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ADME Study PK SDTM/ADaM And Graph

Fan Lin, Gilead Sciences, Inc.

ABSTRACT

ADME (Absorption, Distribution, Metabolism and Excretion) study is usually conducted in early clinical drug development stage to understand the route of drug excretion and its metabolites in human body. It measures the concentrations of the parent/metabolite(s) and determines the amount of radioactivity in plasma, urine and feces (Gerlie Gieser, Investigators Forum 2012). Due to the sample species involving urine/feces and subjects being discharged at different times the complexities of creating CDISC compiled SDTM and ADAM datasets are increased compared to other PK studies. In this paper we will introduce the complexities of ADME PK study and our approaches to resolve these challenges. This paper demonstrates the process of ADME study PKMERGE/PC/ADPC/TF in a flow chart, and then describes the details in each step, followed by a list of challenges existing in current industry. Other challenges also include deriving last record carried forward over for early discharge subjects to maximum discharge visit in the dataset and how to represent this in cumulative graph. This paper provides the detailed steps of resolving each challenges to create CDISC complied data modules and analysis presentations. Referring other industry white paper [1] our process meets industry standard and provides high quality visual plot by utilizing the most powerful SAS graphic template language.

INTRODUCTION

Early Phase studies investigate the safety and tolerability of Pharmacokinetics (PK) and Pharmacodynamics (PD) of investigational drugs in healthy subjects. Different categories of study designs are facilitated to achieve this goal. ADME (mass balance, ^{14}C-labeled) is generally conducted in early phase to investigate recovery of administered ^{14}C-labeled compound from urine and feces. ADME study design is a single dose administered radiolabeled investigational drug in 6 or 8 healthy male patients. The subjects maybe discharged early depending when they met discharge criteria. At the maximum clinical confinement all subjects will be discharged regardless of criterion met or not. Thus generating CDISC compliant datasets of PC/ADPC with imputation methods and developing mean (SD) cumulative excretion plot to elucidate the routes become necessary.

WORK FLOW AND CHALLENGES IN ADME PK STUDY

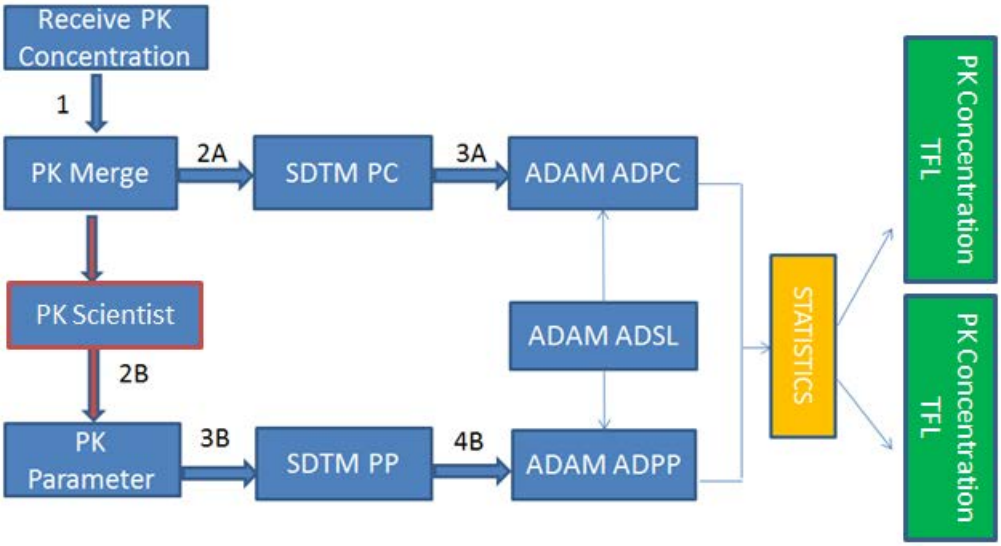

Figure 1 Scheme of the Process

The process work flow as described in above Figure 1 can be summarized as following:

1) PK concentration-time profiles are received from Bioanalytical Lab.
2) PKMERGE is created using actual sample collection date/time and demographic information from CRF and concentration data from BA lab for plasma, whole blood, urine and feces.
3) PKMERGE is used for PK parameter generation by clinical pharmacology group and also as a source for creation of SDTM PC.
4) PK parameters are calculated using specific software for non-compartmental analysis, such as SAS or WinNonlin and used as source for SDTM PP dataset.
5) ADSL is updated to contain the PK population flag variables.
6) ADPC and ADPP datasets are generated by following ADaM IG.
7) PK concentration TFLs are generated from ADPC and PK parameter outputs are generated from ADPP [1].

