

Streamlining Regulatory Submission with CDISC/ADaM Standards for Non-standard Pharmacokinetic/Pharmacodynamic Analysis Datasets

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ABSTRACT

Analysis Data Model (ADaM) which is encouraged by FDA in clinical trial data submission is designed to support analysis datasets. Non-Standard ADaM dataset for Pharmacokinetic (PK) and Pharmacodynamic (PD) analyses have not been clearly discussed. Based on Analysis Data Model v2.1, this paper shares the approaches of how to map non-standard PK/PD data to create ADaM datasets to support the analyses for Thorough QT studies, reproductive safety studies and studies with urine collections. The approaches make the ADaM datasets for these studies consistent with Analysis Data Model v2.1 and submission ready. Detailed mapping methods and examples of these ADaM datasets will be presented.

INTRODUCTION

Analysis Data Model (ADaM) from Clinical Data Interchange Standards Consortium (CDISC) is becoming more and more popular since FDA recommends ADaM as the analysis submission data sets in Study Data Specifications document. ADaM data sets are considered analysis ready, which means it includes all necessary variables needed to perform the statistical analysis of the data. Speeding turn-around time of Pharmacokinetic (PK) and Pharmacodynamic (PD) analyses is critical during the drug development process because it is always good to know a drug's availability as early as possible.

STANDARD APPROACH TO ADAM PK/PD STUDY

In CDISC Analysis Data Model v2.1, the information for PK/PD analysis data set is general. Based on the Basic Data Structure (BDS) specification in the ADaM guide, standard data structure for PK analysis can be generated. The Celerion standard process of creating an ADaM data set for PK analysis has been discussed¹. In this process, SDTM Pharmacokinetic Concentration (PC) data, SDTM Pharmacokinetic Parameter (PP) data, ADaM Pharmacokinetic Concentration (ADPC) data and ADaM Pharmacokinetic Parameters (ADPP) are created based on SDTM/ADaM structure data, clinical data, bioanalytical data and the analysis parameters calculated by scientists. Then, all the related listings, tables and figures can be generated based on ADPC and ADPP data sets.

This process provides a consistent approach from clinical data sets to ADaM data sets for a Celerion standard plasma PK analysis, such as statistical analysis of PK parameters, statistical comparison of difference between treatments. However, some studies require more complex and more involved PK/PD analyses. This paper shares efficient approaches for building ADaM data sets for PK/PD analysis in the situations that go beyond the process discussed in the previous paper.

ADAM DATA SET FOR THOROUGH QT STUDY

BACKGROUND

A thorough QT (TQT) study is expected in the early stages of clinical development for most drugs². Generally, the data for thorough QT analyses come from electrocardiogram (ECG) data set. In TQT studies, some tests are collected multiple times for a particular time point. To get an analysis data set, multiple observations at each time point should be properly mapped according to the analysis specified in the statistical analysis plan, thus the way to handle ADaM TQT data set for cardiac analysis (ADPD or customized ADaM parameter data set for TQT ADZP) are

¹ Xie, Y., Chai, P., Kirby S., Wang N.. 2011. "Pharmacokinetic Data Submission in the CDISC Environment." *American Association of Pharmaceutical Scientists*

² International Conference on Harmonisation. "Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs." October 2005. Available at <http://www.ich.org>

different from the way to handle ADaM safety ECG data set (ADEG). Creating a separate ADaM data sets for TQT analysis from ECG data is suggested.

An example of TQT data set for PD analysis is used to demonstrate the process.

A SAMPLE LIST OF INFORMATION FOR ANALYSIS

1. Delta QT and delta QTc
2. Delta Summary (mean) Heart Rate
3. Delta Summary (mean) PR Rate
4. Delta Summary (mean) QRS Duration
5. Delta Summary (mean) RR Duration
6. Delta T-Wave Amplitude
7. Delta T-Wave Complexity

HOW TO MAP

To create an ADaM data set, there are two different approaches based on the aforementioned requirements. The first approach is used when parameters requested by analysis can be easily calculated, such as delta heart rate, delta pr rate and delta QT. In that case, all the analysis parameters needed can be generated while creating the ADaM data set. The process has two steps. First, create SDTM EG data set. Second, create ADaM ADPD data set based on SDTM EG data set. In this step, the relative information from SDTM EG data set should be selected first and then the calculations for analysis parameters will be performed. For example, to calculate the time-to-time matched change from baseline for QTcF values during ADPD creation.

