Evaluation of Direct Curve Comparison Metrics Applied to Pharmacokinetic Profiles and Relative Bioavailability and Bioequivalence

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Purpose. The intent was to investigate three direct curve comparison metrics, the Rescigno Index, *f1*, and the Chinchilli Metric as tools to assess relative bioavailablity (BA) and bioequivalence (BE). The specific objectives were to 1) estimate relative bioavailability and bioequivalence and 2) compare detection of profile shape differences with typical (i.e. AUC and Cmax) criteria.

Methods. Product bioequivalence was estimated and the degree of concordance with typical criteria in detecting profile differences was determined from the eighteen bioequivalence studies (390 subjects). Descriptive statistical analysis was carried out on the concordant and discordant profile subsets.

Results. 1) Three of the eighteen studies failed typical criteria (AUC and Cmax). Of the curve metrics, 12 studies failed the Chinchilli metric criteria and 13 failed *f1* criteria. Using three different exponents in the Rescigno Index calculation, 17 (exponent = 3), 13 (exponent = 1), and 11 (exponent = 1/3) failed the criteria for bioequivalence. The frequency of profiles found to be different was comparable across the metrics, but the specific profiles found to be different or not different varied across the metrics. The Chinchilli Metric and *f1* agreed 71% and 72% with typical criteria in judging profiles to be different or not different. Descriptive evaluation suggested that the direct curve metrics more effectively detect differences in absorption time lags but less effectively detect differences in Cmax. The Rescigno Index showed dependence on the direction of the difference between test and reference concentrations.

Conclusions. With the limits used here, the direct curve metrics represent a more conservative approach to evaluate product bioequivalence. With further investigation and development, the direct curve approach may be used effectively to evaluate relative BA and BE.

KEY WORDS: bioequivalence metrics; bioequivalence; direct curve comparison.

INTRODUCTION

Drugs statistically similar in bioavailability are considered bioequivalent. BA is usually defined in terms of rate (Cmax) and extent of absorption ($AUC_{(0\text{-infinity})}$) for oral dosage forms. These two parameters alone may not adequately determine the relative BA of an oral dosage form. Because an infinite number of different profiles can calculate to the same AUC, profile shape is not taken into consideration. Further, Cmax is a single point determination, insensitive to changes in input function (1–4), complicated by the presence of flat curves and multiple peaks, and is confounded by the extent of absorption. Because of the use of two parameters, we have no single overall assessment of relative BA/BE. In addition, because Cmax is confounded by the extent of absorption, the traditional BE statistical tests essentially test twice for extent of absorption. A method that takes the shape of the plasma/blood concentration profiles into account may offer increased sensitivity to detect clinically important differences and overcome some of these limitations. In view of this, three direct curve comparison metrics were evaluated for their potential to assess BA and BE and to detect differences in profile shape. Specifically, the Rescigno Index (5), *f1* (6) and Chinchilli Metric (7) were applied to several *in vivo* bioequivalence study data sets.

METHODS

Using data from 18 bioequivalence studies, the each direct curve metrics were used to estimate product bioequivalence and to detect differences in individual profiles and the results were compared with typical (AUC and Cmax) criteria.

Equations

The equations and brief descriptions follow. Some of these approaches have also been used to compare dissolution profiles (8).

Rescigno Index

The general form for calculation of the Rescigno Index is:

$$\xi_j = \left(\frac{\sum_{i=1}^{n} |R_i - T_i|^j}{\sum_{i=1}^{n} |R_i + T_i|^j} \right)^{1/j} \quad (1)$$

R_i = *reference concentration at the ith time*

T_i = *test concentration at the ith time*

n = *number of samples within a profile*

j = *exponent*

Three exponents, j = 3, 1, and 1/3, were used and are referred to as $Rescigno_3$, $Rescigno_1$, and $Rescigno_{1/3}$ in the text, respectively. Each index ranges from 0 to 1 and approaches 0 as the test and reference profiles approach equivalence.

f1

The relative difference, denoted here as *f1*, was applied to compare test and reference profiles:

$$f_1 = \left\{ \frac{\sum_{i=1}^{n} |R_i - T_i|}{\sum_{i=1}^{n} R_i} \right\} \times 100 \quad (2)$$

