

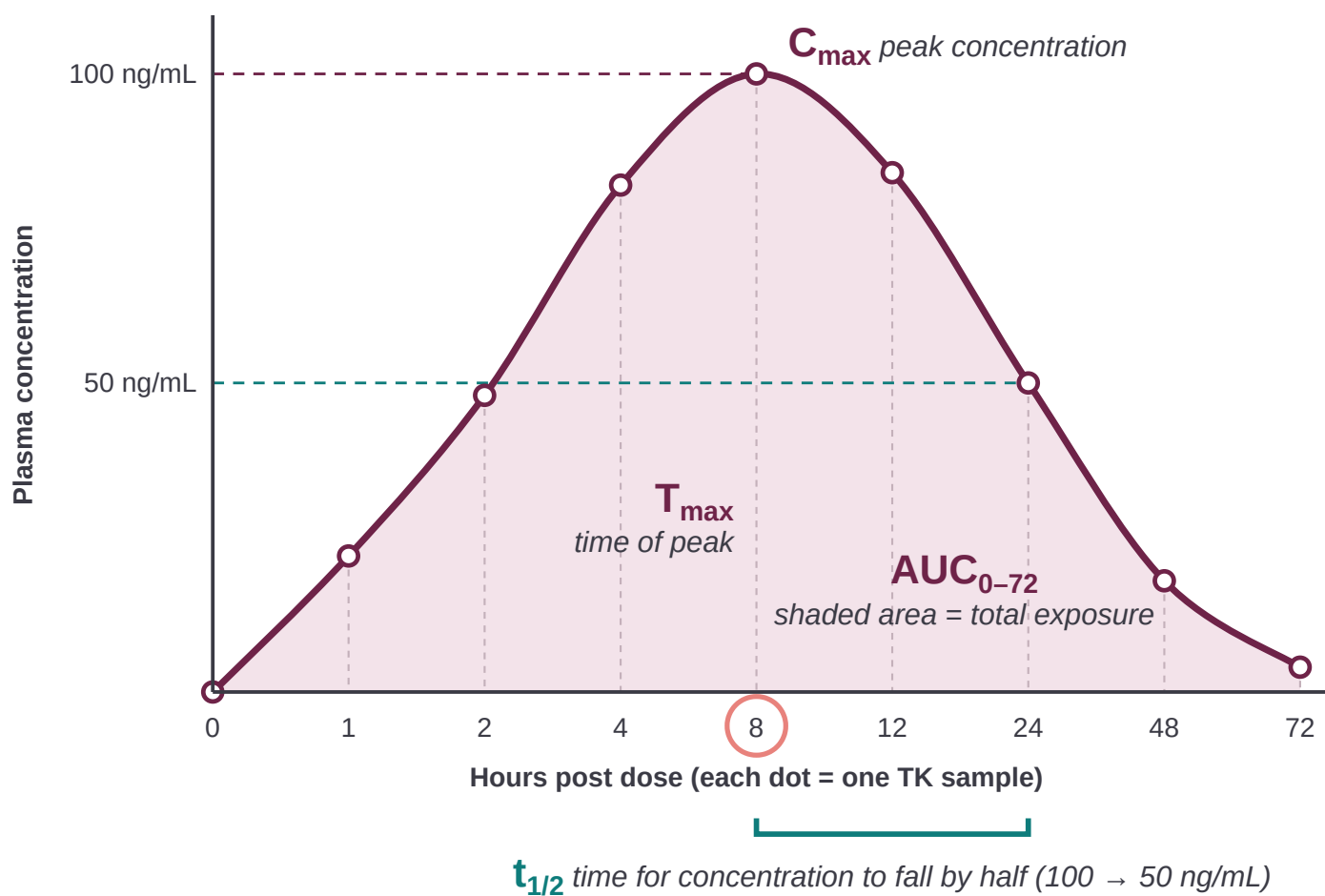


TK Profile Cheat Sheet

A TK profile is a curve, not a coordinate. Every toxicokinetic parameter answers a different question about exposure. Read them together, line them up against your findings, and you can defend your NOAEL, your safety margins, and your first-in-human dose. Read them one at a time and you'll miss the story.

Anatomy of a TK Profile

WHERE EACH NUMBER COMES FROM



Illustrative single-dose profile. Values are for orientation only.

AUC

Total exposure

AREA UNDER THE CONCENTRATION-TIME CURVE

The question it answers: how much drug did the animals actually see?

WHAT IT TELLS YOU

The primary metric for cross-species exposure comparison. It drives safety margins, anchors the NOAEL, and tells you whether your tox program can support clinical doses.

WHAT REGULATORS LOOK FOR

Dose-related increases in AUC. Sex differences greater than 2-fold. The animal-to-human AUC ratio at the NOAEL, which supports the starting dose and dose escalation.

RED FLAGS

Non-linear AUC at high doses (saturation or induction). Wide animal-to-animal variability. Day 1 vs. last-day drift that signals accumulation or autoinduction.

C_{max}

Peak exposure

MAXIMUM OBSERVED PLASMA CONCENTRATION

The question it answers: how high did it spike?

WHAT IT TELLS YOU

C_{max} drives acute toxicity, off-target receptor binding, and CV/CNS findings tied to peak exposure. It sets the upper bound of what tissues actually see.

WHAT REGULATORS LOOK FOR

C_{max} at the NOAEL vs. anticipated clinical C_{max}. The margin to the lowest adverse effect. Whether peaks are sustained or transient.

RED FLAGS

C_{max} spikes that don't scale with dose (often a formulation issue). High peak-to-trough ratios. C_{max} coinciding with clinical signs.

T_{max}

Absorption timing

TIME TO MAXIMUM CONCENTRATION

The question it answers: when did the drug actually arrive?

