

A Peak at PK

An Introduction to Pharmacokinetics



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- Pharmacokinetics = 'Movement of drugs'
- More commonly defined as: 'what the body does to the drug'
- Important in the understanding and development of drugs: dose level, dosing frequency, drug-drug interactions, effect of food, etc
- 4 main processes
 - Absorption
 - Distribution
 - Metabolism
 - Elimination
- We can get a feel for how these 4 processes work by plotting IMP concentration against time

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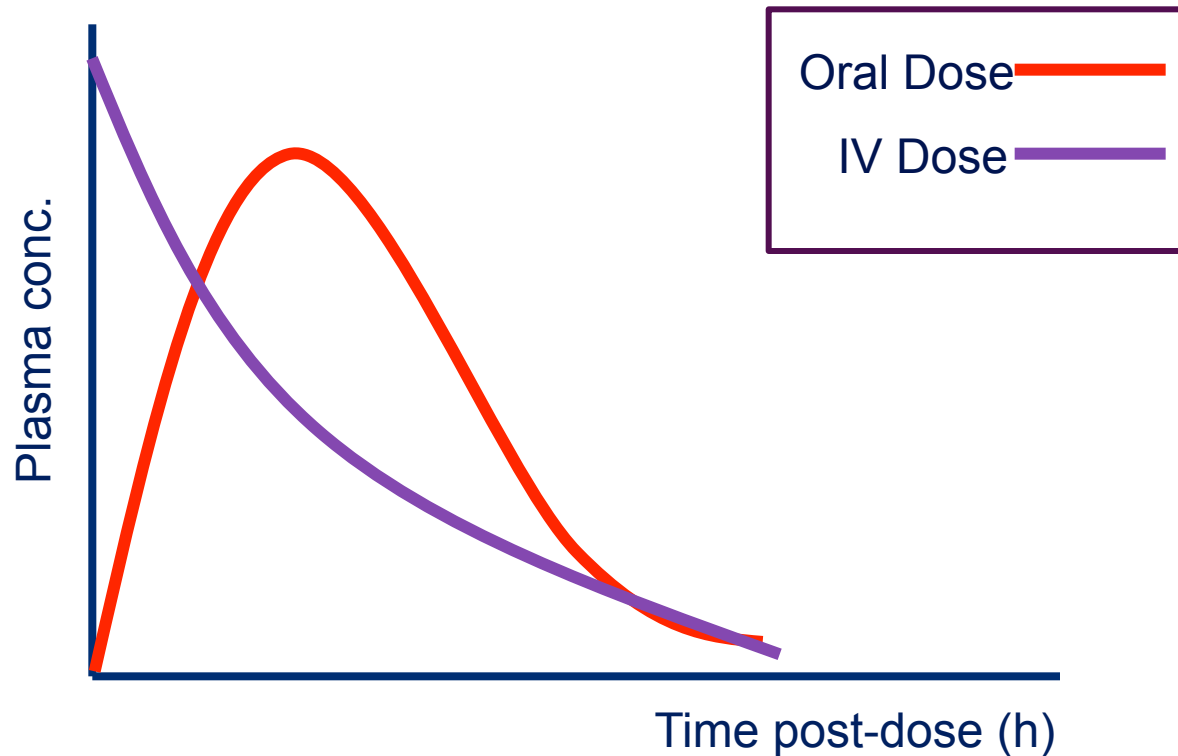
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PK Theory – Dose Response Curve



PK samples taken at predefined time points (from study protocol)

Samples are taken before and after dosing

At the point where plasma concentrations are measurable, all 4 processes are occurring.