R_i = *reference concentration at the ith time*

T_i = *test concentration at the ith time*

n = *number of samples within a profile*

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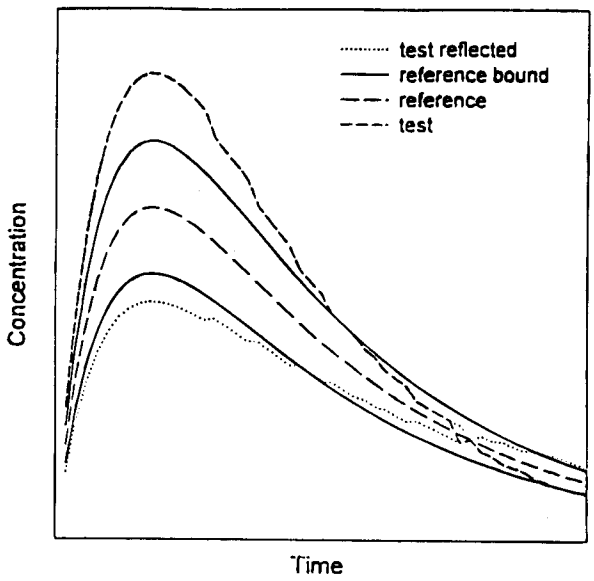

Fig. 1. To calculate the Chinchilli Metric, example of boundaries for the reference region and boundaries for the test region.

f1 approaches 0 as the test and reference profiles approach equivalence.

Chinchilli Metric

The Chinchilli Metric is the ratio of the test region area over the reference region area. Briefly, the reference region was calculated from the reference curve and represents the bioequivalence region. The test region was calculated from the test and reference profile and was calculated by reflecting the test profile off the reference profile (Figure 1). The formulas for calculation of the upper and lower boundaries of the test and reference region for the case where both reference and test concentrations were above the analytical assay limit of quantitation are:

$$R_L(t_i) = \textit{lower acceptance limit}*R_i = 0.80*R_i \quad (3a)$$

$$R_U(t_i) = \textit{upper acceptance limit}*R_i = 1.20*R_i \quad (3b)$$

$$T_L(t_i) = min\{T_i, (R_i/T_i)R_i\} \quad (3c)$$

$$T_U(t_i) = max\{T_i, (R_i/T_i)R_i\} \quad (3d)$$

where $R_L(t_i)$ and $R_U(t_i)$ are the lower and upper boundaries of the reference region and $T_L(t_i)$ and $T_U(t_i)$ are the lower and upper boundaries of the test region. i is the sample number within a profile.

Situations where the reference and/or the test concentrations were below the analytical assay limit of quantitation were handled as described in Chinchilli's derivation of the metric (7). After defining the boundaries, the test region and reference region areas were calculated using the trapezoidal rule:

$$\psi = \frac{\sum_{i=1}^{n} 0.5(t_i - t_{i-1})\{T_U(t_i) - T_L(t_i) + T_U(t_{i-1}) - T_L(t_{i-1})\}}{\sum_{i=1}^{n} 0.5(T_i - t_{i-1})\{R_U(t_i) - R_L(t_i) + R_U(t_{i-1}) - R_L(t_{i-1})\}} \quad (4)$$

Bioequivalence Limits

The criteria used to evaluate product bioequivalence follows.

Cmax(test)/Cmax(ref) and AUC(test)/AUC(ref) (Typical criteria): The 90% confidence intervals of the ratio of the least square means of the log-transformed data was required to be within the 80 to 125% interval to conclude bioequivalence.

f1 The study sample median was required to be less than or equal to 20 to conclude bioequivalence, reflecting an average 20% difference in test and reference profiles.

Rescigno Index The median observed index was required to be less than or equal to 0.100 to conclude bioequivalence. This limit was established by calculating upper and lower boundaries with a 20% difference of the reference concentration between each upper and lower concentration.

Chinchilli Metric The reference curve boundaries were calculated according to equations 3a and 3b and with an acceptance limit of 20%. The median study sample ratio, where each subject ratio was calculated using equation 4, was required to be less than or equal to 1 to conclude bioequivalence. A ratio of less than or equal to one indicates a test region less than or equal to the reference region.

