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Proposal for defining the relevance of drug accumulation derived from single dose study data for modified release dosage forms

Christian Scheerans*, Roland Heinig, and Wolfgang Mueck
Clinical Pharmacology, Bayer Pharma AG, Research Center, Wuppertal, Germany

ABSTRACT: Recently, the European Medicines Agency (EMA) published the new draft guideline on the pharmacokinetic and clinical evaluation of modified release (MR) formulations. The draft guideline contains the new requirement of performing multiple dose (MD) bioequivalence studies, in the case when the MR formulation is expected to show 'relevant' drug accumulation at steady state (SS). This new requirement reveals three fundamental issues, which are discussed in the current work: first, measurement for the extent of drug accumulation (MEDA) predicted from single dose (SD) study data; second, its relationship with the percentage residual area under the plasma concentration–time curve (*AUC*) outside the dosing interval (τ) after SD administration, $\%AUC(\tau\text{-}\infty)_{SD}$; and third, the rationale for a threshold of $\%AUC(\tau\text{-}\infty)_{SD}$ that predicts 'relevant' drug accumulation at SS. This work revealed that the accumulation ratio $R_{A,AUC}$, derived from the ratio of the time-averaged plasma concentrations during τ at SS and after SD administration, respectively, is the 'preferred' MEDA for MR formulations. A causal relationship was derived between $\%AUC(\tau\text{-}\infty)_{SD}$ and $R_{A,AUC}$, which is valid for any drug (product) that shows (dose- and time-) linear pharmacokinetics regardless of the shape of the plasma concentration–time curve. Considering *AUC* thresholds from other guidelines together with the causal relationship between $\%AUC(\tau\text{-}\infty)_{SD}$ and $R_{A,AUC}$ indicates that values of $\%AUC(\tau\text{-}\infty)_{SD} \leq 20\%$, resulting in $R_{A,AUC} \leq 1.25$, can be considered as leading to non-relevant drug accumulation. Hence, the authors suggest that 20% for $\%AUC(\tau\text{-}\infty)_{SD}$ is a reasonable threshold and selection criterion between SD or MD study designs for bioequivalence studies of new MR formulations. © 2014 The Authors *Biopharmaceutics & Drug Disposition* Published by John Wiley & Sons Ltd.

Key words: pharmacokinetics; noncompartmental analysis; drug accumulation; modified release

Introduction

In February 2013, the European Medicines Agency (EMA) published a new draft guideline on the pharmacokinetic and clinical evaluation of modified release (MR) formulations [1]. This draft guideline was discussed at the European Federation for Pharmaceutical Sciences (EUFEPS) Bioavailability and Biopharmaceutics (BABP) Network Open Discussion Forum [2], in June 2013 in Bonn, Germany, together with representatives from the EMA Pharmacokinetic Working Party who were involved in drafting this guideline. During the meeting, one discussion point dealt with the new requirement of performing multiple dose (MD) bioequivalence studies for MR formulations, in the case that the MR formulation is expected to show 'relevant' drug accumulation at steady state (SS). The rationale of this new requirement from the draft guideline was exemplarily presented by EMA representatives, stating that '*multiple dose studies are necessary in*

*Correspondence to: Bayer Pharma AG, Global Drug Discovery - Clinical Sciences, Development Clinical Pharmacology, Aprather Weg 18a, 42113 Wuppertal, Germany.
E-mail: christian.scheerans@bayer.com

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prolonged release products because single dose studies […] do not provide information about the final phase of release, which reflects the absorption rate / release rate of the formulation since absorption is slower than elimination' [3]. In addition, it was pointed out that the multiple dose approach is needed '*[…] only if there is accumulation*' expected [3]. The prediction of 'relevant' drug accumulation was further defined by the representatives from EMA: '*A multiple dose study is needed unless a single dose study has been performed with the highest strength which has demonstrated that the mean AUC(0-τ) [the area under the plasma concentration–time curve within the dosing interval (τ)] after the first dose covers more than 90% of mean AUC(0-∞) [the AUC after single dose administration from time zero to infinity] for both test and reference, and consequently a low extent of accumulation is expected*' [3]. However, the discussions with the representatives from EMA during and after the meeting, revealed that there is obviously no conclusive scientific rationale for the selection of 10% as the threshold. The percentage residual area under the plasma concentration–time curve (*AUC*) outside the dosing interval after single dose (SD) administration, $\%AUC(\tau\text{-}\infty)_{SD} < 10\%$, suggested by EMA as a predictor for 'relevant' drug accumulation at steady state, seemed to be somehow arbitrarily chosen.

Hence, the objective of the current work was to evaluate and discuss the following three fundamental issues, encouraged by initial discussions from the mentioned EUFEPS-BABP network meeting [2], regarding (1) the 'preferred' measurement for the extent of drug accumulation predicted from single dose studies; (2) the relationship between the pharmacokinetic parameter $\%AUC(\tau\text{-}\infty)_{SD}$ and the extent of drug accumulation at steady state; and (3) the rationale for a threshold of $\%AUC(\tau\text{-}\infty)_{SD}$ that predicts a 'relevant' extent of drug accumulation at steady state after multiple dose administration.

