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DRUG METABOLISM & DISPOSITION

Commentary

In Defense of Current Concepts and Applications of Clearance in Drug Development and Therapeutics

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ABSTRACT

Clearance is one of the most widely quoted and applied pharmacokinetic concepts in drug development and therapy. Its foundations and associated models of drug elimination are well embedded and accepted within the scientific community. Recently, however, the prevailing views that have held us in good stead for the past almost 50 years have been challenged with the argument that organ clearance should not be based on elimination rate, now defined by loss across the liver divided by incoming or systemic concentration, as in current practice, but rather, by the mean concentration of drug within the blood in the organ, which is model-dependent. We argue that all needed parameters already exist, and that the proposed new approach to organ clearance is confusing and unnecessary.

SIGNIFICANCE STATEMENT

Clearance concepts are widely applied in drug development and therapy. Historically, hepatic clearance has been defined as the ratio of rate of elimination divided by ingoing blood concentration. Recently, this approach has been challenged arguing that clearance should be referenced to blood concentration within the liver. There is no need for additional, a feature that corresponds to intrinsic clearance of the chosen clearance model, a widely accepted parameter in physiologically based pharmacokinetic (PBPK) and in vitro to in vivo extrapolation (*IVIVE*). There is no need for additional, confusing clearance terms, which offer no material benefit.

Introduction

Clearance is one of the most widely quoted and applied pharmacokinetic concepts in drug development and therapy. Its foundations and associated models of drug elimination are well embedded and generally accepted within the scientific community and have served it well over the past almost 50 years.

Recently, however, Benet et al. (2021) have written a provocative paper rejecting one of the prevailing views, which states that clearance, calculated by relating rate of elimination across the eliminating organ to the systemic or incoming concentration ($\boldsymbol{rate}/\boldsymbol{C}_{\mathrm{in}}$), is independent of any mechanistic models. Rather, they claim, based on chemical engineering principles that the value of organ clearance should be given by dividing the rate of elimination of substance by the mean concentration of drug within the tissue water space within the organ, and advocate that it is model-dependent. In particular, they derive relationships for the common models of organ clearance, the well stirred model (WSM) and the parallel tube model (PTM). In this short commentary, we briefly review the background to Benet's clearance equations and show that what these authors are calculating is the intrinsic clearance of the liver associated with the particular chosen model, a parameter already widely accepted and applied in in vitro to in vivo extrapolation (*IVIVE*), physiologically based pharmacokinetic modeling, and drug development. There is no need for additional clearance terms.

Analysis and Discussion

Clearance ($\boldsymbol{CL}$) is a steady-state concept: rate of elimination = $\boldsymbol{CL} \bullet \boldsymbol{C}$, where the in vivo $\boldsymbol{C}$ is typically the systemic concentration of a drug or solute, in a plasma or blood sample taken from a peripheral venous site, with dimensions of volume per unit time. It is most commonly applied when the kinetics of the drug is linear, that is, when parameters of the system are independent of concentration and time. In such circumstances, $\boldsymbol{CL}$ derived from the systemic exposure (represented by area under the curve from time of dosing to infinite time $\boldsymbol{AUC}_{\infty}$) after single dose intravenous administration ($\boldsymbol{CL} = \boldsymbol{Dose}/\boldsymbol{AUC}_{\infty}$) can serve to predict plasma or blood concentrations at steady state ($\boldsymbol{C}_{ss}$), such as following constant rate input, $\boldsymbol{R_0}$ and ($\boldsymbol{C}_{ss} = \boldsymbol{R_0}/\boldsymbol{CL}$) is a useful and heavily applied property. In such applications, total body clearance is a global estimate of the efficiency of all the eliminating sites within the entire body to remove drug. There is no inherent requirement to know where or how elimination occurs, nor is any structural or mechanistic model of clearance implied. However, to progress further, attention needs to move from global events in the body to relate events occurring in individual organs of elimination. There is also increasing recognition that to ensure mass balance and correctly estimate organ extraction ratio,

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ABBREVIATIONS: DM, dispersion model; *IVIVE*, in vitro to in vivo extrapolation; PTM, parallel tube model; WSM, well stirred model.

