**Clinical Pharmacology**

**openNCA PK Computation Engine Specifications**

**Document version v3.3**

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Prepared for/by:

Pfizer Inc  
Clinical Pharmacology

Document Approval

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| Author | | | | |
|  | I have written this document version to identify the computation rules required for openNCA PK Computation Engine. | | |  |
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| I have written this document to identify the computation rules required for openNCA Computation Engine. | | | | |
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| I agree that this document represents accurate computation rules for openNCA Computation Engine. | | | | |
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Table of Contents

[Table of Contents 3](#_Toc5186395)

[Document History 5](#_Toc5186396)

[1. Overview 6](#_Toc5186397)

[2. Purpose 6](#_Toc5186398)

[3. Document Scope 6](#_Toc5186399)

[4. Non-Compartmental Analysis Models/Parameters 6](#_Toc5186400)

[4.1. Definitions 6](#_Toc5186401)

[4.2. Models 7](#_Toc5186402)

[4.3. Model Configuration Template 7](#_Toc5186403)

[4.1. Secondary Configuration Template 16](#_Toc5186404)

[5. Parameter Units 16](#_Toc5186405)

[5.1. Parameter Unit Classes 16](#_Toc5186406)

[5.2. Parameter Unit Conversions 20](#_Toc5186407)

[6. Parameter significant figures and decimal places 20](#_Toc5186408)

[6.1. Automated Reporting Presentations 21](#_Toc5186409)

[6.2. Publishing Results Presentation 21](#_Toc5186410)

[7. Pre Computation Checks and Dataset or Computation Flag Definitions 21](#_Toc5186411)

[7.1. Data Items Required – Configuration of Dataset 30](#_Toc5186412)

[7.2. FLAGS Dataset 30](#_Toc5186413)

[7.2.1. Example FLAGS Dataset 32](#_Toc5186414)

[8. Primary Parameter Calculations 33](#_Toc5186415)

[8.1. Matrix Independent Parameters 33](#_Toc5186416)

[8.2. Matrix Dependent Parameters 34](#_Toc5186417)

[8.2.1. Blood/Serum/Plasma 34](#_Toc5186418)

[8.2.2. Urine 78](#_Toc5186419)

[8.2.3. Derived PK Parameters with urine and plasma 89](#_Toc5186420)

[8.2.4. Derived PK Parameters for Metabolites 90](#_Toc5186421)

[8.2.5. Derived PK Parameters – Dose Normalization 91](#_Toc5186422)

[8.2.6. Derived PK Parameters - Body Size Normalization 92](#_Toc5186423)

[9. Derived PK Parameters for Absolute and Relative Bioavailability 97](#_Toc5186424)

[10. Computation Engine User Interface Considerations 98](#_Toc5186425)

[10.1. User/Application Interface 98](#_Toc5186426)

[10.2. KEL related user interface computations 98](#_Toc5186427)

[10.3. Parameters on-the-fly 99](#_Toc5186428)

[11. References 99](#_Toc5186429)

[11.1. Project References 99](#_Toc5186430)

[11.2. Technical References 100](#_Toc5186431)

[12. Appendices 101](#_Toc5186432)

[12.1. Calculating AUC, AUMC, and AURC 101](#_Toc5186433)

[12.1.1. Background 101](#_Toc5186434)

[12.1.2. Options 102](#_Toc5186435)

[12.1.3. NCA Computations: General Issues with Data Handling Rules for Partial Areas 103](#_Toc5186436)

[12.2. Significant Figures Definition 105](#_Toc5186437)

[12.2.1. Definition 105](#_Toc5186438)

[12.2.2. Multiplication and Division 105](#_Toc5186439)

[12.2.3. Addition and Subtraction 106](#_Toc5186440)

[12.3. Missing Data 106](#_Toc5186441)

[12.3.1. Missing Data at Time of Dose 106](#_Toc5186442)

[12.3.2. AUC Calculations and Missing Data 106](#_Toc5186443)

[12.4. Study Design Elements (SDE)/Profile Identifier 108](#_Toc5186444)

[12.5. Analysis Ready Dataset (ARD) 110](#_Toc5186445)

[12.6. Other Key Assumptions 122](#_Toc5186446)

[12.7. Footnoting for PK Parameter Estimates 122](#_Toc5186447)

[12.8. Examples of Profiles and Dosing Intervals in openNCA 122](#_Toc5186448)

[12.8.1. Example 1: Single-Dose Profiles 122](#_Toc5186449)

[12.8.2. Example 2: Multiple-Dose Profile 123](#_Toc5186450)

[12.8.3. Example 3: Multiple-Dose Profile Including 2 Doses 125](#_Toc5186451)

[12.8.4. Example 4: Multiple-Dose Profile Including 3 Doses 126](#_Toc5186452)

[12.9. Data Exclusion Flag Fields 128](#_Toc5186453)

[12.10. Multiple Dosing Interval and TAU handling 130](#_Toc5186454)

[12.10.1. Variables 130](#_Toc5186455)

[12.10.2. Example Dataset illustrating Dosing Intervals, TAUi and TOLDi values 132](#_Toc5186456)

[12.10.3. Flow 134](#_Toc5186457)

[12.10.4. Important assumptions 134](#_Toc5186458)

[12.11. Parameter Model Mapping List - Primary and Derived 134](#_Toc5186459)

[12.12. C0 Example 138](#_Toc5186460)

[12.12.1. Example Data 138](#_Toc5186461)

[12.12.2. Estimate C0 139](#_Toc5186462)

[12.12.3. Estimate AUCXBPCTO (observed) 139](#_Toc5186463)

[12.12.4. Estimate AUCXBPCTP (predicted) 140](#_Toc5186464)

[12.13. Volume/Weight conversion for Urine data 140](#_Toc5186465)

[12.13.1. Calculation 140](#_Toc5186466)

[12.13.2. NCA Dataset correction for PKAMT 141](#_Toc5186467)

[12.14. Derivations for Parameter calculations 141](#_Toc5186468)

[12.15. Calling Sequences for openNCA Computation Engine R Package 146](#_Toc5186469)

Document History

| Revision | Issue Date | Comments |
| --- | --- | --- |
| 1.0 | 06-Feb-2006 | Initial release for eNCA release 1.0 |
| 2.0 | 06-Nov-2006 | Updated for eNCA release 1.0 |
| 3.0 | 30-May-2007 | Initial release for eNCA release 2.0 |
| 4.0 | 12-May-2017 | Update required for development of new NCA application environment under the EQuIP program. |
| 4.0 | 18-June-2018 | Updated modifications to Model Configuration Template – updated with additional entries to reflect the dates and times of sample collection and dosing  Remove eNCA references  Add Secondary Configuration Template concept to support analysis of Derived or Secondary Parameters.  Added Urine data handling section  Refined TAUi/TOLDi/DIi details and changed definition of TOLD  Added TID multiple dosing profile |

# Overview

eNCA is an existing (2018) pharmacokinetic (PK) data management and analysis system developed by Pfizer Inc with full audit and security features developed as a web-based multi-tier application.

eNCA provides mathematical and graphical computational capability via “eNCA Computation Engine“ for various functionality within the eNCA application to perform PK Non Compartmental Analysis, reporting and other tasks.

This version of this document is based on the eNCA PK Computation Engine Specifications version 2.0 documentation and reflects an updated version of the PK NCA Computation Engine specifications that will be used to support the development and production utilization of the openNCA PK NCA Computation Engine code base developed in 2017-2018 for the Pfizer Enhanced Quantitative Informatics Platform (EQuIP) project supporting the analysis and content repository for the openNCA PK open source application being developed as one of the EQuIP deliverables through the Pfizer Clinical Pharmacology discipline. As such, this specification effectively describes release 3.0 of the computation engine.

The openNCA PK computation engine is planned for development as one or more R packages and utilizes dependencies from the [CRAN](https://cran.r-project.org/) and [GitHub](https://github.com/) package repositories.

The openNCA package development is itself hosted in [GitHub](https://github.com/tensfeldt/openNCA).

# Purpose

This document provides the openNCA computation engine requirements, a part of Pfizer EQuIP NCA Requirements Package.

# Document Scope

The scope of this document is limited to documenting computing rules to be used for:

1. Calculating Primary and Secondary or Derived Parameter for Non Compartmental Analysis (NCA) based on total plasma/serum/blood/urine concentration
2. Generating Plots of individual profile data to facilitate exploration and selection of the data points for computation of kel and subject inclusion/exclusion for kel and the associated parameters (t1/2 and AUCinf)

**Note:** Pharmacokinetic Parameters are calculated based on Pfizer’s Clinical Pharmacology Guidance documentation (as referenced below) or as identified in the references provided in the Section References.

# Non-Compartmental Analysis Models/Parameters

## Definitions

|  |  |
| --- | --- |
| **Primary Parameters** | Parameters generated by the system for one of the primary pharmacokinetic computation Models in the following scenarios:  Applying computational pharmacokinetic algorithms on the concentration dataset (e.g.: AUC, Tmax, Cmax, etc.)  Applying pre-defined computation algorithms on the combination of concentration dataset and other primary parameters (e.g.: Dose normalized parameters, etc.) |
| **Derived Parameters** | Parameters generated utilizing primary parameters from one or more datasets. incorporating different analytes, cohorts, visits, or periods.  Derived parameters either can be automatically computed by custom script using primary parameters to generate new parameters. (e.g.: AUC Ratios, etc.)  These parameters are calculated by computation engine automatically when feasible or defined by user developed adhoc or stored script based on particular study analysis needs.  Note that ***Derived Parameters***, i.e. parameters that were previously referred to inprior editions of this specification associated with the legacy Pfizer eNCA system as ***Secondary Parameters*** are also listed in the Appendix Section Parameter Model Mapping List - Primary and Derived. |

## Models

The design of the openNCA computation engine specification is intended to be driven by user defined configuration settings. Once the data are selected and all configurations selected and data flags set as desired, execution of the parameter Model with these inputs will create all of the parameters associated with the model specification. The model input configuration requirements for executing the models and associated flags controlling execution and reporting are specified in Section Model Configuration Template and the data requirements supporting the configuration requirements are specified in Section Analysis Ready Dataset (ARD)

All primary parameter computation within openNCA will be grouped in the following PK NCA models:

|  |  |  |
| --- | --- | --- |
| Model | Matrix | Dosing Route |
| M1 (SD/SS) | Plasma/Serum/Blood | Extravascular |
| M2 (SD/SS) | Plasma/Serum/Blood | Bolus IV |
| M3 (SD/SS) | Plasma/Serum/Blood | Constant Infusion |
| M4 (SD/SS) | Urine | Extravascular/Bolus IV/Constant Infusion |

Note: SD = single dose; SS = steady-state

*Refer to the Appendix “*Parameter Model Mapping List - Primary and Derived *” for the summary of parameters to be computed for individual model.*

## Model Configuration Template

The following table outlines the configuration entries for the parameterized data items and settings required for executing a specific model successfully or executing one or more of the pre-model computation data checks or transformations. This is a ***Model Configuration Template***.

Note that the list of Parameters defined for number of Decimal Places and Significant Digits for reporting purposes is extensible and the selection displayed below is for illustration only.

Note also that values of these fields are set or reset from default values by the analyst in defining the specifications for the analysis to be performed.

Note further that reference to FLAGs or FLAGs datasets in this document refers to a data input file that is used to communicate selections associated with the determination of the data points associated with the terminal elimination phase for computation of associated parameters such as KEL or THALF, etc as well as selections associated with definition of dosing intervals and other flags associated with selection of a profile and its analysis results for further summarization and reporting.

| PARAMETER | VALUE | Description |
| --- | --- | --- |
| MODEL[a] | M1 | Model M1 is specified, selected by analyst.  Application Drop Down will present the following options that the analyst can select to override the default in the MCT: M1/M2/M3/M4 |
| DOSINGTYPE[a] | SD | Single Dose identified/set by analyst  Application Drop Down will present the following options that the analyst can select to override the default in the MCT:  SS/SD |
| MAXDOSINGINTERVALS | 5 | Configurable number of dosing intervals. If this is not present in the MCT, the computation engine code will assume a default of 5. The MCT can be updated if more than 5 are necessary. |
| AUCMETHOD[a] | LINLOG | LINLOG AUC method selected by analyst  Application Drop Down will present the following options that the analyst can select to override the default in the MCT:  LINLOG/LIN/LOG/”LINUP-LOGDOWN” |
| SAMPLETYPE[b] | PKCOLL | Interval vs Point sample collection. |
| SDEID[b] | SDEID | “SDEID” is the name of the field identifying the individual profiles of data |
| RETURNCOLS\*[b] | See Footnote for RETURNCOLS below \*\* | Semi-colon delimited list of columns from the INPUT data or FLAGS that are incorporated into the results set and to include all of the parameters from the nca computations for the model selected. |
| PKADT[b] | PKADT | Actual Sample Collection Start Date |
| PKATM[b] | PKATM | Actual Sample Collecton Start Time |
| PKADTE[b] | PKADTE | Actual Sample Collection Stop Date |
| PKATME[b] | PKATME | Actual Sample Collecton Stop Time |
| DRGDATE[b] | DRGDATE | Date of Dosing Start |
| DOSETIM[b] | DOSETIME | Time of Dosing Start |
| DRGDATESTOP\*[b] | ACENDTF | Date of Dosing Stop (For Infusion Dosing) |
| DOSETIMESTOP\*[b] | ACENTMF | Time of Dosing Stop (For Infusion Dosing) |
| NOMTIME[b] | PKPTMS | Nominal time is selected as data field “PKPTMS” |
| NOMTIMEU[b] | PKPTMU | Nominal time units |
| ACTTIME[b] | PKATPD | Actual Time data field |
| ACTTIMEU[b] | PKATPDU | Actual Time Units data field |
| NOMENDTIME[b] | PKPTME | Nominal End of Sample Collection Interval Time field |
| NOMENDTIMEU[b] | PKPTMU | Units for Nominal End of Sample Collection Interval Time field |
| ACTENDTIME[b] | PKATPDE | Actual End of Sample Collection Interval Time field |
| ACTENDTIMEU[b] | PKATPDEU | Units for actual End of Sample Collection Interval Time field |
| CONCRAW\*[b] | PKCNC | Raw input concentration data represented as character values |
| CONC[b] | PKCNCN | Concentration numeric value data field |
| CONCU[b] | PKCNCU | Concentration units data field |
| CONCMOD[b] | PKCNCNMOD | Modified Concentration numeric value data field |
| CONCMODU[b] | PKCNCNMODU | Concentration units data field for Modified Concentration value |
| TIME[b] | Nominal | Time selected to be Nominal as default; Two options are “Nominal” or “Actual”  If TIME resolves to a column name in the supplied dataset, this is the data field that will be utilized. |
| TIMEU[b] | PKPTMU | UNITS for TIME only required if TIME itself resolves to a column name in the supplied dataset. Entry not required if TIME is selected either as “Nominal” or “Actual” value. |
| LLOQPATTERNS\* | LLOQ|BLQ|^[<]{1} | LLOQ Patterns to match in CONC field |
| AMOUNT[b] | PKAMT | Amount data field |
| AMOUNTU[b] | PKAMTU | Amount Units data field |
|  |  |  |
|  |  |  |
| DOSEi[b] (alternate is DOSE) | DOSEi | Dose (DOSEi) data field. There will be as many of these entries in the ***Model Configuration Template*** as the maximum number of doses for individual dosing intervals. The MCT entry for dose can be “DOSE” if there’s a singe dosing interval within a profile, i.e. a single dose profile. |
| DOSEiU[b] (alternate is DOSEU) | DOSEiU | Dose Units (DOSEUi) data field. There will be as many of these entries in the ***Model Configuration Template*** as the maximum number of doses for individual profiles. Alternatively, the MCT entry for dose unit could be simply “DOSEU” if there’s single dosing interval within a profile, i.e. a single dose profile. |
| DOFi\*[b] | TIMEU | Duration of Infusion |
| TOLD*i*\*[b] | TOLD1 | Time of last dose of a specific profile data field.  There will be as many of these entries in the ***Model Configuration Template*** as the maximum number of doses for individual profiles |
| TOLD*i*U\*[b] | TOLD1U | Units for Time of last dose data field. There will be as many of these entries in the ***Model Configuration Template*** as the maximum number of doses for individual profiles |
| TAU*i*[b] | TAU*i*U | Data field for TAUi. There will be as many of these entries in the ***Model Configuration Template*** as the maximum number of doses for individual profiles |
| TAU*i*U[b] | TAU*i*U | Data field for Units for TAUi. There will be as many of these entries in the ***Model Configuration Template*** as the maximum number of doses for individual profiles |
| FLGEXPROF[a] | 1=TRUE  0=FALSE=DEFAULT | If set to 1 then don’t compute PROFILE level parameters but only compute DOSING INTERVAL level parameters. |
| **FLGMERGE**\*[b] | PKDATAROWID | Data item utilized to merge FLAG dataset items into the concentration dataset |
| **FLGEXKEL**[c] | FLGEXKEL | **KEL Exclude Flag Field** |
| **FLGEXAUC**[c] | FLGEXAUC | **AUC Exclude Flag Field** |
| **FLGEXSDE**[c] | FLGEXSDE | **Exclude from ALL computations flag field** |
| **FLGEXST**[c] | FLGEXST | **Data point excluded from concentration summary statistics flag field** |
| **FLGCZERO**[c] | FLGCZERO | **Data point excluded from computation of C0 for Model 2.** |
| **FLGACCEPTKELCRIT**\*[d] | KELRSQ>=0.9, KELNOPT>=3,  AUCXPCTP<=0.2,  KEL>0 | Acceptance criteria for parameters dependent upon the quality of the estimation of KEL. Specification is written as a comma delimited list of Boolean expressions that are evaluated relative to the data and parameter acceptance. The example VALUE illustrates a single Boolean expression. |
| **FLGNOCMAX** | 1=TRUE=Default  0=FALSE | KEL optimal selection algorithm includes CMAX/TMAX data pair or not. |
| **FLGACCEPTTAU**\*[d] | FLGACCEPTTAU |  |
| **FLGACCEPTPREDOSECRIT**\*[d] | *0.05* | *Flag indicating upper limit criteria for identifying a pre-dose concentration value as a percentage of CMAXi for the interval/profile.* |
| **LASTTIMEACCEPTCRIT**\*[d] | 0.95 \* TAUi | LASTTIME Acceptance Limit as a percentage of TAUi |
| **SPANRATIOCRIT**\*[d] | 2 | Flag indicating the criteria to be considered in the evaluation of the duration of the interval over which the THALF is estimated to the estimated THALF. |
| **NORMBS**\*[b] | BW | NORMBS is defined as the name of the data field containing the body size measurement to utilize in parameter body size normalizations. By default, it’s defined to be the “Body Weight”, BW or baseline/screening WT of the subject, typically the baseline body weight. |
| **NORMBSU**\*[b] | BWU | Units data field for **NORMBS** |
| MATRIX[b] | PKBDFLD | Name of the data field recording the bioanalytical matrix. |
| PKTERMPARENT[d] |  | Value identifying the PARENT analyte from the unique values of PKTERM. Assumption is that remaining values are “metabolites” |
| PKPCOM[c] | PKPCOM | PK Analyst Comments |
| TIMEOUTPUTUNIT[d] | HR | Unit Class to convert for TIMEU data item |
| AMOUNTOUTPUTUNIT[d] |  | Unit Class to convert for AMOUNTU data item |
| DOSEOUTPUTUNIT[d] |  | Unit Class to convert for DOSEU data item |
| VOLUMEOUTPUTUNIT[d] |  | Unit Class to convert for VOLUMEU data item |
| CONCOUTPUTUNIT[d] |  | Unit Class to convert for CONCU data item |
| KELOUTPUTUNIT[d] |  | Unit Class to convert for KELU data item |
| CLOUTPUTUNIT[d] |  | Unit Class to convert for CLU data item |
| AUCOUTPUTUNIT[d] |  | Unit Class to convert for AUCU data item |
| AUMCOUTPUTUNIT[d] |  | Unit Class to convert for AUMCU data item |
| AUCNORMOUTPUTUNIT[d] |  | Unit Class to convert for AUCNORMU data item |
| AUROUTPUTUNIT[d] |  | Unit Class to convert for AURCU data item |
| CONCNORMOUTPUTUNIT[d] |  | Unit Class to convert for CONCNORMU data item |
| RATEOUTPUTUNIT\*[d] |  | Unit Class to convert for RATEU data item |
| VOLUMENORMOUTPUTUNIT\*[d] |  | Unit Class to convert for VOLUMEWU data item |
| CLNORMOUTPUTUNIT\*[d] |  | Unit Class to convert for CLWU data item |
| AUCNPAIR[e] | 0 | Indicates # of partial AUCs requested |
| AUC.i.T1[e] | 0 | 1st starting time point T1 of the T1\_T2 time pair for partial AUC computations. There are 0 to AUCNPAIRs of of these values stored in the ***Model Configuration Template***. These entries are included in the ***Model Configuration Template*** if no partial Area computations are specified.  This will be recorded/labelled as AUC.1.T1 for the start of the first interval  If AUCNPAIR == 0, no AUC.i.T1 nor AUC.i.T2 entries need to be incorporated into the ***Model Configuration Template*** |
| AUC.i.T2[e] | 7 | 1st ending time point T2 of the Partial AUC time range.  This will be recorded as AUC.1.T2 for the end of the first interval |
| AUC.i+1.T1[e] | 8 | 2nd starting time point T1 of the set of AUCNPAIR timepairs for partial AUC computations  This will be recorded as AUC.<i+1>.T1 for the start of the i+1 interval |
| AUC.i+1.T2[e] | 48 | 2nd ending time point T2 of the Partial AUC time range.  This will be recorded as AUC.<i+1>.T1 for the end of the i+1 interval |
| AUC.AUCNPAIR.T1[e] | 0 | AUCNPAIRth starting time point T1 of the set of last of the partial AUCNPAIR timepairs for partial AUC computations specified  This will be recorded as AUC.<NPAIR>.T1 for the start of the AUCNPAIRth interval |
| AUC.AUCNPAIR.T2[e] | 64 | AUCNPAIRth ending time point T2 of the last of the partial AUCNPAIR timeparis for partial AUC computations specified.  This will be recorded as AUC.<NPAIR>.T1 for the end of the AUCNPAIRth interval |
| ParameterList[g] |  | Semi-colon delimited list of parameters that are utilized in reporting/publishing.  See footnote for details. |
| DATADISPLAYLIST[b] |  | Semi-colon delimited list of dataset items that are utilized and interactively displayed during analysis of individual profiles in analysis module of the openNCA application. No direct utilization in the Computation Engine code. |
| ParameterDisplayList[g] |  | Semi-colon delimited list of parameters that are utilized in interactively displaying computed parameters during analysis of individual profiles in analysis module of an application (openNCA) that utilizes the computation engine.  See footnote for details. |
| FLAGSDISPLAYLIST[b] | See Representative example in Section FLAGS Dataset | Semi-colon delimited list of data fields (nominal time, actual time, concentration, dose, treatment, etc.), selected analysis selection flags such as **FLGEXKEL** and **FLGEXAUC** and return values from the results of the computation engine model execution, i.e. FLG |
| OPTIMIZEKEL | **1** | Allowed values (1/0)  1=FALSE=Default  OPTIMIZEKEL specifies whether to implement **Set KEL optimal data selection** algorithm or not. |
| INCLUDEINTERPOLATION† | **1** | Allowed values (1/0)  1=TRUE=Default  INCLUDEINTERPOLATION argument specifies whether to implement interpolation for AUC computations or not. |
| INCLUDEEXTRAPOLATION† | 1 | Allowed Values (1/0) 1=TRUE=Default  INCLUDEEXTRAPOLATION argument specifies whether to implement extrapoloation for AUC computations or not. |
| ***DP.<PARAMETERNAME>***[f] | ***<Decimal Places>*** | ***An entry for the # of decimal places for each parameter associated with a Model. The entry in this table is for illustration only.*** |
| DP.DEFAULT[d] | 3 | The default for the # of decimal places if a parameter is not defined in the ***Model Configuration Template***. |
| DP.CMAXi[d] | 2 | For example only |
| DP.AUCALL[d] | 4 | For example only |
| DP.KEL[d] | 4 | For example only |
| DP.KELRSQ[d] | 4 | For example only |
| ***SF.<PARAMETERNAME>***[f] | ***<Significant Figures>*** | ***An entry for the # of significant figures for each parameter associated with a Model. The entry in this table is for illustration only.*** |
| SF.DEFAULT[d] | 3 | The default for the # of significant figures if a parameter is not defined in the ***Model Configuration Template***. |
| SF.AUCALL[d] | 3 | For example only |
| SF.AUCINFP[d] | 3 | For example only |
| SF.AUCINFPN[d] | 3 | For example only |
| SF.AUCLAST[d] | 3 | For example only |
| SF.AUCT[d] | 3 | For example only |
| SF.CLFIP[d] | 3 | For example only |
| SF.CLFO[d] | 3 | For example only |
| SF.CMAXI[d] | 3 | For example only |
| SF.CMAXIN[d] | 3 | For example only |
| SF.CMINI[d] | 3 | For example only |
| SF.CTROUGHI[d] | 3 | For example only |
| SF.KEL[d] | 4 | For example only |
| SF.KELRSQ[d] | 4 | For example only |
| SF.KELRSQA[d] | 4 | For example only |
| SF.THALF[d] | 4 | For example only |

[a] – configuration comes from selected MCT config file. Analyst can select from a dropdown of standard options which override the default presented in the MCT.

[b] – The entries in the MCT represent default data field items in the source dataset, either ARD (or some other file specification) or integration with PIMS or via merging in a Data Transformation utilizing data from an ARD or similar file format and a file representing data from the CRF. The application will permit the analyst to change this default value mapping from the input dataset to a different value also appearing in the input dataset. The user can re-select the default value from one of the existing values in the source dataset. In the case of the TIME MCT value, this entry may either represent a pointer to the selected NOMTIME data field value if “NOMINAL” is selected or the ACTTIME value if “ACTUAL” is selected. Alternatively TIME can be selected to be the name of a datafield in the dataset.

[c] – These are flags set an defined through the FLAGs dataset by the analyst in 1) the NCA Application Analysis Module or 2) in the input dataset. If set in the input dataset, these represent initialization values that set the initial settings or selection of the flags in the NCA Analysis Module. The user can then reset these as desired in the NCA Analysis Module. The flags dataset itself will contain the values that the user has requested from the NCA Analysis Module and will be used to replace any values in the input dataset on merging the flags dataset with the input dataset.

[d] – generally items representing flags that have default values and can be updated through text direct entry in the NCA Analysis Module.

[e] – entries required for the MCT associated with Partial Areas. Note the default MCTs as configuration items to the Computation Engine will ALL have AUCNPAIR = 0 and thus no entries for the endpoints of the AUC time pairs. The entries for the AUC time pairs are only made through the NCA Analysis Module itself through analyst actions take to define them. Once these are set or updated by the user, the value for ANCNPAIR is recalculated to reflect the number of defined pairs requested by the user.

[f] - The particular entry in this table is for illustration only and is not a formal component of the MCT definition.

[g] - Note that section Parameter Model Mapping List - Primary and Derived contains the mapping between Models, dosing regimen (Single vs Multiple or Steady-State dosing) and the parameters available as default in the models output and defined in the PARAMETERLIST and PARAMETERDISPLAYLIST values for the MCT.

\* - New with release 3.0 of the Computation Engine Specifications

\*\* - RETURNCOLS – default example: UDSDEID;SDEID;STUDY;SITEID;SUBJID;RAND;TREATXT;TRTCD;PKCOLL;PKBDFLD;PKTERM;PERIODU;PERIOD;VISITU;VISIT;PHASE;PCANMETH;DSREAS;DSSTAT;HT;WT;AGEDERU;AGEDER;WTUNI;WTRAW;HTUNI;HTRAW;RACEOTH;RACES;SEX;RACIALD;ETHNIC;DOSE;DOSEi;DOSEiU;ACTTRT;ACTTRTC;ACTTRTS;TREATSEQ;FLGEMESIS;FU;UDFNAME1;UDFVALUE1;UDFUNIT1;UDFNAMEn;UDFVALUEn;UDFUNITn;DATASTATUS;PKPCOM;PKSIGFIG;PKDECPL;DATABLINDSTATUS;PCMETHOD;PCLLOQ;PCSTRESU;PCNAM;ROUTE;TAU1;TAI1U;TOLD1;TOLD1U

\*\*\* - FLAGSDISPLAYLIST – example: PKDATAROWID;PKPTMS;PKATPD;PKCNCN;PKCNCNMOD;FLGEXKEL;FLGEXAUC;FLGEXSDE;FLGEXST;FLGCZERO;x`PKPCOM;PKRCOM;FLGEMESIS;TAU1;TOLD1;TAU2;TOLD2;DOSE

**†-** Not yet implemented in openNCA interface to computation engine nor in computation engine code itself.

## Secondary Configuration Template

The secondary configuration template (SCT) specifies for the following derived/secondary parameter types the specific settings and data requirements to finalize the computations for the parameters.

# Parameter Units

## Parameter Unit Classes

Concentration, Time and Dose data units are specified in the PK data file and are identified by the user in the parameter calculation user interface. Parameter units are obtained from the concentration, time and dose data units.

