PhUSE US Connect 2018

Paper DS07

Making PK Analysis Easier: The New ADaM Data Standard ADNCA

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ABSTRACT

Noncompartmental analysis ("NCA") of the pharmacokinetic ("PK") characteristics of a drug is one of the commonly used methods during drug development to investigate what happens to the drug in the body after dose administration. Recently, a subgroup of CDISC's ADaM team has completed the initial draft specification of a data standard (ADNCA") that is ready for noncompartmental analysis and is essentially an ADaM Basic Data Structure ("BDS") for NCA and should be viewed as the ADaM BDS model plus additional NCA variables. This paper presents a preview of some details of the proposed standard and gives some insight into the rationale behind the standard's specification. Because the paper represents the current status of the discussion and the review process of ADNCA, the information contained in this paper should not be used as a guidance until the final release of ADNCA.

To provide additional context, the paper will start with a brief introduction of the base concepts of NCA that will allow to better explain the proposed standard. This is followed by examples for the most critical and maybe controversial concepts of ADNCA – covering the representation of dosing information and the different types of timing variables, the specific additions to represent interval-based data (think urine data), and handling of exclusions.

INTRODUCTION

Looking at the clinical research side from a really high level and ignoring the details of other available and useful standards, the CDISC-defined standards support the general workflow from collection through tabulation and to analysis through the core foundational standards CDASH (Clinical Data Acquisition Standards Harmonization), SDTM (Study Data Tabulation Model), and ADaM (Analysis Data Model). The idea of SDTM and ADaM is that SDTM contains the data for tabulation as they were collected while ADaM contains analysis-ready datasets. Pretty much since the beginning, PK analysis was somewhat of a special case: SDTM not only contains a domain specification for data that are collected as input data for PK analysis (the PC or Pharmacokinetics Concentrations domain) but also includes a specification for the results of the PK analysis (the PP or Pharmacokinetics Parameters domain). Apart from this anomaly ("analysis results are in SDTM"), the basic workflow concept of creating an analysis-ready dataset (based on the ADaM specification) from the tabulated data (typically using data from multiple SDTM domains) applies nicely to PK analysis workflows. Except for the fact that the content for NCA-ready datasets does not really fit well into the restrictions of the basic dataset specified in ADaM, the BDS or Basic Data Structure datasets.

Recognizing the special needs of the PK community, the ADaM leadership team formed a sub team to deal with the requirements of the PK scientists. This team has not completed the initial draft of the NCA-ready ADaM standard ("ADNCA") and submitted for internal review. As this proposal goes through the review and approval process, feedback and additional input is sought to make sure that the release of ADNCA will meet the user's requirements. The goal is to develop a standard that closely follows current ADaM guidance – specifically BDS – and allows for enough flexibility to support the various PK analysis programs that are in use.

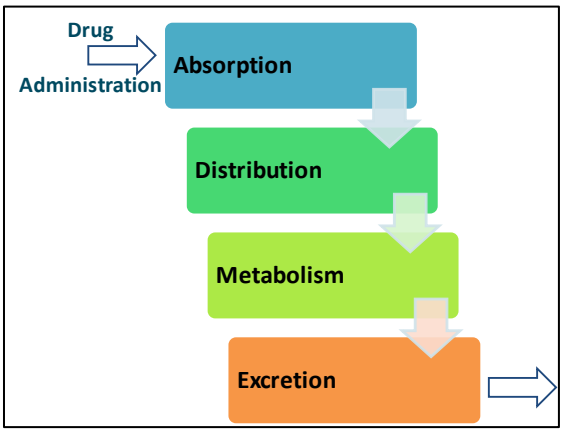
Pharmacokinetic analysis is based on concentration-time profiles that are collected after dose administration. The result are so-called PK parameters, such as the maximum concentration (C_{Max}), the time point of the maximum concentration (T_{Max}), half-life of the drug in the body ($t_{1/2}$), and several areas under the concentration curve (AUC). The PK parameters allow scientists to understand what happens to the drug after administration and assess the characteristics of the drug's distribution in the body. PK analysis is typically performed using existing, often commercial software packages (in contrast to writing specific analysis programs). These packages require complete input datasets with all data, not only the concentration-time profiles but also the doing information, sampling profile and co-factors – including subject-specific data such as weight, sex, etc. Consequently, the flexibility of the BDS specification is deployed in ADNCA to allow users to incorporate the required data from the different SDTM and ADaM sources when creating an ADNCA dataset.