Material and Methods

The 'preferred' measurement for the extent of drug accumulation

The phenomenon of drug accumulation in plasma was described quantitatively via mathematical equations a long time ago, i.e. in 1924 by Widmark and Tandberg [4] via a one-compartment open model approach and a quarter of a century later by Druckrey and Kuepfmueller [5] via a two-compartment open model approach. However, equations for measuring and predicting the extent of drug accumulation are often derived from either imprecise assumptions, e.g. ratios of highly variable single point measurements such as C_{max}, or derived from an overly simplified compartment model [6–9]. Hence, in the following the authors summarize the most fundamental compartmental (A) and compartment-independent (B) approaches for measuring and predicting the extent of drug accumulation in plasma, including considerations of special cases, e.g. influence of lag time, and the underlying assumptions that may limit the application of the respective approach.

(A) Compartmental approaches

One of the first compartmental approaches to describe the accumulation of drug concentration in body fluids was provided by Widmark and Tandberg (1924, in German language), where the periodic fluctuation of acetone concentrations in plasma and similar substances were considered via a one-compartment open model approach for continuous and intermittent intravenous (i.v.) drug administration [4]. In 1949, Druckrey and Kuepfmueller provided (in German language) the complete theory of drug concentration–time courses in the body, including its accumulation after multiple dosing, derived from a two-compartment open model approach for various routes of drug administration [5]. Unfortunately, this unique work did not receive adequate attention at that time and in the following years [10].

Based on the previous work from Widmark [11] and Tandberg [4] and Druckrey and Kuepfmueller [5], the paediatrician Friedrich Hartmut Dost described (1953, in German language), via a one-compartment open model with first order absorption, the accumulation of penicillin concentrations in plasma for intramuscular (i.m.) drug administration, when multiple equal doses are administered at uniform time intervals [12]. In 1960, Ekkehart Krueger-Thiemer used Dost's equation for the accumulation of the asymptotic 'trough' drug concentration immediately prior to the administration of the next dose, in order to derive drug specific loading

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doses (D^*) for orally administered sulfonamide antibiotics, which quickly produce effective (pseudo steady state) drug concentrations in plasma, i.e. already at the beginning of the first dosing interval (τ) when the maintenance dose (D) is given [13,14]. Krueger-Thiemer's dose ratio R^* (Eq. (1)) seems to be the first successful approach for predicting the extent of drug accumulation in plasma for orally administered drugs that show linear pharmacokinetics, considering τ and the two first-order rate constants of absorption and elimination, k_a and k_e, respectively.

$$R^* = \frac{D^*}{D} = \frac{1}{(1 - e^{-k_a \cdot \tau}) \cdot (1 - e^{-k_e \cdot \tau})} \quad (1)$$

For example, in the case $k_a \geq 5 \cdot k_e$ and if the selected τ is equal to the elimination half-life ($t_{1/2} = \ln(2)/k_e$), a two-fold increase in the 'trough' plasma drug concentration immediately prior to the administration of the next dose is obtained at (pseudo) steady state (i.e. $R^* \approx 2$) compared with the 'trough' plasma drug concentration reached at time equals τ after a single administration of the maintenance dose.

In addition, Krueger-Thiemer derived a simplified equation for the parameter R^* (Eq. (1a)) that is valid for the i.v. bolus injection [13], from which Dost later (1968) suggested that this formula can be used more generally, i.e. also as an approximation for extravascular administration, if $k_a >> k_e$, e.g. ≥10-fold [14]. This simplified mono-exponential approach to quantify or predict drug accumulation after extravascular drug administration is similar to previous considerations from Boxer *et al*. [15] and Swintosky *et al*. [16]. However, this approach should not be applied for orally administered drugs or drug products with slow absorption kinetics, as is often the case for many MR formulations.

$$R^* = \frac{D^*}{D} = \frac{1}{(1 - e^{-k_e \cdot \tau})} \quad (1a)$$

Moreover, despite its essential role in the development of rational, i.e. drug specific, dosing regimens for oral sulfonamide antibiotics in the 1960s and beyond, it should be noted that Krueger-Thiemer's equations for R^* are both based on a one-compartment open model approach which does not fit for drugs showing distinctive multi-phasic disposition characteristics [6]. Furthermore, as realized by Wiegand *et al*. [17], it should be mentioned that the formula of the 'accumulation factor' R^* from Equation (1) can only provide sufficiently precise estimates for cases with $k_a \geq 4 \cdot k_e$ [14,18–21], e.g. as it is valid for many sulfonamide antibiotics studied by Krueger-Thiemer, however, which may not necessarily be the case for many orally administered MR formulations.

Overall, compartmental approaches for predicting drug accumulation, as presented above, are in general highly dependent on the precise estimation of the involved rate constants of the respective pharmacokinetic model. Of special importance for correctly predicting the extent of drug accumulation in plasma is the correct detection of the 'true' terminal slope after single dose administration, otherwise wrong predictions will result [22].

