

Implementation of CDISC ADaM in Pharmacodynamics

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ABSTRACT

SGS Life Sciences is a CRO that is one of the pioneers in the implementation of CDISC standards. After implementing the CDISC standards for Pharmacokinetic (PK) analysis, the CDISC standards are now initiated for Pharmacodynamic (PD) analysis. In an SDTM database, pharmacodynamic data can be stored as one record per subject, per time point (PD domain), similar as PK data in the PC domain. For the PD analysis, the generation of Tables, Listings and Figures (TLF), and the statistical analysis on PD observations, an “analysis-ready” dataset is created. The structure of the “analysis-ready” dataset is based upon the Basic Data Structure (BDS) of CDISC ADaM. This paper, supported by case study examples, will explore the approach to create the PD analysis dataset (ADPD) and to capture PD parameters (e.g. E_{max} , AUEC) calculated within SAS® or within other specific software.

INTRODUCTION

The U.S. FDA requires the use of Clinical Data Interchange Standards Consortium (CDISC) standards for submission of clinical trial data. Pharmacodynamic (PD) data can be available in different Study Data Tabulation Model (SDTM) domains, depending on the nature of the PD data, e.g. Laboratory test result (LB), ECG test results (EG) or Pharmacokinetics concentrations (PC)^[1]. At SGS LS, a new findings domain was defined, similar to the LB domain: Pharmacodynamics (PD), with one record per subject, per time point.

To perform the PD analysis, an “analysis-ready” dataset ADPD, based upon the Basic Data Structure (BDS) of the CDISC ADaM^[2] is created. PD parameters like E_{max} (maximum effect) or AUEC (Area under the effect curve) can be estimated either in SAS® or with specific software (e.g. Phoenix® WinNonlin®). The two different approaches will be discussed in the article.

Note, as PD analyses exist in different areas, the scope of this article is limited to lab-like data; however, the principles shown can be implemented in different areas of PD analyses.

ADDED VALUE OF ADAM DATASETS

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

- PD 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 PD parameters

Important information for the PD analysis found in these sections is not covered in the PD domain. In order to obtain “analysis-ready” dataset, ADPD dataset is created in which the specifications of the protocol and SAP can be included. If PD parameters need to be calculated, this can be done either in SAS within the ADPD or alternatively, outside SAS with the ADPD used as input file for PD software (Figure 1). In the latter case, the parameters estimated with the PD software should be imported in a second ADPD dataset for good traceability. The ADPD used as input can be named ADPD1, and the second ADPD with the parameters can be named ADPD2.

