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Pharmacodynamic considerations in bioequivalence assessment: comparison of novel and existing metrics

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Abstract

This study addresses the utility of pharmacodynamic considerations to the assessment of bioequivalence (BE) studies. A novel methodology was developed and the performance of classic, nonclassic and novel BE indices was evaluated using extensive simulations of BE trials generated from a classic pharmacokinetic (PK)/pharmacodynamic (PD) model. Three novel indices based on drug's pharmacodynamics were developed and served as criteria for the assessment of all BE indices. Modified power curves were constructed and used for the analysis of BE trials from a PD point of view. All BE indices of either purely PK or PD nature were classified in a semiquantitative manner according to their strictness in declaring BE. The partial area until the peak concentration followed by the two newly proposed metrics (MARD, $MARD_{w1}$) exhibited the most strict performance in declaring BE irrespective of the PK scenarios examined. The study opens new avenues in BE assessment since it places more emphasis on the PD aspects of the formulations.

Keywords: Bioequivalence; Pharmacodynamics; Direct curve comparison metrics; Simulated trials

1. Introduction

Various sporadic in vivo observations in the early 1960s gave the first intimations of bioequivalence (BE) problems with multisource drug products. It was realized about this time that product efficacy can depend on how much of the drug is ultimately absorbed (extent of absorption) from its formulation and how rapidly the drug is absorbed (rate of absorption). Thus, these two key terms, extent and rate of absorption, formed the basis of bioavailability and bioequivalence testing (Federal Register, 1977). Since then bioequivalence testing is based on the assumption that the therapeutic effect of a drug product is a function of the concentration of the active ingredient or active moiety in the systemic circulation.

Although decision rules for approval of generic drugs have evolved from the first regulations of the Food and Drug Administration issued in 1977 (Federal Register, 1977), approval is still based on the statistical comparison of two parameters, *AUC* (area under the concentration, C–time, t, curve) for the extent of absorption and peak plasma concentration (C_{max}) for the rate of absorption (Chen et al., 2001b; Jackson, 2002). However, C_{max} has been criticized as a metric which also expresses extent of absorption (Basson et al., 1996; Bois et al., 1994a; Rostami-Hodjegan et al., 1994). Thus, concern has been raised during the last decade for the problem of assessing the rate of absorption in BE studies (Chen, 1992; Endrenyi and Al-Shaikh, 1995; Lacey et al., 1994; Macheras et al., 1994, 1996; Reppas et al., 1995; Schall and Luus, 1992; Tothfalusi and Endrenyi, 1995). Furthermore, a variety of metrics, described as direct curve comparison metrics (DCC metrics), have been proposed to quantify the (dis)similarity of the two profiles (Chincilli and Elswick, 1997; Marston and Polli, 1997; Polli and McLean, 2001; Rescigno, 1992). Apart from these efforts, several attempts have been made to move the emphasis towards safety and efficacy issues (Chen et al., 2001a; Dokoumetzidis and Macheras, 2000; Tozer et al., 1996).

In principle, measurement of effect of a physiological process as a function of time after administration of the different products can serve as the basis of bioequivalence assessment. This is the so-called pharmacodynamic (PD) bioequivalence testing which requires comparison of ef-

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fect–time profiles and it has been applied in specific cases e.g. metaproterenol and albuterol aerosols (Chen et al., 2001b). For the majority of drugs, however, effect data may actually be imprecise, not quantifiable and/or less relevant than drug concentration data. PK studies, in general, are less variable than PD studies (Derendorf and Hochhaus, 1995; Levy, 1998).

Another alternative is to rely on pharmacokinetic–pharmacodynamic (PK/PD) considerations and try to develop concentration–effect relationships. In this context, some attempts have been made to utilize pharmacodynamic models in order to assess bioavailability (Forgue and Colburn, 1991). To the best of our knowledge, none of the PK/PD studies has been directed towards development of BE criteria. In this study, we explore the utility of pharmacodynamic considerations in BE assessment using the most frequently encountered model in PK/PD studies (Holford and Sheiner, 1982). To this end, we adopt this classic PK/PD models in order to (i) examine the currently applied 0.80–1.25 limits for AUC and C_{max} in respect to pharmacodynamics, (ii) develop a novel methodology for BE assessment utilizing PD concepts and relevant PD indices, (iii) introduce three new indices based on PK/PD considerations and (iv) evaluate pharmacodynamically the performance of classical, nonclassical and the novel indices using simulated BE trials.

2. Theory

2.1. General

Our study is divided into two major sections. In the first part, we focus on a PD evaluation of the currently applied 0.80–1.25 limits for AUC and C_{max} using simulated PK/PD data. In the second part of the study a novel methodology for BE assessment, based on PD considerations, is proposed. In both parts, simulations were based on a PK/PD model assuming first order input, one- or two-compartment model disposition kinetics with the central compartment indirectly linked with an effect site compartment (Derendorf and Hochhaus, 1995).

The time course of plasma drug concentration for the one-compartment model is given by Eq. (1) (Derendorf and Hochhaus, 1995):

$$C = \frac{FDK_{01}}{V(K_{01} - K_{10})} \cdot (e^{-K_{10}t} - e^{-K_{01}t}) \quad (1)$$

where F is the bioavailable fraction of dose D, V is the apparent volume of drug distribution, $K_{01}$and K_{10} are the absorption and elimination rate constants, respectively. Drug concentration at the effect site changes with time according to Eq. (2) (Derendorf and Hochhaus, 1995).

$$C_e = \frac{FDK_{01}}{V} \frac{(K_{10}-K_{e0})e^{-K_{01}t}+(K_{e0}-K_{01})e^{-K_{10}t}+(K_{01}-K_{10})e^{-K_{e0}t}}{(K_{01}-K_{10})(K_{10}-K_{e0})(K_{01}-K_{e0})} \quad (2)$$

where K_{e0} refers to effect site drug dissipation rate constant.

The time evolution of concentration at the central compartment of two compartment model follows Eq. (3) (Gabrielsson and Weiner, 1997):

$$C = Ae^{-at} + Be^{-\beta t} - (A+B)e^{-K_{01}t} \quad (3)$$

where a, β are the distribution and elimination hybrid rate constants composed from the microconstants K_{10}, K_{12} (central to peripheral rate constant) and K_{21} (peripheral to central constant) and A, B are concentration constants. Drug concentration at the effect site changes with time following Eq. (4) (Gabrielsson and Weiner, 1997):

$$C_e = A\frac{(a-K_{e0})e^{-K_{01}t}+(K_{e0}-K_{01})e^{-at}+(K_{01}-a)e^{-K_{e0}t}}{(a-K_{e0})(K_{01}-K_{e0})} + B\frac{(\beta-K_{e0})e^{-K_{01}t}+(K_{e0}-K_{01})e^{-\beta t}+(K_{01}-\beta)e^{-K_{e0}t}}{(\beta-K_{e0})(K_{01}-K_{e0})} \quad (4)$$

For both one- and two-compartment models, the pharmacological effect (E) was associated with the concentration at the effect site (C_e) with Eq. (5):

$$E = \frac{E_{max}C_e}{C_{e50} + C_e} \quad (5)$$

where E_{max} is the maximum effect and C_{e50} is the concentration at the effect site which elicits half of E_{max}.