(B) Compartment-independent approaches

In 1967, John Garnet Wagner [23] proposed the more general 'drug concentration ratio' (R_c) which aims to quantify the extent of drug accumulation (Eq. (2)), when a fixed dose is administered in a fixed dosing regimen.

$$R_C = \frac{\overline{C_{SS,\tau}}}{\overline{C_{SD,\tau}}} \quad (2)$$

Here, $\overline{C_{SS,\tau}}$ represents the time-averaged plasma concentration during τ at steady state and $\overline{C_{SD,\tau}}$ refers to the time-averaged plasma concentration during τ for the first (single) dose, which can be calculated from the AUC at steady state from time zero to τ, $AUC(0\text{-}\tau)_{SS}$, (Eq. (2a)) and the AUC after the first (single) dose administration from time zero to τ, $AUC(0\text{-}\tau)_{SD}$ (Eq. (2b)), respectively (see Figure 1), divided by τ [23].

$$\overline{C_{SS,\tau}} = \frac{AUC(0-\tau)_{SS}}{\tau} \quad (2a)$$

$$\overline{C_{SD,\tau}} = \frac{AUC(0-\tau)_{SD}}{\tau} \quad (2b)$$

Wagner could show that, considering e.g. a one-compartment open model with first order

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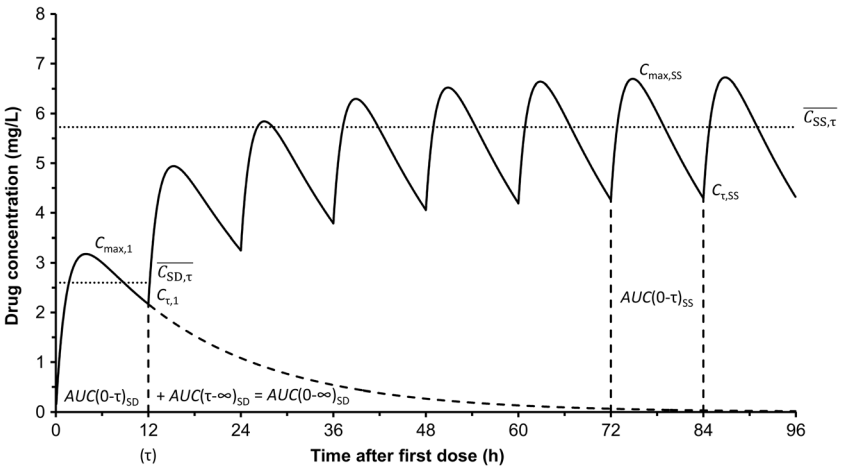

Figure 1. Schematic depiction of the concentration–time course of a hypothetical drug after multiple extravascular, e.g. oral, drug administrations at uniform time intervals, accumulating over time towards (pseudo) steady state, based on a one-compartment open model including first order absorption and elimination with: $D^* = D = 2.0$ mg, $\tau = 12$ h, $t_{lag} = 0$ h, $F = 1$, $V = 42$ L, $k_a = 0.058\ h^{-1}$, $k_e = 0.693\ h^{-1}$, resulting in $\%AUC(\tau\text{-}\infty)_{SD} = 55\%$ and thus $R_{A,AUC} = 2.2$. For the description of parameters see text

absorption as used by Dost and for Krueger-Thiemer's equation for R^* (see above, Eq. (1)), the exact mathematical solution for R_c can be derived algebraically from the general Equation (2) [23], which was confirmed briefly by van Rossum [24]. Although fundamentals for the calculation of $\overline{C_{SS,\tau}}$ had already been provided by Widmark and Tandberg in 1924 [4,21], it took more than four decades (1965) until the formula (Eq. (2a)) was reconsidered by Wagner *et al*. [25]. In 1970, van Rossum and Tomey confirmed that Wagner's general equations for calculating $\overline{C_{SD,\tau}}$ and $\overline{C_{SS,\tau}}$ (Eq. (2a) and (2b)) are valid for any drug showing (dose- and time-) linear pharmacokinetics with mono- or multi-phasic disposition characteristics [26].

Moreover, Wagner *et al*. revealed that $AUC(0\text{-}\tau)_{SS}$ is equal to the *AUC* after single dose administration from time zero to infinity, $AUC(0\text{-}\infty)_{SD}$ (Eq. (2c), see Figure 1) [25], which was again supported by the investigations of van Rossum and Tomey [26].

$$\overline{C_{SS,\tau}} = \frac{AUC(0-\tau)_{SS}}{\tau} = \frac{AUC(0-\infty)_{SD}}{\tau} \quad (2c)$$

The latter mentioned relationship of areas had already been introduced briefly as Dost's 'law of corresponding areas' [14,27]. Dost's assumption is valid for all drugs showing linear pharmacokinetics, i.e. independent of the (one- or multi-compartment) disposition model [28].

