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Applied Translational Medicine

Human ADME Study Design Considerations in Healthy Subjects and in Patients

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Learning Goals and Outline

What is a human ADME study?

- Mass balance in the context of an ADME study
- Why are they required and what information do they provide?

How is a human ADME study conducted?

- Standard designs and special considerations
- Results and interpretation

Expansions of ADME protocols

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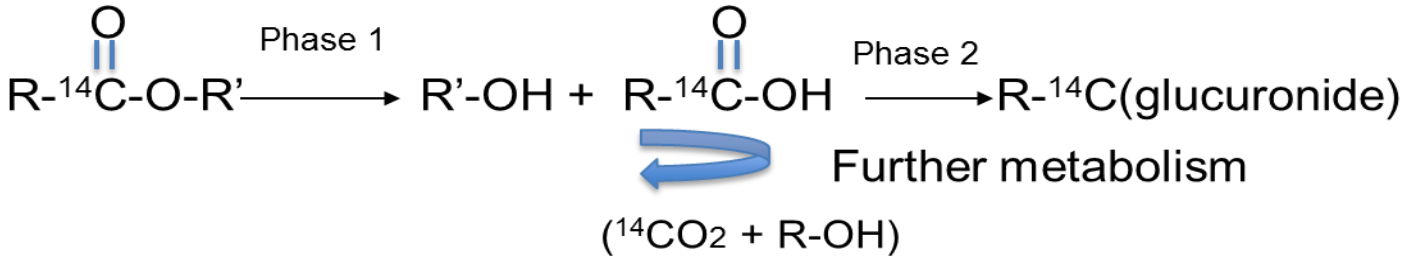
What is Mass Balance?

Human Absorption, Distribution, Metabolism and Elimination (ADME)
hADME = clinical ADME = AME = mass balance study

Mass Balance: What comes in ≈ What comes out



Recovery goal > 90% Administered Dose

Drug Dose = Urine (Drug + Metabolites) + Feces (Drug + Metabolites) + Any Vomited Dose (PO)

- Sometimes collect: toilet tissue, exhalate (i.e. CO_2)
- Generally not collected: sweat, tears

Role of hADME in Drug Development

Conducted to identify the major route of drug removal from the body

- Does the mass balance study suggest renal or hepatic as the major route of elimination?
  - Is a renal or hepatic study required?

Conducted to quantify and identify the major metabolites in the body

- What are the characteristics of drug metabolism?
  - FDA guidance on Safety Testing of Drug Metabolites
    - Additional safety testing prior to Phase III? (if > 10% of parent systemic exposure)
  - FDA guidance on Drug Interaction Studies
    - Need for in vitro or in vivo metabolite DDI? (if ≥25% of parent or active)

hADME Data to Support Objectives

Mass balance in excreta

- % dose in feces + % dose in urine

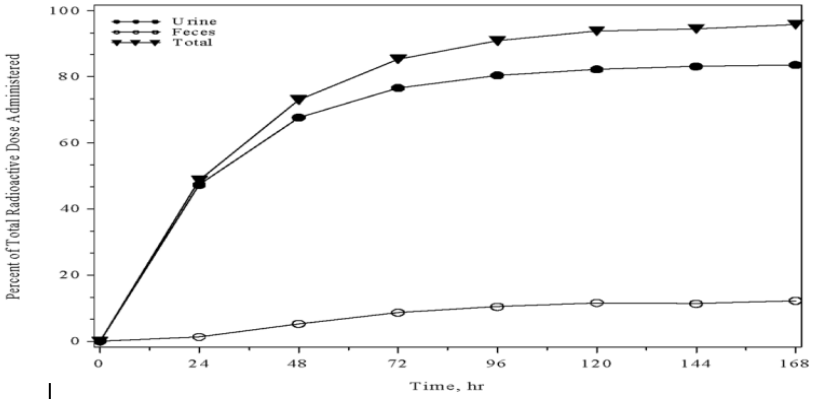
PK in circulation (drug, metabolites, total radioactivity)

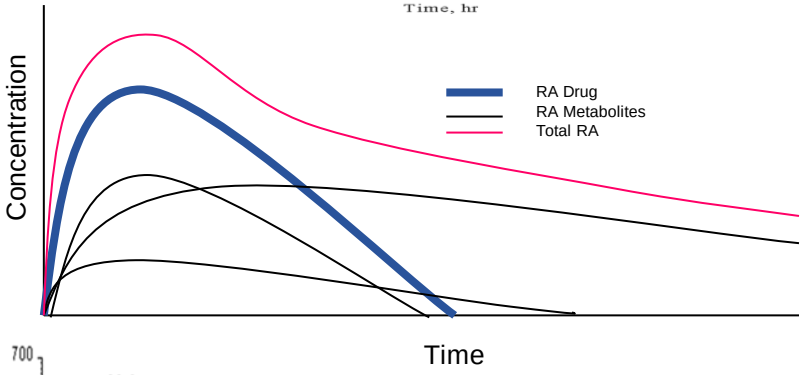
- Plasma (drug, metabolites, total RA) ± WB partitioning ± ETR

