Whats and Whys of combining Clinical and Pharmacokinetic database

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Agenda

1 Introduction

2. PK Data flow

   2.1 Study setup

   2.2 Data collection

   2.3 PK Merge

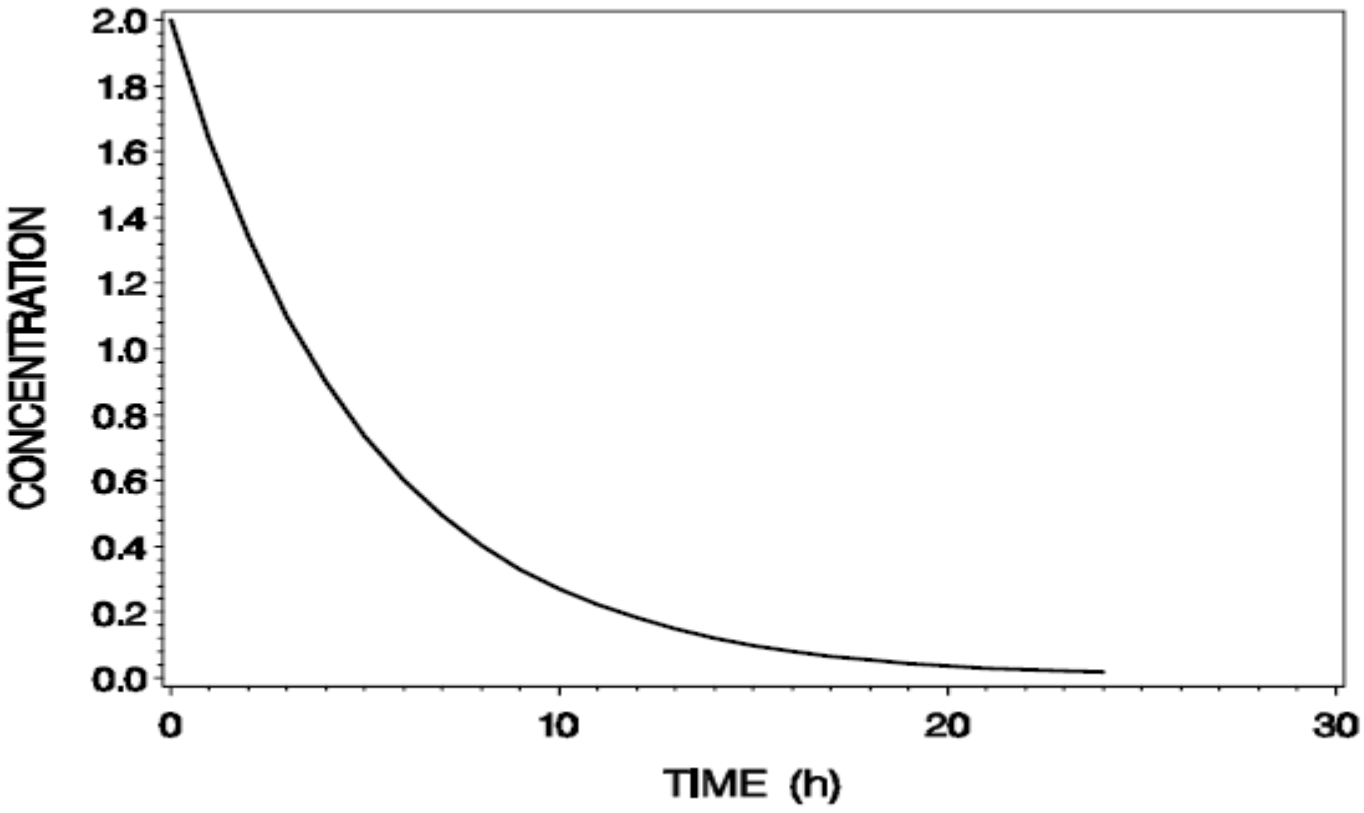
3 Summary

Introduction

- What are Pharmacokinetics ?
  - *What the body does to the drug*
- What Pharmacodynamics are ?
  - *What the drug does to the body*

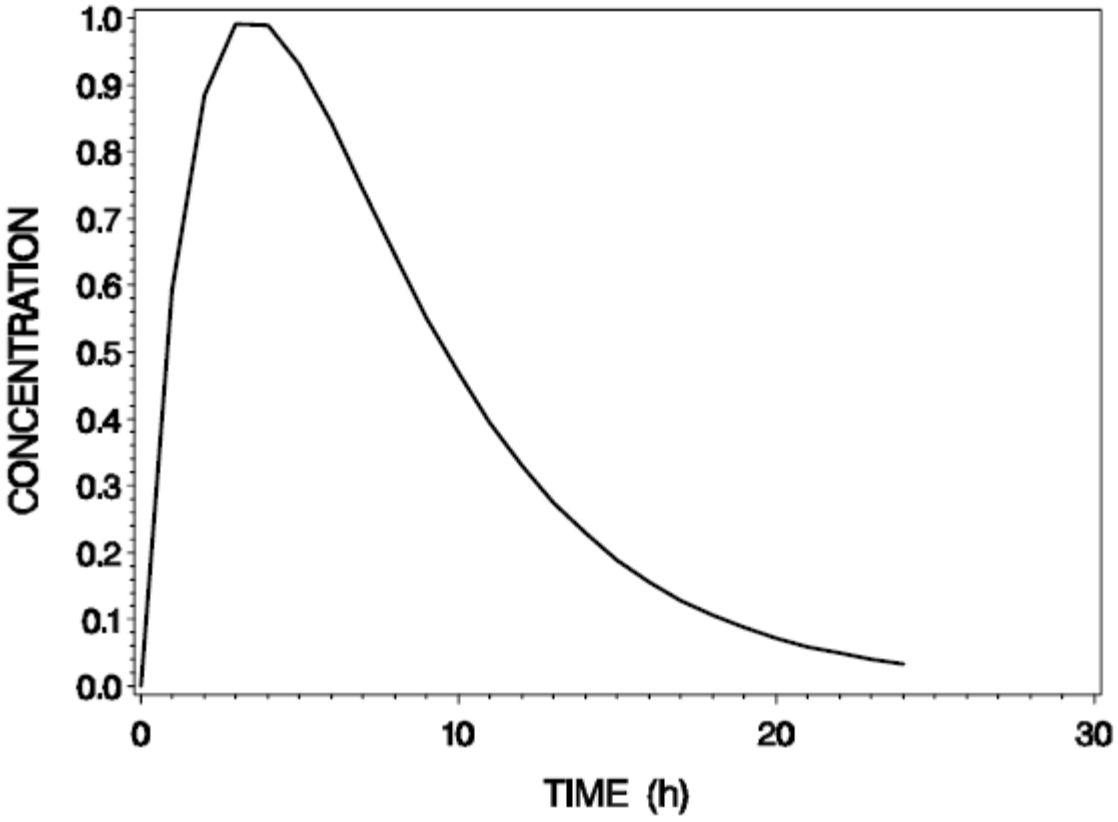
Question?

