NCI Drug Development Workshop: How to Advance A Therapeutic Candidate from Bench to Bedside

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Session II, Topic 2

Preclinical pharmacology in IND-enabling studies and clinical pharmacology in clinical protocol development

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Disclaimers

I have no conflicts of interest

This talk does not necessarily represent official views of OSU (or any other organization), and may conflict with it

Any expressed opinions are not necessarily mine, and probably not necessary

Primary objectives

- Evaluate how and why pharmacokinetics (PK) studies are conducted during drug development and to ultimately facilitate optimal use of drugs
- Understand mechanisms contributing to variability in exposure to small-molecule cancer drugs
- Interpret fundamental PK data, and how they related to drug efficacy, safety and toxicity

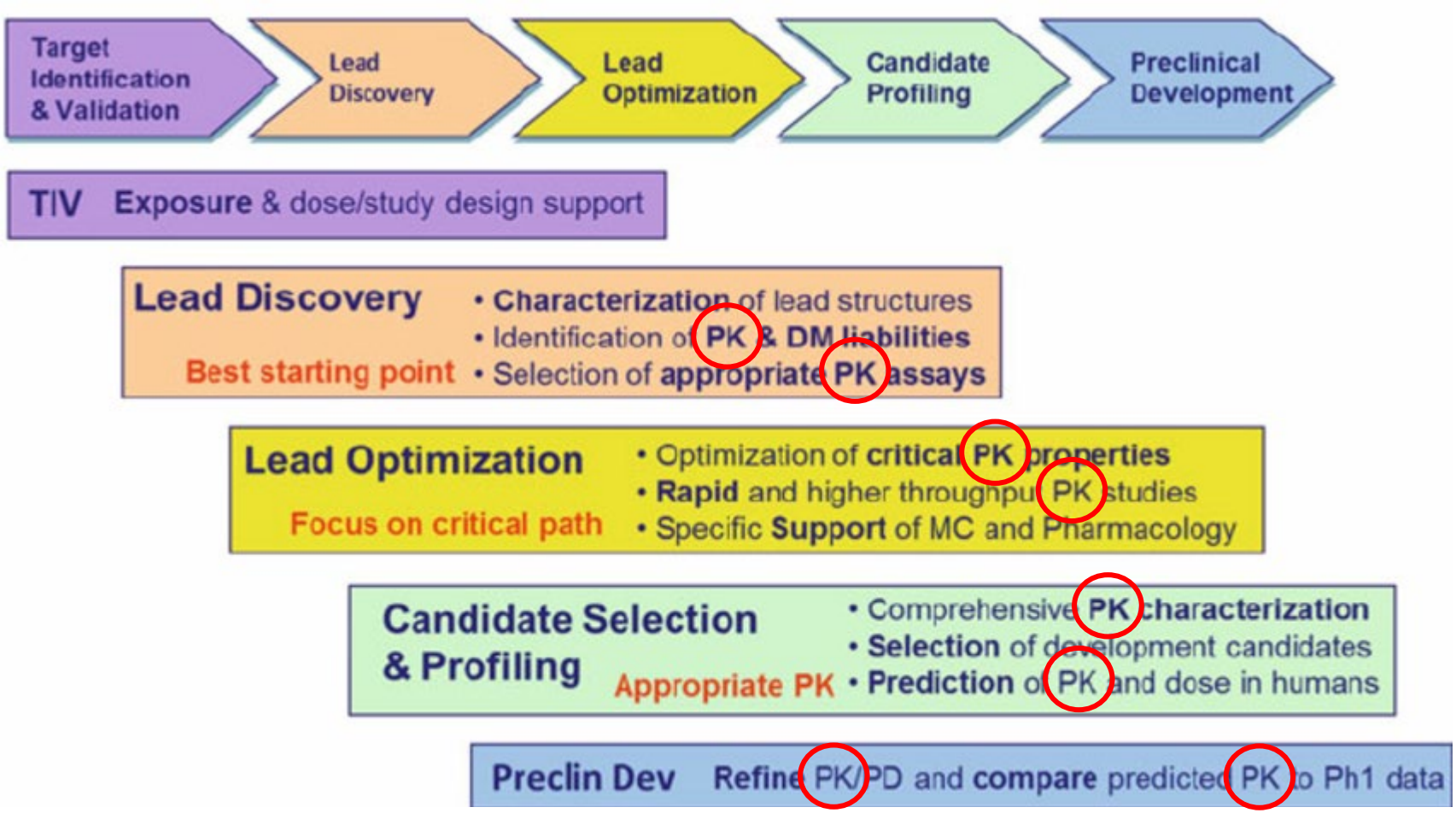
PK and pharmaceutics: intro and definitions

Pharmaceutics is a discipline of pharmacy that deals with the process of turning a new chemical entity (or existing drug) into a medication to be used safely and effectively by patients.

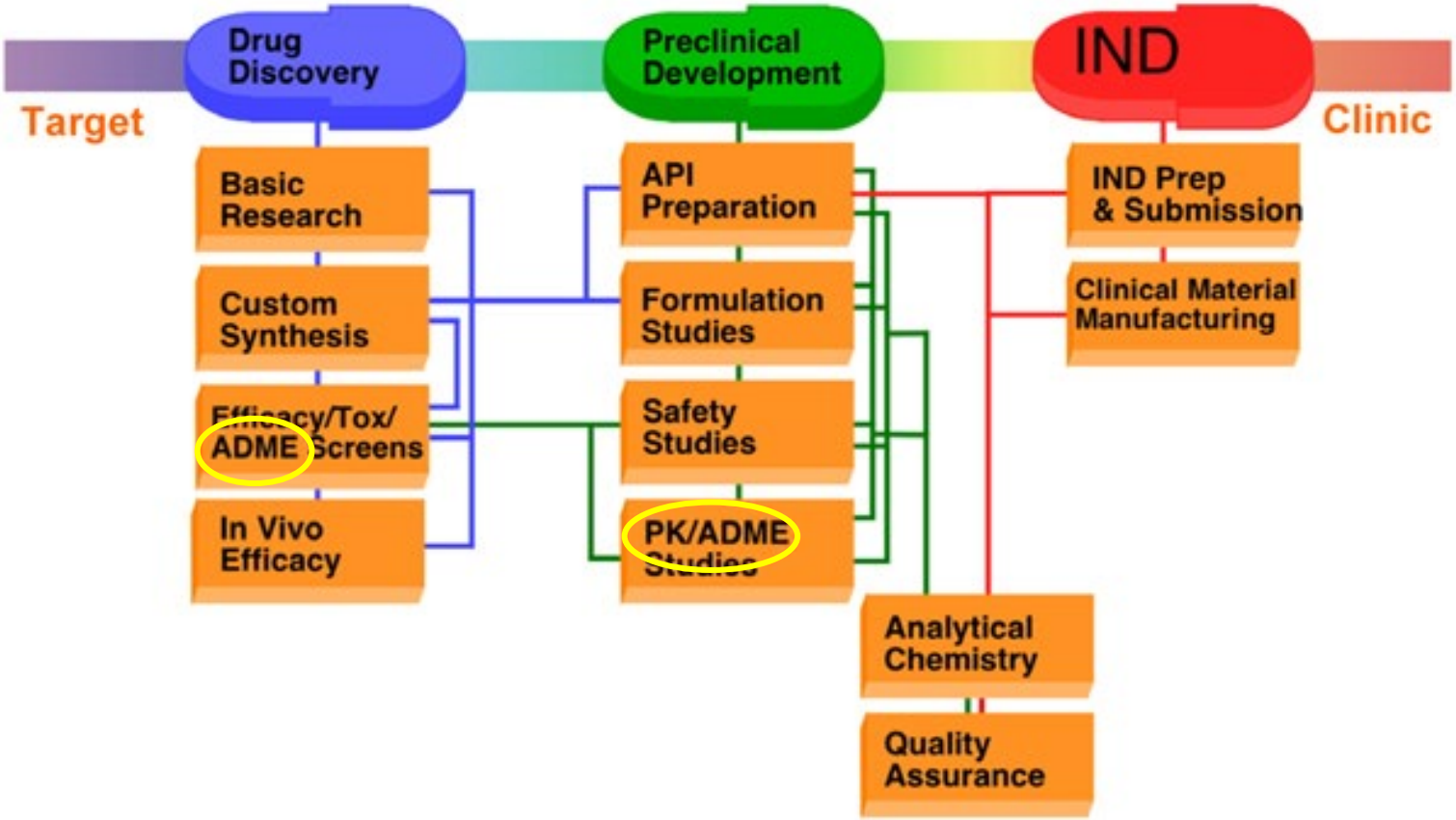
There are many chemicals with pharmacological properties, but most need special measures to help them achieve therapeutically-relevant amounts at their sites of action.

Pharmaceutics helps to relate the delivery of drugs (**formulation**) with absorption/disposition (**PK**) and pharmacological response (**pharmacodynamics; PD**).

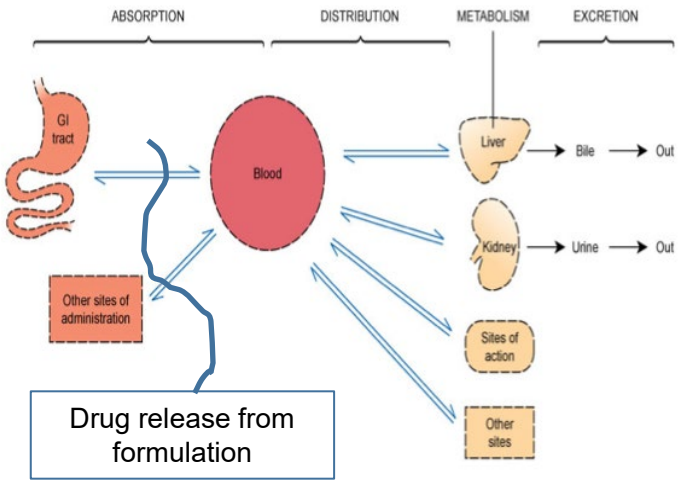
PK in drug discovery and development



Safety pharmacology & drug development



“ADME”



Absorption: movement of a substance from the site of administration to the site of measurement

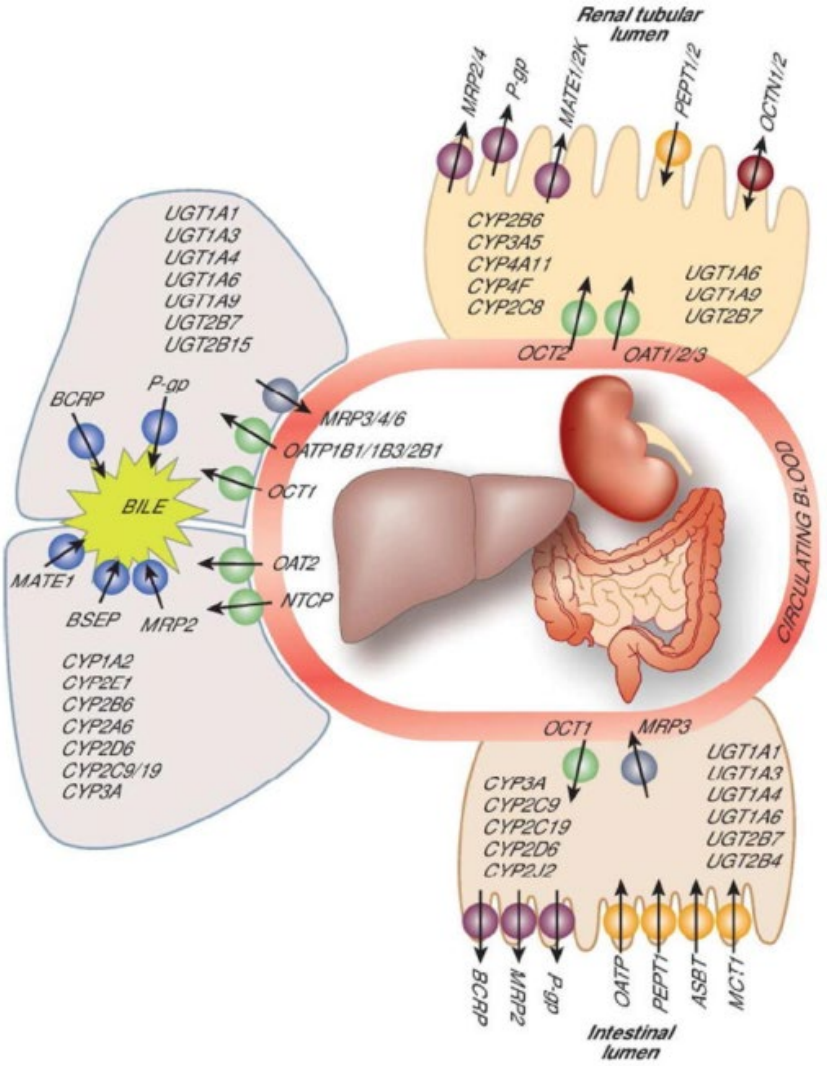
Distribution: reversible movement of a substance to and from the site of measurement