With the expected release of the ADNCA standard, submission of the input data that are used for calculating PK parameters will be easier to review by authorities and overall contribute to a faster and smoother application and review process. ADNCA will help to close a critical gap in the universe of clinical data standards. More so, because it can not only support the PK analysis but also reporting on the concentration data, i.e., an ADNCA dataset can be used to create tables, listings, and figures for reporting on the data. However, it should be noted that ADNCA is focused on individual PK analysis and is not intended or expected to be sufficient for population PK.

NONCOMPARTMENTAL PHARMACOKINETICS ANLYSIS

In short, the pharmacokinetic of a drug describes what happens to the drug in the body after the administration of the drug. PK scientists study the processes in the body that that are related to and driven by the drug concentration levels in the body and use a model with four processes. This is typically referred to as ADME model which is short for

the processes “Absorption”, “Distribution”, “Metabolisms”, and “Excretion”. Because the drug concentration levels at the site of the desired drug effect are critical for a drug efficacy, understanding the PK characteristics are critical for a drug candidate’s failure or success and PK analysis is part of the early stages of the drug development process, pre-clinical or phase I studies.



To study a drug candidate’s PK characteristics, scientists start by collecting and analyzing specimen samples (blood, plasma, urine) at pre-defined time points. From these samples the concentration levels of the drug and related metabolites are determined per subject and per time point. This results in so-called concentration-time profiles per subject. A typical profile after an oral administration of a drug is shown in Figure 1:
Note that the time points for collection are not evenly spaced: Sample time points are typically closer together right after dosing because concentration levels will change faster compared to the final elimination phase when the change of the concentration value is less dynamic. The concentration-time profile shown is typical for so-called full sampling of the concentration values after a single oral dose of a drug. In medical research studies many variations are applied – depending on the purpose of the study and the characteristics of the drug under investigation: Examples include multiple doses with the same or varying amounts of drug, intravenous bolus or infusion administration, sparse sampling where concentration values for a subject are not available for a significant number of time points [1]. The ADNCA standard needs to support the resulting dataset formats.

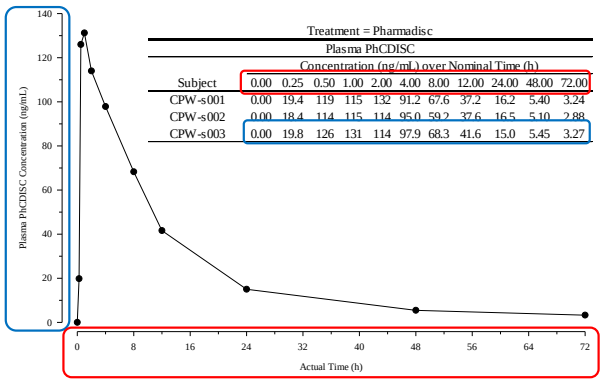


Figure 1: Typical concentration-time profile after Oral administration of a drug

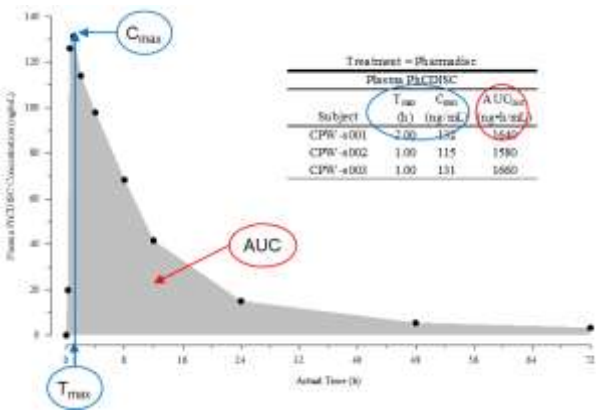


Figure 2: PK Parameters C_{Max}, T_{Max}, AUC_{last} for the concentration-time profile of a subject after oral dosing

In noncompartmental analysis a set of so-called PK parameters is calculated for each of the subjects based on the values in this type of concentration-time profile. Figure 2 shows a few typical PK parameters in the context of a concentration-time profile. The calculations are typical rather simple algebraic formulas, however, a PK scientist will likely make some decisions that impact the results: For example, some values might be excluded from the calculations for some reason or the scientist might define the time points are the ‘tail end’ of the profile, i.e., which part of the profile is considered the elimination phase of the drug. Of course, the ADNCA standard needs to allow for capturing and tracking these analysis decisions. The resulting PK parameters are key concepts that are related to the concentrations levels of the drug in the body and allow scientists to achieve two main objectives:

- They allow to assess the amount of drug that is available to have an effect, be it the desired therapeutic effect or an unwanted side effect.
- Secondly, by comparing the PK parameters across subjects or subgroups of subjects, scientists try to evaluate the effect of the drug across a broader population or within certain sub-populations.