Though Chinchilli proposes calculation of an upper confidence limit for the sample median via a bootstrapping algorithm (7), the upper limit was not calculated for the Chinchilli metric or for *f1* and the Rescigno Index (see Discussion). Medians rather than means were used because of the apparent highly skewed distribution of the curve metrics, noted even with the relatively small sample sizes.

Profile Similarity Limits

In addition to product bioequivalence, the degree of concordance in judging profiles to be the same or different was determined. For that assessment, the criteria used to detect individual profile differences is described below.

Cmax(test)/Cmax(ref) and AUC(test)/AUC(ref) (Typical criteria) A ratio between 0.80 and 1.20 was required to find the profiles similar. Raw concentrations rather than logarithms were used in the calculation.

f1 An index less than or equal to 20 was required to conclude similarity, reflecting an average 20% difference.

Chinchilli Metric The reference boundary was 20% above and below the observed reference profile. A ratio less than or equal to 1 was required to conclude similarity.

Rescigno Index The observed index was required to be less than or equal to 0.100 to conclude similarity.

Experimental Data

Data from 18 randomized 2 × 2 crossover studies enrolling an average of 24 subjects per study was evaluated. Each subject was administered a single dose of test or reference product according to the randomization scheme, with an adequate washout period between drug administrations. At least 17 blood samples were taken at appropriate times and analyzed for drug concentration according to a validated HPLC method. Healthy volunteers participated in the 18 studies used for this research. The Protocol and Informed Consent were approved by an Institutional Review Board and all subjects signed the Informed Consent prior to the start of the study.

The test and reference product AUC(0-t) was calculated for each subject using the trapezoidal rule and Cmax was taken from the observed data. The direct curve comparison metrics were calculated according to the equations above.

The products represent a broad range of drugs and drug products with simple to complex profiles.

RESULTS

Bioequivalence Estimation

Of the 18 standard BE studies, three products failed the typical bioequivalence criteria. Using the median direct curve metric of the study sample as the point estimate; 17 studies failed $Rescigno_3$, 13 studies failed $Rescigno_1$, 12 studies failed *f1*, and 11 studies failed both Chinchilli and $Rescigno_{1/3}$ (Table I). Confidence intervals would increase the failure rate. Results show the direct curve metrics correlate with each other, where the same studies pass according to rank sensitivity. Figure 2 illustrates the relationship between *f1* and the Chinchilli metric.

In contrast, the direct curve metrics appear not to correlate with typical criteria. In addition to increased sensitivity, the direct curve metrics appear to have very different detection properties in relation to typical criteria. More specifically, products with narrow confidence intervals for Cmax and AUC passed and failed the direct curve criteria with equal frequency, suggesting that the metrics detect differences not detected by typical criteria and vice versa. There was no apparent relationship between the $Cmax_{(test)}/Cmax_{(ref)}$ ratio, the $AUC_{(test)}/AUC_{(ref)}$ ratio, or the within-subject variabilities and the median direct curve metric (Table I). Among the products passing the direct curve criteria, the within-subject variability for Cmax was between 11 and 22% and for AUC, between 4 and 16.7%, approximately average for all of the studies.

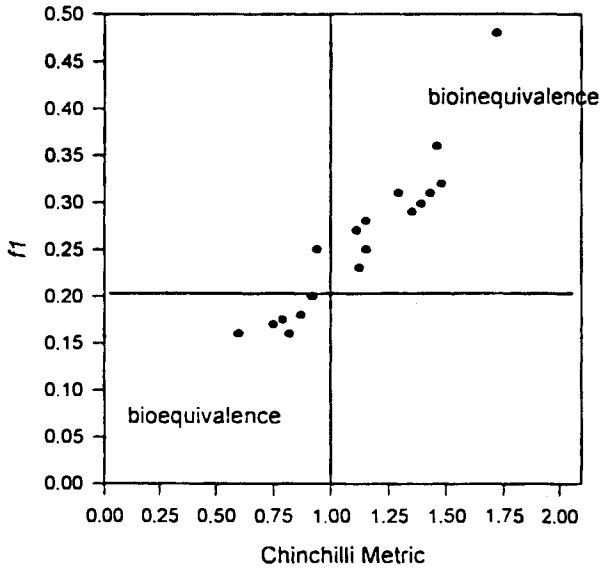

Fig. 2. Plot of the median Chinchilli Metric and *f1* for each bioequivalence study.