Hereafter, the symbols T or R will be used as subscripts of the various parameters of Eqs. (1)–(5) and denote test and reference formulation, respectively.

2.2. PD considerations in Bioequivalence: novel PK/PD metrics

Ideally, the comparison of the effect–time curves of the two drug products has to be used to assess their bio(in)equivalence. This concept is utilized in the present section in order to develop pharmacodynamically based metrics.

Fig. 1A shows the time evolution of the E_T/E_R ratio (where E_T and E_R refer to the effect following the administration of the T and R formulation, respectively) using one-compartment model disposition for a variety of bioavailable fractions, F_T, and absorption rate constants, K_{01T}, for the test formulation. Ideally, both test and reference formulations should have identical effect–time profiles (dashed line in Fig. 1A). Accordingly, a reasonable measure of the magnitude of the difference between the two formulations is the area enclosed between the E_T/E_R–

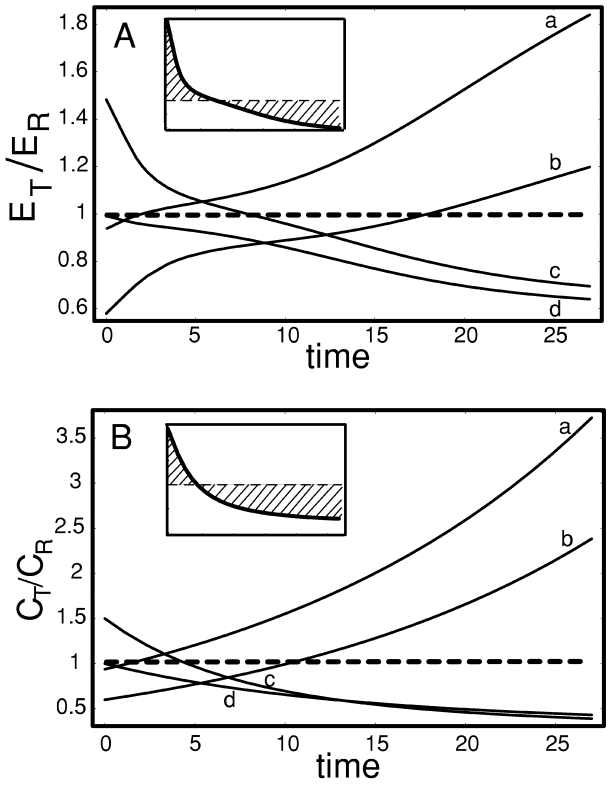

Fig. 1. E_T/E_R (A), and C_T/C_R (B), versus time plots using one-compartment model for a variety of K_{01T} and F_T values (K_{01T}, F_T): (a) 0.3, 1.25 (b) 0.3, 0.8 (c) 0.6, 1 (d) 0.5, 0.8. The values for the remaining parameters were assigned as follows: $K_{01R}=0.4$, $K_{10}=0.355$, $K_{e0}=0.255$, $F_R=1$, $C_{e50}=0.9$, $E_{max}=1$. The insets indicate the areas enclosed between E_T/E_R-1 curve (A), and C_T/C_R-1 curve (B), for $K_{01T}=0.8$ and $F_T=1$.

time curve and the line with ordinate $y=1$ (see the inset of Fig. 1A). Regardless of the positioning of the area (either above or below the line $y=1$), all areas can be summed up to provide an estimate which quantifies the deviation from zero. It is also worth mentioning that it is preferable to have on the numerator of the effect fraction, the drug product which makes the effect ratio to diminish with time, i.e. either $\lambda_{PD}=E_T/E_R$ or $\lambda_{PD}=E_R/E_T$. Otherwise, the ratio of effects during the elimination phase increases with time (e.g. curves labeled as *a* and *b* in Fig. 1A). This is not a desirable feature since this part of the curve (which corresponds to a region of lower importance) would significantly contribute to the total area. Besides, the index can be normalized—in terms of time— by dividing the entire area with the duration of the study. The normalized index, called $MARD_{PD}$, expresses the mean absolute value of the relative difference between the effect–time curves for the two formulations. Mathematically, it corresponds to the mean value of $|E_T/E_R-1|$–or $|E_R/E_T-1|$–time function for the utilized time period. The discrete analogue of $MARD_{PD}$ based on an experimental design of n observations is:

$$MARD_{PD}=\frac{\sum_{i=1}^{n}|\lambda_{PDi}-1|}{n} \quad (6)$$

where λ_{PDi} refers to the E_T/E_R (or E_R/E_T) ratio for the ith observation, and n is the total number of the available time points.

Since effects with higher values can be of greater importance compared to those lying at the two ends of the limbs of the E–t curves, appropriate corrections—'weights' can be applied in order to enhance the sensitivity of $MARD_{PD}$ index. Two different types of weight were formulated, Eqs. (7) and (8):

$$MARD_{PDw1}=\frac{\sum_{i=1}^{n}(E_{Ti}+E_{Ri})|\lambda_{PDi}-1|}{\sum_{i=1}^{n}(E_{Ti}+E_{Ri})} \quad (7)$$

$$MARD_{PDw2}=\frac{\sum_{i=1}^{n}\frac{t_{PDm}}{|t_i-t_{PDm}|+1}|\lambda_{PDi}-1|}{n} \quad (8)$$

where E_{Ti}, E_{Ri} are the effects observed at the ith time point for T and R formulation, respectively; t_i is the time of the ith observation, while t_{PDm} corresponds to the mean value of the time-points where the maximum effect is observed for the T and R formulations. The correction factor applied in Eq. (7) is similar to that used for direct curve metrics (Polli and McLean, 2001). The observations (effects) are corrected in Eq. (8) in terms of the time of the observed maximum effect, t_{PDm}.

Fig. 1B shows the ratios of the two plasma concentrations i.e. C_T/C_R (where C_T and C_R are the plasma concentrations of the test and reference formulation) versus time generated from the one compartment model for a variety of bioavailable fractions, F_T, and absorption rate constants, K_{01T}, for the test formulation. Visual inspection of the corresponding graphs (a–d) in Fig. 1A and B reveals the similarity in the time evolution of E_T/E_R and C_T/C_R curves. The time shift in the graphs (Fig. 1A vs. Fig. 1B) is compatible with the delay character of the PK/PD model. However, the area shown in the inset of Fig. 1B is the PK analogue of the Fig. 1A inset, and it can be used as a measure of the difference of the two formulations in BE assessment. Therefore, PK indices similar to the PD indices described above can be developed following the same reasoning and adjusting appropriately the two types of weight. Three PK metrics were developed (called for reasons of uniformity MARD, $MARD_{w1}$ and $MARD_{w2}$) in full analogy with Eqs. (6)–(8), respectively.

$$MARD=\frac{\sum_{i=1}^{n}|\lambda_i-1|}{n} \quad (9)$$

$$\mathrm{MARD}_{w1} = \frac{\sum_{i=1}^{n}(C_{Ti} + C_{Ri})|\lambda_i - 1|}{\sum_{i=1}^{n}(C_{Ti} + C_{Ri})} \quad (10)$$

$$\mathrm{MARD}_{w2} = \frac{\sum_{i=1}^{n}\frac{t_m}{|t_i - t_m| + 1}|\lambda_i - 1|}{n} \quad (11)$$

where λ_i refers to the C_T/C_R (or C_R/C_T) ratio for the ith observation, and n is the total number of the available time points. The terms C_{Ti}, C_{Ri} denote the concentrations observed at the ith time point (t_i) for T and R formulation, respectively, while t_m corresponds to the mean value of the time-points where the maximum plasma concentrations are observed for the T and R formulations.