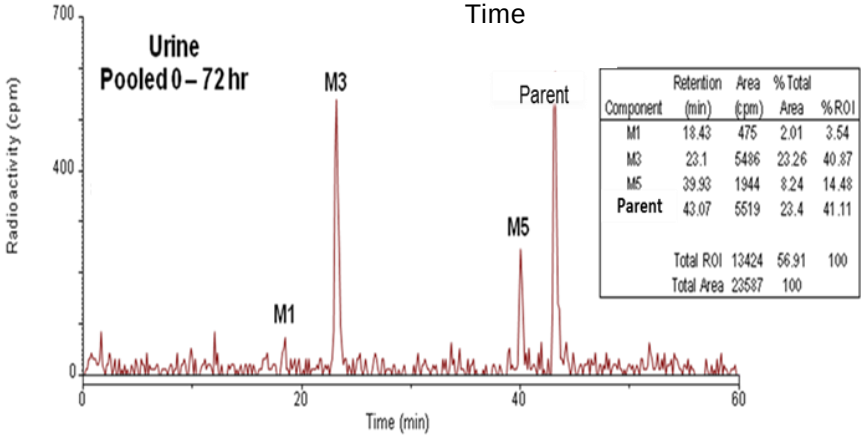
Metabolic profiling in excreta and circulation

- Identification and relative abundancies

Routes and rates of excretion & relative contributions to CL







Standard Study Design Outline

1 Period

Single oral dose

Subjects: 6-8 healthy males

Confinement: planned + early release criteria + contingency for extension

PK (blood, urine, feces) and safety assessments

hADME Design Considerations

Population

- Healthy or Patients

Route of administration

Dose

- API dose
- Radioactive dose

Sample collection and data analysis

Choice of Subjects

Standard ADME in healthy subjects

- Most practical approach if safety favorable
- 6-8 males
  - Women of non-childbearing potential (WNCBP) - if indication only in females

ADME in patients

- Based on safety or scientific considerations
- 4-6 patients
- Individual subject recruitment

Microdose ADME in healthy subjects

- Safety limits pharmacologically active dose in healthy
- 6-8 males (WNCBP as per indication)
- Microdose PK must be predictive of active

hADME Design Considerations

Population

- Healthy or Patients

Route of administration

Dose

- API dose
- Radioactive dose

Sample collection and data analysis

Route of Administration

Oral

- Same as clinical
  - Oral solution or filled capsule

Vascular

- Same as clinical

Inhalation

- 3-period, PO and IV radiolabeled, inhalation cold

hADME Design Considerations

Population:

- Healthy or Patients

Route of administration

Dose

- API dose
- Radioactive dose

Sample collection and data analysis

Dose: Active Pharmaceutical Ingredient (API) and Radiation

API dose: goal for same PK as at therapeutic dose

- Therapeutic or equivalent
- Microdose (predictive of therapeutic dose PK)

Radiation dose: lowest possible

- 21 CFR 361.1:
  - "...the subject receives the smallest radiation dose with which it is practical to perform the study..."
- FDA sets limits for maximum exposure to:
  - Reproductive organs
  - Bone marrow
  - Lens of the eye

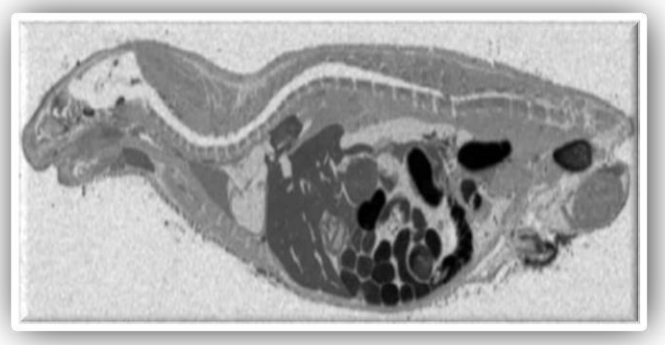
Dosimetry Report: What is it and What is Needed

Estimates radiation exposure to various tissues in human body

- Required when dose > 500 nCi (in NE)

Minimum requirements:

- Proposed radioactive dose
- Animal mass balance
- Organ biodistribution study [i.e. (Q)WBA]



Most Common vs Most Appropriate

Industry standard/most common dose: 100 µCi (US)

- Radiation safety:
  - dosimetry usually favorable
- Regulatory compliance:
  - is it more radioactivity than needed?
- Practicality:
  - is it enough? Can all objectives be achieved at this dose?