Metabolism: conversion of a substance to another species (and *vice versa*)

Excretion: irreversible loss of a substance from the body

N.B. Elimination: Metabolism + Excretion

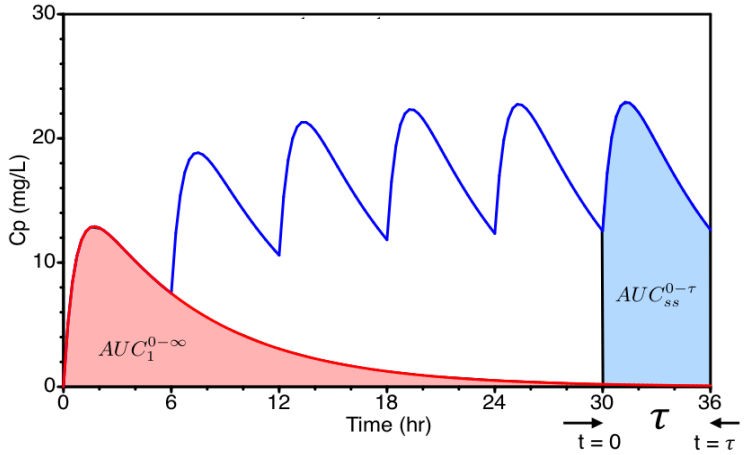
Drug metabolism and transport as key drivers of ADME properties



Why bother with PK?

Why bother with PK?

1. To design safe and effective dose regimens for individual patients



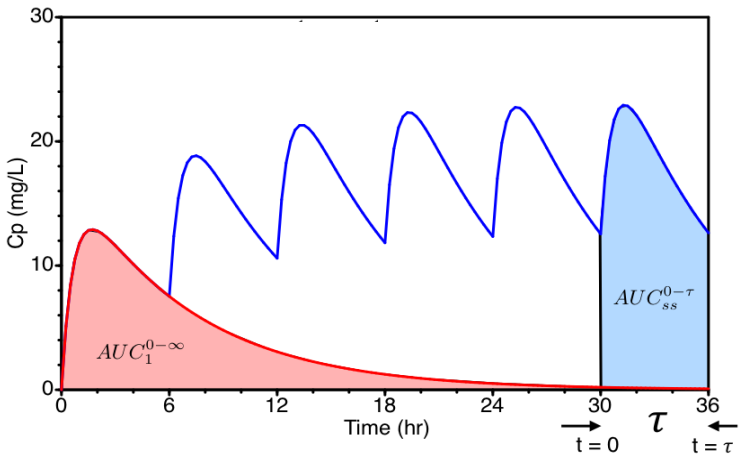
Any dosage regimen includes 3 questions

- How much dose?
- How often (dosing interval)?*
- How long?

* Cf. despite half-life differences (eg, dasatinib, 3 h vs gilteritinib, 159 h), most TKIs are given once daily

Why bother with PK?

1. To design safe and effective dose regimens for individual patients



Any dosage regimen includes 3 questions

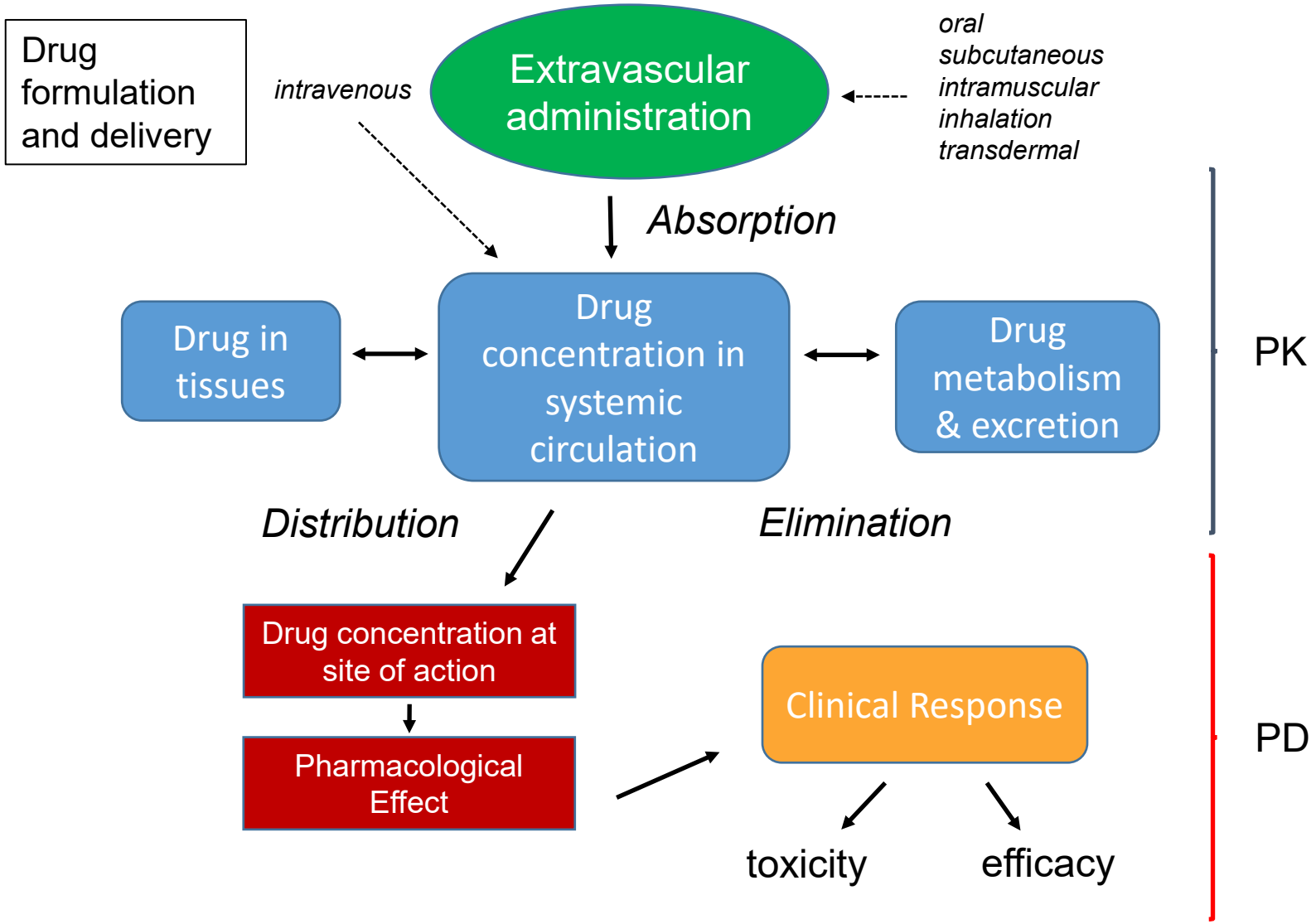
- How much dose?
- How often (dosing interval)?*
- How long?

2. To understand the degree of PK variability between patients

* Cf. despite half-life differences (eg, dasatinib, 3 h vs gilteritinib, 159 h), most TKIs are given once daily

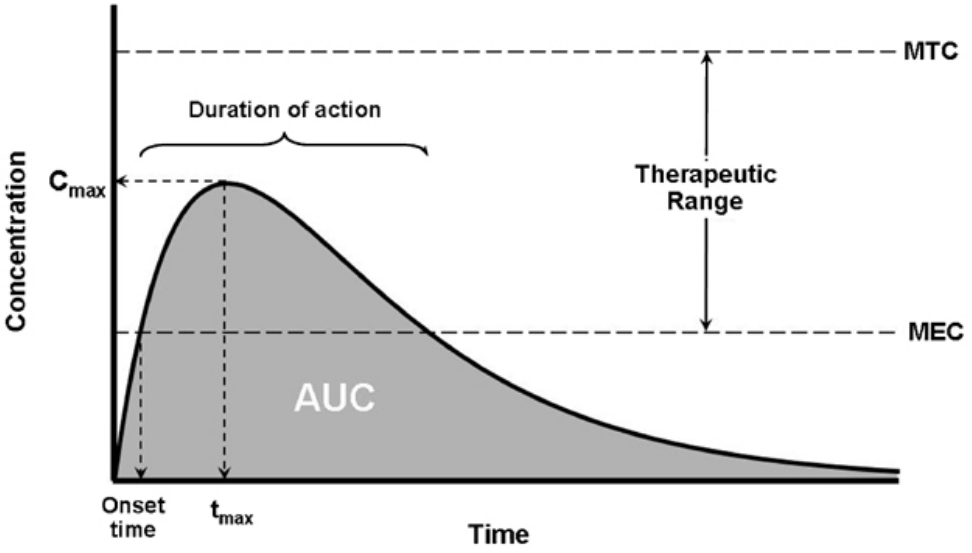
Why consider PK variability?