3. Methods

3.1. Pharmacodynamic evaluation of the 0.80–1.25 limits for AUC and C_{max}

Concentration–time profiles were generated using Eq. (1). In all simulations of this section, the following values were assigned to the parameters: $D/V = 1$ and $K_{10} = 0.355$. In addition, the value for F_R was set equal to 1 while the absorption rate constant of the reference formulation, K_{01R}, was 0.4. The value for F_T was set equal to $0.80F_R$ or $1.25F_R$.

In this part, we study the relationship between the currently applied 0.80–1.25 limits for AUC and C_{max} and a pharmacodynamic index expressed as the ratio E_{peakT}/E_{peakR}, where E_{peakT} and E_{peakR} refer to the maximum effect of test (T) and reference (R) formulation, respectively. The boundary values for the extent and rate of drug absorption i.e. Eqs. (12) and (13) were used as the basis of the calculations:

$$0.8 \le \frac{\mathrm{AUC}_T}{\mathrm{AUC}_R} \le 1.25 \quad (12)$$

$$0.8 \le \frac{C_{maxT}}{C_{maxR}} \le 1.25 \quad (13)$$

These equations were solved in terms of absorption rate constant of the test formulation, K_{01T}, after appropriate substitution of pharmacokinetic expressions for C_{max} [Eq. (14)] and *AUC* [Eq. (15)]:

$$C_{max} = \frac{FD}{V}\left(\frac{K_{01}}{K_{10}}\right)^{\frac{K_{10}}{K_{10}-K_{01}}} \quad (14)$$

$$\mathrm{AUC} = \frac{FD}{VK_{10}} \quad (15)$$

The two (lower and higher) estimates for K_{01T} obtained from the equations satisfying the 0.80 and 1.25 limits, were further used to calculate the quotient E_{peakT}/E_{peakR} from Eqs. (2) and (5) assuming: $E_{max} = 1$, $K_{e0} = 0.255$, and $C_{e50} = 0.9$. Since the value of E_{peakR} was kept constant in all simulations, two values (lower and higher) of E_{peakT}/E_{peakR} were derived from the corresponding K_{01T} estimates.

The reverse route was also followed, namely, estimation of the limiting values for $\mathrm{AUC}_T/\mathrm{AUC}_R$ and C_{maxT}/C_{maxR} which are associated with the pharmacodynamic limits defined in Eq. (16):

$$0.8 \le \frac{E_{peakT}}{E_{peakR}} \le 1.25 \quad (16)$$

Like the aforementioned analysis, two (lower and higher) estimates for K_{01T} were obtained from Eqs. (2) and (5) satisfying the two limiting cases: $E_{peakT}/E_{peakR} = 0.80$ and $E_{peakT}/E_{peakR} = 1.25$. Subsequently, these K_{01T} values were used to calculate the corresponding two quotients of C_{maxT}/C_{maxR} and $\mathrm{AUC}_T/\mathrm{AUC}_R$.

3.2. Assessment of metrics using BE simulated trials

The objective of this section is to examine the performance of: (i) the three new proposed PK metrics (MARD, MARD_{w1}, MARD_{w2}), (ii) the classical metrics, AUC and C_{max}, (iii) the nonclassical metrics C_{max}/AUC (Endrenyi et al., 1991) and the partial area until the peak concentration, AUC_p (Chen, 1992), and (iv) several direct curve comparison (DCC) metrics (Rho, Rho_m, Delta_a, Delta_s, ξ_1) (Polli and McLean, 2001; Rescigno, 1992) with respect to pharmacodynamics. The indices described as DCC metrics were calculated using the relevant methodology described in literature (Polli and McLean, 2001; Rescigno, 1992). AUC and AUC_p values were estimated by using the trapezoidal rule until the smaller generated concentration value, and until the peak concentration, respectively. C_{max} was simply identified as the highest recorded concentration of a given concentration–time curve. In case of ξ_1 index (Rescigno, 1992), the value of 1 was assigned to the appropriate exponent.

The three PD indices presented in the Theory section, served as pharmacodynamic criteria for the assessment of the PK metrics, allowed the ranking of both the PK and PD metrics with respect to their sensitivity to perceive differences in the two drug products in BE studies. To this end, we simulated the conditions of clinical BE trials by developing a computer program in FORTRAN. The whole task was accomplished by following in general the procedure proposed by Bois et al. (1994a), where concentration–time data were generated using Monte-Carlo simulations. This kind of simulations has been extensively used (Bois et al., 1994a,b; El-Tahtawy et al., 1995; Endrenyi et al., 1998a,b) in theoretical BE studies. In our study, however, we carried out additional simulation studies generating effect–time data using the same principles

based on the PK/PD model described in the theoretical section.

The generated data were based on the assignment of statistical distributions to the various PK and PD parameters involved. Two types of variability were incorporated to the PK and PD parameter values. Parameter estimates were sampled from population distributions, while intra-individual variability was added to the PK and PD parameters. Analytical assay error with CV equal to 5% was added to the plasma concentration values. Table 1 summarizes the population means, the variations (CV%) of the PK and PD parameter values, and the type of distribution for each parameter. All PK or PD constants followed lognormal distribution; the only exception was the bioavailable fraction (F) which followed the uniform distribution. The values assigned to parameters were selected to produce reasonable time profiles for C, C_e and E. An arbitrary dose of 100 mg of drug was considered to be administered.

In order to simulate the conditions of a two-period crossover design, a number of 24 subjects were assumed to participate in each trial. The subjects were randomly divided into two sequences of drug administration. Simulated concentration and effect time data were generated for a variety of K_{01} and F ratios. A number of 2000 trials were performed under each condition. The utilized experimental design considered measurements of concentration and effect at times of 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 15, 18 h. This sampling scheme offers an adequate number of observations in the uplimb part of the curves, as well as it gives information for an adequately large time period.

The performance of all metrics was assessed using power 3D curves which provide the percentage of simulated trials of accepting BE for each PK and PD metric when the ratio of bioavailable fractions or absorption rate constants is varied. When one ratio (e.g. F_T/F_R) was varied the other ratio (e.g. K_{01T}/K_{01R}) was set equal to one. This modified version of the power curves allows a pictorial contrast of the performance of PK and PD metrics in BE trials.

