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Implementation of CDISC ADaM in the Pharmacokinetics department

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ABSTRACT

SGS Life Science Services as a leading CRO, is one of the pioneers in the implementation of CDISC standards. Given the positive experiences in the SGS Data Management and Biostatistics departments (implementation of SDTM and ADaM respectively), the Pharmacokinetics (PK) Department recently decided to adopt the CDISC standards as well.

In an SDTM database, pharmacokinetic data is stored as one record per subject, per time point (PC domain) or per pharmacokinetic parameter (PP domain). For the PK analysis, the generation of Tables, Listings and Figures, and the statistical analysis on PK parameters, 'analysis ready' datasets are created. The structure of these 'analysis ready' datasets is based upon the Basic Data Structure (BDS) of CDISC ADaM.

This paper will highlight a practical approach in converting PC into ADPC and PP into ADPP, with the focus on data handling, criteria evaluation and sub-analysis selection, important aspects of PK analysis.

INTRODUCTION

The FDA encourages the use of Clinical Data Interchange Standards Consortium (CDISC) standards for submission of clinical trial data. For submission of pharmacokinetic (PK) data using the Study Data Tabulation Model (SDTM), two domains are available: Pharmacokinetic Concentrations (PC) and Pharmacokinetic Parameters (PP) domain[1]. In addition to SDTM, an Analysis Data Model (ADaM) was developed[2]. The Analysis Dataset containing PK Concentrations (ADPC) and the Analysis Dataset containing PK Parameters (ADPP) are the 'analysis-ready' datasets of PC and PP respectively, based upon the Basic Data Structure (BDS) of the CDISC ADaM[3]. ADPC and ADPP are used for the PK analysis, the statistical analysis on PK parameters and the generation of Tables, Listings and Figures (TLF). At this moment, specific CDISC guidelines to create ADPC and ADPP are not yet available. This article proposes a guideline for converting PC into ADPC and PP into ADPP.

ADDED VALUE OF ADPC/ADPP

In a clinical study, the protocol or the Statistical Analysis Plan (SAP) defines (among others) the following sections:

- PK population
- Data handling:
    - Handling of values above/below a threshold
    - Handling of missing data
    - Handling of missing date/times
    - Handling of outliers
    - Other, sponsor specific data handling
- Time deviations (protocol deviations)
- Calculation of PK parameters

Important information for the PK analysis found in these sections is not covered in the PC/PP domain. Moreover, the PC dataset itself cannot be used directly by PK software. By using ADPC and ADPP, the specifications of the protocol and SAP can be included in the ADPC and ADPP datasets and the ADPC file can be imported directly in Phoenix® WinNonLin for PK analysis.

STRUCTURE OF ADPC/ADPP

In order to compile ADPC (table 1), the PC domain is merged with the Subject-Level Analysis Dataset (ADSL) which contains general subject information (e.g. demographic information), and with the ADAPER (one or more records per subject, per analysis period) analysis dataset which contains start and end times of each period and actual and planned treatment per period. Treatment information from the exposure dataset (EX) is also imported and derived variables are added (figure 1).

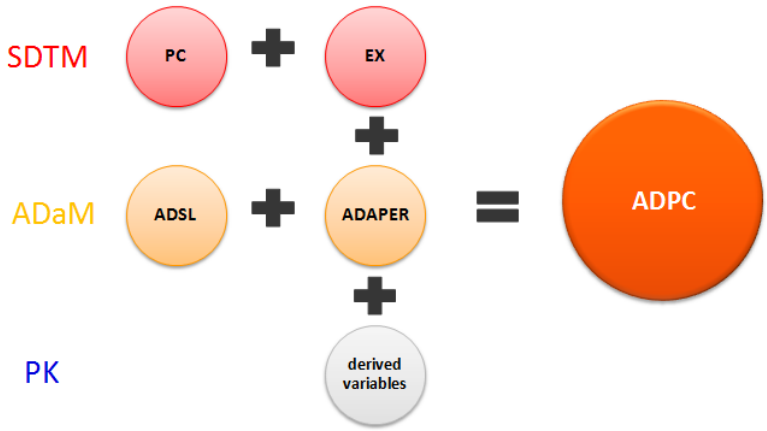

Figure 1: Compiling ADPC

Similar to the creation of ADPC, the PP domain is merged with ADSL and ADAPER and derived variables are added to create ADPP (figure 2, table 2).