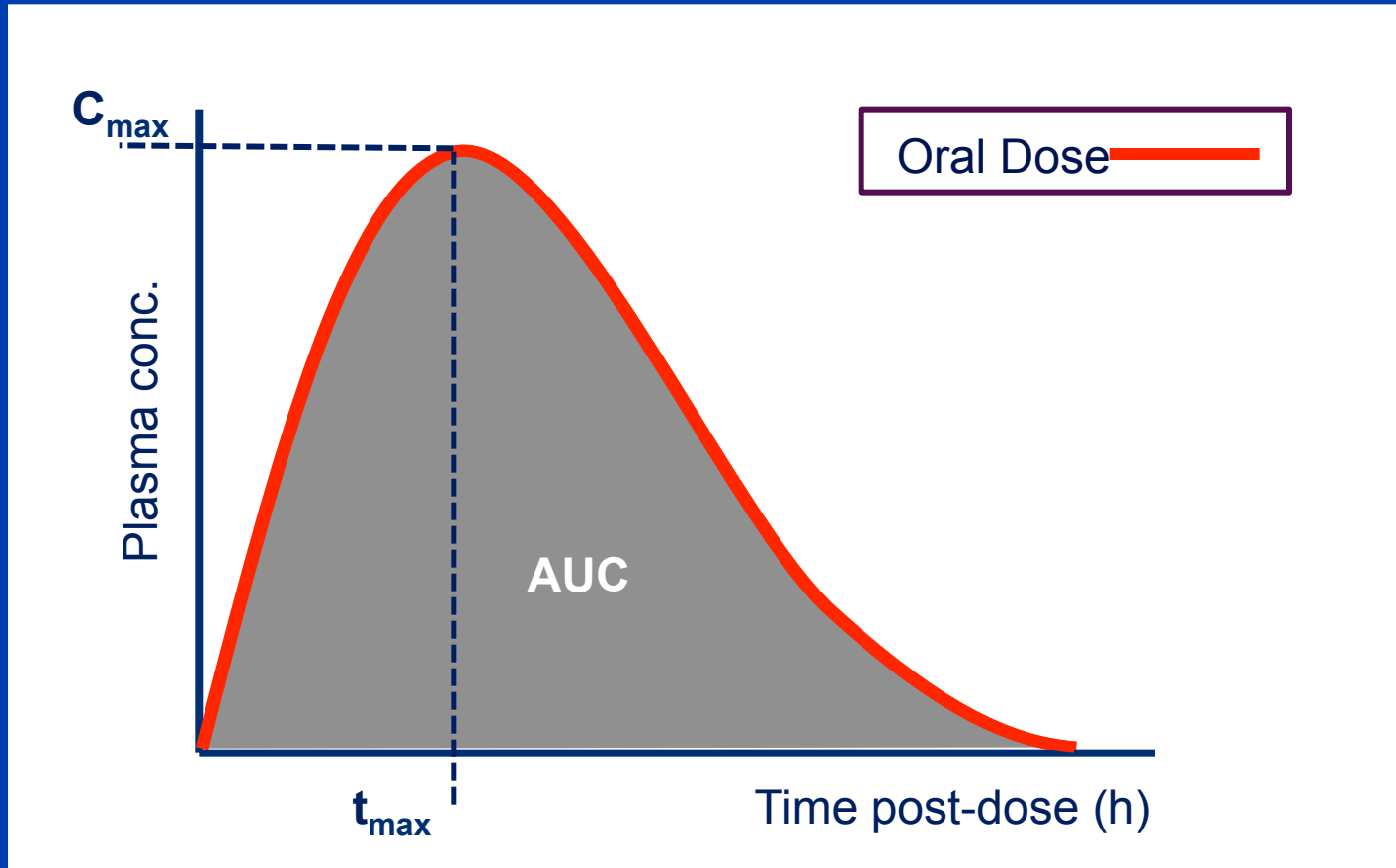
The route of Administration will affect
The absorption phase

The difference in absorption can be seen here between the oral and IV doses

Bioavailability is proportion of drug in the systemic circulation. Here the IV dose is 100% bioavailable. The oral dose has reduced bioavailability e.g. due to first pass metabolism

Dose Proportionality: There is a constant ratio between the dose and PK profile.