For the newly proposed PK metrics as well as the DCC metrics (Rho, Rho_m, $Delta_a$, $Delta_s$, ξ_i) the decision for declaring BE was based on the 90% confidence interval (Schuirmann, 1987). The lower limit for the novel metrics i.e. the situation of complete concordance between two formulations is obviously equal to zero. The upper acceptable limit for MARDs and $MARD_{PD}$s was arbitrarily set at 0.20, which means that two drug products were considered bioequivalent if their mean absolute value of the relative difference of effects (or concentrations) did not exceed 20%. The upper limit for the DCC metrics was set to the values reported in literature (Polli and McLean, 2001). A simulation trial was regarded to denote BE if the upper value of the confidence interval is not greater than the relevant limiting value. The performance of classical and nonclassical metrics (AUC, AUC_p, C_{max}, C_{max}/AUC) was also examined. In this case, two one-sided t-tests (90% confidence interval) were performed after logarithmic transformation of their values by using the standard error derived from ANOVA (analysis of variance) in each trial (Metzler, 1991).

Table 1
Population means and variability of pharmacokinetic and pharmacodynamic parameters used in the simulated bioequivalence trials

Parameter	Distribution	Population mean		CV (%)	
		1-comp.[a]	2-comp.[a]	Inter[b]	Intra[b]
V	Lognormal	70.0	70.0	5	5
K_{01}	Lognormal	0.6	0.8	10	5
K_{10}	Lognormal	0.2	0.2	10	5
F	Uniform	1.0	1.0	±0.1	±0.05
K_{e0}	Lognormal	0.30	0.30	10	5
E_{max}	Lognormal	1.0	1.0	10	5
C_{e50}	Lognormal	0.9	0.5	10	5
K_{12}	Lognormal	–	0.15	10	5
K_{21}	Lognormal	–	0.05	10	5

[a] One- and two-compartment models.
[b] Inter- and intra-individual variation.

4. Results

4.1. Pharmacodynamic evaluation of the 0.80–1.25 limits for AUC and C_{max}

Based on the classical acceptable limits of pharmacokinetic parameters (C_{max}, AUC), an attempt was made to evaluate if these limits ensure pharmacodynamic equivalence too. Assuming that the ratio C_{maxT}/C_{maxR} would lie in the predefined limits 0.80–1.25, the corresponding range for the ratio of pharmacodynamic parameters (E_{peakT}/E_{peakR}) was calculated. The C_{maxT} value was set equal either to $0.80C_{maxR}$, or to $1.25C_{maxR}$; the values of the absorption rate constant of the test formulation, K_{01T}, were derived as described in the Methods section. These values were then used to estimate the lower and upper limits for E_{peakT}, and subsequently the upper and lower ratio for E_{peakT}/E_{peakR}. It is obvious that following this procedure the range of the higher and lower C_{maxT}/C_{maxR} values is always 0.45 (i.e. 1.25 minus 0.80). The corresponding PD range for E_{peakT}/E_{peakR} is obtained by subtracting the two E_{peakT}/E_{peakR} estimates. Fig. 2A and B show the PD range as a function of the bioavailable fraction, F_T, and the absorption rate constant, K_{01R}, respectively. Inspection of the ordinate values in Fig. 2 reveals that the pharmacokinetic limits satisfying the 0.80–1.25 criterion lead to pharmacodynamic values which are confined to a much shorter range. These findings indicate that the 0.80–1.25 acceptable region for C_{maxT}/C_{maxR} seems to be very restrictive for the pharmacodynamic evaluation expressed in terms of E_{peakT}/E_{peakR}. Although

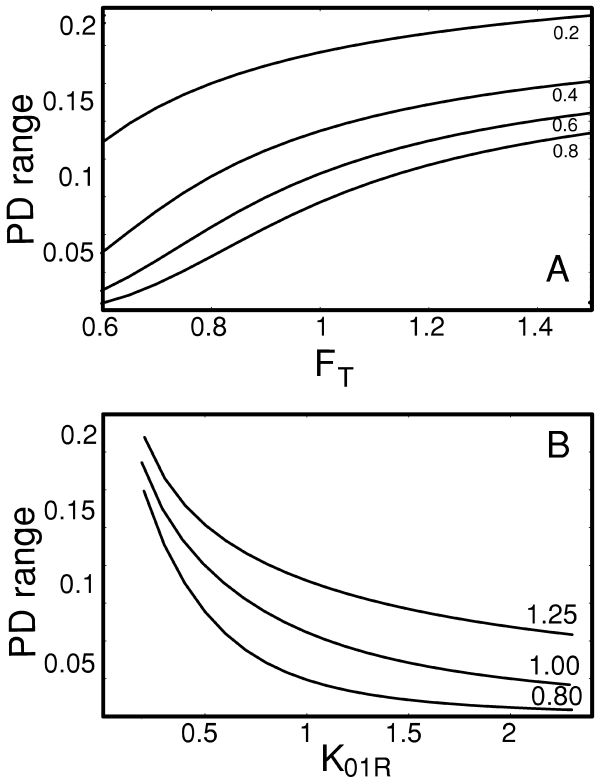

Fig. 2. Pharmacodynamic range (difference between the two limiting values of E_{peakT}/E_{peakR} values) as a function of the bioavailable fraction for the T formulation, F_T, (A), and absorption rate constant, K_{01R}, (B), assuming one-compartment model disposition kinetics. The numbers in plots A and B indicate the values of K_{01R} and F_T, respectively. For comparative purposes one should note that the pharmacokinetic range (upper C_{maxT}/C_{maxR} minus lower C_{maxT}/C_{maxR}) is always equal to 0.45 i.e. 1.25 minus 0.80. Key: $K_{10}=0.355$, $K_{e0}=0.255$, $E_{max}=1$, $C_{e50}=0.9$, and $F_R=1$.

the relative importance of the numerical values of the concentration and effect ratios can be different in the various therapeutic categories, the dimensionless character of the ratios allows their comparative evaluation.

The reverse route was also followed; the fraction E_{peakT}/E_{peakR} was set either equal to 0.80 or to 1.25 and two K_{01T} values were calculated and used to estimate the quotients of C_{maxT}/C_{maxR} (one estimate per K_{01T} value). The PK range was calculated by subtracting the two limiting values. As expected the range for the quotients C_{maxT}/C_{maxR} and AUC_T/AUC_R was found to be broader (not reported) than the currently used 0.80–1.25. This finding is in agreement with the conclusions derived from Fig. 2.

