Pharm Res (2013) 30:191–202
DOI 10.1007/s11095-012-0862-x

RESEARCH PAPER

Use of Partial AUC (PAUC) to Evaluate Bioequivalence—A Case Study with Complex Absorption: Methylphenidate

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Received: 16 March 2012 / Accepted: 9 August 2012 / Published online: 25 September 2012

ABSTRACT

Purpose Methylphenidate modified-release products produce early and late peak concentrations critical for treatment of morning and afternoon symptoms of attention deficit hyperactivity disorder (ADHD). Standard bioequivalence (BE) criteria cannot be applied to these products. The performance of partial area under the drug concentration-time curve (PAUC), Cmax and AUCINF to assess BE were independently evaluated for two products.

Methods A two-stage analysis was performed on plasma data for two methylphenidate modified-release products (Product 1 and 2). Simulations using the fitted parameters determined how changes in fast absorption rate constant (K0Fast) and fraction available (F1) affected curve shape and BE determination using Cmax, AUCINF and PAUC.

Results The sensitivity of the mean PAUC(test)/PAUC(reference) ratios to changes in K0Fast(test) are product dependent. Product 1 mean PAUC(test)/PAUC(reference) ratios for PAUC0-4h are more responsive to both decreases and increases in K0Fast(test) than Product 2. Product 2 showed a greater response in the mean PAUC(test)/PAUC(reference) ratio for PAUC0-4h when the K0Fast(test) is decreased and less response as the value is increased.

Conclusions PAUC estimated curve shape is sensitive to changes in absorption and are product specific, and may require a new PAUC metric for each drug. A non-product specific metric to assess curve shape is warranted.

KEY WORDS bioequivalance · curve shape · methylphenidate · modified release product · partial AUC

ABBREVIATIONS

1-F1	relative bioavailability fraction of the administered dose for the slow release compartment 2
ADHD	attention deficit hyperactive disorder
AUCext	extrapolated area
AUCINF	area-under-the-curve to time infinity
AUCT	area-under-the-curve to time T
BE	bioequivalence
CI	confidence intervals
CL	clearance
D1	duration of zero-order absorption from the fast release compartment
F1	relative bioavailability fraction of the administered dose for the fast release compartment 1
F2	process which was lagged to accommodate the duration of absorption for the fast release relative bioavailability fraction of the administered dose for the slow release compartment
FDA	Food and Drug Administration
IR	immediate-release
k03	elimination rate constant
k13	K0Fast (a zero-order absorption rate constant)
k23	KAslow (first-order absorption process)
LAG	time for absorption delay for slow release

Electronic supplementary material The online version of this article (doi:10.1007/s11095-012-0862-x) contains supplementary material, which is available to authorized users.

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PAUC	partial area under the drug concentration-time curve
proerr	proportional residual error
R	reference
RATIO_04	ratio of PAUC0-4T/PAUC0-4R
RATIO_06	ratio of PAUC0-6T/PAUC0-6R
RMSE	root mean square error
T	test
Vc	apparent volume of central compartment

INTRODUCTION

In 1992 a paper introduced the concept of partial area under the drug concentration-time curve (PAUC) as an alternative metric whenever early onset of action was therapeutically important for the evaluation of the rate of absorption in bioequivalence (BE) trials (1). The PAUC method has been investigated as an indirect measure of rate of absorption for immediate-release formulations, especially when time for onset of action was important (2). The incremental AUC representing 10 to 30% of the total AUC was reported to be more sensitive than either Cmax or Tmax in detecting input rate differences between formulations (3). It was suggested by Chen (1) that, "the method was found to be more discriminating than Cmax and/or Tmax in the evaluation of the absorption rate of drugs."

The optimal cutoff time point for the PAUC metric has been studied. Specifically, it has been investigated whether the Tmax is an appropriate proposed cutoff time for PAUC (4). It was suggested that provided that the quality of experimental data ensures a precise estimation of the parameters, the Tmax of the formulation with the faster absorption characteristics is generally the most practical cutoff time point for calculation of the normalized PAUC, when a drug follows a one-compartment model disposition with linear absorption (5). It has also been proposed that a fixed universal acceptance time interval for BE may be inappropriate (6) with respect to PAUC. Others have indicated that for drugs with two absorption peaks, there is increased power for stating BE when PAUC included the time interval for the earlier rather than the later of two peaks in each subject (7). Similarly, the power for stating BE was comparatively high when PAUC was based upon the Tmax of the reference. The power for stating BE was also high when PAUC was determined until the fixed true population mean time of the reference formulation (7,8). Based upon these investigations the time for the PAUC to be measured remains one of the controversial aspects related to this metric. It has also been recommended that the cutoff time-point for PAUC be a common time for both test and reference products in each individual so that a valid comparison can be made (1). Although an earlier cutoff is associated with greater kinetic sensitivity, the earlier truncation is also accompanied by higher statistical variability in the PAUC measure (2). In addition, authors have suggested that the selection of a truncation point may vary with the clinical indication of the drug under study (1). An author who introduced two new metrics while considering PAUC concluded that indeed PAUC performed well when the drug's pharmacodynamics were developed and served as a criterion for the assessment of all BE indices (9).