PK Theory – PK Parameters



PK response curves allow us to measure certain PK parameters which can be used to understand how the drug interacts with the body

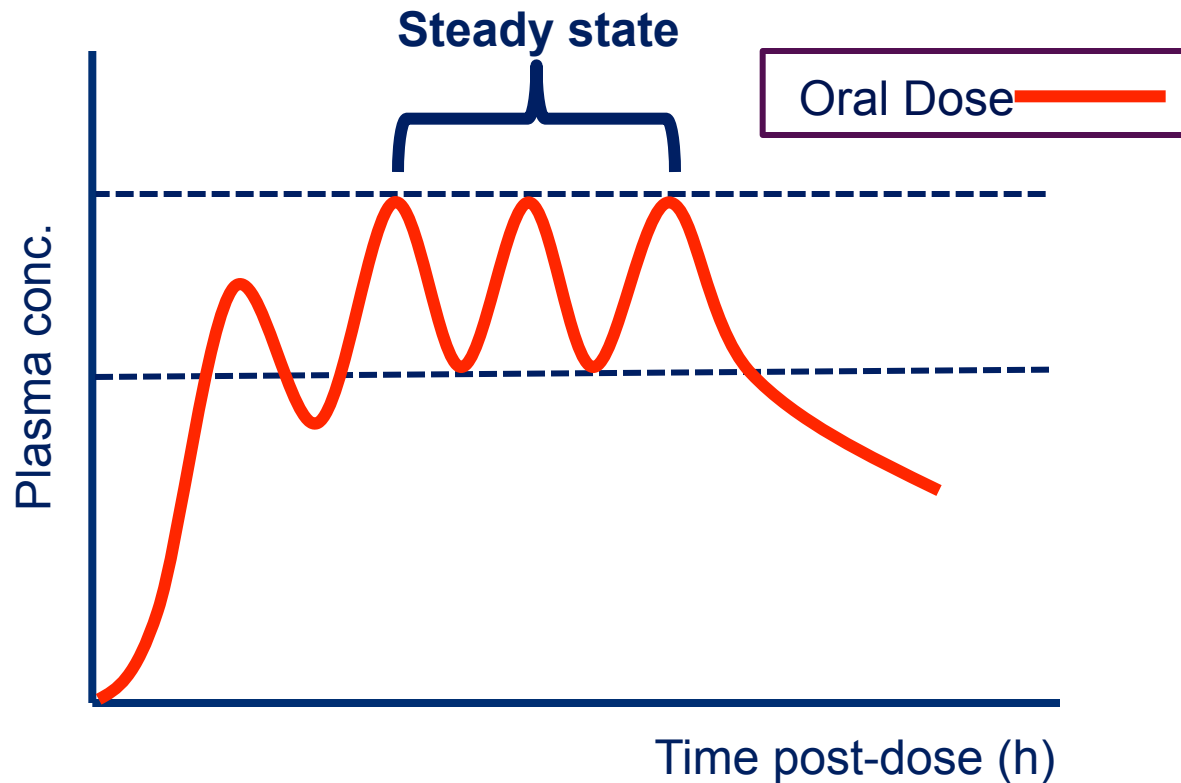
$C_{\max}$ = Maximum plasma concentration recorded

$t_{\max}$ = The time taken to reach $C_{\max}$

AUC = Area Under the Curve – a measure of exposure to the drug

$t_{1/2}$ = Half-Life - the time taken for the plasma concentration to fall by half its original value

PK Theory – Steady State



When the process of absorption is happening at exactly the same rate as Elimination.

Is dependent upon the half-life of the drug (assuming dosing intervals are kept constant)

Here two doses are required for steady-state to be reached. In practice this would happen over a larger number of doses, though a loading dose may be given initially to get to steady state more quickly.