Determining the Minimum Radioactive Dose

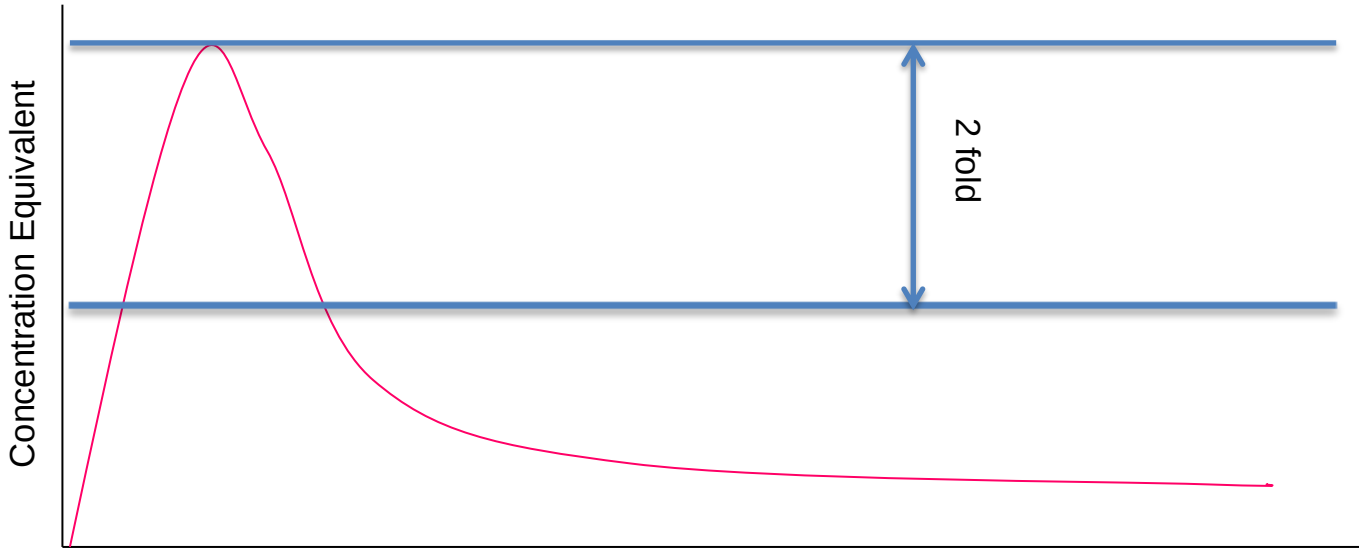
- Proportionality ratio:
- $\frac{C_{max}}{API\ Dose} = \frac{LLOQ}{X}$

X = amount of radioactivity needed to just detect the C_{max}

- Example:

C_{max} (16 mg dose) = 15.4 ng/mL
LLOQ ~ 110 DPM/mL

X = 51.5 µCi



Plasma PK and Radioactive Dose

Plasma Total Radioactivity (nM equivalents) Time (hr)														
AN	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**24**	**48**
0001	0.000	0.000	0.000	157.774	319.459	217.754	156.470	122.568	100.141	77.844	0.000	0.000	0.000	0.000
0002	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
0003	0.000	0.000	0.000	0.000	0.000	0.000	179.940	284.254	157.774	82.929	0.000	0.000	0.000	0.000
0004	0.000	0.000	91.665	136.911	143.431	142.127	101.575	83.451	70.803	0.000	0.000	0.000	0.000	0.000
0005	0.000	65.978	0.000	0.000	89.057	258.175	131.695	92.448	89.449	73.541	0.000	0.000	0.000	0.000
0006	0.000	0.000	0.000	75.757	112.919	117.744	106.399	95.968	85.015	0.000	0.000	0.000	0.000	0.000
Plasma API (nM) Time (hr)														
AN	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**5**	**6**	**8**	**12**	**16**	**24**	**48**
0001	0.000	0.000	50.647	144.042	280.561	160.445	90.619	76.906	47.309	25.811	17.020	9.237	5.133	1.413
0002	0.000	0.000	13.532	35.275	42.589	26.175	19.842	20.562	19.577	17.376	15.854	10.077	6.019	3.227
0003	0.000	0.000	7.096	8.416	21.447	63.840	139.034	226.742	101.235	43.892	22.630	12.109	8.691	2.413
0004	0.000	20.605	86.742	139.727	140.336	108.711	69.610	47.643	40.917	22.122	14.562	12.562	7.275	2.718
0005	0.000	51.499	28.669	37.797	66.003	185.658	83.974	48.854	36.311	21.155	18.564	10.677	6.037	5.628
0006	0.000	20.141	51.470	61.653	84.453	84.745	81.288	75.559	57.855	44.248	36.964	22.280	16.059	5.428

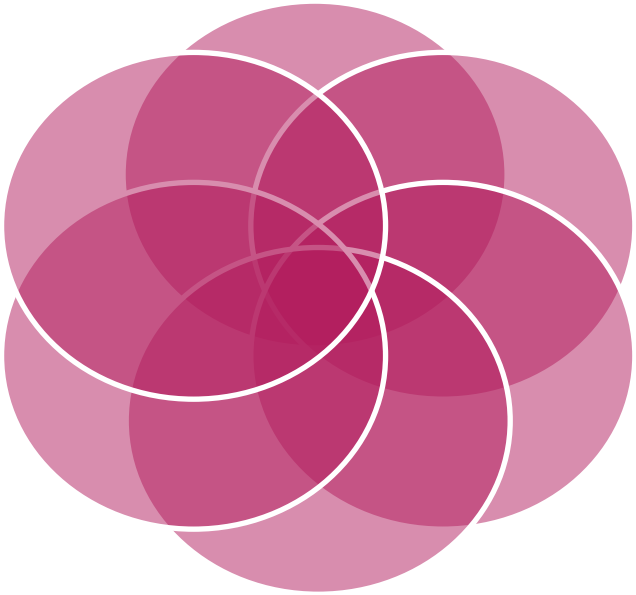
- Problem for total radioactivity PK in plasma
- Problem for metabolic profiling in plasma
- Potential problem for mass balance (if long terminal $t_{1/2}$)