The table below catalogs the unit classes and parameters associated with each class.

| **Unit Class** | **Unit Column Name** | **Parameters** | **Supported Units (for automated conversions)** |
| --- | --- | --- | --- |
| Dimensionless |  | KELNOPT KELRSQ KELRSQA PTR*i*  PTROUGHRi  PTROUGHRENDi PTF*i* THALFF  **F**  **FREL**  **FRELLASTi**  **FTAUi**  MRAUCINF  MRAUCLAST  MRAUCTAUi  MRCMAXi  RACi  RACCMAXi  RACCMINi  RSSi | NA |
| Dimensionless % |  | AUCXPCTO AUCXPCTOi AUCXPCTP AUCXPCTPi  AUMCXPTO AUMCXPTOi  AUMCXPTP  AUMCXPTPi   **AETPCT** **AEPCT**  **AET** **AETAU*PTi*** **AUCXBPCTO** **AUCXBPCTP** AURCXPCTO AURCXPCTP  FA | NA (%) |
| Time  (t) | TIMEU | TOLD*i* TMAX*i* TMIN*i* TLAST  TLASTi TLAG KELTMLO KELTMHI THALF  MRTIVIFP(i)  MRTIVIFP(i)  MRTEVIFP(i)  MRTEVIFO(i)  MRTLAST TMAXRATEi  DOFi  **MIDPTLAST**  MIDPTLASTi | Hour = HR  Minute = MIN |
| Amount  (mass/wt) | AMOUNTU | AT AET AE AETAUi | Grams = GM  Milligrams = MG  Micrograms = UG  Nanograms = NG  Picograms = PG  Femtograms = FG |
| Dose Amount  (mass/wt) or (mass/wt)/(bodywt) | DOSEU | DOSE  DOSEi DOSEC | Grams = GM  Milligrams = MG  Micrograms = UG  Nanograms = NG  Picograms = PG  Femtograms = FG  DPM for ADME studies  ngeq (nanogram equivalent) (ADME)  Body(wt) = kg |
| Volume  (v) | VOLUMEU | VZFO VZFP **VSSO**  VSSP **VSSPi** VZO VZP VOLSUM V0  **VZFTAUi**  **VZFTAUWi**  **VZTAUi** | Liter = L  Deciliter = DL  Centiliter = CL  Milliliter = ML  Nanoliter = NL  Picoliters = PL |
| Amount/Volume  (wt/v) | CONCU | CMAX  CMAX*i*  **CMAXC**  **CMAXCi**  CMIN*i*  CLAST CLASTi CTROUGH*i*  CTROUGHEND*i* CAV  CAV*i* C0 KELC0 | Any combination of Unit Class Amount (mass/wt) and Volume (v)  Eg:  NG/ML  GM/L  MG/ML  PG/ML  DPM/ML  ngeq/ML  (Note: Separator will be “/” with no spaces) |
| 1/Time  (t-1) | KELU | KEL | Hour = HR  Minute = MIN  Output format  1/HR  (Note: Separator will be “/” with no spaces) |
| Volume/Time  (v/t) | CLU | CLFO CLFP CLO CLP  CLFTAUi  CLR  CLRTAUi  CLRT  CLTAUi | Any combination of Unit Class Time (t) and Volume (v)  Examples:  ML/HR  L/HR  ML/MIN  Not acceptable format  {(PG/ML)/MG}/HR  {(MG/ML)/MG}/HR  (Note: Separator will be “/” with no spaces) |
| Amount \*Time/Volume  (wt\*t/v) | AUCU | AUCT AUCT1\_T2 AUCALL  AUCLAST AUCLASTi  **AUCLASTC**  **AUCLASTCi** AUCINFO  AUCINFOi  **AUCINFOC** AUCINFP  AUCINFPi  **AUCINFPC** AUCTAU*i* | Any combination of Unit Class Amount (mass/wt), Volume (v) and Time (t)  Example:  NG.HR/ML  (Note: Separator will be “.” and “/” with no spaces) |
| Amount \*Time2 /Volume  (wt\*t2/v) | AUMCU | AUMCLAST  AUMCLASTi AUMCINFO AUMCINFOi  AUMCINFP AUMCINFPi  AUMCTAUi | Any combination of Unit Class Amount (mass/wt), Volume (v) and Time (t)  Example:  NG.HR.HR/ML  (Note: Separator will be “.” and “/” with no spaces) |
| [Amount \*Time/Volume]/ Amount ((wt\*t/v)/wt) | AUCNORMU | AUCTDN  **AUCLASTDNi**  AUCINFODN  AUCINFPDN  **AUCTAUDNi** | Any combination of Unit Class Amount (mass/wt), Volume (v) and Time (t)  Example:  NG.HR/ML/MG  (Note: Separator will be “.” and “/” with no spaces) |
| [Volume\*Amount]/Volume | AURCU | AURCLAST AURCINFO AURCINFP AURCALL  AURCT1\_T2 | Any combination of Unit Class Amount (mass/wt), Volume (v) and Time (t)  Example:  ML.NG/ML  (Note: Separator will be “.” and “/” with no spaces) |
| [Amount /Volume]/ Amount  (wt/v/wt) | CONCNORMU | **CMAXDN**  **CMAXDNi** | Any combination of Unit Class Amount (mass/wt) and Volume (v)  Example:  NG/ML/MG  (Note: Separator will be “/” with no spaces) |
| Amount/Time (wt/t) | RATEU | **MAXRATE**  **MAXRATEi**  RATELASTi  RATEA  RATEN | Any combination of Unit Class Amount (mass/wt) and Time (t) |
| Volume normalized by body weight  (v/kg) | VOLUMEWU | VZFOW VZFPW  VZFTAUWi VSSOW VSSPWi VZOW VZPW  VZTAUW | Any combination of Unit Class Volume (v) and body weight (kg)  Example:  L/KG |
| Volume/Time normalized by body weight  (v/t/kg) | CLWU | CLFOW CLFPW  CLFTAUWi CLOW CLPW  CLTAUWi | Any combination of Unit Class Time (t), Volume (v) and body weight (kg)  Examples:  ML/HR/KG  L/HR/KG  ML/MIN/KG  (Note: Separator will be “/” with no spaces) |

## Parameter Unit Conversions

By default, parameter units are derived based on the units of the primary quantities involved.

For system to process required automated unit conversions:

1. User must specify the required conversions for a particular unit classes in the application UI, based on the supported units columns of the table above.
2. The source data units must be in the supported units format for the system to automatically compute and convert units and scale associated parameter values where necessary.

# Parameter significant figures and decimal places

**Note:**

1. All parameters are calculated and stored with double precision in the application at all times.
2. For definition and application logic to calculate significant figures and decimal places, refer to the Appendix “Significant Figures Definition”
3. The default settings and configuration items defining the number of decimal places and significant figures to be utilized for specific parameters are outlined in the table appearing in Section Model Input/Calling Arguments and Data Flags.

## Automated Reporting Presentations

For all automated reports generated by the NCA computation engine the following requirements apply for numeric value handling and presentation:

| Parameter Data within the openNCA database | Double Precision |
| --- | --- |
| Significant figures | NA |
| Decimal places | 3 |

## Publishing Results Presentation

For parameter publishing, the NCA application will use the following numeric value presentations by default. Note the approach here requires that the fields DECPL or SIGFIG are incorporated into the published data.

| Parameter Data within the NCA database | Double Precision |
| --- | --- |
| Parameter Data within the NCA database view (Published parameter views or publishing portal) | Double Precision |
| Populate SIGFIG column in the NCA Published Parameter views/publishing portal | Default value = 3  OR  Value defined by users for a particular parameter at the time of publishing |
| Populate DECPL column in the NCA Published Parameter views/publishing portal | Default value = (value in the decimal places column in the “Primary Parameters Calculations” section)  OR  Value defined by users for a particular parameter at the time of publishing |

# Pre Computation Checks and Dataset or Computation Flag Definitions

The following pre-computation checks will be performed with the concentration data and analysis info/setup information before computing any parameter.

Flag definitions are identified here as dataset flags (data field items intended to be provided with the analysis dataset) or as computation flags, flags that are generated as the analysis is performed and may be represented as dependencies for other computatons.

|  |  |
| --- | --- |
| 1 | **Set/Manage Data Exclusion Flag Fields**  System will identify the following flag data fields which are carried as data items with the concentration data or similar datastructure. The PK Analyst sets these flag field values via the NCA application interface (or could be set by creating the flag fields in batch/direct calls to the computation engine) to exclude/include data points from certain computations and summaries. If NCA analysis parameters have not been calculated the flag fields do not appear as data items in the dataframes associated with concentration and parameter data, depending upon computation engine implementation.  If any of the Data Exclusion Flag Fields isn’t present in the dataset(s), the computation engine sets FLGEXKEL flag field to 1 (i.e. exclude all data points in a profile) and all other data exclusion flag fields to 0 as default values.  Note that data checks are still performed and an associated data point can be excluded if the point fails a data check.  Definitions for each of the following data exclusion flag fields appear in Section Data Exclusion Flag Fields   * **FLGEXKEL**– KEL Exclude flag field   KEL Exclude Flag Based on selections made by PK Analyst. Flag value set to 1 for a data point excludes the data point from Kel calculation and all Kel associated parameter calculations. Flag value set to 0 for a data point includes the data point in the Kel calculation and all Kel associated parameter calculations.   * **FLGEXAUC**– AUC Exclude flag field   AUC Exclude Flag Based on selections made by PK Analyst. Flag value set to 1 for a data point excludes the data point from the AUC calculation and all AUC associated parameter calculations. When the FLGEXAUC Flag value is set to 0 the data point is specifically included in AUC parameter type calculations.   * **FLGEXSDE**– Exclude from ALL computations flag field   Exclude Concentration and Time Data from All Calculations Flag. When the FLGEXSDE Data Flag field is set to 1 for a particular datapoint, it is excluded from all parameter calculations. To exclude an entire SDE/profile completely, all FLGEXSDE values for each of the data point records within the SDE/profile need to be set to 1. This flag is also used to exclude subject from calculations if the analyst excludes an entire subject from all computations by setting the FLGEXSDE flag for all data points from each of the subjects profiles to 1. When the FLGEXST Flag value is set to 0 for an individual data point record, that data point is specifically included in calculations.   * **FLGEXST**– Exclude from summary statistics flag field   Data point excluded from concentration summary statistics flag. Flag set to 1 will cause the specified data point to be excluded from all summary statistic calculations. This Flag does not affect the calculation of Primary or Derived Parameters. Flag set to 0 for a specified data point specifically includes the data point in summary statistic calculations. Note that data checks are still performed and the data point can be excluded if the point fails a data check.  Note: Note that the legacy Pfizer eNCA system only set the default FLGEXKEL value to 1 when the option/argument to estimate KEL automatically for a profile was not selected to estimate KEL, i.e. the argument SetKelFlag==0.  For this edition of the openNCA Computation Engine specification, if the MCT valueOPTIMIZEKEL==1, an algorithm to compute the optimal selection of concentration time data points to select to optimize the linear regression defining KEL is executed. See discussion below for automated selection of data points for KEL estimation. |
| 2 | **FLGACCEPTKELCRIT**  Default acceptance criteria for KEL based parameters based upon guidance from the Clinical Pharmacology Chapter 23 PK and NCA Conventions. Note that the criteria specifications are structured as follows: <DATAITEM><BOOLEAN OPERATOR><NUMERIC CRITERIA>. The Defaults are as follows:   * KELRSQ>=0.9 * KELNOPT>=3 * AUCXPCTP <=20% * KEL>0 (ensure negative slope; KEL is positive for negative terminal elimination phase slope) |
| 3 | **FLGACCEPTKEL**  **Terminal Phase Acceptance/Rejection Criteria Flag Data Field**  The terminal elimination half-life, THALF, and the associated slope or rate constant, KEL, and other parameters based upon the KEL value, should only be reported/accepted when the terminal phase is well characterized. The criteria guidance from the Pfizer [Clinical Pharmacology Chapter 23 PK and NCA Conventions](http://sharepoint.pfizer.com/sites/CPAccelerator/Clin%20Pharm%20Guidance%20Documents/Ch_23_PK%20Data%20and%20NCA%20Conventions_Final_17April2012.pdf?Web=1) specifies the following quantitative criteria:   * A minimum of 3 data values not to include the data value representing the Cmax value * The goodness-of-fit statistic for the regression (r2) should be ≥ 0.9 * The percent of AUCinf based upon extrapolation (AUCXPCTO and/or AUCXPCTP) should be ≤20%. Note that this criteria should be considered for reporting of KEL even for multiple dose data when AUCinf is not otherwise reported. * Terminal elimination phase slopes must be negative. * In addition, THALFF is defined as the ratio of the duration of time over which THALF is estimated to the actual THALF estimate may be considered. A ratio ≥ 2 is preferred but is not required if other criteria are considered acceptable.   The terminal phase acceptance/rejection flag is automatically recorded as a 0 or 1 for the parameters and the associated set of data for the profile based upon the criteria for acceptability as described above for Pfizer Clinical Pharmacology Chapter 23 PK and NCA Conventions Guidance or as a system configuration as described below in other circumstances.  The terminal phase acceptance criteria themselves must be implemented as a configurable method or function so that the criteria can 1) be localized for a particular implementation 2) can be customized for a particular project/drug candidate 3) can be redefined by the analyst to implement analysis specific considerations.  The system should permit these flags to be automated, defined by standard methods (scripts/etc) that are specific to types of analyses/study designs or analysis models, and added to or expanded upon within the library without redevelopment of the system, i.e. if implemented through R scripting/programming, the business could add to these or modify the criteria as system configuration and/or global library content.  Note that the approach here could be implemented on a case by case basis if the criteria are differentially applied by parameter. This may require user script development similar to the code example below to implement.   * **Acceptance/Rejection Criteria for Terminal Elimination Phase**   Example R code follows to illustrate the concept , not intended to represent a specific implementation. Note the acceptance/rejection criteria would be specified as a configuration item in the ***Model Configuration Template***. This example illustrates the Pfizer Chapter 23 Conventions Guidance but can be customized to other NCA conventions.  # Note function parse.reg definition not shown here but available on request  evalflgacceptcrit <- function(d, FLGACCEPTKELCRIT) {  FLGACCEPTKELCRIT <- unlist(strsplit(FLGACCEPTKELCRIT, ","))  x <- regexpr("^[[:space:]]\*?([[:alnum:]\_.+]+?)([<>=!]+?)([[:digit:].]+?)$", FLGACCEPTKELCRIT, ignore.case=TRUE, perl=TRUE)  y <- parse.reg(FLGACCEPTKELCRIT, x)  names(y) <- c("VAR", "OPR", "CRIT")  FLGACCEPTKEL <- rep(TRUE, nrow(d))  for(i in 1:nrow(y)) {  x <- d[,as.character(y$VAR[i])]  textcrit <- paste("x",y$OPR[i],y$CRIT[i],sep='')  FLGACCEPTKEL <- FLGACCEPTKEL & eval(parse(text=textcrit))  }  return(FLGACCEPTKEL)  }  FLGACCEPTKELCRIT <- "KELRSQ>=0.9, KELNOPT>=3, AUCXPCTP<=20, KEL>0"  Params$FLGACCEPTKEL <- evalflgacceptcrit(params, FLGACCEPTKELCRIT)  # Set KEL,THALF to missing if FLGACCEPTKEL is false, i.e. 0.  params <- within(params, {  KEL <- ifelse(FLGACCEPTKEL, KEL, NA)  THALF <- ifelse(FLGACCEPTKEL, THALF, NA)  })  Params$FLGACCEPTAUC <- evalflgacceptcrit(params, “AUCXPCTP<20”)  # Set AUCINF,etc to missing if FLGACCEPTKEL is false, i.e. 0.  params <- within(params, {  AUCINFO <- ifelse(FLGACCEPTAUC, AUCINFO, NA)  AUCINFP <- ifelse(FLGACCEPTAUC, AUCINFP, NA)  AUCINFOC <- ifelse(FLGACCEPTAUC, AUCINFOC, NA)  AUCINFPC <- ifelse(FLGACCEPTAUC, AUCINFPC, NA)  })  vlist <- c("KELRSQ", "KELNOPT", "FLGACCEPTKEL", "KEL", "THALF","AUCXPCTP", "FLGACCEPTAUC", "AUCINFO", "AUCINFP")  params[,vlist]  KELRSQ KELNOPT FLGACCEPTKEL KEL THALF AUCXPCTP FLGACCEPTAUC  1 0.9955421 4 TRUE 0.03273358 21.175418 7.68404767 TRUE  2 1.0000000 3 FALSE NA NA 2.99165240 TRUE  3 0.9997271 3 FALSE NA NA 4.66602992 TRUE  4 0.9988047 3 FALSE NA NA 2.96074170 TRUE  5 0.9889092 3 FALSE NA NA 14.58611253 TRUE  6 0.9951571 4 TRUE 0.08330574 8.320521 1.99934371 TRUE  7 0.9999235 3 FALSE NA NA 2.70851854 TRUE  8 0.9887088 5 FALSE NA NA 1.10940746 TRUE  9 0.9848178 3 FALSE NA NA 9.84141179 TRUE  10 0.9613906 5 FALSE NA NA 9.76685944 TRUE  11 0.9655010 4 FALSE NA NA 6.23791345 TRUE  12 0.9991340 3 FALSE NA NA 2.70867797 TRUE  13 0.9823067 6 FALSE NA NA 4.70630987 TRUE  14 0.9863159 6 FALSE NA NA 5.92845655 TRUE  15 0.9988961 3 FALSE NA NA 7.23522456 TRUE  16 0.9968212 3 FALSE NA NA 1.88276503 TRUE  17 0.9998668 4 TRUE 0.03852380 17.992700 5.42144297 TRUE  18 0.9407686 5 FALSE NA NA 5.71496594 TRUE  19 0.9955633 6 TRUE 0.04133378 16.769507 0.52463423 TRUE  20 0.9918967 6 TRUE 0.04579767 15.134987 0.26211759 TRUE |
| 4 | **FLGEMESIS**  Analysis dataset flag indicating that emesis occurred during or prior to a dosing interval/profile. Since this is an analysis dataset flag, it is stored 1 value/record as a data field of the dataset and can vary across study periods depending upon the design of the study.  FLGEMESIS is recorded as  0 – no emesis occurred during the dosing interval or during or prior to the visit  1 – emesis occurred during the dosing interval or during or prior to the visit  Note that the analysis dataset for the computation engine can introduce other similar flags for information and summarization purposes. For example, a flag indicating the PK analysis population that represents the subjects matching the statistical rule book requirements for analysis of pharmacokinetic data could be incorporated. The analyst can use this to guide which subjects and profiles results would be generated and potentially use this information in preparing summaries and reporting items (Tables, Listings, Plots) of the concentration and parameter data from the dataset. |
| 5 | **FLGACCEPTTMAX**  Parameter flag computed based upon indicating the Acceptance/Rejection criteria for TMAXi for subjects who experienced emesis. Used to accept/reject other parameters as well, CMAXi in particular.  **Accept if computed TMAXi for profile < 2 \* median TMAXi for the treatment.**  This uses the FLGEMESIS value and produces a value for the FLGACCEPTTMAX flag. Note this “code” assumes the treatment or period, denoted by [SDEID], has already been selected for consideration.  uconc <- concdata[!duplicated(concdata$SDEID), c(“SUBJID”, “SDEID”, “FLGEMESIS”)]  params <- merge(x=params, y=uconc, by=c(“SUBJID”, “SDEID”), all.x=TRUE)  params$FLGACCEPTTMAX <- ifelse(params$FLGEMESIS==1 & params$TMAX1 <2\*median(params$TMAX1),1,0) |
| 6 | **FLGACCEPTPREDOSECRIT**  Value defining the threshold or upper limit criteria for identifying a pre-dose concentration value as a percentage of CMAXi for the interval/profile. |
| 7 | **FLGACCEPTPREDOSE**  **Flag for Pre-dose Concentrations exceeding the FLGACCEPTPREDOSECRIT**  **(typically 5% by default but configurable in the *Model Configuration Template*) of Cmax for an individual profile**  This flag is set to indicate when a pre-dose concentration value exceeds a threshold limit as a percentage of CMAX and defined by the **FLGACCEPTPREDOSECRIT** configuration item.  Example code illustrates the technique for a single profile of a single subject.  FLGACCEPTPREDOSECRIT <- 0.05 # This would be a configuration item in the system/system library  dataset <- conc  params <- ref  i <- 1  subj <- unique(dataset$SUBJID)  iprofile <- unique(dataset$SDEID[dataset$SUBJID==subj[i]])[i]  kc <- dataset$SUBJID==subj[i] & dataset$SDEID==iprofile  d <- dataset[kc,] # select the concentration data associated with a profile  # initialize FLGACCEPTPREDOSE  params$FLGACCEPTPREDOSE <- rep(TRUE, nrow(params))  kp <- params$SUBJID==subj[i] & params$SDEID==iprofile  p <- params[kp,] # select the parameter data associated with a profile  if(is.element(0, d$PKPTMR)) { params$FLGACCEPTPREDOSE[kp] <- ifelse(d$PKCNCN[d$PKPTMR==0] > FLGACCEPTPREDOSECRIT \* p$CMAX1, 0, 1) } # Note here PKCNCN is numeric concentration and PKPTMS is nominal time post dose. |
| 8 | **LASTTIMEACCEPTCRIT**  Criteria value, defining the threshold limit, for identifying the length of the time profile over which estimate AUCTAUi can be considered acceptable. This is defined as a percentage of the TAUi value. |
| 9 | **FLGACCEPTTAU**  Flag for Acceptance of AUCTAU and associated parameters for an individual profile based upon the LASTTIMEACCEPTCRIT criteria.  FLGACCEPTTAU only is considered if LASTTIME is >= LASTTIMEACCEPTCRIT and FLGACCEPTKEL is 1, i.e. “ACCEPT”  Example code illustrates management of the FLGACCEPTTAU flag and LASTTIMEACCEPTCRIT for several AUCTAU parameters.  This criteria is applied for the last TAUi in the profile.  # Following criteria for FLGACCETTAU is implemented by Computation Engine  LASTTIMEACCEPTCRIT <- 0.95 \* TAUi # 0.95 value is an analysis setting with default of 0.95 or 95% of TAUi  parameters$FLGACCEPTTAU <- ifelse(parameters$LASTTIME>=LASTIMEACCEPTCRIT, 1, 0)  # Following are “Business or Reporting Rules” set outside the Computation Engine  # Note below that  # If FLGACCEPTTAU==1, i.e. “ACCEPT”, **AND**  # FLGACCEPTKEL==1, “ACCEPT”, **AND**  #If t½ is estimable and accepted as per acceptance criteria  # ThenreportAUCTAU*i* if AUCTAU*i* <= 120% \* AUCLASTi; If t½ is not estimated**,** do not reportAUCTAU*i*.  # Report AUCTAU, AUCTAUDN, CLPTAU, or Not  parameters$AUCTAU <- ifelse(FLGACCEPTTAU, parameters$AUCTAU, ifelse(FLGACCEPTKEL, parameters$AUCTAU, NA)  parameters$AUCTAUDN <- ifelse(FLGACCEPTTAU, parameters$AUCTAUDN, ifelse(FLGACCEPTKEL, parameters$AUCTAUDN, NA)  parameters$CLPTAU <- ifelse(FLGACCEPTTAU, parameters$CLTAU, ifelse(FLGACCEPTKEL, parameters$CLTAU, NA) |
| 10 | **SPANRATIOCRIT**  **SPANRATIOCRIT** is the criteria value set in the ***Model Configuration Template*** as the default criteria value for evaluation of the THALFF flag value. The default is typically a value of 2 but can be modified as needed by setting the value of SPANRATIOCRIT. |
| 11 | **Default Dataset Sorting**  Prior to analysis, each study design element identifier (SDEID), or Profile Identifier, defined profile is sorted in ascending order with regard to time.  Following columns are used for sorting  SDEID (or “profile ID”, “PROID”)  NOMTIME (a dataset field is mapped to or defined as NOMTIME)  *Refer to Appendix “*Study Design Elements (SDE)*” for details* |
| 12 | **Set dosing intervals for each study design**  Scenario 1: If data items TAU1 to TAU5 (TAU*i*) and TOLD1 to TOLD5 (TOLD*i*) are available in the dataset and defined as data fields through the ***Model Configuration Template***  If DOSINGTYPE = SD  Then set NDOSE to 1  If DOSINGTYPE = SS  Then set NDOSE = I from the last TAU*i* populated for a specific profile, i.e. representing the total number of dosing intervals in a profile.  Scenario 2: TAU and TOLDi are data items provided through the ***Model Configuration Template***.  System will look for following columns  TAU  TOLD  DOSINGTYPE  System creates a new column NDOSE and sets initial value to 0  If DOSINGTYPE = SD  Then set NDOSE to 1  If DOSINGTYPE = SS  Then set NDOSE = (TOLD) / (TAU)  Note: Computation Engine is designed to allow for a maximum of 5 user defined TAU*i* and TOLD*i* intervals. |
| 13 | **FLGNOCMAX**  FLGNOCMAX specifies the behavior of the KEL optimal data selection algorithm to permit incorporation of the TMAX/CMAX data pair in the computation of KEL optimal result or not.   * FLGNOCMAX = 1 – computation of KEL **should not include** the TMAX/CMAX data pair in the dataset utilized to generate the terminal elimination phase rate constant. * FLGNOCMAX = 0 - – computation of KEL **permits inclusion of** the TMAX/CMAX data pair in the dataset utilized to generate the terminal elimination phase rate constant. |
| 14 | **Set KEL optimal data selection**  The computation engine will utilize an optimal regression approach to determine the optimal selection of concentration time data values, subject to constraints specified in the **FLGACCEPTKELCRIT** criteria setting for the selection of initial KEL exclude (**FLGEXKEL**) flags  **When** the computation engine is called with the MCT value, OPTIMIZEKEL set to 1, i.e. TRUE, to estimate KEL Flag values, the computation engine will execute a regression selection approach to selecting an “optimal” selection of concentration time data points maximizing the constraints associated with the **FLGACCEPTKELCRIT** settings.  For example, if **FLGACCEPTKELCRIT** is set to the default “KELRSQ>=0.9, KELNOPT>=3, AUCXPCTP<=0.2, KEL>0” value, the constraints will be specified as   * KELRSQ >= 0.9 AND KELNOPT >= 3 AND AUCXPCTP<=0.2 AND KEL>0   Which will translate to the following constraints   * Maximize R2 value of the regression * Maximize (number of data points) * Maximize (1-extrapolated AUCINF) * Require negative Terminal Elimination Phase slopes   Note that the constraint critiera, **FLGACCEPTKELCRIT** can be set to alternative values as desired by the analyst by updating the value stored in the MCT. For example, if desired, the criteria could be set to KELRSQ>=0.9 & KELNOPT>=3 & AUCXPCTP<=0.2  Note that if FLGNOCMAX is set to the default value of 1 (i.e. TRUE), the concentration time data point selection algorithm will not permit incorporation of values prior to nor including the CMAX value. If FLGNOCMAX is set to 0 (i.e. FALSE), the concentration time data point selection algorithm will permit incorporation of values from and including CMAX/TMAX to TLAST but not prior to CMAX/TMAX. If the user desires to incorporate values prior to CMAX/TMAX, the optimal data selection algorithm cannot be used.  Note that if there are sets of these points that represent ties, i.e. with values of R2 within 0.0001, the set with the maximum number of data points is chosen. |
| 15 | **Unit Consistency Checks**  System checks following variables to make sure:   1. Same unit value exists in all rows of same column 2. Unit value is a either a Pfizer Data Standard (PDS) value or has been configured via an EQuIP openNCA data standard template  * NOMTIMEU * ACTTIMEU * CONCU * AMOUNTU * DOSEU * TOLDU * TAUU |
| 16 | **Insert missing data**  If concentration data is not available at AUC start or end times (including user-defined partial areas), data points are inserted into the dataset where possible based on rules for handling missing data.  Note: The missing time point is only added at the time of the calculation of the parameter. So Kel would not see a missing datapoint for example. It is not a “Pre”- calculation check.  *Refer to Appendix “*Missing Data*” for details* |
| 17 | **Data point exclusion**   1. Data points proceeding the initial dose time are excluded. If the time value for a data point is earlier than the dosing time, then the point is excluded from the NCA computations 2. Data points that contain no time value or no concentration value are excluded from calculations unless otherwise indicated |
| 18 | **BLQ/LLOQ Processing**  The legacy Pfizer eNCA system and data format utilize a convention for reporting values of the Lower Limit of the Quantitative (LLOQ) curve for a bioanalytical batch run as part of the concentration data itself. Thus for each bioanalytical method and each bioanalytical batch run, the provider of the raw concentration data can define the LLOQ for each run, taking into account whether the quality control samples met required specification and other requirements as predefined for the analytical method itself.  The manner in which this is communicated through the data is, for Pfizer Standard PK Definition File format is by   1. reporting each concentration value in the field name, PKCNC, as a character string. 2. For a bioanalytical run whose quality control samples met acceptance criteria for the run/method, samples which fall below the LLOQ are reported as “<xxx.xxx” where xxx.xxx is the numeric value of the LLOQ for the method. 3. For a bioanalytical run whose lower quality control samples failed acceptance criteria for the run/method, the LLOQ is adjusted as a new LLOQ, i.e. yyy.yyy, for that specific bioanalytical run. Samples whose quantitation fall below this batch run specific LLOQ, are reported as “<yyy.yyy”.   Example (here Method LLOQ, i.e. PCLLOQ, is defined as “1.0 ng/mL” and the bioanalytical batch run 1, met all quality control sample criteria and run 2, failed the lowest QC changing the reported LLOQ for the run to “<5.0”):   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Bioanalytical Batch | Time (hr) | PKCNC | PKCNCU | PKCNCN (ng/mL) | PKCNCNU | | 1 | 0 | “<1.0” | ng/mL | 0.0 | ng/mL | | 1 | 0.5 | “<1.0” | ng/mL | 0.0 | ng/mL | | 1 | 1 | “1.5” | ng/mL | 1.5 | ng/mL | | 1 | 2 | “2.3” | ng/mL | 2.3 | ng/mL | | 1 | 4 | “4.7” | ng/mL | 4.7 | ng/mL | | 2 | 0 | “<5.0” | ng/mL | 0.0 | ng/mL | | 2 | 0.5 | “<5.0” | ng/mL | 0.0 | ng/mL | | 2 | 1 | “7.8” | ng/mL | 7.8 | ng/mL | | 2 | 2 | “1.7” | ng/mL | 1.7 | ng/mL | | 2 | 4 | “<5.0” | ng/mL | 0.0 | ng/mL |   With the introduction of required CDISC compatibility, the PCLLOQ data item will also be a required data element for the Pfizer Standard PK Data Definition for PK Definition Files/LCD files/ARD files and Data loads to the EQuIP. This value, PCLLOQ, is related to PCMETHOD and PCANMETH, and represents the LLOQ as a attribute of the bioanalytical method operational characteristics and not for a specific bioanalytical batch run.  The legacy Pfizer eNCA system sets any value reported as “<xxx.xxx”, with xxx.xxx the numeric value of the LLOQ to a numeric ZERO value in the field PKCNCN as default behavior.  If the PK analysis requires a different replacement value, other than ZERO, the system will permit the user to implement a user defined method to convert the PKCNC and PKCNCN fields to a user definable PKCNCNMOD and PKCNCNMODU fields. This is a standard mechanism in the legacy Pfizer eNCA system to permit modifications, typically for baseline correction methods, to the supplied and system controlled PKCNC/PKCNCN values. Thus, as an example, the user could set values reported as “<xxx.xxx” in the PKCNC field to ½ the reported PCLLOQ value in the PKCNCNMOD field. This could be provided as a standard method for data transformation in the EQuIP NCA application or as a standard computation engine method for function. See LLOQPATTERNS for how flexible identification of values defined as below the limit of quantification are defined. |
| 19 | **Baseline Correction**  The baselinecorrect function/method implements baseline correction of concentration data. The primary rationale for using this function is to compute the correction and prepare or update the dataset for analysis with the corrected baseline values.  The individual timepoint data are grouped as profiles for correction by unique values of study design elements defined in the sdelist argument. One or more concentration datapoints are specified by the criteria defined in the "baseline index" (bslindex) argument selecting concentration data from each profile defined through the unique elements of sdelist.  The correction is implemented as the offset of the concentration data by the single predose concentration data point identified by the bslindex or, if more than one data point for each profile is available data from each profile, the mean of the concentration values indexed by bslindex for each profile.  The corrected concentration value is returned in the original PKCNC and PKCNCN fields. The correction itself is returned in the CORRECTION field. The original concentration data is returned as PKCNC.orig and an updated PKTERM field is returned as described in the arguments below. |
| 20 | **FLGSMPLPOSTDOSE**  FLGSMPLPOSTDOSE a dataset flag that is used to indicate whether a sample planned to be taken prior to the planned dose, is actually taken following the planned dose. When available it is incorporated into the analysis dataset.   |  |  | | --- | --- | | FLGSMPLPOSTDOSE | Criteria | | 0 | pk sample occurs prior to the planned dose rather than prior | | 1 | pk sample occurs following to the planned dose rather than as planned prior to the dose | |
| 21 | **FLGMERGE**  Data item utilized as a merge key to merge FLAG dataset items into the concentration dataset |
| 22 | FLGEXPROF† - Parameter generation control flag. If FLGEXPROF is set to 1 then don’t compute PROFILE level parameters, for example **CMIN**, but only compute DOSING INTERVAL level parameters, for example **CMIN*i***. |
| 23 | FLGTIME  Name of the FLGTIME data item in the FLAGS Dataset.  In the FLAGS Dataset, the value of FLGTIME is set on a concentration-time datapoint by datapoint basis for a profile. The purpose of FLGTIME is to permit selection of a TIME OVERRIDE on a point by point basis. The value of FLGTIME defaults to zero (0) for each data point in the profile which indicates that the computation engine code should utilize the value of the time variable set by the ***Model Configuration Template*** (MCT) variable TIME.  For example, if the TIME value in the MCT is set to “ACTUAL”, a FLGTIME value of 0 indicates to the computation engine that the “ACTUAL” time should be used as specified in the TIME variable.  If the FLGTIME for a particular data point in the profile is set to 1 while TIME is set to “ACTUAL”, this indicates to the computation engine that the alternate value, the “NOMINAL” value pointed to in the MCT by NOMTIME is to be utilized.  Note that if MCT TIME variable is defined as a direct data field item, the FLGTIME variable is not utilized.  The valid values of FLGTIME are set to   * 0=Use Value Set by MCT TIME Variable=DEFAULT * 1=Use Alternate Value Not Set by MCT Time Variable=OVERRIDE   See FLAGS Dataset for an example. |

## †- Not yet implemented in openNCA interface to computation engine nor in computation engine code itself.

## Data Items Required – Configuration of Dataset

The following are some of the data items that may be required in the dataset provided to the computation engine for certain parameter calculations, defined by the computation engine as automatically computed as part of a computation Model or via analyst action as a data transformation or user defined analysis method. The details are outlined in the description for each parameter calculation. Note that the full requirements for the Analysis Ready Dataset (ARD) specification that will form the basis of the dataset template specification for the Pfizer standard dataset appears in Section Analysis Ready Dataset (ARD). Some of these items will be reiterated in that dataset specification.

| **Release\*** | **Name** | **Description** | **Unit Class** |
| --- | --- | --- | --- |
|  | DOFi | Duration of Infusion | TIMEU |
|  | DOSE*i* | Dose amount for the ith dose administered | DOSEU |
|  | DOSE*i*U | Dose amount for the ith dose administered | DOSEU |
|  | MW | Molecular Weight | g/mole |
|  | Fu | Fraction Unbound |  |
|  | **FLGSMPLPOSTDOSE** |  | Predefined (0/1) |
|  | **FLGEMESIS** |  | Predefined  (0/1) |
|  | **NORMBS** | NORMBS is defined as the name of the data field containing the body size measurement to utilize in parameter body size normalizations. By default, it’s defined to be the “Body Weight”, BW or baseline/screening WT of the subject, typically the baseline body weight. |  |
|  | **NORMBSU** | Units for NORMBS |  |

## FLAGS Dataset

The FLAGS dataset is provided to identify which data points in a profile are to be utilized for derivation of the parameters dependent upon the terminal elimination rate phase constant or to be included in computation of AUC based parameters or included in summary statistics.