BEYOND NCA

Certainly, even this short overview on PK analysis would not be complete without mentioning that NCA is just one of several methods that are used to analyze the interaction between the body and a drug after dose administration.

[1] Note that special methods – so-called sparse analysis methods – are applied in this case. Sparse sampling is very common in pre-clinical studies with small rodents.

based data profiles over time. Figure 3 shows a brief description of the most commonly used methods. Again, as a reminder, the ADNCA standard is dedicated to NCA – additional standard development efforts are certainly required.

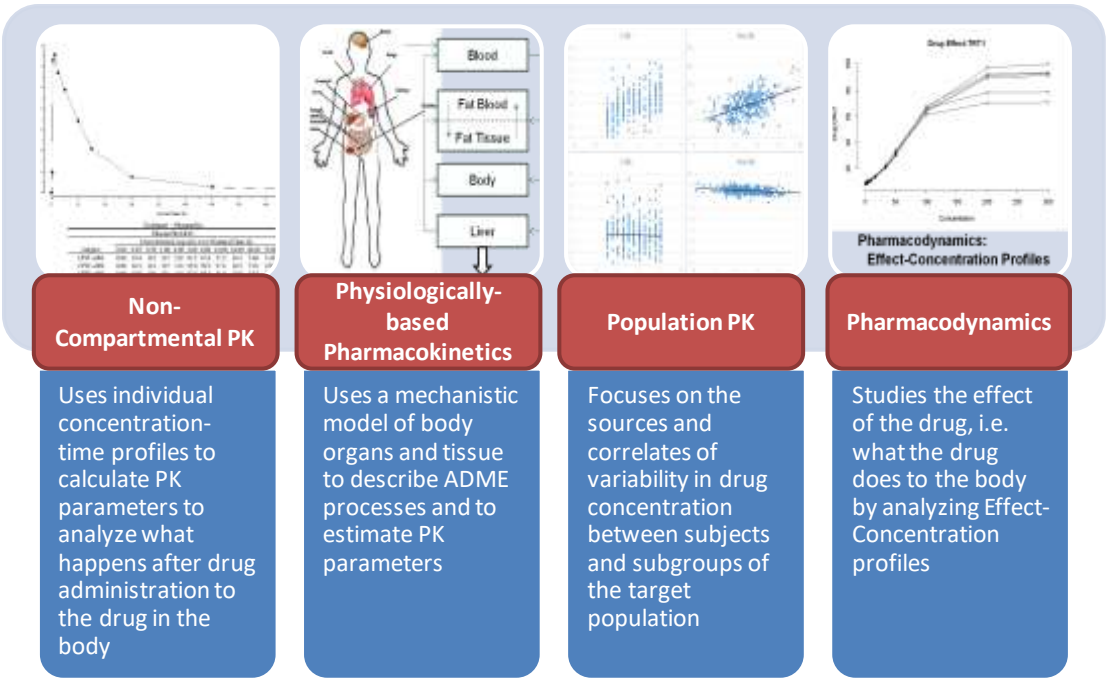


Figure 3: PK/PD Analysis Methods: NCA, PBPK, Population PK, PD

THE ADNCA DATASET

Pharmacokinetic NCA is a method to calculate PK parameters from concentration-time profiles collected after administration of a drug, i.e., the analysis algorithms use pairs of time and concentration values and the corresponding dosing data as input for the calculation.
The ADNCA dataset is structured as one record per subject per parameter per analysis visit per analysis timepoint. For NCA, the records which belong to a unique profile for a specific subject under specific conditions need to be extracted for analysis. The record keys (that uniquely identify each record) are the usual variables STUDYID, USUBJID, PARAMCD, AVISIT, ATPT and for NCA additional 'profile key' variables are used that identify all profile records.
The timing variables in ADNCA belong either to the analysis variable, i.e., they contain the time of a concentration value or some other analysis variable, or to the treatment information, i.e., the they contain the time and if applicable duration of dose administration.
The concentration values are the analysis variables, i.e., they are contained in the standard BDS variable AVAL and related variables.
To summarize, the data required for noncompartmental PK analysis can be categorized into the following three main categories which need to be supported by the ADNCA data format:

- **Profile data**: Concentration-time profiles uniquely identified by a set of 'profile key' variables which allow to select all records for a unique profile
- **Subject data**: Per subject demographics (such as age, race, etc.), additional findings (such as weight, alcohol usage, smoking habits, etc.) or subject characteristics (for example, skin type, genetic disposition, or other relevant conditions)
- **Treatment and dosing data**: Information such as treatment, route, dose amount with dose time parameters (dosing interval for multiple doses, duration of IV administration, etc.) using the same key variables as observations

In the following sections, the paper will describe the main concepts and variables that are used in ADNCA to represent these data. How the values for these variables are derived from collected and tabulated data is not in the scope of this document. In addition, there is a set of flag variables in ADNCA that are analysis related, some of which will be described in the section about Exclusions.