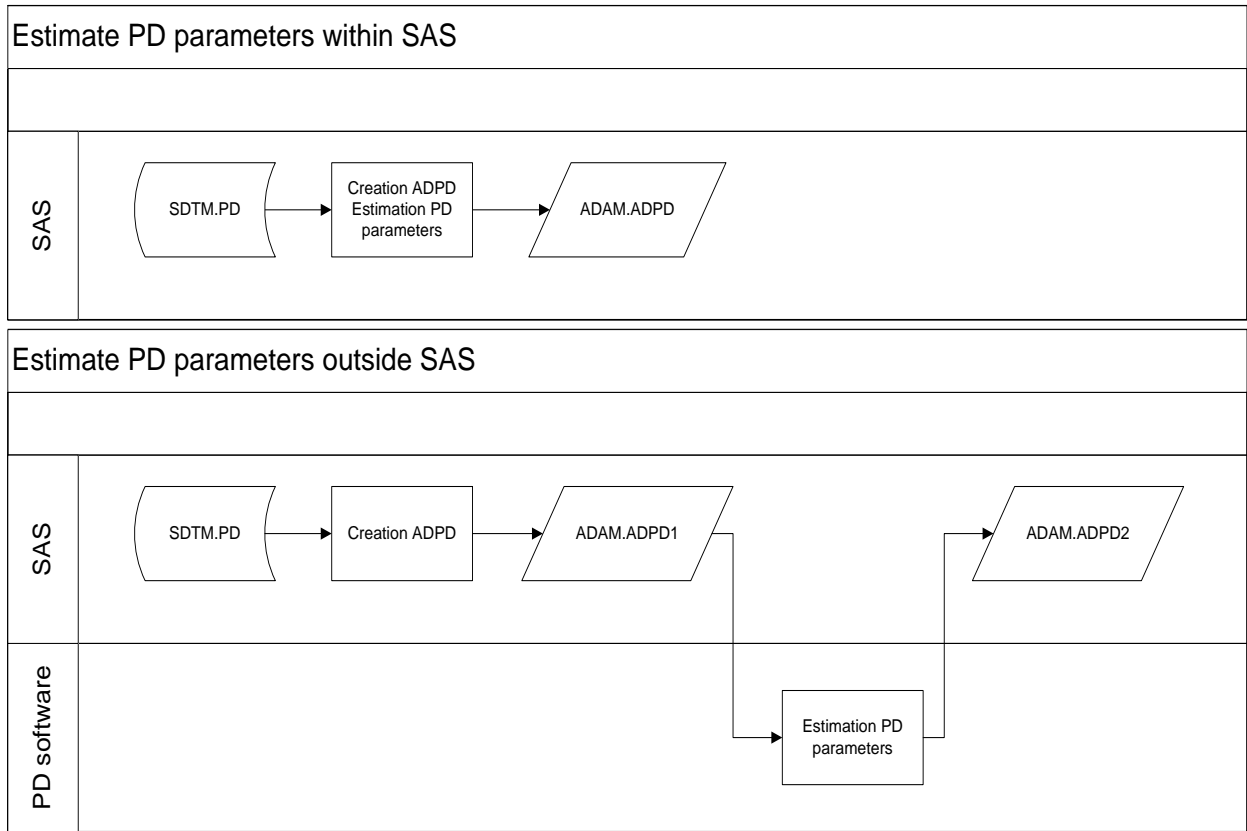


Figure 1: Compiling ADPD - Flowcharts

COMPOSITION OF DATASETS

STRUCTURE OF ADPD(1)

In order to compile ADPD, the SDTM PD domain is merged with the ADaM Subject-Level Analysis Dataset (ADSL) and with ADPHASE analysis dataset. ADSL contains general subject information (e.g. demographic information), where ADPHASE contains the start and end date/times of each phase [and period (if applicable)] together with the actual and planned treatment. Treatment information from the exposure dataset (EX) is also imported into the ADPD if needed (e.g. when the analysis should be done by actual time and not by planned time) and derived variables are added (Figure 2).

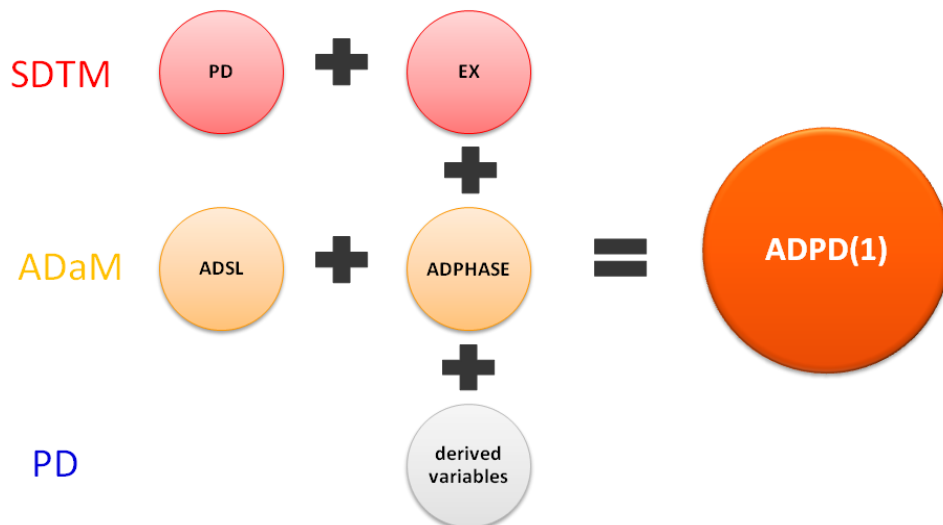


Figure 2: Compiling ADPD(1)

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STRUCTURE OF ADPD2

The ADPD2 will have the same identifier variables, record-level treatment and dose variables, and time variables (e.g. visit, aperiod, aphase) as ADPD1, to link the parameters unambiguously to the PD profile in ADPD1, however, the analysis parameter variables are derived.

BDS VARIABLES

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

- **PARAM, PARAMN, PARAMCD**

The variable PARAM (examples 1, 2, 3 and 4) contains the description of the analysis parameter with the unit, and is abbreviated in the variable PARAMCD. The numeric counterpart PARAMN can also be included for sorting purposes.