Note that when the “Best Guess” algorithm is invoked to select the optimal selection of data points from the concentration time profile relative to the criteria specified in the **FLGACCEPTKELCRIT** value, the FLAGS dataset will be returned as an output from the computation engine. This is necessary since updates to the points selected for the computation of KEL based parameters as selected/specified via the **FLGEXKEL** flag value will document and communicate the results of this algorithm.

The basic structure of the FLAGS dataset for a single profile of concentration-time data (note that the FLAGS dataset could incorporate ALL profiles in the dataset depending on the data provided for a computation engine call) is as follows:

### Example FLAGS Dataset

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| SDEID | PKDATAROWID | NOMTIME | ACTTIME | FLGTIME | CONC | CONCMOD | FLGEXKEL | FLGEXAUC | FLGEXSDE | FLGEXST | FLGCZERO | PKPCOM | PKRCOM | FLGEMESIS | TAU1 | TOLD1 | TAU2 | TOLD2 | DOSE1 | DOSE2 |
| 2346546482 | 25009244 | 0.5 | 0.5 | 0 | 1580 |  | 1 | 0 | 0 | 0 | 1 | Profile comment |  | 0 | 12 | 0 | 12 | 12 | 30 | 30 |
| 2346546482 | 25009245 | 1.0 | 1.0 | 0 | 2700 |  | 1 | 0 | 0 | 0 | 1 | Profile comment | Inconsistent time | 0 | 12 | 0 | 12 | 12 | 30 | 30 |
| 2346546482 | 25009246 | 2.0 | 2.0 | 0 | 3040 |  | 1 | 0 | 0 | 0 | 1 | Profile comment |  | 0 | 12 | 0 | 12 | 12 | 30 | 30 |
| 2346546482 | 25009247 | 3.0 | 3.5 | 0 | 3060 |  | 1 | 1 | 0 | 0 | 1 | Profile comment |  | 0 | 12 | 0 | 12 | 12 | 30 | 30 |
| 2346546482 | 25009248 | 4.0 | 4.0 | 0 | 2830 |  | 0 | 0 | 0 | 0 | 1 | Profile comment |  | 0 | 12 | 0 | 12 | 12 | 30 | 30 |
| 2346546482 | 25009249 | 6.0 | 6.0 | 0 | 2620 |  | 0 | 0 | 0 | 0 | 1 | Profile comment |  | 0 | 12 | 0 | 12 | 12 | 30 | 30 |
| 2346546482 | 25009250 | 8.0 | 8.2 | 0 | 2600 |  | 1 | 0 | 0 | 0 | 1 | Profile comment |  | 0 | 12 | 0 | 12 | 12 | 30 | 30 |
| 2346546482 | 25009251 | 10.0 |  | 1 | 2320 |  | 0 | 0 | 0 | 0 | 1 | Profile comment |  | 0 | 12 | 0 | 12 | 12 | 30 | 30 |
| 2346546482 | 25009252 | 12.0 | 12.0 | 0 | 2200 |  | 0 | 0 | 0 | 0 | 1 | Profile comment |  | 0 | 12 | 0 | 12 | 12 | 30 | 30 |
| 2346546482 | 25009254 | 24.0 | 24.0 | 0 | 1660 |  | 1 | 0 | 0 | 0 | 1 | Profile comment |  | 0 | 12 | 0 | 12 | 12 | 30 | 30 |

Note that the FLAGS dataset could incorporate additional data items including the nominal and actual time post dose fields, the concentration data field, the modified concentration data field (PKCNCNMOD for example), and other informational items from the dataset as defined in the FLAGSDISPLAYLIST MCT field. The default dataitems, flags, MCT items that will be displayed in the FLAGs dataset include SDEID, PKDATAROWID, NOMTIME, ACTTIME, FLGTIME, CONC, CONCMOD, FLGEXKEL, FLGEXAUC, FLGEXAUC, FLGEXSDE, FLGEXST, FLGCZERO, PKPCOM, PKRCOM, FLGEMESIS, TAU1-5, TOLD1-5, DOSE1-5. Up to 5 additional dataitems/fields/columns will be displayed in the FLAGS dataset from the input dataset through the specification of these fields in the FLAGDISPLAYLIST as defined in the MCT.

## Estimated Concentration Dataset

The estimated concentation dataset is returned by the computation engine and incorporates the results of concentration values generated by the computation engine for

* Estimated values of concentration for data points selected for inclusion in the terminal elimination phase regression
* Estimated values of concentration data for the **C0** (Czero) concentration value.
* Interpolated values of concentration for data points generated in the computation of partial AUCs (**AUCT1\_T2**) where planned concentration time data points were not incorporated into the sampling design for the profile
* Extrapolated values of concentration for data points generated in the computation of partial AUCs (**AUCT1\_T2**) where missing concentration-time data points occur.

See Sections Interpolation of Missing Data for AUC and AUMC Calculations and Missing Data for the circumstances that trigger these computations.

An example Estimated Concentration Dataset appears as follows:

### Example Estimated Concentration Dataset

The following represents an example Estimated Concentration Dataset that the Computation Engine produces to communicate the estimated concentrations for the selected terminal elimination phase, C0 and TLAST datapoints, as well as interpolated and extrapoloated concentration values for partial AUC and other parameter computations.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **SDEID** | **PKDATAROWID** | **TIME** | **CEST\_KEL** | **CEST\_INT** | **CEST\_EXT** | **CEST\_C0** | **CEST\_TLAST** |
| 2346546482 |  | 12 |  | 4.1 |  |  |  |
| 2346546482 | 8 | 12 | 3.232205 |  |  |  |  |
| 2346546482 | 9 | 18 | 2.513906 |  |  |  |  |
| 2346546482 | 10 | 24 | 1.955237 |  |  |  |  |
| 2346546482 | 11 | 72 | 0.261819 |  |  |  |  |
| 2346546482 | 12 | 96 | 0.095808 |  |  |  |  |
| 2346546482 |  | 120 |  |  | 0.035059 |  |  |
| 2346546482 |  | 96 |  |  |  |  | 0.095808 |
| 3318683525 | 22 | 13 | 7.74048 |  |  |  |  |
| 3318683525 | 23 | 16 | 6.73048 |  |  |  |  |
| 3318683525 | 24 | 20 | 5.58578 |  |  |  |  |
| 3318683525 | 25 | 26 | 4.22318 |  |  |  |  |
| 3318683525 | 26 | 72 | 0.49496 |  |  |  |  |
| 3318683525 |  | 8 |  |  | 9.771725 |  |  |
| 3318683525 |  | 8 |  | 11.9 |  |  |  |
| 3318683525 |  | 12 |  |  | 8.109773 |  |  |
| 136927602 | 32320941 | 3 |  |  |  | 109.784 |  |
| 136927602 | 32320942 | 5 |  |  |  | 105.3919 |  |
| 136927602 | 32320945 | 24 | 58.34286 |  |  |  |  |
| 136927602 | 32320946 | 48 | 38.56274 |  |  |  |  |
| 136927602 | 32320947 | 72 | 25.48873 |  |  |  |  |
| 136927602 | 32320948 | 96 | 16.84722 |  |  |  |  |
| 136927602 | 32320949 | 120 | 11.13547 |  |  |  |  |
| 136927602 |  | 0 |  |  |  | 168.2768 |  |
| 86418313525 | 20 | 10 | 10.60000 |  |  |  |  |
| 86418313525 | 21 | 13 | 8.30000 |  |  |  |  |
| 86418313525 | 22 | 16 | 6.50000 |  |  |  |  |
| 86418313525 | 23 | 20 | 5.50000 |  |  |  |  |
| 86418313525 | 24 | 26 | 4.10000 |  |  |  |  |
| 86418313525 | 25 | 72 | 0.50000 |  |  |  |  |
| 423081137 | 47 | 13 | 7.74048 |  |  |  |  |
| 423081137 | 48 | 16 | 6.73048 |  |  |  |  |
| 423081137 | 49 | 20 | 5.58578 |  |  |  |  |
| 423081137 | 50 | 26 | 4.22318 |  |  |  |  |
| 423081137 | 51 | 72 | 0.49496 |  |  |  |  |
| 7823189456 | 21 | 13 | 7.74048 |  |  |  |  |
| 7823189456 | 22 | 16 | 6.73048 |  |  |  |  |
| 7823189456 | 23 | 20 | 5.58578 |  |  |  |  |
| 7823189456 | 24 | 26 | 4.22318 |  |  |  |  |
| 7823189456 | 25 | 72 | 0.49496 |  |  |  |  |

# Primary Parameter Calculations

## Matrix Independent Parameters

**Note:** All parameter calculations are for models specified in Appendix “Parameter Model Mapping List - Primary and Derived ”, unless otherwise specified.

**Important Naming Convention Note**: steady state parameters are generally named with the suffix “i”, i.e. “NAMEi”. This permits computation and naming of multiple values of the parameter, one per each defined dosing interval, i.e. if there is a multiple dose profile specified in the data. For either single dose or multiple dosing regimens, parameters for both the entire profile as well as for each dosing interval may be generated (see Section 12.11 Parameter Model Mapping List - Primary and Derived for details of which parameter may generated/requested for each Model) named named both with the suffix “i” for parameters computed over individual dosing intervals, i.e. “NAME” as well as without the suffice “I” for parameters computed over the entire profile of data. *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*

| **Release\*** | **Name†** | **Description** | **Decimal Places** | **Unit Class** |
| --- | --- | --- | --- | --- |
| 1.0 | **DOSE*i*** | The dose amount for the ith dose administered within a pharmacokinetic profile,where *i* is an integer. For single dosing *i* = 1. *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  Primary Source: Obtained from NCA concentration data load process or dataset as DOSE1 for the first dose. Note that if there’s only one dose, DOSE is a synonym.  Secondary Source: User Input or edit before parameter computation.  Corresponding DOSE unit would be DOSEiU. | NA | DOSEU |
| 2.0 | **DOSEC** | **Corrected Dose**  At the time of parameter calculations, system converts DOSE*i* to match concentration units for CL and Volume calculations. The result of this correction is DOSEC.  DOSEC is used for CL and Volume calculations.  Example:  DOSE in MG  CONC in NG/ML  DOSE in MG would be converted to DOSEC in NG to match concentration units. DOSE values would be multiplied in this case by 10^6 to convert from MG to NG. |  | DOSEU |
| 2.0\* | **TOLD*i*** | **Time of Last Dose**  This is the nominal time that the last dose administered prior to the ith dosing interval within a profile.  Primary Source: Obtained from the NCA concentration input dataset or from the FLAGs dataset used to communicate data selections from the NCA application.  Note that if there’s only one dose and one TOLD or time of last dose, then TOLD is a synonym for TOLD1.  Secondary Source: User Input or edit before parameter computation Example:   |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Dose.** | | 1 | 0hr | 50ng | | 1 | 8hr | 50ng | | 1 | 16hr | 50ng |   Time of last dose (TOLD1) = 16  Default TOLD value to zero if TOLDi column has a null value or is missing. | NA | TIMEU |
| 3.0 | **TOLD*i*U** | **Units for Time of Last Dose,** TOLDi  Note that TOLDiU data fields are recorded in either the input dataset or in the FLAG dataset or both. If in the input dataset, these TOLDi values are used as starting values or the openNCA application analysis module. Changes implemented by the analyst in the Analysis Module are stored in the FLAGs dataset to be communicated to the Computation Engine. | NA | TIMEU |

\* - Note that Release version indicates which release the parameter was included in the legacy Pfizer eNCA computation engine. Entries marked “3.0” indicate introduction through the first version of the EQuIP open source code base for the computation engine.

† - Parameter Name utilized in this computation engine.

## Matrix Dependent Parameters

Blood/Serum/Plasma

Typical NCA pharmacokinetic parameters for blood, serum, plasma are defined in the following Table below.

**Note:** All parameter calculations are for models specified in Appendix “Parameter Model Mapping List - Primary and Derived ”, unless otherwise specified.

**Note:** For mixed model M1 and M4 (i.e. the way it is available in release 1.0) SAMPLETYPE column is used to distinguish “INTERVAL” from “POINT”. Value in the SAMPLETYPE data field column is used case insensitive for matching to determine which model, M1 or M4 to select.

**Note:** **Parameter Normalization**

In this version of the specification, parameter normalization is defined for a select set of commonly normalized parameters and is limited to unit dose normalization. Parameter normalization to reference doses or to body size measurements such as body weight (BW), body mass index (BMI) or body surface area (BSA) is not defined explicitly in this version of the specification.