Pharmacokinetics (PK) vs Pharmacodynamics (PD)

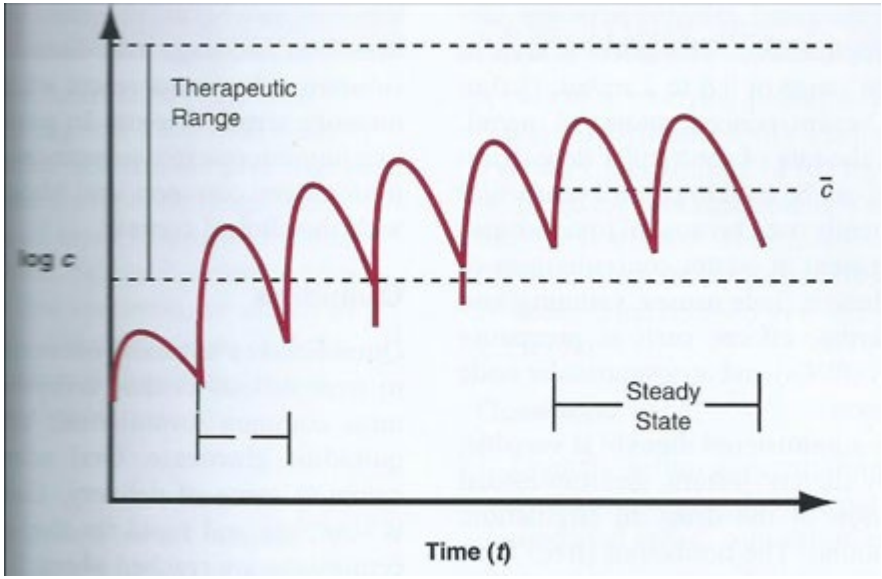


Therapeutic range or “window” or “index”

Single-dose regimen

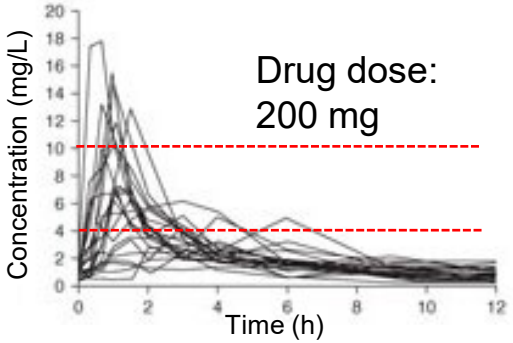


Multiple-dose regimen



C_{max} - maximum plasma concentration
T_{max} - time to maximum plasma concentration
AUC - area under the concentration-time (C-T) curve
MEC - minimum effective concentration
MTC – minimum toxic concentration

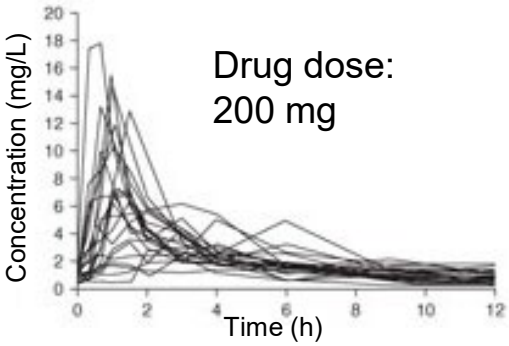
Inter-patient variability in plasma C-T curve



Sources of variation in drug plasma concentrations (PK variability)

Morphometric:
Body size
Body composition

Drug Specific:
Dose & schedule
Dosage form
Delivery systems



Demographic:
Age
Race/ethnicity
Sex

Variability

Genetics:
Drug metabolism
Drug transport

Physiologic:
Disease
Hepatic function
Renal function

Environment:
Drug-drug interactions
Drug-CAM interactions
Drug-formulation interactions
Drug-food constituent interactions

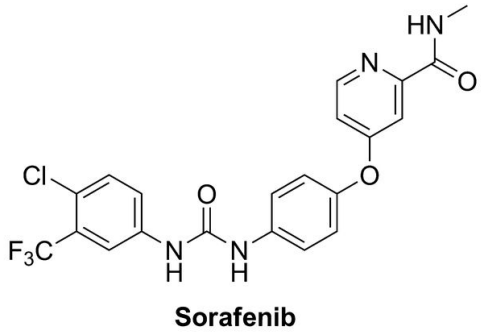
“Pre-work” to perform PK studies

- Questions related to sampling “the system”
- Design of PK sampling schemes
- Preparation & documentation

Questions related to sampling “the system”

- Parent drug and/or metabolites?
- Plasma vs whole blood?
- Cells vs biological fluids?
- Bioanalytical method development & validation
- When to administer drugs? (diurnal and seasonal variation)
- Should posture, age, strain, and sex be considered?

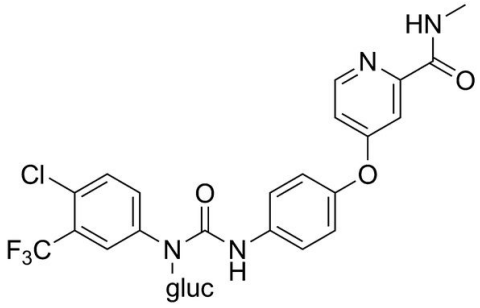
Measurement of metabolites?



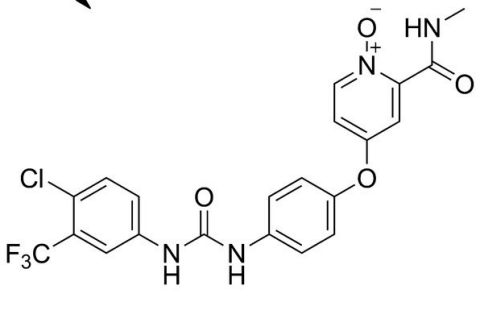
Sorafenib

UGT1A9

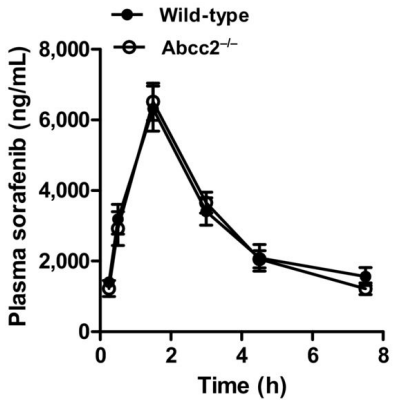
CYP3A4

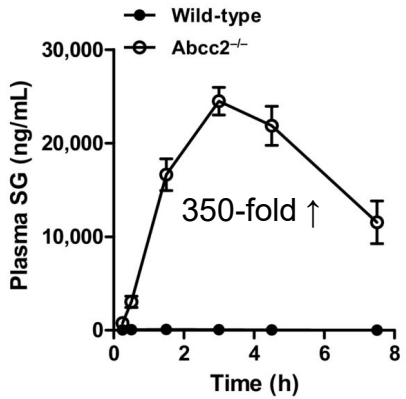


Glucuronide



N-oxide





Major inactive metabolite but contributes to enterohepatic recirculation in humans

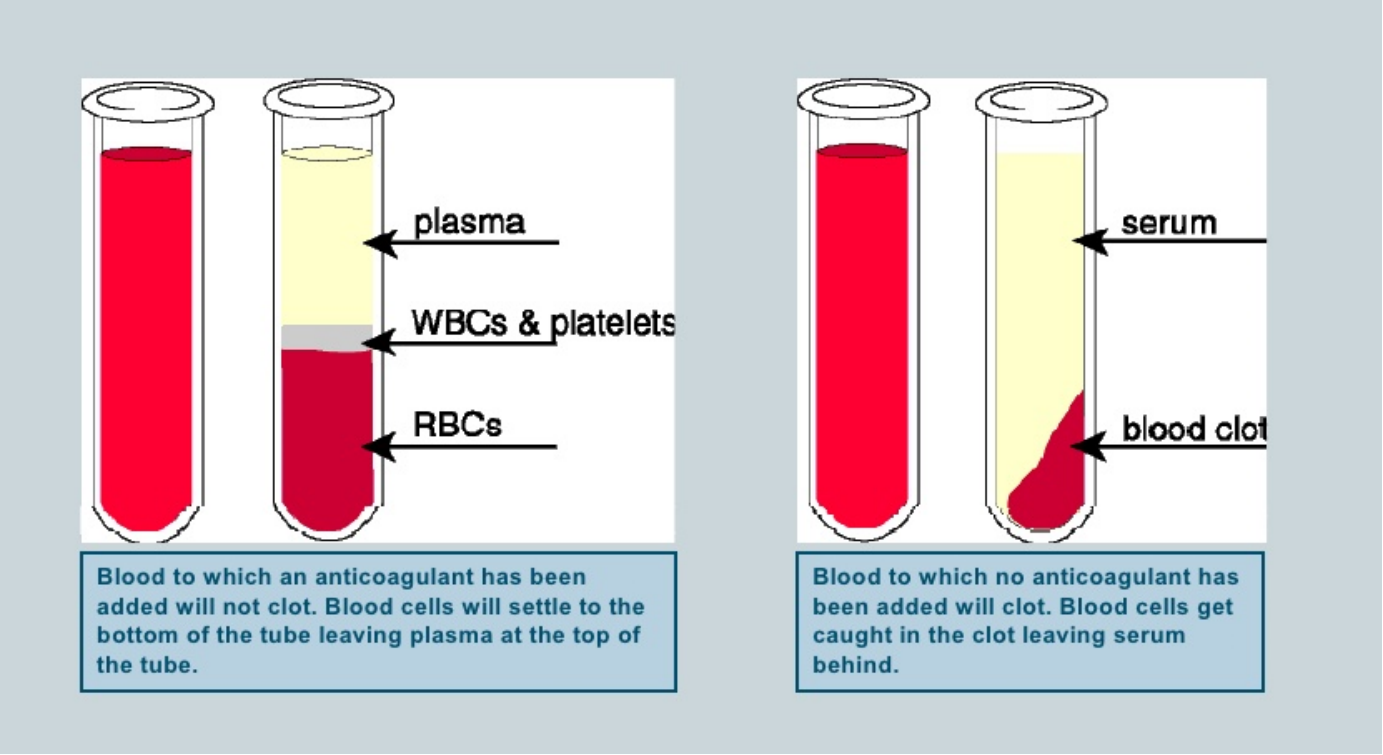
Minor active metabolite

Vasilyeva et al, Cancer Res 2015
(SG, sorafenib-glucuronide)

PK Sampling Site

- Measurement of a drug in the body is usually limited to the blood or plasma (or serum)

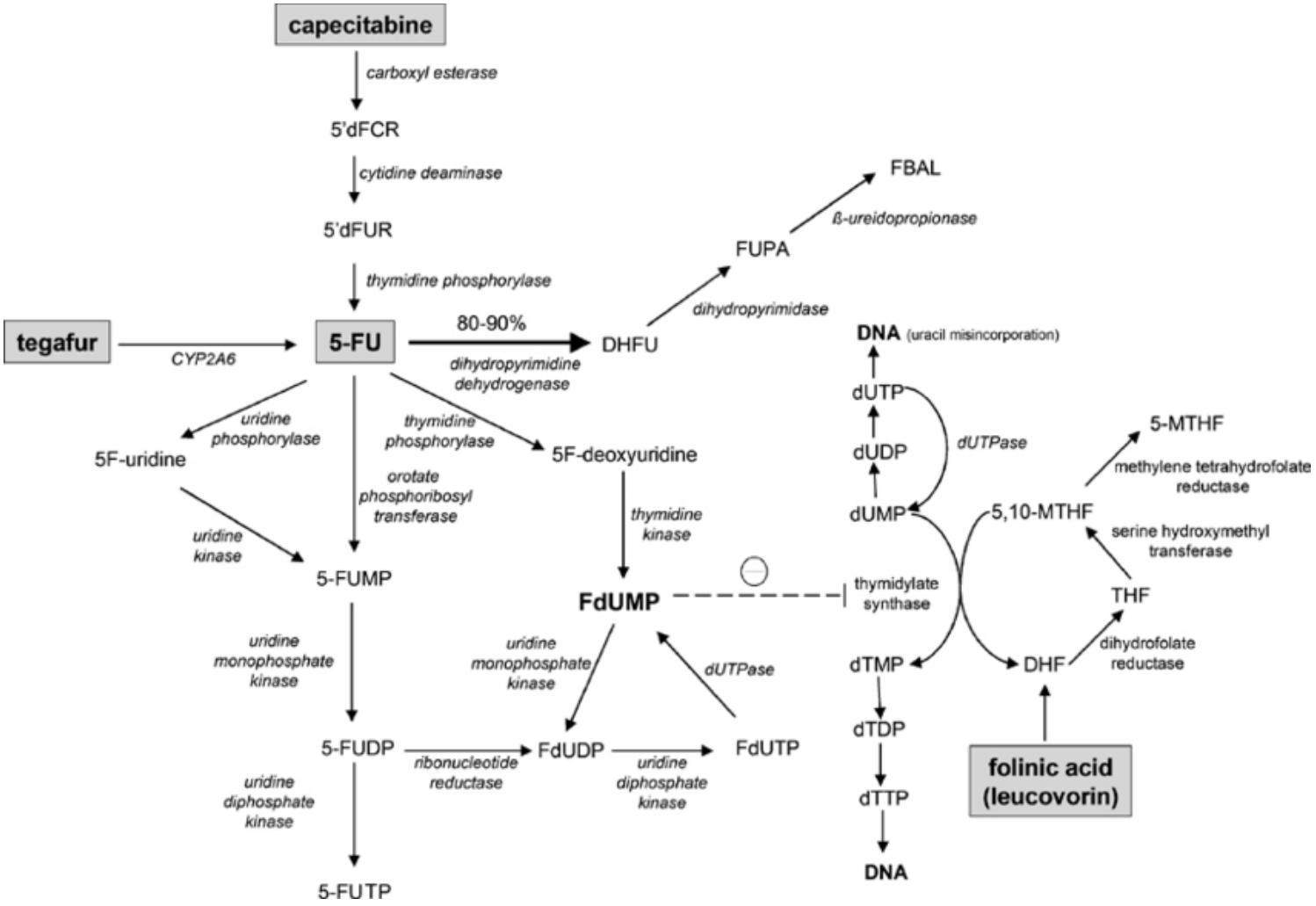
  Practical and convenient site of measurement