Can you say something about the drug from this?

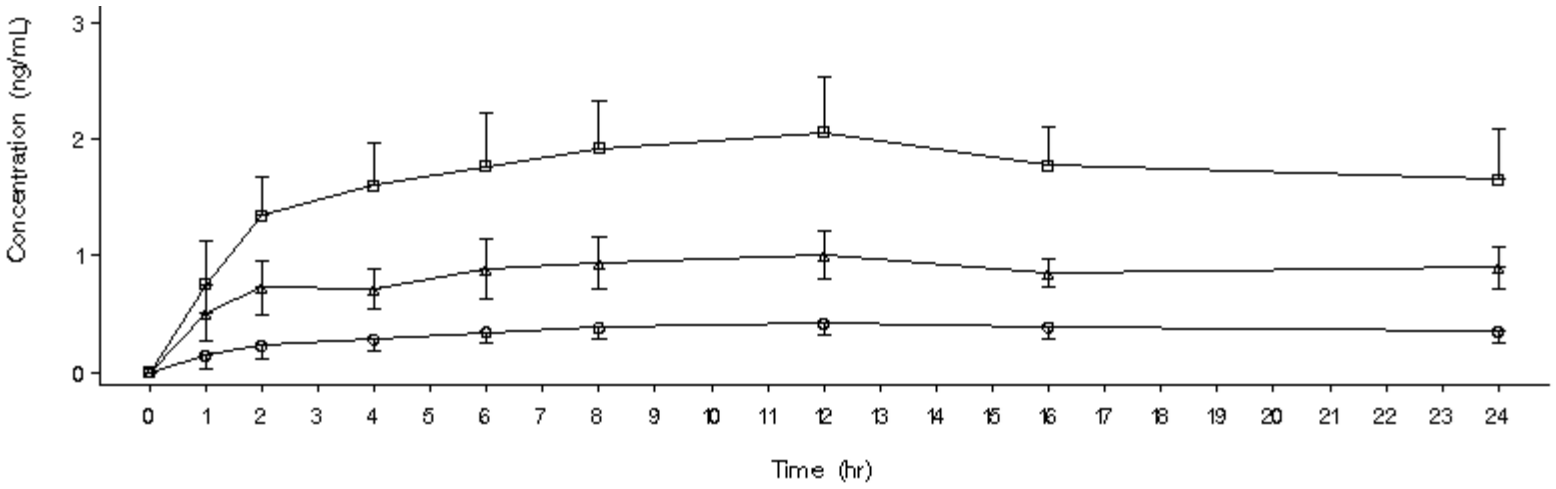


Question ?

Typical concentration-time profile of an oral dose



In reality what kind of graph we get



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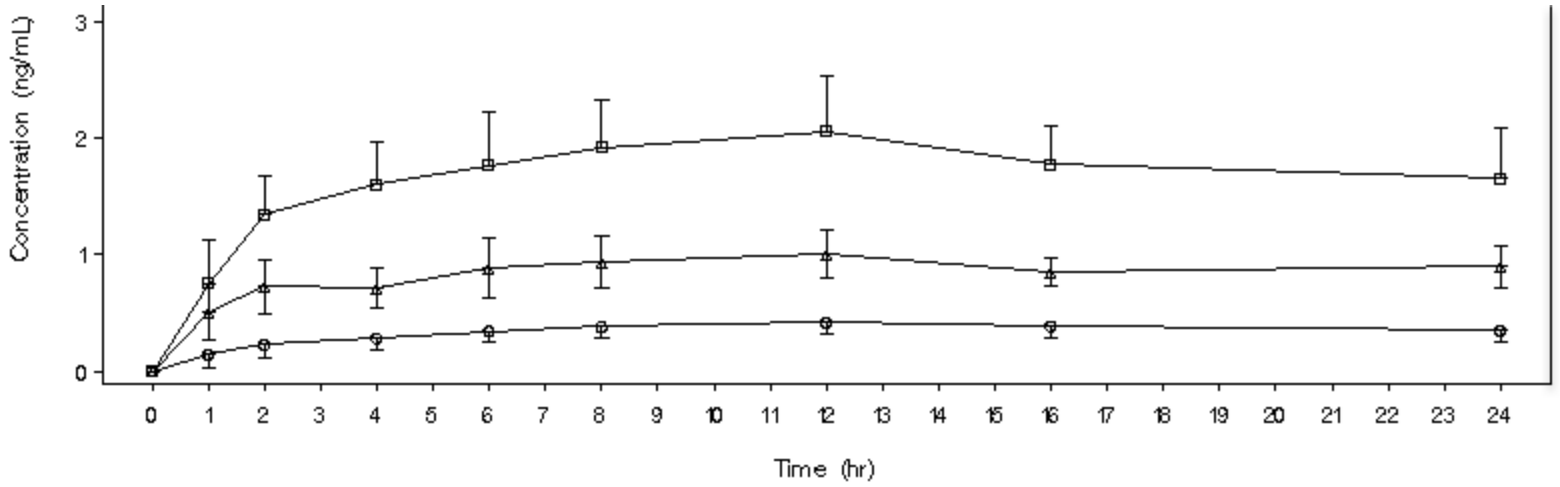
Question?

What info we loose in this graph?



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PK depends on?

- PK of a drug may depend on:
  - Formulation of the drug
  - Route of administration
  - Presence of co-administered drug
  - Ethnicity
  - And many more factors… (Don’t ask me what are they☺)

Why do we study Pharmacokinetics in Drug discovery?

Why do we study Pharmacokinetics in Drug discovery??

To Answer:

- How much drug gets into the body?
- How fast does the drug enter the body?
- Where does it go into the body?
- How the drug moves from the blood?
- How fast does the drug disappear?

Why do we study Pharmacokinetics in Drug discovery??

- Does the **bioavailability of a drug** change when it is given together **with another drug**
- What is the **bioavailability** of the drug in **special populations**?
  - Do they need **dose adjustment**?
- How do drug **concentrations change with dose**?
  - Are they proportional to dose?
- Are two (or more) different **formulations of the same drug comparable**
- Are the kinetics of drug XXX in **Caucasian and Japanese** subjects comparable?
- Does the intake **of food have an impact on the bioavailability** of a drug?

2.7.1.1 Background and Overview

This section should provide the reviewer with an overall view of the formulation development process, the *in vitro* and *in vivo* dosage form performance, and the general approach and rationale used in developing the bioavailability (BA), comparative BA, bioequivalence (BE), and *in vitro* dissolution profile database. Reference should be made to any guidelines or literature used in planning and conducting the studies. This section should also provide the reviewer with an overview of the analytical methods used, with emphasis on the performance characteristics of assay validation (e.g., linearity range, sensitivity, specificity) and quality control (e.g., accuracy and precision). This section should not include detailed information about individual studies.