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reference must be given to measurement of drug in whole blood and not plasma, as many drugs partition into blood cells, some extensively, and potentially be available for elimination. Plasma concentrations must be multiplied by the blood-to-plasma concentration ratio (R_b) to give blood concentrations.

Bradley et al. (1945) estimated hepatic blood flow Q_H in man using bromosulfophthalein, a compound exclusively eliminated via the liver. They infused bromosulfophthalein at a known constant rate to steady state when this rate is matched by the rate of elimination across the liver, given by the difference between the rate in, $Q_H \cdot C_{in,ss}$, and rate out, $Q_H \cdot C_{out,ss}$, i.e., $Q_H \cdot (C_{in,ss} - C_{out,ss})$, an application of Fick's Principle of Perfusion, in which $C_{in,ss}$ and $C_{out,ss}$ are the (measured) hepatic input and output blood concentrations at steady state, respectively. The basis of this calculation is that at steady state, the only reason for a drop in concentration across the organ is elimination; prior to then, output is due to a mixture of elimination and tissue uptake/binding. Given that clearance is rate of elimination divided by concentration, adopting a similar approach as Bradley et al. (1945) and keeping to directly measurable quantities, Rowland (1972) propose Eq. 1 for the estimation of organ (hepatic) clearance.

$$CL_{H,b} = \frac{Q_H \cdot (C_{in,ss} - C_{out,ss})}{C_{in,ss}} = Q_H \cdot E_H \quad (1)$$

where $CL_{H,b}$ is hepatic clearance based on measurements in whole blood, and E_H is the hepatic extraction ratio, the fraction of the inputted drug that is eliminated during a single passage through the liver at steady state, a measure of the efficiency of elimination of the process. The difference, $1 - E_H$, is the fraction escaping single-pass elimination, often referred to as the organ (hepatic) availability (to the systemic circulation) F_H. This concept of clearance applies to all eliminating organs.

Eq. 1 has been adopted consistently and almost universally by the pharmaceutical, medical, and biological communities as the definition of hepatic drug clearance. It should be noted that the equivalent of F_H in the chemical reaction engineering literature is the fraction of compound emerging unchanged in the exit stream from a chemical reactor F_c. Importantly, this literature shows that, for a given amount of catalyst (enzyme) and first-order kinetics, F_c varies with the flow characteristics within the reactor (Levenspiel, 1999; Fogler, 2016). Given that the flow characteristics inside the liver are not well stirred in nature (Roberts and Rowland, 1986a), Eq. 1 does not, as repeatedly proposed by Benet et al. (2018; 2021), confer a WSM property to hepatic clearance (discussed later). Also, this property was not, as claimed, required for the definition of clearance as implied in the paper on clearance concepts in pharmacokinetics by Rowland et al. (1973). The only requirement stated in the 1973 paper, which deals with the WSM and applies to other flow models as well, is that the rate of elimination across the perfused organ at steady state associated with the chosen model must equal that obtained directly from measurement of drug entering and leaving the organ. More recently, we have restated that Eq. 1 is not based on the WSM (Rowland and Pang, 2018; Pang et al., 2019). However, Eq. 1 is a helpful representation of hepatic clearance on at least two counts. First, it indicates that there is a physical upper limit to the value of clearance, that is organ blood flow, when the extraction ratio approaches its upper limit of 1. This feature is not apparent from the general formulation, rate of elimination $= CL \bullet C$. Second, in most cases, peripheral venous blood, the most common sampling site in pharmacokinetic studies, drains from non-eliminating tissues, typically skin and muscle, in which case the venous concentration of drug at steady state (or the integral of the concentration over time after a single bolus dose, area under the curve to infinity) equals that in the entering arterial concentration, which is generally the same as that entering the eliminating organ. Accordingly, the value of organ clearance obtained by applying Eq. 1 adds directly as part of total body clearance, estimated following intravenous administration.