Another possible mapping approach suggested is similar to the Celerion standard process. In this case, some analysis parameters need to be calculated by a scientist. The process has five steps. First, all the ECG information from clinical collected in ECG data set is mapped to SDTM EG data set. Second, based on the information from SDTM EG data set, an ADaM data set (ADZC) is created for scientists to do the parameters calculation. The name ADZC is used to distinguish from the name ADPC used for ADaM pharmacokinetic concentration data set in the Celerion standard process. It is more appropriate to name the data set ADZC for TQT study since it is considered as a customized ADaM concentration data set. When preparing ADZC data set, different methods can be used for dealing with the multiple observations at the same time point. Depending on the protocol or Statistical Analysis Plan, mean, median, maximum and minimum could be calculated for the multiple observations to make the data analysis ready. Third, analysis parameters will be calculated by scientists based on ADZC data set. Fourth, based on the information of analysis parameters provided by scientists, create SDTM ZP data set. Fifth, ADZP, the customized ADaM parameter data set for TQT study, is created for further analysis usage.

#	Unique Subject Identifier	visit	Actual Tr.	Parameter	Parameter Code	Analysis Value	Analysis Value (C)	Analysis Unit	Complete	PK Analysis Record Level Flag	PK Analy
100	BigPharma-001-0002-0001	DAY 1	A	Delta QTcB - Bazett's Correction Formula	D_QTCB	1.1		msec	Y	Y	Y
101	BigPharma-001-0002-0001	DAY 1	A	Delta QTcF - Fridericia's Correction For	D_QTCF	0.0		msec	Y	Y	Y
102	BigPharma-001-0002-0001	DAY 1	A	Delta Summary (Mean) Heart Rate	D_HRMEAN	1.1		BEATS/MIN	Y	Y	Y
103	BigPharma-001-0002-0001	DAY 1	A	Delta Summary (Mean) PR Duration	D_PRMEAN	5.7/5.2		msec	Y	Y	Y
104	BigPharma-001-0002-0001	DAY 1	A	Delta Summary (Mean) QRS Duration	D_QRSOUR	1.5/1.5		msec	Y	Y	Y
105	BigPharma-001-0002-0001	DAY 1	A	Delta Summary (Mean) QT Duration	D_QTMEAN	-2/-2		msec	Y	Y	Y
106	BigPharma-001-0002-0001	DAY 1	A	Delta Summary (Mean) RR Duration	D_RRMEAN	-14/-14		msec	Y	Y	Y
107	BigPharma-001-0002-0001	DAY 1	A	Delta T-Wave Amplitude	D_TAMP	65.4/65.4		msec	Y	Y	Y
108	BigPharma-001-0002-0001	DAY 1	A	Delta T-Wave Complexity	D_TCOMP	0.0		msec	Y	Y	Y
109	BigPharma-001-0002-0001	DAY 1	A	QTcB - Bazett's Correction Formula	QTcB	391.391		msec	Y	Y	Y
110	BigPharma-001-0002-0001	DAY 1	A	QTcF - Fridericia's Correction Formula	QTcF	389.389		msec	Y	Y	Y
111	BigPharma-001-0002-0001	DAY 1	A	Summary (Mean) Heart Rate	HRMEAN	62.62		msec/MIN	Y	Y	Y
112	BigPharma-001-0002-0001	DAY 1	A	Summary (Mean) PR Duration	PRMEAN	155.5/155.5		msec	Y	Y	Y
113	BigPharma-001-0002-0001	DAY 1	A	Summary (Mean) QRS Duration	QRSOUR	79.5/79.5		msec	Y	Y	Y