Examination of the pharmacokinetics of the various products, a reflection profile shape, provides some insight into the different sensitivities of the curve metrics as compared to typical criteria. Of particular interest, the products passing the direct curve metrics showed rapid absorption kinetics. Looking specifically at these products, all three of the oral suspension products

Table I. Comparing Typical Criteria with the Direct Curve Metrics in the Assessment of Product Bioequivalence

			Bioequivalence results[b]						Within-subject variability (CV%)[c]		
Drug-study #	Formulation	N[a]	Typical	Chinchilli	Rescigno 1/3	*f1*	Rescigno 1	Rescigno 3	Cmax	AUCt	AUCi
a1	gelcap	8	BE	BinE	BinE	BinE	BinE	BinE	17.6	6.9	6.4
b1	tablet	27	BE	BinE	BinE	BinE	BinE	BinE	23.0	10.0	11.0
c1	tablet	11	BinE	BinE	BinE	BinE	BinE	BinE	25.0	24.0	25.0
d1	oral susp.	25	BE	BE	BE	BE	BE	BinE	11.0	10.0	9.5
e1	tablet	58	BE	BinE	BinE	BinE	BinE	BinE	51.0	34.0	30.0
f1	tablet	25	BE	BE	BE	BE	BE	BinE	15.0	10.0	11.0
g1	oral susp.	15	BE	BE	BE	BE	BE	BE	17.0	4.0	3.5
a2	gelcap	8	BE	BinE	BinE	BinE	BinE	BinE	14.0	7.2	7.5
h1	tablet	22	BE	BinE	BinE	BinE	BinE	BinE	23.0	16.0	14.0
b2	tablet	23	BE	BinE	BinE	BinE	BinE	BinE	16.0	12.0	12.0
i1	tablet	24	BE	BE	BE	BE	BE	BinE	14.0	16.7	7.4
j1	tablet	18	BinE	BE	BE	BE	BinE	BinE	22.0	8.8	11.0
d2	oral susp.	18	BE	BE	BE	BE	BE	BinE	11.7	15.0	15.0
h2	tablet	25	BE	BE	BE	BinE	BinE	BinE	12.0	7.0	5.7
i2	enteric coat	16	BinE	BinE	BinE	BinE	BinE	BinE	15.4	3.3	3.3
a3	tablet	17	BE	BinE	BinE	BinE	BinE	BinE	15.0	5.3	5.9
h3	tablet	25	BE	BinE	BinE	BinE	BinE	BinE	21.0	12.0	11.0
h4	tablet	25	BE	BinE	BinE	BinE	BinE	BinE	14.5	9.0	9.8

[a] Number of subjects in the study.
[b] Evaluated as described in **Methods, Bioequivalence Limits**; 'BE' = bioequivalent, 'BinE' = bioinequivalent.
[c] Within-subject variability estimated from the ANOVA residual mean square for log-transformed Cmax, AUC from 0 to the last timpoint, and AUC from 0 to infinity.

(g1, d1, and d2) and two of the tablet products (f1 and i1) met at least four of the 5 direct curve criteria for equivalence. In addition to rapid absorption kinetics, the tablet products were somewhat distinguished by slow elimination and relatively long sampling times (48 and 72 hours). One product, j1, passed *f1*, Chinchilli, and $Rescigno_{1/3}$ criteria, but failed Cmax. A slow elimination and long sampling time (36 hours) was also associated with this product. In view of the high direct curve metric failure rate, the finding of a product failing Cmax but passing the direct curve metric suggests the new metrics may, under some conditions, show less sensitivity to large differences in peak concentrations.

Only one of the 7 products with fast absorption (a2) failed each direct curve criteria. This product also exhibited relatively large mean partial AUC calculated to the reference Tmax, a sensitive indicator of absorption lag time differences (1,9). Further, from the mean data, there appears to be a correlation between the partial AUC and the median direct curve (Table II).