The systemic exposure of a drug is often well correlated with its efficacy and/or toxicity, and hence it is generally used as an index for dose optimization. For these reasons, a recent Food and Drug Administration (FDA) guidance (10) as well as Chen and colleagues (11) have recommended a change in focus from measures of absorption rate to measures of systemic exposure. According to the FDA proposal, a plasma/serum profile can be characterized by three fundamental exposure attributes: early exposure, peak exposure and total exposure. Reliance on these systemic exposure measures would achieve the underlying goal of assuring comparable therapeutic effects between formulations. This concept of exposure becomes more relevant for modified-release formulations with different rates of absorption as indicated by their differences in curve shapes. With respect to immediate-release (IR) formulations, the FDA guidance recommends the use of PAUC as an early exposure measure, and that PAUC be truncated at the population median of Tmax value for the reference formulation.

It has been pointed out that for many modified-release dosage forms, assurance of comparable profiles is essential for demonstration of BE and therapeutic equivalence. Thus, early exposure may become important (3). To further investigate this relationship between PAUC i.e., as a surrogate for not only rate but curve shape, we chose methylphenidate as a representative modified-release dosage form (12,13). Different release rates for a product with a dual release mechanism such as methylphenidate could result in different shaped plasma concentration time curves and non-equivalent formulations.

Methylphenidate was selected as a model drug to study since all of the currently marketed products have a dual release plasma profile. The drug is widely prescribed for attention deficit hyperactive disorder (ADHD). It has been marketed in several controlled release formulations such as Focalin XR, Ritalin LA, Metadate CD, Concerta and Metadate ER. What is very unique about this class of compounds is that each drug has a very distinctive dual release profile. The methylphenidates have been manufactured to have an early release and a late release component. The clinical importance of this type of profile was highlighted in an article by Swanson and colleagues (14). These drugs are all prescribed for once daily administration. The study by Swanson and colleagues reported that an ascending regimen

i.e., designed to produce increasing methylphenidate concentrations from a low drug concentration established early in the morning to a high drug concentration (i.e., the bid peak level) by the end of the day was most effective in the treatment of ADHD. We investigated the potential role of PAUC by comparing its performance in the determination of the BE for two marketed reference products with different curve shapes, reference product 1 and reference product 2 (15). Both products have been deemed to be clinically effective for the treatment of ADHD.

The focus of the current study was to investigate the use of PAUC not as the singular metric for BE but in combination with current established metrics (i.e., Cmax and area-under-the-curve to time infinity (AUCINF)). It is highly unlikely that a small portion of an area-under-the-curve such as AUC0-2h, or even smaller may be used to determine BE without consideration of the rest of the concentration-time profile. Therefore, this investigation focused on the proposed use of PAUC in addition to Cmax and AUCINF as measures of exposure, especially when clinical response has been related to curve shape (14,15).

MATERIALS AND METHODS

Experimental study data for both reference product 1 and reference product 2 were submitted to the FDA. Both studies were designed as single-dose, open-label, randomized, two-period crossover studies conducted under fasted conditions. The dose for product 1 was 54 mg (N=34) while that for product 2 (N=19) was 40 mg. Sampling times for both drugs were 0 (pre-dose), 0.25, 0.50, 1, 1.5, 2, 3, 4, 5, 6, 6.5, 7, 7.5, 8, 10, 12, 16, and 24h. Methylphenidate was assayed by a validated high performance liquid chromatography mass spectroscopy assay in both studies with a limit of quantitation of 0.25 ng/ml.

Structural Model

Reference Product 1

The structural model for reference product 1 is described by two parallel inputs (Fig. 1). The first input is for the fast-release component which mimics the products immediate-release drug overcoat which is fast dissolving and represented in the model with a rapid zero-order (K0Fast) input into plasma (12). This is followed by the second input which is for the slow first-order release of drug (KAslow) due to water permeation into the product's core and controlled drug delivery/release through a membrane. This observed delayed release in the model is represented by a delayed first-order drug release. Graphical analysis of the concentration-time profiles indicated that a one-compartment model with these fast and slow absorption components adequately described the time course for product 1.

