Predicting the Onset of Nonlinear Pharmacokinetics

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When analyzing the pharmacokinetics (PK) of drugs, one is often faced with concentration \( C \) vs. time curves, which display a sharp transition at a critical concentration \( C_{\text{crit}} \). For \( C > C_{\text{crit}} \), the curve displays linear clearance and for \( C < C_{\text{crit}} \) clearance increases in a nonlinear manner as \( C \) decreases. Often, it is important to choose a high enough dose such that PK remains linear in order to help ensure that continuous target engagement is achieved throughout the duration of therapy. In this article, we derive a simple expression for \( C_{\text{crit}} \) for models involving linear and nonlinear (saturable) clearance, such as Michaelis-Menten and target-mediated drug disposition (TMDD) models.

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✔ Mathematical models of nonlinear PK and TMDD of mAbs are widely used to guide drug development. Often, it is important to choose a high enough dose such that PK remains linear to help ensure that continual target engagement is achieved throughout the duration of therapy. There has not yet been a demonstration for how the PK/pharmacodynamic parameters impact the onset concentration at which the nonlinearity is observed.

WHAT QUESTION DID THIS STUDY ADDRESS?

✔ How the PK and binding properties of the drug impact the onset of nonlinear PK.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

✔ \( C_{\text{crit}} \) was derived and was found to be equal to \( V_{\text{max}}/\text{Cl} \) for the Michaelis-Menten model or \( k_{\text{syn}}/(\text{Cl}/V_{\text{c}}) \) for the TMDD model.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?

✔ The \( C_{\text{crit}} \) parameter can be used to provide better intuition for how the PK parameters impact drug concentration profiles and, in particular, guide the modeler in understanding where the random effects may need to be added and what parameters of the model are identifiable.

When analyzing the pharmacokinetics (PK) of drugs, one is often faced with concentration vs. time curves which display a sudden increase in the elimination rate below a certain critical concentration \( (C_{\text{crit}}) \). Examples of this phenomenon, in which the PK exhibit this nonlinear behavior, are shown in Figure 1 for efalizumab (anti-CD11a),1 mavrilimumab (antigranulocyte-macrophage colony-stimulating factor receptor),2 and romosozumab (antisclerostin).3

This nonlinearity shown in Figure 1 results from a combination of two pathways of drug clearance: (i) a linear, nonspecific clearance due to endocytosis; and (ii) a nonlinear, saturable clearance due to internalization of the target receptor:

- At high drug concentrations, the target receptor is saturated and the rate of elimination is governed by the nonspecific clearance.
- At lower drug concentrations, when the target receptor is no longer saturated, both the nonspecific route and the saturable route contribute to drug clearance and, hence, the rate of elimination increases as the concentration decreases.

A common goal when selecting the dose and regimen of a drug is to maintain a drug concentration that stays above the \( C_{\text{crit}} \). There are two reasons for this goal.

1. Ensure lower PK variability in the population, because \( C_{\text{crit}} \) may vary between subjects.
2. Ensure that target occupancy remains high, as maintaining drug concentrations above \( C_{\text{crit}} \) is thought to be a necessary (although not sufficient) condition to maintain target saturation.4

In this article, we show examples of systems that have a simple critical value for the drug concentration \( C_{\text{crit}} \) such that as long as the drug concentration remains above this value, target mediated elimination is saturated and the PK is linear. In Figure 1, \( C_{\text{crit}} \) is illustrated; when the concentration falls below \( C_{\text{crit}} \), the elimination rate suddenly increases.

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We derive an analytical expression for $C_{\text{crit}}$ for both the Michaelis-Menten model\textsuperscript{1,5} and the target-mediated drug disposition model (TMDD).\textsuperscript{6–8} Both models have two routes of clearance: nonspecific-linear elimination and saturable-nonlinear elimination. Both analyses will be discussed in the absence and in the presence of a peripheral compartment. In the presence of a peripheral compartment, the analysis becomes more complex, but it is still transparent in common cases, such as rapid exchange between the two compartments. In all cases, $C_{\text{crit}}$ is independent of drug dose and volume of distribution.

**METHODS**

For modeling the onset of the PK nonlinearity, we focus on the two models that are frequently used by the pharmacometrics community: Michaelis-Menten and TMDD. A more general theoretical derivation of $C_{\text{crit}}$ for any PK model is beyond the scope of this article. We start by focusing on the simpler case of the one-compartment model and then extend this analysis to the two-compartment scenario. The two-compartment models are shown schematically in Figure 2 below. The corresponding one-compartment models are identical with the models shown in Figure 2, except that the peripheral compartments ($C_p$) are removed.