114	BigPharma-001-0002-0001	DAY 1	A	Summary (Mean) QT Duration	QTMEAN	384.384		msec	Y	Y	Y
115	BigPharma-001-0002-0001	DAY 1	A	Summary (Mean) RR Duration	RRMEAN	86.4/86.4		msec	Y	Y	Y
116	BigPharma-001-0002-0001	DAY 1	A	T-Wave Amplitude	TAMP	296.2/296.2		msec	Y	Y	Y
117	BigPharma-001-0002-0001	DAY 1	A	T-Wave Complexity	TCOMP	1.1		msec	Y	Y	Y
118	BigPharma-001-0002-0001	DAY 1	A	Delta QTcB - Bazett's Correction Formula	D_QTCB	3.3		msec	Y	Y	Y
119	BigPharma-001-0002-0001	DAY 1	A	Delta QTcF - Fridericia's Correction For	D_QTCF	-2.2		msec	Y	Y	Y
120	BigPharma-001-0002-0001	DAY 1	A	Delta Summary (Mean) Heart Rate	D_HRMEAN	5.6		BEATS/MIN	Y	Y	Y
121	BigPharma-001-0002-0001	DAY 1	A	Delta Summary (Mean) PR Duration	D_PRMEAN	9.5/9.5		msec	Y	Y	Y
122	BigPharma-001-0002-0001	DAY 1	A	Delta Summary (Mean) QRS Duration	D_QRSOUR	1.7/1.7		msec	Y	Y	Y
123	BigPharma-001-0002-0001	DAY 1	A	Delta Summary (Mean) QT Duration	D_QTMEAN	9.9/9.9		msec	Y	Y	Y
124	BigPharma-001-0002-0001	DAY 1	A	Delta Summary (Mean) RR Duration	D_RRMEAN	-68/-68		msec	Y	Y	Y
125	BigPharma-001-0002-0001	DAY 1	A	Delta T-Wave Amplitude	D_TAMP	43.3/43.3		msec	Y	Y	Y
126	BigPharma-001-0002-0001	DAY 1	A	Delta T-Wave Complexity	D_TCOMP	0.0		msec	Y	Y	Y
127	BigPharma-001-0002-0001	DAY 1	A	QTcB - Bazett's Correction Formula	QTcB	392.392		msec	Y	Y	Y
128	BigPharma-001-0002-0001	DAY 1	A	QTcF - Fridericia's Correction Formula	QTcF	388.388		msec	Y	Y	Y
129	BigPharma-001-0002-0001	DAY 1	A	Summary (Mean) Heart Rate	HRMEAN	64.64		BEATS/MIN	Y	Y	Y
130	BigPharma-001-0002-0001	DAY 1	A	Summary (Mean) PR Duration	PRMEAN	156/156		msec	Y	Y	Y
131	BigPharma-001-0002-0001	DAY 1	A	Summary (Mean) QRS Duration	QRSOUR	79.5/79.5		msec	Y	Y	Y
132	BigPharma-001-0002-0001	DAY 1	A	Summary (Mean) QT Duration	QTMEAN	381.3/381.3		msec	Y	Y	Y
133	BigPharma-001-0002-0001	DAY 1	A	Summary (Mean) RR Duration	RRMEAN	845.845		msec	Y	Y	Y
134	BigPharma-001-0002-0001	DAY 1	A	T-Wave Amplitude	TAMP	273.0/273.0		msec	Y	Y	Y
135	BigPharma-001-0002-0001	DAY 1	A	T-Wave Complexity	TCOMP	1.1		msec	Y	Y	Y
136	BigPharma-001-0002-0001	DAY 1	A	Delta QTcB - Bazett's Correction Formula	D_QTCB	1.1		msec	Y	Y	Y
137	BigPharma-001-0002-0001	DAY 1	A	Delta QTcF - Fridericia's Correction For	D_QTCF	3.3		msec	Y	Y	Y
138	BigPharma-001-0002-0001	DAY 1	A	Delta Summary (Mean) Heart Rate	D_HRMEAN	-1/-1		BEATS/MIN	Y	Y	Y
139	BigPharma-001-0002-0001	DAY 1	A	Delta Summary (Mean) PR Duration	D_PRMEAN	2.7/2.7		msec	Y	Y	Y
140	BigPharma-001-0002-0001	DAY 1	A	Delta Summary (Mean) QRS Duration	D_QRSOUR	1.1/1.1		msec	Y	Y	Y
141	BigPharma-001-0002-0001	DAY 1	A	Delta Summary (Mean) QT Duration	D_QTMEAN	4.4		msec	Y	Y	Y
142	BigPharma-001-0002-0001	DAY 1	A	Delta Summary (Mean) RR Duration	D_RRMEAN	14/14		msec	Y	Y	Y
143	BigPharma-001-0002-0001	DAY 1	A	Delta T-Wave Amplitude	D_TAMP	-6.6/-6.6		msec	Y	Y	Y