However, as written, Eq. 1 does not describe the likely causes for change in hepatic clearance, and hence in exposure of drug within the body, as a result of changes in hepatic blood flow, binding within blood, enzymatic activity, and permeability, situations that arise during drug therapy. To progress to this desired state of affairs, models have been developed incorporating postulated blood flow behavior and transport within liver sinusoids and Disse space linking output to input, and in particular, disposition in hepatocytes, where elimination occurs. Historically, there was also the common assumption that elimination is driven by unbound concentration of drug at the site of elimination. This led to the concept of intrinsic clearance, CL_{int} (Wilkinson and Shand, 1975), with dimensions of flow per unit time, so named because it describes the intrinsic ability of the hepatocyte to eliminate substrate (rate of elimination $= CL_{int} \cdot Cu_{H,cell}$, where $Cu_{H,cell}$ is the unbound drug concentration in hepatocyte water), which in the context of the model is considered independent of such external factors as blood flow and binding within blood. When elimination occurs via metabolism that is characterized by Michaelis–Menten kinetics operating under linear conditions $CL_{int} = {}^{V_{max}}/_{K_m}$, where V_{max} is the maximum velocity of the reaction(s) and K_m is the Michaelis-Menten constant of the respective enzymes involved. In principle, intrinsic clearance may also describe biliary excretion and active transport processes. At steady state, it should be readily apparent that rate of elimination occurring globally within the liver equals that determined externally across the liver.

Physiologically oriented clearance models that are particularly applied to hepatic elimination have been widely discussed (Roberts et al., 1988; Hung et al., 2001; Pang et al., 2019). The first, least physiologic, but still the most widely applied in pharmacokinetics (Wilkinson and Shand, 1975; Pang et al., 2019), is the WSM (Pang and Rowland, 1977), alternatively called the continuously stirred tank model. Assumptions of this model, shared in common with other models of elimination described below, are that only unbound drug permeates cells and that permeation of the drug is so fast that radial distribution is blood flow rate-limited, such that unbound drug in hepatocyte water equals the unbound concentration in blood within the organ. Specific assumptions of the WSM are that the organ is well-mixed such that there is no concentration gradient of drug within the organ in the direction of bulk (vascular) flow, and that the unbound concentration of drug in the venous outflow (Cu_{out}) equals the unbound concentration in hepatocyte water ($Cu_{H,cell}$), a condition also known as venous equilibration. Accordingly, the equalities of the rates of elimination globally within and across the liver for the WSM at steady state are:

$$\begin{aligned} CL_{int,WSM} \cdot Cu_{H,cell,ss} &= CL_{int,WSM} \cdot Cu_{out,ss} \\ &= fu_b \cdot CL_{int,WSM} \cdot C_{out,ss} \\ &= Q_H \cdot (C_{in,ss} - C_{out,ss}) \end{aligned} \quad (2)$$

where $CL_{int,WSM}$ is the intrinsic clearance associated with the WSM, and $fu_b = Cu/C$ is the ratio of unbound plasma concentration to whole blood concentration. On collecting terms and applying the definition for hepatic clearance expressed in Eq. 1, the familiar solution of the WSM is obtained.

$$CL_{H,b,WSM} = Q_H \cdot \left[\frac{fu_b \cdot CL_{int,WSM}}{Q_H + fu_b \cdot CL_{int,WSM}}\right] \quad (3)$$

To re-emphasize, as defined here, for a given $CL_{H,b}$ that is the based on observations without reference to a structure (Eq. 1), hepatic clearance is now related to the WSM, $CL_{H,b,WSM}$.