**Michaelis-Menten elimination**

**One-compartment model.** The basic model for linear and nonlinear drug elimination involves a single (central) compartment and a single differential equation for the concentration $C$ of the drug involving linear and saturable elimination side by side:

$$V_c \frac{dC}{dt} = -Cl \cdot C - V_{\text{max}} \frac{C}{C + K_M}.$$  \hspace{1cm} (1)

Here, $V_c$ is the volume of the central compartment, $Cl$ a first order clearance rate, $V_{\text{max}}$ is the maximum rate of saturable elimination and $K_M$ is the Michaelis-Menten constant. For an initial i.v. bolus dose $D$, the initial concentration is given by $C(0) = D/V_c$.

**Two-compartment model.** When the drug is distributed over a central compartment with concentration $C_c$ and a peripheral compartment $C_p$ with linear and nonlinear elimination occurring only from the central compartment, the PK are described by the system of equations:

$$\begin{align*}
V_c \frac{dC_c}{dt} &= -Cl \cdot C_c - V_{\text{max}} \frac{C_c}{C_c + K_M} - Q(C_c - C_p) \\
V_p \frac{dC_p}{dt} &= +Q(C_c - C_p)
\end{align*}$$  \hspace{1cm} (2)

in which exchange between the compartments is driven by the difference in drug concentration in the two compartments (i.e., by the term $Q(C_c - C_p)$ where $Q$ denotes a non-specific clearance rate).

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Figure 1  Nonlinear pharmacokinetics for efalizumab, mavrilumab, and romosozumab. Note that for all three drugs, as the concentration drops below the critical concentration ($C_{\text{crit}}$), the elimination rate suddenly increases.

Figure 2  Structural scheme of the basic model describing (a) Michaelis-Menten kinetics and (b) target-mediated drug disposition (TMDD) where a drug $C$ binds a target receptor $R$ which is synthesized by a zero order reaction and degenerates according to a first order reaction. Drug and target form a complex $CR$, which internalizes through a first-order reaction.
Table 1 Parameters for mavrilimumab, efalizumab, and romosozumab, based on fits to data

|                    | Mavrilimumab | Efalizumab | Romosozumab | Units     |
|--------------------|--------------|------------|-------------|-----------|
| Weight-based dose  | 10           | 10         | 10          | mg/kg     |
| Equivalent molar dose | 4667       | 4667       | 4667        | nmol      |
| $V_c$              | 2.8          | 2.4        | 2.4         | L         |
| $V_p$              | 5.6          | 3.6        | 2.6         | L         |
| $CI$               | 0.3          | 0.46       | 0.25        | L/d       |
| $Q$                | 1.7          | 9.7        | 0.54        | L/d       |
| $k_{syn} = V_{max}/V_c$ | 2.4       | 8.5        | 6.1         | nM/d      |
| $k_{SS} = K_M$     | 1.1          | 1.2        | 12          | nM        |
| $k_{eff}$          | 2.2          | 4400       | 860         | 1/d       |
| $k_{tot}$          | 2.2          | 4400       | 860         | 1/d       |
| $k_{on}$           | 10           | –          | –           | 1/d       |
| $k_{off}$          | 11           | –          | –           | 1/(nM·d)  |

Note that the on-rate and the off-rate constants $k_{on}$ and $k_{off}$ no longer appear in these equations.

If initially, an i.v. bolus dose $D$ is supplied to the central compartment while the peripheral compartment is empty, the initial conditions are here $C_c(0) = D/V_c$ and $C_p(0) = 0$.

### Target-mediated drug disposition

In its most elementary form, TMDD target kinetics is assumed to follow a zero-order production rate $k_{syn}$ and a first-order elimination rate $k_{eff}$. The formation of drug-target complex $CR$ takes place via a second-order process $k_{syn}C \cdot R$, a first-order loss of the drug-receptor complex via $k_{eff}CR$, and an irreversible first-order elimination process $k_{tot}CR$.

In Figure 2 this system of reactions is shown schematically.

