# Streamlining Regulatory Submission with CDISC/ADaM Standards for Non-standard Pharmacokinetic/Pharmacodynamic Analysis Datasets Xiaopeng Li, Katrina E. Canonizado, Chun Feng and Nancy Wang Celerion, 621 Rose Street, Lincoln, NE 68502

# 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 to perform the statistical analysis of the data. Quick turn-around time of Pharmacokinetic (PK) and Pharmacodynamic (PD) analyses is critical during the drug development process, because it is always desirable 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 provided 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 discussed<sup>1</sup>. 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.

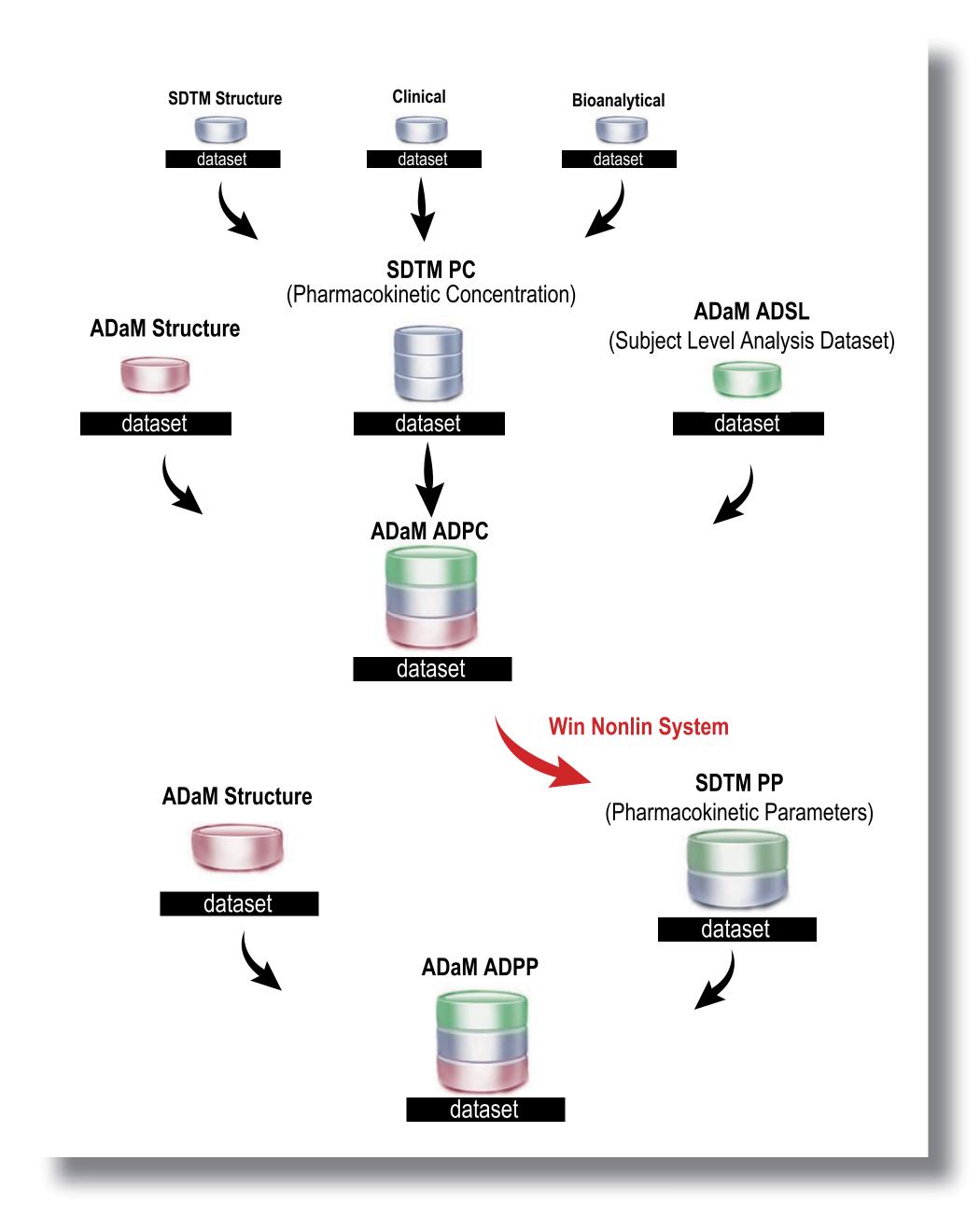


Figure 1: Celerion standard process of creating an ADaM data set for PK analysis

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 and statistical comparison of difference between treatments. However, some studies require more complex and more involved PK/PD analyses. The following section shares efficient approaches for building ADaM data sets for PK/PD analysis in the situations that go beyond the Celerion standard process.