4.2. Assessment of metrics using BE simulated trials

Figs. 3–6 provide a global picture of the modified power curves for the various kinetic scenarios and metrics utilized. A total of 144 curves are presented in Figs. 3–6 corresponding to the 12 utilized PK metrics derived from 696 000 BE trials. Each one of the curves in Figs. 3–6 indicates the relationship between the percentage of trials accepting PD bioequivalence versus the percentage of trials declaring bioequivalence in pharmacokinetic terms for a variety of F_T/F_R or K_{01T}/K_{01R} ratios. Obviously, the maxima for percentage PK and percentage PD power coincide when the ratio F_T/F_R or K_{01T}/K_{01R} is equal to unity. The assessment of the performance of the various PK metrics is based on the comparison of the percentage power values with the corresponding percentage power values of the three PD indices. When the value of the percentage power of a metric is smaller compared with the percentage power of another metric, then the first metric is considered more ‘strict’ i.e. it is more sensitive to detect differences between the two formulations. When the various PK metrics are assessed with the same PD criterion, a ranking of the PK metrics can be obtained. In an analogous manner, the relative order of the PD metrics in declaring BE was derived by comparing their performance with the performance of the various PK metrics. Thus, the results presented in Figs. 3–6 allowed the ranking of PK and PD metrics in terms of their strictness in declaring BE in a comparative, semiquantitative manner, Fig. 7.

For the data generated from the one compartment model when the F_T/F_R ratio is varied, visual inspection and analysis of the results shown in Fig. 3 reveals that the PK metrics can be divided in three major groups as shown in Fig. 7A. The more strict group includes *AUC*, AUC_p, C_{max}, ξ_1, and the three MARD metrics. The second group of moderate strictness consists of Rho_m, $Delta_a$, $Delta_s$ while the Rho index exhibits remarkably lower strictness. The ranking of the three PD indices derived from a similar analysis indicates that $MARD_{PDw2}$ agrees (in the percentage power) with the more strict group of PK metrics, while the $MARD_{PD}$ and $MARD_{PDw1}$ indices exhibit similar behavior with the moderate group and Rho, respectively, Fig. 7A. The same analysis was also performed for the data generated from the one-compartment model using a variety of K_{01T}/K_{01R} ratios, Fig. 4. In this case, three major groups of PK metrics were identified and classified in accord with their performance as shown in Fig. 7B; the performance of the ξ_1 index lies between the two more strict groups (Fig. 7B).

The PK and PD indices were also evaluated using data generated from a two compartment model varying either the F_T/F_R or the K_{01T}/K_{01R} ratio. The results obtained (Figs. 5 and 6) were roughly similar to those derived from the one compartment model. When the F_T/F_R was varied, the positioning of the PK metrics was shifted towards the left-hand side relative to the PD indices (Fig. 7C). This applies also for the PK metrics adhering to the data generated for a variety of K_{01T}/K_{01R} ratios, Fig. 7D, with the exception of $MARD_{w2}$, which became less strict (moved to the right-hand side), in respect to the rest PK and PD metrics. As far as the ranking of the PD indices is concerned, this was found to be identical to both sets of data Fig. 7A and B and Fig. 7C and D. In general, the semiquantitative classification of metrics in Fig. 7 implies

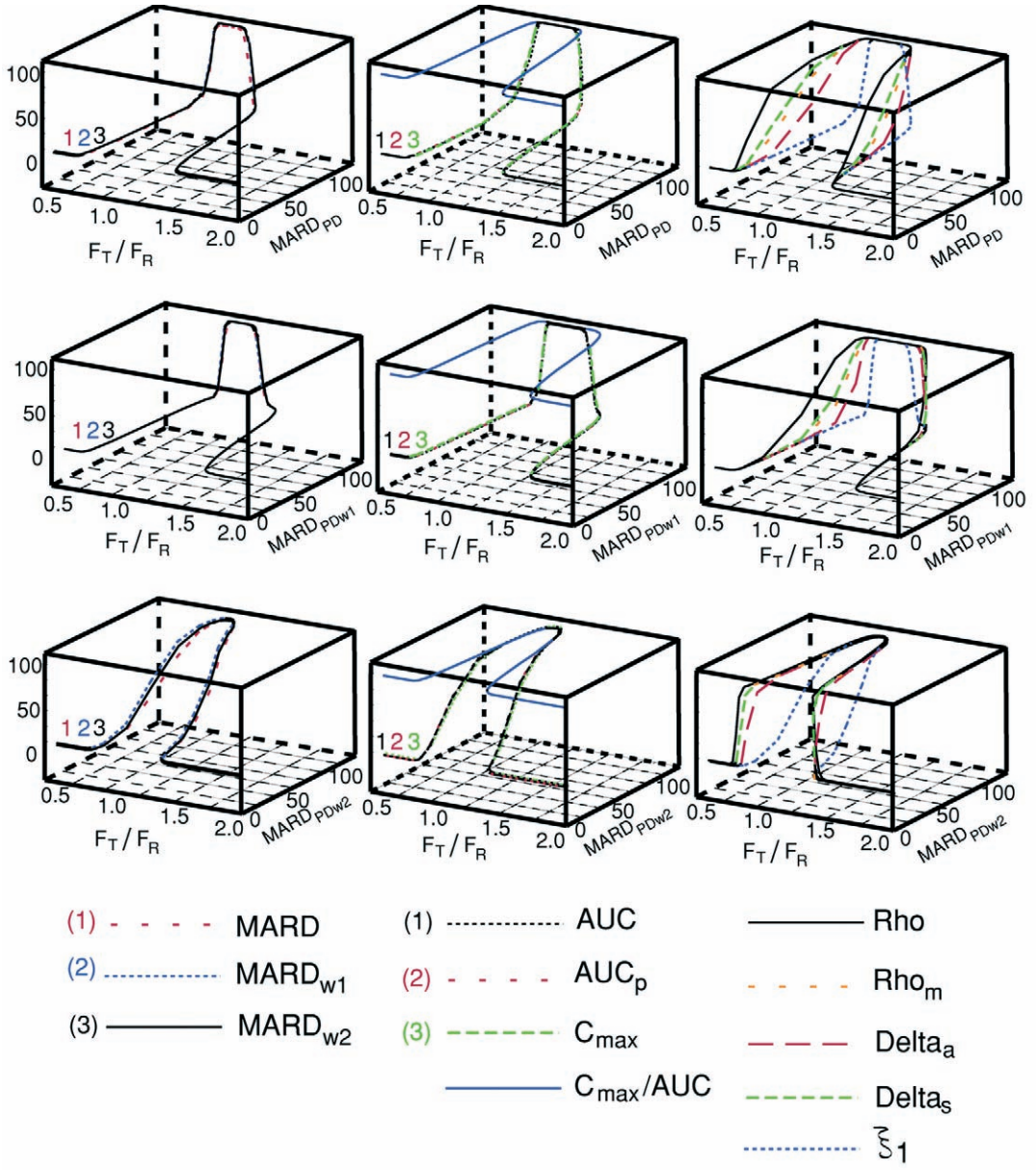

Fig. 3. Power curves showing the relationship between the percentage acceptance number for the PK metrics (*z* axis) which are quoted at the bottom of the graph for each one of the three columns and the percentage acceptance number of PD metrics for a variety of F_T/F_R ratios, assuming one-compartment model disposition kinetics. Each curve is constructed from 61 data points (not shown for clarity reasons). Since visual inspection of the plots becomes uncertain when complete concordance exists between two or more curves, some of the curves are also labeled with a different number.

that the consumer risk in BE terms is augmented when one moves from left to right.