Display 1: ADPD for Thorough QT analysis Display (Only show part of data from dummy ADaM data set)

Special attention need to be paid to making sure ADEG and ADPD do not have overlapped information, because both analysis data sets ADEG and ADPD share information from SDTM EG data set. The overlapped information may cause confusion when end users review ADaM data sets and work on listings, tables and figures. Additionally, the overlapped information may cause queries during the submission review.

ADAM DATA SET FOR REPRODUCTIVE SAFETY STUDY

BACKGROUND

Reproductive safety is a concern in certain drugs. It is usually collected through a different specimen such as semen. The analysis for this type of matrix is unique, thus the customized ADaM PK/PD data set should be created separately. A male reproductive safety study with semen samples is used as an example.

A SAMPLE LIST OF INFORMATION FOR ANALYSIS

1. Gross Physical Characteristics
2. Neat Sample
3. Quantitative Microscopic Characteristics
4. Quantitative Morphology
5. Sample Collection Information

HOW TO MAP

Compared to the standard PK ADaM data sets, semen data do not quite fit into ADPC data set. Some parameters in semen data sets require averages or changes from baseline. Deriving parameters are not commonly done in a plasma concentration data sets. Additionally, semen analysis not only includes concentration information, but also includes other types of information, such as physical characteristics, thus it makes more sense to consider semen ADaM data set as a customized data. Accordingly, ADZS for semen data set name is suggested. To generate ADZS, there are two steps. First, starting from clinical semen data set, SDTM ZS data set is created. ZS data set is a customized SDTM data set which contains semen information in this study. Second, based on the protocol and statistical analysis plan, ADaM ADZS data set can be created. ADZS data set is similar to safety ADaM data set, such as ADEG data set, because some analysis of semen tests are required to calculate the change from baseline information which is often seen in safety ADaM data set, but not in ADPC and ADPP data sets. Furthermore, ADZS may include concentration information and volume information which is usually used in ADPC data set. All semen tests are implemented in the data set as parameters. All change from baseline information can be calculated as needed and the baselines need to be marked with baseline flags in ADaM ADZS data set.