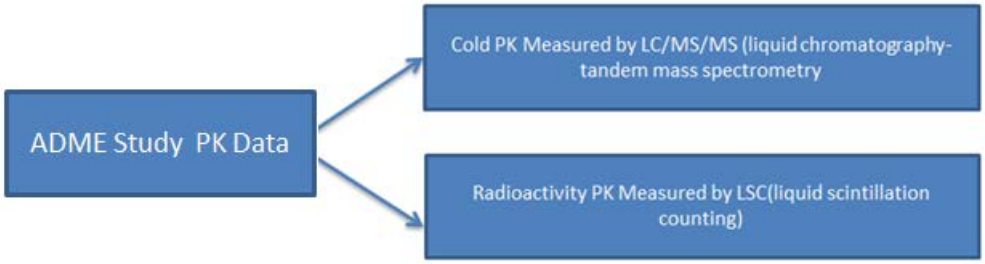

Figure 2 Components of ADME Study PK Data

In ADME study PK data contains two parts as shown in above Figure 2: regular cold PK and radio activity PK. Compared to regular PK study which only includes cold PK, the radio activity PK brings more complexities:

1) The sample species involve urine and feces which have interval time points. The sum of urine and feces species was required in analysis.

2) PK tests include amount of excrete, cumulative amount of excrete, percent of dose administration, cumulative percent of dose administration. These tests require derived records to carry over the last available result.

3) CRF data does not collect cumulative time points.

Our solutions to these challenges are:

- Derived DTYPE=SUM to add urine and feces for all intervals. Urine collection interval has a start and end time, the end time is more accurate to planned time point, the scheduled/deviation time is calculated by end collection time.
- Because some subjects were discharged early the cumulative concentration should be carried to last time point. The LOCF imputation technique was applied. This brought challenge to the cumulative figure since on the plot the LOCF values were displayed and at the bottom the number of subjects displayed was actual number remained at the time point. The challenge will be discussed at the figure section.
- Since CRF did not collect cumulative time points, time points from 0 to each end time point were derived in order to merge with PK concentration cumulative test results.

We will elaborate the steps of the process flow chart from Figure 1 and describe solutions of the challenges in following sections.

STEP 1 (CREATION OF PKMERGE):

In this step, individual concentration-time profiles are reviewed and pkmerge is created. PKMERGE is not only served as rawdata to sdtm.PC, but also the source file provided to PK scientist for generating PK parameters. Figure 3 shows urine collection start and end date/time. URENTIM is the end time column which is more accurate to planned time point. Actual scheduled end times (SCHENTMC) are calculated; derivation end times (ENDEV) between actual and scheduled are also calculated.

URSTDAT_RAW	URENDAT_RAW	URSTTIM	URENTIM	URTPT
11 OCT 2017	12 OCT 2017	20:10	08:11	Predose
12 OCT 2017	12 OCT 2017	11:03	12:10	0-4.0 h postdose
12 OCT 2017	12 OCT 2017	13:49	16:10	4.0-8.0 h postdose
12 OCT 2017	12 OCT 2017	18:20	20:11	8.0-12.0 h postdose
12 OCT 2017	13 OCT 2017	22:07	08:10	12.0-24.0 h postdose
13 OCT 2017	13 OCT 2017	12:28	20:10	24.0-36.0 h postdose
13 OCT 2017	14 OCT 2017	23:09	08:10	36.0-48.0 h postdose
14 OCT 2017	15 OCT 2017	12:43	08:10	48.0-72.0 h postdose
15 OCT 2017	16 OCT 2017	12:32	08:11	72.0-96.0 h postdose
16 OCT 2017	17 OCT 2017	12:26	08:10	96.0-120.0 h postdose

Figure 3 Urine Collection Time Points and End Time

STEP 2 (CREATION OF SDTM DATASET):

The SAS dataset PKMERGE will be used as source for PK parameter generation and to create SDTM.PC. PC domain contains typically one record per analyte per planned time point per time point reference per visit per subject. The important columns in PC, such as PCSPEC, PCTEST, PCTESTCD, PCDTC, PCORRES and PCSTRESC etc. are shown in Table 1 Important Variable in SDTM PC/PP. (Dr.Peter Schaefer www.phusewiki.org/docs/posters2013CSS/pp02.pdf).

The PK parameter file will be used to generate SDTM.PP. PP domain contains one record per PK parameter per time-concentration profile per modeling per method per subject. The PK parameter is specified by variables of PPTESTCD and PPTEST; the calculated values are stored in the result variables of PPORES, PPSTRESC and PPSTRESN. The important PP variables are also shown in Table 1. The reference time that references the dosing, PPRFTDTC and PCRFTDTC are the relation variables between the two datasets [2].

Important Variables in PC Domain		Important Variables in PP Domain	
PCSPEC	Containing Specimen		
PCTESTCD	Test Code	PPTESTCD	Test Code
PCTEST	Test Name	PPTEST	Test Name
VISIT	Visit		
VISITNUM	Visit Number		
PCDTC	Date/Time Specimen Collection		
PCENDTC	End Date/Time Specimen Collection		
PCTPTREF	Reference Time Point to Dosing		
PCRFTDTC	Reference Time Point Date/Time	PPRFTDTC	Reference Time Point Date/Time
PCORRES	Original Result	PPORRES	Original Result
PCSTRESC	Standard Character Result	PPSTRESC	Standard Character Result
PCSTRESN	Standard Numeric Result	PPSTRESN	Standard Numeric Result

Table 1 Important Variable in SDTM PC/PP

STEP 3 (CREATION OF ADAM DATASET):