- **AVAL**

The analysis value is reported in AVAL (examples 1, 2, 3 and 4). Adjustments can be done, as specified in protocol or SAP, with the derivation specified in DTYPE. An example of this is the imputation of values below or above quantification limit.

- **AVALCATY(N)**

AVALCATy(N) (example 2) is a categorization of AVAL within a parameter.

- **BASE, CHG, PCHG**

BASE (examples 1, 2 and 4) is the baseline analysis value. CHG (example 1) is the change from baseline analysis value, equal to AVAL-BASE. PCHG (examples 1 and 4) is the percent change from baseline analysis value, equal to $((AVAL-BASE)/BASE)*100$.

If CHG or PCHG is used for a given PARAM, it should be populated for all post-baseline records of that PARAM regardless of whether that record is used for analysis.

- **CHGCATY(N), PCHGCATY(N)**

CHGCATy(N) or PCHGCATy(N) (example 1) is a categorization of CHG or PCHG within a parameter.

- **AVISIT, AVISITN**

AVISIT (examples 1, 2, 3 and 4) and its numeric counterpart AVISITN are derived from the variables VISIT and VISITNUM from the PD domain. In the examples below, the baseline record is duplicated, with AVISIT set to 'BASELINE' and DTYPE to 'LVPD' (Last Value Prior to Dosing). Other baseline derivation methods are possible, e.g. average of predose samples.

- **ATPT, ATPTN**

The planned analysis time points are presented in ATPT (examples 3 and 4) and ATPTN. ATPT and ATPTN are derived from PDTPT and PDTPTNUM (variables from the PD domain). The value of PDTPTNUM, which is in general negative for predose samples, can be put to zero in ATPTN to derive PD parameters. If the variable PDTPTNUM contains the planned time points in minutes, it can be converted to e.g. hours in ATPTN.

- **ANLZZFL, ANLZZFD**

Analysis flags (ANLzzFL) can be used to select a set of records for one or more analyses. 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 needed to define the different analysis groups: ANLzzFD (Analysis Flag zz Description). In ADPD, the main analysis groups are: 'PD analysis', 'Descriptive statistical analysis' and 'Inferential statistical analysis'. Subjects, time points or PD parameters can be included or excluded from analyses based upon criteria or as specified in the protocol/SAP.

- **CRITY, CRITYFL, CRITYFN**

Analysis criteria are evaluated in CRITy. The "y" is used to categorize the different criteria and will be replaced with an integer digit: 1-99.

EXAMPLES

- **EXAMPLE 1: CHANGE FROM BASELINE**

PARAM	AVISIT	AVAL	DTYPE	ABLFL	BASE	CHG	CHGCAT1	PCHG	PCHGCAT1
PD measurement (unit)	SCREENING	36							
PD measurement (unit)	BASELINE	36	LVPD	Y	36				
PD measurement (unit)	DAY 1	30			36	-6]-10, 0] unit	-16.67]-20, 0] %
PD measurement (unit)	DAY 2	26			36	-10]-20, -10] unit	-27.78]-40, -20] %
PD measurement (unit)	DAY 3	22			36	-14]-20, -10] unit	-38.89]-40, -20] %
PD measurement (unit)	DAY 7	14			36	-22]-30, -20] unit	-61.11]-80, -60] %

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For the records originating from PD, the value of PARAM is the name of the PD measurement with the unit, derived from PDTEST and PDSTRESU. AVAL is derived from PDSTRESN, the numeric result in standard unit. CHG and PCHG are populated for the post-baseline records. CHGCAT1 is used to categorize the CHG; PCHGCAT1 is used to categorize the PCHG.

- **EXAMPLE 2: PERCENT REDUCTION FROM BASELINE**

PARAM	AVISIT	AVAL	DTYPE	ABLFL	BASE	AVALCAT1
PD measurement (unit)	SCREENING	36				
PD measurement (unit)	BASELINE	36	LVPD	Y	36	
PD measurement (unit)	DAY 1	30			36	
PD measurement (unit)	DAY 2	26			36	
PD measurement (unit)	DAY 3	22			36	
PD measurement (unit)	DAY 7	14			36	
Reduction PD (%)	DAY 1	16.67				[0, 20[%
Reduction PD (%)	DAY 2	27.78				[20, 40[%
Reduction PD (%)	DAY 3	38.89				[20, 40[%
Reduction PD (%)	DAY 7	61.11				[60, 80[%

For derived records, the value of PARAM is the name of the derived PD parameter with the unit. AVAL is derived from AVAL and BASE: $100-(AVAL/BASE)*100$. Derivation rules should be specified in the define.xml. AVALCAT1 is used to categorize AVAL.