Unique Subject Identifier	Analysis Visit	Parameter	Parameter Code	Parameter Category 2	Analysis Value	Analysis V...	Baseline Value	Baseline Value (C)	Change fr...	Baseline R
BigPharma-001-0002-0006	DAY-2	Dilution	DILUTN	NEAT SAMPLE	2/2		2/2			Y
BigPharma-001-0002-0007	DAY-2	Dilution	DILUTN	NEAT SAMPLE	0/0		0/0			Y
BigPharma-001-0002-0008	DAY-2	Dilution	DILUTN	NEAT SAMPLE	0/0		0/0			Y
BigPharma-001-0002-0009	DAY-2	Dilution	DILUTN	NEAT SAMPLE	0/0		0/0			Y
BigPharma-001-0002-0010	DAY-2	Dilution	DILUTN	NEAT SAMPLE	2/2		2/2			Y
BigPharma-001-0002-0011	DAY-2	Dilution	DILUTN	NEAT SAMPLE	0/0		0/0			Y
BigPharma-001-0002-0012	DAY-2	Dilution	DILUTN	NEAT SAMPLE	0/0		0/0			Y
BigPharma-001-0002-0013	DAY-2	Dilution	DILUTN	NEAT SAMPLE	0/0		0/0			Y
BigPharma-001-0002-0014	DAY-2	Dilution	DILUTN	NEAT SAMPLE	0/0		0/0			Y
BigPharma-001-0002-0015	DAY-2	Dilution	DILUTN	NEAT SAMPLE	0/0		0/0			Y
BigPharma-001-0002-0017	DAY-2	Dilution	DILUTN	NEAT SAMPLE	2/2		2/2			Y
BigPharma-001-0002-0018	DAY-2	Dilution	DILUTN	NEAT SAMPLE	0/0		0/0			Y
BigPharma-001-0002-0001	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	90/90		90/90			Y
BigPharma-001-0002-0002	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	94/94		94/94			Y
BigPharma-001-0002-0003	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	91/91		91/91			Y
BigPharma-001-0002-0004	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	99/99		99/99			Y
BigPharma-001-0002-0005	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	92/92		92/92			Y
BigPharma-001-0002-0006	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	95/95		95/95			Y
BigPharma-001-0002-0007	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	95/95		95/95			Y
BigPharma-001-0002-0008	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	94/94		94/94			Y
BigPharma-001-0002-0009	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	93/93		93/93			Y
BigPharma-001-0002-0010	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	95/95		95/95			Y
BigPharma-001-0002-0011	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	96/96		96/96			Y
BigPharma-001-0002-0012	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	94/94		94/94			Y
BigPharma-001-0002-0013	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	95/95		95/95			Y
BigPharma-001-0002-0014	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	94/94		94/94			Y
BigPharma-001-0002-0015	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	95/95		95/95			Y
BigPharma-001-0002-0017	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	97/97		97/97			Y
BigPharma-001-0002-0018	DAY-2	Forward Progress (Heartland)	PROGRESS	QUANT. MICROSCOPIC CHARACTERISTICS	99/99		99/99			Y
BigPharma-001-0002-0001	DAY-2	Forward Progress (WHO)	PROGWHO	QUANT. MICROSCOPIC CHARACTERISTICS	55/55		55/55			Y
BigPharma-001-0002-0002	DAY-2	Forward Progress (WHO)	PROGWHO	QUANT. MICROSCOPIC CHARACTERISTICS	61/61		61/61			Y
BigPharma-001-0002-0003	DAY-2	Forward Progress (WHO)	PROGWHO	QUANT. MICROSCOPIC CHARACTERISTICS	60/60		60/60			Y
BigPharma-001-0002-0004	DAY-2	Forward Progress (WHO)	PROGWHO	QUANT. MICROSCOPIC CHARACTERISTICS	88/88		88/88			Y
BigPharma-001-0002-0005	DAY-2	Forward Progress (WHO)	PROGWHO	QUANT. MICROSCOPIC CHARACTERISTICS	63/63		63/63			Y
BigPharma-001-0002-0006	DAY-2	Forward Progress (WHO)	PROGWHO	QUANT. MICROSCOPIC CHARACTERISTICS	78/78		78/78			Y
BigPharma-001-0002-0007	DAY-2	Forward Progress (WHO)	PROGWHO	QUANT. MICROSCOPIC CHARACTERISTICS	67/67		67/67			Y
BigPharma-001-0002-0008	DAY-2	Forward Progress (WHO)	PROGWHO	QUANT. MICROSCOPIC CHARACTERISTICS	73/73		73/73			Y
BigPharma-001-0002-0009	DAY-2	Forward Progress (WHO)	PROGWHO	QUANT. MICROSCOPIC CHARACTERISTICS	63/63		63/63			Y
BigPharma-001-0002-0010	DAY-2	Forward Progress (WHO)	PROGWHO	QUANT. MICROSCOPIC CHARACTERISTICS	78/78		78/78			Y
BigPharma-001-0002-0011	DAY-2	Forward Progress (WHO)	PROGWHO	QUANT. MICROSCOPIC CHARACTERISTICS	91/91		91/91			Y
BigPharma-001-0002-0012	DAY-2	Forward Progress (WHO)	PROGWHO	QUANT. MICROSCOPIC CHARACTERISTICS	70/70		70/70			Y
BigPharma-001-0002-0013	DAY-2	Forward Progress (WHO)	PROGWHO	QUANT. MICROSCOPIC CHARACTERISTICS	90/90		90/90			Y
BigPharma-001-0002-0014	DAY-2	Forward Progress (WHO)	PROGWHO	QUANT. MICROSCOPIC CHARACTERISTICS	69/69		69/69			Y