ADaM ADPC and ADPP are the next steps to build by following ADaM IG after creation of SDTM.PP and PC. In ADPC we derived three DTYPE: 1) DTYPE=LOCF. In step1 we mentioned that one of complexity in ADME PK study is the early discharge subjects who were required to have values at the protocol defined last time point in cumulative test. Thus the last observation carried forward (LOCF) was applied on those subjects. Figure 4 shows cumulative percent of dose administration (CUMUPERC) in feces at each time interval from 0-24 hour to 0-504 for one subject. This subject met discharge criterion on Day 13 and discharged on Day 14, so from Day 14 through Day 22 there was no feces sample available which was noted in SAMPCOM variable. However the maximum clinical confinement for this study is up to Day 22. LOCF was performed after Day 13, the last available value 93.5 was carried over from Day 13 to Day 22 and DTYPE=LOCF was given. The similar imputation was applied to urine species where the last available value 4.46 was carried over from Day 13 to Day 22 as shown in Figure 5.

PARAMCD	AVAL	AVALC	PCSTRESC	VISITNUM	VISIT	AVISIT	AVISITN	DTYPE	ATPT	ATPTN	EXDOSDTM	EXACTDT	PCSPEC	SAMPCOM	ANL01FL
CUMUPERC	0	0.00	0.00	2	Day 2	Day 2	2		0 to 24 hr post-dose	24	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	13.9	13.9	13.9	3	Day 3	Day 3	3		0 to 48 hr post-dose	48	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	27.6	27.6	27.6	4	Day 4	Day 4	4		0 to 72 hr post-dose	72	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	58.2	58.2	58.2	5	Day 5	Day 5	5		0 to 96 hr post-dose	96	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	77.5	77.5	77.5	6	Day 6	Day 6	6		0 to 120 hr post-dose	120	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	82	82.0	82.0	7	Day 7	Day 7	7		0 to 144 hr post-dose	144	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	85.9	85.9	85.9	8	Day 8	Day 8	8		0 to 168 hr post-dose	168	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	90.4	90.4	90.4	9	Day 9	Day 9	9		0 to 192 hr post-dose	192	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	92.1	92.1	92.1	10	Day 10	Day 10	10		0 to 216 hr post-dose	216	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	93	93.0	93.0	11	Day 11	Day 11	11		0 to 240 hr post-dose	240	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	93.4	93.4	93.4	12	Day 12	Day 12	12		0 to 264 hr post-dose	264	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	93.5	93.5	93.5	13	Day 13	Day 13	13		0 to 288 hr post-dose	288	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC		N.S.	N.S.	14	Day 14	Day 14	14		0 to 312 hr post-dose	312	12OCT17:08:30:00	12OCT2017	FECES	No sampl...	
CUMUPERC		N.S.	N.S.	15	Day 15	Day 15	15		0 to 336 hr post-dose	336	12OCT17:08:30:00	12OCT2017	FECES	No sampl...	
CUMUPERC		N.S.	N.S.	16	Day 16	Day 16	16		0 to 360 hr post-dose	360	12OCT17:08:30:00	12OCT2017	FECES	No sampl...	
CUMUPERC		N.S.	N.S.	17	Day 17	Day 17	17		0 to 384 hr post-dose	384	12OCT17:08:30:00	12OCT2017	FECES	No sampl...	
CUMUPERC		N.S.	N.S.	18	Day 18	Day 18	18		0 to 408 hr post-dose	408	12OCT17:08:30:00	12OCT2017	FECES	No sampl...	
CUMUPERC		N.S.	N.S.	19	Day 19	Day 19	19		0 to 432 hr post-dose	432	12OCT17:08:30:00	12OCT2017	FECES	No sampl...	
CUMUPERC		N.S.	N.S.	20	Day 20	Day 20	20		0 to 456 hr post-dose	456	12OCT17:08:30:00	12OCT2017	FECES	No sampl...	
CUMUPERC		N.S.	N.S.	21	Day 21	Day 21	21		0 to 480 hr post-dose	480	12OCT17:08:30:00	12OCT2017	FECES	No sampl...	
CUMUPERC		N.S.	N.S.	22	Discharge/Day 22	Discharge/Day 22	22		0 to 504 hr post-dose	504	12OCT17:08:30:00	12OCT2017	FECES	No sampl...	
CUMUPERC	93.5	93.5	N.S.	14	Day 14	Day 14	14	LOCF	0 to 312 hr post-dose	312	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	93.5	93.5	N.S.	15	Day 15	Day 15	15	LOCF	0 to 336 hr post-dose	336	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	93.5	93.5	N.S.	16	Day 16	Day 16	16	LOCF	0 to 360 hr post-dose	360	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	93.5	93.5	N.S.	17	Day 17	Day 17	17	LOCF	0 to 384 hr post-dose	384	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	93.5	93.5	N.S.	18	Day 18	Day 18	18	LOCF	0 to 408 hr post-dose	408	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	93.5	93.5	N.S.	19	Day 19	Day 19	19	LOCF	0 to 432 hr post-dose	432	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	93.5	93.5	N.S.	20	Day 20	Day 20	20	LOCF	0 to 456 hr post-dose	456	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	93.5	93.5	N.S.	21	Day 21	Day 21	21	LOCF	0 to 480 hr post-dose	480	12OCT17:08:30:00	12OCT2017	FECES		Y
CUMUPERC	93.5	93.5	N.S.	22	Discharge/Day 22	Discharge/Day 22	22	LOCF	0 to 504 hr post-dose	504	12OCT17:08:30:00	12OCT2017	FECES		Y