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We and others have also described physiologically based models of hepatic elimination that will be addressed in more depth in a separate communication. Here, we will confine ourselves to two simple, more realistic models of hepatic elimination that take into account the observed continuous decline in drug concentration along the sinusoidal flow path within the liver (Gumucio, 1983). These are the dispersion model (DM) (Roberts and Rowland, 1986b), which also accommodates the observed spread in transit times of compound as it is conveyed by blood traveling through liver sinusoids, and a limiting case in which no such dispersion is assumed – frequently called the parallel-tube model (PTM) (Bass et al., 1976; Pang and Rowland, 1977). As pointed out by Pang and Rowland (1977) and Benet et al. (2021), the latter model is classified as a plug flow reactor. In contrast to the WSM, where the unbound concentration is assumed constant throughout the liver, in the PTM, for which the enzymes (and associated intrinsic clearance) are assumed to be distributed uniformly along identical lengths and hence parallel tubes within the liver, the unbound concentration in blood within the liver, that unbound in hepatocyte water, and the associated rate of elimination all incrementally decline monoexponentially with distance along the sinusoidal flow path from input to output. The corresponding overall rate of elimination across the organ is the integral of the rate–distance profile within the organ, for which there is a corresponding average rate.

Accordingly, the equalities for the PTM globally within and across the liver at steady state are:

$$\begin{aligned} \boldsymbol{CL_{int,PTM} \cdot Cu_{H,logav,cell,ss}} &= \boldsymbol{CL_{int,PTM} \cdot Cu_{logav,ss}} \\ &= \boldsymbol{fu_b \cdot CL_{int,PTM} \cdot C_{logav,ss}} \\ &= \boldsymbol{Q_H \cdot (C_{in,ss} - C_{out,ss})} \end{aligned} \quad (4)$$

where $\boldsymbol{C_{logav,ss}}$ is the logarithmic average blood concentration at steady state within the liver (Winkler et al., 1973), which for a monoexponential decline is given by $\boldsymbol{C_{logav,ss} = (C_{in,ss} - C_{out,ss})/[ln(C_{in,ss}/C_{out,ss})]}$, and $\boldsymbol{Cu_{H,logav,cell,ss}}$ is the corresponding log average unbound concentration in hepatocyte water. On collecting terms and applying the definition for hepatic clearance given in Eq. 1 yields Eq. 5 for $\boldsymbol{CL_{H,b,PTM}}$

$$\boldsymbol{CL_{H,b,PTM} = Q_H \cdot \left(1 - e^{-\left(\frac{fu_b \cdot CL_{int,PTM}}{Q_H}\right)}\right)} \quad (5)$$

where $\boldsymbol{CL_{int,PTM}}$ is the intrinsic clearance for the whole liver that is associated with the PTM.

The WSM (infinite mixing, bulk flow) and the PTM (no mixing, plug flow) set limits for model prediction, and these models therefore serve as extremes of the boundary conditions of how blood flow, binding within blood and intrinsic clearance affect hepatic clearance (Pang and Rowland, 1977; Pang et al., 2019). The DM predictions are, in principle, intermediate between these two extremes, noting that DM predictions are also dependent on other physiologic determinants, such as hepatic flow rate-induced dispersive changes in liver transit times.

In contrast to the above, Benet et al. (2021) argue that the only correct hepatic clearance associated with PTM, which they designated as $\boldsymbol{CL_{H,b,PTM}}$, is given by Eq. 6.

$$\boldsymbol{CL_{H,b,PTM} = Q_H \cdot ln\left(\frac{C_{in,ss}}{C_{out,ss}}\right)} \quad (6)$$