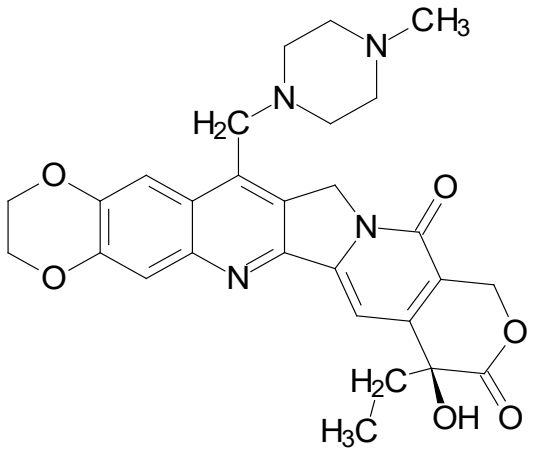
Sample selection: is plasma sufficient (and/or efficient)?

Alternative	Example
Saliva:	CPT-11, carboplatin
RBCs:	6-mercaptopurine
WBCs:	cisplatin
Tumor:	capacitabine
Urine:	liposomal drugs

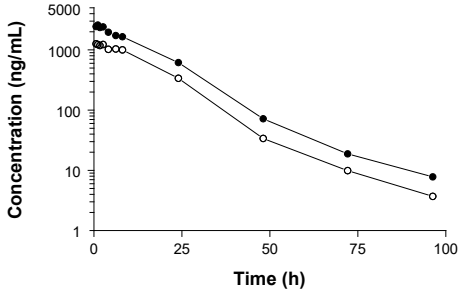
When plasma levels are not useful predictors: Capecitabine disposition pathways



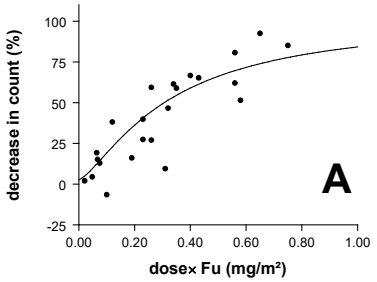
Urine as a surrogate for unbound drug



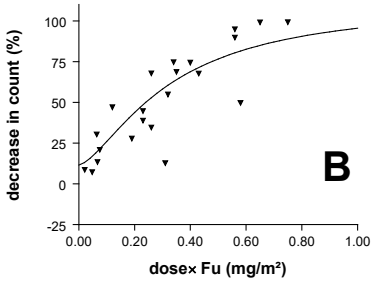
Liposomal lurtotecan (NX 211)



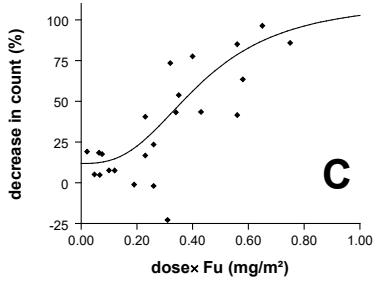
AUC >50-fold higher than OSI211



WBC



ANC

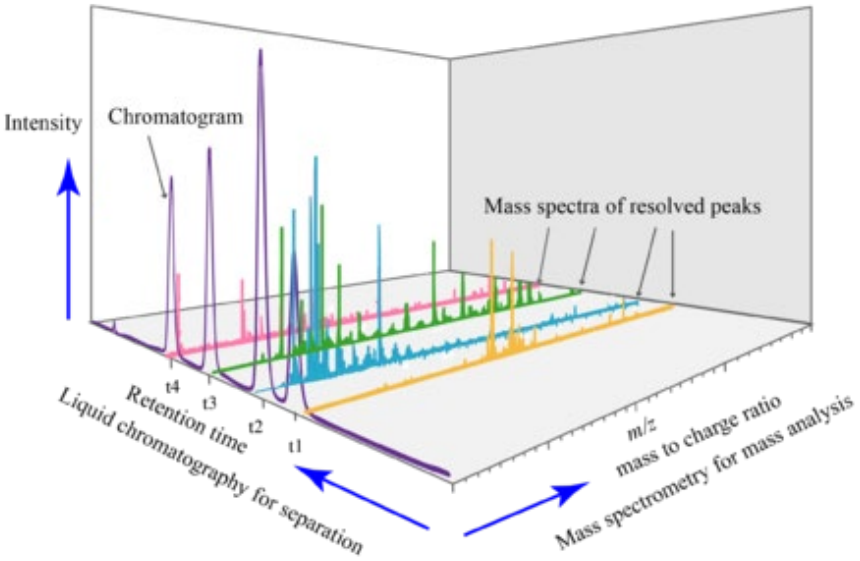


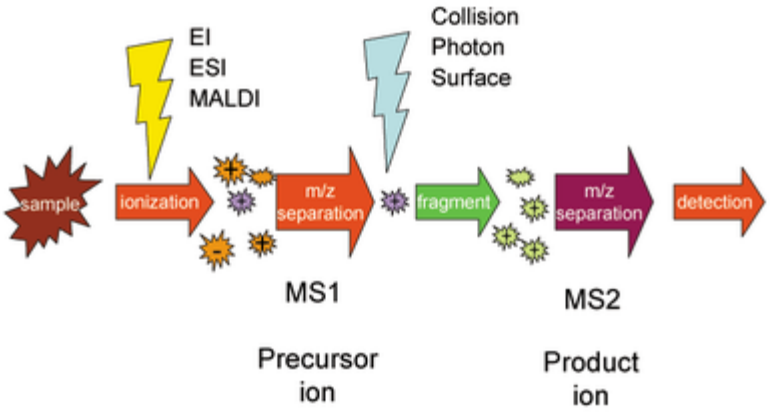
Platelets

Loos et al, CCR 2002; Kehrer et al, JCO 2002

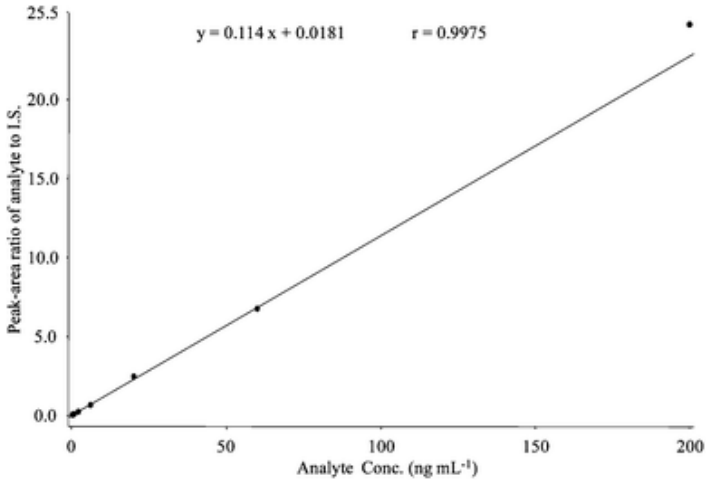
Bioanalytical method development

LC-MS/MS system





Calibration curve



Bioanalytical method validation

Parameter	Definition
Accuracy	an assessment of the difference between the measured value and the real value
Precision	a measure of the agreement for multiple measurements on the same sample
Specificity	the ability to assess the analyte when in the presence of other components
Limits of detection and quantitation	the lowest amounts of analyte that can be detected / determined accurately, respectively
Linearity and range	the proportionality of the measurement to the concentration of the analyte within a specified range
Robustness	a check of the effect of deliberate small changes to the method on the results

https://www.fda.gov/downloads/drugs/guidances/ucm368107.pdf

Planning a non-clinical PK study: things to consider that you may not think about

Type of formulation (excipient effects)

Time of drug administration (diurnal effects)

Month of experiment (seasonal effects)

Location of experiment (environmental effects)

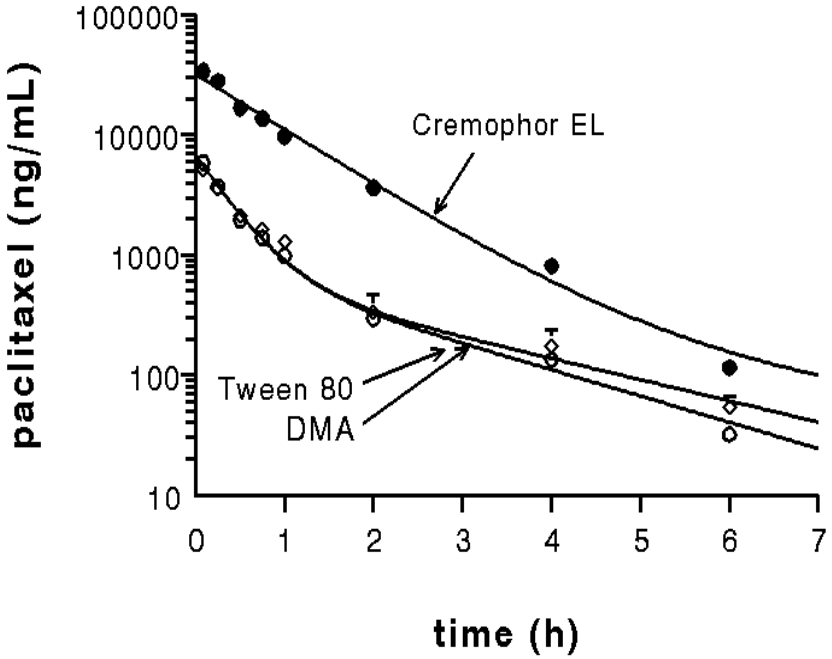
Body position of animal (posture effects)

Genetic make-up of animal (strain effects)

Documentation of experimental conditions

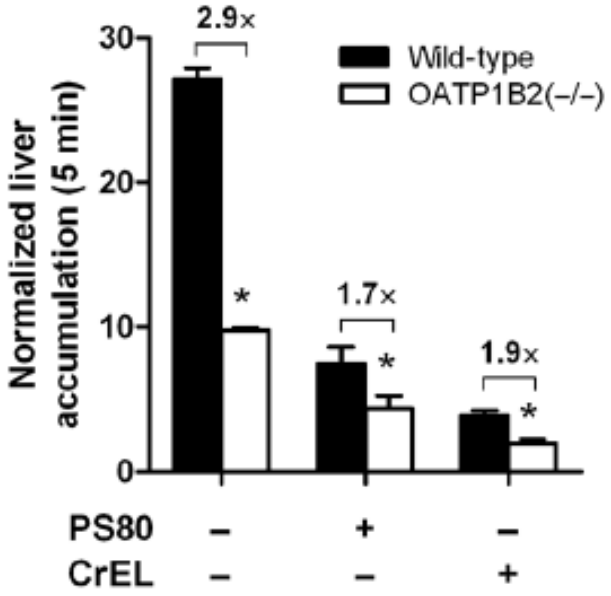
Planning a non-clinical PK study: Excipient effects