# STUDY

## Background

Thorough QT (TQT) study is often required in the early stages of clinical development for many drugs<sup>2</sup>. Generally, the data for TQT 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, The way to handle ADaM TQT data set for cardiac analysis (ADPD or customized ADaM parameter data set for TQT ADZP) is different from the way to handle ADaM safety ECG data set (ADEG). Creating a separate ADaM data set 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

- 6. Delta T-Wave Amplitude

## How to map

To create an ADaM data set, there are two different approaches based on the aforementioned requirements.

- The first approach: 1. Create SDTM EG data set.
- purpose.



# **ADAM DATA SET FOR THOROUGH QT**

2. Delta Summary (mean) Heart Rate 3. Delta Summary (mean) PR Rate 4. Delta Summary (mean) QRS Duration 5. Delta Summary (mean) RR Duration 7. Delta T-Wave Complexity

2. Create ADaM ADPD data set based on SDTM EG data set (calculations for analysis parameters will be performed, such as the time-to-time matched change from baseline for QTcF values). • Another possible mapping approach:

1. All the ECG information from the clinic collected in ECG data set is mapped to SDTM EG data set. 2. Based on the information from SDTM EG data set, an ADaM data set (ADZC, a customized ADaM data set) is created for scientists to perform the parameters calculation. Multiple observations from SDTM EG data set will be calculated as mean, median, maximum or minimum for analysis

3. Analysis parameters will be calculated by scientists based on ADZC data set.

4. Based on the information of analysis parameters provided by scientists, create SDTM ZP data set. 5. ADZP, the customized ADaM parameter data set for TQT study, is created for further analysis usage.