#### One-compartment model

Mathematically, the one-compartment TMDD model is described by the system of differential equations below:

\[
\begin{align*}
\frac{dC}{dt} &= -k_{on}C \cdot R + k_{off}CR - k_{eff}C; \quad k_{eff} = \frac{CI}{V_c} \\
\frac{dR}{dt} &= k_{syn} - k_{on}C \cdot R + k_{off}CR - k_{eff}R \\
\frac{dCR}{dt} &= k_{syn}C \cdot R - k_{off}CR - k_{tot}CR
\end{align*}
\]

(3)

Note that in the absence of drug, the steady-state target concentration is given by $R_c = k_{syn}/k_{eff}$. Here, we assume that the drug is supplied through an i.v. bolus dose $D$ to the system when it is free from drug and the target is at steady state (i.e., $C(0) = D/V_c$, $R(0) = R_c$, and $CR(0) = 0$).

By adding the first and the third equations, we obtain an equation for the total amount of drug $C_{tot} = C + CR$ and, similarly, by adding the second and the third equations we obtain an equation for the total amount of the target, $R_{tot} = R + CR$:

\[
\begin{align*}
\frac{dC_{tot}}{dt} &= -k_{on}C \cdot R + k_{off}CR - k_{eff}C \\
\frac{dR_{tot}}{dt} &= k_{syn} - k_{off}R - k_{tot}CR
\end{align*}
\]

(4)

Note that the on-rate and the off-rate constants $k_{on}$ and $k_{off}$ no longer appear in these equations.

In practice, drug binding and complex internalization is fast, so that after a short time drug, target, and drug-target complex are in quasi-steady-state (QSS) (i.e., $C$, $R$, and $CR$) are approximately related through the expressions:

\[
CR = R_{tot} \frac{C}{C + K_{SS}} \quad \text{and} \quad R = R_{tot} \frac{K_{SS}}{C + K_{SS}}
\]

(5)

where

\[
K_{SS} = \frac{k_{off} + k_{eff}CR}{k_{on}}
\]

(6)

### Two-compartment model

The two-compartment model is similar to the one-compartment model with the addition of a peripheral compartment with the initial condition $C_{p}(0) = 0$.

\[
\begin{align*}
\frac{dC}{dt} &= -k_{on}C \cdot R + k_{off}CR - k_{eff}C + Q(C - C_p) \\
\frac{dC_p}{dt} &= +Q(C - C_p) \\
\frac{dR}{dt} &= k_{syn} - k_{off}R - k_{eff}CR
\end{align*}
\]

(7)

### Model analysis, fitting, and simulation

A mathematical analysis of the above equations was performed to derive $C_{crit}$ for each model above. To test the theory, the data from Figure 1 was fit to the two-compartment TMDD model from Eq. 7 where it was assumed that $k_{eff} = k_{eff}CR$. This assumption is typically made when fitting the PK for membrane-bound targets where it can be especially difficult to estimate $k_{eff}^{10}$. Good fits can still be achieved even when implementing this constraint.

Sensitivity analyses were performed for the one-compartment Michaelis-Menten and TMDD models and the
two-compartment Michaelis-Menten model. In the sensitivity analysis, one parameter at a time was changed while all other parameters were held fixed, and the calculated \( C_{\text{crit}} \) was plotted together with the simulated PK data.

Because dosing of monoclonal antibodies (mAbs) is usually reported in mg/kg, but the binding model requires doses of nmol and concentrations of nM, a dose of 10 mg/kg is converted to nanomoles for the model simulations using the formula below, which assumes a 70 kg patient and a 150 kDa drug (typical antibody).

\[
\frac{10 \text{ mg}}{\text{kg}} \times \frac{70 \text{ kg}}{\text{patient}} \times \frac{1 \text{ g}}{1000 \text{ mg}} \times \frac{1 \text{ mol}}{150 \times 10^3 \text{ g mol}} = 467 \text{ nmol}
\]

RESULTS

Model fit

The model fits to the data are shown in the Supplementary Material and the parameters from the fits that are subsequently used for simulations are listed in Table 1. These parameters were also used to compute the \( C_{\text{crit}} \) lines, as described below. Note that the large values for \( k_{\text{e(f)}} \) and \( k_{\text{e(CR)}} \) for romosozumab and efalizumab are due to the practical unidentifiability of these parameters.\(^\text{11}\)

Michaelis-Menten elimination

One-compartment model. For drug concentrations, which are either large or small with respect to \( K_M \), Eq. 1 can be approximated by the following simpler equations:

\[
\begin{align*}
V_c \frac{dC}{dt} &= -Cl \cdot C - V_{\text{max}} \approx -Cl \cdot C \quad \text{for} \ C \gg K_M, \\
V_c \frac{dC}{dt} &= - (Cl + \frac{V_{\text{max}}}{K_M})C \quad \text{for} \ C < K_M.
\end{align*}
\]

(8)

Thus, on a logarithmic scale, the graph of \( C(t) \) will be approximately linear for both large and small values of \( C \); for

the range of concentrations in between, the graph curves down connecting the upper linear segment with the lower linear segment (see Figure 3).