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Single Ascending Dose Studies - SAD

	Week 1	2	3	4	5	6	7
Dose level 1							
Dose level 2							
Dose level 3							
Dose level 4							
Dose level 5							
Dose level 6							
Dose level 7							

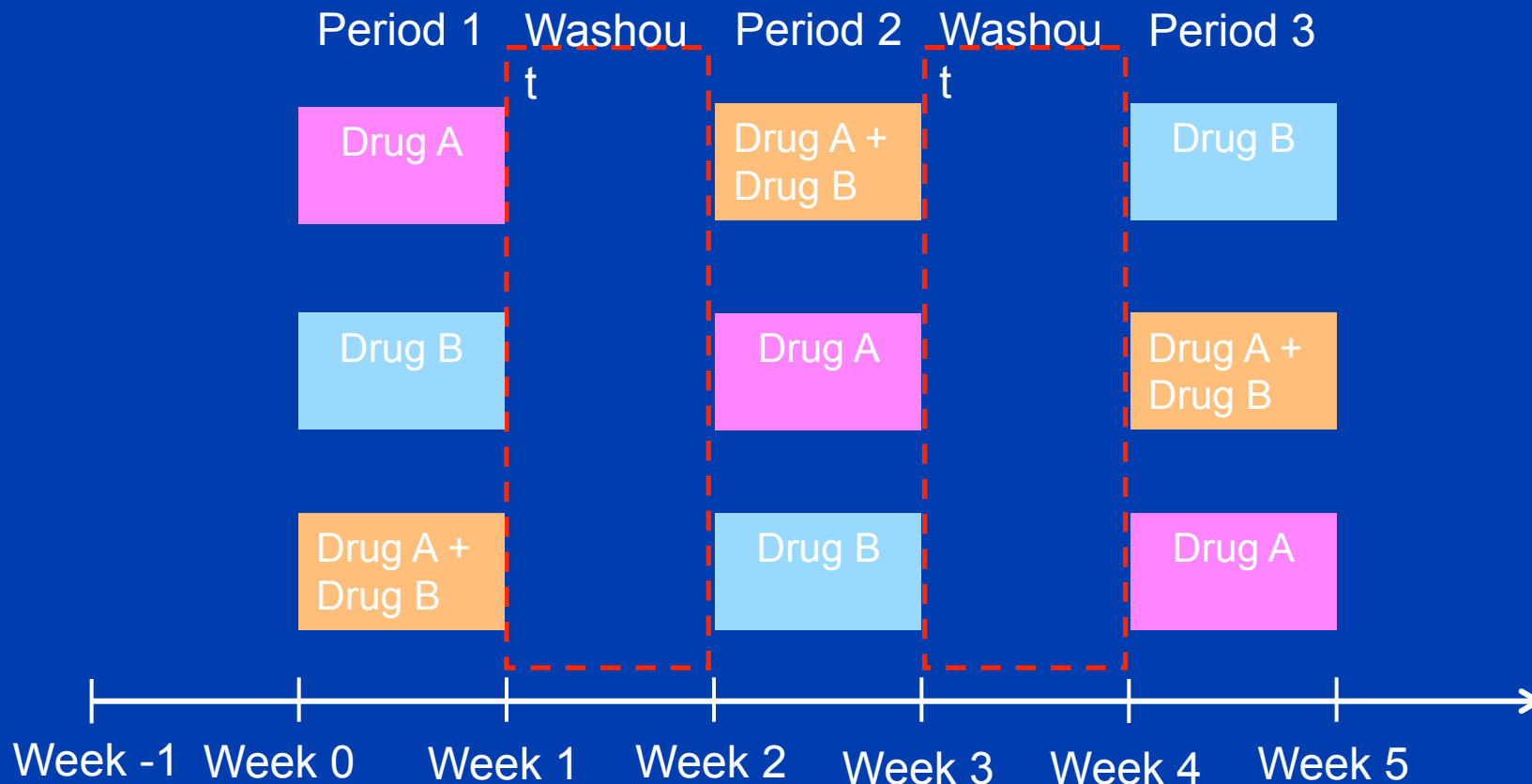
- First time drug has been given to humans
- Specified number of subjects at each dose level
- Dose can be either active or placebo
- Used to assess safety and tolerability
- Used to assess PK profile across a range of doses
 - Is the drug is dose proportional?
 - MTD

