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A Practical and Efficient Method of Calculating Actual Time Since Last Dose Data in PK Analysis

Yingqiu Yvette Liu, PAREXEL International, Billerica, USA

ABSTRACT

Pharmacokinetic (PK) and Pharmacodynamic (PD) data analysis is an important component in drug development and clinical trials. PK data at each time point consists of two sets of data pairing up together: time point data (nominal/planned, and actual), and drug concentration data (parent drug or its metabolite) in serum, urine, etc.. Besides nominal time point data which is pre-planned and up-stream data that can be directly sourced from central lab, calculating actual time point data, such as Actual Time Since First Dose (ATSFD) and Actual Time Since Last (i.e. intermediate previous) Dose (ATSLD), is one of the major tasks in developing analysis PK dataset: ADaM Analysis Dataset of Pharmacokinetic Concentration (ADPC) or non-ADaM dataset Non-Compartmental PK Analysis (PKNCA), and Population PK dataset (popPK). In this paper, the author will demonstrate a practical and efficient method of calculating Actual Time Since Last Dose (ATSLD) data.

INTRODUCTION

Pharmacokinetics (PK): is what the body does to the drug, it characterizes the time course of concentrations of the drug and/or the drug metabolite after drug administration in order to obtain information on drug disposition in the body. There are four phases of PK process inside the body: Absorption, Distribution, Metabolism, and Excretion (ADME). Pharmacodynamics (PD): is what the drug does to the body, it studies the body's pharmacological response to a drug (measured in terms of AEs & Efficacy). And PKPD studies the dose-effect relationship. [1,3]

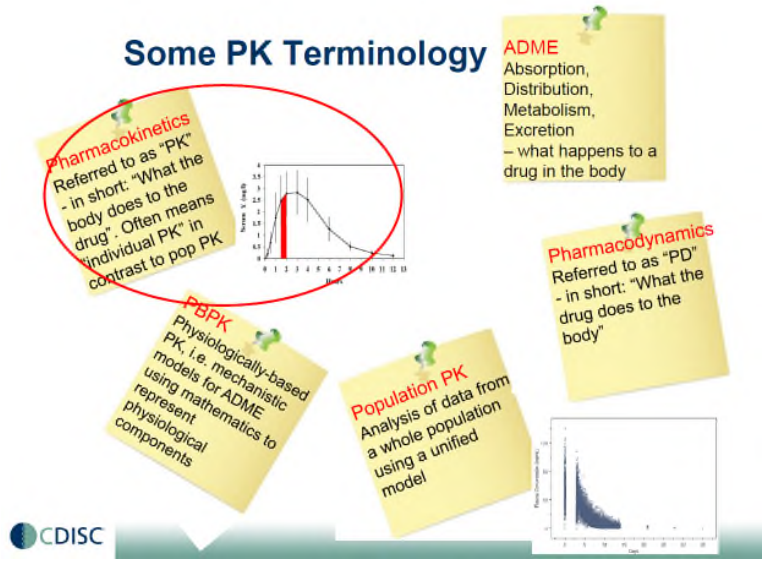

Figure 1: PK Terminology. Source [1].

1. PC (PK CONCENTRATION) AND ADPC (ANALAYSIS PK CONCENTATION) DATASET

An exmaple of EX data:

Data not showed in EX dataset below (using fake data of USUBUID and EXTRT just for demonstration purpose):

USUBJID = "StudyA-000-100"

	EXSEQ	EXTRT	EXDOSE	EXDOSU	EXDOSFRM	EXROUTE	VISITNUM	VISIT	EPOCH	EXSTDTC	EXENDTC	EXSTDY	EXENDY
1	1	PLACEBO	2000	mg		ORAL	20	DAY 1	SINGLE BLIND TREATMENT	2012-02-21T09:50	2012-02-21T09:50	1	1
2	2	PLACEBO	2000	mg		ORAL	20	DAY 1	SINGLE BLIND TREATMENT	2012-02-21T21:59	2012-02-21T21:59	1	1
3	3	PLACEBO	2000	mg		ORAL	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T10:10	2012-02-22T10:10	2	2
4	4	DRUGA	2000	mg		ORAL	40	DAY 3	SINGLE BLIND TREATMENT	2012-02-23T10:40	2012-02-23T10:40	3	3
5	5	DRUGA	2000	mg		ORAL	40	DAY 3	SINGLE BLIND TREATMENT	2012-02-23T22:39	2012-02-23T22:39	3	3
6	6	DRUGA	2000	mg		ORAL	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T10:50	2012-02-24T10:50	4	4

Figure 2: EX dataset.