Of particular interest is the situation when the rate of elimination increases substantially at low concentrations. According to Eq. 8, this is the case when:

\[
\frac{V_{\text{max}}}{K_M} \gg Cl \quad \Rightarrow \quad K_M \ll \frac{V_{\text{max}}}{Cl}.
\]

(9)

Throughout this article, it will be assumed that Eq. 9 holds. The sensitivity analysis for romosozumab in the Supplementary Material demonstrates that for small values of \( V_{\text{max}} \) or large values of \( K_M \), the shoulder (where the onset of the PK nonlinearity is observed) disappears entirely and the PK appears linear.

As the concentration drops, the elimination rate increases, and it is important to know at which concentration this transition takes place. We define this critical concentration, \( C_{\text{crit}} \), as the value of \( C \) where the rate of elimination doubles from its value at large drug concentrations. This definition was chosen because when the rate of elimination doubles, that means the linear and nonlinear components of elimination contribute equally. \( C_{\text{crit}} \) is derived by dividing Eq. 1 by \( C \), which gives:

\[
V_c \frac{d}{dt} \log (C) = - \left( Cl + \frac{V_{\text{max}}}{C+K_M} \right)
\]

(10)

It can readily be seen that for large concentrations, the slope is \( Cl \) and, thus, the rate of elimination doubles when:

\[
\frac{V_{\text{max}}}{C+K_M} = Cl \quad \text{or} \quad C = \frac{V_{\text{max}}}{Cl} - K_M
\]

(11)

By assumption of Eq. 9, we may neglect \( K_M \) in the right expression in Eq. 11 and, thus, define the critical concentration to be:
Note that neither the drug dose nor the volume $V_c$ of the central compartment enters the definition of $C_{\text{crit}}$. In Figure 3, we show simulations of concentration graphs based on Eq. 1 for data from mavrilimumab in which $Cl = 0.3 \text{ L/d}$, $V_{\text{max}} = 6.7 \text{ nmol/d}$, and $K_M = 1.1 \text{ nM}$ (Table 1). Then, according to Eq. 12, $C_{\text{crit}} = 22 \text{ nM}$. Note that here $C_{\text{crit}}$ is large compared to $K_M$ so that for the base values condition Eq. 9 is satisfied.

Figure 3 shows how $C_{\text{crit}}$ computed from Eq. 12 and indicated by a dot, changes when one of the parameters involved in the model is varied. In addition, it shows where $C_{\text{crit}}$ fits in the concentration-time curve of the drug. The graph for the largest parameter value is drawn in red and the graph for the smallest is drawn in magenta.

In the first panel in Figure 3, in which the dose is varied while keeping $C(0) > C_{\text{crit}}$, it is shown how both numerically and geometrically $C_{\text{crit}}$ corresponds to the kink in the graph, irrespective of the dose value. According to Eq. 12, as $V_{\text{max}}$ increases, $C_{\text{crit}}$ moves up, while as $Cl$ increases $C_{\text{crit}}$ moves down, and this is observed in the second and third panels. Because $C_{\text{crit}}$ does not depend on either $V_c$ or $K_M$, it does not move in the fourth and the fifth panels.

**Two-compartment model.** As we shall see, for initial drug concentrations that are large enough, the switch from linear to nonlinear drug elimination is apparent in this situation as well, and it is possible to identify a critical drug concentration $C_{\text{crit}}$. Here, we only derive the formula for $C_{\text{crit}}$ for the special case when drug exchange between the two compartments is fast relative to the nonspecific clearance ($Cl$) and the saturable clearance ($V_{\text{max}}$), such as when:

$$Q \gg Cl \quad \text{and} \quad Q \gg V_{\text{max}}. \quad (13)$$

Under these conditions, it is found that the two concentrations, $C_c$ and $C_p$, rapidly coalesce (i.e., $C_c(t) - C_p(t) \to 0$), and $C_{\text{crit}}$ in both the central and peripheral compartments is given by the same formula as for the one-compartment model (i.e., by Eq. 12):

$$C_{\text{crit}} = \frac{V_{\text{max}}}{Cl}. \quad (14)$$

The details of the derivation of Eq. 14 are provided further below.