WHAT IT TELLS YOU

T_{max} reveals absorption kinetics and formulation behavior. It tells you when to look for PD effects and clinical signs.

WHAT REGULATORS LOOK FOR

T_{max} consistency across days and sexes. Evidence that PD endpoints, safety pharmacology windows, and clinical observations were timed to it.

RED FLAGS

Highly variable T_{max} within a dose group. Delayed T_{max} at high doses (saturated absorption). Double peaks suggesting enterohepatic recirculation.

t_{1/2}

Persistence

TERMINAL ELIMINATION HALF-LIFE

The question it answers: how long does it stay?

WHAT IT TELLS YOU

t_{1/2} drives accumulation in repeat-dose studies, recovery-period length, and dosing interval. It also informs human PK projection.

WHAT REGULATORS LOOK FOR

Accumulation consistent with half-life and dosing interval. A recovery period long enough for washout. Cross-species t_{1/2} used in human projection.

RED FLAGS

Half-life that lengthens with dose (saturated clearance). A species t_{1/2} too short to maintain exposure between doses. Too few terminal-phase points to trust the estimate.

$C_{\text{trough}} / C_{\text{min}}$

Concentration at the end of the dosing interval. Tells you whether target coverage is continuous or intermittent.

Watch for: levels falling to BLQ between doses when the mechanism needs sustained coverage.

Dose Proportionality

Does exposure rise in step with dose? Less than proportional points to absorption or solubility limits. More than proportional points to saturated clearance.

Watch for: an exposure plateau, which can justify your top dose but must be shown, not assumed.

Bioavailability (F)

The fraction of an extravascular dose that reaches systemic circulation, compared with IV exposure. Explains whether low exposure is an absorption problem.

Watch for: low or species-variable F that caps the exposure you can reach at high doses.

Control & Pre-dose Samples

Control animals and Day 1 pre-dose samples should be BLQ.

Watch for: measurable drug in controls. It can call the whole study into question.

Accumulation Ratio (R_{ac})

Last-day AUC compared with Day 1 AUC. Above 1 means accumulation. Below 1 can mean induction or reduced absorption.

Watch for: a ratio that doesn't fit the half-life and dosing interval.

Sex Differences

Always report TK by sex. Large differences can mean sex-specific metabolism, especially in rats.

Watch for: margins calculated on pooled data that hide a lower-exposed sex.

Metabolite Exposure

Human metabolites must be adequately covered in at least one tox species.

Watch for: a disproportionate human metabolite discovered after your tox studies are done.

Immunogenicity (Biologics)

Anti-drug antibodies can clear drug, sustain it, or neutralize it.

Watch for: exposure falling over time with no ADA data to explain it.

TK Design Checks Before the Study Starts

GET THE DATA RIGHT UP FRONT

Sampling Timepoints

Enough early points to catch absorption and T_{max} , and enough late points to define the terminal phase and $t_{1/2}$.

Satellite Groups vs. Microsampling

Rodent TK often uses satellite animals. Microsampling can sample main-study animals directly and reduce animal use.

Fit-for-Purpose Bioanalytical Method

GLP studies need a method validated for the matrix and species. For non-GLP studies, a qualified method is sufficient. Either way, the lower limit of quantitation must be low enough to see the terminal phase.

Sampling Days

Sample on Day 1 and near the end of dosing so you can see accumulation, induction, or loss of exposure.

Both Sexes, Every Dose Group

Plan TK for males and females at every dose level, including controls.

Metabolites & Test Article

Decide early which metabolites to measure, and confirm the tox batch impurity profile will cover the clinical batch.

#	Step	What to do	What you're looking for
1	Check the controls	Review control-group and Day 1 pre-dose samples.	All BLQ. Measurable drug in controls calls the exposure data into question.
2	Confirm data quality	Confirm the bioanalytical concentration data have been QC'd or QA-audited, based on the study's GLP compliance.	Verified data before margins are built on them.
3	Read across dose groups	Compare AUC and C_{max} across dose levels.	Proportional, less than proportional, or plateaued exposure.
4	Compare to Day 1	Compare last-day exposure with Day 1.	Accumulation, induction, or loss of exposure over time.
5	Correlate exposure with findings	Map clinical signs and pathology to the exposure that produced them, not just the dose.	A dose response: findings that increase in incidence or severity as exposure rises.
6	Build margins: target organs	Compare exposure at which target organ findings occur with projected human exposure.	How much room you have before target organ effects, and whether they're monitorable and reversible.
	Build margins: NOAEL	Compare NOAEL AUC and C_{max} with projected human exposure.	The margins that support your starting dose and escalation plan.

Regulatory Anchors

CLICK A GUIDANCE TO OPEN IT ON FDA.GOV

Guidance	Where TK matters
<u>ICH S3A</u>	Toxicokinetics in toxicity studies, plus its Q&A on microsampling.
<u>ICH M3(R2)</u>	Exposure-based high-dose selection (exposure margin, saturation of exposure, maximum feasible dose, limit dose) and metabolite safety testing at a high level.
<u>ICH M10</u>	Bioanalytical method validation for the assays that generate GLP TK data.
<u>ICH Q3A(R2) / Q3B(R2)</u>	Impurities in drug substance and drug product: qualification thresholds, and why your tox batch impurity profile has to cover the clinical batch.
<u>ICH M7(R2)</u>	Mutagenic impurities: assessment and control.
<u>ICH S6(R1)</u>	Biologics: exposure and immunogenicity in species selection and interpretation.
<u>ICH S9</u>	Oncology: exposure considerations for dose selection in advanced-cancer programs.

Not sure what your TK data is telling you? Dessi Turner, MS, DABT, helps biotech teams interpret TK data, build defensible safety margins, and get IND-ready. Book a call at dessiturner.com.