Multiple Ascending dose studies - MAD

	Month 1	2	3	4	5	6	7
Dose level 1							
Dose level 2							
Dose level 3							
Dose level 4							
Dose level 5							
Dose level 6							
Dose level 7							

- drug is safe and tolerable when a subject is dosed multiple times
- compare PK of multiple dose data against single dose PK data to see if any changes over time, determine if there is any accumulation

Crossover – Drug Drug Interaction (DDI) /Food Effect



Aim : Does one drug enhances or reduces the effect of another drug.

Aim: To test the effect of food on the rate and extent of absorption of a drug when given just after a meal compared to when given under fasted conditions.

Bioavailability vs. Bioequivalence



Study	Relative Bioavailability	Absolute Bioavailability	Bioequivalence
Design	2 Period Crossover Drug A formulation 1 vs. Drug A formulation 2	2 Period Crossover IV vs. Oral dose	2 Period Crossover Drug A vs. Generic Drug A or Drug A formulation 1 vs. Drug A formulation 2
Aim	Tests the rate and extent of absorption of the drug when compared to another formulation or product of the same drug. Used to Compare and contrast the PK profiles.	Since an IV infusion is 100% bioavailable an oral dose is given to measure the bioavailability of the oral dose compared to the IV dose i.e. how much of the oral IMP reaches the systemic circulation compared to the IV dose?	To show that the two formulations are statistically the same (the confidence intervals within certain bound (generally between 0.8-1.25)) in terms of PK parameters (C_{max} and AUC).

Renal + Hepatic Impairment Studies:

Group
Normal
Mild
Moderate
Severe

Patients are grouped on certain criteria

Matched on age, gender and weight

Aim: Do impaired patients need a dose adjustment?

Mass Balance Studies:

Administering a certain amount of radiolabelled drug.

The radioactive marking is used to keep track of the drug and its metabolites by collecting the subject's blood, urine and faeces and assaying them for radioactive label.

Aim: determine the routes and rates of excretion and the metabolic profile of the IMP.