In Figure 4, we show simulations for the two-compartment Michaelis-Menten model for parameter values, which are varied around the base parameters listed in Table 1, as indicated in the headings of the different panels. The graphs in the different panels are comparable to those shown in Figure 3 for the one-compartment model, except that many show a weak point of inflection below the $C_{\text{crit}}$.

Evidently, the location of $C_{\text{crit}}$ on the graphs, as defined by Eq. 14, has not changed much from what was seen in Figure 3. This is remarkable because the condition in Eq. 13 is not satisfied by the base values of the parameters. Specifically, the value of the intercompartmental clearance $Q$ is not large compared to $V_{\text{max}}$. On the other hand, $Q$ is indeed large compared to the nonspecific clearance $Cl$, as is also borne out by the different graphs shown in Figure 4, which exhibit a clear two-phase structure during the initial development.

**Figure 4** Mavrilimumab two-compartment Michaelis-Menten model, in which the base parameter values are listed in Table 1, and each plot shows a sensitivity analysis in which the parameter in the title is changed from 0.1-fold to 10-fold. The dot shows critical concentration. $Cl$, clearance; $V_{\text{max}}$, maximal rate of metabolism.
Rapid exchange between central and peripheral compartments
Suppose that \( Q \gg C_{\text{L}} \) and \( Q \gg V_{\text{max}} \). Then, when we divide the system of Eq. 2 by \( Q \), and scale the time variable according to \( \tau = Qt \), we obtain, with \( x(t) = C_{c}(t/Q) \) and \( y(t) = C_{p}(t/Q) \),

\[
\begin{align*}
V_{c} \frac{dx}{d\tau} &= -e \cdot x - (x - y) - v(\tau), \\
V_{p} \frac{dy}{d\tau} &= x - y
\end{align*}
\]  
(15)

where

\[
e = \frac{C_{\text{L}}}{Q} \ll 1 \quad \text{and} \quad v(\tau) = \frac{V_{\text{max}}}{Q} \frac{C_{c}}{C_{c} + K_{M}} \ll 1
\]  
(16)

Adding the two equations we find for the total amount of drug:

\[
A(\tau) \overset{\text{def}}{=} V_{c}x(\tau) + V_{p}x(\tau),
\]  
(17)

the conservation law:

\[
\frac{d}{d\tau}(V_{c}x + V_{p}y) = -e \cdot x - v \approx 0
\]  
(18)

Thus, there is very little loss of drug: on the fast time scale \( \tau = O(1) \) (i.e., \( t = O(1/Q) \)). Similarly, by dividing the equations by their respective volumes and then subtracting the two equations we obtain:

\[
\frac{d}{d\tau}(x - y) \approx -\left( \frac{1}{V_{c}} + \frac{1}{V_{p}} \right)(x - y)
\]  
(19)

so that \( C_{c}(t) - C_{p}(t) \approx 0 \) on the fast time scale as well. Therefore, within a very short time, we may write \( A(t) \approx (V_{c} + V_{p})C(0) \).

We now go back to Eq. 18 and multiply it by \( Q \) so that the original time variable \( t \) is returned. In light of Eq. 19, this yields the following equation:

\[
\frac{d}{d\tau}(x - y) \approx -\left( \frac{1}{V_{c}} + \frac{1}{V_{p}} \right)(x - y)
\]  
(19)

Thus, when we subtract the second equation in Eq. 23 from the first we obtain for \( 0 < t < t_{0} \)

\[
\frac{dC}{dt} = -k_{e}(C)C - k_{\text{syn}}
\]  
(24)

or, when we multiply by \( V_{c} \),

\[
V_{c} \frac{dC}{dt} = -C_{c} - V_{\text{max}}
\]  
(25)

This equation is formally the same as the first equation in the system of Eq. 8. Following the reasoning used in the Michaelis-Menten elimination Subsection to derive \( C_{\text{crit}} \), we assume, as in Eq. 9, that:

\[
\frac{V_{\text{max}}}{Cl} \gg K_{ss} \quad \text{or} \quad \frac{k_{\text{syn}}}{k_{e}(C)} \gg K_{ss}
\]  
(26)

and show that

\[
C_{\text{crit}} = \frac{V_{\text{max}}}{Cl} = \frac{k_{\text{syn}}}{k_{e}(C)}
\]  
(27)

Thus, by assuming rapid drug binding and complex internalization, drug clearance can be seen as the sum of linear and Michaelis-Menten type elimination resulting in the same expression for the \( C_{\text{crit}} \).