Display 1: Partial dummy data of ADPD for Thorough QT analysis

Unique Subject Identifier	avisit	Actual Tr	Parameter	Parameter Code	Analysis Value	Analysis Value (C)	Analysis Unit	Complete	PK Analysis Record-Level Flag	PKAnaly
igPharma-001~0002~0001	DAY 1	A	Delta QTcB - Bazett's Correction Formula	D_QTCB	1	1	msec	Y	Y	Y
iqPharma-001~0002~0001	DAY 1	A	Delta QTcF - Fridericia's Correction For	D_QTCF	0	0	msec	γ	Y	Y
igPharma-001~0002~0001	DAY 1	A	Delta Summary (Mean) Heart Rate	D_HRMEAN	1	1	BEATS/MIN	Y	Y	Y
igPharma-001~0002~0001	DAY 1	A		D_PRMEAN	5.2	5.2	msec	Y	Y	Y
igPharma-001~0002~0001	DAY 1	A	Delta Summary (Mean) QRS Duration	D_QRSDUR	1.5	1.5	msec	Y	Y	Y
igPharma-001~0002~0001	DAY 1	A	Delta Summary (Mean) QT Duration	D_QTMEAN	-2	-2	msec	γ	Y	Y
igPharma-001~0002~0001	DAY 1	A	Delta Summary (Mean) RR Duration	D_RRMEAN	-14	-14	msec	Y	Y	Y
igPharma-001~0002~0001	DAY 1	A	Delta T-Wave Amplitude	D_TAMP	65.4	65.4	msec	Y	Y	Y
igPharma-001~0002~0001	DAY 1	A	Delta T-Wave Complexity	D_TCOMP	0	0	msec	Y	Y	Y
igPharma-001~0002~0001	DAY 1	A		QTCB	391		msec	Y	Y	Y
igPharma-001~0002~0001	DAY 1	A		QTCF	389		<u>msec</u>	Y	Y	Y
igPharma-001~0002~0001	DAY 1			HRMEAN	62		msec S/MIN	Y	Y	Y
igPharma-001~0002~0001	DAY 1			PRMEAN	155.5		msec	•	Y	Y
igPharma-001~0002~0001	DAY 1			QRSDUR	79.5		msec	Y	Y	Y
igPharma-001~0002~0001	DAY 1			QTMEAN	384		msec	-	Y	Υ
igPharma-001~0002~0001	DAY 1		· · · · ·	RRMEAN	964		msec	Y	Y	Y
igPharma-001~0002~0001	DAY 1	A	T-Wave Amplitude	TAMP	296.2	296.2	msec	Υ	Y	Y
igPharma-001~0002~0001	DAY 1		T-Wave Complexity	TCOMP	1		msec	•	Y	Y
igPharma-001~0002~0001	DAY 1			D_QTCB	3		msec	-	Y	Υ
igPharma-001~0002~0001	DAY 1			D_QTCF	-2		msec	Υ	Y	Υ
igPharma-001~0002~0001	DAY 1			D_HRMEAN	5		BEATS/MIN	Υ	Y	Υ
igPharma-001~0002~0001	DAY 1			D_PRMEAN	9.5		msec	Υ	Υ	Υ
igPharma-001~0002~0001	DAY 1			D_QRSDUR	1.7		msec	Υ	Y	Υ
igPharma-001~0002~0001	DAY 1			D_QTMEAN	-9.9		msec	•	Υ	Υ
igPharma-001~0002~0001	DAY 1			D_RRMEAN	-68			•	Y	Υ
igPharma-001~0002~0001	DAY 1			D_TAMP	43.3				Υ	Y
igPharma-001~0002~0001	DAY 1	A		D_TCOMP	0			•	Y	Υ
igPharma-001~0002~0001	DAY 1	A		QTCB	392		msec	Y	Y	Υ
igPharma-001~0002~0001	DAY 1			QTCF	388		msec	Υ	Y	Υ
igPharma-001~0002~0001	DAY 1			HRMEAN	64				Υ	Y
igPharma-001~0002~0001	DAY 1	A		PRMEAN	156			•	Y	Υ
igPharma-001~0002~0001	DAY 1			QRSDUR	79.5		msec	1	Y	Υ
igPharma-001~0002~0001	DAY 1			QTMEAN	381.3		msec	•	Y	Y
igPharma-001~0002~0001	DAY 1		· · · ·	RRMEAN	945		msec	•	Y	Y
igPharma-001~0002~0001	DAY 1	A		TAMP	273.8			•	Υ	Υ
igPharma-001~0002~0001	DAY 1	A	T-Wave Complexity	TCOMP	1	· .	msec	•	Υ	Υ
igPharma-001~0002~0001	DAY 1			D_QTCB	1		msec	Y	Y	Y
igPharma-001~0002~0001	DAY 1			D_QTCF	3		msec	Y	Y	Y
igPharma-001~0002~0001	DAY 1			D_HRMEAN	-1		BEATS/MIN	•	Y	Y
igPharma-001~0002~0001	DAY 1			D_PRMEAN	2.7		msec	Y	Y	Y
igPharma-001~0002~0001	DAY 1				1.1		msec	Y	Y	Y
igPharma-001~0002~0001	DAY 1		Delta Summary (Mean) QT Duration	D_QTMEAN	· · ·		msec	•	Y	Y
igPharma-001~0002~0001	DAY 1	A		D_RRMEAN	14		msec	Y	Y	Y
awaarma 1011 .0007 .0001	111AV 1	10	U LOITO L VAIOVO APOPUTURIO		66	LE K	meat	~ .	~	I V

Special attention is needed in 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.

## 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.** Forward progress 2. Dilution
- 3. Color
- 4. Motility
- 5. Total Sperm Count 6. Volume

## How to map

requirements.