In 1979, Chiou used the reciprocal of Wagner's R_C term to quantify the 'mean fraction ($f_{n\tau}$) of the steady state level achieved during the *n*th τ' (Eq. (3)) from compartment-independent equations [29], based on the principle of superposition [30]. For $n = 1$, $\overline{C_{n\tau}}$ becomes equal to $\overline{C_{SD,\tau}}$ from Wagner's R_C formula, which can be calculated by Equation (3a).

$$f_{n\tau} = \frac{\overline{C_{n\tau}}}{\overline{C_{SS,\tau}}} = \frac{AUC(0-n\tau)}{AUC(0-\infty)_{SD}} \quad (3)$$

$$\overline{C_{n\tau}} = \frac{AUC(0-n\tau)}{\tau} \quad (3a)$$

Furthermore, Chiou showed that this general equation (Eq. (3)) holds true for any linear compartment open model, e.g. a constant-rate absorption or intravenous infusion for a two-compartment open model [31]. In 1982, Perrier and Gibaldi took Chiou's approach (Eq. (3)) and refined it as 'mean fraction of steady state', f_{SS}, for its predictability from single dose data in the form of Equation (3b) [32,33], where $AUC(\tau\text{-}\infty)_{SD}$ refers to the *AUC* after single dose administration from τ to infinity (see Figure 1).

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$$f_{SS} = \frac{\overline{C_{SD,\tau}}}{\overline{C_{SS,\tau}}} = \frac{\left[AUC(0-\infty)_{SD} - AUC(\tau-\infty)_{SD}\right]}{AUC(0-\infty)_{SD}} = \frac{AUC(0-\tau)_{SD}}{AUC(0-\infty)_{SD}} \quad (3b)$$

Overall, the equations (Eq. 2-2b) from Wagner provide a compartment-independent measure for the extent of drug accumulation which can be summarized as the 'accumulation ratio' $R_{A,AUC}$ (Eq. (4)).

$$R_{A,AUC} = \frac{AUC(0-\tau)_{SS}}{AUC(0-\tau)_{SD}} \quad (4)$$

Alternatively, the extent of accumulation of a given drug has also been approached via the ratio of the ('trough') plasma drug concentration (C_τ) immediately before the next dose at (pseudo) steady state ($C_{\tau,SS}$) to the ('trough') plasma drug concentration immediately prior to the administration of the second dose ($C_{\tau,1}$, see Figure 1) [8,9,33], which can be defined as the accumulation ratio $R_{A,C\tau}$ (Eq. (4a)).

$$R_{A,C_\tau} = \frac{C_{\tau,SS}}{C_{\tau,1}} \quad (4a)$$

Another compartment-independent measurement for the extent of drug accumulation is based on the respective maximum (or 'peak') plasma drug concentrations (C_{max}) during τ at (pseudo) steady state ($C_{max,SS}$) and after the first dose ($C_{max,1}$, see Figure 1) [9], which can be defined as the accumulation ratio $R_{A,Cmax}$ (Eq. (4b)).

$$R_{A,C_{max}} = \frac{C_{max,SS}}{C_{max,1}} \quad (4b)$$

The advantage of these compartment-independent measurements is that the underlying pharmacokinetic parameters, i.e. AUC, C_{max} and C_τ can be calculated via standardized non-compartmental analysis (NCA). Regarding the three accumulation ratios (Eq. 4-4b) as measurements for the extent of drug accumulation, essential differences in precision and accuracy should be considered, as explained in the following.

With $R_{A,Cmax}$ and $R_{A,C\tau}$ only one data point per concentration–time profile determines the estimate of the accumulation ratio, which can be seen as an inherent disadvantage of these two measurements. In contrast, for $R_{A,AUC}$ all the concentration–time points from the two profiles (during τ) after the first dose and at steady state are used [9]. Furthermore, if C_τ approaches the lower limit of quantification (LLOQ) of the assay, the analytical error (introduced by the assay) may be higher compared with C_{max} [34]. At drug concentrations > LLOQ modern bioanalytical techniques usually have heteroscedastic variance with a constant coefficient of variation [9]. However, due to the inter-subject variation in t_{max} (the time at which C_{max} occurs) the accuracy and precision of C_{max} is generally limited, which may affect the correctness of $R_{A,Cmax}$. In contrast, the time at which C_τ occurs is usually less uncertain [34]. Nevertheless, occasionally $C_{\tau,1}$ will not be available due to bioanalytical limitations, i.e. if $C_{\tau,1}$ is below the LLOQ. In such cases, additionally monitored 'trough' concentrations during the increasing accumulation from the first dose until (pseudo) steady state, can be supportive [9].

In the case of oral drug administration, including MR formulations, several other factors, e.g. the dosing interval (τ), lag time (t_{lag}) and the ratio of absorption to elimination rate constants (k_a/k_e), can influence the three accumulation ratios differently. As shown via deterministic *in silico* simulations, if absorption becomes slower, as is typically the case for oral formulations with 'controlled' drug release, the resulting values of the three accumulation ratios are in the order: $R_{A,AUC} > R_{A,C\tau} > R_{A,Cmax}$ [6,8]. Moreover, with decreasing τ, the number of administered doses (n) increases, which shortens the time required to attain C_{max}, i.e. t_{max} within each interval becomes progressively shorter. The possible decrease in t_{max} should be considered when selecting the time points for blood sampling for the steady state profile. If this is neglected, i.e. blood sampling for $C_{max,SS}$ is at the same (relative) t_{max} as for the first dose, it may lead to underestimation of $C_{max,SS}$, and thus, also of $R_{A,Cmax}$ [6].