Plasma levels



Sparreboom et al, Cancer Res 1996
(DMA, dimethylacetamide)

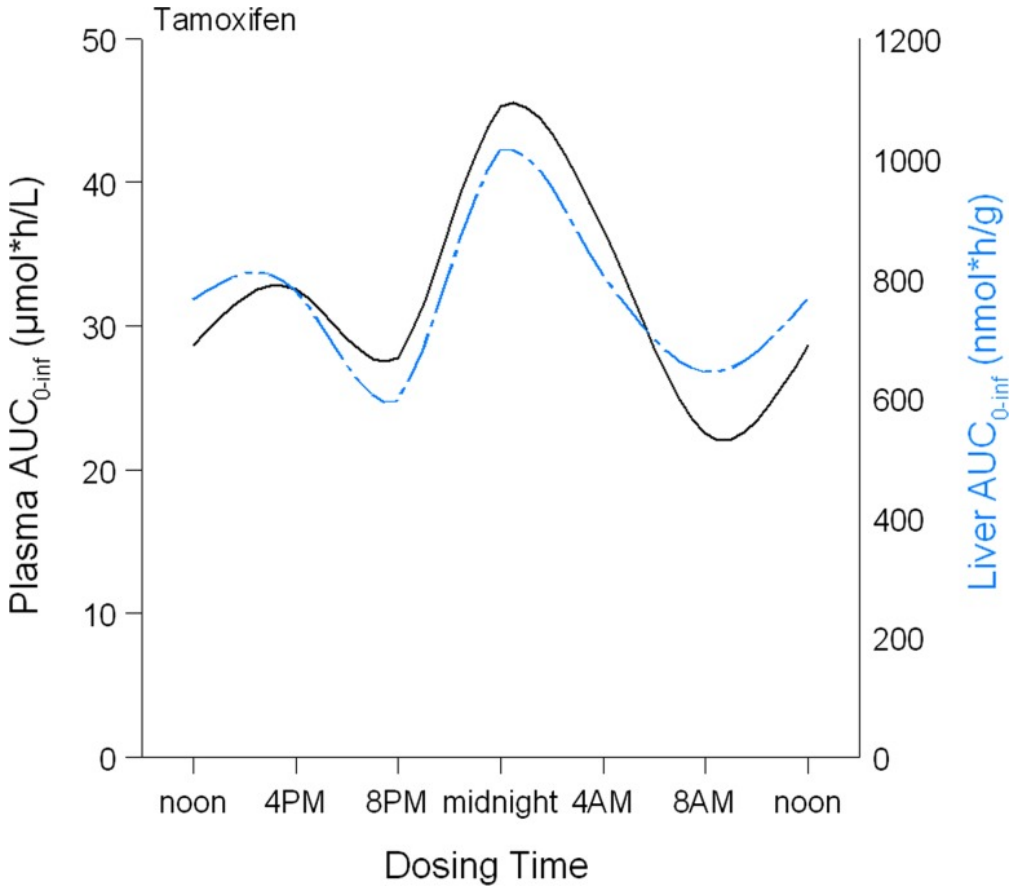
Liver levels



Nieuweboer et al, Cancer Res 2014
(PS80, Tween 80; CrEL, Cremophor EL)

Clinical relevance of this has been documented in comparative studies of paclitaxel administered with and without Cremophor EL (EG, Gardner et al, CCR 2008)

Planning a non-clinical PK study: Diurnal effects



Influence of dosing time on tamoxifen pharmacokinetics in mice (highest at midnight)

Binkhorst et al, Breast Cancer Res Treat. 2015

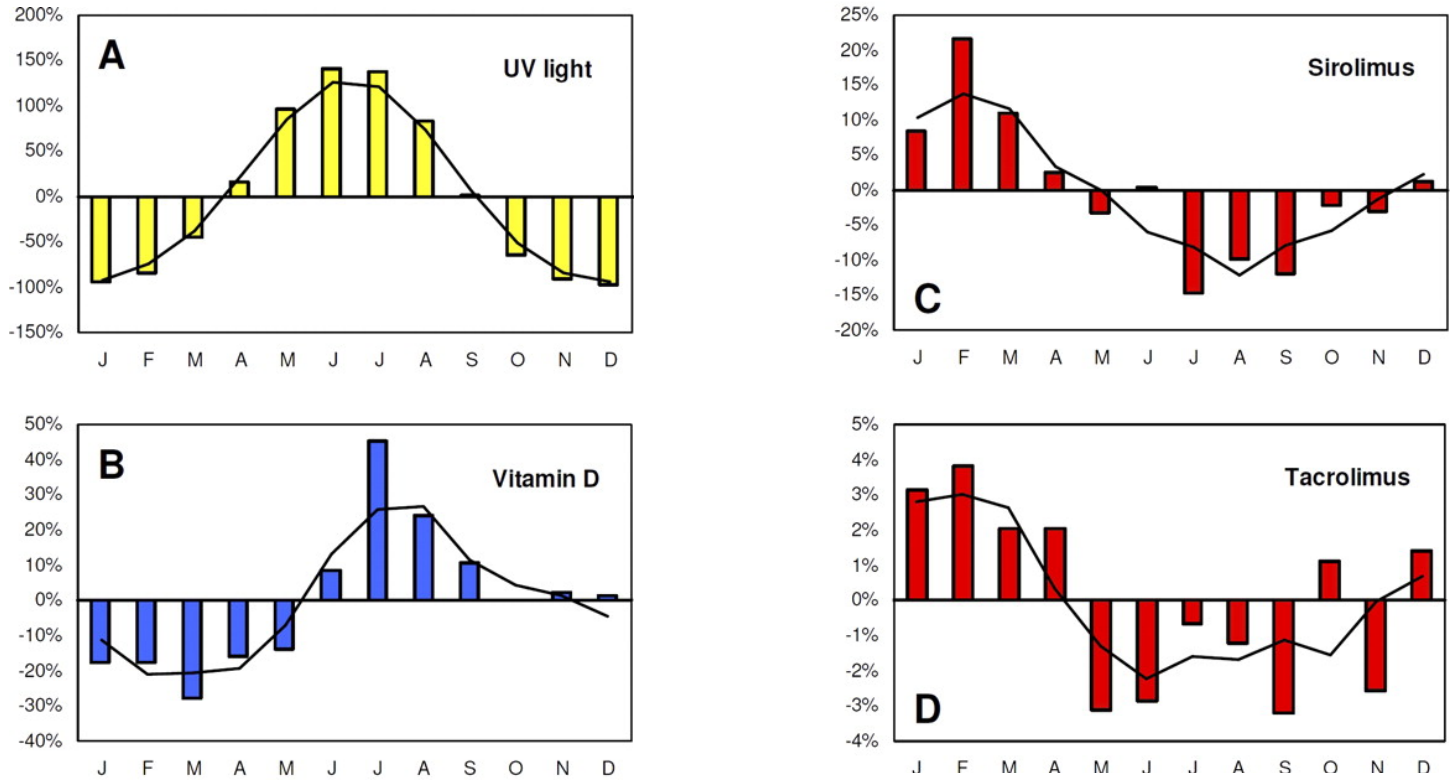
Diurnal effects on PK properties in humans

Retrospective studies suggest that administration of mercaptopurine (6-MP) in the evening results in a better prognosis

The area under the curve (AUC) of 6-MP is about 3-fold higher when administered in the evening, and associated with worse myelosuppression

Koren et al, Am J Dis Child 1990

Seasonal effects on PK properties



A, monthly UV radiation in Stockholm, Sweden. B, monthly serum levels of vitamin D (25OH vitamin D) in a Finnish cohort (*n* = 1136). C, monthly sirolimus dose-corrected concentration (C/D ratio) in 344 patients. D, monthly tacrolimus C/D ratios in 1671 patients. All values are presented as deviations from the yearly average. Lines represent moving average of three adjacent months. Lindh et al, DMD 2011

Are lab animals (mice) affected by the changing of seasons?

Unlike C57BL/6J mice, A/J mice somehow retain the breeding characteristics of a wild mouse (many pups in the spring and summer months, and a much lower output in the winter), even though they have been inbred for nearly 300 generations.

SPRET/EiJ, derived from wild *Mus spretus*, also shows seasonal lulls in breeding performance.

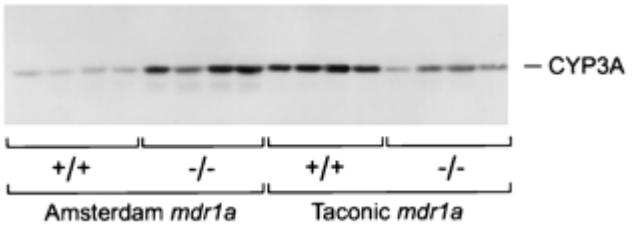
In addition to litter size, other reproductive traits can change with the seasons, including: gestation length, bone density, and response to stressful situations (eg, drug dosing and blood sampling).

Seasonal effects in drug PK in mice are uncertain but anecdotal evidence supports the possibility

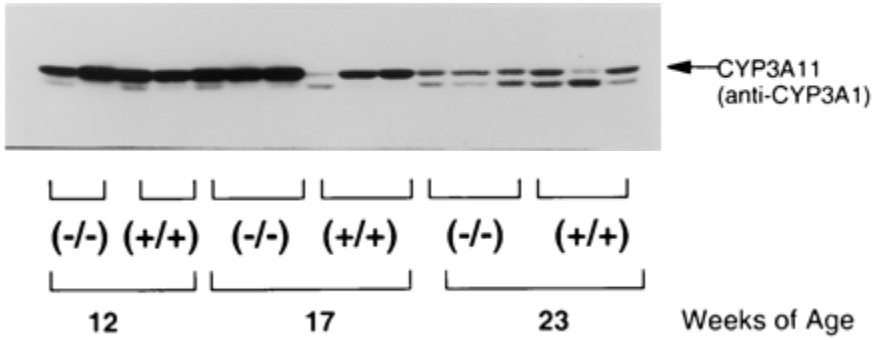
Planning a non-clinical PK study: Environmental effects

Mice knockout for *mdr1a/1b* (Pgp) kept in Amsterdam have dramatically increased levels of CYP3A protein

However, expression of CYP3A is unchanged in identical mice housed in Memphis (Taconic)



And expression depends on age of the mice…



Schuetz et al, Mol Pharmacol 2000

Planning a non-clinical PK study: Posture effects

Body position may influence physiological characteristics, such as perfusion, gastrointestinal function and plasma volume.

These characteristics may interact with key factors determining dissolution, and ADME of various drugs including nifedipine and methotrexate.