Subject Level Analysis

To gain insight into the sensitivity of the direct curve metrics to differences in shape, subject level analysis was carried out. Counting the number of subjects (N = 390) passing and failing the profile similarity criteria for each study and for each metric, and using the limits stated above, 53% of the subjects failed to meet either the AUC(0-t) criteria or the Cmax criteria; 21% failed the AUC(0-t) criteria, 45% failed the Cmax criteria, and 12% failed both. The proportion failing the curve criteria was as follows: $Rescigno_3$ (86%), $Rescigno_1$ (64%), *f1* (63%), Chinchilli (54%), and $Rescigno_{1/3}$ (52%). Though the frequencies suggest strong concordance among at least some of the metrics, the specific profiles judged to be different varied when comparing the direct metrics and typical criteria. Focusing on the Chinchilli Metric and *f1*, and counting the cases where the direct curve metrics and typical metrics both conclude different or not different, the degree of concordance with typical criteria averaged across studies was 71% for the Chinchilli Metric and 72% for *f1* (Table II). Descriptive statistics were carried out on the discordant subsets and are examined below.

Cases That Fail Typical Limits but Pass the Direct Curve Limits

The direct curve metrics detected differences in 96% (Chinchilli) and 98% (*f1*) of the cases failing AUC and Cmax, and in 91% (Chinchilli) and 94% (*f1*) of the cases failing AUC. But for the cases failing Cmax, the indices detected differences in only 71% (Chinchilli) and 82% (*f1*). Of the subset failing Cmax, but passing the Chinchilli Metric, the median absolute percent difference between Cmax test and reference was 27% (20 to 73%). Of the subjects failing Cmax but passing *f1*, the median absolute percent difference between Cmax test and reference was 24% (21 to 40%).

The studies demonstrating the highest frequency of subjects failing typical criteria, but passing the direct curve criteria

Table II. Subject Level Analysis, The Degree of Concordance in Detecting Profile Differences Comparing Chinchilli and *f1* Criteria with Typical (Cmax and AUC) Criteria

					Mean (Chinchilli and *f1*) Percent of Profiles by Study[a]						
					concordance			discordance		concordance	
Drug-study #	Elim. Rate[b]	Abs. Rate[c]	AUCP[d]	PK Model[e]	yy + nn	yy	nn	ny	yn	Chinchilli yy + nn	*f1* yy + nn
a1	mod	mod	0.01	1-c	88	25	63	0	13	88	88
b1	slow	mod	0.13	1 to 2-c	83	33	50	2	15	81	85
c1	mod	slow	0.20	1-c	82	9	73	9	9	73	91
d1	mod	fast	0.14	1-c	80	50	30	14	6	76	84
e1	slow	slow	0.06	1-c	79	8	72	9	11	81	78
f1	slow	fast	0.05	1-c	78	52	26	14	8	76	84
g1	fast	fast	0.04	1-c	77	63	13	20	3	73	80
a2	mod	fast	0.45	1-c	75	38	38	13	13	75	75
h1	mod	mod	0.03	mltple pks	73	23	50	9	18	73	73
b2	slow	mod	0.07	2-c	72	26	46	11	17	65	78
i1	slow	fast	0.18	1-c	71	52	19	19	10	71	71
j1	slow	fast	0.26	2-c	67	22	44	28	6	72	61
d2	mod	fast	0.06	1-c	64	44	19	25	11	61	67
h2	mod	mod	0.15	mltple pks	64	38	26	6	30	68	60
i2	slow	slow	0.68	1-c	59	22	38	6	34	63	56
a3	mod	mod	0.37	1-c	59	32	26	6	21	53	65
h3	mod	mod	0.21	mltple pks	58	6	52	16	26	60	56
h4	mod	mod	0.21	mltple pks	52	24	28	8	40	52	52