| **Release** | **Name†** | **Description** | **Decimal Places** | **Unit Class** |
| --- | --- | --- | --- | --- |
| 1.0 | **CMAX** | **Maximum observed concentration** is obtained by inspection of the data. For steady-state data, CMAX is obtained by inspection of the data over all dosing intervals *within a profile.*  **For Example**   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | **Profile** | **Dosing Interval** | **TOLD (h)** | **TAU (h)** | **Time (h)** | **Conc.** | | 1 | 1 | 0 | 6 | 1 | 0.53 | | 1 | 1 | 0 | 6 | 2 | 1.7 | | 1 | 1 | 0 | 6 | 3 | 0.76 | | 1 | 1 | 0 | 6 | 4 | 0.36 | | 1 | 1 | 0 | 6 | 5 | BLQ | | 1 | 1/2 | 0 | 6 | 6 | BLQ | | 1 | 2 | 6 | 6 | 7 | 0.74 | | 1 | 2 | 6 | 6 | 10 | 1.6 | | 1 | 2 | 6 | 6 | 11 | 0.3 | | 1 | 2 | 6 | 6 | 12 | BLQ |   As per above example table  Then CMAX = 1.7   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | CMAX = 0 | |  ≤ 0 | Should be a part of data preparation and validation | | 3 | CONCU |
| 1.0 | **CMAX*i*** | **Maximum observed concentration** is obtained by inspection of the data. For steady-state data, CMAXi is obtained by inspection of the data during each dosing interval *i*, i.e. *the dosing interval index, i.e. the number of the ith dose administered within a profile.*  Note that the algorithm for the legacy Pfizer eNCA application and computation engine, for 2 or more dosing intervals within a profile, reports a CMAXi for each dosing interval defined within the profile. For example, CMAX1 and CMAX2 are computed for morning and evening dosing intervals. Note that the dosing interval does not need to be of equal length, i.e. can be unegual in duration. This behavior applies to each parameter defined within the ith dosing interval.  **For Example**   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | **Profile** | **Dosing Interval** | **TOLD (h)** | **TAU (h)** | **Time (h)** | **Conc.** | | 1 | 1 | 0 | 6 | 1 | 0.53 | | 1 | 1 | 0 | 6 | 2 | 1.7 | | 1 | 1 | 0 | 6 | 3 | 0.76 | | 1 | 1 | 0 | 6 | 4 | 0.36 | | 1 | 1 | 0 | 6 | 5 | BLQ | | 1 | 1/2 | 0 | 6 | 6 | BLQ | | 1 | 2 | 6 | 6 | 7 | 0.74 | | 1 | 2 | 6 | 6 | 10 | 1.6 | | 1 | 2 | 6 | 6 | 11 | 0.3 | | 1 | 2 | 6 | 6 | 12 | BLQ |  |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Conc.** | | 1 | 1hr | 0.53 | | 1 | 2hr | 1.26 | | 1 | 3hr | 1.56 | | 1 | 4hr | 1.55 | | 1 | 5hr | 1.57 |   As per above example table  If TOLD1 = 6h (used for single dose analyses)  Then CMAX1 = 1.7  If TOLD2  = 6h (for multiple dose analyses)  Then CMAX2 = 1.6   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | CMAXi = 0 | |  ≤ 0 | Should be a part of data preparation and validation | | 3 | CONCU |
|  | **CENDINF** | **Observed Concentration at end of infusion**  **Model M3**  **CENDINF** is the observed concentration at the time of the end of the infusion. If there is no observed concentration identified at time of the end of the infusion, the **CENDINF** is imputed as the **CMAX** value. | 3 | CONCU |
|  | **CENDINFDN** | **Observed Concentration at end of infusion (Dose normalized)**  **Model M3** | 3 | CONCU/normalized |
|  | **TENDINF** | **Time of the Observed Concentration (CEND) at end of infusion**  **Model M3**  **TENDINF**is the time of the **CENDINF** at the end of the infusion. If there is no observed concentration identified at the time of the end of the infusion, the **TENDINF** is imputed as the **TMAX** value. |  | TIMEU |
| 1.0 | **CEST** | **Estimated concentration at time of occurrence of TLAST.**  **CEST** is utilized directly in the computation of **AUCINFP**, **AUCINFPi**, **AUMCINFP**, **AUMCINFPi**.  **Method of Calculation**  Calculate the predicted concentration (**CEST**) at the time of the last measurable concentration:    **CEST** = Predicted concentration at time TLAST  TLAST = Time of the last observed measurable concentration  KEL = Terminal or elimination phase rate constant  KELC0 = Y-intercept (concentration at time zero) from log-linear regression for KEL | 3 | CONCU |
| 1.0 | **CLAST** | **Last measurable (non-zero) plasma concentration** is obtained by inspection of the data within a profile.  **For Example**   |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Conc.** | | 1 | 1h | 0.53 | | 1 | 2h | 1.26 | | 1 | 3h | 0.76 | | 1 | 4h | BLQ | | 1 | 5h | BLQ |   *CLAST in above example is 0.76*   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | Return “NA”  (Missing/Not Determined) | | 3 | CONCU |
| 1.0 | **CLASTi** | **Last measurable (non-zero) plasma concentration** is obtained by inspection of the data. *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **For Example**   |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Conc.** | | 1 | 1h | 0.53 | | 1 | 2h | 1.26 | | 1 | 3h | 0.76 | | 1 | 4h | BLQ | | 1 | 5h | BLQ |   *CLASTi in above example is 0.76*   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | Return “NA”  (Missing/Not Determined) | | 3 | CONCU |
| 1.0 | **CMIN** | For steady-state data, the **minimum observed concentration** in a profile by inspection of the data.  **For Example**   |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Conc.** | | 1 | 0 | 0.20 | | 1 | 0.5h | 0.20 | | 1 | 1h | 2.45 | | 1 | 4h | 1.26 | | 1 | 12h | 0.65 | | 1 | 16h | BLQ | | 1 | 24h | 0.20 |   As per above example table  CMIN = 0   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | Return “NA”  (Missing/Not Determined) | | 3 | CONCU |
| 1.0 | **CMIN*i*** | For steady-state data, the **minimum observed concentration** in a dosing interval *i*obtained by inspection of the data. *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **For Example**   |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Conc.** | | 1 | 0 | 0.20 | | 1 | 0.5h | 0.20 | | 1 | 1h | 2.45 | | 1 | 4h | 1.26 | | 1 | 12h | 0.65 | | 1 | 16h | BLQ | | 1 | 24h | 0.20 |   As per above example table  If  = 12h Then CMINi = 0.20  If  = 24h, then CMINi = 0   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | Return “NA”  (Missing/Not Determined) | | If  ≤ 0 | Should be a part of data entry validation at front end level | | 3 | CONCU |
| 1.0 | **TMAX** | **First Time at which Cmax is observed within full pharmacokinetic profile** and is obtained by inspection of the data.  **Example**   |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Conc.** | | 1 | 0 | 0.20 | | 1 | 0.5h | 2.45 | | 1 | 1h | 2.45 | | 1 | 4h | 1.26 | | 1 | 12h | 0.65 | | 1 | 16h | BLQ | | 1 | 24h | 0.20 | | 1 | 72h | 2.45 | | 1 | 72.5h | 2.45 | | 1 | 73h | 3.21 | | 1 | 76h | 3.58 | | 1 | 84h | 3.01 | | 1 | 88h | 2.54 | | 1 | 96h | 2.0 |   As per above example table  If  = 0h (used for single dose analyses)  Then TMAX = 76h  If  = 24h (for multiple dose analyses)  Then TMAX = 0.5h   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | Return “NA”  (Missing/Not Determined) | | 2 | TIMEU |
| 1.0 | **TMAX*i*** | **First Time at which Cmax*i* is observed within a dosing interval** and is obtained by inspection of the data. For steady-state, Tmax is obtained by inspection of the data during the dosing interval *i.* *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **For Example**   |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Conc.** | | 1 | 0 | 0.20 | | 1 | 0.5h | 2.45 | | 1 | 1h | 2.45 | | 1 | 4h | 1.26 | | 1 | 12h | 0.65 | | 1 | 16h | BLQ | | 1 | 24h | 0.20 | | 1 | 72h | 2.45 | | 1 | 72.5h | 2.45 | | 1 | 73h | 3.21 | | 1 | 76h | 3.58 | | 1 | 84h | 3.01 | | 1 | 88h | 2.54 | | 1 | 96h | 2.0 |   As per above example table  If  = 0h (used for single dose analyses)  Then TMAX = 76h  If  = 24h (for multiple dose analyses)  Then TMAX = 0.5h   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | Return “NA”  (Missing/Not Determined) | | 2 | TIMEU |
| 1.0 | **TLAST** | Time of Last measurable (non-zero) concentration obtained by inspection of the data *for the entire profile*.  E.g.:   |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Conc.** | | 1 | 1h | 0.53 | | 1 | 2h | 1.26 | | 1 | 3h | 0.76 | | 1 | 4h | BLQ | | 1 | 5h | BLQ |   *TLAST in above example is 3h*   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | Return “NA”  (Missing/Not Determined) | | 2 | TIMEU |
| 1.0 | **TLASTi** | Time of Last measurable (non-zero) concentration obtained by inspection of the data *for a dosing interval within the profile indexed from the start of the profile, not the dosing interval*.  E.g.:   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | **Profile** | **Dosing Interval** | **TOLD (h)** | **TAU (h)** | **Time (h)** | **Conc.** | | 1 | 1 | 0 | 6 | 1 | 0.53 | | 1 | 1 | 0 | 6 | 2 | 1.26 | | 1 | 1 | 0 | 6 | 3 | 0.76 | | 1 | 1 | 0 | 6 | 4 | 0.36 | | 1 | 1 | 0 | 6 | 5 | BLQ | | 1 | 1/2 | 0 | 6 | 6 | BLQ | | 1 | 2 | 6 | 6 | 7 | 0.74 | | 1 | 2 | 6 | 6 | 10 | 1.6 | | 1 | 2 | 6 | 6 | 11 | 0.3 | | 1 | 2 | 6 | 6 | 12 | BLQ |   *TLAST1 in above example is 4h*  *TLAST2 in above example is 11h*   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | Return “NA” | | 2 | TIMEU |
| 3.0 | **LASTTIME** | This is the time of the last measured concentration point of the profile INCLUDING any points at or below the Lower limit of Quantitation, BLQ’s . This observation can be later than TLAST.  LASTTIME serves, in one use case as criteria for acceptability or quality flags to ensure there’s sufficient data to report certain parameters, for example, AUCTAU. If AUCTAU not of sufficient quality, then analyst would also not likely report CL. See the discussion in Pre Computation Checks and Dataset or Computation Flag Definitions for **FLGACCEPTTAU**  **Model: M1(SD/SS), M2(SD/SS), M3(SD/SS)**  Example:   |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Conc.** | | 1 | 1h | 0.53 | | 1 | 2h | 1.26 | | 1 | 3h | 0.76 | | 1 | 4h | BLQ\* | | 1 | 5h | BLQ |   *LASTTIME in above example is 5h*  \* - Note that BLQ is specifically identified here since consideration is based upon BLQ values NOT missing samples.  If there are no BLQ samples, LASTTIME=TLAST | 2 | TIMEU |
| 3.0 | **LASTTIMEi** | This is the time of the last measured concentration point of the profile INCLUDING any points at or below the Lower limit of Quantitation, BLQ’s . This observation can be later than TLAST.  LASTTIMEi serves, in one use case as criteria for acceptability or quality flags to ensure there’s sufficient data to report certain parameters, for example, AUCTAUi. If AUCTAUi not of sufficient quality, then analyst would also not likely report CL. See the discussion in Pre Computation Checks and Dataset or Computation Flag Definitions for **FLGACCEPTTAU**  **Model: M1(SD/SS), M2(SD/SS), M3(SD/SS)**  Example:   |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Conc.** | | 1 | 1h | 0.53 | | 1 | 2h | 1.26 | | 1 | 3h | 0.76 | | 1 | 4h | BLQ\* | | 1 | 5h | BLQ |   *LASTTIMEi in above example is 5h*  \* - Note that BLQ is specifically identified here since consideration is based upon BLQ values NOT missing samples.  If there are no BLQ samples, LASTTIMEi=TLASTi | 2 | TIMEU |
| 1.0 | **TMIN** | For steady-state data, the **First Time at which CMIN is observed** **within the profile** and is obtained by inspection of the data.  **For Example**   |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Conc.** | | 1 | 0 | 0.20 | | 1 | 0.5h | 0.20 | | 1 | 1h | 2.45 | | 1 | 4h | 1.26 | | 1 | 12h | 0.65 | | 1 | 16h | BLQ | | 1 | 24h | 0.20 |   As per above example table  TMIN = 0h   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | Return “NA” | | 2 | TIMEU |
| 1.0 | **TMIN*i*** | For steady-state data, the **First Time at which CMIN*i* is observed** **within dosing interval *i*** and is obtained by inspection of the data. *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **For Example**   |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Conc.** | | 1 | 0 | 0.20 | | 1 | 0.5h | 0.20 | | 1 | 1h | 2.45 | | 1 | 4h | 1.26 | | 1 | 12h | 0.65 | | 1 | 16h | BLQ | | 1 | 24h | 0.20 |   As per above example table  If TAU = 12h Then TMINi = 0h  If TAU = 24h, then TMINi = 16h   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | Return “NA” | | If Tau ≤ 0 | Return “NA” | | 2 | TIMEU |
| 1.0 | **TLAG** | **Model M1:**  Lag time is described as the **time before the start of absorption phase** and is directly observed from the concentration-time profile. This time is defined as the sample time immediately prior to the first quantifiable concentration (non-zero). If all concentrations have a value greater than 0 then TLAG is 0.  **For Example**   |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Conc.** | | 1 | 1hr | BLQ | | 1 | 2hr | BLQ | | 1 | 3hr | BLQ | | 1 | 4hr | 0.53 | | 1 | 5hr | 1.26 |   As per above example table  TLAG = 3hrs   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | Return “NA” | | 2 | TIMEU |
| 1.0 | **KEL** | **Terminal or elimination phase rate constant** is estimated as the absolute value of the slope of a least-squares linear regression during the terminal phase of the **natural-logarithm (ln) transformed** concentration-time profile.  **First calculate slope**          S = Slope†  *b* = KEL*C0* (the y intercept)  *Ci* = ith concentration  *Ti* = ith Time  n = the number of data points  †Slope is being calculated using the ***lm*** function in R.-  See <http://mathworld.wolfram.com/LeastSquaresFitting.html> for reference to equataions.  **Terminal log-linear phase** = The phase in the natural-log transformed concentration-time profile selected by user at the time of primary parameter computations via interactive concentration-time plots (refer to KEL tab on the front end)  Set time of last dose to 0 and shift Ti accordingly in calculation of Kel. This impacts the KELC0 intercept used in other parameter calculations AUCINF.  **Equation for KEL**    S = Slope   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If n < 2 | Return “NA” | | If C = “NA” | Exclude the C and corresponding T and reduce n by 1 | | If value of C is <=0 | Exclude this C with corresponding T and reduce n by 1 | | If KEL <=0 | Return the value of KEL |   *Other names (for reference only)*   * *Lambda Z* * *Elimination Phase Rate Constant* | 3 | KELU |
| 1.0 | **KELC0** | KELC0 is the intercept on natural log of plasma drug concentration axis (y-intercept)  See calculation in parameter KEL for equation |  | CONCU |
| 1.0 | **KELTMLO** | Initial timepoint used in the calculation of kel  User Input or curve stripping   |  |  | | --- | --- | | **Data Checks** | **Actions** | | KELTMLO ≠ KETMHI | Return “NA” | | KETMLO must be < KELTMHI | Return “NA” | | KEL = NA | KETMLO = NA | | 2 | TIMEU |
| 1.0 | **KELTMHI** | Final timepoint used in the calculation of kel  User Input or curve stripping   |  |  | | --- | --- | | **Data Checks** | **Actions** | | KELTMHI ≠ KETMLO | Return “NA” | | KETMHI must be > KELTMLO | Return “NA” | | KEL = NA | KELTMHI = NA | | 2 | TIMEU |
| 1.0 | **KELNOPT** | Number of timepoints used in the calculation of kel  See “*n”* in the definition of KEL | NA | None |
| 1.0 | **KELRSQ** | Goodness of fit statistic (r2) † for the terminal phase rate constant (**KEL**)  **Equation**          C*i* = Concentration at each point for a profile  T*i* = Time at each point for a profile  N = Number of provided time/concentration data points in a profile  †r2 is being calculated using the ***lm*** function in Splus 7.0   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If N < 2 | Then Return “NA” | | If C = “NA” | Exclude the C and corresponding T and reduce N by 1 | | If value of C is <=0 | Exclude this C with corresponding T and reduce N by 1 | | **KEL** = NA | KELRSQ = NA |   **NOTE:** If curve stripping is checked then follow curve stripping logic before outputting KELRSQ value | 3 | None |
| 1.0 | **KELRSQA** | Goodness of fit statistic (r2) for the terminal phase rate constant (**KEL**) adjusted for the number of points used for the estimation of (**KEL**)  **Equation**    r2 = Another primary parameter (see above)  n = Number of provided times/concentrations in a profile   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If N < 2 | Then Return “NA” | | Refer to r2 |  | | 3 | None |
| 2.0 | **KELR** | Goodness of fit statistic (r) † for the terminal phase rate constant (**KEL**) |  | None |
| 1.0 | **THALF** | Terminal phase **half-life**    KEL = Terminal or elimination phase rate constant   |  |  | | --- | --- | | **Data Checks** | **Actions** | | THALF must be > 0 | Return “NA” | | KEL = NA | THALF = NA | | 1 | TIMEU |
| 2.0 | **THALFF** | THALF Flag  Flag if the ratio of the duration over which the THALF is estimated to the actual THALF estimate is less than 2. Legacy Pfizer standards referred to this as the “***Spanratio***” for evaluation of quality of the estimated KEL and THALF.  If  (KELTMHI – KELTMLO) / THALF >= **SPANRATIOCRIT**  Then  Value = 0  Else  Value = 1  **SPANRATIOCRIT** is the criteria value set in the ***Model Configuration Template***. The default is typically a value of 2 but can be modified as needed by setting the value of **SPANRATIOCRIT**. |  | None |
| 2.0\* | **All AUC Calculations** | **For all AUC Calculations:**   1. Use the appropriate trapezoidal rules and related equations as specified by the user 2. Apply rules for missing data at start times for AUC 3. Apply rules for missing data at end time for AUCTAU and Partial Areas 4. Always assume time of initial dose is zero   *(refer to Appendix “*Calculating AUC, AUMC, and AURC*” for details)* |  | AUCU |
| 1.0 | **AUCT** | **Area under the concentration versus time curve** from time 0 to time T for all recorded times T.  **Calculation**   1. Calculate using the appropriate trapezoidal AUC rule for each interval. 2. Add the AUCs for each interval from 0 to time T to compute total AUC  |  |  | | --- | --- | | **Data Checks** | **Actions** | | If C corresponding T is “NA” | Return “NA” | | If all Cs = 0 | AUCT = 0 | | 2 | AUCU |
| 1.0 | **AUCT1\_T2** | **Partial Area under the concentration versus time curve** from time T1 until time T2, where T1 and T2 are user-specified times.  AUCNPAIR indicates the number of requested partial area parameters to be computed. T1 and T2 specifications are defined in the ***Model Configuration Template***  **Calculation**   1. Calculate using the appropriate trapezoidal AUC rule for each interval. 2. Add the AUCs for each interval to compute total AUCT1T2.  |  |  | | --- | --- | | **Data Checks** | **Actions** | | If T1<Dose time | Return “NA” | | T1 ≠ T2 | Return “NA” | | If T2<T1 | Return “NA” | | If C corresponding to either time T1 or T2 is not available (after applying rules for “AUC Calculations and Missing Data”; See Appendix Missing Data) | Return “NA” | | If all Cs = 0 | AUCT1T2 = 0 | | 2 | AUCU |
| 1.0 | **AUCALL** | **Area under the concentration versus time curve** **from zero time until the last time point.**  As illustrated in the following figure, AUCALL includes the trapezoidal area from the time of the last measurable concentration to the next time point. Although there may be additional time points, there is no additional AUC since by definition all subsequent concentrations are zero.  AUC_plot  **Calculation**   1. If the last measurable concentration is also the last time point, then AUCALL = AUCLAST. 2. Otherwise, calculate the trapezoidal AUC for the interval from Tlast (time of the last measurable concentration, Clast) to the next time point. 3. Add this AUC to AUCLAST to calculate AUCALL.  |  |  | | --- | --- | | **Data Checks** | **Actions** | | If TLAST = last time point | AUCALL = AUCLAST | | If all Cs = 0 | AUCALL = 0 | | 2 | AUCU |
| 1.0 | **AUCLAST** | **Area under the concentration versus time curve** **from zero time until the time (TLAST) of the last measurable concentration (CLAST) during the profile.**  In the following example, CLAST is 0.76 and TLAST is 3 hr:   |  |  |  | | --- | --- | --- | | **Observation** | **Time** | **Conc.** | | 1 | 1hr | 0.53 | | 2 | 2hr | 1.26 | | 3 | **3hr** | **0.76** | | 4 | 4hr | BLQ | | 5 | 5hr | BLQ |   **Calculation**   1. Calculate using the appropriate trapezoidal AUC rule for each time interval. 2. Add the AUCs for each time interval to calculate total AUCLAST.  |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | AUCLAST = 0 | | 2 | AUCU |
| 1.0 | **AUCLASTi** | **Area under the concentration versus time curve** **from zero time until the time (TLASTi) of the last measurable concentration (CLASTi) during the ith dosing interval.** *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  In the following example, CLASTi is 0.76 and TLASTii is 3 hr:   |  |  |  | | --- | --- | --- | | **Observation** | **Time** | **Conc.** | | 1 | 1hr | 0.53 | | 2 | 2hr | 1.26 | | 3 | **3hr** | **0.76** | | 4 | 4hr | BLQ | | 5 | 5hr | BLQ |   **Calculation**   1. Calculate using the appropriate trapezoidal AUC rule for each time interval. 2. Add the AUCs for each time interval to calculate total AUCLASTi.  |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | AUCLASTi = 0 | | 2 | AUCU |
| 1.0 | **AUCINFO** | **Area under the concentration versus time curve from zero time to infinity (Observed):** Observed value for the time of the last measurable concentration is used to calculate extrapolated AUC.  **Calculation**   1. Calculate extrapolated AUC:   CLAST = Last observed measurable (non-zero) plasma concentration during the selected dosing interval  KEL = Terminal or elimination phase rate constant  E.g:   |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Conc.** | | 1 | 1hr | 0.53 | | 2 | 2hr | 1.26 | | 3 | 3hr | 0.76 | | 4 | 4hr | BLQ | | 5 | 5hr | BLQ |   *CLAST in above example is 0.76*   1. **Final Equation**   AUCLAST = Area under the concentration versus time curve from zero time until the time (TLAST) of the last measurable concentration (CLAST).   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUCINFO < 0 | Return “NA” | | If KEL = NA | Return “NA” | | If all Cs = 0 | AUCINFO = 0 | | 2 | AUCU |
| 1.0 | **AUCINFOi** | **Area under the concentration versus time curve from start of the dosing interval (TOLDi) to infinity (Observed):** Observed value for the time of the last measurable concentration is used to calculate extrapolated AUC.  **Calculation**   1. Calculate extrapolated AUC:     CLASTi = Last observed measurable (non-zero) plasma concentration during the selected dosing interval  KEL = Terminal or elimination phase rate constant  E.g:   |  |  |  | | --- | --- | --- | | **Profile** | **Time** | **Conc.** | | 1 | 1hr | 0.53 | | 2 | 2hr | 1.26 | | 3 | 3hr | 0.76 | | 4 | 4hr | BLQ | | 5 | 5hr | BLQ |   *CLAST1 in above example is 0.76*   1. **Final Equation**   AUCLASTi = Area under the concentration versus time curve from zero time until the time (TLASTi) of the last measurable concentration (CLASTi).   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUCINFO < 0 | Return “NA” | | If KEL = NA | Return “NA” | | If all Cs = 0 | AUCINFO = 0 | | 2 | AUCU |
| 1.0 | **AUCINFP** | **Area under the concentration versus time curve from zero time to infinity** **(Predicted):** Estimated concentration at the time of the last measurable concentration is used to calculate extrapolated AUC.  **Calculation**  1). Calculate the predicted concentration (Cest) at the time of the last measurable concentration:    Cest = Predicted concentration at time TLAST  TLAST = Time of the last observed measurable concentration  KEL = Terminal or elimination phase rate constant  KELC0 = Y-intercept (concentration at time zero) from log-linear regression for KEL  2). Calculate the extrapolated AUC:    3). Calculate AUCINFP    AUCLAST = Area under the concentration versus time curve from zero time until the time (TLAST) of the last measurable concentration (CLAST).   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If KEL = NA | Return “NA” | | If all Cs = 0 | Return “NA” | | If AUCINFP < 0 | Return “NA” | | 2 | AUCU |
| 1.0 | **AUCINFPi** | **Area under the concentration versus time curve from start of the dosing interval (TOLDi) to infinity** **(Predicted):** Estimated concentration at the time of the last measurable concentration is used to calculate extrapolated AUC.  **Calculation**  1). Calculate the predicted concentration (Cest) at the time of the last measurable concentration:    Cest = Predicted concentration at time TLAST  TLASTi = Time of the last observed measurable concentration  KEL = Terminal or elimination phase rate constant  KELC0 = Y-intercept (concentration at time zero) from log-linear regression for KEL  2). Calculate the extrapolated AUC:    3). Calculate AUCINFPi    AUCLASTi = Area under the concentration versus time curve from zero time until the time (TLASTii) of the last measurable concentration (CLASTi).   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If KEL = NA | Return “NA” | | If all Cs = 0 | Return “NA” | | If AUCINFPi < 0 | Return “NA” | | 2 | AUCU |
| 1.0 | **AUCXPCTO** | **Percentage of AUCINFO obtained by forward extrapolation.**  **Calculation:**    AUCINFO = Area under the concentration versus time curve from zero time to infinity (Observed)  AUCLAST = Area under the concentration versus time curve from zero time until the time (TLAST) of the last measurable concentration (CLAST).     |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | AUCXPCTO= ”NA”  (since AUCINFO is NA) | | If AUCINFO = NA | Return “NA” | | If AUCINFO = 0 | Return “NA” | | If AUCLAST = NA | Return “NA” | | 1 | None % |
| 1.0 | **AUCXPCTOi** | **Percentage of AUCINFO obtained by forward extrapolation.**  **Calculation:**  AUCINFOi = Area under the concentration versus time curve from start of the dosing interval (TOLDi) to infinity (Observed)  AUCLASTi = Area under the concentration versus time curve from start of the dosing interval (TOLDi) until the time (TLASTi) of the last measurable concentration (CLASTi).     |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | AUCXPCTOi= “NA” | | If AUCINFOi = NA | Return “NA” | | If AUCINFOi = 0 | Return “NA” | | If AUCLASTi = NA | Return “NA” | | 1 | None % |
| 1.0 | **AUCXPCTP** | **Percentage of AUCINFP obtained by forward extrapolation.**  **Calculation:**    AUCINFP = Area under the concentration versus time curve from zero time to infinity (Predicted)  AUCLAST= Area under the concentration versus time curve from zero time until the time (TLAST) of the last measurable concentration (CLAST).   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | AUCXPCTP= ”NA” | | If AUCINFP = NA | Return “NA” | | If AUCINFP = 0 | Return “NA” | | If AUCLAST = NA | Return “NA” | | 1 | None % |
| 1.0 | **AUCXPCTPi** | **Percentage of AUCINFP obtained by forward extrapolation.**  **Calculation:**  AUCINFPi = Area under the concentration versus time curve from start of the dosing interval (TOLDi) to infinity (Predicted)  AUCLASTi = Area under the concentration versus time curve start of the dosing interval (TOLDi) time until the time (TLASTi of the last measurable concentration (CLASTi).   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | AUCXPCTPi= “NA” | | If AUCINFP = NA | Return “NA” | | If AUCINFP = 0 | Return “NA” | | If AUCLASTi = NA | Return “NA” | | 1 | None % |
| 1.0 | **AUCTAU*i*** | **For steady-state data, the Area under the concentration versus time curve from** from start of the dosing interval (TOLDi)  **until the end of the dosing interval** *i***.** *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Calculation:**   1. Calculate using the appropriate trapezoidal AUC rule for each interval. 2. Add the AUCs for each interval to calculate total AUCTAU.  |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | AUCTAU = 0 | | If C corresponding to time T is not available (after applying rules for “AUC Calculations and Missing Data”; See Appendix Missing Data) | Return “NA” | | 2 | AUCU |
| 1.0 | **AUMCLAST** | The **area under the first moment curve** from zero time until the last measurable concentration is calculated using the trapezoidal rule.  **Calculation:**   1. Use the appropriate trapezoidal rule (see section “Calculating AUC and AUMC” for reference) and related equation as selected by the user 2. Calculate AUMC for each time observed interval and then add each of them to compute total AUMC  |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | AUMC = 0 | | 2 | AUMCU |
| 1.0 | **AUMCLASTi** | **For steady-state data,** the **area under the first moment curve** from the start of the dosing interval (TOLDi) until the last measurable concentration within the dosing interval i is calculated using the trapezoidal rule. *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Calculation:**   1. Use the appropriate trapezoidal rule (see section “Calculating AUC and AUMC” for reference) and related equation as selected by the user 2. Calculate AUMC for each time observed interval and then add each of them to compute total AUMC  |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | AUMC = 0 | | 2 | AUMCU |
| 1.0 | **AUMCINFO** | **The** **area under the first moment curve from zero time to infinity** **(Observed)**  **Equations:**  **1. First calculate extrapolated AUMC:**    TLAST = Time of last measurable (non-zero) plasma concentration  CLAST =,Observed concentration at the time of the last measurable (non-zero) plasma concentrations  KEL = Terminal or elimination phase rate constant  **2.Final Equation**    AUMCLAST = Area under the first moment curve from zero time until the last measurable concentration.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUMCINFO < 0 | Return “NA” | | If THALF = NA | Return “NA” | | If KEL = NA | Return “NA” | | If all Cs = 0 | AUMCINFO = “NA” | | 2 | AUMCU |
| 1.0 | **AUMCINFOi** | **The area under the first moment curve from start of the dosing interval (TOLDi) to infinity (Observed)**  **Equations:**  **1. First calculate extrapolated AUMC:**    TLASTi = Time of last measurable (non-zero) plasma concentration  CLASTi =,Observed concentration at the time of the last measurable (non-zero) plasma concentrations  KEL = Terminal or elimination phase rate constant  **2.Final Equation**    AUMCLASTi = Area under the first moment curve from zero time until the last measurable concentration.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUMCINFOi < 0 | Return “NA” | | If THALF = NA | Return “NA” | | If KEL = NA | Return “NA” | | If all Cs = 0 | AUMCINFOi = “NA” | | 2 | AUMCU |
| 1.0 | **AUMCINFP** | **The area under the first moment curve from zero time to infinity** **(Predicted)**  **Equations**  **1.** Calculate the estimated concentration (Cest) at the time of the last measurable concentration:    TLAST = Time of the last measurable (non-zero) plasma concentration  KEL = Terminal or elimination phase rate constant  KELC0 = Y-intercept (concentration at time zero) from linear regression for KEL.  **2. First calculate extrapolated AUMC**    TLAST = Time of last measurable (non-zero) plasma concentration  CLAST = Predicted concentration at the time of the last measurable (non-zero) plasma concentration  KEL = Terminal or elimination phase rate constant  **2. Final Equation**    AUMCLAST = Area under the first moment curve from zero time until the last measurable concentration.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUMCINFP < 0 | Return “NA” | | If THALF = NA | Return “NA” | | If KEL = NA | Return “NA” | | If all Cs = 0 | AUMCINFP = “NA” | | 2 | AUMCU |
| 1.0 | **AUMCINFPi** | The area under the first moment curve from start of the dosing interval (TOLDi) to infinity (Predicted)  **Equations**  **1.** Calculate the estimated concentration (Cest) at the time of the last measurable concentration:    TLASTi= Time of the last measurable (non-zero) plasma concentration  KEL = Terminal or elimination phase rate constant  KELC0 = Y-intercept (concentration at time zero) from linear regression for KEL.  **2. First calculate extrapolated AUMC**    TLASTi = Time of last measurable (non-zero) plasma concentration  CLASTi = Predicted concentration at the time of the last measurable (non-zero) plasma concentration  KEL = Terminal or elimination phase rate constant  **2. Final Equation**    AUMCLAST = Area under the first moment curve from zero time until the last measurable concentration.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUMCINFP < 0 | Return “NA” | | If THALF = NA | Return “NA” | | If KEL = NA | Return “NA” | | If all Cs = 0 | AUMCINFPi = “NA” | | 2 | AUMCU |
| 1.0 | **AUMCXPTO** | **Percentage of AUMCINFO obtained by forward extrapolation.**  **Calculation:**    AUMCINFO = Area under the first moment curve from zero time to infinity (Observed)  AUMCLAST = Area under the first moment curve from zero time until the last measurable concentration.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | AUMCXPTO= “NA” | | If AUMCINFO = NA | Return “NA” | | If AUMCINFO = 0 | Return “NA” | | 1 | None % |
| 1.0 | **AUMCXPTOi** | **Percentage of AUMCINFOi obtained by forward extrapolation.**  **Calculation:**    AUMCINFOi = Area under the first moment curve from zero time to infinity (Observed)  AUMCLASTi = Area under the first moment curve from zero time until the last measurable concentration.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | AUMCXPTOi= “NA” | | If AUMCINFOi = NA | Return “NA” | | If AUMCINFOi = 0 | Return “NA” | | 1 | None % |
| 1.0 | **AUMCXPTP** | **Percentage of AUMCINF obtained by forward extrapolation.**  **Calculation:**    AUMCINFP = Area under the first moment curve from zero time to infinity (Predicted)  AUMCLAST = Area under the first moment curve from zero time until the last measurable concentration.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | AUMCXPTP= “NA” | | If AUMCINFP = NA | Return “NA” | | If AUMCINFP = 0 | Return “NA” | | 1 | None % |
| 1.0 | **AUMCXPTPi** | **Percentage of AUMCINFi obtained by forward extrapolation.**  **Calculation:**    AUMCINFPi = Area under the first moment curve from zero time to infinity (Predicted)  AUMCLASTi = Area under the first moment curve from zero time until the last measurable concentration.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | AUMCXPTPi= “NA” | | If AUMCINFPi = NA | Return “NA” | | If AUMCINFPi = 0 | Return “NA” | | 1 | None % |
| 1.0 | **AUMCTAU*i*** | **For steady-state data, the Area under the first moment curve from zero time until the end of the dosing interval *i*.** *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Calculation:**   1. Calculate using the appropriate trapezoidal AUMC rule for each interval. 2. Add the AUMCs for each interval to calculate total AUCTAU.  |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all Cs = 0 | AUMC = 0 | | If C corresponding to time T is not available (after applying rules for “AUMC Calculations and Missing Data”) | Return “NA” | | 2 | AUMCU |
| 3.0 | **MRTIVIFP(i)** | **The mean residence time (MRT) extrapolated to infinity for a substance administered by intravascular dosing, calculated using the predicted value of the last non-zero concentration.**  **Note that the parameter naming convention for Release 2 of the Computaton Engine Specifications referred to MRTIVIFP(i) as MRTPi for intravascular administration. This has been changed to MRTIVIFP(i) with Release 3 to distinguish between intra- and extravascular administration.**  **Single Dose Equation:**  **For Model M2**    **For Model M3**    **Steady-State Equation:**  **For Model M2**    **For Model M3**    AUMCINFP = Area under the first moment curve from zero time to infinity (Predicted)  AUCINFP= Area under the concentration versus time curve from zero time to infinity (Predicted)  AUMCTAUi = Area under the first moment curve from zero time until the end of the ith dosing interval.  AUCTAUi = Area under the concentration versus time curve from zero time until the end of the ith dosing interval.  TAU*i* = Duration of the ith Dosing interval  DOFi = duration of infusion, Used for constant infusion models.  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUMCINFP <0 | Return “NA” | | AUCINFP <=0 | Return “NA” | | AUCTAUi <=0 | Return “NA” | | 3 | TIMEU |
| 3.0 | **MRTIVIFO(i)** | **The mean residence time (MRT) extrapolated to infinity for a substance administered by intravascular dosing, calculated using the observed value of the last non-zero concentration.**  **Note that the parameter naming convention for Release 2 of the Computaton Engine Specifications referred to MRTIVIFO(i) as MRTOi for intravascular administration. This has been changed to MRTIVIFO(i) with Release 3 to distinguish between intra- and extravascular administration.**  **Single Dose Equation:**  **For Model M2**    **For Model M3**    **Steady-State Equation:**  **For Model M2**    **For Model M3**    AUMCINFO = Area under the first moment curve from zero time to infinity (Observed)  AUCINFO= Area under the concentration versus time curve from zero time to infinity (Observed)  AUMCTAUi = Area under the first moment curve from zero time until the end of the ith dosing interval.  AUCTAU = Area under the concentration versus time curve from zero time until the end of the ith dosing interval.  TAU*i* = Duration of the ith Dosing interval  DOFi = duration of infusion, used for constant infusion models.  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUMCINFO <0 | Return “NA” | | AUCINFO <=0 | Return “NA” | | AUCTAUi <=0 | Return “NA” | | 3 | TIMEU |
| 3.0 | **MRTEVIFP(i)** | The mean residence time (MRT) extrapolated to infinity for a substance administered by extravascular dosing, calculated using the predicted value of the last non-zero concentration.  **Note that the parameter naming convention for Release 2 of the Computaton Engine Specifications referred to MRTEVIFP(i) as MRTPi for extravascular administration. This has been changed to MRTEVIFP(i) with Release 3 to distinguish between intra- and extravascular administration.**  **Single Dose Equation:**  **For Model M1**    **Steady-State Equation:**  **For Model M1**    AUMCINFP = Area under the first moment curve from zero time to infinity (Predicted)  AUCINFP= Area under the concentration versus time curve from zero time to infinity (Predicted)  AUMCTAUi = Area under the first moment curve from zero time until the end of the ith dosing interval.  AUCTAUi = Area under the concentration versus time curve from zero time until the end of the ith dosing interval.  TAUi = Duration of the ith Dosing interval  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUMCINFP <0 | Return “NA” | | AUCINFP <=0 | Return “NA” | | AUCTAUi <=0 | Return “NA” | | 3 | TIMEU |
| 3.0 | **MRTEVIFO(i)** | **The mean residence time (MRT) extrapolated to infinity for a substance administered by extravascular dosing, calculated using the observed value of the last non-zero concentration.**  **Note that the parameter naming convention for Release 2 of the Computaton Engine Specifications referred to MRTEVIFO(i) as MRTOi for extravascular administration. This has been changed to MRTEVIFO(i) with Release 3 to distinguish between intra- and extravascular administration.**  **Single Dose Equation:**  **For Model M1**    **Steady-State Equation:**  **For Model M1**    AUMCINFO = Area under the first moment curve from zero time to infinity (Observed)  AUCINFO= Area under the concentration versus time curve from zero time to infinity (Observed)  AUMCTAUi = Area under the first moment curve from zero time until the end of the ith dosing interval.  AUCTAUi = Area under the concentration versus time curve from zero time until the end of the ith dosing interval.  TAUi = Duration of the ith Dosing interval  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUMCINFO <0 | Return “NA” | | AUCINFO <=0 | Return “NA” | | AUCTAU <=0 | Return “NA” | | 3 | TIMEU |
| 2.0 | **MRTLAST** | **Mean residence time from the time of dosing to the last measurable concentration.**  **For Models M1 and M2**    **For Model M3**    AUMClast = Area under the first moment curve from zero time until the last measurable concentration.  AUClast = Area under the concentration versus time curve from zero time until the time (TLAST of the last measurable concentration (CLAST).  DOFi = duration of infusion, used for constant infusion models   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUMCLAST <0 | Return “NA” | | AUCLAST <=0 | Return “NA” | | 1 | TIMEU |
| 2.0 | **MRTLASTi** | **Mean residence time from the time of dosing to the last measurable concentration within a dosing interval**  **For Models M1(ss) and M2(ss)**  **For Model M3(ss)**  **AUMCLASTi** = Area under the first moment curve from zero time until the last measurable concentration.  **AUCLASTi** = Area under the concentration versus time curve from zero time until the time (TLAST of the last measurable concentration (CLAST).  DOFi = duration of infusion, used for constant infusion models   |  |  | | --- | --- | | **Data Checks** | **Actions** | | **AUMCLASTi** <0 | Return “NA” | | **AUCLASTi** <=0 | Return “NA” | | 1 | TIMEU |
| 2.0\* | **CLFO** | **Apparent clearance (observed)** of drug from e.g. plasma, for **extravascular** routes of administration.  **Model M1**  Single Dose Equation only; not calculated at steady-state.  Note: For steady-state CLFTAUi is calculated using AUCTAUi:    F = fraction of dose absorbed [value is unknown for extravascular model  Dose = sum of dosei to dosen  AUCINFO = Area under the first moment curve from zero time to infinity (Observed)   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUCINFO = NA | Return “NA” | | Dose = 0 | Return “NA” | | 1 | CLU |
| 2.0 | **CLO** | **Total clearance of drug (observed)**  **Models M2 and M3**  Single Dose Equation only; not calculated at steady-state. For steady-state CLTAUi is calculated using AUCTAUi:    Dose = sum of dosei to dosen  AUCINFO = Area under the first moment curve from zero time to infinity (Observed)   |  |  | | --- | --- | | AUCINFO = Area under the first moment curve from zero time to infinity (Observed)  **Data Checks** | **Actions** | | AUCINFO = NA | Return “NA” | | Dose = 0 | Return “NA” | |  | CLU |
| 2.0\* | **CLFP** | **Apparent clearance (predicted)** of drug from e.g. plasma, for extravascular routes of administration.  **Model M1(SD)**  Single Dose Equation**:**    F = fraction of dose absorbed assumed to be since value is unknown for extravascular model  AUCINFP = Area under the first moment curve from zero time to infinity (Predicted).  DOSE = dose unit value for drug dosing interval.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUCINFP = NA | Return “NA” | | DOSE = 0 | Return “NA” | | 1 | CLU |
| 3.0 | **CLFTAUi** | The total body clearance for extravascular administration divided by the fraction of dose absorbed, calculated using AUCTAUi. *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Note that the parameter naming convention for Release 2 of the Computaton Engine Specifications referred to CLFTAUi as CLFiP for steady-state data. This has been changed to CLFTAUi with Release 3 to distinguish between the single dose and steady-state parameters.**  **Model M1(SS)**  Steady-State Equation:    AUCTAUi = Area under the concentration versus time curve from zero time until the end of the ith dosing interval.  DOSEi = dose value for the ith drug dosing interval.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUCTAUi = NA | Return “NA” | | DOSEi = 0 | Return “NA” | | 3 | CLU |
| 2.0 | **CLP** | **Total clearance (predicted)** of drug from e.g. plasma.  **Models M2(SD) and M3(SD)**  Single Dose Equation:    Where F (fraction of dose absorbed) is assumed to be 1  AUCINFP = Area under the first moment curve from zero time to infinity (Predicted).  DOSE = dose amount for drug.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUCINFP = NA | Return “NA” | | DOSEi = 0 | Return “NA” | |  | CLU |
| 3.0 | **CLTAUi** | The total body clearance for intravascular administration, calculated using AUCTAU. *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Note that the parameter naming convention for Release 2 of the Computaton Engine Specifications referred to CLTAUi as CLiP for steady-state data. This has been changed to CLTAUi with Release 3 to distinguish between the single dose and steady-state parameters.**  **Model M2 (SS) and M3 (SS)**  Steady-State Equation:    AUCTAUi = Area under the concentration versus time curve from zero time until the end of the ith dosing interval.  DOSEi = dose value for drug ith dosing interval.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUCTAUi = NA | Return “NA” | | DOSEi = 0 | Return “NA” | | 3 | CLU |
| 2.0\* | **VZFO** | **Apparent volume of distribution (observed)** based on the terminal phase for **extravascular** routes of administration.  **Model M1(SD)**  Single Dose Equation only; not calculated at steady-state    F = fraction of dose absorbed [value is unknown for extravascular model].  KEL = Terminal or elimination phase rate constant.  AUCINFO = Area under the first moment curve from zero time to infinity (Observed).  DOSE = dose value for the profile.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUCINFO<0 | Return “NA” | | KEL = NA | Return “NA” | | Dose = 0 | Return “NA” | | 0 | VOLUMEU |
| 2.0\* | **VZFP** | **Apparent volume of distribution (predicted)** based on the terminal phase for extravascular routes of administration.  **Model M1(SD)**  Single Dose Equation:    F = fraction of dose absorbed [value is unknown for extra vascular model].  KEL = Terminal or elimination phase rate constant.  AUCINFP = Area under the first moment curve from zero time to infinity (Predicted).  DOSE = dose value for the profile.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUCINFP = NA | Return “NA” | | AUCTAUi = NA | Return “NA” | | KEL = NA | Return “NA” | | Dose = 0 | Return “NA” | | 0 | VOLUMEU |
| 3.0 | **VZFTAUi** | The volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed, calculated using AUCTAUi. *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Note that the parameter naming convention for Release 2 of the Computaton Engine Specifications referred to VZFTAUi as VZFiP for steady-state data. This has been changed to VZFTAUi with Release 3 to distinguish between the single dose and steady-state parameters.**  **Model M1(SS)**  Steady-State Equation:    AUCTAUi = Area under the concentration versus time curve from zero time until the end of the ith dosing interval.  DOSEi = dose value for ith drug dosing interval.  KEL = Terminal or elimination phase rate constant.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUCTAUi = NA | Return “NA” | | KEL = NA | Return “NA” | | DOSEi = 0 | Return “NA” | | 3 | VOLUMEU |
| 2.0 | **VZO** | **Volume of distribution (observed)** based on the terminal phase.  **Models M2(SD) and M3(SD)**  Single Dose Equation only not calculated at steady-state (only VZTAU is calculated using AUCTAU as the correct PK variable):    where F (fraction of dose absorbed) is assumed to be 1  KEL = Terminal or elimination phase rate constant.  AUCINFO = Area under the first moment curve from zero time to infinity (Observed).  DOSEi = dose value for drug dosing interval *i*.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUCINFO<0 | Return “NA” | | KEL = NA | Return “NA” | | DOSEi = 0 | Return “NA” | |  | VOLUMEU |
| 2.0 | **VZP** | **Volume of distribution (predicted)** based on the terminal phase.  **Models M2(SD) and M3(SD)**  Single Dose Equation:    AUCINFP = Area under the first moment curve from zero time to infinity (Predicted).  DOSEi = dose value for drug dosing interval *i*.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUCINFP = NA | Return “NA” | | KEL = NA | Return “NA” | | DOSEi = 0 | Return “NA” | |  | VOLUMEU |
| 3.0 | **VZTAUi** | The volume of distribution associated with the terminal slope following intravascular administration, calculated using AUCTAU.  **Note that the parameter naming convention for Release 2 of the Computaton Engine Specifications referred to VZTAUi as VZiP for steady-state data. This has been changed to VZTAUi with Release 3 to distinguish between the single dose and steady-state parameters.**  **Model M2(SS) and M3 (SS)**  Steady-State Equation:    AUCTAUi = Area under the concentration versus time curve from zero time until the end of the ith dosing interval.  DOSEi = dose value for ith drug dosing interval.  KEL = Terminal or elimination phase rate constant.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | AUCTAUi= NA | Return “NA” | | KEL = NA | Return “NA” | | DOSEi = 0 | Return “NA” | | 3 | VOLUMEU |
| 2.0 | **VSSO** | Steady-state (observed) volume of distribution for non-steady state or steady state data.  **Models M2(SD) and M3(SD)**  MRTO/**MRTIVIFO(i)** = Mean residence time (observed) extrapolated to infinity.  **CLO** = Total clearance of drug (observed)   |  |  | | --- | --- | | **Data Checks** | **Actions** | | **CLO** = NA | Return “NA” | | MRTO/**MRTIVIFO(i)** = NA | Return “NA” | | MRTO/**MRTIVIFO(i)** = 0 | Return “NA” | | 0 | VOLUMEU |
| 2.0 | **VSSOi** | Steady-state (observed) volume of distribution for non-steady state or steady state data.  **Models M2(SS) and M3(SS)**  MRTO/**MRTIVIFO(i)** = Mean residence time (observed) extrapolated to infinity.  **CLO** = Total clearance of drug (observed)   |  |  | | --- | --- | | **Data Checks** | **Actions** | | **CLTAUi** = NA | Return “NA” | | MRTOi/**MRTIVIFO(i)** = NA | Return “NA” | | MRTOi/**MRTIVIFO(i)** = 0 | Return “NA” | | 0 | VOLUMEU |
| 2.0 | **VSSP** | Steady-state (observed) volume of distribution for non-steady state or steady state data.  **Models M2(SD) and M3(SD)**  MRTP/**MRTIVIFP(i)** = Mean residence time (predicted) extrapolated to infinity.  **CLP** = Total clearance of drug (observed)   |  |  | | --- | --- | | **Data Checks** | **Actions** | | **CLP** = NA | Return “NA” | | MRTP/**MRTIVIFP(i)** = NA | Return “NA” | | MRTP/**MRTIVIFP(i)** = 0 | Return “NA” | | 0 | VOLUMEU |
| 2.0 | **VSSPi** | Steady-state (predicted) volume of distribution for non-steady state or steady state data.*i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Models M2(SS) and M3(SD)**  MRTP = Mean residence time (predicted) extrapolated to infinity.  **CLTAUi** = Total clearance of drug (predicted) for ith dosing interval  **Note this parameter was named “VSSiP” in Computation Engine Release 2.0.**   |  |  | | --- | --- | | **Data Checks** | **Actions** | | CLTAUi = NA | Return “NA” | | MRTPi/**MRTIVIFP(i)** = NA | Return “NA” | | MRTPi/**MRTIVIFP(i)** = NA | Return “NA” | | 0 | VOLUMEU |
| 1.0 | **PTR*i*** | **Peak/Trough (CMAX*i* to CMIN*i*) Ratio over the dosing interval *i.*** *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  Steady-State Equation:    CMAXi = Maximum observed concentration  CMINi = Minimum observed concentration  Example:   |  |  | | --- | --- | | **Time** | **Conc.** | | Predose | 0.25 | | 1hr | 0.53 | | 2hr | 1.26 | | 8hr | 0.76 | | 12hr | 0.57 | | 24hr | 0.23 |   TAU=24 hrs  PTR = 1.26/0.23 = 5.48 at steady-state.  Not calculated for single dose.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If CMAXi = 0 | Return “NA” | | If CMINi = 0 | Return “NA” | | 1 | None |
| 3.0 | **PTROUGHRi** | The maximum concentration during the ith dosing interval divided by the pre-dose concentration. *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Models M1(SS), M2(SS), M3(SS)**  Steady-State Equation:    CMAXi = Maximum observed concentration in the ith dosing interval  CTROUGHi = Pre-dose concentration in the ith dosing interval  Example:   |  |  | | --- | --- | | **Time** | **Conc.** | | Predose | 0.25 | | 1hr | 0.53 | | 2hr | 1.26 | | 8hr | 0.76 | | 12hr | 0.57 | | 24hr | 0.23 |   TAU=24 hrs  PTR = 1.26/0.25 = 5.04 at steady-state.  Computed for steady-state only, not calculated for single dose.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If CMAXi = 0 | Return “NA” | | If CTROUGHi = 0 | Return “NA” | | 3 | None |
| 3.0 | **PTROUGHRENDi** | The maximum concentration during a dosing interval divided by the concentration at the end of the dosing interval. *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Models M1(SS), M2(SS), M3(SS)**  Steady-State Equation:    CMAXi = Maximum observed concentration in the ith dosing interval  CTROUGHENDi = Concentration at the end of ith dosing interval  E.g.:   |  |  | | --- | --- | | **Time** | **Conc.** | | Predose | 0.25 | | 1hr | 0.53 | | 2hr | 1.26 | | 8hr | 0.76 | | 12hr | 0.57 | | 24hr | 0.23 |   TAU=24 hrs  PTROUGHREND = 1.26/0.23 = 5.48 at steady-state.  Computed for steady-state only, nnot calculated for single dose.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If CMAXi = 0 | Return “NA” | | If CTOUGHENDi = 0 | Return “NA” | | 3 | None |
| 1.0 | **PTF*i*** | **Fluctuation between the peak and trough concentrations during a dosing interval *i.*** *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  Steady-State Equation:    CMAXi = Another parameter, maximum observed concentration for interval i  CMINi = Another parameter, minimum observed concentration for interval i  CAVi = Another parameter; average concentration at steady-state for interval i.  Example:   |  |  | | --- | --- | | **Time** | **Conc.** | | Predose | 0.25 | | 1hr | 0.53 | | 2hr | 1.26 | | 8hr | 0.76 | | 12hr | 0.57 | | 24hr | 0.23 |   TAU=24  PTF = (1.26-0.23)/0.62 = 1.66 as steady-state.  Not calculated for single dose.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If CMAX = 0 | Return “NA”  (Not Determined) | | If CMIN = 0 | Return “NA” | | If CAVi = 0 | Return “NA” | | 1 | None |
| 1.0 | **CAV*i*** | **Average concentration at steady state.**  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*    **Steady-State Equation:**    Not calculated for single dose  PK Analyst Note: User to re-calculate CAVi with AUCINF if steady-state is not obtained.  **Secondary parameter report**   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If  ≤ 0 | Return “NA”  (Not Available) | | If AUCTAU is NA | Return “NA” | | If AUCTAU ≤ 0 | Return “NA” | | If  is not one of the existing times associated with concentration data | Return “NA” | | 3 | CONCU |
| 1.0 | **CTROUGH*i*** | **Pre-dose concentration** defined as nominal time 0 during multiple dosing.  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  This is the concentration that corresponds to the nominal time of dosing  Models: M1(SS), M2(SS), M3(SS)  Example:   |  |  | | --- | --- | | Predose | 0.25 | | 1hr | 0.53 | | 2hr | 1.26 | | 8hr | 0.76 | | 12hr | 0.57 | | 24hr | 0.23 |   CTROUGH*i*=0.25 | 3 | CONCU |
| 3.0 | **CTROUGHEND*i*** | Concentrations at the end of the ith dosing interval, defined as the observed concentration at the time of nominal time TAU during multiple dosing. *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Models M1(ss), M2(ss), M3(ss)**    This is the concentration that corresponds to the nominal time of dosing for the next dosing interval, jth+1.   |  |  | | --- | --- | | Predose | 0.25 | | 1hr | 0.53 | | 2hr | 1.26 | | 8hr | 0.76 | | 12hr | 0.57 | | 24hr | 0.23 |   TAUi=24hr  CTROUGHEND*i*=0.23 | 3 | CONCU |
| 2.0 | **C0** | **Initial concentration resulting immediately after an IV bolus administration.**  **Model M2 (IV bolus).**  **Note for PK Analysts:** This not **KELC0**  C0 can be estimated by the following methods:  1) C0 is the first observed concentration value if that value occurs at the dose time.  Example:   |  |  | | --- | --- | | **Time** | **Conc** | | ***0*** | ***10*** | | 2 | 6.3 | | 4 | 4 | | ***6*** | ***2.5*** | | 8 | 1.6 | | 10 | 1 | | 12 | 0.63 | | 18 | 0.16 | | 24 | 0.04 | | 36 | 0 | | 48 | 0 |   From the example table above:  If time of last dose is at 0 hr, then C0 equals 10.  If time of last dose is at 6 hr, then C0 equals 2.5.  2) Otherwise, C0 is estimated by back-extrapolating from the first two concentration values using the  log-linear regression to perform on the first two data points (where C2<C1) to back-extrapolate C0.  Equations:  First find slope of the first two data point:    Where C1 and C2 are the 1st and 2nd concentration value, respectively and T1 and T2 are the times when C1 and C2 occur, respectively.  Then calculate C0:    Where C1 is the 1st concentration and T1 is the actual time post-dose of the 1st concentration and K is the slope of the first two data points.  Example:   |  |  | | --- | --- | | **Time** | **Conc** | | 2 | 6.3 | | 4 | 4 | | 6 | 2.5 | | 8 | 1.6 | | 10 | 1 | | 12 | 0.63 | | 18 | 0.16 | | 24 | 0.04 | | 36 | 0 | | 48 | 0 |   From example table above, the slope of the first two data points and C0 are calculated as follows:  K = (ln(4 ) – ln( 6.3)) / (4-2) = - 0.227 hr-1  C0 = 6.3 exp(-(-0.227)\*2) = 9.9225 ng/mL  3) However, in the instance that the regression yields a slope >= 0 (where, C2>C1) or at least one of the first two y-values is 0, then the first observed positive y-value will be used as an estimate for C0.  Example:   |  |  | | --- | --- | | **Time** | **Conc** | | 2 | 3 | | 4 | 4 | | 6 | 5 | | 8 | 6 | | 10 | 6.3 | | 12 | 10 | | 18 | 7.9 | | 24 | 5 | | 36 | 4 | | 48 | 1 |   From example table above, the slope of the first two data points is 0.148 hr-1 (i.e. >=0), then C0 is 3.0 ng/mL.  *Refer to Appendix “*C0 Example*” for detailed example* |  | CONCU |
| 2.0 | **AUCXBPCTO** | The percentage of AUCINF (observed) that was due to back extrapolation to estimate C0.  **Model M2**  AUCINFO corrected for the back extrapolated area, AUCT0-T1    AUCXBPCTO    AUCT0-T1 = area under the concentration curve that was back extrapolated (i.e. from T0 to T1). See Section Estimate AUCXBPCTO (observed) for details.  AUCINF = AUCINFO not including AUC T0-T1  AUCINFO = **Area under the concentration versus time curve from zero time to infinity (Observed)**. |  | None % |
| 2.0 | **AUCXBPCTP** | The percentage of AUCINF (predicted) that was due to back extrapolation to estimate C0.  **Model M2**  AUCINFP corrected for the back extrapolated area, AUCT0-T1    AUCXBPCTP    AUCT0-T1 = area under the concentration curve that was back extrapolated (i.e. from T0 to T1). See Section Estimate AUCXBPCTP (predicted) for details.  AUCINF = AUCINFP not including AUC T0-T1  AUCINFP = **Area under the concentration versus time curve from zero time to infinity** **(Predicted)**. |  | None % |
| 2.0 | **V0** | Initial Volume of Distribution  **Model M2 (IV Bolus)**    Note: automated computation of V0 for Model M2 (IV Bolus) are not implemented in the legacy Pfizer eNCA computation engine release 2 code base.  Use DOSE1 in the case where there are multiple dosing intervals. |  | Volume |
| 3.0 | **CMAXC** | **Corrected CMAX**  **Model M2 (IV Bolus)**  CMAX corrected using estimates of **KEL** and **C0**.  The corrected CMAXC **(and the other corrections below)** should be triggered for computation when the FLAG for predose concentrations >5% of Cmax are observed has been set. This would ordinarily apply to CMAXC. | 3 | CONCU |
| 3.0 | **CMAXCi** | **Corrected CMAXi**  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Model M2 (IV Bolus)**  CMAXi corrected using estimates of **KEL** and **C0**.  The corrected CMAXCi **(and the other corrections below)** should be triggered for computation when the FLAG for predose concentrations >5% of Cmax are observed has been set. This would ordinarily apply to CMAXC1, i.e. the first dosing interval of a concentration time profile. | 3 | CONCU |
| 3.0 | **AUCINFOC** | **Corrected AUCINFO**  AUCINFO corrected using estimates of KEL and C0    C0 is the residual plasma concentration observed at time zero (i.e. the predose concentraton).  KEL is the terminal phase rate constant for the concentration-time profile of interest. | 3 | AUCU |
| 3.0 | **AUCINFPC** | **Corrected AUCINFPC**  AUCINFP corrected using estimates of KEL and C0    C0 is the residual plasma concentration observed at time zero (i.e. the predose concentraton).  KEL is the terminal phase rate constant for the concentration-time profile of interest. | 3 | AUCU |
| 3.0 | **AUCLASTC** | **Corrected** AUCLAST  AUCLAST corrected using estimates of KEL and C0    CLAST(res) is the predicted residual concentration at TLAST and is computed as follows:    C0 is the residual plasma concentration observed at time zero (i.e. the predose concentraton).  KEL is the terminal phase rate constant for the concentration-time profile of interest. | 2 | AUCU |
| 3.0 | **AUCLASTCi** | **Corrected** AUCLAST**i**  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  AUCLASTi corrected using estimates of KEL and C0    CLASTi(res) is the predicted residual concentration at TLASTi and is computed as follows:    C0 is the residual plasma concentration observed at time zero (i.e. the predose concentraton).  KEL is the terminal phase rate constant for the concentration-time profile of interest. | 2 | AUCU |
| 3.0 | **Fu** | **Fraction Unbound**  Fraction unbound, Fu, should be reported and summarized as a unitless value (i.e., the fraction unbound should be provided rather than the % unbound).  Note Fu is not computed by the computation engine but defined here so it can be reported as a PK parameter.  Fu should be treated as a PK parameter and summarized/listed in the same fashion as AUC or CMAX. | As reported | None - unitless |