Queckenberg and Fuhr, EJCP 2009
Blaney et al, JCO 1995

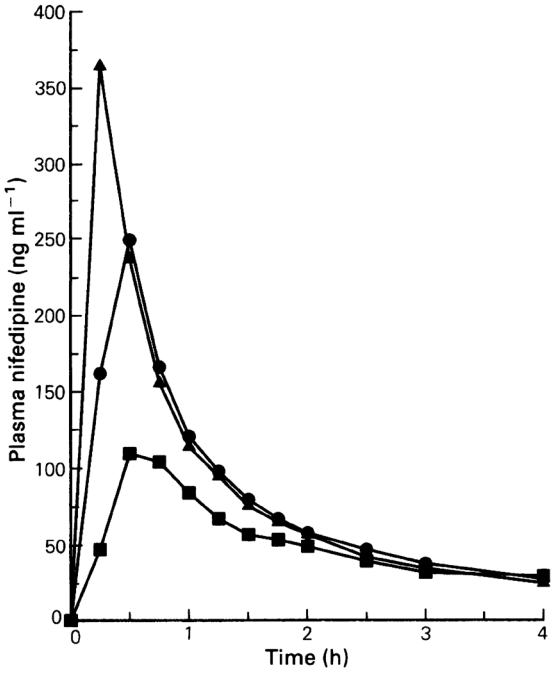
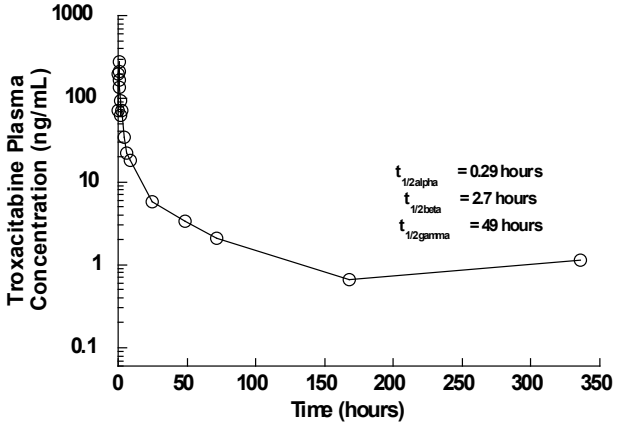


Figure 1 Plasma concentrations of nifedipine following the administration of 20 mg as capsules while lying on the left side (■), lying on the right side (●) or standing (▲). Statistically significant differences were detected between standing and lying on the left at 0.25 h and between left and right supine postures at 0.5 h.

Renwick et al, BJCP 1992

Planning a non-clinical PK study: Design of sampling schemes (1)

- Intensive (frequent) sampling:
  - enough data to describe plasma absorption and disposition (distribution, elimination) phases
- Extensive (prolonged) sampling (e.g., 72 h, 1 week)
  - allows for accurate description of the terminal disposition phase of the drug
- Limited sampling – utilizes population PK approaches



Prolonged sampling

Sample-collection period & half-life: SN-38

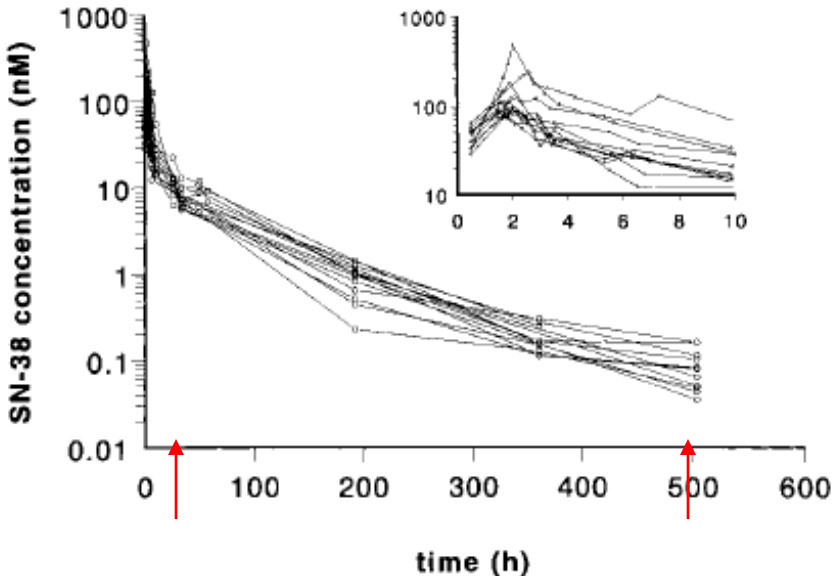


Table 1 Summary of plasma pharmacokinetics[a]

	CPT-11	SN-38	SN-38G
C_{max}[b] (μM)	7.53 ± 2.20	0.168 ± 0.115	0.639 ± 0.258
AUC_{0-56} (μM·h)	41.7 ± 13.9	1.12 ± 0.570	11.0 ± 9.26
AUC_{0-inf} (μM·h)	ND[c]	1.99 ± 0.790	26.9 ± 18.2
$T_{1/2,\ 0-56}$ (h)	13.9 ± 3.20	29.4 ± 18.6	26.6 ± 9.23
$T_{1/2,\ 0-inf}$ (h)	ND[c]	47.0 ± 7.90	39.2 ± 24.3
CL (l/h/m^2)	15.6 ± 4.32		

Kehrer et al, CCR 2000

Sample-collection period & half-life: docetaxel

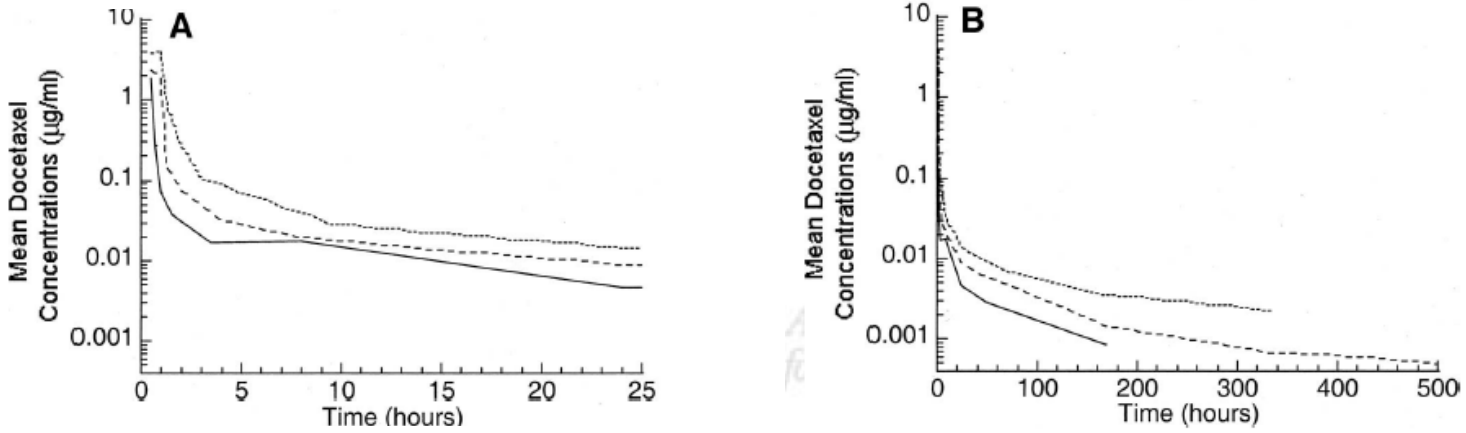


Table 3 Docetaxel pharmacokinetic parameters: extended sampling to days 8–22 post-treatment

Schedule	Concurrent drug	No. of patients[b]	Parameter[a] AUC[c] (µg·h/ml)	CL (liter/h/m^2)	$t_{1/2,\lambda z}$ (h)	Concentration[d] (µg/ml) Day 8	Day 15	Day 22
3-Weekly								
60	Doxorubicin	5	3.74 ± 0.77	16.6 ± 3.64	135 ± 21.9	ND	ND	0.00077 ± 0.00044
75	None	9	3.41 ± 0.98	23.2 ± 5.66	91.7 ± 32.1	0.0014 ± 0.00043	0.00067 ± 0.00025[e]	0.00047 ± 0.00008[e]
100	None	4	7.87 ± 2.90	14.4 ± 6.37	120 ± 80.5	0.0036 ± 0.0022	0.0022 ± 0.0019	0.0073[f]

Wikipedia: "…half-life of mean 12.2 hours represent the slow efflux of docetaxel from the peripheral compartment." (??)

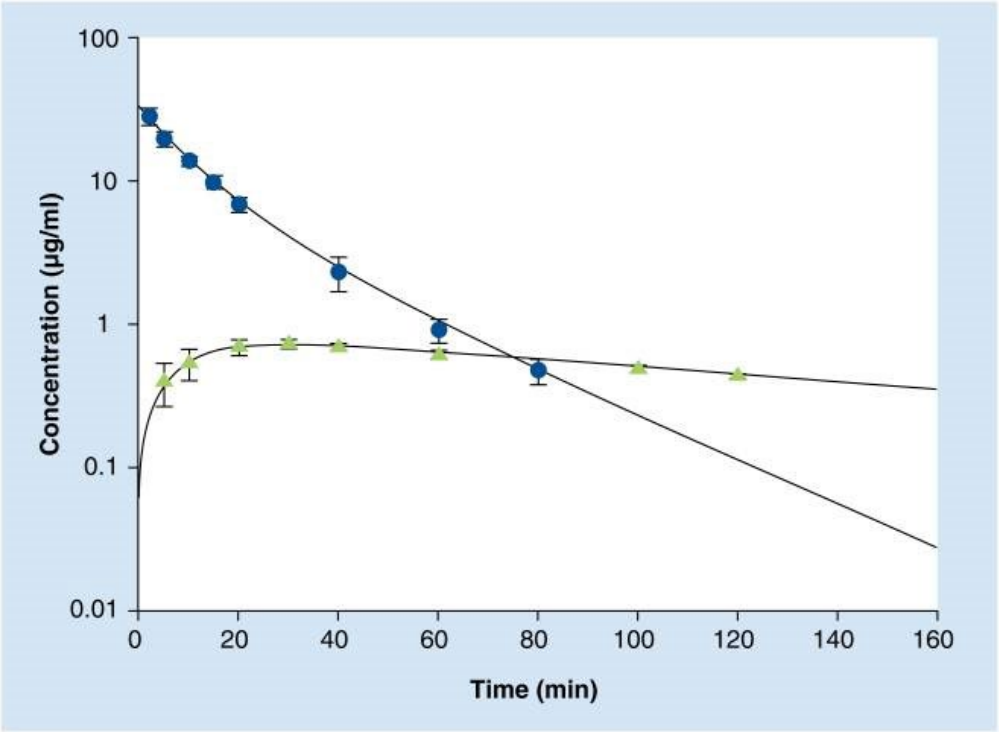
Baker et al, CCR 2004

Design of PK sampling schemes (2)

- Timing of sampling depends on:
  - the route of administration (e.g., iv vs. oral)
  - typically involves geometric spacing of samples after drug administration (examples below)
    - iv infusion (eg, 6 h) - pre-dose, during the infusion at 1, 2, 4 and 6 h (end of infusion), and post-infusion at 15 and 30 min, and 1, 2, 4, 8, 12, and 24 h
    - oral administration - intensive sampling for the first few hours after ingestion of drug to characterize absorption parameters (e.g.,15, 30, 60 and 90 min) and geometric spacing thereafter (e.g., 2, 4, 6, 8, 12, 24 h)

Flip-flop PK – reversal of disposition

In flip-flop PK, k_a (absorption constant) << than k_e (elimination constant)



Acamprosate PK after i.v. or oral administration of 9.3 mg/kg (Yanez et al, Ther Deliv 2011)

F-F PK is more common that currently believed and impacts selection of proper time points for sample collection!