- **EXAMPLE 3: WITH PARAMETERS ASSESSED IN SAS**

PARAM	AVISIT	ATPT	AVAL
PD measurement (unit)	DAY 1	PRE-DOSE	0.08
PD measurement (unit)	DAY 1	0.5H	96.58
PD measurement (unit)	DAY 1	0.75H	95.39
PD measurement (unit)	DAY 1	1H	96.77
PD measurement (unit)	DAY 1	2H	99.75
PD measurement (unit)	DAY 1	4H	88.82
PD measurement (unit)	DAY 1	8H	75.59
PD measurement (unit)	DAY 1	24H	67.06
PD measurement (unit)	DAY 1	48H	56.03
PD measurement (unit)	DAY 1	96H	62.37
PD measurement (unit)	DAY 1	168H	32.05
PD measurement (unit)	DAY 1	336H	0.17
PD measurement (unit)	DAY 1	672H	0.20
PD measurement (unit)	DAY 1	1344H	0.20
PD measurement (unit)	DAY 1	2016H	0.34
AUEC (unit)	DAY 1		10504
E _{max} (unit)	DAY 1		99.75
tE _{max} (unit)	DAY 1		2

Additional PD parameters (AUEC, E_{max}, tE_{max}) are derived in SAS from AVAL of the PD measurement. AVAL for these parameters contains the result of the derivation. Derivation rules should be specified in the define.xml.

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- EXAMPLE 4: WITH PARAMETERS ASSESSED IN PHOENIX WINNONLIN

ADPD1

PARAM	AVISIT	ATPT	AVAL	DTYPE	ABLFL	BASE	PCHG
PD measurement (unit)	DAY 1	PRE-DOSE	9380				
PD measurement (unit)	DAY 1	BASELINE	9380	LVPD	Y	9380	0.00
PD measurement (unit)	DAY 1	2H	9870			9380	5.22
PD measurement (unit)	DAY 1	4H	8770			9380	-6.50
PD measurement (unit)	DAY 1	8H	9590			9380	2.24
PD measurement (unit)	DAY 1	24H	8860			9380	-5.54
PD measurement (unit)	DAY 1	48H	7270			9380	-22.49
PD measurement (unit)	DAY 1	72H	6700			9380	-28.57
PD measurement (unit)	DAY 1	96H	5920			9380	-36.89
PD measurement (unit)	DAY 1	144H	4970			9380	-47.01
PD measurement (unit)	DAY 1	336H	3340			9380	-64.39
PD measurement (unit)	DAY 1	504H	4140			9380	-55.86
PD measurement (unit)	DAY 1	672H	4360			9380	-53.52

ADPD2

PARAM	AVISIT	AVAL
AUEC (unit)	DAY 1	-33762
Emax (unit)	DAY 1	-64.39
tEmax (unit)	DAY 1	336

Additional PD parameters (AUEC, E_{max} , tE_{max}) are here derived in Phoenix WinNonlin from PCHG. AVAL contains the result of the derivation. The Phoenix WinNonlin project is referred to in the define.xml.

CONCLUSION

The ADaM BDS variables provide sufficient flexibility to support PD analysis. By working according to the ADaM rules, and thus increasing standardization in the datasets, the time to perform PD analysis decreases. In addition, the information from the protocol and SAP, needed for PD analysis, can be integrated in these standardized datasets.

When PD assessments require the estimation of PD parameters (e.g., AUEC, E_{max} and tE_{max}), two different approaches can be followed. PD parameters can be estimated within SAS during creation of ADPD or the PD parameters are estimated in a PD software (like Phoenix WinNonlin). In the latter case, the ADPD1 will contain the PD measurements and serve as input for the software; the ADPD2 will contain the estimated PD parameters that were exported from the software. This flow will ensure good traceability of the PD analysis.

REFERENCES

- [1] CDISC SDTM Implementation Guide (Version 3.2). Available at www.CIDSC.org
- [2] CDISC ADaM Implementation Guide (Version 1.1). Available at www.CDISC.org

CONTACT INFORMATION

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