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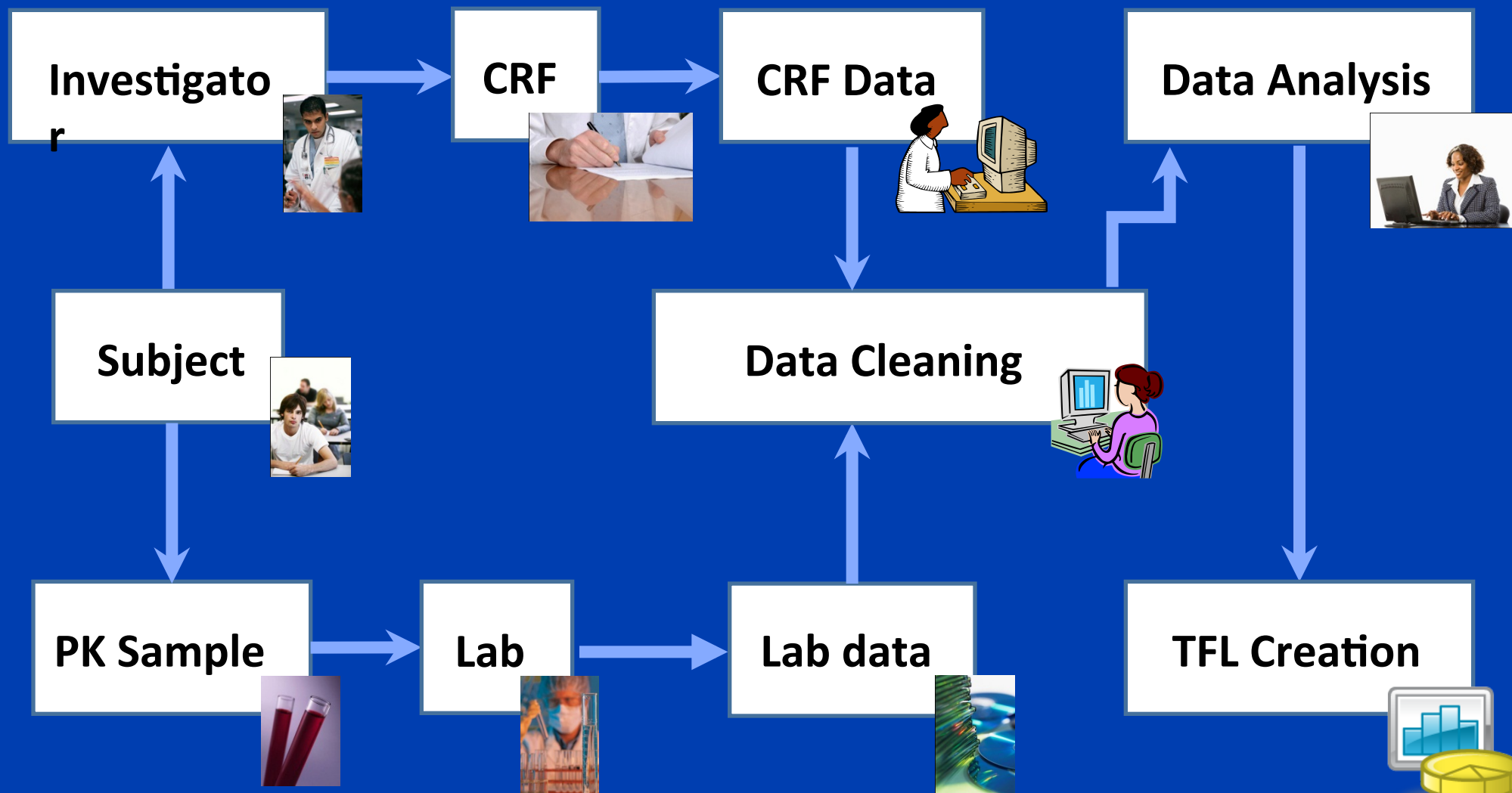
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Example PK Scheduling from a

Procedure	Day 1													Day 2
	Pre-dose	0 h	0.25 h	0.5 h	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h	12 h	15 h	24 h
Drug Administration		x												
Pharmacokinetic Sampling	x		x	x	x	x	x	x	x	x	x	x	x	x

Example CRF page

#	Sample Number	Sample schedule	Date of Sample dd mon yyyy	Time of Sample (24 hr clock)	Sample comments
1	101	PREDOSE			
2	102	0.25 H			
3	103	0.5 H			
4	104	1 H			
5	105	1.5 H			
6	106	2 H			
7	107	3 H			
8	108	4 H			
9	109	6 H			
10	110	8 H			
11	111	12 H			
12	112	15 H			

An example of part of a PK dataset created by the Statistical Group

<u>Subject</u>	<u>Sample #</u>	<u>Visit</u>	<u>Scheduled sampling time</u>	<u>PK Analyte</u>	<u>Plasma Conc</u>	<u>Unit</u>	<u>Datetime of IMP dosing</u>	<u>Datetime of PK sample</u>	<u>Actual time from last dose</u>
1001	101	Day 1	PREDOSE	Drug A	BLQ	NG/ML	31OCT2011:08.00	31OCT2011:07.21	-0.65
1001	102	Day 1	0.25 H	Drug A	BLQ	NG/ML	31OCT2011:08.00	31OCT2011:08.15	0.25
1001	103	Day 1	0.5 H	Drug A	BLQ	NG/ML	31OCT2011:08.00	31OCT2011:08.30	0.5
1001	104	Day 1	1 H	Drug A	BLQ	NG/ML	31OCT2011:08.00	31OCT2011:09.05	1.08
1001	105	Day 1	1.5 H	Drug A	BLQ	NG/ML	31OCT2011:08.00	31OCT2011:09.30	1.5
1001	106	Day 1	2 H	Drug A	BLQ	NG/ML	31OCT2011:08.00	31OCT2011:10.10	2.17
1001	107	Day 1	3 H	Drug A	11.1	NG/ML	31OCT2011:08.00	31OCT2011:11.00	3
1001	108	Day 1	4 H	Drug A	54	NG/ML	31OCT2011:08.00	31OCT2011:12.00	4
1001	109	Day 1	6 H	Drug A	534	NG/ML	31OCT2011:08.00	31OCT2011:14.04	6.07
1001	110	Day 1	8 H	Drug A	194	NG/ML	31OCT2011:08.00	31OCT2011:16.02	8.03
1001	111	Day 1	12 H	Drug A	105	NG/ML	31OCT2011:08.00	31OCT2011:20.00	12
1001	112	Day 1	15 H	Drug A	78.7	NG/ML	31OCT2011:08.00	31OCT2011:23.08	15.13
1001	113	Day 1	24 H	Drug A	57.9	NG/ML	31OCT2011:08.00	01NOV2011:08.00	24