Options When 100 µCi is Not Enough

Dose > 100 µCi

Microtracer ADME and AMS

↑ Count time for plasma and whole blood



LSC until BLQ then AMS

↑ Aliquot size for plasma and whole blood

Urine and feces →LSC
Plasma and whole blood →AMS

When to Consider Microtracer Dose

Dosimetry not favorable	▪ Recalculate dosimetry if > 500 nCi
Missing data for a dosimetry report	▪ Dose ≤ 500 nCi
Option for long $t_{1/2}$ drugs	▪ Dilution in excreta reduces recovery

Study Design Considerations with Microtrace Dose

Same basic ADME design

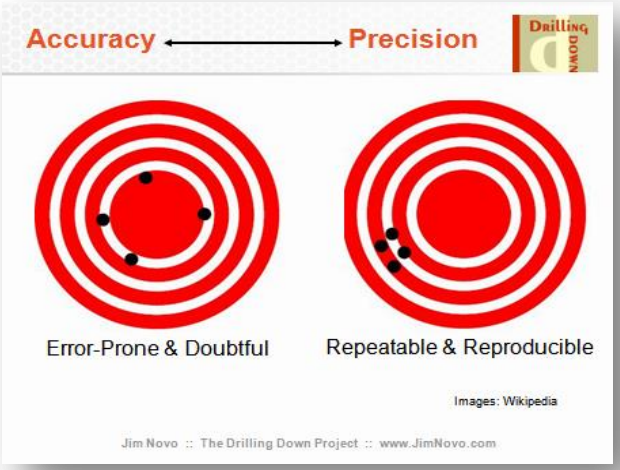
- Single therapeutic dose or equivalent
- 6-8 Males (or WNCBP if indicated)
- Standard safety, PK assessments

Main difference

- Delayed data analysis (long sample preparation time for AMS)
  - No early release criteria
  - No evaluation for possible extension

Final Product

Therapeutic or equivalent dose:	▪ Extemporaneous compounding required
Microdose:	▪ Less extemporaneous compounding
Precision more important than accuracy	▪ Easier to backtrack with dosing solution than capsules



Subject #	API Dose (mg)	Total Radioactivity (DPM)	Total Radioactivity (µCi)
1	61.2	227805770	102.6
2	61.3	228209397	102.8
3	61.3	228336002	102.9
4	60.8	226566519	102.1
5	61.1	227396170	102.4
6	61.1	227620931	102.5
Specific activity in each mL of dosing solution = 7858778 DPM/2.11 mg			

hADME Design Considerations

Population:

- Healthy or Patients

Route of administration

Dose

- API dose
- Radioactive dose

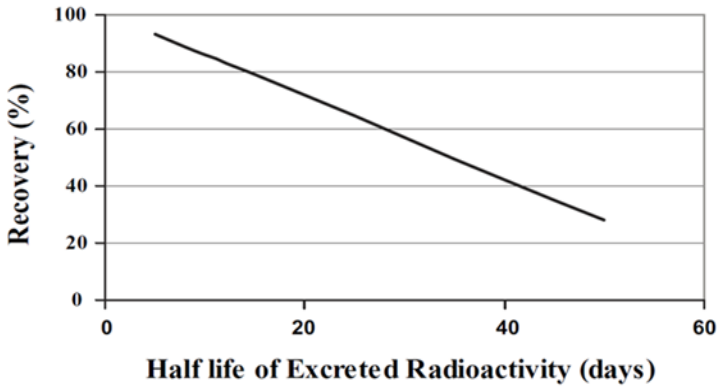
Sample collection and data analysis

Confinement, Duration of Sampling and $t_{1/2}$

Recovery goal > 90% Administered Dose

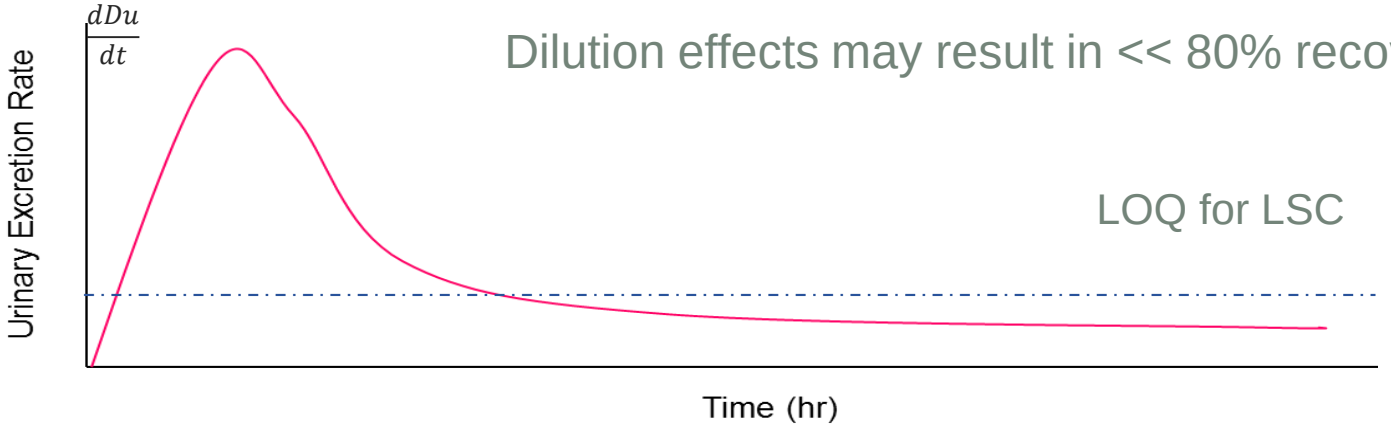
- Short $t_{1/2}$
  - 7 days if predominantly urinary excretion
  - 14 days if predominantly fecal excretion
- Long $t_{1/2}$
  - 21 days with potential extensions
- Include:
  - Early release criteria (i.e. 2 consecutive days with < 1% dose)
  - Contingency for study extension (i.e. confinement, returns, at-home collections)