2.7.2 Summary of Clinical Pharmacology Studies

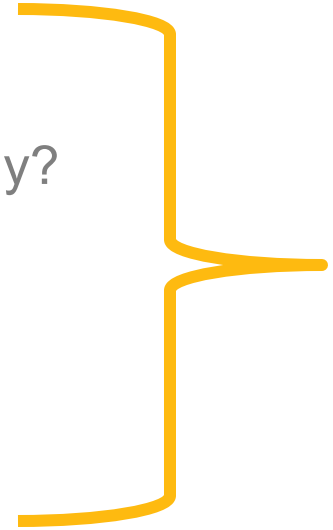
2.7.2.1 Background and Overview

This section should provide the reviewer with an overall view of the clinical pharmacology studies. These studies include clinical studies performed to evaluate human pharmacokinetics (PK), and pharmacodynamics (PD), and *in vitro* studies performed with human cells, tissues, or related materials (hereinafter referred to as human biomaterials) that are pertinent to PK processes. For vaccine products, this section should provide the reviewer with immune response data that support the selection of dose, dosage schedule, and formulation of the final product. Where appropriate, relevant data that are summarised in sections 2.7.1, 2.7.3 and 2.7.4 can also be referenced to provide a comprehensive view of the approach and rationale for the development of the pharmacokinetic, pharmacodynamic, PK/PD and human biomaterial database. This section should not include detailed information about individual studies.

Why do we study Pharmacokinetics in Drug discovery?? *Study Types*

To Answer:

- How much drug gets into the body?
- How fast does the drug enter the body?
- Where does it go into the body?
- How the drug moves from the blood?
- How fast does the drug disappear?



A-D-M-E

Why do we study Pharmacokinetics in Drug discovery??

- Does the **bioavailability of a drug** change when it is given together **with another drug**
  - Drug-Drug Interaction studies
- What is the **bioavailability** of the drug in **special populations**?
  - Do they need **dose adjustment**?

  - Studies in special populations (elderly, children, persons with renal or hepatic impairment)
- How do drug **concentrations change with dose**?
  - Are they **proportional to dose?**

  - Dose Proportional studies
- Are two (or more) different **formulations of the same drug comparable**

- Bioequivalence Studies

Why do we study Pharmacokinetics in Drug discovery??

- Are the kinetics of drug XXX in **Caucasian and Japanese** subjects comparable?

  - PK Bridging Studies

- Does the intake **of food have an impact on the bioavailability** of a drug?

  - Food Effect Studies

Contribution to drug label

Adobe Acrobat Document

- **Contributes greatly to the label** once the drug has been approved

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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What we do in the end?

Example of some output that we finally produce

Table 11-3 Geometric mean ratio (test/reference) and 90% confidence intervals for PK variables
Pharmacokinetic Analysis Population
Compound: [redacted], Biological Matrix: Blood, Analyte: [redacted]
Ratio: Fed/Fasted

	Adjusted geo-mean*		Geo-mean ratio*		
Parameter (Unit)	**Fed**	**Fasted**	**Estimate**	**Lower 90% CL**	**Upper 90% CL**
Cmax (ng/mL)	1.264	1.378	0.92	0.88	0.96
AUClast (h*ng/mL)	225.887	230.104	0.98	0.91	1.06
AUCinf (h*ng/mL)	252.171	255.459	0.99	0.92	1.06

Another example (AM SD graph)

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

GILENYA is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.

2 DOSAGE AND ADMINISTRATION

Recommended Dose

The recommended dose of GILENYA is 0.5 mg orally once daily. Fingolimod doses higher than 0.5 mg are associated with a greater incidence of adverse reactions without additional benefit. GILENYA can be taken with or without food.

12.3 Pharmacokinetics

Absorption

The T_{max} of fingolimod is 12-16 hours. The apparent absolute oral bioavailability is 93%.

Food intake does not alter C_{max} or exposure (AUC) of fingolimod or fingolimod-phosphate. Therefore GILENYA may be taken without regard to meals.

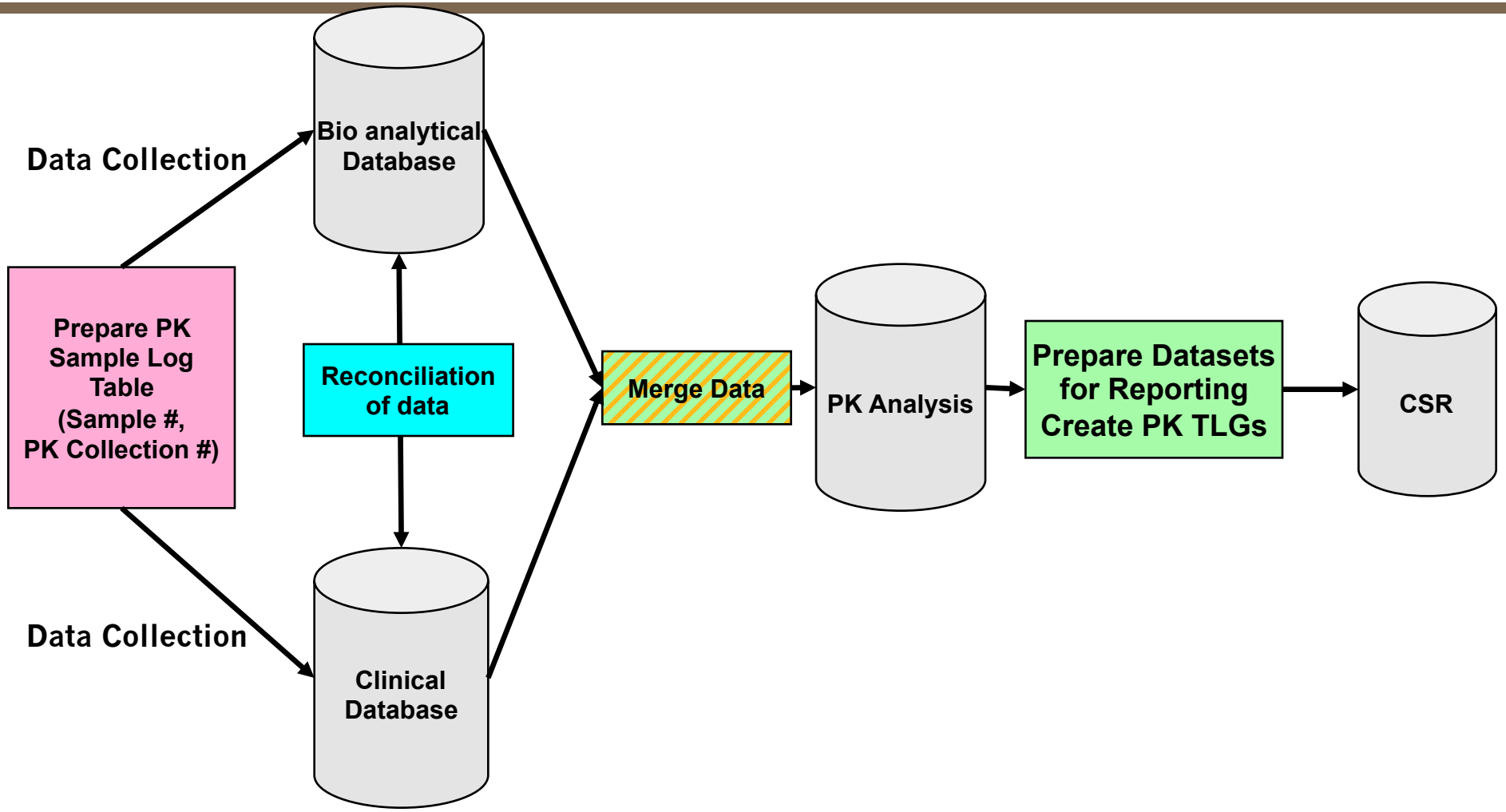
Example of a simpler output (Listing)