[a] YY: AUC and Cmax = similar, curve metric = similar NN: AUC and Cmax = different, curve metric different NY: AUC and Cmax = different, curve metric = similar YN: AUC and Cmax = similar, curve metric different.
[b] mean elimination (/hr) of ref product estimated from terminal phase of each profile: slow: ke <= 0.10, moderate: 0.11 <= ke < .99, fast: ke >= .99.
[c] rate of absorption roughly estimated from mean ref Tmax (hr): slow: Tmax >= 2.2, moderate: 1.2 <= Tmax < 2.2, fast: Tmax <= 1.2.
[d] absolute difference from 1 of the ratio of test and ref log-transformed partial AUC, calculated up to the reference Tmax.
[e] pharmacokinetic model roughly estimated from mean plots: 1-c = 1 compartment, 2-c = 2 compartment, mltple pks = multiple peaks.

were: the products labeled j1 (28%), d2 (25%), g1 (20%), and i1 (19%) (Table II). The pharmacokinetics of these products tended to be somewhat distinguished by rapid absorption resulting in single, sharp peaks (Figure 3). The oral suspension products g1 and d2 demonstrate very rapid absorption and moderate to rapid elimination. The tablet product j1, also a fast absorbing product, failed Cmax. Finally, all 7 of the rapid absorption products show the highest degree of discordance on examination of cases failing typical criteria but passing direct curve criteria. The discordance can be largely attributed to a relative insensitivity to large differences in peak concentrations under some conditions.

Cases That Pass Typical Limits but Fail the Direct Curve Limits

The direct curve metrics detect differences in 32% (Chinchilli) and 41% (*f1*) of the subjects passing Cmax and AUC limits. The median absolute percent difference between Cmax test and reference and between AUC test and reference was about 10% for this subset.

In most cases, a curve shift could account for the difference detected by the Chinchilli Metric and by *f1*. In some cases, both Cmax and AUC ratios were very close to the limit. The median absolute percent difference between Tmax test and reference was 38% and 33% for subjects failing the Chinchilli and *f1* criteria and passing the typical criteria, but 20% for subjects passing the direct curve limits and failing the typical criteria.

The studies demonstrating the highest frequency of cases passing typical criteria, but failing the direct curve limits were: products labeled h, studies 1 to 4 (18, 26, 30, 40%), i2 (34%), and a3 (21%) (Table II). Multiple peaks and flat profiles were evident in all of the product h studies. Both i2 and a3 products demonstrated large curve shifts (Figure 4), evident even in the mean data (mean profiles not shown). The average partial AUC ratio, calculated up to the reference Tmax for both test and reference profiles, supports the observation of curve shifts associated with the majority of the subject profiles for these products.

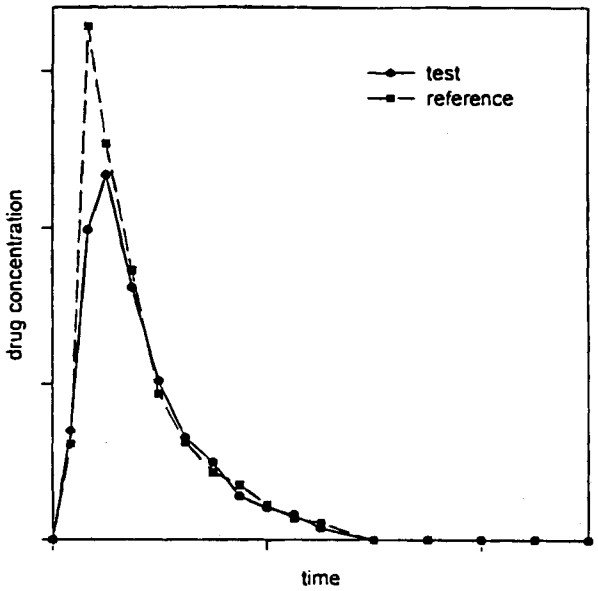

Fig. 3. Example of a profile passing the direct curve metric profile similarity criteria, but failing typical criteria.