An example of PC data:
Data not showed in PC dataset below (using fake data of USUBUID and PCTEST just for demonstration purpose):

USUBJID = “StudyA-000-100”
PCTEST = “DRUGA”

	PCSTRESN	PCSTRESU	PCSPEC	VISITNUM	VISIT	EPOCH	PCDTC	PCDY	PCTPT	PCTPTNUM	PCELTM	PCTPTREF
1		ug/L	PLASMA	20	DAY 1	SCREENING	2012-02-21T09:46	1	BASELINE	1		DOSE
2		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T09:57	2	PRE-DOSE	11		DOSE
3		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T11:15	2	1 HOUR POST DOSE	35	PT1H	DOSE
4		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T12:17	2	2 HOURS POST DOSE	55	PT2H	DOSE
5		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T13:15	2	3 HOURS POST DOSE	75	PT3H	DOSE
6		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T14:19	2	4 HOURS POST DOSE	95	PT4H	DOSE
7		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T16:15	2	6 HOURS POST DOSE	115	PT6H	DOSE
8		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T18:15	2	8 HOURS POST DOSE	135	PT8H	DOSE
9		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T20:15	2	10 HOURS POST DO...	155	PT10H	DOSE
10		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T22:15	2	12 HOURS POST DO...	175	PT12H	DOSE
11		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-23T10:25	3	24 HOURS POST DO...	195	PT24H	DOSE
12		ug/L	PLASMA	40	DAY 3	SINGLE BLIND TREATMENT	2012-02-23T10:25	3	BASELINE	1		DOSE
13	2633.5	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T10:45	4	PRE-DOSE	11		DOSE
14	2981.68	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T11:55	4	1 HOUR POST DOSE	35	PT1H	DOSE
15	3246.91	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T12:55	4	2 HOURS POST DOSE	55	PT2H	DOSE
16	3599.17	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T13:55	4	3 HOURS POST DOSE	75	PT3H	DOSE
17	3558.94	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T14:55	4	4 HOURS POST DOSE	95	PT4H	DOSE
18	3042.47	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T16:55	4	6 HOURS POST DOSE	115	PT6H	DOSE
19	2355.75	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T18:55	4	8 HOURS POST DOSE	135	PT8H	DOSE
20	2249.3	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T20:55	4	10 HOURS POST DO...	155	PT10H	DOSE
21	2123.6	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T22:55	4	12 HOURS POST DO...	175	PT12H	DOSE
22	1197.3	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-25T10:55	5	24 HOURS POST DO...	195	PT24H	DOSE

Figure 3: PC dataset.

We can tell from the related PC data and EX data:
PC data row 1 - 11 correspond to EX data row 1 – 3 of PLACEBO. Then there’s no doubt why the PCSTREN value for these rows are missing because of placebo drug administered. PC data row 12 - 22 (blue highlighted) correspond to EX data row 4 - 6 (blue highlighted) of DRUGA.

PCELTM should be populated with the planned elapsed time but not the actual elapsed time. There is no place in the PC domain for the actual elapsed time, though it can be derived from the difference between PCDTC (date/time of sample collection) and PCRFTDTC (date/time of reference time point, which is usually a dose). [2]

An example of ADPC dataset:
Data not showed in ADPC dataset below (using fake data of USUBUID and treatment variables just for demonstration purpose):

USUBJID = “StudyA-000-100”
TRTA = “DRUGA”
TRTP = “DRUGA”
TRTSEQA = “Placebo/ DrugA”
TRTSEQP = “Placebo/ DrugA”