Designing a non-clinical PK study: Documentation

- Actual (exact) amount of drug administered
- Site of drug administration
- Time of drug administration
- Start and stop times for drug infusion
- Timing of PK sampling relative to drug administration
- Site of PK sampling (eg, blood/plasma, urine, tissue)

Serial bleeding for collection of samples from a single mouse to yield a complete PK profile

bio-protocol

www.bio-protocol.org/e3056

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Murine Pharmacokinetic Studies

Alix F. Leblanc, Kevin M. Huang, Muhammad Erfan Uddin,
Jason T. Anderson, Mingqing Chen and Shuiying Hu*

Materials and Reagents

Equipment

Software

Procedures

Drug preparation
Drug administration
Blood collection

Data analysis

Planning a clinical PK study: things to consider that you may not think about

(in addition to the things nobody thinks about when planning a non-clinical PK study)

Single-dose vs steady-state conditions

Influence of disease and disease type

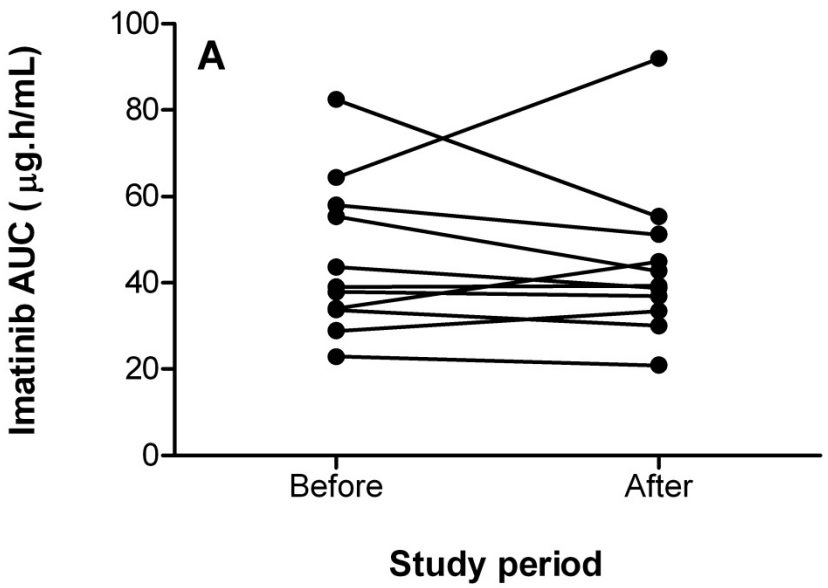
Pursuing compounds with low oral bioavailability

Timing of sample analysis relative to trial enrollment

Asking about use of herbal remedies, food intake, etc

Planning a clinical PK study: Single-dose vs steady-state conditions

The AUC of a single dose of imatinib is increased ~40% by the CYP3A4 inhibitor ketoconazole and “evaluation of ketoconazole/imatinib co-administration in multi-dose regimens warranted as drug-drug interactions may be greater under such conditions” (Dutreix et al. Blood 2002)



Ritonavir has no effect on imatinib AUC (N=12)

At steady-state imatinib likely (1) inhibits its own primary elimination, and (2) becomes dependent on other enzymes/transporters that are not affacted by ritonavir

van Erp et al, CCR 2007

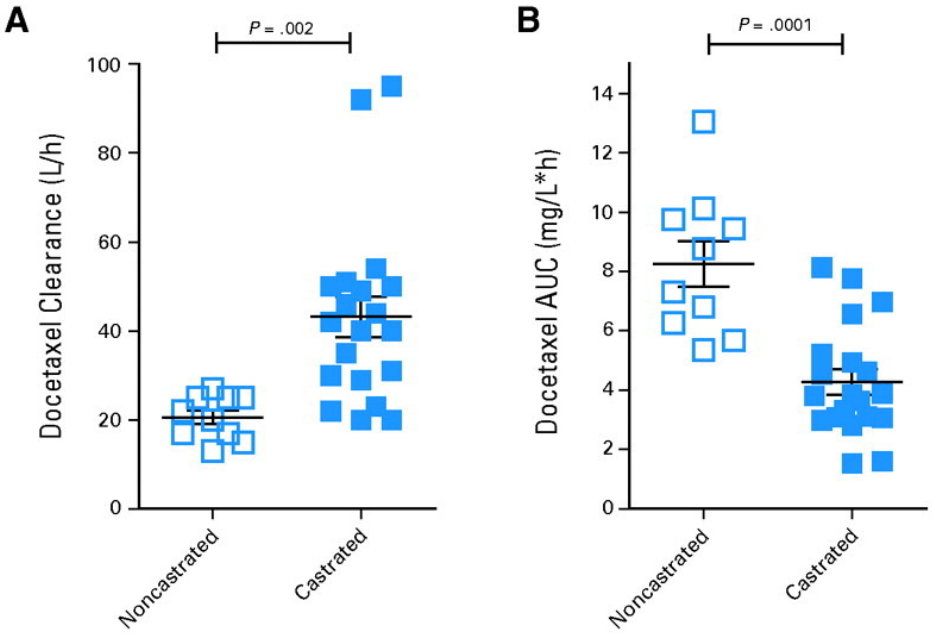
Planning a clinical PK study: Influence of disease and disease type (1)

Table 1. Incidence of Docetaxel-Induced Neutropenia by Disease Type

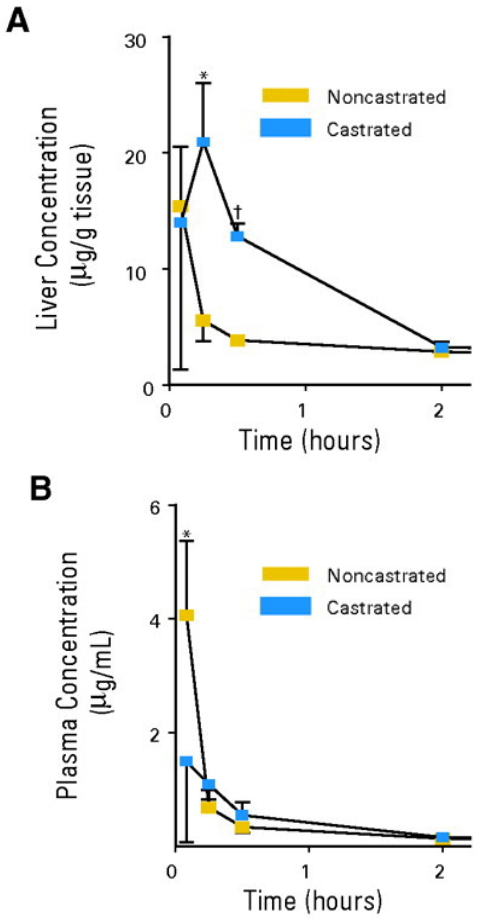
Disease	Dose (mg/m^2)	% Grade 3/4 Neutropenia
Prostate cancer (castrated patient)	60	16
Breast cancer	60	49
Prostate cancer (castrated patient)	75	32
Breast cancer	75	66
Non–small-cell lung cancer	75	74
Head and neck cancer	75	76
Gastric cancer	75	82
Prostate cancer (noncastrated patient)	75	88

NOTE. Source: Product insert for Taxotere (docetaxel; sanofi-aventis, Bridgewater, NJ).[6]

Planning a clinical PK study: Influence of disease and disease type (2)



Franke et al, JCO 2010



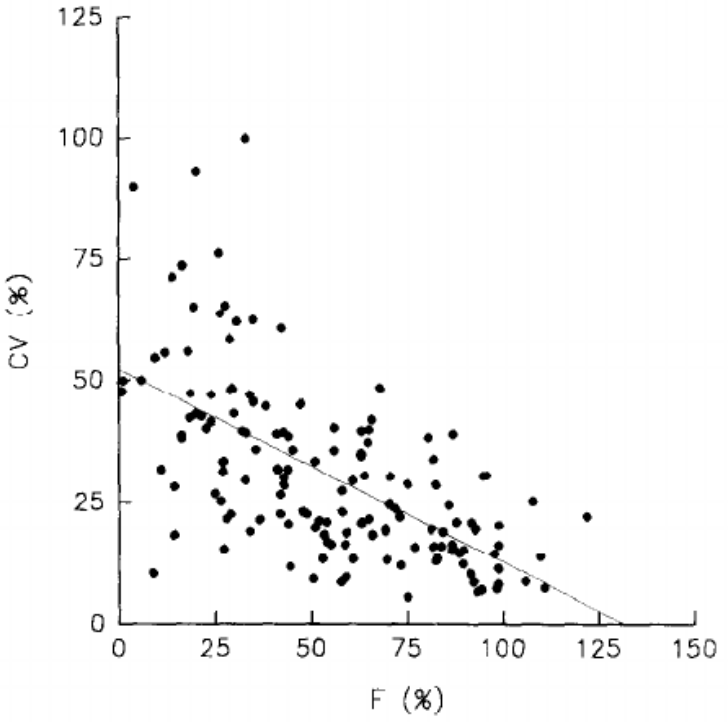
"The exposure to docetaxel was significantly lower in prostate cancer patients as compared to patients with other types of solid tumours" (Vermunt et al, CCP 2021)

Planning a clinical PK study: Compounds with low oral bioavailability (F)

Why is low oral F problematic? Can't we give a higher dose?

Variability increases!

Fig. 1. Relationship between absolute bioavailability *(F)* and intersubject variability (CV) in absolute bioavailability for all studies evaluated ($n = 149$). Data were obtained from a total of 143 references reporting absolute oral bioavailability data in *Clinical Pharmacology & Therapeutics* between 1970 and 1994. The total number of drugs studied was 100, the majority of which were cardiovascular system agents (38), central nervous system agents (25), and antiinfective agents (9).



Hellriegel et al, CPT 1996

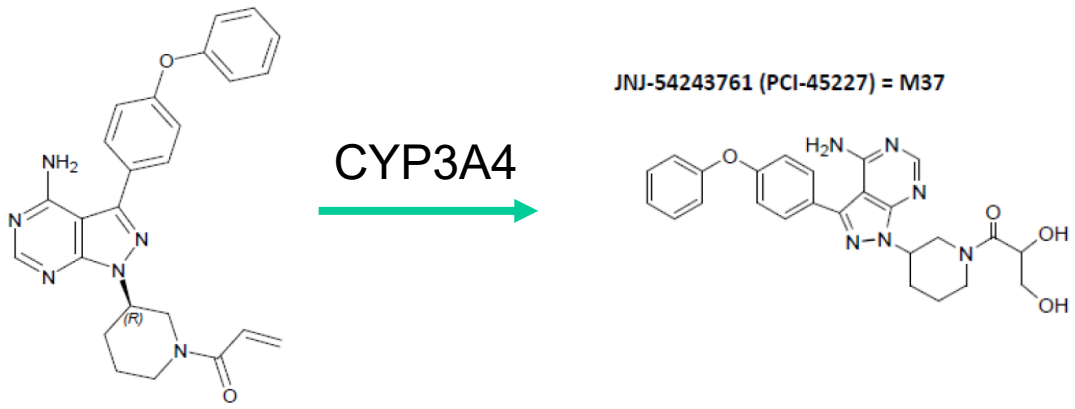
Oral bioavailability (F) examples of kinase inhibitors

Drug		Oral F	Reference
Imatinib			
	Capsule	98.3%	Peng et al, JCP 2004
	Solution	97.2%	ibid.
Sorafenib		unknown	(no i.v. formulation available)
Ibrutinib		3.9%	De Vries et al, BJCP 2015*
		2.9%	Imbruvica prescribing information

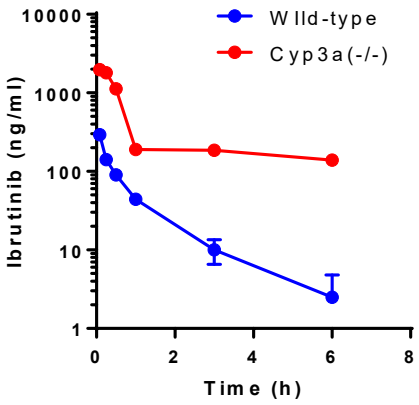
*Design involved simultaneous administration of an i.v. isotope-labeled microdose (100 µg) and an oral unlabeled dose (560 mg)

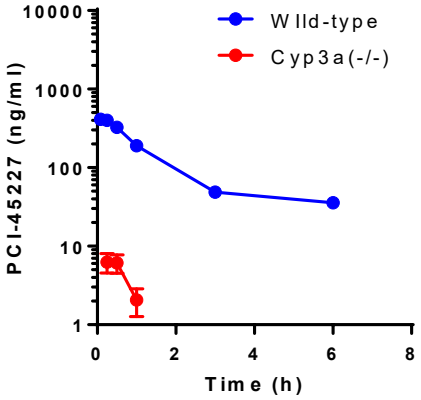
The interindividual variability in exposure (AUC) to ibrutinib is >70%, and the low oral bioavailability is likely associated with extensive, pre-systemic metabolism (first-pass) mediated by CYP3A isoforms.