They derived this equation by dividing the rate of elimination across the organ by the mean concentration of drug in blood within the organ. Kochak (2020) has the same equation and uses the same terminology as Benet et al. (2021). A comparison clearly shows that the $\boldsymbol{CL_{H,b,PTM}}$ term, as defined in Eq. 6, is numerically greater than the clearance given by Eqs. 1 or 5 for the PTM, for a given $\boldsymbol{E_H}$ and $\boldsymbol{Q_H}$. The problem of defining hepatic clearance in this way, by referencing rate of organ elimination to the mean liver blood concentration, is that it has the seemingly absurd value of approaching infinity as $\boldsymbol{E_H}$ approaches a value of 1 because $\boldsymbol{C_{out,ss}}$ approaches zero. This does not arise when referencing elimination to $\boldsymbol{C_{in,ss}}$ as then clearance is limited at high $\boldsymbol{E_H}$ values by organ blood flow rate. So, what exactly is the meaning of Eq. 6? This is shown by recognizing that, $\boldsymbol{C_{out,ss}/C_{in,ss} = 1 - E_H = F_H = e^{-\left(\frac{fu_b \cdot V_{max}/K_m}{Q_H}\right)} = e^{-\left(\frac{fu_b \cdot CL_{int,PTM}}{Q_H}\right)}}$, which upon inverting, taking logarithms, and rearranging can be seen to give

$$\boldsymbol{Q_H \cdot ln\left(\frac{C_{in,ss}}{C_{out,ss}}\right) = fu_b \cdot CL_{int,PTM}} \quad (7)$$

This relationship (Eq. 7) has been described previously by Keiding (1987) for $\boldsymbol{fu_b = 1}$. Thus, Eq. 6 is just a direct way of calculating the intrinsic clearance, multiplied by the unbound fraction of drug in blood, estimated from experimental data ($\boldsymbol{C_{in,ss}}$, $\boldsymbol{C_{out,ss}}$, and $\boldsymbol{Q_H}$), and is not the clearance $\boldsymbol{CL_{H,b,PTM}}$ as defined in Eq. 5. The same discrepancy was noted by Jusko and Li (2021). As such, it does not warrant the creation of a new clearance term; we have already defined it earlier in the form of intrinsic clearance, $\boldsymbol{CL_{int}}$.

Now, it should be readily apparent from a comparison between the WSM and PTM (Eqs. 2 and 4) that the rate of elimination across the organ equals the product of the model-defined intrinsic clearance multiplied by its corresponding hepatocyte unbound concentration:

$$\underset{\textit{Rate of elimination}}{[\boldsymbol{Q_H \cdot (C_{in,ss} - C_{out,ss})}]} = \underset{\textit{WSM}}{\boldsymbol{CL_{int,WSM} \cdot Cu_{H,cell,ss}}} = \underset{\textit{PTM}}{\boldsymbol{CL_{int,PTM} \cdot Cu_{H,logav,cell,ss}}} \quad (8)$$

and, since all unbound concentrations within the liver associated with the PTM (except for $\boldsymbol{Cu_{in,ss}}$ at the entry point) are greater than WSM, other than at the exit to the liver when they are equal, it follows that $\boldsymbol{CL_{int,PTM} < CL_{int,WSM}}$. Restated, the PTM predicts that a lower amount of enzyme activity is needed than the WSM for a given extraction ratio or clearance.