Figure 4 ADPC in FECES DTYPE=LOCF

PARAMCD	AVAL	AVALC	PCSTRESC	VISITNUM	VISIT	AVISIT	AVISITN	DTYPE	ATPT	ATPTN	EXDOSDTM	EXACTDT	PCSPEC	SAMPCOM	ANL01FL
CUMUPERC	0.756	0.756	0.756	1	Day 1	Day 1	1		0 to 4 hr post-dose	4	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	1.25	1.25	1.25	1	Day 1	Day 1	1		0 to 8 hr post-dose	8	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	1.46	1.46	1.46	1	Day 1	Day 1	1		0 to 12 hr post-dose	12	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	1.71	1.71	1.71	2	Day 2	Day 2	2		0 to 24 hr post-dose	24	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	1.99	1.99	1.99	2	Day 2	Day 2	2		0 to 36 hr post-dose	36	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	2.27	2.27	2.27	3	Day 3	Day 3	3		0 to 48 hr post-dose	48	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	2.88	2.88	2.88	4	Day 4	Day 4	4		0 to 72 hr post-dose	72	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	3.43	3.43	3.43	5	Day 5	Day 5	5		0 to 96 hr post-dose	96	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	3.88	3.88	3.88	6	Day 6	Day 6	6		0 to 120 hr post-dose	120	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	4.14	4.14	4.14	7	Day 7	Day 7	7		0 to 144 hr post-dose	144	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	4.35	4.35	4.35	8	Day 8	Day 8	8		0 to 168 hr post-dose	168	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	4.46	4.46	4.46	9	Day 9	Day 9	9		0 to 192 hr post-dose	192	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	4.46	4.46	4.46	10	Day 10	Day 10	10		0 to 216 hr post-dose	216	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	4.46	4.46	4.46	11	Day 11	Day 11	11		0 to 240 hr post-dose	240	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	4.46	4.46	4.46	12	Day 12	Day 12	12		0 to 264 hr post-dose	264	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	4.46	4.46	4.46	13	Day 13	Day 13	13		0 to 288 hr post-dose	288	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC		N.S.	N.S.	14	Day 14	Day 14	14		0 to 312 hr post-dose	312	12OCT17:08:30:00	12OCT2017	URINE	No sampl...	
CUMUPERC		N.S.	N.S.	15	Day 15	Day 15	15		0 to 336 hr post-dose	336	12OCT17:08:30:00	12OCT2017	URINE	No sampl...	
CUMUPERC		N.S.	N.S.	16	Day 16	Day 16	16		0 to 360 hr post-dose	360	12OCT17:08:30:00	12OCT2017	URINE	No sampl...	
CUMUPERC		N.S.	N.S.	17	Day 17	Day 17	17		0 to 384 hr post-dose	384	12OCT17:08:30:00	12OCT2017	URINE	No sampl...	
CUMUPERC		N.S.	N.S.	18	Day 18	Day 18	18		0 to 408 hr post-dose	408	12OCT17:08:30:00	12OCT2017	URINE	No sampl...	
CUMUPERC		N.S.	N.S.	19	Day 19	Day 19	19		0 to 432 hr post-dose	432	12OCT17:08:30:00	12OCT2017	URINE	No sampl...	
CUMUPERC		N.S.	N.S.	20	Day 20	Day 20	20		0 to 456 hr post-dose	456	12OCT17:08:30:00	12OCT2017	URINE	No sampl...	
CUMUPERC		N.S.	N.S.	21	Day 21	Day 21	21		0 to 480 hr post-dose	480	12OCT17:08:30:00	12OCT2017	URINE	No sampl...	
CUMUPERC		N.S.	N.S.	22	Discharge/Day 22	Discharge/Day 22	22		0 to 504 hr post-dose	504	12OCT17:08:30:00	12OCT2017	URINE	No sampl...	
CUMUPERC	4.46	4.46	N.S.	14	Day 14	Day 14	14	LOCF	0 to 312 hr post-dose	312	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	4.46	4.46	N.S.	15	Day 15	Day 15	15	LOCF	0 to 336 hr post-dose	336	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	4.46	4.46	N.S.	16	Day 16	Day 16	16	LOCF	0 to 360 hr post-dose	360	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	4.46	4.46	N.S.	17	Day 17	Day 17	17	LOCF	0 to 384 hr post-dose	384	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	4.46	4.46	N.S.	18	Day 18	Day 18	18	LOCF	0 to 408 hr post-dose	408	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	4.46	4.46	N.S.	19	Day 19	Day 19	19	LOCF	0 to 432 hr post-dose	432	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	4.46	4.46	N.S.	20	Day 20	Day 20	20	LOCF	0 to 456 hr post-dose	456	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	4.46	4.46	N.S.	21	Day 21	Day 21	21	LOCF	0 to 480 hr post-dose	480	12OCT17:08:30:00	12OCT2017	URINE		Y
CUMUPERC	4.46	4.46	N.S.	22	Discharge/Day 22	Discharge/Day 22	22	LOCF	0 to 504 hr post-dose	504	12OCT17:08:30:00	12OCT2017	URINE		Y