It has been further shown that if t_{lag} occurs before drug absorption, which is typical for some MR formulations, t_{lag} reduces the $AUC(0\text{-}\tau)_{SD}$, whereas the $AUC(0\text{-}\tau)_{SS}$ is not affected by t_{lag}.

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Consequently, the value for $R_{A,AUC}$ is higher compared with the situation without t_{lag} prior to the onset of absorption. This relevant influence of t_{lag} on $R_{A,AUC}$, reflecting the 'true' accumulation, is less pronounced for $R_{A,C\tau}$ [8]. Although the influence of t_{lag} on $R_{A,Cmax}$ has not been tested in the cited literature, this influence is also expected to be less pronounced compared with the other accumulation ratios. Hence, it can be assumed that $R_{A,C\tau}$ and $R_{A,Cmax}$ are less suitable parameters to reflect the influence of t_{lag}, and thus, for oral MR formulations $R_{A,AUC}$ should be the 'preferred' accumulation ratio.

In a recent publication, Li *et al*. [34] reviewed 96 articles where the different utilized accumulation ratios (R_As) were calculated. In about two-thirds of the cases only one type of accumulation ratio was used, while in the other third two or three approaches for R_A were applied. The most frequently used approach was $R_{A,AUC}$ (73%*), whereas $R_{A,Cmax}$ (26%*) and $R_{A,C\tau}$ (6%*) were used much less. Thus, the applied scientific work also reveals $R_{A,AUC}$ as the 'preferred' measurement for the extent of drug accumulation.

Predicting the extent of drug accumulation from single dose studies

Predicting the extent of drug accumulation by means of single dose data was originally done by using compartment open model approaches, under the assumption of linear pharmacokinetics (see above, Eq. 1-1a). Based on Wagner's general equation for the extent of drug accumulation (see above, Eq. 2-2b) and Dost's 'law of corresponding areas' [14,27,28], NCA approaches can also be used. Hence, the accumulation ratio $R_{A,AUC}$ (see above, Eq. (4)) can be predicted (Eq. (5)) from the ratio of the *AUC* after single dose administration from time zero to infinity, $AUC(0\text{-}\infty)_{SD}$, and the *AUC* after single dose administration from time zero to τ, $AUC(0\text{-}\tau)_{SD}$ (see Figure 1) [8,33].

$$R_{A,AUC,predSD} = \frac{AUC(0-\infty)_{SD}}{AUC(0-\tau)_{SD}} \tag{5}$$

In the current work, the accumulation ratio $R_{A,AUC}$ predicted from single dose data ($R_{A,AUC,predSD}$) was used as a basis to derive the mathematical relationship between the pharmacokinetic parameter $\%AUC(\tau\text{-}\infty)_{SD}$ and the extent of drug accumulation at steady state.

Results

In the following, the relationship between the percentage residual *AUC* outside τ after single dose administration, $\%AUC(\tau\text{-}\infty)_{SD}$, and the predicted 'preferred' accumulation ratio $R_{A,AUC,predSD}$ was mathematically derived.

Derivation of the mathematical relationship

The *AUC* after single dose administration from time zero to infinity, $AUC(0\text{-}\infty)_{SD}$, can be calculated (Eq. (6)) from the sum of the *AUC* after single dose administration from time zero to τ, $AUC(0\text{-}\tau)_{SD}$, and the *AUC* after single dose administration from τ to infinity, $AUC(\tau\text{-}\infty)_{SD}$ (see Figure 1).

$$\begin{aligned} AUC(0-\infty)_{SD} = {} & AUC(0-\tau)_{SD} \\ & + AUC(\tau-\infty)_{SD} \end{aligned} \tag{6}$$

Rearranging of Equation (6) results in:

$$\begin{aligned} AUC(0-\tau)_{SD} = {} & AUC(0-\infty)_{SD} \\ & - AUC(\tau-\infty)_{SD} \end{aligned} \tag{6a}$$

and subsequently combining Equations (6a) with (5) gives:

$$R_{A,AUC,predSD} = \frac{AUC(0-\infty)_{SD}}{\left[AUC(0-\infty)_{SD} - AUC(\tau-\infty)_{SD}\right]} \tag{5a}$$

The parameter $\%AUC(\tau\text{-}\infty)_{SD}$ can be calculated from Equation (7):

$$\%AUC(\tau-\infty)_{SD} = \left[\frac{AUC(\tau-\infty)_{SD}}{AUC(0-\infty)_{SD}}\right] \cdot 100\% \tag{7}$$

Rearranging Equation (7) reveals:

$$AUC(\tau-\infty)_{SD} = \left[\frac{\%AUC(\tau-\infty)_{SD}}{100\%}\right] \cdot AUC(0-\infty)_{SD} \tag{7a}$$

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Combining Equations (5a) and (7a) results in:

$$R_{\mathrm{A,AUC,predSD}} = \frac{1}{1 - \left[\%AUC(\tau - \infty)_{\mathrm{SD}}/100\%\right]} \tag{5b}$$

It should be mentioned that the intermediate Equation (5a) equals the reciprocal of the 'mean fraction of steady state' (see above, Eq. (3b)) derived by Perrier and Gibaldi [32,33]. As an exemplary test of validity for Equation (5b), this formula has been successfully used to derive the known formula for the extent of drug accumulation for a one-compartment open model with first order absorption, see Appendix A.