CONCENTRATION-TIME PROFILES

In noncompartmental analysis, the data that are analyzed are concentration-time profiles, i.e., a set of pairs of time and concentration values for each subject after the administration of a drug. However, there are two fundamentally

different types of profiles to be considered depending on the specimen that is collected: There are discrete time-point profiles (typical for plasma or serum measurements) and interval-based profiles for specimen collections that happen over an interval (typical for urine studies).
In time point-based profiles, the analysis variable AVAL contains the concentration value at the time point specified by the timing variables of the record. In addition to the concentration, information about the sample is available in ADNCA as required or useful for NCA. This includes information about the analyte (specimen type, analyte name, unit), and optional indicator to record any derivation applied to the value, and a special flag to indicate that the analyte is not the parent drug but a metabolite. For interval-based profiles, additional variables contain the amount of material that was collected: The typical NCA tool will use the amount of material and the concentration in the material to calculate the amount of metabolite which is actually used for calculating the applicable PK parameters.

TIMING VARIABLES

The time values for concentration-time profiles in ADNCA are contained in several sets of timing variables that provide the flexibility to represent a variety of situations:

- Variables for actual and for nominal / planned sampling times
- Variables for elapsed time from dose administration and for absolute date/time values.
- Variables for time-point sampling (typical for plasma or serum measurements) and for interval-based sampling for collections over an interval (typical for urine studies).

The table below describes the resulting categories and gives some insight into the variety of different timing variables.

	Sample Time relative to Reference Dose	**Sample Time relative to First Dose**	**Absolute Sample Time**
Description	• Variables contain the elapsed time since the administration of the reference dose for the concentration-time profile • Separate variables for actual and nominal / planned times	• Variables contain the elapsed time since the first dose administration to the subject • Separate variables for actual and nominal / planned times	• Variables contain the absolute date and/or time of the sampling • Separate variables for the date, the time, and the date and time
Data type	Numerical value indicating the time in units specific by unit variable	Numerical value indicating the time in units specific by unit variable	Numerical value indicating the absolute date and/or time • Note that the current proposal does not specify the date/time representation (SAS, Excel, R, others?)
For time-point sampling	Separate variables for the actual and nominal time point of sampling	Separate variables for the actual and nominal time point of sampling	Separate variables for the actual and nominal time point of sampling
For interval-based sampling	• Uses time-point variables for start of sampling interval • Additional variables for actual and nominal endpoint of sampling interval	• Uses time-point variables for start of sampling interval • Additional variables for actual and nominal endpoint of sampling interval	• Uses time-point variables for start of sampling interval • Additional variables for actual and nominal endpoint of sampling interval

Table 1: Overview on Timing Variables for Concentration Data

TREATMENT AND DOSING DATA

In pharmacokinetic analysis, using dosing data relevant to the concentration-time profile is a crucial part of the process. The treatment information – such as the treatment name and route of treatment – is pretty much always one of the keys used to identify and extract each specific and unique concentration-time profile. In addition, the dose amount is an important factor for the calculation of dose-adjusted PK parameters. And finally, the time of the dose administration is critical in matching a concentration-time profile to the correct reference dose amount.
But before talking about how dosing data are represented in ADNCA, a brief digression to how dosing data are collected and tabulated in SDTM. The SDTM_EX domain is the relevant domain for the reference dose for PK analysis. EX allows to record dosing by using an individual record for each dose administration or to represent multiple doses in one record – this is called the “one record per constant dosing interval per subject” tabulation. When

tabulating dosing data in the EX domain for PK analysis using a separate dosing record for each dose administration will make processing and analyzing the data easier.
In ADNCA, treatment and dosing data are represented by variables to contain the planned and actual treatment respectively dosing information. Treatment variables contain the description of the treatment, typically the name of the drug, the amount, and the unit. There are also additional variables for supplemental treatment information such as route, treatment sequence (if applicable), or treatment intervals in case of multiple dose studies – which crosses the line to the timing variable for dose and treatment data. Dose variables contain the amount of the administered drug during treatment as numerical value to be used for PK parameter calculations.