Ibrutinib PK in Cyp3a-deficient mice



After oral administration of ibrutinib in humans, only 1% of the dose is recovered as unchanged drug [prescribing information], suggesting that 99% of the dose is metabolized.

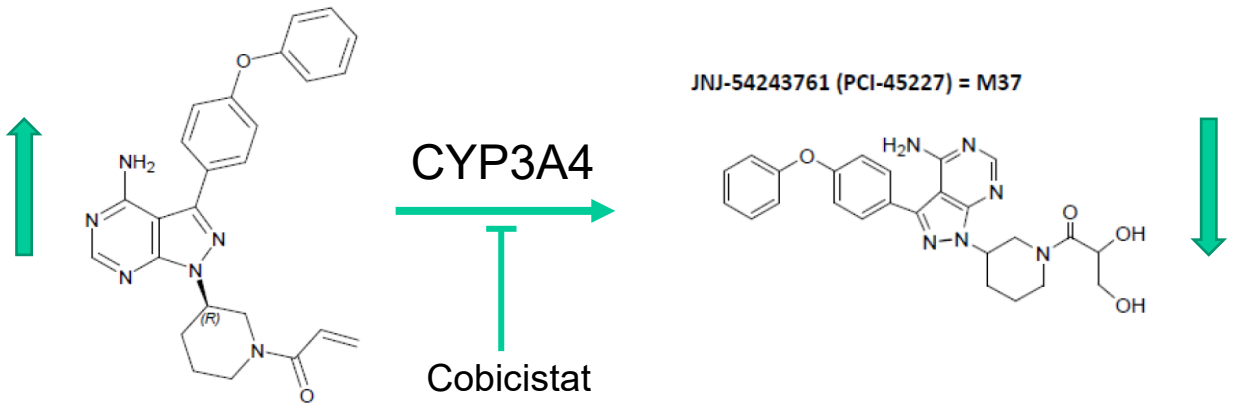


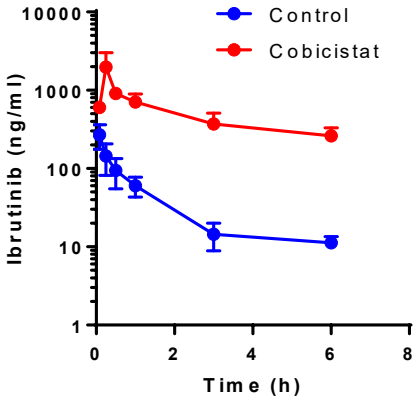


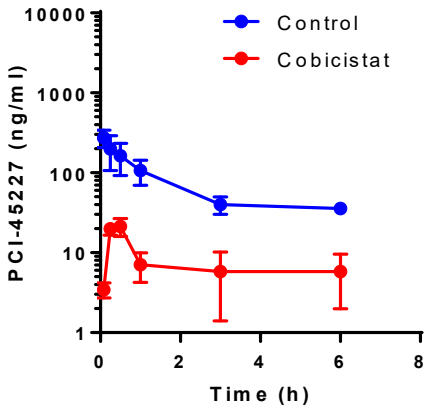
Group	Ibrutinib AUC (ng×h/ml)	PCI-45227 AUC (ng×h/ml)
Wild-type	184 ± 21	669 ± 74
Cyp3a(-/-)	2428 ± 161	4.1 ± 1.1

Eisenmann et al, submitted (2021)

Ibrutinib boosting with a CYP3A4 inhibitor







Group	Ibrutinib AUC (ng×h/ml)	PCI-45227 AUC (ng×h/ml)
Control	228 ± 69	423 ± 112
Cobicistat	3024 ± 900	45 ± 15

Compare with:

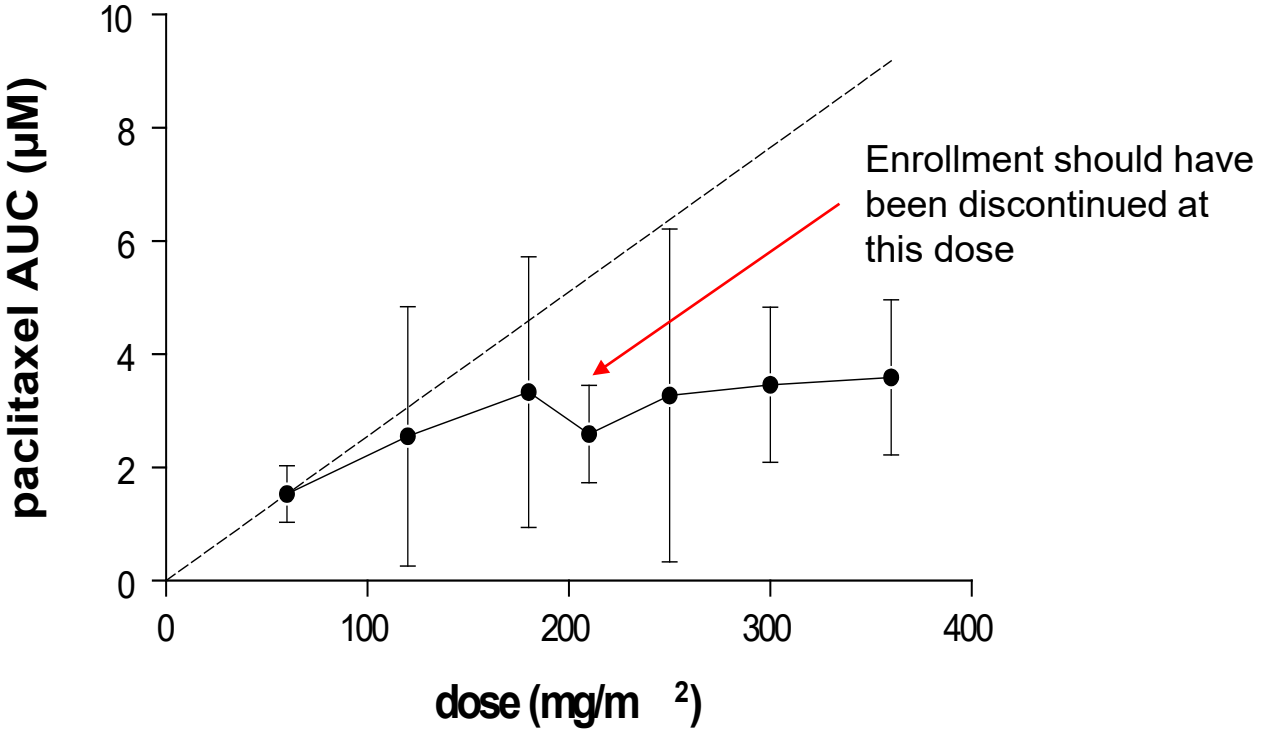
Wild-type	184 ± 21	669 ± 74
Cyp3a(-/-)	2428 ± 161	4.1 ± 1.1

Similar observations were made in male and female mice, and with ketoconazole, another CYP3A4 inhibitor.

Studies in Cyp3a(-/-) mice have confirmed that the observed DDIs are due to effects on CYP3A-mediated metabolism.

Eisenmann et al, submitted (2021)

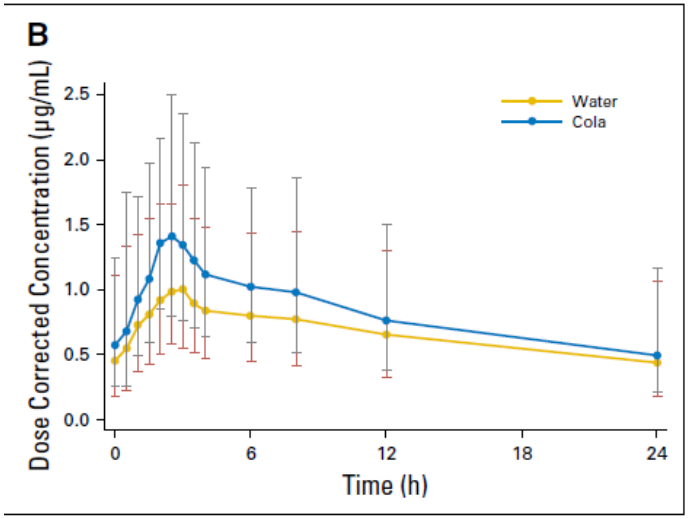
Planning a clinical PK study:
Timing of sample analysis: a case for “real-time PK”



Malingré et al, JCO 2000

Planning a clinical PK study: Unexplained variability: of cheeseburgers and coke

Drug	Food	Effect on drug exposure	Manufacturer's recommendations
Abiraterone	High-fat meal	↑ AUC 1,000%	Without food
Dasatinib	High-fat meal	↑ AUC 14%	With or without food
Erlotinib	High-fat, high-calorie breakfast	Single dose, ↑AUC 200% Multiple dose, ↑AUC 37-66%	Without food[a]
Gefitinib	High-fat breakfast High-fat breakfast	↓ AUC 14%, ↓ Cmax 35% ↑ AUC 32%, ↑ Cmax 35%	With or without food
Imatinib	High-fat meal	No change Variability (% CV) ↓ 37%	With food and a large glass of water[b]
Lapatinib	Low-fat meal (5% fat, 500 calories) High-fat meal (50% fat, 1000 calories	↑ AUC 167%, ↑ Cmax 142% ↑ AUC 325%, ↑ Cmax 203%	Without food[c]
Nilotinib	High-fat meal	↑ AUC 82%	Without food
Sorafenib	Moderate-fat meal (30% fat, 700 calories) High-fat meal (50% fat, 900 calories	No change in bioavailability ↓ bioavailability 29%	Without food
Sunitinib	High-fat, high-calorie meal	↑ AUC 18%	With or without food
Everolimus	High-fat meal	↓ AUC 16%, ↓ Cmax 60%	With or without food
Vismodegib	High-fat meal	↑ AUC 74% for single dose; no effect at steady-state	With or without food
Vorinostat	High-fat meal	↑ AUC 37%	With food[d]



MENU

CHEST Physician
THE NEWSPAPER OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS

NEWS

Cola enhances absorption of erlotinib in NSCLC

Publish date: February 8, 2016

By: Jennifer Shepphird, Frontline Medical News

Van Leeuwen et al, JCO 2016

Conclusions

PK studies constitute an important component of various stages of the drug discovery and development processes

Proper integration of such studies can guide treatment optimization and identify important contributors to variation (unpredictability) in treatment outcome (efficacy and/or toxicity)

Tailoring drug dose to achieve a desired PK parameter can improve therapy with drugs (but this is rarely done)

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