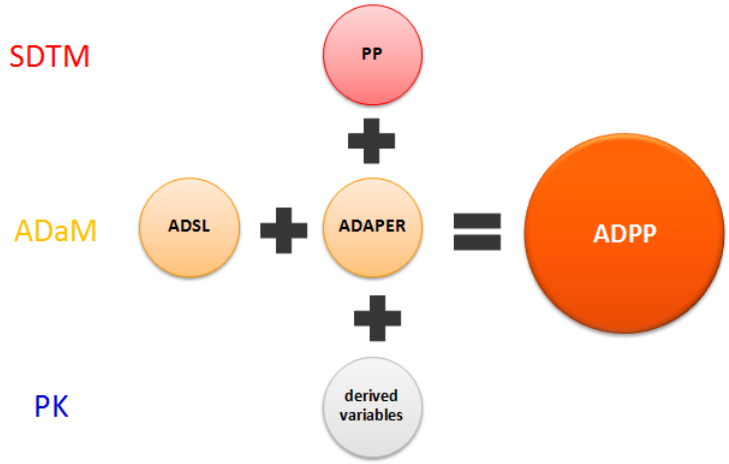

Figure 2: Compiling ADPP

In the CDISC ADaM Implementation Guide (IG) following variables are defined for the Basic Data Structure (BDS):

PARAM, PARAMN, PARAMCD

The variable PARAM contains the description of the analysis parameter. In ADPC files, the value of PARAM represents the analyzed compound with its unit (e.g. 'Compound X (ng/mL)'); the abbreviation of the analyzed compound is stored in the variable PARAMCD. In ADPP files, the value of PARAM is the PK parameter with its unit (e.g. 'Cmax (ng/mL)'); the abbreviation of the PK parameter is stored in the variable PARAMCD. The numeric counterpart is presented in PARAMN.

ADTM, ASTDTM, AENDTM

In the ADTM variable (table 1, var 1), the Date/Time associated with the analysis value (AVAL) is stored. It is the numeric version of the variable PCDTC (Date/Time of Specimen collection) from the PC domain. ASTDTM and AENDTM are associated with the start and end time of an analysis interval, e.g. for urine collection. These variables are not present in ADPP.

AVISIT, AVISITN

AVISIT and its numeric counterpart AVISITN (table 1 and 2, var 2) are derived from the variables VISIT and VISITNUM from the PC domain. All PK concentrations (in ADPC) or all PK parameters (in ADPP) that refer to the same exposure will have the same AVISIT(N) value.

ATPT, ATPTN

The planned analysis time points are presented in ATPT and ATPTN (table 1, var 3). Only for predose values they differ from the PCTPT and PCTPTNUM (variables from the PC domain). The value of PCTPTNUM, which is in general negative for predose samples, is put to zero in ATPTN. If the variable PCTPTNUM contains the planned time points in minutes, it can be converted to e.g. hours in ATPTN. These variables are not present in ADPP.

ARELTM, ARELTMU

The analysis relative time, needed for PK analysis, is stored in the variable ARELTM (table 1, var 4). The anchor time, which is the reference time, can be covered in different variables as e.g. PCRFTDTC (Date/Time of reference intake in PC domain), TRTSDTM (Datetime of First Exposure to Treatment, from ADSL) or EXSTDTC (start Date/Time of treatment in EX domain). If ARELTM is calculated based upon the reference intake time, the value will be negative for predose values, but for PK analysis, the predose value is considered as the zero hour value. To cover this difference, two ARELTMs are used: ARELTM1 with the real relative time and ARELTM2 with the predose value put to zero. For the other time points, ARELTM2 will be equal to ARELTM1. Because of this modification to the ARELTM, two ANCHOR variables need to be added, one for ARELTM1, with the reference intake time variable as value of ANCHOR1, and one for ARELTM2, with only for the predose value the PCDTC as value for ANCHOR2; for the other PK samples, ANCHOR2 will be equal to ANCHOR1. ARELTM1/ANCHOR1 and ARELTM2/ANCHOR2 are modified variables from the BDS variable ARELTM. These variables are not present in ADPP.

ANLzzFL

Analysis record flags (ANLzzFL) can be used to select a set of records for one or more analyses (table 1 and 2, var 5). The “zz” represents an index for a record selection algorithm, and will be replaced with 01-99. As multiple analysis flags can be assigned, a new variable, analogue to ANLzzFL, is created within our company to define the different analysis groups: ANLzzFD (Analysis Record Flag zz Description). The selection of different sub-analysis sets is discussed in the section on PK specific requirements.