Display 2: ADZS for Semen analysis (Only show part of data from dummy ADaM data set)

Another possible mapping approach is when some parameters are needed to be calculated from semen concentration and volume information by scientists. In this case, ADSC (ADaM semen concentration data set) and ADSP (ADaM semen concentration parameter data set) will be created. First, create SDTM SC semen concentration data set which includes semen concentration bioanalysis data set information and the relevant clinical information. Second, create ADaM ADSC data set based on SDTM SC data set. SC stands for semen concentration. Similarly, ADSC is the name of analysis data set for semen concentration. ADSC contains information such as semen concentration, semen volume, total sperm count and total motile count. A scientist will use the ADSC data set to calculate the parameters needed. Generally, time intervals are used in semen clinical data set instead of individual time points. While programming ADSC, merging clinical data set with semen bioanalytical data is challenging. The reason is that clinical data usually has individual time point. Usually, using endpoint of an interval is one way for data merging. Third, when the semen parameters are calculated based on ADSC data set by a scientist, SDTM SP data set can be created. Finally, ADSP, analysis data set for semen parameters, can be created using the SDTM SP data set.

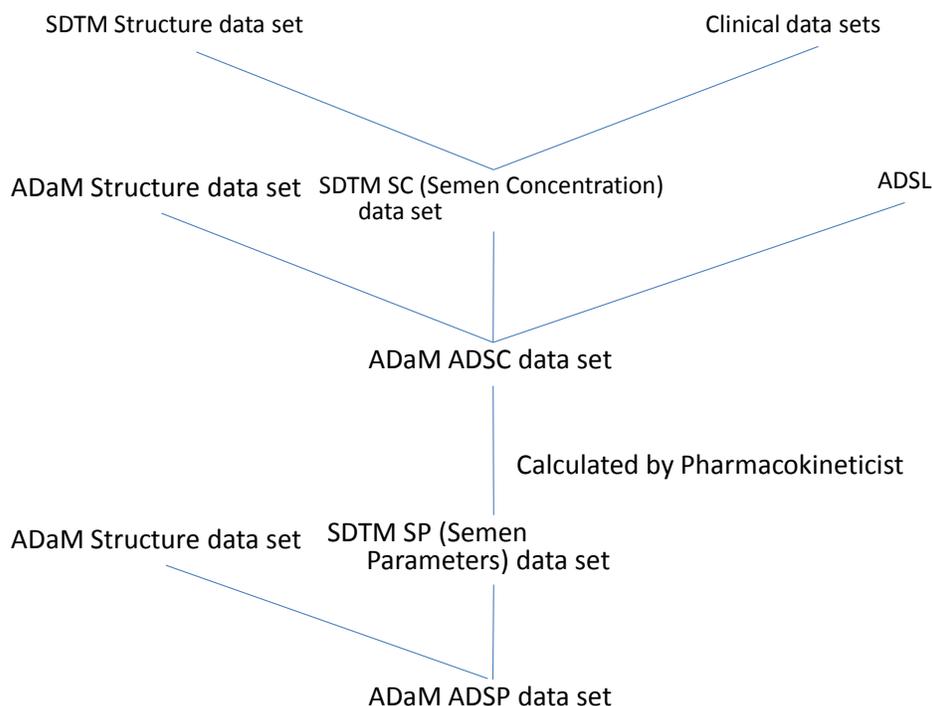


Figure 1: Process to get ADaM ADSP data set for Semen analysis study

ADAM DATA SET FOR URINE PHARMACOKINETIC ANALYSIS STUDY

BACKGROUND

Urine analysis includes Pharmacokinetics analysis and Pharmacodynamics analysis. The Urine Pharmacokinetic analysis is simple, but unique. A study with urine Pharmacokinetic analysis results is used as an example.