	PCSEQ	AUNIT	AVISITN	AVISIT	ADY	ATPTREF	ATPTN	ATPT	AEXLSDTM	ADTM	APRELTM	APRELTMU	ARELTM	ARELTMC	ARELTMU	AVAL	EXDOSE	APERADY	APERIOD	PARAMCD
1	13	ug/L	50	DAY 4	4	DOSE	11	PRE-DOSE	24FEB12:10:50:00	24FEB12:10:45:00			-0.0666...	-0h 4m	HRS	2633.5	2000	2	2	CONC
2	14	ug/L	50	DAY 4	4	DOSE	35	1 HOUR POST DOSE	24FEB12:10:50:00	24FEB12:11:55:00	1	HRS	1.1	1h 6m	HRS	2981.68	2000	2	2	CONC
3	15	ug/L	50	DAY 4	4	DOSE	55	2 HOURS POST DOSE	24FEB12:10:50:00	24FEB12:12:55:00	2	HRS	2.1	2h 6m	HRS	3246.91	2000	2	2	CONC
4	16	ug/L	50	DAY 4	4	DOSE	75	3 HOURS POST DOSE	24FEB12:10:50:00	24FEB12:13:55:00	3	HRS	3.1	3h 6m	HRS	3599.17	2000	2	2	CONC
5	17	ug/L	50	DAY 4	4	DOSE	95	4 HOURS POST DOSE	24FEB12:10:50:00	24FEB12:14:55:00	4	HRS	4.1	4h 6m	HRS	3558.94	2000	2	2	CONC
6	18	ug/L	50	DAY 4	4	DOSE	115	6 HOURS POST DOSE	24FEB12:10:50:00	24FEB12:16:55:00	6	HRS	6.1	6h 6m	HRS	3042.47	2000	2	2	CONC
7	19	ug/L	50	DAY 4	4	DOSE	135	8 HOURS POST DOSE	24FEB12:10:50:00	24FEB12:18:55:00	8	HRS	8.1	8h 6m	HRS	2355.75	2000	2	2	CONC
8	20	ug/L	50	DAY 4	4	DOSE	155	10 HOURS POST DOSE	24FEB12:10:50:00	24FEB12:20:55:00	10	HRS	10.1	10h 6m	HRS	2249.3	2000	2	2	CONC
9	21	ug/L	50	DAY 4	4	DOSE	175	12 HOURS POST DOSE	24FEB12:10:50:00	24FEB12:22:55:00	12	HRS	12.1	12h 6m	HRS	2123.6	2000	2	2	CONC
10	22	ug/L	50	DAY 4	5	DOSE	195	24 HOURS POST DOSE	24FEB12:10:50:00	25FEB12:10:55:00	24	HRS	24.1	24h 6m	HRS	1197.3	2000	3	2	CONC

Figure 4: ADPC dataset.

APRELTM stores planned / nominal elapsed time (since last / immediate previous dose), while ARELTM stores actual

elapsed time (since last / immediate previous dose).

Pay attention to row 1 where ARELTM (actual elapsed time) has negative value -0.66666 and APRELTM (planned elapsed time) has missing value. Negative and missing pre-dose sampling times are typically set to zero for PK analysis. [1]

ADPC data row 1 – 10 corresponds to PC data row 13 – 22 (PREDOSE to 24 HOURS POST DOSE).

But, there're no variables in ADPC to store planed elapsed time since first dose (PTSFD) and actual elapsed time since first dose (ATSFD). So in the section below we will take a detailed look at PKNCA dataset which accommodates both planed and actual time since first dose and last dose.

2. PKNCA: NON-COMPARTMENTAL PK ANALASISI DATAST.

2.1 CALCULATING ATSLD (ACUTAL TIME SINCE LAST / INTERMEDIATE PREVIOUS DOSE)

Step 1: Create a common variable DTM in both PK and EX datasets.

```
data ex1(keep=usubjid exdtm dtm extrt exdose);
set ex;
exdtm = input (exstdtc, is8601dt.);
dtm = exdtm;
format exdtm dtm is8601dt.;
run;

data pk1;
set pk;
pkdtm = input (pkdtc, is8601dt.);
dtm = pkdtm;
format pkdtm dtm is8601dt.;
run;
```

Step 2: Set PK and EX together into PKEX. Using numeric flag SRCFN to differentiate data source whether data comes from EX of PK.

```
data pkex1;
set ex(in=a) pk1(in=b)  ;
if a then srcfn = 1;
if b then srcfn = 0;
run;
```

NOTE: sort variable SRCFN to ensure PK record always on top of EX record when they have same value of DTM (i.e. when having same value of DTM, PK record is pre-dose record which should definitely be on top EX records for the sake of populating correct dosing date time for the pre-dose PK records which should have the previous EX date time as its dosing date time).