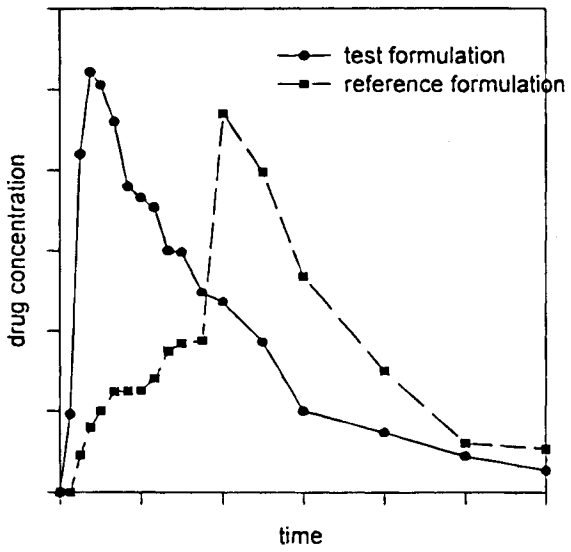

Fig. 4. Example of a profile failing the direct curve metric profile similarity criteria, but passing typical criteria.

Direct Curve Metric Comparisons

A small simulation study showed that the Chinchilli Metric, *f1*, and the Rescigno Index are all independent of the number of sampling points and the concentration units (data not shown). However the Rescigno Index shows dependence on the direction of change between test and reference curves. Test concentrations greater than reference concentrations calculate to a smaller index than test concentrations less than reference concentrations. As a consequence, three profiles, each with an AUC test and reference difference of about 20% (ratio of 1.20 or 0.80), calculate to three different indices. The asymmetry increases with increasing percent difference in test and reference concentrations, but is constant for the three exponents (Figure 5).

DISCUSSION

Two general approaches were taken and compared to evaluate profile differences and BA/BE, and the two approaches lead to different conclusions. Simply taking the mean or the median direct curve metric of the study participants often indicated bioinequivalence, whereas under the typical analysis, only 3 of the products were bioinequivalent. Despite individual profiles passed and failed the curve criteria with the same frequency as the typical criteria, the mean or median curve metric suggested bioinequivalence more often than the typical criteria. Even without calculation of the upper confidence limit, the high failure suggests the new metrics are more sensitive than desirable for reasonable assessment of clinically important differences. Because of this high failure rate, calculation of the upper confidence limit was not pursued with this research. Rather, attention was focused on studying the detection properties of the new metrics. To that end, characterization of the mean data according to pharmacokinetics and comparison of conclusions of bioequivalence and bioinequivalence offered

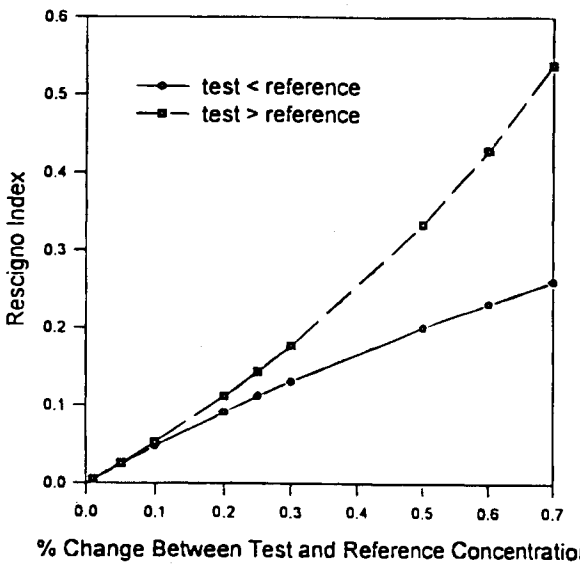

Fig. 5. The dependence of the Rescigno Index on the direction of the difference between the test and reference concentrations.

some insight into the specific sensitivities of the different approaches. Moreover, subject level analysis, where the degree of concordance with typical criteria in judging profiles to be the same or different, was also conducted. Results show that although the number of profiles found to be different was consistent among the metrics, the specific profiles passing and failing each metrics' criteria varied. In other words, the direct curve metrics detect differences not detected by the typical criteria, and the typical criteria, specifically Cmax, detect differences not detected by the direct curve metrics.

The extent of agreement between typical assessment and the curve metric approach does appear to relate to the drug product profile shape. More specifically, the observations of discordance indicate a relative insensitivity to large differences in Cmax and an increased sensitivity to absorption time lag differences as compared to typical criteria. Confirmation of these findings could come from controlled simulation studies or larger experimental datasets. But from the current study, these findings of discordance help characterize the specific sensitivities of the two general approaches as discussed below.