%Recovery vs $t_{1/2}$ with release criteria of <1% dose over 24 hr



From: Roffey S, et al. *What is the Objective of the Mass Balance Study? A Retrospective Analysis of Data in Animal and Human Excretion Studies Employing Radiolabeled Drugs*. Drug Metabolism Reviews, 39: 17–43, 2007

Dilution Effects and Long $t_{1/2}$



If conventional radioactive dose:

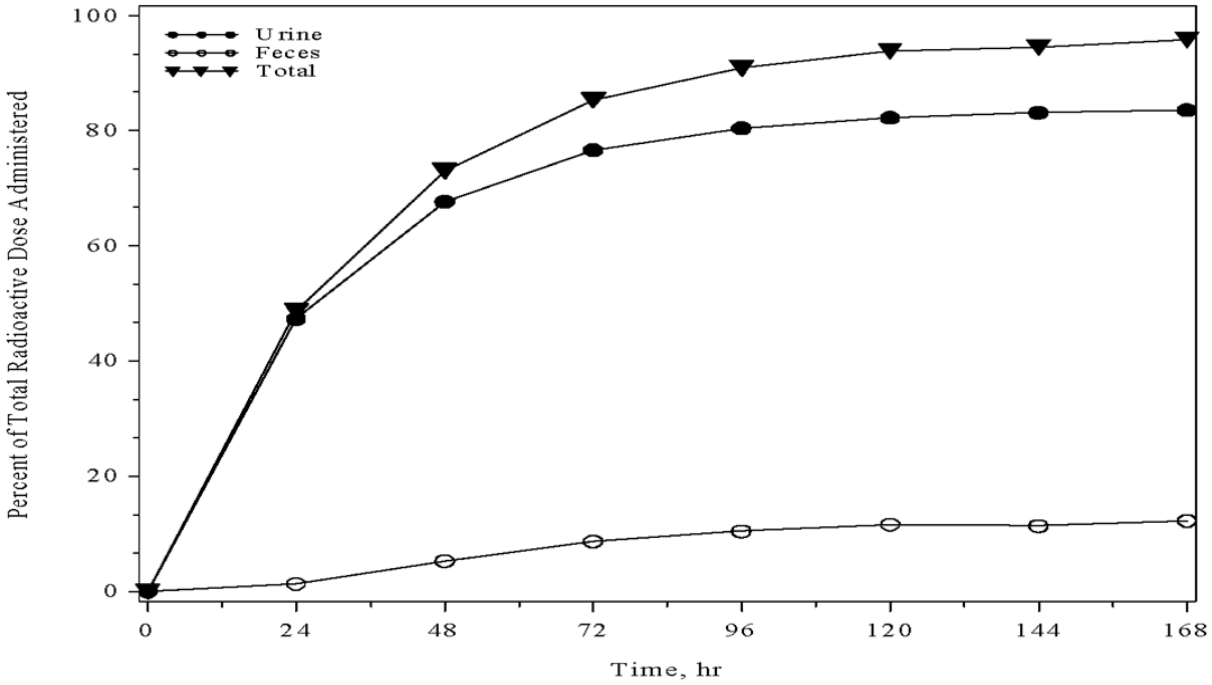
- Confinement 2-3 × $t_{1/2}$, then weekly (or QOW) 24 hr returns
  - Mass balance from excretion rate vs time plots
  - AMS for samples from return visits

If microtracer radioactive dose:

- Same approach, with all radioactivity determined using AMS

Data Analysis and Results: Mass Balance Data

Cumulative Excretion Plots for Mass Balance

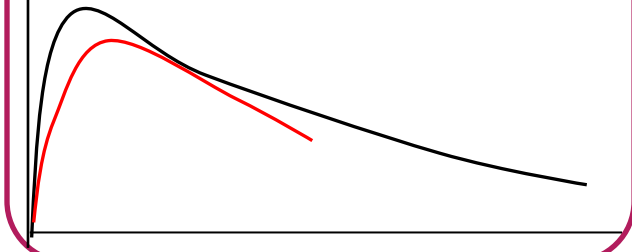


% Dose Administered (Total RA in Dose – any vomited) ≈ % Urine (Total RA) + % Feces (Total RA)