Step 3: Sort PKEX by USUBJID, DTM, SRCFN.

```
proc sort data = pkex;
by usubjid dtm srcfn;
run;
```

Step 4: Using LAG( ) function and RETAIN statement to populate LDOSEDTM for each post-dose PK record.

```
data pkex2;
set pkex1;
by usubjid dtm;

format lagexdtm ldosedtm is8601dt. ;
retain ldosedtm;
lagexdtm = lag(exdtm);

if first.an then do;
```

```
        lagexdtm = .;
        ldosedtm = .;
    end;

    if lagexdtm ne . then ldosedtm = lagexdtm;
    run;
```

Step 5: Only keep PK records.

```
    data pkex3;
    set pkex2;
    by usubjid dtm;
    where srcfn = 0;
    run;
```

Step 6: Calculate ATSLD for each post-dose PK record, set ATSLD = 0 for pre-dose record.

```
    data pkex4;
    set pkex3;
    if n(pkdtm,ldosedtm) = 2 then atsld= (pkdtm - ldosedtm)/3600;
    if index(upcase(TPT), “PRE-DOSE”) > 0 then ATSLD = 0;
    run;
```

2.2 CALCULATING ATSFD (ACUTAL TIME SINCE FIRST DOSE)

Step 1: keep only first dose record for each subject in EX dataset.

```
    data ex2(keep=usubjid fdosedtm);
    set ex1;
    by usubjid dtm;
    if first.usubjid;
    fdosedtm = exdtm;
    format fdosedtm is8601dt.;
    run;
```

Step 2: merge EX2 with PKEX4 by USUBJID, now each PK record has FDOSEDTM.

```
    data pkex5;
    merge pkex4(in=a) ex2(in=b);
    by usubjid;
    if a;
    if n(pkdtm,fdosedtm) = 2 then atsfd = (pkdtm - fldosedtm)/3600;
    run;
```

Step 3: calculating ATSFD, set ATSFD = 0 for pre-dose record.

```
    data pkex6;
    set pkex5;
    if n(pkdtm,fdosedtm) = 2 then atsfd = (pkdtm - fldosedtm) / 3600;
    if index(upcase(TPT), “PRE-DOSE”) > 0 then ATSFD = 0;
    run;
```

3. ATSFD VS. ATSLD

In general, ATSFD should only be set to 0 for the pre-dose associated with the very first dose of the drug associated with the analyte (i.e. parent drug or its metabolite) of interest, across all periods. ATSFD should also include the time spent during the washout between periods.

NTSFD, however, should be calculated for each period, with the reference day corresponding to the day that the first dose of the drug of interest was given.

So basically, NTSFD is used to keep track of the time since the first dose of the drug given within a period (note, this isn't always Day 1). While ATSFD is keeping track of the real time since the subject took the very first dose of the drug of interest (which includes the washout periods).

CONCLUSION

Once we finish preparation of source input data of EX and PK records that is ready for use (i.e. they are sorted well enough by USUBID and DATE and TIME), we can utilize LAG( ) function to grab the corresponding last (i.e. intermediate previous) dosing date and time from EX record into the first post-dose PK data, and then by using RETAIN statement to populate this last dosing date and time value into the rest of post-dose PK records for this dose. At this point, calculating ATSLD (Actual Time Since Last Dose) is quite straight forward by getting the difference of PKDTM (PK sample collection date and time) and the last dosing date and time. We think this strategy is practical and efficient in our programming work of PK analysis.

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CONTACT INFORMATION

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

Yingqiu Yvette Liu
PAREXEL International
Yvette.liu@PAREXEL.com

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