Listing 16.2.5-2.1 Listing of concentrations per treatment (Page 1 of 130)
Safety Population
Compound: [redacted], Biological Matrix: Blood, Analyte: [redacted]

Treatment	Subject	Gender	Sequence	Scheduled sample time (h)	Elapsed time	Concentration (ng/ml)
[redacted] Fed	0001_05101	Male	A	0	0.00	0
				0.5	0.50	0
				1	1.00	0
				1.5	1.50	0
				2	2.00	0.113
				3	3.00	0.255
				4	4.00	0.246
				6	6.00	0.431
				8	8.00	0.644
				12	12.00	0.771
				16	16.00	1.04
				24	24.00	1.02
				36	36.00	1.08
				48	48.00	0.987
				72	72.00	0.758
				96	96.00	0.677
				168	168.00	0.342
				240	240.00	0.216
				336	336.00	0.121
				504	504.00	0
				672	672.00	0
				864	864.00	0

PK Data Flow in PK Data Project

PK Data Flow in PK Data Project



PK data flow – Protocol - Primary objective

Example:

An open-label study in healthy adult male volunteers to assess the absorption, distribution, metabolism, and excretion of a single oral dose of 10 mg [^{14}C][redacted]

Primary objective(s)

- To identify and quantify the metabolites of [redacted] in plasma, urine, and feces as feasible following a single oral 10 mg of ^{14}C-labeled [redacted]
- To determine the rate and routes of excretion and the mass balance of total radioactivity in urine and feces

PK data flow – Protocol - Sample collection

Pharmacokinetic/ADME assessments

Sample collections:

- Blood collection: plasma samples will be collected over up to 28 days following dose administration at the following times: pre-dose, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, 192, 240, 312, 408, 504 and, if necessary, up to 672 hr post-dose.
- Urine collection: A predose sample will be collected within one day prior to dosing. All urine produced will be collected during the following time intervals: 0-6, 6-12, 12-18, 18-24, and over 24 h time intervals thereafter for up to 672 hr post-dose.
- Feces collection: A predose sample will be collected within one day prior to dosing. All feces produced will be collected during 24 hr time intervals from day one and up to 672 hr post-dose.
- Vomitus collection: Any vomitus produced during the first 24 hours after dosing will be collected.

PK data flow – Protocol - Blood Log

- Blood Log from Protocol:

Table 7-1 **Blood collection schedule and sample numbers for PK assessments and metabolite characterization**

	Blood Volumes (mL) Collected			
	Tube A	**Tube B**	**Tube C**	**Tube D**
	2mL/sample	**3mL/sample**	**3mL/sample**	**10mL/sample**
Time Post [^{14}C]-[redacted] Dose (hours)	Whole blood total radioactivity analysis	Plasma total radioactivity analysis	Plasma PK analysis	Plasma metabolite characterization
	Sample Number	Sample Number	Sample Number	Sample Number
0	101	201	301	401
1	102	202	302	402
2	103	203	303	403

PK data flow – Protocol - Sample analyses

Sample analyses:

- [redacted] will be measured in plasma by a validated LC/MS/MS method (DMPK-BA, Novartis, EH, USA)
- Total radioactivity determinations in blood, plasma, and excreta (urine, feces) will be performed by clinical site or CRO using liquid scintillation counting (LSC)
- Quantitation and structural characterization of metabolites in plasma and excreta will by done by HPLC/LSC or LC/MS as feasible (DMPK-BT, Novartis, EH, USA)

PK data flow – Protocol - Sample analyses

- **What is in the sample?**

  (or)

- **How much is in the sample?**

- **Analytical Methods in Drug Discovery**
  - High Performance Liquid Chromatography (**HPLC**)
  - Liquid Chromatography)–Mass spectrometry **(LC-MS**)

  Most analytical methods designed for plasma analysis

Study Setup & Data Collection

Study Setup & Data Collection

Protocol Review

- It is essential to correctly setup the PK Sample Log Table/ Blood Log Table in the Protocol
  → determines how CRFs (Dose administration & Blood collection) will be set up
  → determines how data are stored in the clinical database
  → impacts on the data merge
- Unique sample number within subject
- Information on how to handle Unscheduled samples
- Unique PK collection number per dose – **Key for PK Merge**

Study Setup & Data Collection

CRF Review

- It is very important for the programmer and eCRF developer to work together and identify eCRF issues in advance
- In order to have a successful merge the following should be key while doing an eCRF
  - Identification of trough and profile samples
  - Identification of dose to which a sample is required to be link
  - PK collection numbers are appropriately incorporated in CRF and should not become redundant
  - Period information is present in Dosage administration/Treatment

Study Setup & Data Collection

CRF- Dosage Administration page

ID 0 0 0 1 | _____ (Center No. | Subject No.)

Subject's initials _____ _____ (1. 2. | fam.)