Evidence supporting the relative insensitivity to Cmax differences stems from one product failing Cmax but passing three of the five direct curve metric criteria, despite the high direct curve metric bioinequivalence rate. Additionally, from the individual subject profile analysis, the curve metrics failed to detect a profile difference in 18% (*f1*) and 29% (Chinchilli) of the cases failing Cmax. Yet the direct curve metrics failed to detect a difference in only 6% or fewer of the cases failing AUC or AUC and Cmax. Thus the degree of concordance with typical criteria was relatively high when comparing cases failing AUC or AUC and Cmax, but not with cases failing Cmax. Further, simulation studies suggest the curve metrics demonstrate a relative insensitivity to large differences in a small number of data points (data not shown). Consequently, if the entire profile is used in the calculation of the metric, large differences in Cmax may go undetected.

At least two factors might contribute to the discordance in concluding inequivalence when greater than 20% differences in Cmax exist: 1) the inherent weakness of the Cmax metric, a single point determination, and 2) the inherent weakness in the curve comparison approach, where large differences in a few timepoints might be diluted by small differences in a large number of timepoints.

Though the direct curve metrics demonstrate relative insensitivity to detect differences in peak concentrations, the metrics may offer the potential to detect curve shifts and also to better detect differences in the case of multiple peaks and flat profiles. The Chinchilli Metric detected differences in 32%, and *f1* in 59%, of the subjects considered similar by typical criteria. These profiles demonstrate multiple peaks and large curve shifts. In some cases, AUC and Cmax both approach the limit, and if taken together (i.e. direct curve metric), exceed the limit. The mean data also suggests an increased sensitivity to absorption lag time differences, differences not detected by Cmax and AUC.

Bioequivalence Limits

The limits influence all of the findings of this study. As a reasonable starting point, limits corresponding to those typically used to evaluate Cmax and AUC were used. The observed absolute percent difference between each subject's test and reference concentration at each time point was calculated and averaged over the entire subject's profile and then, over all of the studies. This mean difference (the mean of each subject's mean) was 32% (16.5 to 46.6%) and the mean of the median difference was 20.4% (8.2 to 29.6%). These numbers represent a combination of the within-subject variability and the true product difference. Another approach to establishing equivalence criteria, and regardless of the metric used, might be to use the estimate of the reference vs reference within-subject variability in establishing appropriate limits (10). A replicate design offers some potential to partition the variabilities and better estimate the true product differences.

Other criteria could be evaluated, although this study focused on the detection properties of the metrics. For example, widening the limits could bring the overall conclusions of bioequivalence in sync; however, at the expense of passing products with clinically important differences in Cmax.

An additional note, in establishing appropriate limits, it is of interest to consider the frequency of different profiles were comparable for some of the metrics: 53% failed typical criteria, 52% failed $\text{Rescigno}_{1/3}$, 53% failed Chinchilli criteria, 63% failed *f1* criteria, 64% failed Rescigno_1, and 86% failed Rescigno_3.

CONCLUSIONS

This study was initiated based on the premise that clinically relevant information may be lost (in some cases) by limiting relative BA and BE assessment to Cmax and AUC.

The direct curve metrics use the entire profile and as a consequence, offer some potential to improve detection of clinically important differences. But using the study sample median as an estimate of average bioequivalence, and without calculating the upper confidence limit, over 60% of the eighteen typical BE trials failed bioequivalence. This result suggests unreasonable stringency. At the same time, though lacking in statistical rigor, the evaluation suggests a relative insensitivity to potentially clinically significant differences in peak concentrations. But the evaluation also suggests direct curve metrics

better detect curve shifts, differences of possible clinical importance not detected by AUC and Cmax. Further, the discordance with typical criteria was highest for the case of multiple peaks, suggesting important information may be lost in these cases. Controlled simulation studies or larger experimental data sets might be used to confirm the observations in this study. In view of the limitations associated with typical BE evaluation, with further development and research, the direct curve approach may eventually provide a more complete assessment of relative BA/BE.

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