† - Parameter Name utilized in this computation engine.

Urine

These are the parameters that are calculated when the matrix in the study design element indicates that the data is associated with urine sample collections. To calculate these parameters, the user identifies the columns containing the appropriate volume, volume units, concentration, concentration units, starting and ending time of each collection interval as part of the configuration settings for model execution.

**Note:** All parameter calculations are for models specified in Appendix “Parameter Model Mapping List - Primary and Derived ”, unless otherwise specified.

**Note:** For mixed model M1 and M4 the SAMPLETYPE data field is used to distinguish “INTERVAL” from “POINT”. Value in SAMPLETYPE data field is used case insensitive for matching to determine which data goes to M1 or M4 models.

**Note:** If urine amount data is received in mass units then system will automatically convert it before computing any parameters. *(Refer to Appendix “*Volume/Weight conversion for Urine data*”)*

#### Urine Data Handling

The premise of urine data handling/reporting is based on a complete urine collection. In order to address issues arising from incomplete bladder emptying or missing urine collection intervals the following data handling approaches are to be implemented.

* If any interval within a collection period is missing such that a urine volume wasn’t measured or a urine sample was not analyzed this is considered a true missing or NA as such a complete total urine collection cannot be assumed thus associated urine parameters cannot be calculated (Ae, Ae%, CLr).
* If at the discretion of the PK analyst, a collection interval or concentration values appears to be anomalous and excluded this is also considered an incomplete urine collection and no urine parameters are reported (Ae, Ae%, CLr).
* The final scenario is where a subject did not void within a urine interval.

This can arise from short frequent urine collection intervals or reduced renal function consideration for lengthening intervals when possible can reduce incomplete urine emptying. If the subject did not void and no volume was measure for this interval, the standard clinical pharmacokinetic assumption based on linear renal excretion is that the next urine interval collection will contain the prior interval drug amounts and the interval would be recorded as a 0 for urine volume and all calculations and values would be reported as 0 for that interval. Note that the associated urinary parameters (Ae, Ae%, CLr) would still be reported since not voiding is not considered an incomplete urine collection. However, it is advisable to review the volume outputs before and after the no void interval and confirm with the clinical site the subject truly didn’t void if urine outputs seem reasonable surrounding this no void suggesting no diminished urine output or renal insufficiency at the analyst discretion urinary PK parameters for this subject can be considered for exclusion noting that the default is to assume a 0 volume is a complete collection and report urine PK parameters.

**Reporting Scenarios for Urine Data Handling**

**Example 1- Urine Concentration Missing or Anomalous with Urine Measured Urine Volume**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Collection Interval | Urine Volume1 | Urine Concentration | Urine Amount | Total Ae | Ae% | CLr |
| 0-4 Hrs | 400 mL | 1.50 ng/mL | 1050 ng |  |  |  |
| 4-8 Hrs | 700 mL | NA or Excluded (1800 ng/mL) | NA |  |  |  |
| 8-12 Hrs | 500 mL | 10.5 mg/mL | 5250 ng |  |  |  |
| 12-24 Hrs | 900 mL | 5.0 ng/mL | 4500 ng | NA | NA | NA |

1If urine volume is a measured weight urine specific gravity correction of 1.020 g/mL is applied.

**Example 2-Urine Volume not Recorded with Measured Concentration**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Collection Interval | Urine Volume | Urine Concentration | Urine Amount | Total Ae | Ae% | CLr |
| 0-4 Hrs | 400 mL | 1.50 ng/mL | 1050 ng |  |  |  |
| 4-8 Hrs | NA | 8.0 ng/mL | NA |  |  |  |
| 8-12 Hrs | 500 mL | 10.5 ng/mL | 5250 ng |  |  |  |
| 12-24 Hrs | 900 mL | 5.0 ng/mL | 4500 ng | NA | NA | NA |

**Example 3-Urine Volume 0 Subject Didn’t Void**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Collection Interval | Urine Volume | Urine Concentration | Urine Amount | Total Ae | Ae% | CLr |
| 0-4 Hrs | 400 mL | 1.50 ng/mL | 1050 ng | 1050 ng |  |  |
| 4-8 Hrs | 0 | 0 | 0 | 0 |  |  |
| 8-12 Hrs | 500 mL | 10.5 ng/mL | 5250 ng | 6300 |  |  |
| 12-24 Hrs | 900 mL | 5.0 ng/mL | 4500 ng | 10,800 | 1.8% | 0.35 mL/min |

| **Release** | **Name†** | **Description** | **Decimal Places** | **Unit Class** |
| --- | --- | --- | --- | --- |
| 2.0\* | **AT** | **Definition as per Clinical Pharmacology Guidance:** Amount of Drug in the body at time T, where T can have a numerical value.  **Model M4**  Use the appropriate equation to calculate the **amount** of drug recovered unchanged in the urine at **each time post-dose.**  Equations:  If urine is reported as volume then the following equation should be used:  Default  If urine is reported as weight, then system automatically will apply specific gravity corrections where 1.020a g/mL is the approximate specific gravity of urine.  *Refer to Appendix “*Volume/Weight conversion for Urine data*” for details*  a - Value obtained from Pagana, KD. Mosby’s Diagnostic and Laboratory Test Reference (Eighth Edition). 2007, Page 968. The range for adult is 1.005-1.030, with a median derived value of 1.020 g/mL. | 3 | AMOUNTU |
| 1.0 | **AET** | **Cumulative (running sum) amount of drug** recovered unchanged in the urine up to **time t post-dose**, where t can have a numerical value.  **Model M4**  Equation:  *AET = AT1 + AT2 + AT3…….*  AET = cumulative amount of drug (wt) up to time t post dose.  ATt= amount of drug (wt), where t can have a numerical  value  Example:   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Start Time | End Time | V | C | AT | AET | | 0 | 4 | 200 | 3 | 600 | **600** | | 4 | 8 | 350 | 4.2 | 1470 | **2070** | | **8** | **12** | 300 | 4 | 1200 | **3270** | | 12 | 16 | 275 | 3.9 | 1073 | 4343 | | 16 | 20 | 250 | 3.5 | 875 | 5218 | | 20 | 24 | 200 | 0 | 0 | 5218 |   As per example table, the cumulative amount of drug at each post-dose or collection interval will be calculated as follows:  *AE4 @ end of 4 hours = 600 ng*  *AE8 @ end of 8 hours =600 ng + 1470 ng = 2070 ng*  *AE12 @ end of 12 hours =600 ng +1470 ng + 1200 ng =3270 ng*  etc.  NOTE: correct for units. | 3 | AMOUNTU |
| 1.0 | **AE** | **Total amount** of drug recovered unchanged in the urine, from **time zero to infinity**  **Model M4**  **Equation**  *AE = ATt + ATt + ATt…….+ ATlast*  AE = cumulative total amount from time zero to infinity (wt)  ATt = amount of drug (wt), where t can have a numerical  value  ATlast = Last measurable amount of drug (wt)  Example:   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Start Time | End Time | V | C | AT | AET | | 0 | 4 | 200 | 3 | 600 | 600 | | 4 | 8 | 350 | 4.2 | 1470 | 2070 | | 8 | 12 | 300 | 4 | 1200 | 3270 | | 12 | 16 | 275 | 3.9 | 1073 | 4343 | | 16 | 20 | 250 | 3.5 | 875 | **5218** | | 20 | 24 | 200 | 0 | 0 | 5218 |   As per example table, if last measurable urine concentration is at the end of 20 hours, then cumulative total amount of drug recovered from time zero to infinity will be calculated as follows:  *AE =600 + 1470 + 1200 + 1073 + 875 = 5218 ng*  NOTE: correct for units | 3 | AMOUNTU |
| 1.0 | **AETAUi** | **Cumulative amount of drug** recovered unchanged in the urine during a **dosing interval *i* post dose.**  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Model M4**  **Equation**  *AETAUi = ATt + ATt + ATt…….+ ATtau*  AETAUi = Cumulative amount at of drug during a dosing interval (wt)  ATt = amount of drug (wt), where t can have a numerical  value  ATtau = amount of drug (wt) at end of the dosing interval  Example:   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Start Time | End Time | V | C | AT | AET | | 0 | 4 | 200 | 3 | 600 | 600 | | 4 | 8 | 350 | 4.2 | 1470 | 2070 | | 8 | **12** | 300 | 4 | 1200 | **3270** | | 12 | 16 | 275 | 3.9 | 1073 | 4343 | | 16 | 20 | 250 | 3.5 | 875 | 5218 | | 20 | 24 | 200 | 0 | 0 | 5218 |   As per example table, if the dosing interval (i.e., tau) is 12 hours, then cumulative amount of drug recovered during a dosing interval will be calculated as follow:  *AETAU =600 + 1470 +1200 = 3270 ng*  NOTE: correct for units | 3 | AMOUNTU |
| 1.0 | **AETPCT** | **Cumulative amount of drug** recovered unchanged in the urine up to **time *T* post-dose**, where t can have a numerical value, **expressed as percentage of administered dose**  **Model M4, DERIVED**  **Equation**    AET = cumulative amount at of drug at time t (wt)  Dose = administered dose (wt)  Example:   |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Start Time | End Time | V | C | AT | AET | AETPCT | | 0 | 4 | 200 | 3 | 600 | 600 | 1.2 | | 4 | **8** | 350 | 4.2 | 1470 | 2070 | **4.14** | | 8 | 12 | 300 | 4 | 1200 | 3270 | 6.54 | | 12 | 16 | 275 | 3.9 | 1073 | 4343 | 8.67 | | 16 | 20 | 250 | 3.5 | 875 | 5218 | 10.4 | | 20 | 24 | 200 | 0 | 0 | 5218 | 10.4 |   As per example table, if cumulative amount of drug at the end of 8 hours and unit dose administered is 5 mg, then AETpct will be calculated as follow:  AE8pct = (2070 ng / 50000 ng) x 100 = 4.14%    NOTE: correct for units | 1 | None % |
| 1.0 | **AEPCT** | **Cumulative total amount of drug** recovered unchanged in the urine, **from time zero to infinity, expressed as percentage of administered dose**  **Model M4, DERIVED**  **Equation**    AE = Cumulative total amount of drug from time zero to infinity (wt)  Dose = administered dose (wt)  Example:   |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Start Time | End Time | V | C | AT | AE | AEPCT | | 0 | 4 | 200 | 3 | 600 | 600 | 1.2 | | 4 | **8** | 350 | 4.2 | 1470 | 2070 | **4.14** | | 8 | 12 | 300 | 4 | 1200 | 3270 | 6.54 | | 12 | 16 | 275 | 3.9 | 1073 | 4343 | 8.67 | | 16 | **20** | 250 | 3.5 | 875 | 5218 | **10.4** | | 20 | 24 | 200 | 0 | 0 | 5218 | 10.4 |   As per example table, if last measurable urine concentration is at the end of 20 hours and unit dose administered is 5 mg, then cumulative total amount of drug from zero to infinity is at 20 hrs, then AEPCT will be calculated as follow:  As per example table, if last measurable urine concentration is at the end of 20 hours, then cumulative total amount of drug recovered from time zero to infinity will be calculated as follows:  AEpct = (5218 ng/ 50000 ng) x 100 = 10.4%    NOTE: correct for units if necessary | 1 | None % |
| 1.0 | **AETAU*PTi*** | **Cumulative amount of drug** recovered unchanged in the urine during a **dosing interval i, expressed as fraction/percentage of administered dose.** *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Model M4**  **Equation**    AETAUi = Cumulative amount at of drug during a dosing interval *i* (wt)  Dose = dose administered at interval TAU*i* (wt)  Example:   |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | | Start Time | End Time | V | C | AT | AET | AETPCT | | 0 | 4 | 200 | 3 | 600 | 600 | 1.2 | | 4 | 8 | 350 | 4.2 | 1470 | 2070 | 4.14 | | 8 | **12** | 300 | 4 | 1200 | 3270 | **6.54** | | 12 | 16 | 275 | 3.9 | 1073 | 4343 | 8.67 | | 16 | 20 | 250 | 3.5 | 875 | 5218 | 10.4 | | 20 | 24 | 200 | 0 | 0 | 5218 | 10.4 |   As per example table, if cumulative total amount of drug during a dosing interval (tau = 12 hrs) and unit dose administered is 5 mg, then **AETAU*PTi*** will be calculated as follow:  **AETAU*PTi*** = (3270 ng / 50000 ng) x 100 = 6.54%    NOTE: correct for units | 1 | None % |
| 2.0 | **VOLSUM** | **Cumulative Sum of Urine Volumes**  Example:   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Start Time | End Time | MIDPT | V | C | RATE | | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 4 | 2 | 200 | 3 | 150 | | 4 | 8 | 6 | 350 | 4.2 | 368 | | 8 | 12 | 10 | 300 | 4 | 300 | | 12 | 16 | 14 | 275 | 3.9 | 268 | | 16 | 20 | 18 | 250 | 3.5 | 219 | | 20 | 24 | 22 | 200 | 0 | 0 |   VOLSUM = 200 + 350 +300 + 275 + 250 +200 = 1575 mL |  | VOLUMEU |

#### Midpoint and Rate dependent parameters

**Note:** **Midpoint (Nominal/Actual)** and **Rate** are derived by the system and are included as part of the concentration dataset (Data Prep). *See Appendix* Derivations for parameters calculations *for details*.

| **Release** | **Name** | **Description** | **Decimal Places** | **Unit Class** |
| --- | --- | --- | --- | --- |
| 2.0 | KELRSQ | Refer to plasma/serum/blood for definition and calculation methods.  Note: Use MIDPOINT for time and RATE for concentration in calculation. |  | None |
| 2.0 | KELRSQA | Refer to plasma/serum/blood for definition and calculation methods.  Note: Use MIDPOINT for time and RATE for concentration in calculation. |  | None |
| 2.0 | KELR | Refer to plasma/serum/blood for definition and calculation methods. |  | None |
| 2.0 | KELNOPT | Refer to plasma/serum/blood for definition and calculation methods.  Note: Use MIDPOINT for time and RATE for concentration in calculation. |  | None |
| 2.0 | KEL | Refer to plasma/serum/blood for definition and calculation methods.  Note: Use MIDPOINT for time and RATE for concentration in calculation. |  | KELU |
| 2.0 | KELTMLO | Refer to plasma/serum/blood for definition and calculation methods.  Note: Use MIDPOINT for time and RATE for concentration in calculation. |  | TIMEU |
| 2.0 | KELC0 | Refer to plasma/serum/blood for definition and calculation methods.  Note: Use MIDPOINT for time and RATE for concentration in calculation. |  | CONCU |
| 2.0 | KELTMHI | Refer to plasma/serum/blood for definition and calculation methods.  Note: Use MIDPOINT for time and RATE for concentration in calculation. |  | TIMEU |
| 2.0 | THALF | Refer to plasma/serum/blood for definition and calculation methods.  Note: Use MIDPOINT for time and RATE for concentration in calculation. |  | TIMEU |
| 2.0 | TLAG | Refer to plasma/serum/blood for definition and calculation methods.  Note: Use MIDPOINT for time and RATE for concentration in calculation. |  | TIMEU |
| 3.0 | **TMAXRATE** | Midpoint of collection interval associated with the maximum observed excretion rate.  Example:   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Start Time | End Time | MIDPT | V | C | RATE | | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 4 | 2 | 200 | 3 | 150 | | 4 | 8 | **6** | 350 | 4.2 | **368** | | 8 | 12 | 10 | 300 | 4 | 300 | | 12 | 16 | 14 | 275 | 3.9 | 268 | | 16 | 20 | 18 | 250 | 3.5 | 219 | | 20 | 24 | 22 | 200 | 0 | 0 |   TMAXRATE in above example is 6 hr.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all RATE = 0 | Return “NA” | |  | TIMEU |
| 3.0 | **TMAXRATEi** | Midpoint of collection interval associated with the maximum observed excretion rate. *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  Example:   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Start Time | End Time | MIDPT | V | C | RATE | | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 4 | 2 | 200 | 3 | 150 | | 4 | 8 | **6** | 350 | 4.2 | **368** | | 8 | 12 | 10 | 300 | 4 | 300 | | 12 | 16 | 14 | 275 | 3.9 | 268 | | 16 | 20 | 18 | 250 | 3.5 | 219 | | 20 | 24 | 22 | 200 | 0 | 0 |   TMAXRATE in above example is 6 hr.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all RATE = 0 | Return “NA” | |  | TIMEU |
| 2.0† | **MAXRATE** | **Maximum observed excretion rate**  *Computed within the profile.*  Example:   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Start Time | End Time | MIDPT | V | C | RATE | | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 4 | 2 | 200 | 3 | 150 | | 4 | 8 | 6 | 350 | 4.2 | **368** | | 8 | 12 | 10 | 300 | 4 | 300 | | 12 | 16 | 14 | 275 | 3.9 | 268 | | 16 | 20 | 18 | 250 | 3.5 | 219 | | 20 | 24 | 22 | 200 | 0 | 0 |   MAXRATE in above example is 368 ng/hr   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all RATE = 0 | MAXRATE = 0 | |  | RATEU |
| 2.0† | **MAXRATEi** | **Maximum observed excretion rate**  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  Example:   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Start Time | End Time | MIDPT | V | C | RATE | | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 4 | 2 | 200 | 3 | 150 | | 4 | 8 | 6 | 350 | 4.2 | **368** | | 8 | 12 | 10 | 300 | 4 | 300 | | 12 | 16 | 14 | 275 | 3.9 | 268 | | 16 | 20 | 18 | 250 | 3.5 | 219 | | 20 | 24 | 22 | 200 | 0 | 0 |   MAXRATE in above example is 368 ng/hr   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all RATE = 0 | MAXRATE = 0 | |  | RATEU |
| 2.0† | **MIDPTLAST** | **Midpoint of collection interval associated with last measurable (nonzero) rate.**  Example:   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Start Time | End Time | MIDPT | V | C | RATE | | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 4 | 2 | 200 | 3 | 150 | | 4 | 8 | 6 | 350 | 4.2 | 368 | | 8 | 12 | 10 | 300 | 4 | 300 | | 12 | 16 | 14 | 275 | 3.9 | 268 | | 16 | 20 | **18** | 250 | 3.5 | 219 | | 20 | 24 | 22 | 200 | 0 | 0 |   MIDPTLAST in above example is 18 hr.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all RATE = 0 | Return “NA” | |  | TIMEU |
| 2.0† | **MIDPTLASTi** | **Midpoint of collection interval associated with last measurable (nonzero) rate.**  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  Example:   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Start Time | End Time | MIDPT | V | C | RATE | | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 4 | 2 | 200 | 3 | 150 | | 4 | 8 | 6 | 350 | 4.2 | 368 | | 8 | 12 | 10 | 300 | 4 | 300 | | 12 | 16 | 14 | 275 | 3.9 | 268 | | 16 | 20 | **18** | 250 | 3.5 | 219 | | 20 | 24 | 22 | 200 | 0 | 0 |   MIDPTLAST in above example is 18 hr.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all RATE = 0 | Return “NA” | |  | TIMEU |
| 2.0† | **RATELASTi** | **Last measurable (nonzero) rate**  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  Example:   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Start Time | End Time | MIDPT | V | C | RATE | | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 4 | 2 | 200 | 3 | 150 | | 4 | 8 | 6 | 350 | 4.2 | 368 | | 8 | 12 | 10 | 300 | 4 | 300 | | 12 | 16 | 14 | 275 | 3.9 | 268 | | 16 | 20 | 18 | 250 | 3.5 | **219** | | 20 | 24 | 22 | 200 | 0 | 0 |   RATELAST in above example is 219 ng/hr.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If all RATE = 0 | Return “NA” | |  | RATEU |
| 2.0† | **AURCLAST** | **Area under the urinary excretion rate curve from time 0 to the last measurable rate.**  Same as plasma/serum/blood calculations  Note: Use MIDPOINT for time and RATE for concentration in calculation.  **Determination of T0**  First midpoint is always equal to time of last dose and the RATE is assumed to be zero. So T0 is the first midpoint. | 2 | AURCU |
| 2.0† | **AURCALL** | **Area under the urinary excretion rate curve from time 0 to the last rate.**  This equals AURCLAST if the last rate is measurable.  Refer to AUCALL in plasma/serum/blood for calculation methods.  Note: Use MIDPOINT for time and RATE for concentration in calculation. | 2 | AURCU |
| 2.0† | **AURCINFO** | **Area under the urinary excretion rate curve extrapolated to infinity (observed)**  Refer to AUCINFO in plasma/serum/blood for calculation methods.  Note: Use MIDPOINT for time and RATE for concentration in calculation. | 2 | AURCU |
| 2.0† | **AURCT1\_T2** | **Area under the urinary excretion rate curve** from time T1 until time T2, where T1 and T2 are user-specified times.  **Note:** T1 and T2 for this parameter are the nominal MIDPOINTs, i.e. variable MIDPTN  **Calculation**   1. Calculate using the appropriate trapezoidal AUC rule for each interval. 2. Add the AURCs for each interval to compute total AURCT1T2.  |  |  | | --- | --- | | **Data Checks** | **Actions** | | If T1<Dose time | Return “NA” | | T1 = T2 | Return “NA” | | If T2<T1 | Return “NA” | | If C corresponding to either time T1 or T2 is not available (after applying rules for “AUC Calculations and Missing Data” in Appendix Missing Data) | Return “NA” | | If all Cs = 0 | AUCT1T2 = 0 |   Note that MCT definitions for AURCT1\_T2 have no “partial AUC” equivalent in the MCT. Thereby, the partial AUC definitions in the MCT are used as the input to the AURCT1\_T2 values. Note that this applies for MIDPTN computations as well. | 2 | AURCU |
| 2.0† | **AURCXPCTO** | **Percent of AURCINFO that is extrapolated.**  Refer to AUCXPCTO in plasma/serum/blood for calculation methods.  Note: Use MIDPOINT for time and RATE for concentration in calculation. |  | None % |
| 2.0† | **AURCINFP** | **Area under the urinary excretion rate curve extrapolated to infinity (predicted)**  Refer to AUCINFP in plasma/serum/blood for calculation methods.  Note: Use MIDPOINT for time and RATE for concentration in calculation. | 2 | AURCU |
| 2.0† | **AURCXPCTP** | Percent of AURCINFP that is extrapolated.  Refer to AUCXPCTP in plasma/serum/blood for calculation methods.  Note: Use midpoint for time. |  | None % |

† - Parameter Name utilized in this computation engine.