Figure 5 ADPC in URINE DTYPE=LOCF

2) DTYPE=SUM. The ADME PK needs to calculate URINE+FECES species for percent dose administered related tests. This brings in another complexity. From Figure 6, we can see that the time collection intervals before 48 hours post-dose were different between urine and feces, but were same after 48 hour post dose. In order to calculate percent dose administered (PERCADM) in URINE+FECES we need to align the time points among urine and feces. We first summed the percent dose in urine in 0 to 4hr post-dose, 4 to 8hr post-dose, 8 to 12hr post-dose and 12 to 24hr post-dose to make 0-24hr post-dose value in urine. Similarly we calculated the sum of 24 to 36hr post-dose and 36 to 48hr post-dose values which was used as 24 to 48hr post-dose time point. After these done we have the same time points in urine and feces to calculate the sum of the values in both species for corresponding test. Here are some more detail discussions. From Figure 4 and Figure 5 we can see when subjects early discharged the N.S. was entered as result at the rest of time points. In these cases when both urine and feces had N.S. the sum of urine and feces result was N.S. When both urine and feces had BLQ the sum of urine and feces result was BLQ. If one species had N.S. and the other had BLQ the sum of urine and feces had result as N.S. Figure 7 shows the DTYPE=SUM for percent of dose administered records. After Day 13 both urine and feces had N.S. the sum of the two species had results of N.S. Figure 8 shows the DTYPE=SUM for cumulative percent of dose administered (CUMUPERC) records. Because after Day 13 the cumulative tests had LOCF performed as described previously the sum of urine and feces are the sum of LOCF values in two species, the DTYPE=SUM OF LOCF. To do a quick cross check, from Figure 5 urine at 0-24hr had value of 1.71 and from Figure 4 feces at 0-24hr had value of 0, thus the sum of urine and feces at 0-24hr had value of 1.71+0=1.71 with rounding up as shown on Figure 7 the first record.

ATPT	PCSPEC
0 to 4 hr post-dose	URINE
4 to 8 hr post-dose	URINE
8 to 12 hr post-dose	URINE
12 to 24 hr post-dose	URINE
24 to 36 hr post-dose	URINE
36 to 48 hr post-dose	URINE
48 to 72 hr post-dose	URINE
72 to 96 hr post-dose	URINE
96 to 120 hr post-dose	URINE
120 to 144 hr post-dose	URINE
144 to 168 hr post-dose	URINE
168 to 192 hr post-dose	URINE
192 to 216 hr post-dose	URINE
216 to 240 hr post-dose	URINE
240 to 264 hr post-dose	URINE
264 to 288 hr post-dose	URINE
288 to 312 hr post-dose	URINE
312 to 336 hr post-dose	URINE
336 to 360 hr post-dose	URINE
360 to 384 hr post-dose	URINE
384 to 408 hr post-dose	URINE
408 to 432 hr post-dose	URINE
432 to 456 hr post-dose	URINE
456 to 480 hr post-dose	URINE
480 to 504 hr post-dose	URINE

ATPT	PCSPEC
0 to 24 hr post-dose	FECES
24 to 48 hr post-dose	FECES
48 to 72 hr post-dose	FECES
72 to 96 hr post-dose	FECES
96 to 120 hr post-dose	FECES
120 to 144 hr post-dose	FECES
144 to 168 hr post-dose	FECES
168 to 192 hr post-dose	FECES
192 to 216 hr post-dose	FECES
216 to 240 hr post-dose	FECES
240 to 264 hr post-dose	FECES
264 to 288 hr post-dose	FECES
288 to 312 hr post-dose	FECES
312 to 336 hr post-dose	FECES
336 to 360 hr post-dose	FECES
360 to 384 hr post-dose	FECES
384 to 408 hr post-dose	FECES
408 to 432 hr post-dose	FECES
432 to 456 hr post-dose	FECES
456 to 480 hr post-dose	FECES
480 to 504 hr post-dose	FECES