- If 100% >>recovery<<80% verify precise dose to each subject and $t_{1/2}$ estimates (i.e. from renal excretion of total radioactivity)

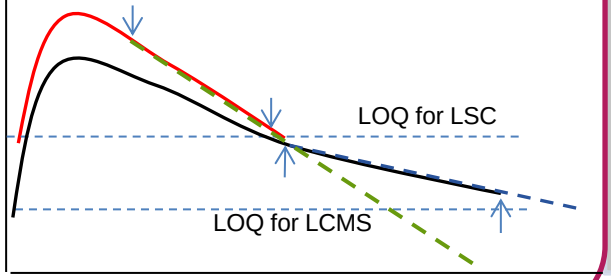
Plasma Exposure Logistics

Total RA C_{max} < Drug C_{max}



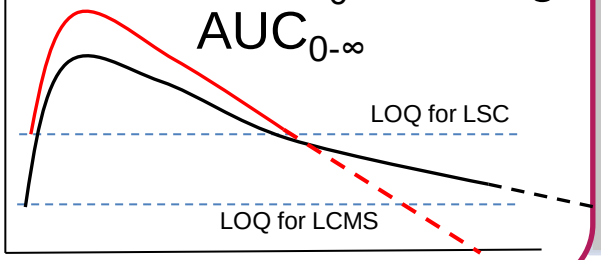
- SA incorrect
  - Calculation error
  - Radiochemistry or stability

Total RA $t_{1/2}$ < Drug $t_{1/2}$



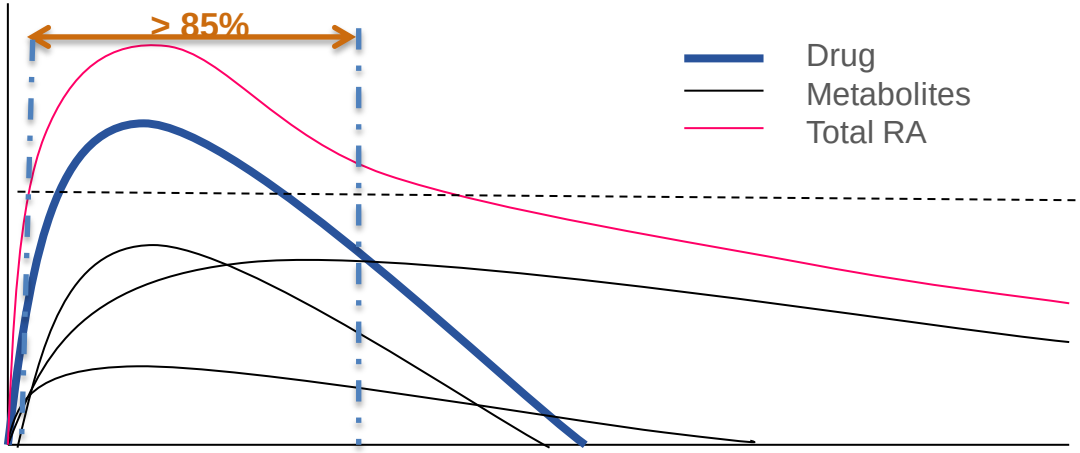
- LOQ differences
- $t_{1/2}$ of total RA is in the “distribution” phase

Total RA $AUC_{0-\infty}$ < Drug $AUC_{0-\infty}$

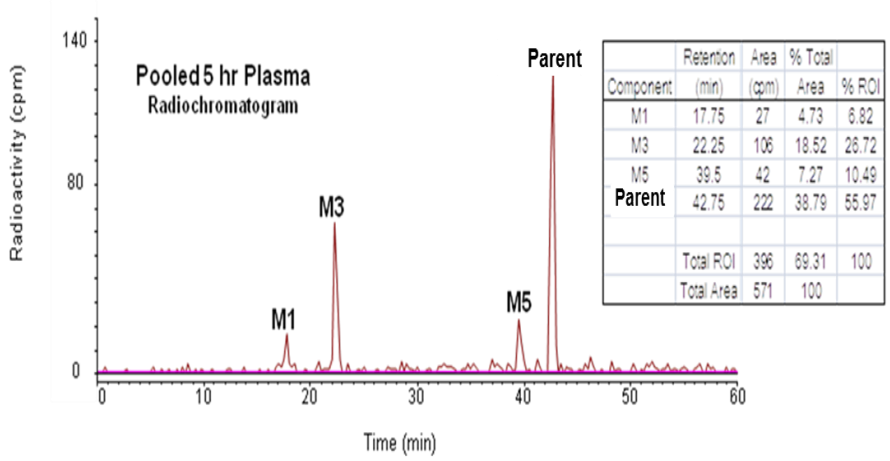


- LOQ differences

Metabolic Profiling vs. PK



For plasma, urine and feces, pooling is across samples accounting for > 85% RA for the given matrix