9.2.3 Derived PK Parameters for Multiple Dose Studies

| Release | Name | Description | Decimal Places | Unit Class |
| --- | --- | --- | --- | --- |
| 3.0 | **RACi** | AUCTAUi,Steady-State (ss) / AUCTAUi, Single Dose (first dose).  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  Can be specified as RAC instead of RAC1 if there is only a single multiple dose profile. These are synonyms. | 3 | None ratio |
| 3.0 | **RACCMAXi** | CMAXi,Steady-State (ss) / Cmax, Single Dose (first dose).  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  Can be specified as RACCMAX instead of RACCMAX1 if there is only a single multiple dose profile. These are synonyms. | 3 | None ratio |
| 3.0 | **RACCMINi** | CMINi,Steady-State (ss) / CTROUGHEND (first dose).  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  CTROUGHEND (first dose) is the concentration at the end of the dosing interval (TAU) after the first dose.  Can be specified as RACCMIN instead of RACCMIN1 if there is only a single multiple dose profile. These are synonyms. | 3 | None ratio |
| 3.0 | **RSSi** | AUCTAUi, Steady-State (ss)/AUCinf Single Dose (first dose)  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  Can be specified as RSS instead of RSS1 if there is only a single multiple dose profile. These are synonyms. | 3 | None ratio |

† - Parameter Name utilized in this computation engine.

### Derived PK Parameters with urine and plasma

| **Release** | **Name†** | **Description** | **Decimal Places** | **Unit Class** |
| --- | --- | --- | --- | --- |
| 3.0 | **CLR** | The clearance of a substance from the blood by the kidneys.  **Model: Derived**  Calculated for single dose studies.    AE = Total amount of drug recovered unchanged in the urine, from time zero to infinity. AEinf is achieved following 5\* terminal phase estimation for collection period.  AUCINFP = Area under the concentration versus time curve from zero time to infinity (Predicted). | 3 | CLU |
| 3.0 | **CLRT** | The clearance of a substance from the blood by the kidneys.  **Model: Derived**  Calculated for single dose studies.    **AET** = Total amount of drug recovered unchanged in the urine, from time zero to time T. AEinf is achieved following 5\* terminal phase estimation for collection period.  **AUCT** = Area under the concentration versus time curve from zero time to time T. | 3 | CLU |
| 3.0 | **CLRTAUi** | The clearance of a substance from the blood by the kidneys, calculated using AUCTAUi.  Calculated for steady state.  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Model: M4, Derived**    **AETAUi** = Cumulative amount of drug recovered unchanged in the urine during a specified dosing interval, i.  **AUCTAU*i*** = For steady-state data, the area under the concentration versus time curve from zero time until the end of the specified dosing interval, i.  Can be specified as CLRTAU instead of CLRTAU1 if there is only a single multiple dose profile. These are synonyms. | 3 | CLU |

† - Parameter Name utilized in this computation engine.

### Derived PK Parameters for Metabolites

Note that the value of PKTERMPARENT stored in the ***Model Configuration Template*** is used to identify the parent analyte data. Multiple values of each of the parameters identified in the table below are generated, one for each metabolite.

| **Release** | **Name†** | **Description** | **Decimal Places** | **Unit Class** |
| --- | --- | --- | --- | --- |
| 3.0 | **MRAUCINF** | (AUCINF metabolite/AUCINF parent )\*MWparent/MWmetabolite  **Model: Derived**  Note multiple values of MRAUCINF and other derived PK Parameters for Metabolites will be generated, one for each metabolite. The parent data is identified throught the PKTERMPARENT value from the ***Model Configuration Template*** | 3 | None ratio |
| 3.0 | **MRAUCLAST** | (AUCLAST metabolite/AUCLAST parent)\*MWparent/MWmetabolite  **Model: Derived** | 3 | None ratio |
| 3.0 | **MRAUCTAUi** | (AUCTAUi metabolite/AUCTAUi parent)\*MWparent/MWmetabolite  **Model: Derived**  Can be specified as MRAUCTAU instead of MRAUCTAU1 if there is only a single multiple dose profile. These are synonyms. | 3 | None ratio |
| 3.0 | **MRCMAX** | (CMAX metabolite/CMAX parent)\*MWparent/MWmetabolite  **Model: Derived**  Can be specified as MRCMAX instead of MRCMAX1 if there is only a single multiple dose profile. These are synonyms. | 3 | None ratio |
| 3.0 | **MRCMAXi** | (CMAXi metabolite/CMAXi parent)\*MWparent/MWmetabolite  **Model: Derived**  Can be specified as MRCMAX instead of MRCMAX1 if there is only a single multiple dose profile. These are synonyms. | 3 | None ratio |

MW = Molecular Weight

† - Parameter Name utilized in this computation engine.

### Derived PK Parameters – Dose Normalization

The following table describes the method utilized to dose normalize parameters to unit doses. Note that this table is not all inclusive in that not all parameters that may be desirable to present as dose normalized are incorporated. Note that the naming convention supporting unit dose normalization renames the associated dose normalized parameter to incorporate the letters “DN” as the suffix of the name.

| **Release** | **Name†** | **Description** | **Decimal Places** | **Unit Class** |
| --- | --- | --- | --- | --- |
| 1.0 | **<AUC>DN** | Dose Normalized AUC (unit dose) **for ANY AUC parameter value**  To normalize **ANY AUC parameter** to a unit dose.  **Calculation for all AUC parameters excluding incremental AUC’s**    AUC : Any AUC value (AUCINF, AUCLASTi, AUCT1T2, etc.)  Dose: Administered unit dose, defined in primary parameter analysis information, i.e. the ***Model Configuration Template***.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | Dose = 0 | Return “NA” | | Dose = Missing | Return “NA” | | AUC = NA | Return “NA” |   Note: automated computation of Dose Normalized Parameters is not implemented in the legacy Pfizer eNCA computation engine release 2 code base. |  | AUCNORMU  *For example, if AUC is ng\*hr/mL and dose is mg, units for the dose-normalized values would be ng\*hr/mL/mg (not hr/mL).*  *It’s simpler, and easier to relate to the observed (non-normalized) values.* |
| 3.0 | **AUCTDN** | Dose Normalized AUCT to a unit dose value    DOSEi: Administered unit dose for the dosing interval.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | DOSEi = 0 | Return “NA” | | DOSEi = Missing | Return “NA” | | AUCT = NA | Return “NA” | | 2 | AUCNORMU |
| 3.0 | **AUCALLDN** | Dose normalized AUCALL  -See above equation for <AUC>DN | 3 | AUCNORMU |
| 3.0 | **AUCINFODN** | Dose normalized AUCINF (OBSERVED)  -See above equation for <AUC>DN | 3 | AUCNORMU |
| 3.0 | **AUCINFPDN** | Dose normalized AUCINF (PREDICTED)  -See above equation for <AUC>DN | 3 | AUCNORMU |
| 3.0 | **AUCLASTDN** | Dose normalized AUCLAST  -See above equation for <AUC>DN | 3 | AUCNORMU |
| 3.0 | **AUCLASTDNi** | Dose normalized AUCLASTi  -See above equation for <AUC>DN | 3 | AUCNORMU |
| 3.0 | **AUCTAUDNi** | Dose normalized AUCTAUi  -See above equation for <AUC>DN | 3 | AUCNORMU |
| 3.0 | **CMAXDN** | Dose normalized CMAX | 3 | CONCNORMU |
| 3.0 | **CMAXDNi** | Dose normalized CMAX*i* | 3 | CONCNORMU |
| 3.0 | **CMINDN** | Dose normalized CMIN | 3 | CONCNORMU |

† - Parameter Name utilized in this computation engine.

### Derived PK Parameters - Body Size Normalization

Body size normalization for selected pharmacokinetic parameters is performed as indicated in the parameter definitions below. Note that while these definitions indicate that the body size measurement is body weight in each case, this is the default. The configuration value of **NORMBS** indicates the body size measurement to be used, by default the Body Weight, BW, of the subject associated with the data values. See Section Model Input/Calling Arguments and Data Flags for **NORMBS**definition.

| **Release** | **Name†** | **Description** | **Decimal Places** | **Unit Class** |
| --- | --- | --- | --- | --- |
| 3.0 | **VSSPW**  **VSSPWi** | The volume of distribution at steady state based on the predicted Clast for a substance administered by intravascular dosing divided by the weight.  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Model M2(SD) and M3(SD), Derived**  **Model M2(SS) and M3(SS), Derived**  **VSSPi** = Steady-state (predicted) volume of distribution for non-steady state or steady state data.  By default, **NORMBS** = BW = Body weight | 3 | VOLUMEWU |
| 3.0 | **VSSOW**  **VSSOWi** | The volume of distribution at steady state based on the observed Clast for a substance administered by intravascular dosing divided by the weight.  **Model M2(SD) and M3(SD), Derived**  **Model M2(SS) and M3(SS), Derived**  **VSSO** = Steady-state (observed) volume of distribution for non-steady state or steady state data.  By default, **NORMBS** = BW = Body weight | 3 | VOLUMEWU |
| 3.0 | **CLPW** | The total body clearance for intravascular administration, calculated using the predicted value of the last non-zero concentration, divided by the weight.  **Model M2 (SD) and M3 (SD), Derived**    CLP = Total clearance of drug (predicted).  By default, **NORMBS** = BW = Body weight | 3 | CLWU |
| 3.0 | **CLOW** | The total body clearance for intravascular administration, calculated using the observed value of the last non-zero concentration, divided by the weight.  **Model M2 (SD) and M3 (SD), Derived**    CLO = Total clearance of drug (observed).  By default, **NORMBS** = BW = Body weight | 3 | CLWU |
| 3.0 | **CLTAUWi** | The total body clearance for intravascular administration, calculated using AUCTAU, divided by the weight.  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Model M2 (SS) and M3 (SS), Derived**    CLTAUi = Total clearance of drug calculated using AUCTAUi from the ith dosing interval.  By default, **NORMBS** = BW = Body weight | 3 | CLWU |
| 3.0 | **CLFPW** | The total body clearance for extravascular administration divided by the fraction of dose absorbed, calculated using the predicted value of the last non-zero concentration, divided by the weight.  **Model M1 (SD), Derived**    CLFP = Apparent clearance (predicted)of drug for extravascular routes of administration.  By default, **NORMBS** = BW = Body weight | 3 | CLWU |
| 3.0 | **CLFOW** | The total body clearance for extravascular administration divided by the fraction of dose absorbed, calculated using the observed value of the last non-zero concentration, divided by the weight.  **Model M1 (SD), Derived**    CLFO = Apparent clearance (observed)of drug for extravascular routes of administration.  By default, **NORMBS** = BW = Body weight | 3 | CLWU |
| 3.0 | **CLFTAUWi** | The total body clearance for extravascular administration divided by the fraction of dose absorbed, calculated using AUCTAU, divided by the weight.  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Model M1 (SS), Derived**    CLFTAUi = The total body clearance for extravascular administration divided by the fraction of dose absorbed, calculated using AUCTAUi for the ith dosing interval.  By default, **NORMBS** = BW = Body weight | 3 | CLWU |
| 3.0 | **VZPW** | The volume of distribution associated with the terminal slope following intravascular administration, calculated using the predicted value of the last non-zero concentration, divided by the weight.  **Model M2 (SD) and M3 (SD), Derived**    VZP = The volume of distribution associated with the terminal slope following intravascular administration, calculated using the predicted value of the last non-zero concentration.  By default, **NORMBS** = BW = Body weight | 3 | VOLUMEWU |
| 3.0 | **VZOW** | The volume of distribution associated with the terminal slope following intravascular administration, calculated using the observed value of the last non-zero concentration, divided by the weight.  **Model M2 (SD) and M3 (SD), Derived**    VZP = The volume of distribution associated with the terminal slope following intravascular administration, calculated using the observed value of the last non-zero concentration.  By default, **NORMBS** = BW = Body weight | 3 | VOLUMEWU |
| 3.0 | **VZTAUWi** | The volume of distribution associated with the terminal slope following intravascular administration, calculated using AUCTAU, divided by the body weight of the subject.  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Model M2 (SS) and M3 (SS)**    VZP = The volume of distribution associated with the terminal slope following intravascular administration, calculated using AUCTAUi for the ith dosing interval.  By default, **NORMBS** = BW = Body weight | 3 | VOLUMEWU |
| 3.0 | **VZFPW** | The volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed, calculated using the predicted value of the last non-zero concentration, divided by the body weight of the subject.  **Model M1 (SD), Derived**    VZFP = The volume of distribution associated with the terminal slope following extravascular administration, calculated using the predicted value of the last non-zero concentration.  By default, **NORMBS** = BW = Body weight | 3 | VOLUMEWU |
| 3.0 | **VZFOW** | The volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed, calculated using the observed value of the last non-zero concentration, divided by the body weight of the subject.  **Model M1 (SD), Derived**    VZFO = The volume of distribution associated with the terminal slope following extravascular administration, calculated using the observed value of the last non-zero concentration.  By default, **NORMBS** = BW = Body weight | 3 | VOLUMEWU |
| 3.0 | **VZFTAUWi** | The volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed, calculated using AUCTAUi, divided by the body weight of the subject.  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Model M1(SS), Derived**    VZFTAUi = The volume of distribution associated with the terminal slope following extravascular administration divided by the fraction of dose absorbed, calculated using AUCTAUi for the ith dosing interval, divided by the body weight of the subject.  By default, **NORMBS** = BW = Body weight | 3 | VOLUMEWU |

† - Parameter Name utilized in this computation engine.

# Derived PK Parameters for Absolute and Relative Bioavailability

| **Release** | **Name†** | **Description** | **Decimal Places** | **Unit Class** |
| --- | --- | --- | --- | --- |
| 3.0 | **F** | **Absolute Bioavailability**  **Model: Derived**  (AUCINF,po or s.c/AUCINF,iv)\*(DOSEIV/DOSEPO)  This computation requires that ROUTE be defined in the dataset or be introduced during the pre-computation transformations. | 3 | None ratio |
| 3.0 | **FREL** | **Relative Bioavailability**  **Model: Derived**  (AUCINF,test/AUCINF,reference)\*(DOSEref/DOSEtest)  This computation requires a flag FRELFLAG be defined in the dataset or be introduced during the pre-computation transformations defining test and reference. | 3 | None ratio |
| 3.0 | **FRELLASTi** | **Relative Bioavailablity based upon AUCLAST**  **Model: Derived**    (AUCLASTi,test/AUCLASTi,reference)\*(DOSEref/DOSEtest)  This computation requires a flag FRELFLAG be defined in the dataset or be introduced during the pre-computation transformations defining test and reference. | 3 | None ratio |
| 3.0 | **FA** | **% Fraction Absorbed**  **Model: Derived**  100\*(Hot Urine (AEPCT or AE) po)/(Hot Urine (AEPCT or AE) iv)  Urine ADME studies | 3 | percentage |
| 3.0 | **FTAUi** | **Estimate of Absolute Bioavailability based upon AUCTAUi from specific dosing interval**  *i refers to the dosing interval index, i.e. the number of the ith dose administered within a profile.*  **Model: Derived**  (AUCTAUi,po or s.c /AUCINF,iv)\*(DOSEIV/DOSEPO)  Applicable to individual subjects for crossover study design or calculating FTAUi based on average of the AUC’S.  This computation requires that ROUTE be defined in the dataset or be introduced during the pre-computation transformations.  Can be specified as FTAU instead of FTAU1 if there is only a single multiple dose profile. These are synonyms. | 3 | None ratio |

† - Parameter Name utilized in this computation engine.

# Computation Engine User Interface Considerations

## User/Application Interface

## KEL related user interface computations

Regressions are repeated using the last three points with non-zero concentration, then the last four points etc. Points prior to Cmax are not used unless the user specifically requested that time range. Points with a value of zero for the dependent variable are left out of the regression. For each regression, an adjusted R2 is computed:



where n is the number of data points in the regression and R2 is the square of the correlation coefficient.

The regression with the largest adjusted R2 is selected to estimate KEL, with these caveats:

* If the adjusted R2 does not improve, but is within .0001 of the largest R2 value, the regression with the larger number of points is used
* KEL must be positive
* At least three points must have been used in the computation

Once the times have been determined, KEL is estimated by performing a regression of the natural logarithm of the concentrations on sampling time, for those times in the specified time range.

KEL = -1 times the estimated slope

## Parameters on-the-fly

The EQuIP NCA application will compute following primary and derived parameters *on-the-fly*. Which parameters are displayed in the user interface will be controlled by a configuration template that the user can update and save as a configuration or preference item. The dynamically generated parameters are presented within the UI element/control displaying individual profiles of data during selection of data points for estimating the terminal elimination phase or setting other flags for control of which data points are used during terminal elimination phase estimation, summary data presentations, etc. See Section

Refer to the Appendix Section Parameter Model Mapping List - Primary and Derived for the specification of default parameters to be displayed during terminal elimination phase profile definition and estimation.

*Refer to* Primary Parameter Calculations*sections above for individual parameter calculations*

# References

## Project References

| Ref # | Reference | Revision | Document/File Location |
| --- | --- | --- | --- |
| 1 | Clinical Pharmacology Guidance |  | http://sharepoint.pfizer.com/sites/CPAccelerator/SitePages/Guidance%20Documents.aspx |
| 2 | Ch 23 PK data & NCA Conventions of Clinical Pharmacology Guidance | Dated: 17April2012 | <http://sharepoint.pfizer.com/sites/CPAccelerator/Clin%20Pharm%20Guidance%20Documents/Ch_23_PK%20Data%20and%20NCA%20Conventions_Final_17April2012.pdf?Web=1http://insight.pfizer.com/llfetch/livelink.exe?func=pfpublic.fetch&nodeid=24769075> |
| 3 | NCA Data File Specifications | Dated:  02Apr2018 | http://sharepoint.pfizer.com/sites/EQuIPsite/EQuIPDocument/Workstreams/03.%20NCA/Data%20Standards/2018-04-02%20NCA%20Data%20File%20Specifications.xlsx?Web=1 |

## Technical References

| Ref # | Title |
| --- | --- |
| 1 | R Core Team. R: A language and environment for statistical computing. R Foundation for StatisticalComputing, Vienna, Austria. <https://www.R-project.org/> |
| 2 | Leon Shargei, Andrew B.C. Yu , (1993). Applied Pharmaceutics and Pharmacokinetics. Third Edition |
| 3 | J. Gabrielsson and D. Weiner , (1998). Pharmacokinetic and Pharmacodynamic Data Analysis. Second Edition |
| 4 | Rowland and Tozer 3rd Edition, (1995). Clinical Pharmacokinetics:Concepts and Applications. Philadelphia, Pennsylvannia. |
| 5 | Gibaldi and Perrier 2nd Edition, (1982) Pharmacokinetics. New York, NY. |

# Appendices

## Calculating AUC, AUMC, and AURC

**Note:** For AURC, system will use the rules specified below for AUC calculations.

### Background

Area under the curve (AUC) is calculated from observed concentration-time data as the sum of trapezoidal area for each part of the profile, as illustrated in figure below.



Trapezoidal area for each part of a profile can be calculated using either linear or logarithmic methods using the equations in the table below.

|  |  |  |
| --- | --- | --- |
| **Trapezoidal Area Calculations** | | |
|  | AUC | AUMC |
| Linear Method |  |  |
| Logarithmic Method |  |  |
| AUC = Area under the curve  AUMC = Area under the first moment curve  Ci = Concentration 1  Ci+1 = Concentration 2  ti = Time 1  ti+1 = Time 2  ln = Natural Logarithm | | |



*Difference between Linear and Logarithmic Methods for Calculation of Trapezoidal Area*

Options

The following AUC calculations options are available in openNCA

|  |  |
| --- | --- |
| **Option** | **Description** |
| Linear-Log Trapezoidal Rule  **(Default Option)** | The linear method is used up to Tmax (the first occurrence of Cmax), and the log trapezoidal method is used for the remainder of the profile. If Ci or Ci+1 is 0 then the linear trapezoidal rule is used.  **Note:** This method is used by default unless the user specifies one of the other methods. The same method is used for all AUC and AUMC calculations. |
| Linear Trapezoidal Rule | The linear method is used for the entire profile. |
| Log Trapezoidal Rule | The logarithmic method is used for the entire profile. If Ci or Ci+1 is 0 then the linear trapezoidal rule is used |
| Linear Up - Log Down Trapezoidal Rule | Linear trapezoidal while concentrations are increasing, and log trapezoidal while concentrations are decreasing; the assessment is made on a step by step basis for each portion of the profile i.e. t1 to t2. If Ci or Ci+1 is 0 then the linear trapezoidal rule is used. |

#### Interpolation of Missing Data for AUC and AUMC Calculations

If concentration at a specified time (t\*) is missing, and t\* falls between two time points where concentration values are available, the missing concentration C\* at time t\* will be interpolated as shown in table below.

|  |  |
| --- | --- |
| Linear Interpolation Method |  |
| Logarithmic Interpolation Method |  |
| C\* = Concentration at t\*  t\* = Time between t1 and t2  C1 = Concentration at t1  C2 = Concentration at t2  t1 = Time 1  t2 = Time 2  ln = Natural logarithm | |

The interpolation method will depend on the AUC calculation method specified:

* Linear interpolation will be used where the linear trapezoidal rule applies
* Logarithmic interpolation will be used where the log trapezoidal rule applies

### NCA Computations: General Issues with Data Handling Rules for Partial Areas

Illustrations below are all using TAUi = 24 hours

A) TLAST is > TAUi

This is a common scenario where following the last dose in a multiple-dose study, sampling continues after time TAUi.

| Example | Data | Plot | AUCtau reported? |
| --- | --- | --- | --- |
| (A)  Actual time of last sample is ≥ TAUi.  Data is quantifiable to time ≥ TAUi.  If no concentration was collected at time=TAUi, concentration values are estimated via interpolation between observed concentrations as necessary. | |  |  | | --- | --- | | Conc | Actual Time | | 0 | 0 | | 27.2 | 0.5 | | 207 | 1 | | 359 | 2 | | 458 | 4 | | 316 | 6 | | 266 | 8 | | 226 | 12 | | 155 | 24 | |  | openNCA: yes |
| (B)  Actual time of last sample is ≥ TAUi.  Data is BLQ (zero) before time = TAUi. | |  |  | | --- | --- | | Conc | Actual Time | | 0 | 0 | | 0 | 0.5 | | 60.7 | 1 | | 382 | 2 | | 447 | 4 | | 412 | 6 | | 0 | 8 | | 0 | 12 | | 0 | 24 | |  | openNCA: yes |
| (C)  Actual time of last sample is *slightly* < TAUi, that is LASTTIME is >= **LASTTIMEACCEPTCRIT** (set by default as 0.95\*TAUi but configurable in the ***Model Configuration Template***) | |  |  | | --- | --- | | Conc | Actual Time | | 0 | 0 | | 0 | 0.5 | | 89 | 1 | | 181 | 2 | | 287 | 4 | | 321 | 6 | | 278 | 8 | | 231 | 12 | | 158 | 23.917 | |  | openNCA: yes  Note: If t½ is estimated, i.e. FLGACCEPTKEL==1 and THALF is not missing**,** AUCTAUi is slightly >AUCLAST (including the small area extrapolated from TLAST to TAUi); If t½ is not estimated**,** AUCTAUi =AUCLAST. |
| (D)  Last available data point is *much* < TAUi, that is LASTTIME is < **LASTTIMEACCEPTCRIT** (set by default as 0.95\*TAUi) | |  |  | | --- | --- | | Conc | Actual Time | | 0 | 0 | | 32.4 | 0.5 | | 175 | 1 | | 469 | 2.017 | | 389 | 4 | | 339 | 6 |   [no additional data] |  | openNCA: Compute AUCTAUi but – follow Business/Reporting Rule:  If t½ is estimable and accepted as per acceptance criteria**,** reportAUCTAU*i* if AUCTAU*i* <= 120% \* AUCLASTi; If t½ is not estimated**,** do not reportAUCTAU*i*. |

Example (C) is normal for PK data collected during ongoing dosing: samples at nominal time tau consistently have actual time slightly < tau, because they are collected *before* the next dose which is administered at time = tau.

In scenario (C), if THALF is estimated as per the acceptance criteria for KEL, **FLGACCEPTKELCRIT** and the associated acceptance flag, **FLGACCEPTKEL,** AUCTAUi estimated to incorporate the extrapolate area from TLAST to end of the interval (to TAUi) and accepted as per criteria set for **LASTTIMEACCEPTCRIT.**

In scenario (D), if THALF is estimated, AUCTAU*i* is computed by the computation engine. However, any business reporting rules governing acceptability relative to AUCLASTi would be followed for reporting of values subsequent to generation of the results by the Computation Engine. See the entry under Section Pre Computation Checks and Dataset or Computation Flag Definitions for **FLGACCEPTTAU**.

## Significant Figures Definition

Definition

The number of significant figures is the number of digits needed to express a value within the uncertainty of the measurement.

For example; 5.678 +/- 0.003 has 4 significant digits.

Multiplication and Division

The number of significant figures in the result of multiplying or dividing two or more quantities equals the least number of significant figures of the original quantities.

For example; 8.02 × 8.02 = 64.3

Addition and Subtraction

With addition and subtraction the number of significant digits is determined using the least number of decimal places of the quantities involved.

For example; 123.25 + 46.0 + 86.26 = 255.5

## Missing Data

Missing Data at Time of Dose

If the dataset does not include a data point (no time value, or the corresponding concentration value is null or “NA”) at the dose time, estimate a value according to the following diagram. This concentration value is used in all AUC calculations where applicable.



AUC Calculations and Missing Data

If the dataset does not include data points (no time value, or the corresponding concentration value is null or “NA”) at AUC start or end times, use concentration values estimated as shown in the following diagrams.

#### AUC Start time has no data



\*Use linear or logarithmic interpolation depending on AUC method specified

#### AUC End time has no data



\*Use linear or logarithmic interpolation depending on AUC method specified

## Study Design Elements (SDE)/Profile Identifier

A Study Design Element (SDE) value or SDEID defines a set of data concentration time records associated with a single profile and thus represents a Profile Identifier. The legacy Pfizer eNCA system implementation utilizes a set of 14 data fields in combination (1-14 below) data fields, consistent with Pfizer PK data standards, to uniquely identify a profile of data records within a subject within a protocol from the data loaded to the system.

For the new EQuIP based NCA system, the list of data fields (1 or more) will be identified in data format specification represented as one or more templates that are defined as system configuration items. The list of data fields uniquely identifies profiles of data by default. A single field can serve this purpose but where more than one field is identified the system will generate a numeric equivalent unique to the level of profile, i.e. the Profile Identifiier or SDEID. This will permit the analyst or dataload process or role to tailor the Profile Identifier for particular sources of data. The definition templates for data loading will also identify the fields utilized as contributing to the Profile Identifier.

Note that the analyst will be able to re-define which data fields are utilized or a single Profile Identifier field for a particular analysis to define profiles. The analyst can introduce new Profile Identifier fields via *Data Transformation* actions within the EQuIP NCA application. Standardized methods will be introduced into this system to facilitate this.

The Pfizer default list/template definition for SDEIDs/Profile Identification will be updated to to the following list of data field items. Note this list adds PCANMETH to the legacy list of fields used for the Pfizer legacy eNCA system.

| # | Study Design Elements (SDE) | eNCA / PDS\* Name |
| --- | --- | --- |
| 1 | STUDY ID | STUDY |
| 2 | CENTER NUMBER | SITEID |
| 3 | SSID | SUBJID |
| 4 | RANDOMIZATION NUMBER | RAND |
| 5 | TREATMENT DESCRIPTION | TREATXT |
| 6 | TREATMENT CODE | TRTCD |
| 7 | COLLECTION | PKCOLL |
| 8 | MATRIX | PKBDFLD |
| 9 | ANALYTE NAME | PKTERM |
| 10 | PERIOD UNIT | PERIODU |
| 11 | PERIOD | PERIOD |
| 12 | VISIT UNIT | VISITU |
| 13 | VISIT | VISIT |
| 14 | PHASE | PHASE |
| 15 | PCANMETH | PCANMETH |
| 16 | PKUSMID SAMPLE ID | PKUSMID |

\* PDS – Pfizer Data Standard

Note: PKUSMID is equivalent to NOMTIME. Data elements assigned as NOMTIME could potentially be considered a surrogate from PKUSMID. PKUSMID is considered unique within a SDE or profile of data records across subjects within a study or dataset.

## Analysis Ready Dataset (ARD)

The Analysis Ready Dataset (ARD) is a representation of one of many data formats that can be utilized with the computation engine specifications to perform NCA analyses. The required and some optional elements of the ARD are included in the table below. Note that columns required are required for the this particular ARD format but may not be required for computation engine model execution.