- The first approach:
  - 1. 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.
- 2. Create ADaM ADZS data set based on the protocol and statistical analysis plan. ADZS data set could include
- Display 2: Partial dummy data of ADZS for Semen analysis

- semen concentration - semen volume
- total sperm count
- total motile count
- Time intervals (merging clinical data set with semen bioanalytical data)

Figure 2: Process to get ADaM ADSP data set for semen analysis study

# **ADAM DATA SET FOR REPRODUCTIVE** SAFETY STUDY

To create an ADaM data set, there are two different approaches based on the aforementioned

- Baseline value
- Change from baseline
- Change from baseline flag

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				NEAT SAMPLE	2		2 2		Y
BigPharma-001~0002~0007				NEAT SAMPLE	0		0		Y
BigPharma-001~0002~0008		Dilution		NEAT SAMPLE	0		0 0		Y
BigPharma-001~0002~0009				NEAT SAMPLE	0		0 0		.Υ
BigPharma-001~0002~0010				NEAT SAMPLE	2		2 2		Y
BigPharma-001~0002~0011		Dilution		NEAT SAMPLE	0		0 0		Y
BigPharma-001~0002~0012				NEAT SAMPLE	0		0 0		.Y
BigPharma-001~0002~0013				NEAT SAMPLE	0		0 0		Y
BigPharma-001~0002~0014				NEAT SAMPLE	0		0 0		.Y
BigPharma-001~0002~0015				NEAT SAMPLE	0		0 0		.Y
BigPharma-001~0002~0017				NEAT SAMPLE	2		2 2		Y
BigPharma-001~0002~0018				NEAT SAMPLE	0		0 0		.Y
BigPharma-001~0002~0001				QUANT. MICROSCOPIC CHARACTERISTICS	90		90 90	· · ·	.Y
BigPharma-001~0002~0002				QUANT. MICROSCOPIC CHARACTERISTICS	94		94 94	· · ·	.Y
BigPharma-001~0002~0003				QUANT. MICROSCOPIC CHARACTERISTICS	91		91 91		.Y
BigPharma-001~0002~0004				QUANT. MICROSCOPIC CHARACTERISTICS	99		99 99	· · ·	.Y
BigPharma-001~0002~0005				QUANT. MICROSCOPIC CHARACTERISTICS	92		92 92		Y
BigPharma-001~0002~0006				QUANT. MICROSCOPIC CHARACTERISTICS	95		95 95		.Y
BigPharma-001~0002~0007				QUANT. MICROSCOPIC CHARACTERISTICS	95		95 95		Y
BigPharma-001~0002~0008				QUANT. MICROSCOPIC CHARACTERISTICS	94		94 94		Y
BigPharma-001~0002~0009				QUANT. MICROSCOPIC CHARACTERISTICS	93		93 93		.Y
BigPharma-001~0002~0010				QUANT. MICROSCOPIC CHARACTERISTICS	95		95 95		Y
BigPharma-001~0002~0011				QUANT. MICROSCOPIC CHARACTERISTICS	96		96 96		.Y
BigPharma-001~0002~0012				QUANT. MICROSCOPIC CHARACTERISTICS	94		94 94		.Y
BigPharma-001~0002~0013				QUANT. MICROSCOPIC CHARACTERISTICS	95		95 95		Y
BigPharma-001~0002~0014				QUANT. MICROSCOPIC CHARACTERISTICS	94		94 94		.Y
BigPharma-001~0002~0015				QUANT. MICROSCOPIC CHARACTERISTICS	95		95 95		Y
BigPharma-001~0002~0017				QUANT, MICROSCOPIC CHARACTERISTICS	97		97 97		Y
BigPharma-001~0002~0018				QUANT. MICROSCOPIC CHARACTERISTICS	99		99 99		Y
BigPharma-001~0002~0001				QUANT. MICROSCOPIC CHARACTERISTICS	55		55 55		.Y
BigPharma-001~0002~0002				QUANT, MICROSCOPIC CHARACTERISTICS	61		61 61		.Y
BigPharma-001~0002~0003				QUANT. MICROSCOPIC CHARACTERISTICS	60		60 60		Y
BigPharma-001~0002~0004				QUANT. MICROSCOPIC CHARACTERISTICS	88		88 88		.Y
BigPharma-001~0002~0005				QUANT. MICROSCOPIC CHARACTERISTICS	63		63 63		.Y
BigPharma-001~0002~0006				QUANT. MICROSCOPIC CHARACTERISTICS	78		78 78		Y
BigPharma-001~0002~0007				QUANT, MICROSCOPIC CHARACTERISTICS	67		67 67		Y
BigPharma-001~0002~0008				QUANT. MICROSCOPIC CHARACTERISTICS	73		73 73		.Y
BigPharma-001~0002~0009				QUANT. MICROSCOPIC CHARACTERISTICS	63		63 63		.Y
BigPharma-001~0002~0010				QUANT. MICROSCOPIC CHARACTERISTICS	78		78 78		<u>Y</u>
BigPharma-001~0002~0011				QUANT. MICROSCOPIC CHARACTERISTICS	81		81 81		Y
BigPharma-001~0002~0012				QUANT. MICROSCOPIC CHARACTERISTICS	70		70 70		Y
BigPharma-001~0002~0013		Forward Progress (WHO)	PROGWHO	QUANT. MICROSCOPIC CHARACTERISTICS	80		80 80		.Y
RinPharma-001~0007~0014	IDAY-2	Fonward Progress (M(HO)	IPROGWHO	QUANT MICROSCOPIC CHARACTERISTICS	ନସ	คด	ี ธุรุโคร	I	lY .