5. Discussion

The analysis presented above allowed us to classify the currently used, our newly proposed, and a variety of PK metrics according to their ability in suggesting or rejecting BE. This task was performed using as the basis of the assessment three PD indices, Eqs. (6)–(8). Thus, instead of comparing the various PK metrics in respect to the percentage of trials accepting BE for a variety of F_T/F_R or K_{01T}/K_{01R} ratios, the objective of the evaluation has been altered in this study. The reason for this different approach is the widely acknowledged notion that even when a metric ensures PK bioequivalence, the therapeutic equivalence of the two formulations is not guaranteed. In this work, PD indices were developed based on the (dis)similarity of the effect–time curves of the two drug products. These PD metrics served as varying degree measures for the assessment of the difference in pharmacological effect of the two drug products. Based on extensive BE simulations, the contrast between the various PK metrics and the PD

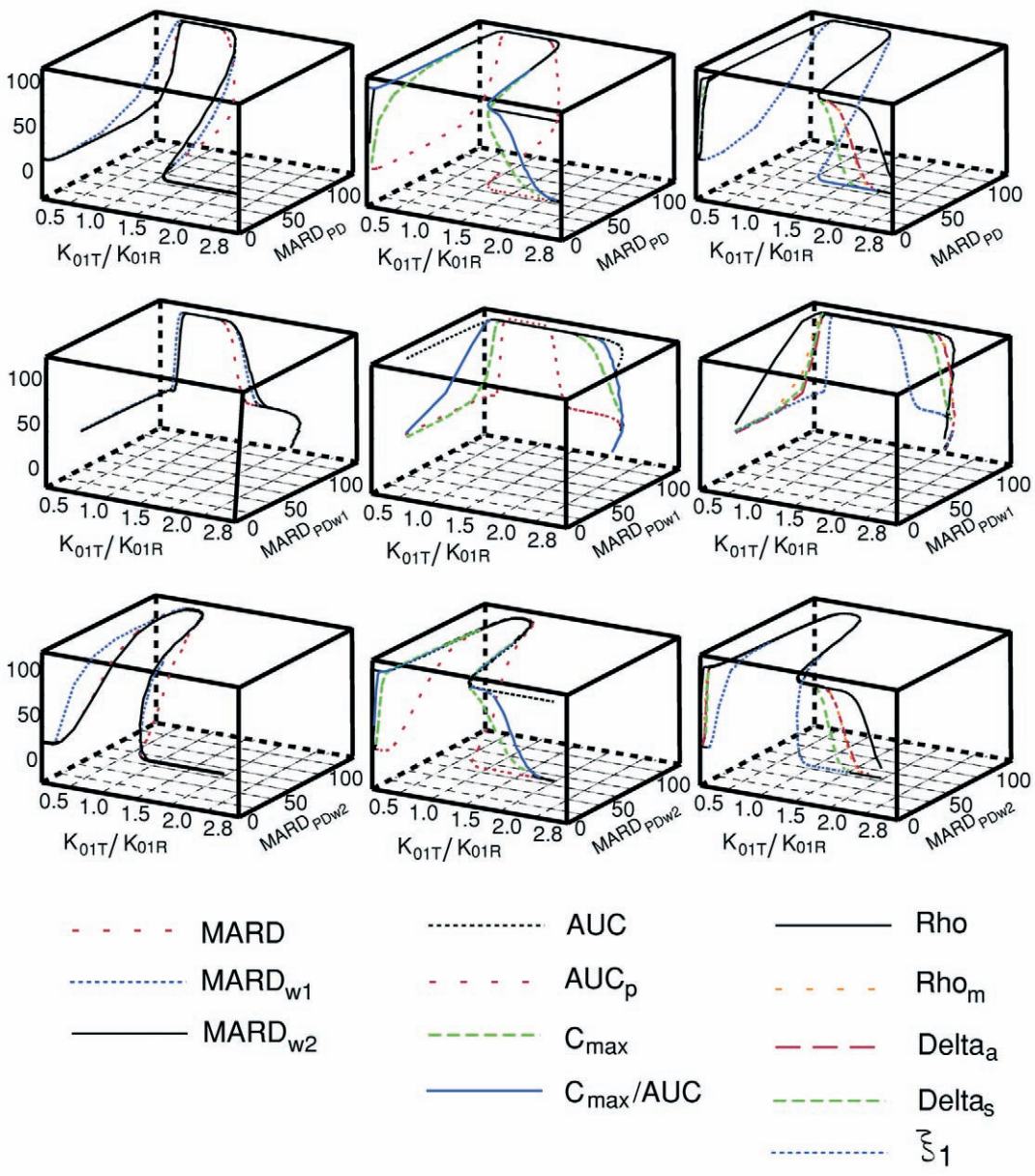

Fig. 4. Power curves showing the relationship between the percentage acceptance number for the PK metrics (z axis) which are quoted at the bottom of the graph for each one of the three columns and the percentage acceptance number of PD metrics for a variety of K_{01T}/K_{01R} ratios, assuming one-compartment model disposition kinetics. Each curve is constructed from 93 data points (not shown for clarity reasons).

indices allowed us to unveil their underlying relationships using different PK scenarios. MARD, $MARD_{w1}$, and AUC_p were found to be always the most strict metrics in declaring BE (Fig. 7). $MARD_{w2}$ and ξ_1 exhibited high or moderate strictness depending on the PK scenario used (Fig. 7). On the contrary, the four DCC metrics (Rho, Rho_m, $Delta_a$, $Delta_s$) appeared to be always the most insensitive to detect BE differences. As expected AUC does not respond to both PK scenarios involving variations in absorption rate (Fig. 7B and D); however, AUC is classified in the strictest groups when alterations in the extent of absorption are studied (Fig. 7A and C). C_{max} is also included in the strictest groups of metrics when the bioavailable fraction is altered, Fig. 7A and C; C_{max} exhibits weak (Fig. 7B) or moderate (Fig. 7D) strictness when absorption rate alterations were applied. This is probably due to the hybrid nature of C_{max}. Similarly, C_{max}/AUC did not respond to changes in the extent of absorption (Fig. 7A and C), while weak performance was noted in PK scenarios with changes in the rate of absorption (Fig. 7B and D).