Alternatively, the relationship from Equation (5b) can be further modified (Eq. (5c)) when reconsidering Equation (7) and introducing the auxiliary quantity 'fractional $AUC(\tau\text{-}\infty)_{\mathrm{SD}}$', $f_{\mathrm{AUC}(\tau-\infty)\mathrm{SD}}$, as defined in Equation (7b).

$$f_{\mathrm{AUC}(\tau-\infty)\mathrm{SD}} = \frac{\%AUC(\tau - \infty)_{\mathrm{SD}}}{100\%} = \frac{AUC(\tau - \infty)_{\mathrm{SD}}}{AUC(0 - \infty)_{\mathrm{SD}}} \tag{7b}$$

$$R_{\mathrm{A,AUC,predSD}} = \frac{1}{\left[1 - f_{\mathrm{AUC}(\tau-\infty)\mathrm{SD}}\right]} \tag{5c}$$

Considering the basic assumption of linear pharmacokinetics, i.e. that the administered dose is proportional to $AUC(0\text{-}\infty)_{\mathrm{SD}}$, it can be shown that $f_{\mathrm{AUC}(\tau-\infty)\mathrm{SD}}$ is equal to the 'fraction of the dose remaining', $f_{\mathrm{DR1}(\tau)}$, i.e. the fraction of the remaining drug amount, $D_{\mathrm{R1}}(\tau)$, at the end of the first dosing interval compared with the administered (maintenance) dose, D (Eq. (7c)). A similar formula to Equation (7c) was derived by Riegelman *et al*. [35] and Gibaldi and Perrier [36,37] based on an i.v. two-compartment open model, and in a more general form (see also above, Eq. (3b) and Figure 1) again by Perrier and Gibaldi [32].

$$f_{\mathrm{AUC}(\tau-\infty)\mathrm{SD}} = \frac{AUC(\tau - \infty)_{\mathrm{SD}}}{AUC(0 - \infty)_{\mathrm{SD}}} = 1 - \left[\frac{AUC(0 - \tau)_{SD}}{AUC(0 - \infty)_{SD}}\right] = \frac{D_{\mathrm{R1}}(\tau)}{D} = f_{\mathrm{DR1}(\tau)} \tag{7c}$$

The latter mentioned relationship has also been used by Notari (Eq. (7d) and (5c)), considering the previous work from Boxer *et al*. [15,16] together with Krueger-Thiemer's dose ratio, R^*, (see above, Eq. 1-1a) and the basic definition of steady state, i.e. assuming that if a constant dosing regimen is applied, at steady state the equivalent of a single dose will be eliminated during each dosing time interval [38,39].

$$f_{\mathrm{DR1}(\tau)} = \frac{D_{\mathrm{R1}}(\tau)}{D} \tag{7d}$$

$$R^* = \frac{D^*}{D} = \frac{1}{\left[1 - f_{\mathrm{DR1}(\tau)}\right]} \tag{5d}$$

However, Notari estimated $f_{\mathrm{DR1}(\tau)}$, based on the intercept and slope of each exponential phase of the 'feathered' semi-logarithmic drug concentration–time course in plasma, which becomes complicated and imprecise, if multi-phasic disposition profiles are considered. In contrast to Notari's feathering approach, the derived relationship (see above, Eq. (5b) and (5c)) between the predicted extent of drug accumulation at steady state and the fractional or percentage $AUC(\tau\text{-}\infty)_{\mathrm{SD}}$ seems to be better applicable and more robust, if 'rich' blood sampling is applied also after the end of the planned dosing interval. The *AUC*s can be calculated via NCA by simply using the trapezoidal rule [40].

Hyperbolic graphical relationship

The derived formula in Equation (5b) (see above) clearly shows the causal relationship between the parameter $\%AUC(\tau\text{-}\infty)_{\mathrm{SD}}$ and the predicted extent of drug accumulation at steady state, which is valid for any drug (product) that shows (dose- and time-) linear pharmacokinetics, regardless of the shape of the plasma concentration–time curve, i.e. mono- or multi-phasic, and chosen route of administration. Moreover, no other pharmacokinetic parameters have to be additionally considered for predicting the extent of drug accumulation from single dose data. The graphical relationship between the parameters $\%AUC(\tau\text{-}\infty)_{\mathrm{SD}}$ and $R_{\mathrm{A,AUC,predSD}}$ results in a (concave upwards) hyperbolic curve (Figure 2). As two examples, in