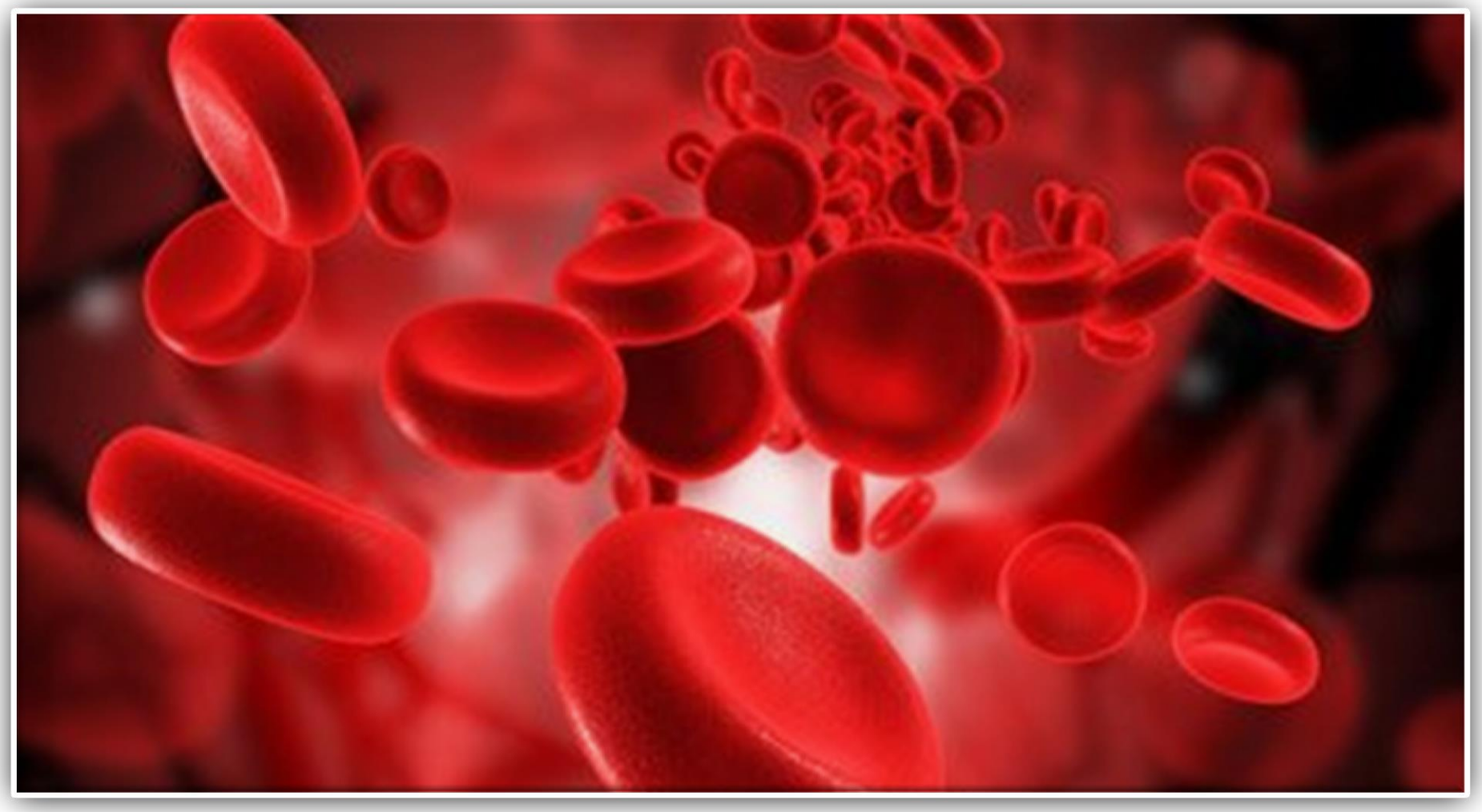
Component	Retention (min)	Area (cpm)	% Total Area	% ROI
M1	17.75	27	4.73	6.82
M3	22.25	106	18.52	26.72
M5	39.5	42	7.27	10.49
Parent	42.75	222	38.79	55.97
	Total ROI	396	69.31	100
	Total Area	571	100	

Component	m/z	Retention Time (min)	Plasma Pooled 5 hr	% of DRM*	Plasma Pooled 0.5 – 36 hr	% of DRM
M1	273	18.2	✓	6.8	Trace	5.2
M2	449	19.9	Trace		Trace	
M3	287	23.1	✓	27	Trace	27
M4	329	25.0	Trace		Trace	
M8	412	ND	ND		ND	
M5		40.0	✓	10	Trace	8
M6	426	41.7	Trace		Trace	
Parent	410	43.2	✓	56	Trace	60
M7	426	46.8	Trace		Trace	