Basis
Treatment Period
Day 1

(3)

Dosage administration record - Oral

Did the subject vomit within 4 hours of dosing
0=No
1=Yes *(please complete the Adverse events page)*

Reason for dose/Reason for change
1=As per protocol
2=Adverse event/lab or test abnormality
5=Dosing error
30=Dispensing error

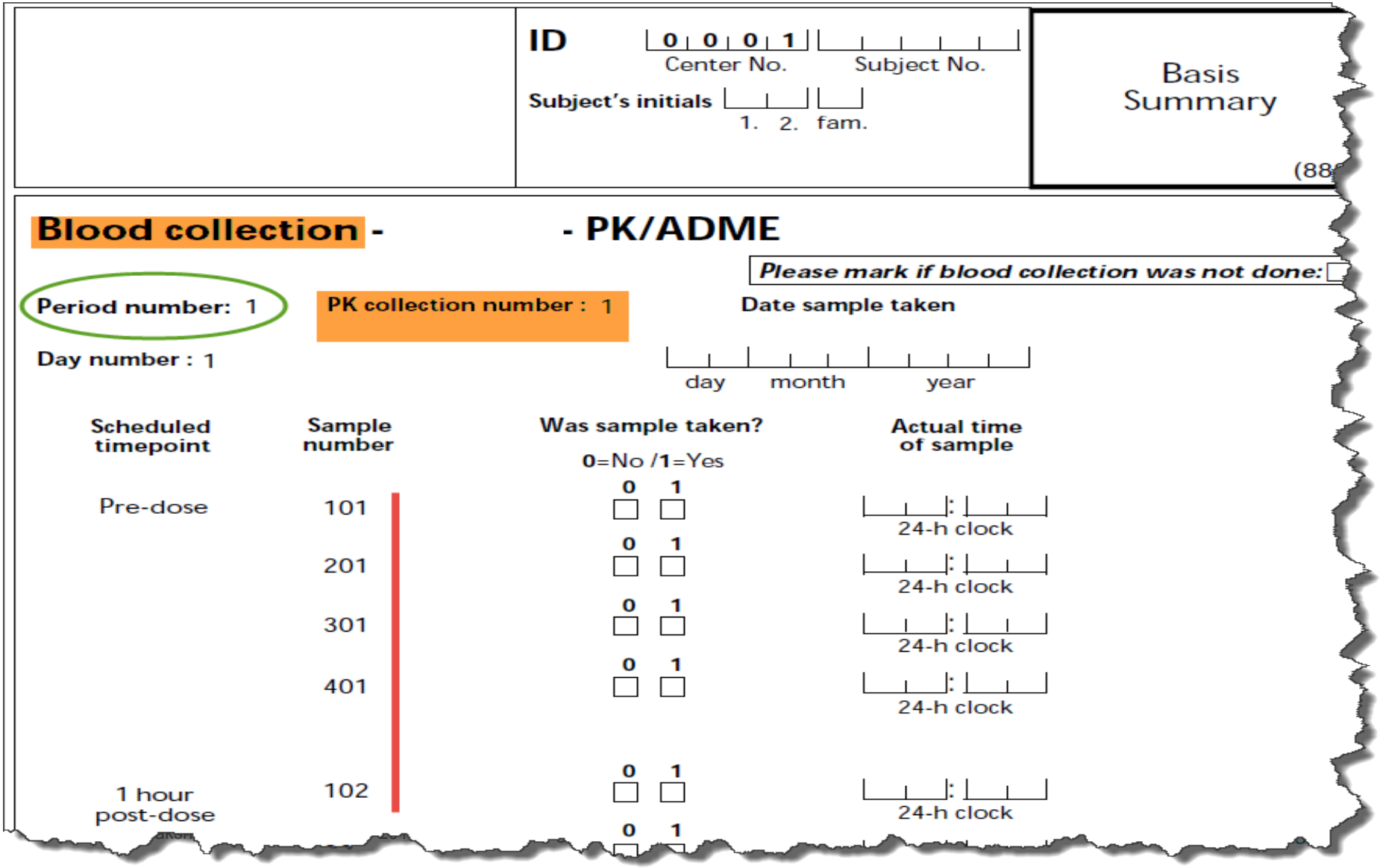
Period number: 1

PK collection number	Day	Date of dosing	Time of dosing	Dose administered
1	1	day month year	24-h clock	mg

Did the subject vomit within 4 hours of dosing?	Time of vomiting	Reason
0 ☐ 1 ☐	24-h clock	1 ☐ 2 ☐ 5 ☐ 30 ☐

Study Setup & Data Collection

CRF – Blood collection Page



ID 0 0 0 1 | _____
Center No. Subject No.

Subject's initials _____ _____
1. 2. fam.

Basis Summary

(88

Blood collection - - PK/ADME

Please mark if blood collection was not done: ☐

Period number: 1

PK collection number : 1

Date sample taken

Day number : 1

day month year

Scheduled timepoint	Sample number	Was sample taken? 0=No /1=Yes	Actual time of sample
Pre-dose	101	0 ☐ 1 ☐	___:___ 24-h clock
	201	0 ☐ 1 ☐	___:___ 24-h clock
	301	0 ☐ 1 ☐	___:___ 24-h clock
	401	0 ☐ 1 ☐	___:___ 24-h clock
1 hour post-dose	102	0 ☐ 1 ☐	___:___ 24-h clock
		0 ☐ 1	

Data (Blood collection , PK & Dosage)

Subject number	Visit Report Name	Sample (ORACLE date)	Sample number	Scheduled timepoint (single or upper)
5101	P1 V3 Day1	22APR2010:08:35:00	1	0.000
5101	P1 V3 Day1	22APR2010:09:05:00	2	0.250
5101	P1 V3 Day1	22APR2010:09:35:00	3	0.750
5101	P1 V3 Day1	22APR2010:09:50:00	4	1.000
5101	P1 V3 Day1	22APR2010:10:20:00	5	1.500
5101	P1 V3 Day1	22APR2010:10:50:00	6	2.000
5101	P1 V3 Day1	22APR2010:11:50:00	7	3.000
5101	P1 V3 Day1	22APR2010:12:50:00	8	4.000
5101	P1 V3 Day1	22APR2010:14:50:00	9	6.000
5101	P1 V3 Day1	22APR2010:20:50:00	10	12.000
5101	P1 V4 Day2	23APR2010:08:50:00	11	24.000
5101	P1 V4 Day2	23APR2010:20:50:00	12	36.000
5101	P1 V5 Day3	24APR2010:08:50:00	13	48.000

Blood collection

Subjec numbe	Sample number	Period	Schedulec timepoint (single or upper)	Analyzed biological Matrix	Calculated concentration	Concentration unit
5101	1	1	0.000	Plasma	0	ng/mL
5101	2	1	0.250	Plasma	441	ng/mL
5101	3	1	0.750	Plasma	4200	ng/mL
5101	4	1	1.000	Plasma	4480	ng/mL
5101	5	1	1.500	Plasma	4140	ng/mL
5101	6	1	2.000	Plasma	3760	ng/mL
5101	7	1	3.000	Plasma	2530	ng/mL
5101	8	1	4.000	Plasma	1600	ng/mL
5101	9	1	6.000	Plasma	647	ng/mL
5101	10	1	12.000	Plasma	123	ng/mL
5101	11	1	24.000	Plasma	24.3	ng/mL
5101	12	1	36.000	Plasma	7.13	ng/mL
5101	13	1	48.000	Plasma	2.17	ng/mL

PK data

Subject number	Dosing (ORACLE date)		Dose amount
5101	22APR2010:08:50:00	1	150.000

Dosage

PK Merge

What is PK Merge

- PK merge is to combine information from two databases and provide the combined file to DMPK for processing

- In PK merge we need to collate information from several panels and prepare a dataset which contains everything together. Along with the Derived **ELAPSED TIME**

This includes:

- Age, sex, race from - Demography
- Height, Weight from - Vitals
- Treatment/Randomization
- Actual Sample time from – Blood collection
- Dose Administration time from - Dosage
- PK concentration - (LIMS)
- Others

PK Merge – Key Information

- PK Concentration file has the following information:
  - Study
  - Subject
  - Sample number
  - Concentration
- Clinical data has the following information
  - Study
  - Subject
  - Sample number
  - **Dose administration date/time**
  - Actual sample date/time
  - Treatment

Question?