All PD indices for the two-compartment model data (Fig. 7C and D) move to the right, with identical order, relative to the PK indices. This behavior indicates that all PD indices become less strict compared to the PK metrics when the scenario changes from one to two compartment

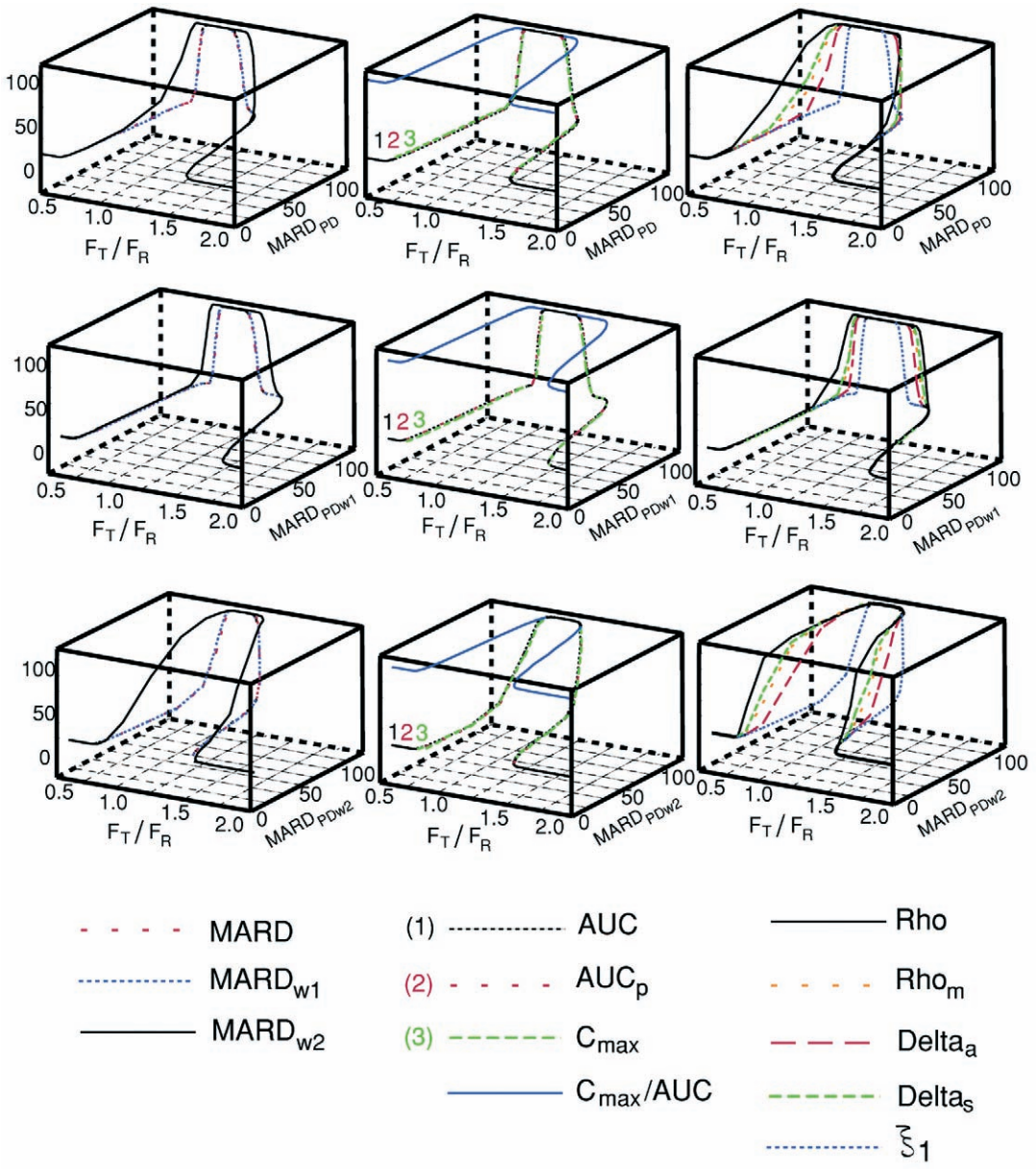

Fig. 5. Power curves showing the relationship between the percentage acceptance number for the PK metrics (*z* axis) which are quoted at the bottom of the graph for each one of the three columns and the percentage acceptance number of PD metrics for a variety of F_T/F_R ratios, assuming two-compartment model disposition kinetics. Each curve is constructed from 61 data points (not shown for clarity reasons). Since visual inspection of the plots becomes uncertain when complete concordance exists between two or more curves, some of the curves are also labeled with a different number.

model. In other words, the differences observed in the plasma concentrations of the reference and test formulation, generated from the two-compartment model and assessed with the PK metrics, are diminished when their effects are considered on the basis of the PD indices.

The conclusions derived from the simulated BE trials using the one-compartment model, Fig. 7A and B, can be contrasted with the results of the first part of the study, Fig. 2. Visual inspection of Fig. 7A and B reveals that the positioning of the PD indices varies in relation to the PK metrics. However, it was shown that the acceptable range for the ratio of indices E_{peakT}/E_{peakR} is significantly smaller than the range 0.45 for the classical ratios of PK indices, AUC_T/AUC_R and $C_{maxT}C_{maxR}$, Fig. 2. This smaller range indicates that E_{peak} is a less sensitive index to detect BE differences compared to *AUC* and C_{max}. In other words, if the E_{peak} index was classified in the ranking of Fig. 7, it would have been positioned on the right hand-side of AUC and C_{max}.

The level of acceptance of the newly proposed PK and PD metrics was arbitrarily set equal to 20%, which is in accord with the currently used limits for *AUC* and C_{max}. The overall analysis of the results indicates that three of the indices tested, namely, AUC_p, MARD and $MARD_{w1}$