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Listing of PK Concentration Data

Listing of Individual Concentrations by Visit

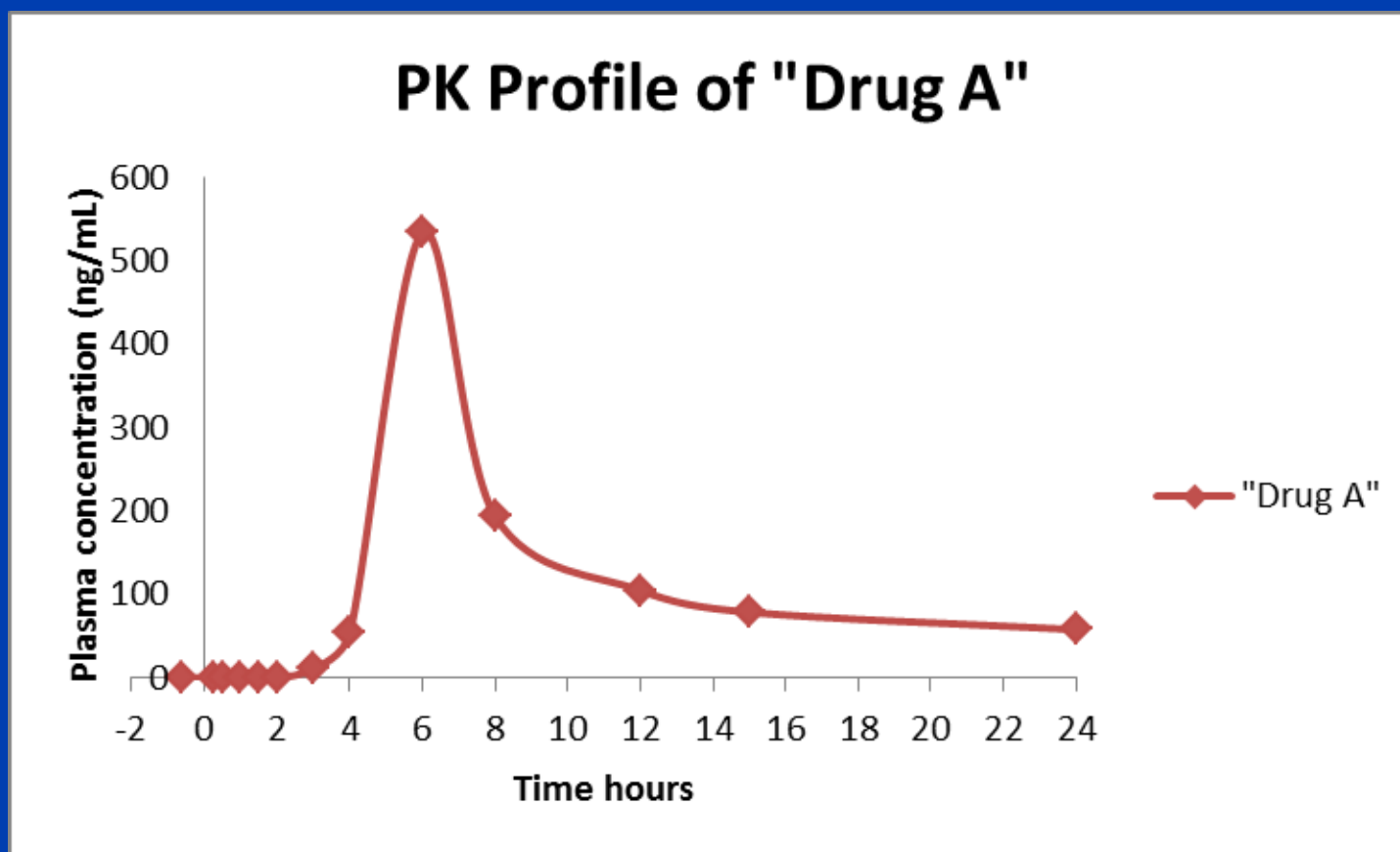
CRTN/Pt. No.	Sex	Baseline Age (years)	Visit	Study Day	Drug	Nominal time from first dose (h)	Actual time from first dose (h)	Drug Concentration (ng/mL)
123456/1001	Male	29	DAY 1	1	Drug A	-0.5	-0.65	BLQ
			DAY 1	1		0.25	0.25	BLQ
			DAY 1	1		0.5	0.5	BLQ
			DAY 1	1		1	1.08	BLQ
			DAY 1	1		1.5	1.5	BLQ
			DAY 1	1		2	2.17	BLQ
			DAY 1	1		3	3	11.1
			DAY 1	1		4	4	54
			DAY 1	1		6	6.07	534
			DAY 1	1		8	8.03	194
			DAY 1	1		12	12	105
			DAY 1	1		15	15.13	78.7
			DAY 1	2		24	24	57.0