Pooled samples = cannot do traditional PK analysis on these data

Qualitative, but only semi-quantitative = will not match the PK data exactly

Expansions of hADME Protocols

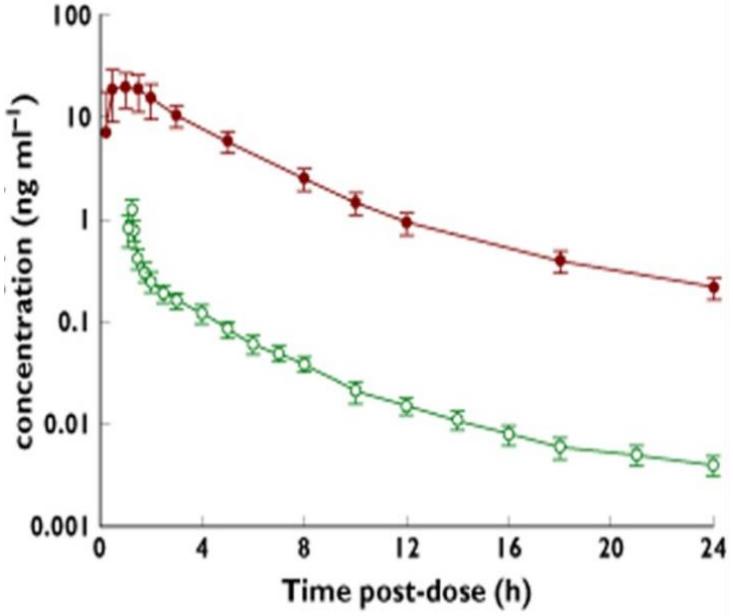


Most Common: Absolute Bioavailability Arm

Part 1, hADME (N = 6)

Part 2, absolute BA (N ≥ 3)

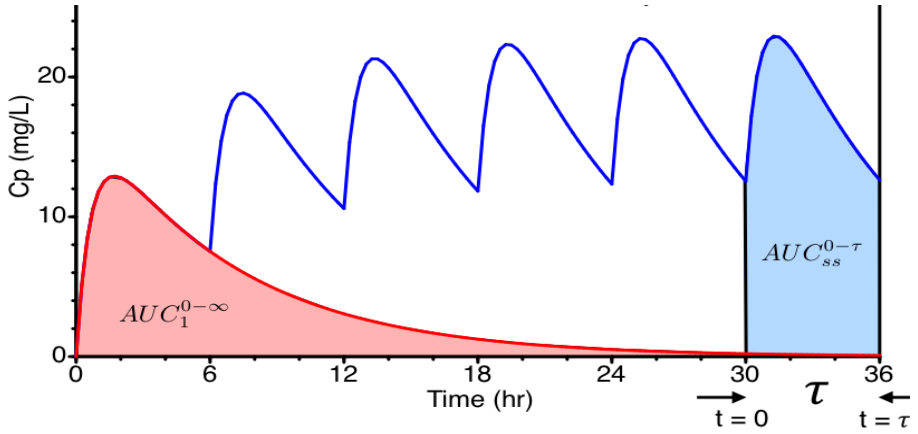
- PO and IV in 1 Period
- Dose PO 1st (therapeutic dose)
- At PO T_{max} administer ^{14}C-labled IV microdose
  - Timing of IV & PO samples
  - IV dosing window
- PO dose drives IV dose PK



Other Types of Expansions:

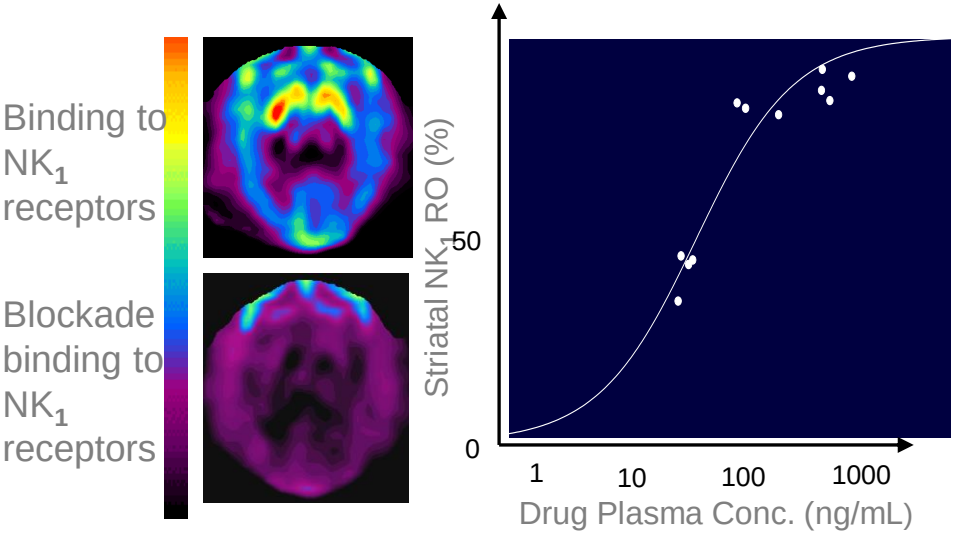
1st dose ^{14}C ADME followed by MD

- To supplement PK data for therapeutic dose
- No time or dose-dependent PK



Site of action PK

- When plasma PK does not reflect site of action PD
  - I.e. biopsy, CSF, specific cell types



Dual isotope approach

- PK & ADME with AMS and PD with PET

Learning Goals and Summary

What is a human ADME study

- PK study conducted to:
  - identify the major route of removal from the body (hepatic or renal)
  - characterize metabolites and their relative abundancies

How is a human ADME study conducted

- Standard design
- Special considerations
  - Population
  - Route of Administration
  - Dose
  - PK characteristics

Expansions of ADME protocols

Thank you