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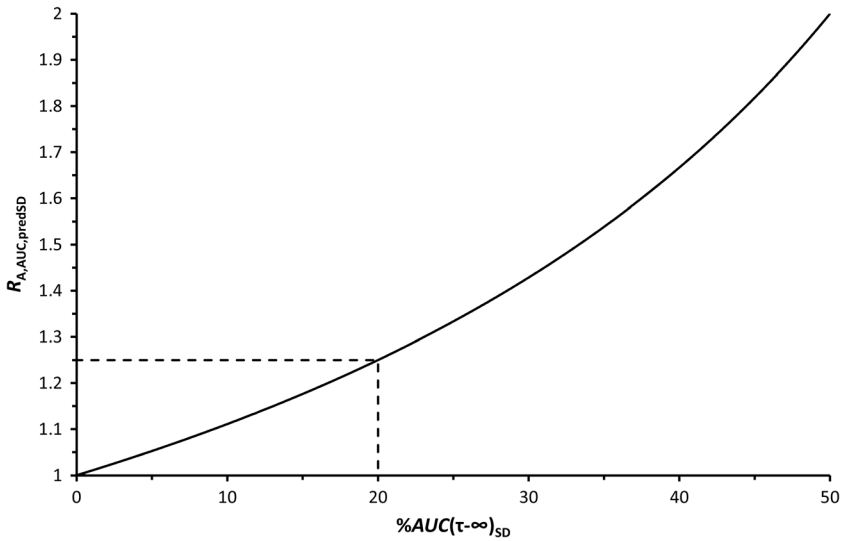

Figure 2. Graphical diagram of the concave upwards hyperbolic relationship (solid curve) between the percentage *AUC* outside τ after single dose administration, $\%AUC(\tau\text{-}\infty)_{SD}$, and the predicted accumulation ratio $R_{A,AUC,predSD}$, the dashed lines highlight the case that $\%AUC(\tau\text{-}\infty)_{SD} = 20\%$ resulting in $R_{A,AUC,predSD} = 1.25$ (or 125%)

the case of $\%AUC(\tau\text{-}\infty)_{SD} = 10\%$ and 20% the expected values for the predicted accumulation ratio are $R_{A,AUC,predSD} = 1.11$ (or 111%) and 1.25 (or 125%), respectively (Table 1). These two cases are further discussed below in the context of its potential to predict 'relevant' drug accumulation.

Discussion

This work clearly identified the most frequently used accumulation ratio $R_{A,AUC}$ as the 'preferred' measurement for the extent of drug accumulation.

Table 1. Tabular diagram of the relationship between the percentage *AUC* outside τ after single dose administration, $\%AUC(\tau\text{-}\infty)_{SD}$ and the predicted accumulation ratio $R_{A,AUC,predSD}$

$\%AUC(\tau\text{-}\infty)_{SD}$	$R_{A,AUC,predSD}$
5.04	1.05
10.07	1.11
15.05	1.18
20.02	1.25
25.00	1.33
30.02	1.43
35.04	1.54
40.03	1.67
45.00	1.82
50.00	2.00

A causal relationship was derived between the parameter $\%AUC(\tau\text{-}\infty)_{SD}$ and the accumulation ratio $R_{A,AUC}$ predicted from single dose data, $R_{A,AUC,predSD}$, which is valid for any drug (product) that shows (dose- and time-) linear pharmacokinetics, regardless of the shape of the plasma concentration–time curve, i.e. mono- or multiphasic, and route of administration. Thus, the parameter $\%AUC(\tau\text{-}\infty)_{SD}$, which can be simply determined via NCA (using the trapezoidal rule) with available standardized commercial software tools, turns out to be the most potent predictor for the extent of drug accumulation that is expected at steady state when multiple doses of the considered drug (product) are administered with the respective constant dosing regimen (D, τ).

Rational threshold for predicting 'relevant' drug accumulation at steady state

In order to define a rational threshold for $\%AUC(\tau\text{-}\infty)_{SD}$ that is predictive for 'relevant' drug accumulation at steady state, the derived relationship (see above, Eq. (5b)) with the predicted accumulation ratio $R_{A,AUC,predSD}$ should be considered. For $\%AUC(\tau\text{-}\infty)_{SD} = 10\%$, as suggested in the draft EMA guideline for MR formulations [1], the predicted extent of drug accumulation is only $R_{A,AUC,predSD} = 1.11$ or 111%. It should be

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noted that this small magnitude of the *AUC* ratio is far below the thresholds used in other EMA guidelines.

In the EMA bioequivalence (BE) guideline for immediate release (IR) formulations [41] and in the draft EMA guideline for MR formulations [1], the upper BE limit for the confidence interval of *AUC* ratios (test/reference) is 125%. The same guideline further states that average dose-normalized *AUC* differences between different dose strengths of ≤25% are considered as acceptable for assuming linear pharmacokinetics for the respective drug (product) [41]. In addition, the EMA drug–drug interaction (DDI) guideline [42] considers that mean changes in *AUC* of <1.25-fold can be seen as not relevant in the context of enzyme inhibition. Hence, most EMA guidelines judge changes in the mean *AUC* ratios or differences of up to 125% or 25%, respectively, as not clinically relevant.