A SAMPLE LIST OF INFORMATION FOR ANALYSIS

1. Urine volume
2. Urine sample collection interval (Start time and end time)
3. Rate of drug excretion
4. Cumulative amount of drug excreted in urine
5. Renal clearance (or other parameters to support main Pharmacokinetic analysis)

HOW TO MAP

Different from Plasma Pharmacokinetics analysis, information needed for the ADaM urine Pharmacodynamics data set, such as volume, collection interval, derived rate of drug excretion, and cumulative drug excretion, is from the urine data set or can be calculated based on the urine data set. Based on the urine data set and urine concentration data set, SDTM UR data set can be created. According to analysis requirement, all the urine analysis parameters can be calculated. For example, rate of drug excretion is calculated by Cumulative amount of drug excreted in urine, which can be calculated by the concentration and the urine volume, during a certain time period divide by the duration of this time period. Then based on the SDTM UR data set and other PD information from other SDTM data set, the ADaM ADPD data set can be created. The urine analysis data set ADPD needs PD record level flags and population flags. Urine concentration, urine volume and the time interval could be included as a parameter in the ADPD data set for better understanding of the data set and for other analysis purpose. Adding flags for urine PD analysis is necessary, because urine analysis parameters may be handled separately from other PD parameters. Additionally, change from baseline information may be included as needed for the analysis.

Unique Subject Identifier	Actual Tre...	Analysis Visit	Parameter	Parameter Code	Analysis Value	Analysis Value (C)	PK Analys...	PK
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	16.02	16.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	-0.17	-0.17	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	1.02	1.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	2.02	2.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	3.02	3.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	4.02	4.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	5.02	5.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	6.02	6.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	7.02	7.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	8.02	8.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	10.02	10.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	12.02	12.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	16.02	16.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	-0.17	-0.17	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	1.02	1.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	2.02	2.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	3.02	3.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	4.02	4.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	5.02	5.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	6.02	6.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	7.02	7.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	8.02	8.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	10.02	10.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	12.02	12.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	16.02	16.02	Y	Y
BigPharma-001~0002~0011	P	DAY 5	Rate of Drug Excretion	EXC	24.02	24.02	Y	Y
BigPharma-001~0002~0001	P	DAY 5	Renal clearance	RCLC	1.02	1.02	Y	Y
BigPharma-001~0002~0001	P	DAY 5	Renal clearance	RCLC	2.02	2.02	Y	Y
BigPharma-001~0002~0001	P	DAY 5	Renal clearance	RCLC	3.02	3.02	Y	Y
BigPharma-001~0002~0001	P	DAY 5	Renal clearance	RCLC	4.02	4.02	Y	Y
BigPharma-001~0002~0001	P	DAY 5	Renal clearance	RCLC	5.02	5.02	Y	Y
BigPharma-001~0002~0001	P	DAY 5	Renal clearance	RCLC	6.02	6.02	Y	Y
BigPharma-001~0002~0001	P	DAY 5	Renal clearance	RCLC	7.02	7.02	Y	Y
BigPharma-001~0002~0001	P	DAY 5	Renal clearance	RCLC	8.02	8.02	Y	Y
BigPharma-001~0002~0001	P	DAY 5	Renal clearance	RCLC	10.02	10.02	Y	Y
BigPharma-001~0002~0001	P	DAY 5	Renal clearance	RCLC	12.02	12.02	Y	Y
BigPharma-001~0002~0001	P	DAY 5	Renal clearance	RCLC	16.02	16.02	Y	Y
BigPharma-001~0002~0001	P	DAY 5	Renal clearance	RCLC	24.02	24.02	Y	Y

Display 3: ADPD for Urine PD analysis (Only show part of data from dummy ADaM data set)

CONCLUSION

In general, non-standard PK/PD analysis data can be prepared two ways. In the first situation when analysis parameters can be easily calculated by a programmer, then the programmer creates the analysis data set. In the second situation when the scientist is involved in calculating the parameters, two analysis data sets will be created. One is the analysis data set for concentration and the other is the analysis data set for parameters.

Comparing with the Celerion standard ADaM PK approach, the approaches to ADaM data sets for Thorough QT study, reproductive safety study and Urine PD study are different and not detailed in the Analysis Data Model v2.1, but all of them can be successfully handled based on the similar definitions and the similar concepts. Additionally, based on these information and experience, other ADaM PK/PD approaches could be accomplished.

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