The formal data specification for this ARD format is provided separately at the link in the References section.

| ***Column/Field Name*** | ***SDEID/ Profile ID*** | **Required?** | ***Value can be NULL?*** | ***Data Type [Data Format]*** | ***Allowed Values*** | ***Short Descriptive Name*** | ***Description*** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| STUDY | TRUE | **TRUE** | **FALSE** | VARCHAR2 (100 Byte) | N/A | Study ID | UNIQUE Protocol defined Study Identifier. Cannot have missing values. Need to concatenate Project and Protocol Number for Pfizer Legacy Files/studies, i.e. studies with protocol format of '128-013'.  Note that this study identifier value MUST match what is in the Registry/DIF/RightTrack II database as the "official study identifier")  This may equate to Pfizer Study Alias Identifier since, as an example, it permits both Pfizer and legacy Wyeth standards. |
| SITEID | TRUE | **TRUE** | **FALSE** | VARCHAR2 (100 Byte) | N/A | Site ID | Site or Center ID. |
| SUBJID | TRUE | **TRUE** | **FALSE** | VARCHAR2 (100 Byte) | N/A | Subject ID | Subject ID (Optional: Entered into legacy eNCA application from file if available otherwise eNCA autofills this field from the RAND) (Note that SUBJID can be alpha-numeric and can have more than 8 characters) |
| RAND | TRUE | **TRUE** | **FALSE** | NUMBER | N/A | Randomization Number | Randomization Number |
| TREATXT | TRUE | **TRUE** | **FALSE** | VARCHAR2 (4000 Byte) | N/A | Treatment Description | Treatment Description associated with the specific data/concentration value. |
| TRTCD | TRUE | **TRUE** | **FALSE** | VARCHAR2 (100 Byte) | N/A | Treatment Code | Treatment Code FOR Non-crossover study. Treatment SEQUENCE FOR crossover study. Typically alphabetic code. |
| PKCOLL | TRUE | **TRUE** | **FALSE** | VARCHAR2 (100 Byte) | POINT INTERVAL | Sample Collection Type | Only value values are POINT or INTERVAL. Point samples refer to collections not aggregated over time such as blood or plasma draws and single urine samples. Interval samples refer to collections aggregated over time such as urine (0-24 hour urint collection for example) or fecal collections. Cannot have missing values. |
| [PKBDFLD](#RANGE!Matrices) | TRUE | **TRUE** | **FALSE** | VARCHAR2 (100 Byte) | N/A | Body Fluid - Matrix | BODY Fluid/Matrix |
| PKTERM | TRUE | **TRUE** | **FALSE** | VARCHAR2 (200 Byte) | N/A | Analyte Name | Verbatim Text of Analyte (Each File Associated CPW file should only have 1 analyte/file) Note that the value is currently intended to be consistent with the Pfizer instance of WHODRUG |
| PERIODU | TRUE | **TRUE** | TRUE | VARCHAR2 (100 Byte) | N/A | Period Unit | PERIOD unit cannot have missing values if the corresponding PERIOD value is provided. |
| PERIOD | TRUE | **TRUE** | TRUE | VARCHAR2 (100 Byte) | N/A | Period Identifier | Period Identifier |
| VISITU | TRUE | **TRUE** | **FALSE** | VARCHAR2 (100 Byte) | N/A | Visit Unit | VISIT unit cannot have missing values if the corresponding PERIOD value is provided. |
| VISIT | TRUE | **TRUE** | **FALSE** | VARCHAR2 (100 Byte) | N/A | Visit Identifier | Visit Identifier |
| PHASE | TRUE | **TRUE** | TRUE | VARCHAR2 (100 Byte) | N/A | Study Phase or Cycle | Phase or Cycle of the study. |
| PCANMETH | TRUE | **TRUE** | TRUE | CHAR | N/A | Analysis Method | See format CDISC definition: "Analysis method applied to obtain a summarized result. Analysis method describes the method of secondary processing applied to a complex observation result (e.g. an image or a genetic sequence)." |
| PKUSMID | FALSE | **TRUE** | TRUE | VARCHAR2 (100 Byte) | N/A | Unique Sample ID | Unique Sample Identifier PKUSMID must be unique for each sample collected for a subject.  For ARD and PKDEF files for NON-PIMS studies, PKUSMID must be the same values as provided in the Planned PK Definition file, when definition files are used to transmit data.  For PIMS studies, PKUSMID will be NULL in the FINAL PKDEF file but populated with the PIMS BAR CODE # in the ARD file.  For LCD files, If definition files are not being used for a particular data type, PKUSMID should be populated as above, with a unique value for each sample collected for a subject, using DIFFERENT PKUSMID values than those in any definition files for the study. While only necessary on rare occasion, it's recommended to use values for non-PK datatypes at a value greater than any of those defined in any of the planned PK definition files, e.g. starting at 1001. |
| PKACES | FALSE | **TRUE** | TRUE | VARCHAR2 (100 Byte) | N/A | Vendor Sample Accession ID | Pfizer/Vendor Accession Number: Sample Management Number |
| PKSCOM | FALSE | **TRUE** | TRUE | VARCHAR2 (4000 Byte) | N/A | Pfizer Sponsor Comments | Pfizer comments that provide additional protocol or study design information for clarification of the collection details for the sample |
| PKAACES | FALSE | **TRUE** | TRUE | VARCHAR2 (100 Byte) | N/A | Analytical Lab Accession ID | Analytical Laboratory Accession Number |
| NTPDU | FALSE | **TRUE** | TRUE | VARCHAR2 (100 Byte) | H MIN HR | Nominal Time Post Dose Unit | Nominal TIME Post Dose Unit (could be generated by NCA application produced if not a data element) |
| PKPTMR | FALSE | **TRUE** | TRUE | VARCHAR2 (100 Byte) | N/A | Nominal TPD or Interval Value | Nominal TIME Post Dose OR Interval Value: (pkptmr+ntpdmn cann't be null) |
| NTPDMN | FALSE | **TRUE** | TRUE | NUMBER | N/A | Nominal TPD Minute Value | Nominal TIME Post Dose OR Interval MINUTE Value: (pkptmr+ntpdmn can't be null) |
| PKATPD | FALSE | FALSE | TRUE | VARCHAR2 (100 Byte) | N/A | Actual TPD Value | Actual Time Post Dose or Actual Post Dose Start (Value) |
| PKATPDU | FALSE | FALSE | TRUE | VARCHAR2 (100 Byte) | H MIN HR | Actual TPD Unit | Actual Time Post Dose Start (Units) (Datafile provided; could be generated by openNCA application produced if not a data element) |
| PKCNC | FALSE | **TRUE** | TRUE | VARCHAR2 (100 Byte) | N/A | Concentration Value | Analytical Results/Concentration Value |
| [PKCNCU](#RANGE!PKCNCU) | FALSE | **TRUE** | **FALSE** | VARCHAR2 (100 Byte) | N/A | Concentration Unit | Analytical Results Units |
| PKAMT | FALSE | FALSE | TRUE | NUMBER | N/A | Sample Amount | Amount - Urine Volue; Tissue Weight |
| PKAMTU | FALSE | FALSE | TRUE | VARCHAR2 (100 Byte) | N/A | Sample Amount Unit | Amount Unit - Urine Volume Units; Tissue Weight Units |
| PKSAMQA | FALSE | **TRUE** | **FALSE** | VARCHAR2 (200 Byte) | FINAL DRAFT | Sample QA Status | Sample QA Status - Has SAMPLE been QA'd |
| [PKCOML](#RANGE!Comment.Codes) | FALSE | **TRUE** | TRUE | VARCHAR2 (4000 Byte) | [See Comment Codes (Free Text also permitted)](#RANGE!A1) | Central Lab Sample Comment | Central Laboratory Comment Codes or Text (Semi-colon ";" delimited); Required field but can be empty if no sample handling events occur |
| [PKACOM](#RANGE!Comment.Codes) | FALSE | **TRUE** | TRUE | VARCHAR2 (4000 Byte) | [See Comment Codes (Free Text also permitted)](#RANGE!A1) | Analytical Lab Sample Comment | Analytical Laboratory Comments Codes or Text (Semi-Colon ";" delimited); Required field but can be empty if no sample handling events occur |
| PKCOMC | FALSE | **TRUE** | TRUE | VARCHAR2 (4000 Byte) | N/A | PK CRF Comment | Comments provided by clinical site on PK CRF page. |
| HT | FALSE | FALSE | TRUE | NUMBER | N/A | Baseline Subject Height | Subject Height (CM) at baseline derived |
| WT | FALSE | FALSE | TRUE | NUMBER | N/A | Baseline Subject Weight | Subject Weight (KG) at baseline derived |
| AGEDERU | FALSE | FALSE | TRUE | VARCHAR2 (100 Byte) | N/A | Baseline Derived Age Units | Subject Age Unit at baseline |
| AGEDER | FALSE | FALSE | TRUE | NUMBER | N/A | Baseline Derived Age | Subject Age at baseline |
| WTUNI | FALSE | FALSE | TRUE | VARCHAR2 (100 Byte) | N/A | Baseline Subject Raw Weight Units | Subject Raw Weight Unit at baseline |
| WTRAW | FALSE | FALSE | TRUE | NUMBER | N/A | Baseline Subject Raw Weight | Subject Raw Weight Value at baseline |
| HTUNI | FALSE | FALSE | TRUE | VARCHAR2 (100 Byte) | N/A | Baseline Subject Raw Height Units | Subject Raw Height Unit |
| HTRAW | FALSE | FALSE | TRUE | NUMBER | N/A | Baseline Subject Raw Height | Subject Raw Height Value |
| RACEOTH | FALSE | FALSE | TRUE | VARCHAR2 (100 Byte) | N/A | Race Other | Race Other - Text for other race |
| RACES | FALSE | FALSE | TRUE | VARCHAR2 (100 Byte) | N/A | Races | Subject Race |
| SEX | FALSE | FALSE | TRUE | VARCHAR2 (100 Byte) | M F | Sex | Subject Gender / Sex |
| RACIALD | FALSE | FALSE | TRUE | VARCHAR2 (100 Byte) | N/A | Racial Designation | Racial Designation |
| ETHNIC | FALSE | FALSE | TRUE | VARCHAR2 (100 Byte) | N/A | Ethnicity | Subject Ethnicity |
| COLLDATE | FALSE | FALSE | TRUE | DATE [YYYY-MM-DD] | N/A | PK Sample Collection Date | Collection DATE OF CRF Page |
| PKATM | FALSE | FALSE | TRUE | VARCHAR2 (200 Byte) [HH24:MM] | N/A | Actual Start Time | Actual Time of Start of Sample Collection |
| PKADT | FALSE | FALSE | TRUE | DATE [YYYY-MM-DD] | N/A | Actual Start Date | Actual Date of Start of Sample Collection |
| PKSMND | FALSE | FALSE | TRUE | VARCHAR2 (200 Byte) | DONE NOT DONE | Sample Not Done | PK Sample Record Not Done Status |
| PKND | FALSE | FALSE | TRUE | VARCHAR2 (200 Byte) | DONE NOT DONE | Module Not Done | PK Sample CRF Module/Page Not Done Status |
| PKSMMSU | FALSE | FALSE | TRUE | VARCHAR2 (200 Byte) | N/A | Matrix Mass Units | Matrix Mass Units |
| PKSMMS | FALSE | FALSE | TRUE | VARCHAR2 (200 Byte) | N/A | Matrix Mass | Matrix Mass |
| PKSMVLU | FALSE | FALSE | TRUE | VARCHAR2 (200 Byte) | N/A | Matrix Volume Units | Matrix Volume Units |
| PKSMVL | FALSE | FALSE | TRUE | VARCHAR2 (200 Byte) | N/A | Matrix Volume | Matrix Volume |
| PKATME | FALSE | FALSE | TRUE | VARCHAR2 (200 Byte) [HH24:MM] | N/A | Actual End Time | Actual Time of End of Sample Collection |
| PKADTE | FALSE | FALSE | TRUE | DATE [YYYY-MM-DD] | N/A | Actual End Date | Actual Date of End of Sample Collection |
| DOSE | FALSE | FALSE | TRUE | NUMBER | N/A | Dose | Numeric Amount of Dose Prior to Sampling event Dose used by reporting software |
| DOSEUNI | FALSE | FALSE | TRUE | VARCHAR2 (100 Byte) | N/A | Dose Unit | Unit of Reporting Dose Administered |
| DOFi | FALSE | FALSE | TRUE |  |  | Duration of Infusion | Duration of Infusion |
| DRGDATE | FALSE | FALSE | TRUE | DATE [YYYY-MM-DD] | N/A | Dose Date | Date of Dosing Default for DRGDATE is to record the Date of the most recent dose prior to the PK sampling event/collection. There are certain sample types and study designs that may require different approaches. One notable example is that for PRE-DOSE or TROUGH samples, typically the analysis requires that DATE of the NEXT dose in the treatment period rather than the prior dose.  For infusion administration, this is the DATE of the Start of the infusion. |
| DOSETIM | FALSE | FALSE | TRUE | VARCHAR2 (200 Byte) [HH24:MM] | N/A | Dose Time | Time of Dosing Default for DOSETIM is to record the TIME of day of the most recent dose prior to the PK sampling event/collection. There are certain sample types and study designs that may require different approaches. One notable example is that for PRE-DOSE or TROUGH samples, typically the analysis requires that TIME of the NEXT dose in the treatment period rather than the prior dose.  For infusion administration, this is the TIME of day of the Start of the infusion. |
| INFDATE | FALSE | FALSE | TRUE | DATE [YYYY-MM-DD] | N/A | Dose Date End | For infusion administration, this is the DATE of day of the End of the infusion. |
| INFTIME | FALSE | FALSE | TRUE | VARCHAR2 (200 Byte) [HH24:MM] | N/A | Dose Time End | For infusion administration, this is the TIME of day of the End of the infusion. |
| ACTTRT | FALSE | FALSE | TRUE | VARCHAR2 (200 Byte) | N/A | Actual Treatment Test/Label | Actual Treatment per Period |
| ACTTRTC | FALSE | FALSE | TRUE | VARCHAR2 (100 Byte) | N/A | Actual Treatment Code | Actual treatment code per period |
| ACTTRTS | FALSE | FALSE | TRUE | VARCHAR2 (200 Byte) | N/A | Actual Treatment Sequence | Actual treatment sequence for crossover study. Same as ACTTRTC for parallel (non-crossover) study.  Generally will be a single letter code for a treatment code. |
| TREATSEQ | FALSE | **TRUE** | TRUE | VARCHAR2(100 Byte) | N/A | Planned Treatment Sequence | Treatment Sequence # |
| PCMETHOD | FALSE | **TRUE** | TRUE | VARCHAR2(200 Byte) | CDISC CL.C85492.METHOD Code List | Method of Test or Examination | See formal CDISC definition: "Method of the test or examination. Examples: EIA (Enzyme Immunoassay), ELECTROPHORESIS, DIPSTICK." https://evs.nci.nih.gov/ftp1/CDISC/SDTM/SDTM%20Terminology.html#CL.C85492.METHOD |
| PCNAM | FALSE | **TRUE** | TRUE | VARCHAR2(200 Byte) | N/A | Bioanalytical Lab Name | See formal CDISC definition |
| PCLLOQ | FALSE | **TRUE** | TRUE | VARCHAR2(100 Byte) | N/A | Bioanalytical Method LLOQ | See formal CDISC definition |
| PCSTRESU | FALSE | **TRUE** | **TRUE** | VARCHAR2(100 Byte) | N/A | Unit of the standardized result | See formal CDISC definition (PKUNIT) |
| ROUTE | FALSE | **TRUE** | **FALSE** | VARCHAR2(100 Byte) | IV/PO/SC/Topical | Route of Administration | Configurable list of administration modalities (Enteral, Parenteral, Topical):  Enteral: PO - oral, Sublingual, Buccal, Rectal Parenteral: IV - intravenous, IM, SC - subcutaneous, intra-arterial, intra-articular, intrathecal, intradermal, inhalation Topical  If ROUTE is included in ARD, it can potentially contribute to the SDEID/Profile ID. This would be under analyst control. |
| UDSDEID | FALSE | **TRUE** | TRUE | NUMBER | N/A | User Defined Study Design Element | Add this to the file format. I think we agreed to make this optional, i.e. part of FORMAT2 but please check the review meeting notes. This field permits the PK Analyst to create a different encoding than the automatically generated 14 field derived SDEID to reassign data to individual profiles. |
| FLGEMESIS | FALSE | FALSE | **FALSE** | NUMBER | N/A | Emesis Occurrence Flag | Flag indicating that emesis occurred prior to or during dosing interval |
| FLGSMPLPOSTDOSE | FALSE | FALSE | **FALSE** | NUMBER | N/A | Sample collected post dose as planned Flag | FLGSMPLPOSTDOSE a dataset flag that is used to indicate whether a sample planned to be taken prior to the planned dose, is actually taken following the planned dose. When available it is incorporated into the analysis dataset.   0 = pk sample occurs prior to the planned dose rather than prior 1 = pk sample occurs following to the planned dose rather than as planned prior to the dose |
| FU | FALSE | FALSE |  | NUMBER | N/A | Fraction unbound for a specific Analyte/PKTERM | Fraction of the drug circulating free/unbound in blood. |
| DATAPREPFILECOM | FALSE | TRUE | TRUE | VARCHAR2(4000) | N/A | Data Preparation Comment | DATAPREPFILECOM will capture an overall data preparation comment for the file. |
| DATAPREPROWCOM | FALSE | FALSE | TRUE | VARCHAR2(4000) | N/A | Data Preparation Comment | Comments as noted by the data preparer  For Production and Legacy LCD and legacy LPD files, every row may have a value but the value MUST be the same since ONLY the VALUE entered on the first will take effect.   APS, CRDC or external CROs will not populate this field for Production LCD Files. If this field is populated in error, the autoloader will not read/apply this field for Production LCD Files. The autoloader code for Production LCD Files will stop at the creation of an Analysis Dataset within eNCA.  This field should ONLY be applicable to files for Legacy Data loading and NOT for production data loading for parameters. There is no production data loading for PK parameters. If this file is inadvertently included with a production LCD, it should not be loaded. Loading of data from external vendors, when applicable, will be treated as for Legacy Data loading.  These will be record by record individual comments that the data programmer can add to the data file directly. |
| DATASTATUS | FALSE | TRUE | **FALSE** | VARCHAR2 (100 Byte) | DRAFT FINAL | Data Status | QA status of supplied data such as DRAFT or FINAL Note that this does not refer to the QA status of the bioanalytical result (see PKSAMQA) but rather the CRF data merged/added to the file.   Note may be included in V4.0 of eNCA Data Standard for LCD, ARD file formats  For Legacy LPD Files, every row will have a value but the value MUST be the same since ONLY the VALUE entered on the first record will take effect.  This field should ONLY be applicable to files for Legacy Data loading and NOT for production data loading for parameters. There is no production data loading for PK parameters. If this file is inadvertently included with a production LCD, it should not be loaded. Loading of data from external vendors, when applicable, will be treated as for Legacy Data loading.  Note for PKPView, DATASTATUS in the view will be updated when PK analyst updates data status on the Analysis Page of eNCA. |

## Other Key Assumptions

|  |  |
| --- | --- |
| 1 | Parameters that are extrapolated to infinity, such as AUCinf, AUMCinf, and AURCinf can be computed in two ways. One extrapolation is based on the last observed concentration, while the second extrapolation is based on the last predicted concentration, where the predicted value is based on the log-linear regression preformed to estimate kel. Parameters that are derived from AUCinf ,AUMCinf, and AURCinf can be represented as observed or predicted as well. |
| 2 | Pfizer’s Clinical Pharmacology Guidance recommends use of the predicted value of Clast for calculation of extrapolated parameters. Both versions will be calculated by the openNCA application but those based on the predicted value will be the default versions for reporting purposes when only one parameter is reported. |
| 3 | System allows the definition of more than one dose per profile to accommodate study designs where the PK sampling profile continues across consecutive dosing intervals.  If more than one Dose is defined, for example am and pm dosing within a study design element:   * 1. Parameters calculated based on the dosing interval TAU are determined for each dosing interval   2. KEL is determined following the last dose   Refer to Appendix “Examples of Profiles and Dosing Intervals in openNCA” for details |

## Footnoting for PK Parameter Estimates

|  |  |  |
| --- | --- | --- |
| NA | Not applicable | NA is visible in S-plus data  It will appear as NULL in excel |

## Examples of Profiles and Dosing Intervals in openNCA

### Example 1: Single-Dose Profiles





|  |  |
| --- | --- |
|  | Study design element: defined in this case by Subject and Treatment |
|  | Time of last/prior dose (TOLD) to end of the pk profile |

For single-dose model, parameters are determined for the entire profile from time of Dose to end of study design element.

### Example 2: Multiple-Dose Profile





|  |  |
| --- | --- |
|  | Study design element: defined in this case by Subject, Treatment, Day |
|  | Dosing Interval 1: from “time of dose 1” to “time of dose 1” + TAU) |
|  | Time of last/prior dose (TOLD) to end of pk profile |

For multiple-dose model, parameters calculated based on the dosing interval TAU (such as Cmax, Tmax, AUCTAU) are determined for the defined dosing interval; kel and related parameters are determined for the entire profile.

### Example 3: Multiple-Dose Profile Including 2 Doses



|  |  |
| --- | --- |
|  | Study design element: defined in this case by Subject, Treatment, Day |
|  | Dosing Interval 1: from “time of dose 1” to “time of dose 1” + TAU) |
|  | Dosing Interval 2: (from “time of dose 2” to “time of dose 2” + TAU) |
|  | Time of last/prior dose (TOLD) to end of pk profile |

For multiple-dose model with more than one dose defined, parameters calculated based on the dosing interval TAU (such as Cmax, Tmax, AUCTAU) are determined for each dosing interval; kel and related parameters are determined following the last dose.

### Example 4: Multiple-Dose Profile Including 3 Doses





For multiple-dose model with more than one dose defined, parameters calculated based on the dosing interval TAU (such as Cmax, Tmax, AUCTAU) are determined for each dosing interval; kel and related parameters are determined following the last dose.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Profile for this example defined by Subject, Treatment, and Day | | | | |  |  |  |  |  |  |  |  |  |  |
|  | Dosing Interval (**DIi**) |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | **DI1** derived from setting nominal time of 0 HR (**start** of the 1st dosing interval) to nominal time of 8HR (**end** of the 1st dosing interval ) | | | | | | | | | | | | | | |
|  | **DI2** derived from setting nominal time of 8 HR (**start** of the 2nd dosing interval) to nominal time of 16 HR (**end** of the 2nd dosing interval ) | | | | | | | | | | | | | | |
|  | **DI3** derived from setting nominal time of 16 HR (**start** of the 3rd dosing interval) to nominal time of 24 HR (**end** of the 3rd dosing interval ) | | | | | | | | | | | | | | |
|  | Duration of Dosing Interval (**TAUi**) | |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  | **TAU1** derived from nominal time of 12 HR (**end** of the 1st dosing interval) minus nominal time of 0HR (**start** of the 1st dosing interval ) | | | | | | | | | | | | | | |
|  | **TAU2** derived from nominal time of 24 HR (**end** of the 2nd dosing interval) minus nominal time of 12HR (**start** of the 2nd dosing interval ) | | | | | | | | | | | | | | |
|  | **TAU3** derived from nominal time of 24 HR (**end** of the3rd dosing interval) minus nominal time of 16HR (**start** of the 3rd dosing interval ) | | | | | | | | | | | | | | |
|  | **TOLDi (Time of Last Dose for the dosing interval, i.e. the most recent prior dose)** | | | | | | | | |  |  |  |  |  |  |
|  | For the above example TOLD =0 for nominal time start of 1st dosing interval | | | | | | |  |  |  |  |  |  |  |  |
|  | For the above example TOLD =8 for nominal time start of 2nd dosing interval | | | | | | |  |  |  |  |  |  |  |  |
|  | For the above example TOLD =16 for nominal time start of 3rd dosing interval | | | | | | |  |  |  |  |  |  |  |  |
|  | Concentration, Time records that appear outside the final dosing interval but included in the profile | | | | | | | | | |  |  |  |  |  |

## Data Exclusion Flag Fields

The NCA Computation Engine uses data exclusion flag fields to communicate analyst decisions to exclude individual data points from individual analysis profiles from specific or global calculations. Note that data checks are still performed and the data point can be excluded if the point fails a data check.

| **Name** | **Description** |
| --- | --- |
| **FLGEXKEL** | **KEL Exclude Flag Field**  Flag value set to 1 means exclude data point from Kel calculation and all Kel associated parameter calculations.  Flag value set to 0 for a individual data point/record includes it in KEL calculation and all KEL associated parameter calculations. |
| **FLGEXAUC** | **AUC Exclude Flag Field**  Flag value set to 1 means excludes the data point from the AUC calculation and all AUC associated parameter calculations.  When the FLGEXAUC Flag value is set to 0 the data point is specifically included in all AUC parameter type calculations |
| **FLGEXSDE** | **Exclude from ALL computations flag field.**  When the FLGEXSDE Data Flag field is set to 1 for a particular datapoint, it is excluded from all parameter calculations. To exclude an entire SDE/profile completely, all FLGEXSDE values for each of the data point records within the SDE/profile need to be set to 1. This flag is also used to exclude subject from calculations if the analyst excludes an entire subject from all computations by setting the FLGEXSDE flag for all data points from each of the subjects profiles to 1.  When the FLGEXST Flag value is set to 0, the data point is specifically included in parameter computations. |
| **FLGEXST** | **Data point excluded from concentration summary statistics flag field.**  Flag set to 1 will cause the specified data point to be excluded from all summary statistic calculations. This Flag does not affect the calculation of Primary or Derived Parameters.  Flag set to 0 for a specified data point specifically includes the data point in summary statistic calculations. Note that data checks are still performed and the data point can be excluded if the point fails a data check. |
| **FLGCZERO** | **Data point excluded from computation of C0 for Model 2.**  See Section **C0** Example for additional details on the computation of **C0**.  Flag value set to 1 means exclude data point from **C0** calculation and all **C0** associated parameter calculations.  Flag value set to 0 for a individual data point/record includes it in **C0** calculation and all **C0** associated parameter calculations. |
| FLGEXPROF**†** | Parameter generation control flag. If FLGEXPROF is set to 1 then don’t compute PROFILE level parameters, for example **CMIN**, but only compute DOSING INTERVAL level parameters, for example **CMIN*i***. Default is 0 = compute/include PROFILE level parameters. |

## †- Not yet implemented in openNCA interface to computation engine nor in computation engine code itself.

## Multiple Dosing Interval and TAU handling

Variables

| **Name** | **Description** | **Source** | **Notes** |
| --- | --- | --- | --- |
| **DIi**  DI1 to DI5 | This is the value of Dosing Interval to be specified by PK Analysts in the following format, so that system can automatically generate appropriate TAU values and compute parameters appropriately.   |  |  |  | | --- | --- | --- | | Nominal time of **start** of dosing interval | hyphen | Nominal time of **end** of dosing interval |   E.g.: 0-8, 8-12, 12-18, 18-24, etc.  Note that the Computation Engine will accept the DIi ranges from TAUi and TOLDi entries as input and record them with output fields but not use these to define Dosing Intervals. | To be specified by PK Analyst in the script at the time of data prep  Secondary: Can be supplied as a data field item. | Up to a maximum of 5 dosing intervals are allowed |
| **TAU*i***  **TAU**  TAU1 to TAU5 | The true duration of dosing interval, to be determined automatically by application based on the DI specified by users  TAU = TAU1 if only one dosing interval to consider. TAU is a synonym for TAU1 when only one dosing interval is considered.   |  |  |  | | --- | --- | --- | | Nominal time of **end** of dosing interval | minus | Nominal time of **start** of dosing interval |   E.g.:   |  |  | | --- | --- | | **DI** | **TAU** | | 0-8 | 8 | | 8-12 | 4 | | 24-48 | 24 |   Note that TAUi data fields are recorded in either the input dataset or in the FLAG dataset or both. If in the input dataset, these TAUi values are used as starting values for the openNCA application analysis module. Changes implemented by the analyst in the Analysis Module are stored in the FLAGs dataset to be communicated to the Computation Engine. | To be automatically computed by application at the time of parameter calculations  Secondary: Can be supplied as a data field item identified via the ***Model Configuration Template*** | Up to a maximum of 5 TAU*i* are allowed |
| **TAU*i*U** | Units for TAU*i* |  |  |
| **TOLD**  **TOLDi**  TOLD1 to TOLD5 | Time of last or most recent prior dose.  Note that TOLDi data fields are recorded in either the input dataset or in the FLAG dataset or both. If in the input dataset, these TOLDi values are used as starting values or the NCA application analysis module. Changes implemented by the analyst in the Analysis Module are stored in the FLAGs dataset to be communicated to the Computation Engine. |  | Up to a maximum of 5 TOLD*i* are allowed |
| TOLD*i*U | Units of TOLD*i* |  |  |
| DIiF | Dosing interval flags  Just used to visually explain the logic of dosing intervals and how the overlaps are managed, in the example below. | None | Not a true variable within the application |

Example Dataset illustrating Dosing Intervals, TAUi and TOLDi values

Note that DOSEi, DOSEiU, TAUiU nor TOLDiU values not illustrated in the table below but would be expected to be available for the computation engine.

| SDEID | NomTime | Conc. | DI1F | DI2F | DI3F | DI4F | DI5F | DI1 | DI2 | DI3 | DI4 | DI5 | TAU1 | TAU2 | TAU3 | TAU4 | TAU5 | TOLD1 | TOLD2 | TOLD3 | TOLD4 | TOLD5 |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 1 | 0 | 1.5 | 1 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 1 | 1 | 3.5 | 1 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 1 | 2 | 9.75 | 1 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 1 | 4 | 6.5 | 1 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 1 | 6 | 4.5 | 1 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 1 | 8 | 6.4 | 1 | 1 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 1 | 10 | 9.9 | 0 | 1 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 1 | 12 | 4.1 | 0 | 1 | 1 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 1 | 18 | 2.7 | 0 | 0 | 1 | 1 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 1 | 24 | 1.5 | 0 | 0 | 0 | 1 | 1 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 1 | 72 | 0.2 | 0 | 0 | 0 | 0 | 1 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 1 | 96 | 0.12 | 0 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 2 | 0 | 1.5 | 1 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 2 | 1 | 3.5 | 1 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 2 | 2 | 9.75 | 1 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 2 | 4 | 6.5 | 1 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 2 | 6 | 4.5 | 1 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 2 | 8 | NA | 1 | 1 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 2 | 10 | 9.9 | 0 | 1 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 2 | 12 | 4.1 | 0 | 1 | 1 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 2 | 18 | 2.7 | 0 | 0 | 1 | 1 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 2 | 24 | 1.5 | 0 | 0 | 0 | 1 | 1 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 2 | 72 | 0.2 | 0 | 0 | 0 | 0 | 1 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 2 | 96 | 0.12 | 0 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 3 | 0 | 1.5 | 1 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 3 | 1 | 3.5 | 1 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 3 | 2 | 9.75 | 1 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 3 | 4 | 6.5 | 1 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 3 | 6 | 4.5 | 1 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 3 | NA | NA | 1 | 1 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 3 | 10 | 9.9 | 0 | 1 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 3 | 12 | 4.1 | 0 | 1 | 1 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 3 | 18 | 2.7 | 0 | 0 | 1 | 1 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 3 | 24 | 1.5 | 0 | 0 | 0 | 1 | 1 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 3 | 72 | 0.2 | 0 | 0 | 0 | 0 | 1 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |
| 3 | 96 | 0.12 | 0 | 0 | 0 | 0 | 0 | 0-8 | 8-12 | 12-18 | 18-24 | 24-48 | 8 | 4 | 6 | 6 | 24 | 0 | 8 | 12 | 18 | 24 |

### Flow

1. Normal Flow
   1. At the time of SS parameter calculations in flash module
   2. System will check for the existence of 1 to 5 DI columns in the data prep
   3. 1 to 5 DI columns are found
   4. System will use value within these 1 to 5 columns to compute TAU and parameters
2. Alternative Flow
   1. At the time of SS parameter calculations in flash module
   2. System will check for the existence of 1 to 5 DI columns
   3. 1 to 5 DI columns are NOT found
   4. System will display existing user interface for users to specify TOLD
   5. System will compute parameters in the way its done currently (i.e. release 1.0)

### Important assumptions

1. Users can only specify up to a maximum of 5 dosing intervals
2. If first or last concentration data point for a dosing interval are missing (SDEID=2 and NomTime=8 in the above example) then system with automatically interpolate the concentration value for calculations
3. If complete row is missing (very rare scenario) (SDEID=3 and after NomTime=6 in the above example) then system will insert a time point and will interpolate the concentration value for calculations

## Parameter Model Mapping List - Primary and Derived

The following table displays which parameters are computed for each computation model selected and whether the parameter is *primary or* is a combined parameter *derived* from one or more primary parameters.