In Figure 5, we show simulations for the one-compartment Michaelis-Menten and TMDD models and we see that for mavrilimumab, a typical antibody for which Eq. 26 is satisfied, simulations give corresponding results and, as we have seen in Figures 3 and 4 for the Michaelis-Menten model, \( C_{\text{crit}} \) fits snuggly in the arm of the concentration curves.

In the first five graphs, in which simulations for the Michaelis-Menten model and the TMDD model are shown together (the Michaelis-Menten model is dashed and the TMDD is solid), the Michaelis-Menten model curves lie below the TMDD curves. This can be understood by comparing the equations for \( C_{\text{tot}} \) and \( R_{\text{tot}} \) in Eqs. 4 and 23 and remembering that \( CR < R_{\text{tot}} \).

The similarity between the Michaelis-Menten and TMDD models has been reported elsewhere.10,11 Comparable findings were observed for the two-compartment model as well. Note that the similarity of the Michaelis-Menten and TMDD models may not apply for other biologics, such as bispecific
DISCUSSION

In practice, \( C_{\text{crit}} \) is a useful quantity. We list a few applications below.

One application of \( C_{\text{crit}} \) is in providing an initial estimate for \( V_{\text{max}} \) or \( k_{\text{syn}} \) from a graphical inspection of the data. For large, i.v. doses, Cl can be estimated by non-compartmental analysis by computing the area under the curve (AUC) 0–∞ for a single dose and then computing Cl = Dose/AUC 0-∞. Then, \( C_{\text{crit}} \) can be estimated from a graph of the PK and Eq. 14 is then applied to get \( V_{\text{max}} = C_{\text{crit}} \cdot Cl \) or \( k_{\text{syn}} = C_{\text{crit}} \cdot Cl/V_c \).

Another application is that when fitting a population PK model, there may be patients who have similar PK above \( C_{\text{crit}} \) (and, thus, similar Cl) but different \( C_{\text{crit}} \) levels. When this is observed, we have found that a random effect on \( V_{\text{max}} \) was needed to capture the intersubject variability in the low concentration data.

Finally, \( C_{\text{crit}} \) is also useful in understanding the identifiability of TMDD models when fit to data of the type shown in Figure 1. Here, it has been shown that once the linear PK parameters have been identified (say from high-dose data) \( k_{\text{syn}} \) is the only remaining parameter needed to determine \( C_{\text{crit}} \). Then, given \( k_{\text{syn}}, K_{SS} \) is the only remaining parameter needed to determine the slope of the nonlinearity. Thus, these two parameters are often estimable from the nonlinear PK alone. However, other parameters of the TMDD model, such as the receptor density \( R_0 = k_{\text{syn}}/k_{e(R)} \) (often assumed to be constant with \( k_{e(R)} = k_{e(CR)} \)) is often not identifiable with PK data alone, as previously reported.\(^{10,11}\)

One key assumption for the \( C_{\text{crit}} \) estimate to apply is that initially, the drug concentration is large so that the nonlinear elimination term initially has a negligible contribution to the PK curve. If this assumption does not hold, there may be no kink and hence no \( C_{\text{crit}} \). In addition, there may be a kink, but if the dose is low enough such that the nonlinear component already contributes significantly to the elimination, \( C_{\text{crit}} \) as calculated here will not describe the kink. In the extreme case that Cl \( \rightarrow 0 \) for a drug with only saturable elimination, \( C_{\text{crit}} \rightarrow \infty \) and is essentially unobservable. Thus \( C_{\text{crit}} \) as defined here is no longer of practical value in scenarios where the saturable route of elimination dominates for all observable drug concentrations, as is the case for drugs that are given at low doses, such as bispecific target engagers and cytokines. To describe the kink in the PK curve in these scenarios (shown in more detail in the Supplementary Material) an alternative definition of \( C_{\text{crit}} \) would be needed. \( C_{\text{crit}} \) is of its greatest utility for mAbs (or other drugs) given at sufficiently high doses, such that both linear and nonlinear elimination phases are observable.

In summary, when developing antagonists, it is often the goal to pick a dosing regimen where the drug concentration stays above \( C_{\text{crit}} \). In this article, we have developed a simple formula for this critical concentration: \( C_{\text{crit}} = V_{\text{max}}/Cl = k_{\text{syn}}/K_{SS} \).
Supplementary Information

Supplementary information accompanies this paper on the CPT: Pharmacometrics & Systems Pharmacology website (www.psp-journal.com).

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