AVAL, AVALC

The analysis value is reported in AVAL (table 1 and 2, var 6). In most cases, it is equal to PCSTRESN, the numeric result in standard unit. The character counterpart is reported in AVALC. As mentioned before, several rules for data handling are described in the protocol and/or SAP. These adjustments can be done in AVAL(C).

CRITy, CRITyFL, CRITyFN

Analysis criteria are evaluated in CRITy. The “y” is used to categorize the different criteria and will be replaced with a single digit: 0-9. Different criteria important to PK analysis and statistical analysis of the PK parameters are discussed in the section on PK specific requirements. The outcome of the analysis criteria is presented in CRITyFL, CRITyFN.

PK SPECIFIC REQUIREMENTS

DATA HANDLING

In AVAL(C), adjustments to the values in PCSTRESN can be done. For example, missing pre-dose values or values below the limit of quantification can be put to zero.

CRITERIA EVALUATION

Two important criteria in PK analysis are time deviations and quantifiable predose values. If a sample is taken more than 10% too soon, or too late relative to the scheduled time point, the value can be excluded from the descriptive statistical analysis. In bioequivalence studies, if the predose value is more than 5% of the maximal concentration, the subject will be excluded from the trial.

For statistical analysis on PK parameters, the AUC percent extrapolated (AUCpeo) should be lower than 20% of AUC infinity (AUCifo), if not, AUCifo can be excluded from the statistical analysis.

SELECTION OF SUB-ANALYSIS RECORDS

In PK analysis, different sub-analysis can be performed, each including a different set of records. In ADPC, the main analysis groups are: 'PK analysis', 'Descriptive statistical analysis' and 'Steady state analysis'. In ADPP, the main analysis groups are: 'Inferential statistical analysis' and 'Descriptive statistical analysis', but also 'Formulation effect', 'Food effect' and others are possible. Subjects, time points or PK parameters can be included or excluded from analyses based upon criteria as specified in the protocol/SAP.

CONCLUSION

Despite no CDISC ADaM guidelines exist so far for Pharmacokinetics, the ADaM BDS variables provide sufficient flexibility to support PK analysis. By working according to the ADaM rules, and thus increasing standardization in the datasets, the time to perform PK analysis decreases. In addition, the information from the protocol and SAP, needed for PK analysis, can be integrated in these standardized datasets. Moreover, the PK department can work now on similar platforms as the data management team (SDTM) and statistical department (ADaM).

For PK analysis and statistical analysis on PK parameters, ADPC and ADPP datasets respectively are needed. These datasets are compiled from SDTM (EX and PC or PP) and ADaM (ADSL and ADAPER) datasets, in combination with derived analysis variables. These derived analysis variables are defined by BDS. For PK analysis specifically, a slight modification is made in the variables ARELTM/ANCHOR, and the variable ANLzzFD is added.

Although experience in compiling and using ADPC and ADPP files has been built up over the last years, CDISC standards on ADPC and ADPP files are "a must have" for uniformity between different companies.

REFERENCES

[1] CDISC SDTM Implementation Guide (Version 3.1.3). Available at www.CIDSC.org
[2] CDISC ADaM Implementation Guide (Version 1.0). Available at www.CDISC.org
[3] Y. Xie, P. Chai, X. Li, N. Wang. Pharmacokinetic Data Submission in the CDISC environment. AAPS 2011.

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

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Table 1: ADPC

SUBJID	EXSTDTC	PCDTC	ADTM	VISITNUM	VISIT	AVISIT	AVISITN	PCTPT	PCTPTNUM	ATPT	ATPTN	PCSTRESC
			Var 1			Var 2	Var 2			Var 3	Var 3	
1	2013-07-05T09:00	2013-07-05T08:55	2013-07-05T08:55	1.001	PERIOD1_DAY1	DAY1	1	PRE-DOSE	-1	0H	0	<1
1	2013-07-05T09:00	2013-07-05T09:30	2013-07-05T09:30	1.001	PERIOD1_DAY1	DAY1	1	0.5H	30	0.5H	0.5	1511
1	2013-07-05T09:00	2013-07-05T10:00	2013-07-05T10:00	1.001	PERIOD1_DAY1	DAY1	1	1H	60	1H	1	1852
1	2013-07-05T09:00	2013-07-05T10:30	2013-07-05T10:30	1.001	PERIOD1_DAY1	DAY1	1	1.5H	90	1.5H	1.5	1360
1	2013-07-05T09:00	2013-07-05T11:01	2013-07-05T11:01	1.001	PERIOD1_DAY1	DAY1	1	2H	120	2H	2	1410
1	2013-07-05T09:00	2013-07-05T13:00	2013-07-05T13:00	1.001	PERIOD1_DAY1	DAY1	1	4H	240	4H	4	490
1	2013-07-05T09:00	2013-07-05T17:00	2013-07-05T17:00	1.001	PERIOD1_DAY1	DAY1	1	8H	480	8H	8	74.4
1	2013-07-05T09:00	2013-07-05T21:00	2013-07-05T21:00	1.001	PERIOD1_DAY1	DAY1	1	12H	720	12H	12	16.5
1	2013-07-05T09:00	2013-07-06T09:00	2013-07-06T09:00	1.002	PERIOD1_DAY2	DAY1	1	24H	1440	24H	24	<1
1	2013-07-05T09:00	2013-07-07T09:02	2013-07-07T09:02	1.003	PERIOD1_DAY3	DAY1	1	48H	2880	48H	48	<1