Note that the column marked “Fly” and parameters marked with “C” for “compute and display” indicate that the configuration template for the NCA application will include that parameter to be displayed automatically during profile review and terminal elimination phase estimation, i.e. the analysis tool.

Note that computation FLAGS and FLAG CRITERIA are also incorporated in this table to indicate that these will be included in the output from each of the model executions.

|  | **Data** |  | **M1** | **M1** | **M2** | **M2** | **M3** | **M3** | **M4** | **M4** |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Parameters** | **Field** | **Fly** | **SD** | **SS** | **SD** | **SS** | **SD** | **SS** | **SD** | **SS** | **Derived** |
| **AE** |  |  |  |  |  |  |  |  | X | X |  |
| **AEPCT** |  |  |  |  |  |  |  |  | X | X | X |
| **AET** |  |  |  |  |  |  |  |  | X | X |  |
| **AETAUi** |  |  |  |  |  |  |  |  |  | X |  |
| **AETAU*PTi*** |  |  |  |  |  |  |  |  |  | X |  |
| **AETPCT** |  |  |  |  |  |  |  |  | X | X | X |
| **AT** |  |  |  |  |  |  |  |  | X | X |  |
| **AUCALL** |  |  | X | X | X | X | X | X |  |  |  |
| **AUCALLDN** |  |  | X | X | X | X | X | X |  |  |  |
| **AUCT** (\* placeholder) |  |  | X | X | X | X | X | X |  |  |  |
| **AUCTDN** |  |  | X | X | X | X | X | X |  |  |  |
| **AUCINFO** |  |  | X | X | X | X | X | X |  |  |  |
| **AUCINFOi** |  |  |  | X |  | X |  | X |  |  |  |
| **AUCINFOC** |  |  | X | X | X | X | X | X |  |  | X |
| **AUCINFODN** |  |  | X | X | X | X | X | X |  |  | X |
| **AUCINFP** |  | C | X | X | X | X | X | X |  |  |  |
| **AUCINFPi** |  | C |  | X |  | X |  | X |  |  |  |
| **AUCINFPC** |  |  | X | X | X | X | X | X |  |  | X |
| **AUCINFPDN** |  |  | X | X | X | X | X | X |  |  | X |
| **AUCLAST** |  | C | X | X | X | X | X | X |  |  |  |
| **AUCLASTi** |  | **C** |  | **X** |  | **X** |  | **X** |  |  |  |
| **AUCLASTDN** |  | C | X | X | X | X | X | X |  |  |  |
| **AUCLASTDNi** |  | C |  | X |  | X |  | X |  |  | X |
| **AUCLASTC** |  | C | X | X | X | X | X | X |  |  | X |
| **AUCLASTCi** |  | C |  | X |  | X |  | X |  |  | X |
| **AUCT1\_T2** [T1 & T2 evaluated and incorporated into multiple **AUCT1\_T2** values] (\* placeholder) |  |  | X | X | X | X | X | X |  |  |  |
| **AUCTAU*i*** |  | C |  | X |  | X |  | X |  |  |  |
| **AUCTAUDNi** |  |  |  | X |  | X |  | X |  |  | X |
| **AUCXBPCTO** |  |  |  |  | X | X |  |  |  |  |  |
| **AUCXBPCTP** |  |  |  |  | X | X |  |  |  |  |  |
| **AUCXPCTO** |  |  | X | X | X | X | X | X |  |  |  |
| **AUCXPCTOi** |  |  |  | X |  | X |  | X |  |  |  |
| **AUCXPCTP** |  | C | X | X | X | X | X | X |  |  |  |
| **AUCXPCTPi** |  | C |  | X |  | X |  | X |  |  |  |
| **AUMCINFO** |  |  | X |  | X |  | X |  |  |  |  |
| **AUMCINFOi** |  |  |  | X |  | X |  | X |  |  |  |
| **AUMCINFP** |  |  | X |  | X |  | X |  |  |  |  |
| **AUMCINFPi** |  |  |  | X |  | X |  | X |  |  |  |
| **AUMCLAST** |  |  | X |  | X |  | X |  |  |  |  |
| **AUMCLASTi** |  |  |  | X |  | x |  | X |  |  |  |
| **AUMCTAU*i*** |  |  |  | X |  | X |  | X |  |  |  |
| **AUMCXPTO** |  |  | X |  | X |  | X |  |  |  |  |
| **AUMCXPTOi** |  |  |  | X |  | X |  | X |  |  |  |
| **AUMCXPTP** |  |  | X |  | X |  | X |  |  |  |  |
| **AUMCXPTPi** |  |  |  | X |  | X |  | X |  |  |  |
| **AURCALL** |  |  |  |  |  |  |  |  | X | X |  |
| **AURCINFO** |  |  |  |  |  |  |  |  | X | X |  |
| **AURCINFP** |  | C |  |  |  |  |  |  | X | X |  |
| **AURCLAST** |  | C |  |  |  |  |  |  | X | X |  |
| AURCT (define as for AUCT above but consistent with AURCT1\_T2) (\* placeholder) |  |  |  |  |  |  |  |  | X | X |  |
| **AURCT1\_T2** (\* placeholder) |  |  |  |  |  |  |  |  | X | X |  |
| **AURCXPCTO** |  |  |  |  |  |  |  |  | X | X |  |
| **AURCXPCTP** |  | C |  |  |  |  |  |  | X | X |  |
| **C0** |  |  |  |  | X | X |  |  |  |  |  |
| **CAV*i*** |  |  |  | X |  | X |  | X |  |  |  |
| **CEST** |  | C | X | X | X | X | X | X |  |  |  |
| **CENDINF** |  |  |  |  |  |  | X | X |  |  |  |
| **CENDINFDN** |  |  |  |  |  |  | X | X |  |  |  |
| **CLAST** |  |  | X | X | X | X | X | X |  |  |  |
| **CLASTi** |  |  |  | X |  | X |  | X |  |  |  |
| **CLFO** |  |  | X |  |  |  |  |  |  |  |  |
| **CLFOW** |  |  | X |  |  |  |  |  |  |  | X |
| **CLFP** |  |  | X |  |  |  |  |  |  |  |  |
| **CLFPW** |  |  | X |  |  |  |  |  |  |  |  |
| **CLFTAUi** |  |  |  | X |  |  |  |  |  |  |  |
| **CLFTAUWi** |  |  |  | X |  |  |  |  |  |  |  |
| **CLP** |  |  |  |  | X |  | X |  |  |  |  |
| **CLO** |  |  |  |  | X |  | X |  |  |  |  |
| **CLOW** |  |  |  |  | X |  | X |  |  |  |  |
| **CLPW** |  |  |  |  | X |  | X |  |  |  |  |
| **CLR** |  |  |  |  |  |  |  |  | X |  | X |
| **CLRT** |  |  |  |  |  |  |  |  | X | X | X |
| **CLRTAUi** |  |  |  |  |  |  |  |  |  | X | X |
| **CLTAUi** |  |  |  |  |  | X |  | X |  |  |  |
| **CLTAUWi** |  |  |  |  |  | X |  | X |  |  |  |
| **CMAX** |  |  | X | X | X | X | X | X |  |  |  |
| **CMAX*i*** |  |  |  | X |  | X |  | X |  |  |  |
| **CMAXC** |  |  |  |  | X |  |  |  |  |  |  |
| **CMAXCi** |  |  |  |  |  | X |  |  |  |  |  |
| **CMAXDN** |  |  | X | X | X | X | X | X |  |  |  |
| **CMAXDNi** |  | C |  | X |  | X |  | X |  |  | X |
| **CMIN** |  |  | X | X | X | X | X | X |  |  |  |
| **CMINDN** |  |  | X | X | X | X | X | X |  |  |  |
| **CMIN*i*** |  |  |  | X |  | X |  | X |  |  |  |
| **DOSEC** |  |  | X | X | X | X | X | X |  |  | X |
| **CTROUGH*i*** |  |  |  | X |  | X |  | X |  |  |  |
| **CTROUGHEND*i*** |  |  |  | X |  | X |  | X |  |  |  |
| **DOFi** | X |  |  |  |  |  | X | X |  |  |  |
| **DOSE*i*** | X |  |  | X |  | X |  | X |  | X |  |
| **F** |  |  | X |  | X |  | X |  |  |  | X |
| **FREL** |  |  | X | X | X | X | X | X |  |  | X |
| **FRELLASTi** |  |  | X | X | X | X | X | X |  |  | X |
| **FA** |  |  |  |  |  |  |  |  | X | X | X |
| **FTAUi** |  |  |  | X |  | X |  | X |  |  | X |
| **KEL** |  | C | X | X | X | X | X | X | X | X |  |
| **KELC0** |  |  | X | X | X | X | X | X |  |  |  |
| **KELNOPT** |  |  | X | X | X | X | X | X | X | X |  |
| **KELR** |  | C | X | X | X | X | X | X | X | X |  |
| **KELRSQ** |  | C | X | X | X | X | X | X | X | X |  |
| **KELRSQA** |  |  | X | X | X | X | X | X | X | X |  |
| **KELTMHI** |  |  | X | X | X | X | X | X | X | X |  |
| **KELTMLO** |  |  | X | X | X | X | X | X | X | X |  |
| **LASTTIME** |  |  | X | X | X | X | X | X |  |  |  |
| **LASTTIMEi** |  |  |  | X |  | X |  | X |  |  |  |
| **MAXRATE** |  | C |  |  |  |  |  |  | X | X |  |
| **MAXRATEi** |  | C |  |  |  |  |  |  |  | X |  |
| **MIDPTA** |  |  |  |  |  |  |  |  | X | X |  |
| **MIDPTLAST** |  |  |  |  |  |  |  |  | X | X |  |
| **MIDPTLASTi** |  |  |  |  |  |  |  |  |  | X |  |
| **MIDPTN** |  |  |  |  |  |  |  |  | X | X |  |
| **MRAUCINF** |  |  | X | X | X | X | X | X |  |  | X |
| **MRAUCLAST** |  |  | X | X | X | X | X | X |  |  | X |
| **MRAUCTAUi** |  |  |  | X |  | X |  | X |  |  | X |
| **MRCMAX** |  |  | X | X | X | X | X | X |  |  | X |
| **MRCMAXi** |  |  |  | X |  | X |  | X |  |  | X |
| **MRTLAST** |  |  | X | X | X | X | X | X |  |  |  |
| **MRTLASTi** |  |  |  | X |  | X |  | X |  |  |  |
| **MRTEVIFO(i)** |  |  | X | X |  |  |  |  |  |  |  |
| **MRTIVIFO(i)** |  |  |  |  | X | X | X | X |  |  |  |
| **MRTEVIFP(i)** |  |  | X | X |  |  |  |  |  |  |  |
| **MRTIVIFP(i)** |  |  |  |  | X | X | X | X |  |  |  |
| **PTF*i*** |  |  |  | X |  | X |  | X |  |  | X |
| **PTR*i*** |  |  |  | X |  | X |  | X |  |  | X |
| **PTROUGHRi** |  |  |  | X |  | X |  | X |  |  | X |
| **PTROUGHRENDi** |  |  |  | X |  | X |  | X |  |  | X |
| **RACi** |  |  |  | X |  | X |  | X |  |  | X |
| **RACCMAXi** |  |  |  | X |  | X |  | X |  |  | X |
| **RACCMINi** |  |  |  | X |  | X |  | X |  |  | X |
| **RATEA** |  |  |  |  |  |  |  |  | X | X |  |
| **RATELASTi** |  |  |  |  |  |  |  |  | X | X |  |
| **RATEN** |  |  |  |  |  |  |  |  | X | X |  |
| **RSSi** |  |  |  |  |  |  |  |  |  |  | X |
| **TAU** |  |  |  | X |  | X |  | X |  | X |  |
| **TAU*i*** |  |  |  | X |  | X |  | X |  | X |  |
| **TENDINF** |  |  |  |  |  |  | X | X |  |  |  |
| **THALF** |  | C | X | X | X | X | X | X | X | X |  |
| **THALFF** |  | C | X | X | X | X | X | X | X | X |  |
| **TLAG** |  |  | X | X |  |  |  |  | X | X |  |
| **TLAST** |  | C | X | X | X | X | X | X |  |  |  |
| **TLASTi** |  | C |  | X |  | X |  | X |  |  |  |
| **TMAX** |  |  | X | X | X | X | X | X |  |  |  |
| **TMAX*i*** |  | C |  | X |  | X |  | X |  |  |  |
| **TMAXRATE** |  | C |  |  |  |  |  |  | X | X |  |
| **TMAXRATEi** |  | C |  |  |  |  |  |  |  | X |  |
| **TMIN** |  |  | X | X | X | X | X | X |  |  |  |
| **TMIN*i*** |  |  |  | X |  | X |  | X |  |  |  |
| **TOLD** |  |  |  | X |  | X |  | X |  | X |  |
| **TOLD*i*** |  |  |  | X |  | X |  | X |  | X |  |
| **V0** |  |  |  |  | X | X |  |  |  |  |  |
| **VOLSUM** |  |  |  |  |  |  |  |  | X | X |  |
| **VSSP** |  |  |  |  | X |  | X |  |  |  |  |
| **VSSPi** |  |  |  |  |  | X |  | X |  |  |  |
| **VSSPW** |  |  |  |  | X |  | X |  |  |  |  |
| **VSSPWi** |  |  |  |  |  | X |  | X |  |  |  |
| **VSSO** |  |  |  |  | X |  | X |  |  |  |  |
| **VSSOi** |  |  |  |  |  | X |  | X |  |  |  |
| **VSSOW** |  |  |  |  | X |  | X |  |  |  |  |
| **VSSOWi** |  |  |  |  |  | X |  | X |  |  |  |
| **VZFO** |  |  | X |  |  |  |  |  |  |  |  |
| **VZFOW** |  |  | X |  |  |  |  |  |  |  |  |
| **VZFP** |  |  | X |  |  |  |  |  |  |  |  |
| **VZFPW** |  |  | X |  |  |  |  |  |  |  |  |
| **VZFTAUi** |  |  |  | X |  |  |  |  |  |  |  |
| **VZFTAUWi** |  |  |  | X |  |  |  |  |  |  |  |
| **VZO** |  |  |  |  | X |  | X |  |  |  |  |
| **VZOW** |  |  |  |  | X |  | X |  |  |  |  |
| **VZP** |  |  |  |  | X |  | X |  |  |  |  |
| **VZPW** |  |  |  |  | X |  | X |  |  |  |  |
| **VZTAUi** |  |  |  |  |  | X |  | X |  |  |  |
| **VZTAUWi** |  |  |  |  |  | X |  | X |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |
| **FLAGS and CRITERIA** |  |  |  |  |  |  |  |  |  |  |  |
| **FLGACCEPTKEL**\* |  | C | X | X | X | X | X | X | X | X |  |
| **FLGACCEPTKELCRIT**\*\* |  |  | X | X | X | X | X | X | X | X |  |
| **FLGACCEPTPREDOSE**\* |  | C | X | X | X | X | X | X |  |  |  |
| **FLGACCEPTPREDOSECRIT**\*\* |  |  | X | X | X | X | X | X |  |  |  |
| **FLGACCEPTTAU**\* |  | C | X | X | X | X | X | X | X | X |  |
| **FLGACCEPTTMAX**\* |  | C | X | X | X | X | X | X |  |  |  |
| **FLGEXAUC**\*\* |  |  | X | X | X | X | X | X | X | X |  |
| **FLGEXKEL**\*\* |  |  | X | X | X | X | X | X | X | X |  |
| **FLGEXSDE**\*\* |  |  | X | X | X | X | X | X | X | X |  |
| **FLGEXST**\*\* |  |  | X | X | X | X | X | X | X | X |  |
| **FLGNOCMAX**\*\* |  |  | X | X | X | X | X | X | X | X |  |
| **LASTTIMEACCEPTCRIT**\*\* |  |  | X | X | X | X | X | X | X | X |  |
| **SPANRATIOCRIT**\*\* |  |  | X | X | X | X | X | X | X | X |  |
| **THALFF**\* |  |  | X | X | X | X | X | X | X | X |  |

\* - COMPUTED flag from computation engine

\*\* - INPUT flag to computation engine

## C0 Example

### Example Data

| **TIME** | **CONC** | **AUC** |
| --- | --- | --- |
| 0 | C0 = 9.9225 | 0 |
| 2 | 6.3 | 16.2225 |
| 4 | 4 | 26.349 |
| 6 | 2.5 | 32.7319 |
| 8 | 1.6 | 36.7652 |
| 10 | 1 | 39.3183 |
| 12 | 0.63 | 40.92 |
| 18 | 0.16 | 42.9775 |
| 24 | 0.04 | 43.4969 |
| 36 | 0 | 43.7369 |
| 48 | 0 | 43.7369 |



### Estimate C0

1) First estimate slope of first two (default) data points, or those data points identified in the profile via **FLGCZERO**. If the latter, a linear regression of the ln(concentration) vs time of the selected profile data points is performed to estimate the slope of the regression curve.

K = (ln(C2)-ln(C1)) / (t2-t1) = (ln(4)-ln(6.3)) / (4-2) = -0.227

2) Then calculate C0

C0 = C1exp (-K \* T1) = 6.3 exp (-(-0.227) \* 2) = 9.9225

Where C1 and C2 are the 1st and 2nd concentration, respectively, and T1 and T2 are the time post-dose of the 1st and 2nd concentration, respectively.

### Estimate AUCXBPCTO (observed)

Estimate Percentage of AUCINF (observed) that was due to back extrapolation to estimate C0:

1. First estimate the AUC from T0 to the T1 using the trapezoidal rule

AUCT0-T1= 16.2225

1. Second estimate AUCINF without AUCT0-T1

AUCINF = AUCINFO – AUCT0-T1 *= 43.7 – 16.2 = 27.5*

*3) Last, estimate the percentage:*

*AUCXBPCTO = ((AUCT0-T1) / AUCINFO ) x 100*

*= (16.2/ 43.7)) x 100 = 37.1%*

### Estimate AUCXBPCTP (predicted)

Estimate Percentage of AUCINF (predicted) that was due to back extrapolation to estimate C0:

1. First estimate the AUC from T0 to the T1 using the trapezoidal rule

AUCT0-T1= 16.2225

1. Second estimate AUCINF without AUCT0-T1

AUCINF = AUCINFP – AUCT0-T1 *= 44.5 – 16.2 = 28.3*

*3) Last, estimate the percentage:*

*AUCXBPCTP = ((AUCT0-T1) / AUCINFP ) x 100*

*= ((16.2)/ 44.5)) x 100 = 36.4%*

## Volume/Weight conversion for Urine data

### Calculation

If urine is reported as weight, then the following equation should be used:



V = urine volume at each time post-dose or time interval

C = urine concentration at each time post-dose or time interval

W = urine weight at each time post-dose or time interval

1.020 g/mL = specific gravity of urine

Example:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Start Time** | **End Time** | **V** | **C** | **AT** |
| 0 | 4 | 200 | 3 | 600 |
| 4 | 8 | 350 | 4.2 | 1470 |
| 8 | 12 | 300 | 4 | 1200 |
| 12 | 16 | 275 | 3.9 | 1073 |
| 16 | 20 | 250 | 3.5 | 875 |
| 20 | 24 | 200 | 0 | 0 |

As per example table, if urine volume and concentration is reported, then the AT at the end of each post-dose or collection interval will be calculated as follows:

*A4= (200 mL ) x 3 ng/mL = 600 ng*

*A8= (350 mL ) x 4.2 ng/mL = 1470 ng*

*A12= (300 mL ) x 4 ng/mL = 1200 ng*

*etc.*

StartTime = collection interval start time

EndTime = collection interval stop time

### NCA Dataset correction for PKAMT

Follow the following workflow for volume/weight conversions

**If**

PKBDFLD = Urine

PKAMTU = (In Mass units)

**Then**

Apply specific gravity correction

PKAMTC = Corrected Amount

PKAMTUC = Corrected Amount Unit

**Else**

PKAMTC = <Blank>

PKAMTUC = <Blank>

## Derivations for Parameter calculations

These midpoint time derivations are done at the time of preparing parameter calculations.

| Release | Name | Calculations | Decimal Places | Unit Class |
| --- | --- | --- | --- | --- |
| 2.0 | **MIDPTA**  **MIDPTAU** | Actual midpoint of each collection interval and the unit of the actual time midpoint  **If**  SAMPLETYPE = INTERVAL  **Then**    **Else**  MIDPTA = <Blank>  StartTime = ACTTIME  EndTime = ACTENDTIME  **Example**:   |  |  |  | | --- | --- | --- | | Start Time | End Time | MIDPT | | 0 | 0 | 0\* | | 0 | 4 | 2 | | 4 | 8 | 6 | | 8 | 12 | 10 | | 12 | 16 | 14 | | 16 | 20 | 18 | | 20 | 24 | 22 | | <Blank> | <Blank> | <Blank> | | 2 | <Blank> | <Blank> | | 4 | 3 | NA |   MIDPT at collection interval at 8-12 hrs will be calculated as follow:  MIDPT = (12 - 8) / 2) + 8 = 10 hr  \*If profile does not contain an observation for the dosing time, insert zero.   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If EndTime ≤ StartTime | Return “NA” |   Note: MIDPTA and MIDPTN reflect what the MCT$TIME variable is set to, i.e. either ACTUAL or NOMINAL time. The openNCA computation engine produces MIDPT since the names of the other parameters are not changed if the time source changes but time source used is recorded. | NA | TIMEU |
| 2.0 | **MIDPTN**  **MIDPTNU** | Nominal time midpoint of each collection interval and the unit of the nominal time midpoint  **If**  SAMPLETYPE = INTERVAL  **Then**    **Else**  MIDPTN = <Blank>  StartTime = NOMTIME  EndTime = NOMENDTIME  **Note**: Use example and data checks as above for MIDPTA  Note: MIDPTA and MIDPTN reflect what the MCT$TIME variable is set to, i.e. either ACTUAL or NOMINAL time. The openNCA computation engine produces MIDPT since the names of the other parameters are not changed if the time source changes but time source used is recorded. | NA | TIMEU |
| 2.0 | **RATEA**  **RATEAU** | Actual excretion rate for each collection interval and the unit for the actual excretion rate.  **If**  PKCOLL = INTERVAL  **Then**    **Else**  RATEA = <Blank>  Values for RATEA/RATEAU are recorded with the data record representing the END of the sample collection interval.  **Note:** RATEAU is either a data field supplied in the input dataset or it is assumed that ACTTIMEUis same as ACTEMDTIMEU. If not then make appropriate corrections (HR to MINS) for correct calculations  RATEAU is determined from the units for concentration, PKCNCU, volume, PKSMVLU, actual time post dose start, PKATPDU and end, PKATPDEU.  For example:  RATEAU ~ (PKCNCU x PKSMVLU)/(PKATPDUE-PKATPDU)  = (NG/ML x ML)/HR = NG/HR  StartTime = ACTTIME  EndTime = ACTENDTIME  C = CONC  V = SAMPLEVOLUME (use AMOUNT if SAMPLEVOLUME = <Blank>)  StartTime = collection interval start actual time, ACTTIME  EndTime = collection interval stop actual time, ACTENDTIME  Units for RATEA are expressed as RATEU  **Note:** Derive RATE after Volume/Weight corrections for Urine data  **Example**:   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Start Time | End Time | MIDPT | V | C | RATE | | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 4 | 2 | 200 | 3 | 150 | | 4 | 8 | 6 | 350 | 4.2 | 368 | | 8 | **12** | 10 | 300 | 4 | 300 | | 12 | 16 | 14 | 275 | 3.9 | 268 | | 16 | 20 | 18 | 250 | 3.5 | 219 | | 20 | 24 | 22 | 200 | 0 | 0 | | <Blank> | <Blank> | <Blank> |  |  | <Blank> | | 2 | <Blank> | <Blank> |  |  | <Blank> | | 4 | 3 | NA |  |  | NA |   RATE at collection interval at 0-4 hrs will be calculated as follow:  RATE = (3 ng/mL x 200 mL) / (4 hr – 0 hr) = 150 ng/hr    NOTE: correct for units if needed   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If EndTime ≤ StartTime | Return “NA” |   **Note**: RATE = 0 at Time = 0  Note: RATEA and RATEN reflect what the MCT$TIME variable is set to, i.e. either ACTUAL or NOMINAL time. The openNCA computation engine produces RATE since the names of the other parameters are not changed if the time source changes but time source used is recorded. | NA | RATEU |
| 2.0 | **RATEN**  **RATENU** | Nominal excretion rate for each collection interval and the unit for the nominal excretion rate.  **If**  SAMPLETYPE = INTERVAL  **Then**    **Else**  RATEN = <Blank>  Values for RATEN/RATENU are recorded with the data record representing the END of the sample collection interval.  **Note:** RATENU is either a data field supplied in the input dataset or it is assumed that NOMTIMEU is same as NOMENDTIMEU, If not then make appropriate corrections (HR to MINS) for correct calculations  RATENU is determined from the units for concentration, PKCNCU, volume, PKSMVLU, actual time post dose start, NTPDU, and end, PKPTMU.  For example:  RATENU ~ (PKCNCU x PKSMVLU)/(PKPTMU-NTPDU)  = (NG/ML x ML)/HR = NG/HR  StartTime = NOMTIME  EndTime = NOMENDTIME  C = CONC  V = SAMPLEVOLUME (use AMOUNT if SAMPLEVOLUME = <Blank>)  StartTime = collection interval start nominal time, NOMTIME  EndTime = collection interval stop nominal time, NOMENDTIME  **Note:** Derive RATE after Volume/Weight corrections for Urine data  **Example**:   |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | | Start Time | End Time | MIDPT | V | C | RATE | | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 4 | 2 | 200 | 3 | 150 | | 4 | 8 | 6 | 350 | 4.2 | 368 | | 8 | **12** | 10 | 300 | 4 | 300 | | 12 | 16 | 14 | 275 | 3.9 | 268 | | 16 | 20 | 18 | 250 | 3.5 | 219 | | 20 | 24 | 22 | 200 | 0 | 0 | | <Blank> | <Blank> | <Blank> |  |  | <Blank> | | 2 | <Blank> | <Blank> |  |  | <Blank> | | 4 | 3 | NA |  |  | NA |   RATE at collection interval at 0-4 hrs will be calculated as follow:  RATE = (3 ng/mL x 200 mL) / (4 hr – 0 hr) = 150 ng/hr    NOTE: correct for units if needed   |  |  | | --- | --- | | **Data Checks** | **Actions** | | If EndTime ≤ StartTime | Return “NA” |   **Note**: RATE = 0 at Time = 0  Note: RATEA and RATEN reflect what the MCT$TIME variable is set to, i.e. either ACTUAL or NOMINAL time. The openNCA computation engine produces RATE since the names of the other parameters are not changed if the time source changes but time source used is recorded. | NA | RATEU |
| 2.0 | **RATEU**  RATENU  RATEAU | Excretion rate unit class  Amount/Time (wt/t)  Shall be populated with the appropriate value derived from following variables depending on the columns used for the calculation of RATE above   * PKPTMU * PKATPDU * PKATPDEU * PKAMTC * PKAMTUC | NA | NA |
| 2.0 | TAUi | **Dosing interval** for steady state with multiple dosing intervals.  Primary Source: User input or edit before parameter calculation  See TAUi for definition  Note that if there’s only one dose, TAU is a synonym for TAU1.  *Refer to Appendix “*Multiple Dosing Interval and TAU handling*” for details* | NA | TIMEU |
| 2.0 | **DOFi** | **Duration of Infusion for constant infusion model M3**  If the dataset incorporates a field labeled DOF, then this is utilized directly. Alternatively DOF is derived by the computation engine from Dates and Times of Start and Stop of dosing.  Note that if there’s only one dose, DOF is a synonym for DOF1.  Calculation:  DOF = (Actual Infusion End DateTime) – (Actual Infusion Start DateTime)  DOF = ACTENDTIME - ACTTIME  If Actual Time not available then use nominal time | NA | TIMEU |
| 3.0 | **NDOSE** | NDOSE is the number of dosing intervals within a single pk data profile.  This is computed from the # of TAUi/TOLDi values defined for a pk data profile in the dataset. |  |  |

## Calling Sequences for openNCA Computation Engine R Package

This section of the openNCA Computation Engine Specification provides details of the calling arguments for the run\_computation function/entry point to the Computation Engine from the openNCA Application and for calling the Computation Engine directly in other R scripts.

For the openNCA Application, there are currently two modes of calling the openNCA computation engine.

1. Scenario 1 – compute all profiles
   1. compute-call2.sh – script to pass arguments from openNCA analysis module with all profiles from the dataset, call opennca-kel-calc.R script which in turns calls the run\_computation function/entry point.

Parameters that are passed to compute-call2.sh and passed to opennca-kel-calc.R:

* + 1. INPUT1=<dataset filename>
    2. INPUT2=<filename for MCT in JSON format>
    3. INPUT3=<filename for FLAGS dataset in JSON format>
    4. OUTPUT="." – computation engine output directory location, default = “.”
  1. opennca-kel-calc.R – R script utilized in the computation engine call from the Analysis Module from openNCA when **all** profiles are being processed to compute PK parameters. Called by compute-call2.sh. Note that the MCT/MAP and FLAGS parameters are passed in JSON format and transformed to a dataframe in preparation for the call to run\_computation

1. Scenario 2 – virtual” compute call, i.e. call with data from 1 profile
   1. virtual-compute-call.sh – script to pass arguments from openNCA analysis module with a single profile of data, call opennca-kel-calc-virtual.R script which in turns calls the run\_computation function/entry point.

Parameters that are passed to virtual-compute-call.sh and passed to opennca-kel-calc-virtual.R:

* + 1. INPUT1=<dataset filename>
    2. map=<filename for MCT in JSON format>
    3. flags=<filename for FLAGS dataset in JSON format>
    4. OUTPUT="." – computation engine output directory location, default = “.”
  1. opennca-kel-calc-virtual.R – R script utilized in the computation engine call from the Analysis Module from openNCA when a **single** profile is being processed, Note that the primary difference with opennca-kel-calc.R is that the opennca-kel-calc-virtual.R call incorporates a direct calculation of the terminal elimination half life slope. This was done to ensure that the details of the regression were available to be passed to the calling application for use in displaying the regression line. This is intended to be modified in a future update once the computation engine is closer to finalization and the required data will be generated by the run\_computation call results directly. The update will require run\_computation to return times and and concentrations of the “end points” of the range of datapoints utilized for the computation of the terminal elimination phase constant regression.

Called by virtual-compute-call2.sh. Note that the MCT/MAP and FLAGS parameters are passed in JSON format and transformed to a dataframe in preparation for the call to run\_computation.

Current format for calling run\_computation function/entry point:

run\_computation(data=d, map=mct, flag=flags)

Final call format anticipated:

run\_computation(data=d, map=mct, flag=flags, optimizekel=0, include.interpolation=0, include.extrapolation=0)

Arguments to run\_computation routine

* data – dataframe incorporating the concentration time dataset
  + Required elements (TBD)
* map – dataframe incorporating the MCT dataset
* flag – data frame incorporating the FLAGS dataset