Figure 6 URINE and FECES Time Points

SUBJID	PARAMCD	AVAL	AVALC	PCSTRESC	VISITNUM	VISIT	AVISIT	AVISITN	DTYPE	ATPT	PCSPEC	SAMPCOM	ANL01FL
1442...	PERCADM	1.709	1.709		2	Day 2	Day 2	2	SUM	0 to 24 hr post-dose	URINE + FECES		Y
1442...	PERCADM	14.462	14.462		3	Day 3	Day 3	3	SUM	24 to 48 hr post-dose	URINE + FECES		Y
1442...	PERCADM	14.31	14.31		4	Day 4	Day 4	4	SUM	48 to 72 hr post-dose	URINE + FECES		Y
1442...	PERCADM	31.251	31.251		5	Day 5	Day 5	5	SUM	72 to 96 hr post-dose	URINE + FECES		Y
1442...	PERCADM	19.645	19.645		6	Day 6	Day 6	6	SUM	96 to 120 hr post-dose	URINE + FECES		Y
1442...	PERCADM	4.791	4.791		7	Day 7	Day 7	7	SUM	120 to 144 hr post-dose	URINE + FECES		Y
1442...	PERCADM	4.129	4.129		8	Day 8	Day 8	8	SUM	144 to 168 hr post-dose	URINE + FECES		Y
1442...	PERCADM	4.59	4.59		9	Day 9	Day 9	9	SUM	168 to 192 hr post-dose	URINE + FECES		Y
1442...	PERCADM	1.7	1.7		10	Day 10	Day 10	10	SUM	192 to 216 hr post-dose	URINE + FECES		Y
1442...	PERCADM	0.896	0.896		11	Day 11	Day 11	11	SUM	216 to 240 hr post-dose	URINE + FECES		Y
1442...	PERCADM	0.386	0.386		12	Day 12	Day 12	12	SUM	240 to 264 hr post-dose	URINE + FECES		Y
1442...	PERCADM	0.168	0.168		13	Day 13	Day 13	13	SUM	264 to 288 hr post-dose	URINE + FECES		Y
1442...	PERCADM		N.S.		14	Day 14	Day 14	14	SUM	288 to 312 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	PERCADM		N.S.		15	Day 15	Day 15	15	SUM	312 to 336 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	PERCADM		N.S.		16	Day 16	Day 16	16	SUM	336 to 360 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	PERCADM		N.S.		17	Day 17	Day 17	17	SUM	360 to 384 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	PERCADM		N.S.		18	Day 18	Day 18	18	SUM	384 to 408 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	PERCADM		N.S.		19	Day 19	Day 19	19	SUM	408 to 432 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	PERCADM		N.S.		20	Day 20	Day 20	20	SUM	432 to 456 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	PERCADM		N.S.		21	Day 21	Day 21	21	SUM	456 to 480 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	PERCADM		N.S.		22	Discharge/Day 22	Discharge/Day 22	22	SUM	480 to 504 hr post-dose	URINE + FECES	No sample; ...	Y

Figure 7 ADPC DTYPE=SUM in Percent of Dose Administered

SUBJID	PARAMCD	AVAL	AVALC	PCSTRESC	VISITNUM	VISIT	AVISIT	AVISITN	DTYPE	ATPT	PCSPEC	SAMPCOM	ANL01FL
1442...	CUMUPERC	1.71	1.71		2	Day 2	Day 2	2	SUM	0 to 24 hr post-dose	URINE + FECES		Y
1442...	CUMUPERC	16.17	16.17		3	Day 3	Day 3	3	SUM	0 to 48 hr post-dose	URINE + FECES		Y
1442...	CUMUPERC	30.48	30.48		4	Day 4	Day 4	4	SUM	0 to 72 hr post-dose	URINE + FECES		Y
1442...	CUMUPERC	61.63	61.63		5	Day 5	Day 5	5	SUM	0 to 96 hr post-dose	URINE + FECES		Y
1442...	CUMUPERC	81.38	81.38		6	Day 6	Day 6	6	SUM	0 to 120 hr post-dose	URINE + FECES		Y
1442...	CUMUPERC	86.14	86.14		7	Day 7	Day 7	7	SUM	0 to 144 hr post-dose	URINE + FECES		Y
1442...	CUMUPERC	90.25	90.25		8	Day 8	Day 8	8	SUM	0 to 168 hr post-dose	URINE + FECES		Y
1442...	CUMUPERC	94.86	94.86		9	Day 9	Day 9	9	SUM	0 to 192 hr post-dose	URINE + FECES		Y
1442...	CUMUPERC	96.56	96.56		10	Day 10	Day 10	10	SUM	0 to 216 hr post-dose	URINE + FECES		Y
1442...	CUMUPERC	97.46	97.46		11	Day 11	Day 11	11	SUM	0 to 240 hr post-dose	URINE + FECES		Y
1442...	CUMUPERC	97.86	97.86		12	Day 12	Day 12	12	SUM	0 to 264 hr post-dose	URINE + FECES		Y
1442...	CUMUPERC	97.96	97.96		13	Day 13	Day 13	13	SUM	0 to 288 hr post-dose	URINE + FECES		Y
1442...	CUMUPERC	97.96	97.96		14	Day 14	Day 14	14	SUM of LOCF	0 to 312 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	CUMUPERC	97.96	97.96		15	Day 15	Day 15	15	SUM of LOCF	0 to 336 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	CUMUPERC	97.96	97.96		16	Day 16	Day 16	16	SUM of LOCF	0 to 360 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	CUMUPERC	97.96	97.96		17	Day 17	Day 17	17	SUM of LOCF	0 to 384 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	CUMUPERC	97.96	97.96		18	Day 18	Day 18	18	SUM of LOCF	0 to 408 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	CUMUPERC	97.96	97.96		19	Day 19	Day 19	19	SUM of LOCF	0 to 432 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	CUMUPERC	97.96	97.96		20	Day 20	Day 20	20	SUM of LOCF	0 to 456 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	CUMUPERC	97.96	97.96		21	Day 21	Day 21	21	SUM of LOCF	0 to 480 hr post-dose	URINE + FECES	No sample; ...	Y
1442...	CUMUPERC	97.96	97.96		22	Discharge/Day 22	Discharge/Day 22	22	SUM of LOCF	0 to 504 hr post-dose	URINE + FECES	No sample; ...	Y

Figure 8 DTYPE=SUM/SUM OF LOCF in Cumulative Percent Dose of Administered

3) DTYPE=BLQ. BLQ values are also handled in ADPC for summary reports and have DTYPE=BLQ. The rule of imputation BLQ values are for non-concentration PK tests set BLQ to 0. For concentration PK tests set pre-dose BLQ as 0 and post-dose BLQ as half LLOQ. PCSTRESC from SDTM PC is carried over to keep original values for traceability. Figure 9 shows the imputing value in AVAL when DTYPE=BLQ.