Furthermore, in the Canadian BE guideline for MR formulations [43], released in 1996, relevant drug accumulation is defined as the mean $\%AUC(\tau\text{-}\infty)_{SD} > 20\%$, with the constraint that 80% of $AUC(0\text{-}\infty)_{SD}$ is supported by measured concentration–time points. If $\%AUC(\tau\text{-}\infty)_{SD} \leq 20\%$, i.e. no relevant drug accumulation is expected, the Canadian BE guideline accepts BE via a single dose approach.

Conclusion

Considering the *AUC*-related thresholds from the cited EMA guidelines and the Canadian guideline, together with the derived causal relationship between the $\%AUC(\tau\text{-}\infty)_{SD}$ and the predicted accumulation ratio $R_{A,AUC,predSD}$, values of $\%AUC(\tau\text{-}\infty)_{SD} \leq 20\%$ resulting in $R_{A,AUC,predSD} \leq 1.25$ or 125%, can be considered as leading to non-relevant drug accumulation for any drug (product) that shows (dose- and time-) linear pharmacokinetics. Hence, $\%AUC(\tau\text{-}\infty)_{SD} \leq 20\%$ appears to be a reasonable threshold, as is the case for the Canadian MR guideline, in order to differentiate between relevant and non-relevant drug accumulation for drugs with known linear pharmacokinetics. The authors suggest this value as a reasonable threshold for the EMA guideline for MR formulations in the context of the necessity of multiple dosing BE studies for a specific MR product.

Appendix A: Test of validity for Equation (5b)

As exemplary test of validity for Equation (5b) (see above), in the following the predicted accumulation ratio $R_{A,AUC,predSD}$ for a one-compartment open model with first order absorption and elimination, respectively, was derived and compared with the known formula from the literature.

Equation (5b) can be written as:

$$R_{A,AUC,predSD} = \frac{1}{[1-a]} \tag{8}$$

with

$$a = \frac{\%AUC(\tau-\infty)_{SD}}{100\%} = \frac{AUC(\tau-\infty)_{SD}}{AUC(0-\infty)_{SD}} \tag{8a}$$

Considering the selected pharmacokinetic model, with the parameter F equal to the absorbed fraction of the administered dose (D), $k_a \neq k_e$ as first order absorption and elimination rate constants, respectively, and V equal to the apparent volume of distribution, the drug concentration in plasma at time point t after single dose administration, $C(t)_{SD}$, can be described via the 'Bateman function' (Eq. (9)) [44].

$$C(t)_{SD} = \frac{F \cdot D \cdot k_a}{V \cdot (k_a - k_e)} \cdot \left[\left(e^{-k_e \cdot t}\right) - \left(e^{-k_a \cdot t}\right)\right] \tag{9}$$

The following *AUC*s (see Figure 1) can be calculated from the respective integrals:

$$AUC(0-\infty)_{SD} = \int_0^\infty C(t)_{SD} \cdot dt = \frac{F \cdot D \cdot k_a}{V \cdot (k_a - k_e)} \cdot \left[\left(\frac{1}{k_e}\right) - \left(\frac{1}{k_a}\right)\right] \tag{10}$$

$$AUC(0-\tau)_{SD} = \int_0^\tau C(t)_{SD} \cdot dt = \frac{F \cdot D \cdot k_a}{V \cdot (k_a - k_e)} \cdot \left[\left(\frac{1-e^{-k_e \cdot \tau}}{k_e}\right) - \left(\frac{1-e^{-k_a \cdot \tau}}{k_a}\right)\right] \tag{10a}$$

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$$AUC(\tau-\infty)_{SD} = \int_{\tau}^{\infty} C(t)_{SD} \cdot dt = \frac{F \cdot D \cdot k_a}{V \cdot (k_a - k_e)} \cdot \left[\left(\frac{e^{-k_e \cdot \tau}}{k_e} \right) - \left(\frac{e^{-k_a \cdot \tau}}{k_a} \right) \right] \quad (10b)$$

Combining Equations (10) and (10b) in Equation (8a) reveals:

$$a = \left[\frac{k_a}{(k_a - k_e)} \cdot e^{-k_e \cdot \tau} \right] - \left[\frac{k_e}{(k_a - k_e)} \cdot e^{-k_a \cdot \tau} \right] \quad (8b)$$

Considering the derived formula in Equation (8b) for the value '*a*' in Equation (8) gives the formula shown in Equation (8c):

$$R_{A,AUC,predSD} = \frac{1}{1 - \left[\frac{k_a}{(k_a - k_e)} \cdot e^{-k_e \cdot \tau} \right] - \left[\frac{k_e}{(k_a - k_e)} \cdot e^{-k_a \cdot \tau} \right]} \quad (8c)$$

The same formula results if the predicted accumulation ratio $R_{A,AUC,predSD}$ is calculated by using Equations (5), (10) and (10a), i.e. from the ratio of $AUC(0\text{-}\infty)_{SD}$ and $AUC(0\text{-}\tau)_{SD}$. The derived solution (Eq. (8c)) for $R_{A,AUC,predSD}$ of a one-compartment open model with first order absorption and elimination has been published before by Wagner [23] and van Rossum [24].

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Conflict of Interest

All authors work for pharmaceutical industry.

NOTES

*Explanation: As in some articles more than one approach was used the sum of the percentage values is >100%.

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