TIMING VARIABLES

The timing variables for dosing data in ADNCA allow to specify the time of the dose administration using a similar schema as the timing variables for concentration samples – the table below shows an overview on the types of variables in ADNCA. Note that in this case, all variables are numerical representations of the absolute date and time of the dose administration. As mentioned above, the 'anchor' of the value is not specified by the current ADNCA proposal. In other words, ADNCA does not specify the date and time that is represented by a value of "0" for any of these variables.

	Absolute Time of Reference Dose	Absolute Time of First Dose
Description	• Variables contain the absolute date and/or time of the reference dose for the concentration-time profile • Separate variables for the date, the time, and the date and time	• Variables contain the absolute date and/or time of the first dose for subject • Separate variables for the date, the time, and the date and time
Data type	Numerical value indicating the absolute date and/or time • Note that the current proposal does not specify the date/time representation (SAS, Excel, R, others?)	Numerical value indicating the absolute date and/or time • Note that the current proposal does not specify the date/time representation (SAS, Excel, R, others?)
For time-point dosing	Variables for the actual and nominal date/time point of dose administration	Variables for the actual and nominal time point of dose administration
For interval of IV infusion	• Uses time-point variables for start of dosing interval for IV infusion • Additional variables for actual and nominal endpoint of dosing interval for IV infusion	• Uses time-point variables for start of dosing interval for IV infusion Additional variables for actual and nominal endpoint of dosing interval for IV infusion

Table 2: Overview on Timing Variables for Concentration Data

EXCLUSIONS AND FLAGS

In CDISC datasets, flags exist to allow communication between data consumers and producers about characteristics that are critical in understanding the data. In pharmacokinetic analysis communication about the inclusion or exclusion of data records is a critical part of the interaction between PK scientists and data managers. The decision about exclusions will very often be the result of an iteration where the data are prepared and reviewed which could lead to the setting of so-called-exclusion flags.
The ADNCA proposal contains exclusion flags for single records and for subjects. The team concluded that subject-level exclusion flags will allow for a much-simplified process for the iteration between data managers and PK scientists as described above. The exclusion flags are accompanied by a text variable to be used to capture the reason for the exclusion. These text variables are probably the most critical component in achieving the objective of communicating data issues between data producers and consumers. The table below shows the exclusion and other flags and related variables.

Variable Name	Variable Label	Description
PKEFL	PK Subject-level Exclusion Flag	Flag for exclusion (Y= exclusion, blank = inclusion) of all records for an entire subject from the analysis.
REXSUBJ	Reason for Exclusion of Entire Subjects	This variable should be used to explain why entire subjects were excluded from the analysis.

Variable Name	Variable Label	Description
PKERFL	PK Record-Level Exclusion Flag	Flag for exclusion (Y= exclusion, blank= inclusion) of individual records from the analysis if a subject is supposed to be included in the analysis. It is expected that records flagged in PKEFL would also be flagged in PKERFL.
REXRE	Reason for Exclusion of Ind. Records	This variable should be used to explain why individual records were excluded from the analysis.
MEALFL	Meal Within Defined Time Window of Dose	Variable is applicable for oral doses that should be given in a particular state (e.g,, fasted vs fed).
MRELTM	Rel. Time of Meal to Dose	Relative time between meal described in MEALFL and dose described in DOSEP.
VOMITFL	Vomit Related to Dose	Variable is applicable for oral doses and should indicate whether the subject vomited during the expected absorption phase of an oral drug which may impact the PK analysis.
VRELTM	Rel. Time of Vomit to Dose	Relative time between vomiting and dose given.

Table 3: ADNCA Flags and related variables

CONCLUSION

The ADNCA specification will close a gap in the available standards for representing and submitting data from clinical studies. This will be only the first step, because there are more areas in pharmacokinetics to cover – specifically population PK analysis – and there are groups already working on data standard specifications that use ADNCA as the starting point. All in all, the quick release of ADNCA should be considered a goal for all partied involved, CDISC, regulatory agencies and the pharmaceutical industry.

ADNCA is still in review following the development process for CDISC standards. This paper represents the current status of the draft while it is still under discussion and details will change. The information in this paper should not be taken as a representation of the final release of ADNCA. Stay tuned for public review and to get involved in this standardization effort.

REFERENCES

Reinbolt, L., MacDonald, L., (2018), “Coming soon: ADNCA and the PK submission”, PharmaSUG 2018, Seattle, WA

ACKNOWLEDGMENTS

The ADNCA draft standard is the result of a team effort by a sub-team of the CDISC ADaM team. I want to thank the ADNCA team and the ADaM leadership for their support, their patience and their relentless effort to push this proposal forward and to help closing this critical gap in the landscape of CDISC standards.

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