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SUBJID	PARAMCD	AVAL	AVALC	PCSTRESC	VISITNUM	VISIT	AVISIT	AVISITN	DTYPE	PCLLOQ	ATPT	ATPTN	EXDOSDTM	EXACTDT	EXACTTM	PCSPEC	SAMPCOM	ANL01FL
14423...	CONC	0	0	BLQ	1	Day 1	Day 1	1	BLQ	47.8	Predose	0	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	23.9	23.9	BLQ	1	Day 1	Day 1	1	BLQ	47.8	0.25 hr post-dose	0.25	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	392	392	392	1	Day 1	Day 1	1		47.8	0.5 hr post-dose	0.5	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	667	667	667	1	Day 1	Day 1	1		47.8	1 hr post-dose	1	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	764	764	764	1	Day 1	Day 1	1		47.8	1.5 hr post-dose	1.5	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	771	771	771	1	Day 1	Day 1	1		47.8	2 hr post-dose	2	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	897	897	897	1	Day 1	Day 1	1		47.8	2.5 hr post-dose	2.5	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	1060	1060	1060	1	Day 1	Day 1	1		47.8	3 hr post-dose	3	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	1100	1100	1100	1	Day 1	Day 1	1		47.8	4 hr post-dose	4	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	651	651	651	1	Day 1	Day 1	1		47.8	6 hr post-dose	6	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	474	474	474	1	Day 1	Day 1	1		47.8	8 hr post-dose	8	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	339	339	339	1	Day 1	Day 1	1		47.8	12 hr post-dose	12	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	209	209	209	1	Day 1	Day 1	1		47.8	18 hr post-dose	18	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	182	182	182	2	Day 2	Day 2	2		47.8	24 hr post-dose	24	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	136	136	136	2	Day 2	Day 2	2		47.8	36 hr post-dose	36	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	80.9	80.9	80.9	3	Day 3	Day 3	3		47.8	48 hr post-dose	48	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	23.9	23.9	BLQ	3	Day 3	Day 3	3	BLQ	47.8	60 hr post-dose	60	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	64.7	64.7	64.7	4	Day 4	Day 4	4		47.8	72 hr post-dose	72	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	59.8	59.8	59.8	5	Day 5	Day 5	5		47.8	96 hr post-dose	96	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	23.9	23.9	BLQ	6	Day 6	Day 6	6	BLQ	47.8	120 hr post-dose	120	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	23.9	23.9	BLQ	7	Day 7	Day 7	7	BLQ	47.8	144 hr post-dose	144	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	23.9	23.9	BLQ	8	Day 8	Day 8	8	BLQ	47.8	168 hr post-dose	168	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	23.9	23.9	BLQ	9	Day 9	Day 9	9	BLQ	47.8	192 hr post-dose	192	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	23.9	23.9	BLQ	10	Day 10	Day 10	10	BLQ	47.8	216 hr post-dose	216	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	23.9	23.9	BLQ	11	Day 11	Day 11	11	BLQ	47.8	240 hr post-dose	240	12OCT17:0...	12OCT2017	8:30	BLOOD		Y
14423...	CONC	23.9	23.9	BLQ	12	Day 12	Day 12	12	BLQ	47.8	264 hr post-dose	264	12OCT17:0...	12OCT2017	8:30	BLOOD		Y

Figure 9 ADPC DTYPE=BLQ

GENERATING OUTPUTS

The flow chart in Figure 1 shows, after creating ADaM ADPC and ADPP PK outputs are generated based on the two ADaM datasets. The standard PK outputs include listing of individual PK and summary statistics of PK table. Figures for PK concentration vs time profile include individual plot and mean (SD)/median (Q1,Q3) plots. In the beginning section of this paper the challenge of the ADME study in the cumulative test figure was briefly introduced. In this section we will focus on the detail and resolution of the challenge on this figure output.

FIGURE REQUIREMENT

On the cumulative percent of dose administered graph we want to see urine, feces and urine+feces, mean cumulative excretion percent dose recovery curve with SD error bar on the same plot and labels of the number of subjects remaining at each time point at the bottom outside the plot area.

TOOL USED

Graphic Template Language (GTL) is the most powerful graphing tool. In SAS 9.4 GTL not only makes graphs possible but makes them easy (Sanjay Matange, Paper SAS1780-2015). Figure 10 was the plot created using GTL.