Why Dose administration time is an important information in PK merge?

- Correct map of dosing time to samples is essential to calculate **elapsed time** (the time actually elapsed after dosing based on actual dose time and sample time). This information is derived in PK merge and used by PK scientists to calculate Tmax, AUC, t1/2, CL and all such parameters which depend on time

Simple Merge

Example

Blood collection + PK data by Subject Id, Sample No

Subject number	Visit Report Name	Sample (ORACLE date)	Sample number	Scheduled timepoint (single or upper)
5101	P1 V3 Day1	22APR2010:08:35:00	1	0.000
5101	P1 V3 Day1	22APR2010:09:05:00	2	0.250
5101	P1 V3 Day1	22APR2010:09:35:00	3	0.750
5101	P1 V3 Day1	22APR2010:09:50:00	4	1.000
5101	P1 V3 Day1	22APR2010:10:20:00	5	1.500
5101	P1 V3 Day1	22APR2010:10:50:00	6	2.000
5101	P1 V3 Day1	22APR2010:11:50:00	7	3.000
5101	P1 V3 Day1	22APR2010:12:50:00	8	4.000
5101	P1 V3 Day1	22APR2010:14:50:00	9	6.000
5101	P1 V3 Day1	22APR2010:20:50:00	10	12.000
5101	P1 V4 Day2	23APR2010:08:50:00	11	24.000
5101	P1 V4 Day2	23APR2010:20:50:00	12	36.000
5101	P1 V5 Day3	24APR2010:08:50:00	13	48.000

Blood collection

Subjec numbe	Sample number	Period	Schedulec timepoint (single or upper)	Analyzed biological Matrix	Calculated concentration	Concentration unit
5101	1	1	0.000	Plasma	0	ng/mL
5101	2	1	0.250	Plasma	441	ng/mL
5101	3	1	0.750	Plasma	4200	ng/mL
5101	4	1	1.000	Plasma	4480	ng/mL
5101	5	1	1.500	Plasma	4140	ng/mL
5101	6	1	2.000	Plasma	3760	ng/mL
5101	7	1	3.000	Plasma	2530	ng/mL
5101	8	1	4.000	Plasma	1600	ng/mL
5101	9	1	6.000	Plasma	647	ng/mL
5101	10	1	12.000	Plasma	123	ng/mL
5101	11	1	24.000	Plasma	24.3	ng/mL
5101	12	1	36.000	Plasma	7.13	ng/mL
5101	13	1	48.000	Plasma	2.17	ng/mL

PK data

(Blood collection + PK data) + Dose by Subject Id

Subject number	Dosing (ORACLE date)		Dose amount
5101	22APR2010:08:50:00	1	150.000

Dosage

Question?

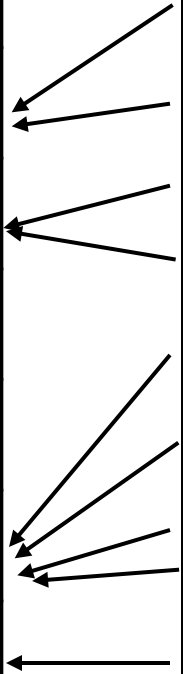
Subject number alone is enough for a successful merge with Dose administration information?

Single dose studies

- For single dose studies it is easy to map dose with PK collections because each subject has only one dose in a period.
- So period and subject number is unique key in merging dosing info with blood collection info
- For multiple dose study it does not provide a good key
- Next slide shows a typical problem for a multiple dose study

Multiple dose

DOSE administration		
Subject	Day	Dose time
1	1	19DEC:08:00
1	2	20DEC:08:00
1	3	21DEC:08:05
1	4	22DEC:08:03
2	1	17JAN:07:03
2	2	18JAN:06:58
2	3	19JAN:07:45



Sample collection			
Subject	Day	Time	Sample time
1	2	0	20DEC:07:50
1	2	8	20DEC:16:05
1	3	16	21DEC:00:03
1	3	24	21DEC:07:55
2	2	0	18JAN:06:55
2	2	8	18JAN:15:10
2	2	12	18JAN:19:01
2	2	16	18JAN:23:05
2	3	24	19JAN:07:00

The Problem

- Inconsistent merge: sometimes we map 16 hours post dose to day 2, sometimes to day 1. This is not the intention at all
- Remember: Correct elapsed time is absolutely necessary in order to obtain correct parameter calculation. This drives the analysis and interpretation of the trial
- As a measure to ease our work we have introduced PK collection number

Multiple dose

Include PK collection Number in the unique Key for Merging

Subject identifier	Sample Number	Scheduled Timepoint (single or upper)	Elapsed Time	Dosing Date and Time	Sampling Date and Time	PK Collection Number
0001_05101	1	0.000	0	02SEP2008 08:00	02SEP2008 07:25	1
0001_05101	2	3.000	3	02SEP2008 08:00	02SEP2008 11:00	1
0001_05101	3	6.000	6.016666666666...	02SEP2008 08:00	02SEP2008 14:01	1
0001_05101	4	9.000	8.983333333333...	02SEP2008 08:00	02SEP2008 16:59	1
0001_05101	5	12.000	12	02SEP2008 08:00	02SEP2008 20:00	1
0001_05101	6	24.000	23.93333333333...	02SEP2008 08:00	03SEP2008 07:56	1
0001_05101	6	0.000	0	03SEP2008 08:00	03SEP2008 07:56	2
0001_05101	7	3.000	3	03SEP2008 08:00	03SEP2008 11:00	2
0001_05101	8	6.000	6	03SEP2008 08:00	03SEP2008 14:00	2
0001_05101	9	9.000	9	03SEP2008 08:00	03SEP2008 17:00	2
0001_05101	10	12.000	12	03SEP2008 08:00	03SEP2008 20:00	2
0001_05101	11	24.000	23.9	03SEP2008 08:00	04SEP2008 07:54	2

PK Merge
Example: A sample is linked to multiple profiles

Blood Log: **Time schedule for blood sampling for safety and pharmacokinetic (PK) assessments**