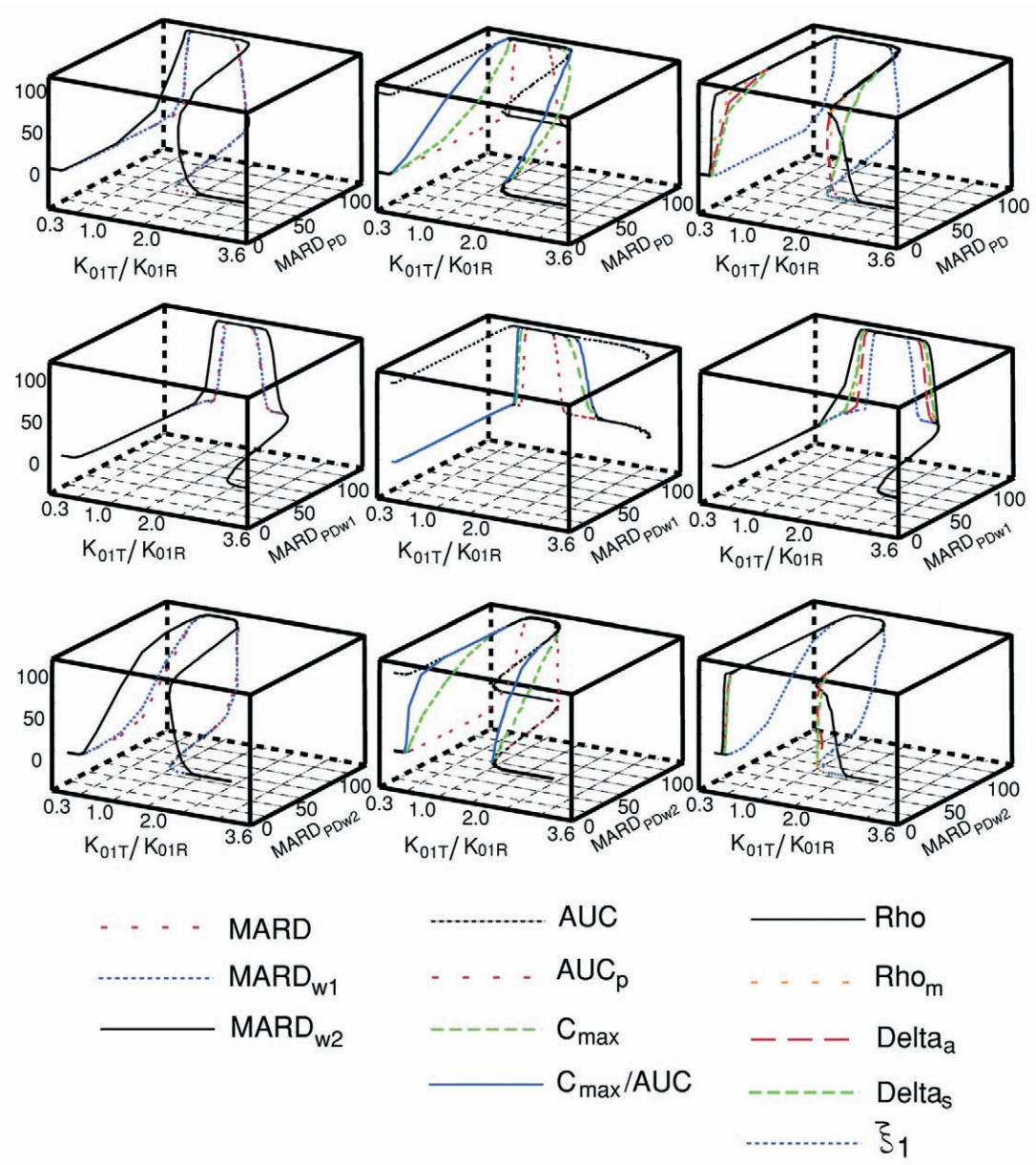

Fig. 6. Power curves showing the relationship between the percentage acceptance number for the PK metrics (z axis) which are quoted at the bottom of the graph for each one of the three columns and the percentage acceptance number of PD metrics for a variety of K_{01T}/K_{01R} ratios, assuming two-compartment model disposition kinetics. Each curve is constructed from 133 data points (not shown for clarity reasons).

exhibit the safest performance in terms of the consumer risk in declaring BE for all scenarios examined. In addition, these indices exhibit either equivalent (one-compartment model, Fig. 7A and B) or stricter performance (two-compartment model, Fig. 7C and D) than $MARD_{PDw2}$, which is the strictest PD index, Fig. 7.

Additional simulations were also carried out to study the distributional characteristics of the proposed indices (MARD, $MARD_{w1}$, $MARD_{w2}$) as well as of the nonclassical metrics (Rho, Rho_m, $Delta_a$, $Delta_s$ and ξ_1). Only, the log-transformed values of MARD calculated from the one-compartment model *C,t* data exhibited normal distribution using the χ^2 goodness of fit criterion. In all other cases, the metrics did not obey normal distribution using either the untransformed or the log-transformed values derived from the one- and two-compartment model *C,t* data.

6. Conclusions

The currently applied 0.80–1.25 acceptable interval for C_{max} and AUC was found to be very restrictive in terms of E_{peakT}/E_{peakR}, using a PK/PD model of indirect link.

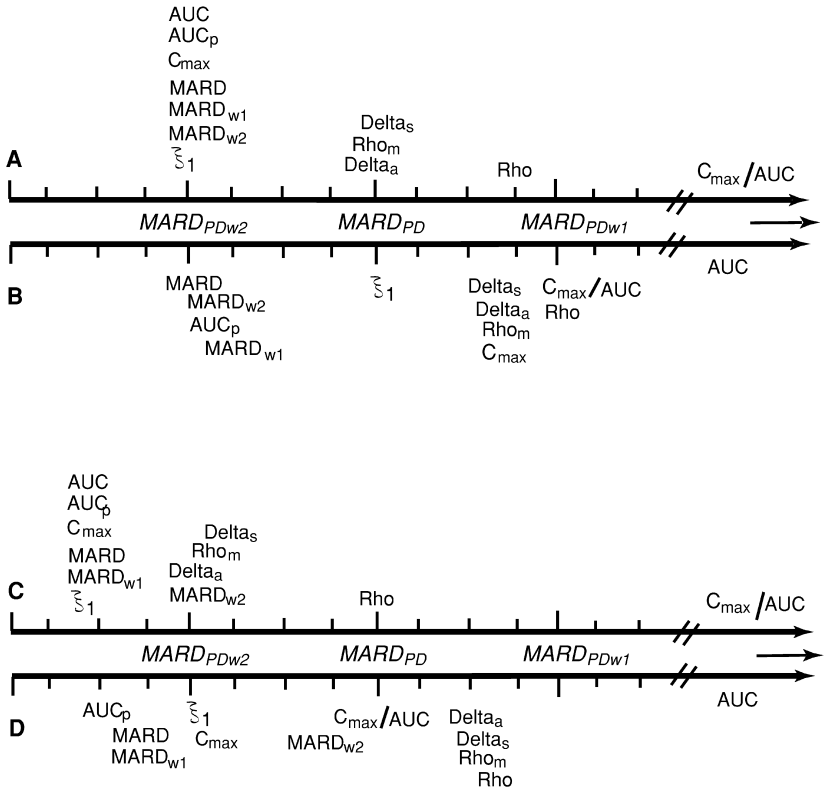

Fig. 7. Classification of the PK and PD metrics in declaring BE for the examined PK scenarios using one-compartment model disposition kinetics for a variety of F_T/F_R (A), or K_{01T}/K_{01R} (B), ratios, and two-compartment model disposition kinetics for a variety of F_T/F_R (C), or K_{01T}/K_{01R} (D), ratios. The arrows indicate the direction of the diminished strictness of metrics in declaring BE. Numerical values for the axes cannot be used since the absolute values in accepting or rejecting BE varies with the F_T/F_R or K_{01T}/K_{01R} values. However, the positioning of the metrics along the *x* axis allows the assessment of their relative strictness.

Ideally, a comparison between two drug formulations would be based on their effect–time profiles. As long as this cannot be achieved in practice, we propose an approach based on PK/PD considerations along with three indices which quantify the deviation from unity of the C_T/C_R profile. In this respect, several PK metrics were ranked according to their ability to detect BE differences using simulated data. Similarly, the PD indices were ranked in terms of their strictness in declaring BE. Three of the indices, namely, AUC_p, MARD and $MARD_{w1}$ exhibited the most strict performance in declaring BE irrespective of the extent and rate of absorption changes considered for both PK scenarios examined. It is hoped that the results of the present study can foster the application of PD considerations in the field of BE assessment.

Acknowledgements

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