So, where does this analysis take the reader in the application of models of organ elimination, and particularly hepatic elimination, in drug development and clinical application? First, and most importantly, there is no need to invent new clearance parameters; all the needed ones have already been defined. Second, given the previously mentioned direct linkage with systemic events, commonly gained from peripheral venous measurements, it is preferable to keep to the simple definition of organ clearance proposed in Eq. 1 by Rowland (1972), which applies equally to all organ models, rather than invent new terminology for clearance dependent on the chosen structural model. Third, for those involved with *IVIVE*, which aims to obtain an in vitro estimate of $\boldsymbol{CL_{int}}$ to predict organ clearance in vivo, the decision as to which model to apply, WSM, PTM, or DM, is the topic of constant and vigorous discussion, often dependent on the characteristic of the drug (Roberts and Rowland, 1986a; Pang et al., 2019; Sodhi et al., 2020), drug interactions, and pathophysiology (Hung et al., 2006). For example, if the in vitro $\boldsymbol{CL_{int}}$ is very low, as is often the case in modern drug development, to help achieve low dosing rate and less frequent dosing, it is immaterial as to which model $\boldsymbol{CL_{int}}$ is applied to predict clearance in vivo; all the above three models predict essentially the same value of clearance (error $< 5\%$ between WSM and DM for $\boldsymbol{E_H \leq 0.4}$) (Roberts and Anissimov, 1999). Even so, this does not guarantee accurate prediction for such compounds, with underprediction frequently encountered (Wood et al., 2017). Still, on the acquisition of in vivo data, the investigator then updates the value of $\boldsymbol{CL_{int}}$ within the chosen model and proceeds forward in the usual manner. Fourth, when basolateral permeability of the compound is low, so that perfusion rate limited distribution no longer applies, the steady-state ratio of intracellular to extracellular unbound concentrations is impacted when active transporters

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are involved, but equally for the WSM and PTM. Fifth, when dealing with clearance following iv administration, it is common practice to subtract renal clearance, and assign the remainder to hepatic clearance, estimate E_H by dividing by the published mean value of Q_H, using Eq. 1, and subsequently chose the WSM, PTM or a related model to predict $CL_{H,b}$ for different scenarios, appreciating all assumptions made. Last, for a given rate of elimination, and therefore rate of administration when the organ is the primary site of elimination, the PTM (and DM) predicts a higher average steady-state unbound hepatic concentration than the WSM (Eq. 8), especially when $E_H > 0.7$, and therefore higher response, in the relatively unusual case of the target residing in the eliminating organ (such as statins acting on hepatic enzymes to lower cholesterol). Also, as a corollary, a lower rate of administration is expected to be needed before internal saturation (exceeding K_m) of enzymes or transporters occurs for such high extraction ratio compounds.

In summary, organ clearance historically has referenced rate of elimination across an eliminating organ to its ingoing blood concentration based on experimental data. Recently, this approach has been challenged by Benet et al. (2021), who argue that clearance should be referenced to the mean blood concentration within the organ, such as the liver, whose value then depends on the choice of the model used to characterize postulating events occurring within the eliminating organ. We show that for the PTM, this definition of organ clearance corresponds to the intrinsic clearance associated with that model, an already widely accepted parameter applied in physiologically based pharmacokinetic modeling and *IVIVE*. There is no need for additional clearance terms, which are confusing and offer no material benefit.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Rowland, Roberts, Pang.

References

Bass L, Keiding S, Winkler K, and Tygstrup N (1976) Enzymatic elimination of substrates flowing through the intact liver. *J Theor Biol* **61**:393–409.

Benet LZ, Liu S, and Wolfe AR (2018) The universally unrecognized assumption in predicting dug clearance and organ extraction ratio. *Clin Pharmacol Ther* **103**:521–525.

Benet LZ, Sodhi JK, Makrygiorgos G, and Mesbah A (2021) There is only one valid definition of clearance: Critical examination of clearance concepts reveals the potential for errors in clinical drug dosing decisions. *AAPS J* **23**:67.

Bradley SE, Ingelfinger FJ, Bradley GP, and Curry JJ (1945) The estimation of hepatic blood flow in man. *J Clin Invest* **24**:890–897.

Fogler HS (2016) *Elements of Chemical Reaction Engineering*, Ed. 5th. Prentice Hall, Hoboken, New Jersey.

Gumucio JJ (1983) Functional and anatomic heterogeneity in the liver acinus: impact on transport. *Am J Physiol* **244**:G578–G582.

Hung DY, Chang P, Weiss M, and Roberts MS (2001) Structure-hepatic disposition relationships for cationic drugs in isolated perfused rat livers: transmembrane exchange and cytoplasmic binding process. *J Pharmacol Exp Ther* **297**:780–789.