Study Phase	Time		Safety mL	PK Coll. No.	[redacted] Number (mL)			[redacted] Number (mL)		
					Sample #	Aliquot #		Sample #	Aliquot #	
Screening	- 21 to -2	d	15							
Treatment Period 1										
Baseline	-1	d	15							
						1	2		1	2
Predose: Day 1	0	h		1	1	2	2	101	2	2
Postdose: Day 1	0.5	h		1	2	2	2	102	2	2
	1	h		1	3	2	2	103	2	2
	1.5	h		1	4	2	2	104	2	2
	2	h		1	5	2	2	105	2	2
	3	h		1	6	2	2	106	2	2
	4	h		1	7	2	2	107	2	2
	6	h		1	8	2	2	108	2	2
	8	h		1	9	2	2	109	2	2
	12	h		1	10	2	2	110	2	2
	16	h		1	11	2	2	111	2	2
Day 2	24	h		1	12	2	2	112	2	2
	36	h		1	13	2	2	113	2	2
Day 3	48	h		1	14	2	2	114	2	2
Day 4	72	h		1	15	2	2	115	2	2
Day 5	96	h		1	16	2	2	116	2	2
Day 8	168	h	15	1	17	2	2	117	2	2
Day 11	240	h		1	18	2	2	118	2	2
Day 15	336	h	15[#]	1	19	2	2	119	2	2
Day 22	504	h		1	20	2	2	120	2	2
Day 29	672	h		1	21	2	2	121	2	2
Day 37*	~864	h		1	22	2	2	122	2	2
Subtotal at end of Period 1			60			88			88	
Total for Period 1			236 mL							

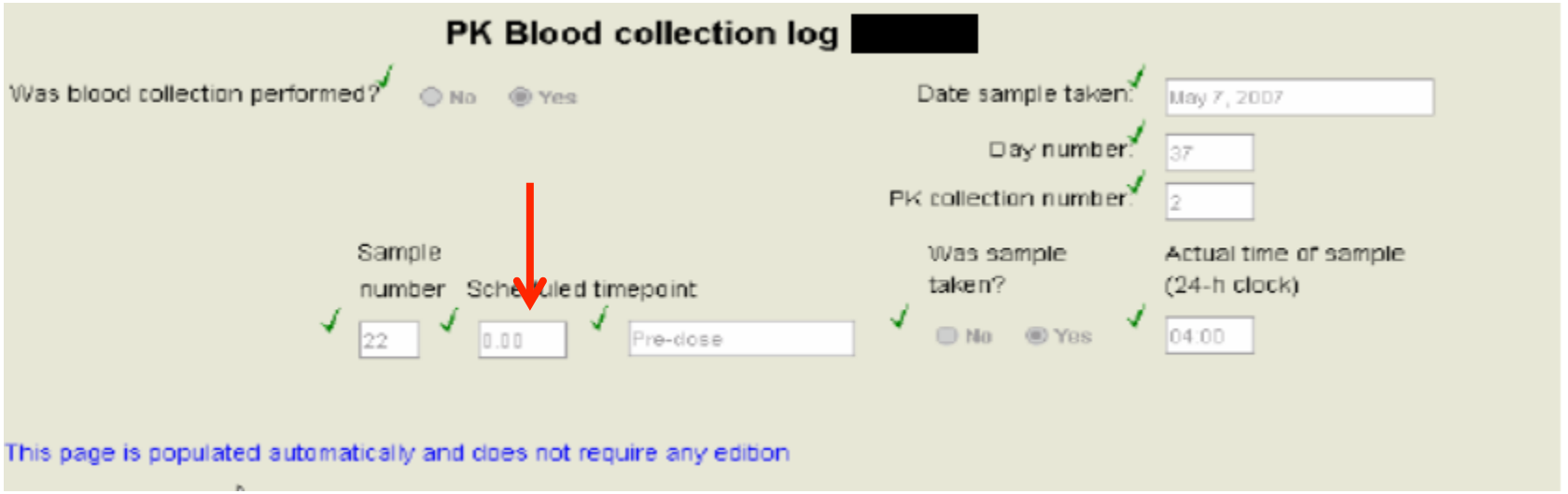
Day 37 is the pre-dose blood sample collected in period 2 treated as last PK sample for period 1

[#] Optional – Safety assessment will be done if required

Time schedule for blood sampling for safety and pharmacokinetic (PK) assessments (continued)

Study Phase	Time		Safety mL	PK Coll. No.	[redacted] Number mL			[redacted] Number mL		
					Sample #	Aliquot #		Sample #	Aliquot #	
Baseline Day 36	-1	d	15							
						1	2		1	2
Post-dose: Day 37	0.5	h		2	23	2	2	123	2	2
	1	h		2	24	2	2	124	2	2
	1.5	h		2	25	2	2	125	2	2
	2	h		2	26	2	2	126	2	2
	3	h		2	27	2	2	127	2	2
	4	h		2	28	2	2	128	2	2
	6	h		2	29	2	2	129	2	2
	8	h		2	30	2	2	130	2	2
	12	h		2	31	2	2	131	2	2
	16	h		2	32	2	2	132	2	2
Day 38	24	h		2	33	2	2	133	2	2
	36	h		2	34	2	2	134	2	2
Day 39	48	h		2	35	2	2	135	2	2
Day 40	72	h		2	36	2	2	136	2	2
Day 41	96	h		2	37	2	2	137	2	2
Day 44	168	h	15	2	38	2	2	138	2	2
Day 47	240	h		2	39	2	2	139	2	2
Day 51	336	h	15[#]	2	40	2	2	140	2	2
Day 58	504	h		2	41	2	2	141	2	2
Day 65	672	h		2	42	2	2	142	2	2
Day 73 (EOS)	~864	h	15	2	43	2	2	143	2	2
Subtotal at end of Period 2			60			84			84	
Total for Period 2			228 mL							
Total for Study			464 mL							