PCSTRESN	PCSTRESU	AVAL	ANCHOR1	ARELTM1	ANCHOR2	ARELTM2	ARELTMU	ANL01FL	ANL01FD	ANL02FL	ANL02FD
		Var 6	Var 4	Var 4	Var 4	Var 4	Var 4	Var 5	Var 5	Var 5	Var 5
.	ng/mL	0	EXSTDTC	-0.0833	PCDTC	0	HOURS	Y	PK ANALYSIS	Y	DESCR STAT
1511	ng/mL	1511	EXSTDTC	0.5	EXSTDTC	0.5	HOURS	Y	PK ANALYSIS	Y	DESCR STAT
1852	ng/mL	1852	EXSTDTC	1	EXSTDTC	1	HOURS	Y	PK ANALYSIS	Y	DESCR STAT
1360	ng/mL	1360	EXSTDTC	1.5	EXSTDTC	1.5	HOURS	Y	PK ANALYSIS	Y	DESCR STAT
1410	ng/mL	1410	EXSTDTC	2.0167	EXSTDTC	2.0167	HOURS	Y	PK ANALYSIS	Y	DESCR STAT
490	ng/mL	490	EXSTDTC	4	EXSTDTC	4	HOURS	Y	PK ANALYSIS	Y	DESCR STAT
74.4	ng/mL	74.4	EXSTDTC	8	EXSTDTC	8	HOURS	Y	PK ANALYSIS	Y	DESCR STAT
16.5	ng/mL	16.5	EXSTDTC	12	EXSTDTC	12	HOURS	Y	PK ANALYSIS	Y	DESCR STAT
.	ng/mL	0	EXSTDTC	24	EXSTDTC	24	HOURS	Y	PK ANALYSIS	Y	DESCR STAT
.	ng/mL	0	EXSTDTC	48.0333	EXSTDTC	48.0333	HOURS	Y	PK ANALYSIS	Y	DESCR STAT

Table 2: ADPP

SUBJID	PPTESTCD	PPTEST	AVISIT	AVISITN	PPSTRESC	PPSTRESN	PPSTRESU	AVAL	ANL01FL	ANL01FD	ANL02FL	ANL02FD
			Var 2	Var 2				Var 6	Var 5	Var 5	Var 5	Var 5
1	AUCPEO	AUC %Extrapolation Obs	DAY1	1	0.215	0.215	%	0.215	Y	INFER STAT	Y	DESCR STAT
1	AUCIFO	AUC Infinity Obs	DAY1	1	4.208	4.208	h*ug/mL	4.208	Y	INFER STAT	Y	DESCR STAT
1	AUCLST	AUC to Last Nonzero Conc	DAY1	1	4.199	4.199	h*ug/mL	4.199	Y	INFER STAT	Y	DESCR STAT
1	CMAX	Max Conc	DAY1	1	1.852	1.852	ug/mL	1.852	Y	INFER STAT	Y	DESCR STAT
1	LAMZHL	Half-Life Lambda z	DAY1	1	3.062	3.062	h	3.062	Y	INFER STAT	Y	DESCR STAT
1	LAMZ	Lambda z	DAY1	1	0.226	0.226	/h	0.226	Y	INFER STAT	Y	DESCR STAT
1	TMAX	Time of CMAX	DAY1	1	1	1	h	1	Y	INFER STAT	Y	DESCR STAT
1	R2ADJ	R Squared Adjusted	DAY1	1	0.984	0.984		0.984	Y	INFER STAT	Y	DESCR STAT