Hung DY, Siebert GA, Chang P, Whitehouse MW, Fletcher L, Crawford DHG, and Roberts MS (2006) Hepatic pharmacokinetics of propranolol in rats with adjuvant-induced systemic inflammation. *Am J Physiol Gastrointest Liver Physiol* **290**:G343–G351.

Jusko WJ and Li X (2021) Commentary: Assessment of the Kochak-Benet equation for hepatic clearance for the parallel-tube model: relevance of classic clearance concepts in PK and PBPK. AAPS J **24**:5 DOI: 10.1208/s1224-021-00656-2.

Keiding S (1987) Hepatic clearance and liver blood flow. *J Hepatol* **4**:393–398.

Kochak GM (2020) Critical analysis of hepatic Clearance based on an advection mass transfer model and mass balance. *J Pharm Sci* **109**:2059–2069.

Levenspiel O (1999) *Chemical Reaction Engineering*, Ed. 3rd. John Wiley & Sons, New York.

Pang KS, Han YR, Noh K, Lee PI, and Rowland M (2019) Hepatic clearance concepts and misconceptions: Why the well-stirred model is still used even though it is not physiologic reality *Biochem Pharmacol* **169**:113596.

Pang KS and Rowland M (1977) Hepatic clearance of drugs. I. Theoretical considerations of a "well-stirred" model and a "parallel tube" model. Influence of hepatic blood flow, plasma and blood cell binding, and the hepatocellular enzymatic activity on hepatic drug clearance. *J Pharmacokinet Biopharm* **5**:625–653.

Roberts MS and Anissimov YG (1999) Modeling of hepatic elimination and organ distribution kinetics with the extended convection-dispersion model. *J Pharmacokinet Biopharm* **27**:343–382.

Roberts MS and Rowland M (1986a) Correlation between in-vitro microsomal enzyme activity and whole organ hepatic elimination kinetics: analysis with a dispersion model. *J Pharm Pharmacol* **38**:177–181.

Roberts MS and Rowland M (1986b) A dispersion model of hepatic elimination: 1. Formulation of the model and bolus considerations. *J Pharmacokinet Biopharm* **14**:227–260.

Rowland M (1972) Influence of route of administration on drug availability. *J Pharm Sci* **61**:70–74.

Roberts MS, Donaldson JD and Rowland M (1988) Models of hepatic elimination: comparison of stochasticmodels to describe residence time distributions and to predict the influence of drug distribution, enzyme heterogeneity, and systemic recycling on hepatic elimination. *J Pharmacokinet Biopharm* **16**:41–83.

Rowland M, Benet LZ, and Graham GG (1973) Clearance concepts in pharmacokinetics. *J Pharmacokinet Biopharm* **1**:123–136.

Rowland M and Pang KS (2018) Commentary on "The universally unrecognized assumption in predicting drug clearance and organ extraction ratio". *Clin Pharmacol Ther* **103**:386–388.

Sodhi JK, Wang HJ, and Benet LZ (2020) Are there any experimental perfusion data that preferentially support the dispersion and parallel-tube models over the well-stirred model of organ elimination? *Drug Metab Dispos* **48**:537–543.

Wilkinson GR and Shand DG (1975) Commentary: a physiological approach to hepatic drug clearance. *Clin Pharmacol Ther* **18**:377–390.

Winkler W, Keiding S, and Tygstrup N (1973) Clearance as a quantitative measure of liver function, In, *"The Liver, Quantitative Aspects of Structure and Function"*, pp. 144–155, Karger Basel 1973.

Wood FL, Houston JB, and Hallifax D (2017) Correction to "Clearance prediction methodology needs fundamental improvement: Trends common to rat and human hepatocytes/microsomes and implications for experimental methodology. *Drug Metab Dispos* **45**:1239.

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