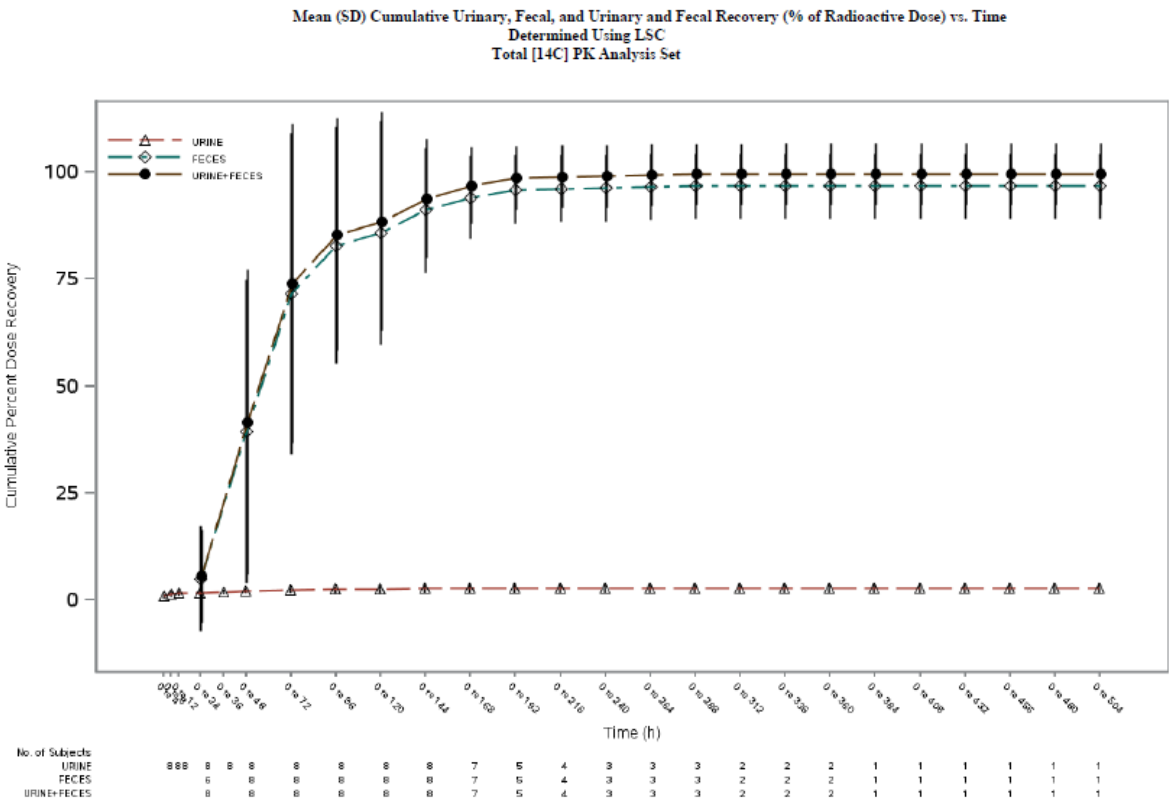

Figure 10 Cumulative Excretion Percent of Dose Administered Plot

STEPS

The graph displays mean and SD of cumulative excretion percent dose administered in three lines and number of subjects, n, at the bottom outside of the plot. On the plot, urine had the lowest curve, then feces had the second lowest curve and urine+feces was on the top. In order to display n at the bottom outside plot, blockplot statement was used, so that the whole graph was able to be split into two rows in ratio of 0.92 and 0.08 where 0.92 portion was holding the plot area and 0.08 for displaying the number of subjects. Layout lattice/row=2 was used for this purpose. Two layout overlay blocks are nested within layout lattice; the first layout overlay was for mean with SD error plot, the second layout overlay for displaying the number of subjects at the bottom. The “No of Subjects” was added as a specimen in the format name as, ntrtgroup, along with urine, feces and urine+feces in order to display it as a label above the three species. This format is used in blockplot statement class option. Since this added specimen has no actual values but appears in the legend as “ -“, using exclude option to exclude missing value specimen in DiscreteLegend statement would allow only three actual species to display in the legend as shown in Figure 10. The code can be provided per request.

CONCLUSION

Although ADME PK study is a single dose study design, the radio activity PK with early discharge subjects brings more challenges than all other regular PK studies. The focus of this paper describes the process flow of ADME PK study, PKMERGE, SDTM, ADaM and final PK outputs, also details each challenge brought by ADME radio PK activity as well as the solutions to the challenges. After reviewing other papers regarding PK standardization in clinical trials we conclude that our process meets the

industry standard. SAS Graphic Template Language is also proved to be a very efficient way to handle complicated graph.

REFERENCES

[1] PhUSE CSS Development of Standard Script for Analysis and Programming Working Group. "Analysis and Displays Associated to Non-Compartmental Pharmacokinetics – With a Focus on Clinical Trials. Final Version1.0. 25 March 2014. Available at http://phusewiki.org/.../PhUSE_CSS_WhitePaper_PK_final_25March2014.pdf

[2] Peter Schaefer 2013.

"Relating PC and PP Domains using RELREC Records" Available at

http://phusewiki.org/docs/posters2013CSS/pp02.pdf

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CONTACT INFORMATION

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

Fan Lin
fan.lin@gilead.com