- How to map

Different from plasma PK analysis, information needed for ADaM urine PD data set, such as volume, collection interval, derived rate of drug excretion, and cumulative drug excretion, is from urine data set or can be calculated based on urine data set. The mapping approach to ADaM urine PK data set

1. Based on the urine data set and urine concentration data set, SDTM UR data set can be created. 2. Based on the SDTM UR data set and other PD information from other SDTM data set, the ADaM ADPD data set can be created. Urine analysis parameters may include:

• 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 data set) and ADSP (ADaM semen concentration parameter data set) will be created.

1. Create SDTM SC semen concentration data set which includes semen concentration bioanalysis data set information and other relevant clinical information.

2. 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.

3. SDTM SP data set can be created when the semen parameters are calculated based on ADSC data set by a scientist.

4. ADSP, ADaM data set for semen analysis parameters, can be created using the SDTM SP data set.

Clinical data sets	accomplished.		
Concentration) ADSL	REFER		
	1 Xie, Y., Chai, I American Associ		
C data set	2 International C Prolongation and		
Calculated by scientists	ich.org		
en analysis data set			
	Clinical data sets Concentration) ADSL data set Calculated by scientists n analysis		





# Celerion

# **ADAM DATA SET FOR URINE** PHARMACOKINETIC ANALYSIS STUDY

## Background

Urine analysis includes PK analysis and PD analysis. Urine PK analysis is simple, but unique. A study with urine PK 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)

- collection interval
- derived rate of drug excretion
- cumulative drug excretion
- rate of drug excretion
- Urine concentration
- urine volume
- time interval

Additionally, baseline flags and values may be included.

### Display 3: Partial dummy data ADPD for Urine PD analysis

Unique Subject Identifier	Actual Tre	Analysis Visit	Parameter	Parameter Code	Analysis Value	Analysis Value (C)	PK Analys	Pł
	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 ~001 1	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 ~001 1	P	DAY 5	Rate of Drug Excretion	EXC	12.02	12.02	Y	Y
BigPharma-001 ~0002 ~001 1	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	Υ
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	<b>1</b> 6.02	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	Υ
BigPharma-001 ~0002 ~0001	P	DAY 5	Renal clearance	RCLC		6.02	Y	Y

## 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 merged raw data 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 PK study are different and not detailed in the Analysis Data Model v2.1, but can be successfully handled based on the similar definitions and the similar concepts. Additionally, with the information and experience, other ADaM PK/PD approaches could be

# ERENCE

Chai, P., Kirby S., Wang N.. 2011. "Pharmacokinetic Data Submission in the CDISC Environment." Association of Pharmaceutical Scientists onal Conference on Harmonisation. "Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval on and Proarrhythmic Potential for Non-Antiarrhythmic Drugs." October 2005. Available at http://www.

# www.celerion.com