PK Merge
Example: A sample is linked to multiple profiles



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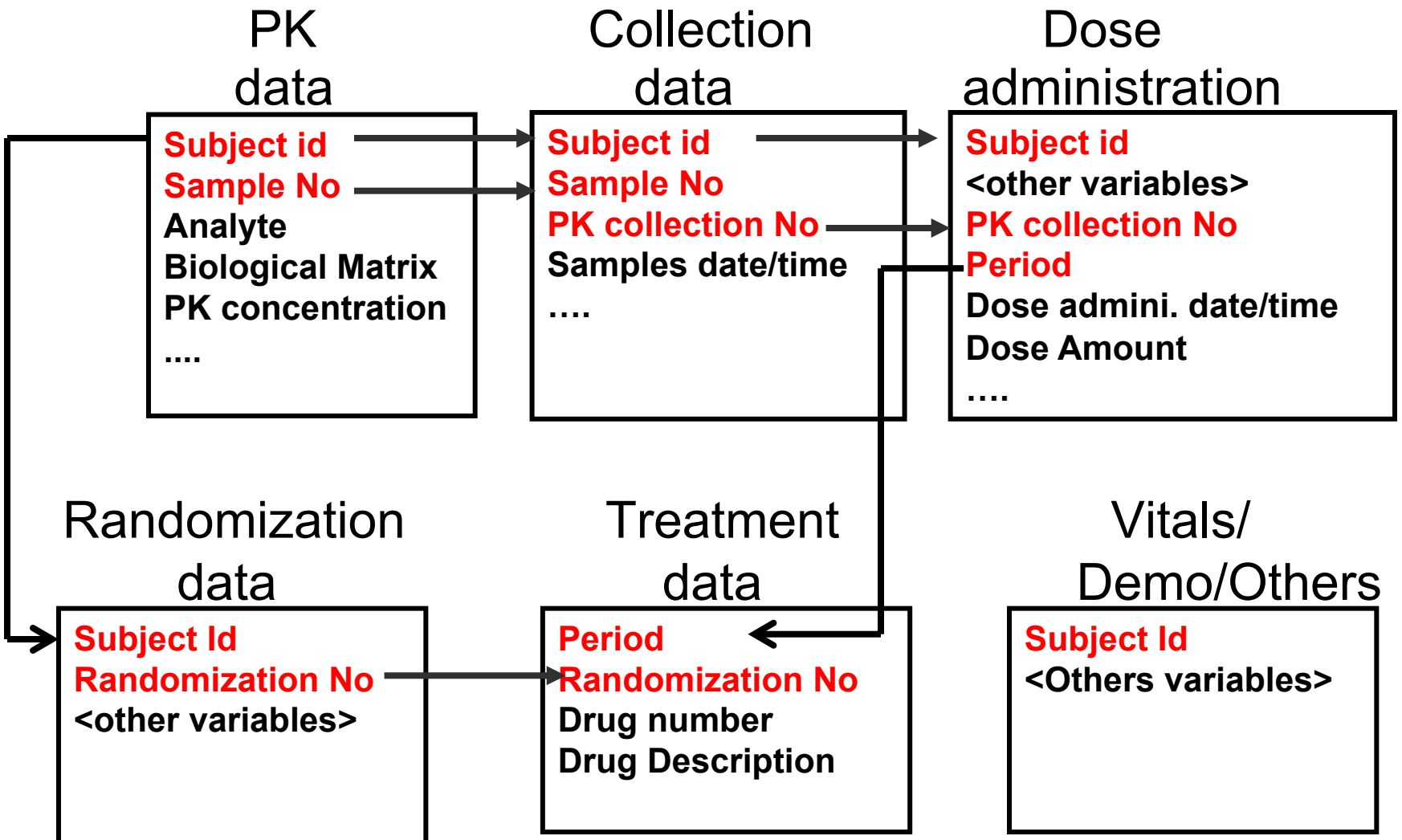
PK Merge - Key variables



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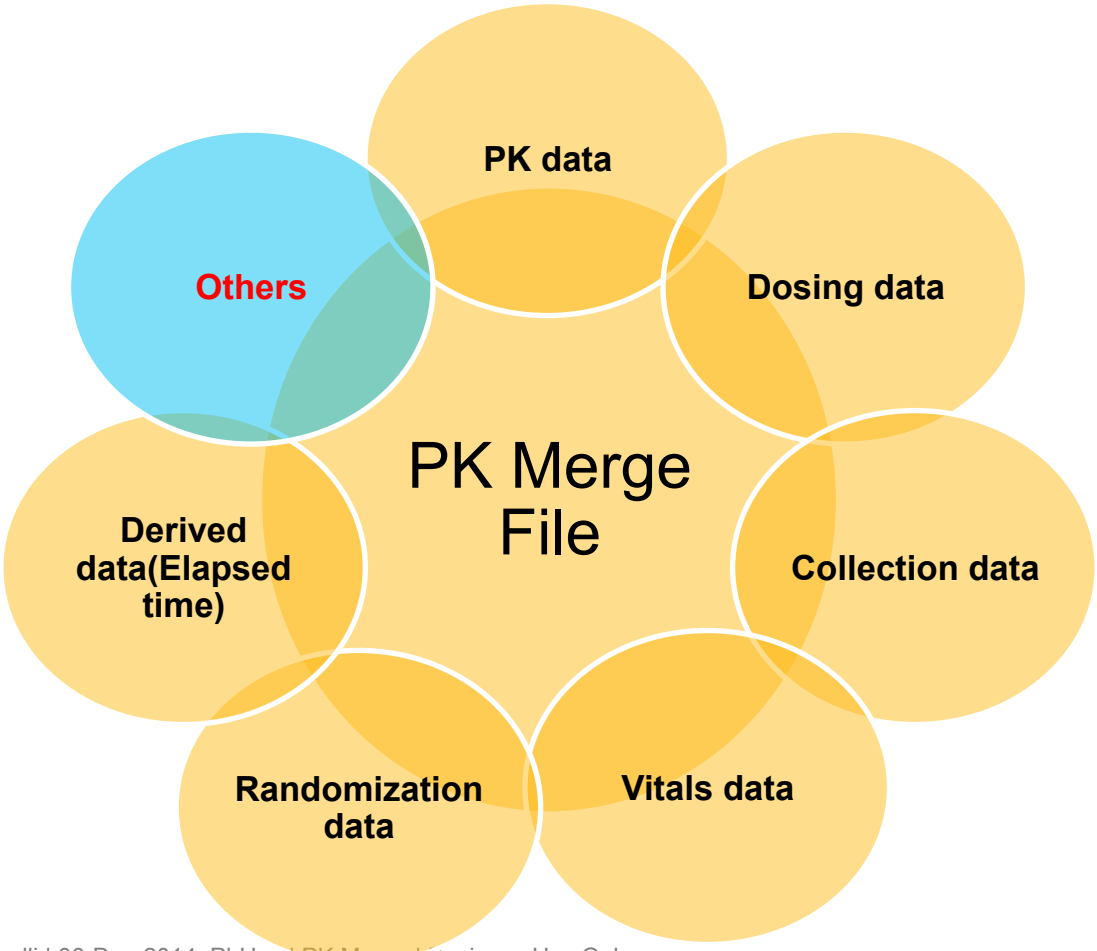
PK merge
Merged data

- The following data are merged for analysis purposes



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Summary

- PK analysis forms a major part of the understanding and development of the Investigational drug
- PK of the drug will also have a big impact on the label of the drug once its approved
- The PK dataflow starts at the protocol stage
- Study setup needs to be planned proper
- Correct Dose and sample time needs to be mapped to get the actual Elapsed time

References

www.fda.gov/

Thank You