CRTN = Clinical Research Task Number (center no.).

Summary of PK Parameters by Trial Treatment in A DDI Study

	Drug A N = 12	Drug A + Drug B N = 11
AUC (ug*day/mL)		
Mean	1692.123	1750.269
SD	375.7369	333.9327
SEM	128.9302	101.9361
Median	1591.932	1630.024
Min-Max	1254.02 - 2333.62	1392.78 - 2151.12
n	12	11
 Cmax (ug/mL)		
Mean	201.927	187.379
SD	35.5269	41.5363
SEM	21.8426	29.6357
Median	205.123	170.341
Min-Max	166.12 - 309.27	121.73 - 315.07
n	12	11

Individual PK profile



Plot of data from
the above dataset
N.B. BLQ is
plotted as 0

Estimated Geometric Mean Ratios of PK Parameters of Drug X for A Bioequivalence Study

Pharmacokinetic Parameter	Comparison (*)	Unit	Geometric Mean Ratio	Confidence Interval		Confidence Level (Percent)
				Lower Limit	Upper Limit	
AUC	B vs A	hr*ng/mL	1.24	1.10	1.40	90
	C vs A	hr*ng/mL	1.11	0.97	1.25	90
Cmax	B vs A	ng/mL	1.23	1.05	1.45	90
	C vs A	ng/mL	1.03	0.86	1.24	90

For AUC B and C were 24% and 11% higher than that of A.

Confidence interval within the bounds of 0.8-1.25

C is bioequivalent to A.

Can't claim that B is bioequivalent to A

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- Introduction into PK theory
- PK parameters
- Phase I studies and how they describe the PK of the drug.
- PK data flow from collection - TFLs and statistical analysis.
- Importance of PK in the development of the drug.
 - If the PK of a drug is undesirable then this can cause the development of the drug to be ceased.
 - Impact on the label:
 - Frequency of dosing
 - Fed or Fasted
 - if the drug should not be taken in conjunction with another drug.
 - Dose adjustment for special populations

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- Carol Reid – Statistical

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