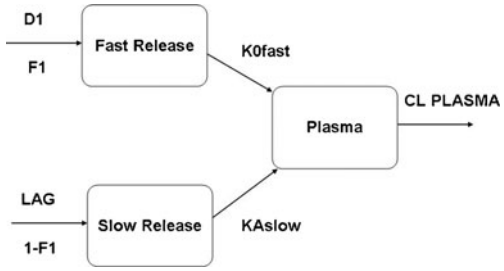

Fig. 1 Model for controlled release reference methylphenidate product 1 and product 2.

A pharmacokinetic model for the oral reference product 1 was developed using the nonlinear mixed effects modeling program (NONMEM, Version VI) with the first-order method of estimation.

A population model was initially used to fit the data, but there were computational difficulties which resulted in a failure of the analysis. Stabilization of the model via log transformation was tried but it did not overcome the computational problems. Graphical analysis indicated that some subjects who received product 1 appeared to have larger input functions for the rapid zero-order input into plasma than others, therefore a mixture model was investigated that could determine the probability of n subpopulations and the probabilities of each subject belonging to the subpopulation n_i (16). However, the mixture model also had numerical difficulties and no solution was obtained.

Due to these problems the data were analyzed by a standard two-stage analysis (STS) since each subject had intensive sampling (17). The data were fit using the PREDPP subroutine ADVAN7 TRANS1. The pharmacokinetic model was parameterized with CL (clearance), Vc (apparent volume of central compartment), absorption rate constant k13, absorption rate constant k23, and the elimination rate constant k30. K13 was defined as K0Fast (a zero-order absorption rate constant), while k23 was defined as KAslow (i.e., first-order absorption process which was lagged (LAG) to accommodate the duration of absorption for the fast zero-order release component). The relative bioavailability fraction of the administered dose for the fast release compartment 1 was defined as F1 while that for the slow release compartment 2 was defined as 1-F1. The value for F1 was defined as a logit function. The final structural model is presented in Fig. 1.

Reference Product 2

Reference product 2 has been described as an extended-release formulation of methylphenidate with a bi-modal release profile due to each bead-filled capsule containing

half the dose as immediate-release beads and half as enteric-coated, delayed-release beads (13). The same model and methods used for reference product 1 were used to fit the data and had similar computational problems during data analysis as observed for reference product 1. Similar to reference product 1, the data were analyzed by a standard two-stage analysis (STS) since each subject had intensive sampling (17). The data were fitted using the PREDPP subroutine ADVAN7 TRANS1. Pharmacokinetic model parameterization was identical to reference product 1 described above.

Parameter Estimation and Residual Variability

Reference Product 1

Preliminary analysis of the pattern of residuals indicated that the residual variability, which represents the discrepancy in observed methylphenidate concentrations and those predicted by the structural model, was best described using a combined additive and proportional error model as shown by Eq. 1.

$$Cp_{ij} = \widehat{C}p_{ij} \cdot (1 + \varepsilon_{ij1}) + \varepsilon_{ij2} \quad (1)$$

$\widehat{C}p_{ij}$ is the individual predicted concentration at time i for subject j, ε_{ij1} is the random variable that quantifies the deviation of the predicted from observed concentration in a manner independent of the magnitude of the prediction. ε_{ij2} is the random variable that quantifies the deviation of the predicted from observed concentration in a manner that is additive to the magnitude of the prediction. The variance for ε_{ij1} is ${\sigma_1}^2$ while for ε_{ij2} the variance is ${\sigma_2}^2$.

Reference Product 2

Parameter estimation was the same as for product 1.

Bootstrap Model Predictive Check: Reference Products 1 and 2

Model qualification was done using a visual predictive check (18). Since curve shape was the most important aspect of the analysis, qualification was based upon visual inspection and comparison of model generated simulated plasma data to the original experimental data. Cp_{ij} values were used for all model qualifications.

The model was used to fit the original data to obtain the estimates for Θ, which is the vector of the estimated individual subject model parameters. The original best fit reference subject parameters for the 34 subject dataset (N=34) were randomly re-sampled (i.e., bootstrapped using SAS, version 9.1) with replacement. This produced 200 parameter data sets of the same size (N=34) with a different combination of subjects. The concentration profiles were simulated in NONMEM based on the 200 (N=34) bootstrapped PK parameters. Evaluation was done by comparing the median plasma-time concentration graphs for each of the resulting 200 simulation studies with the original median experimental plasma data for reference product 1 (N=34). The median curves were compared since parameter distributions were log-normally distributed. A summary of the procedures are presented in Fig. 2.

The same methodology was employed for reference product 2 except the dataset was comprised of 19 subjects.

Parameter Correlation

Correlations between the final fitted parameters were investigated using proc correlation in SAS version 9.1. This was done to assess the impact of correlations on data fitting and parameter interpretation.

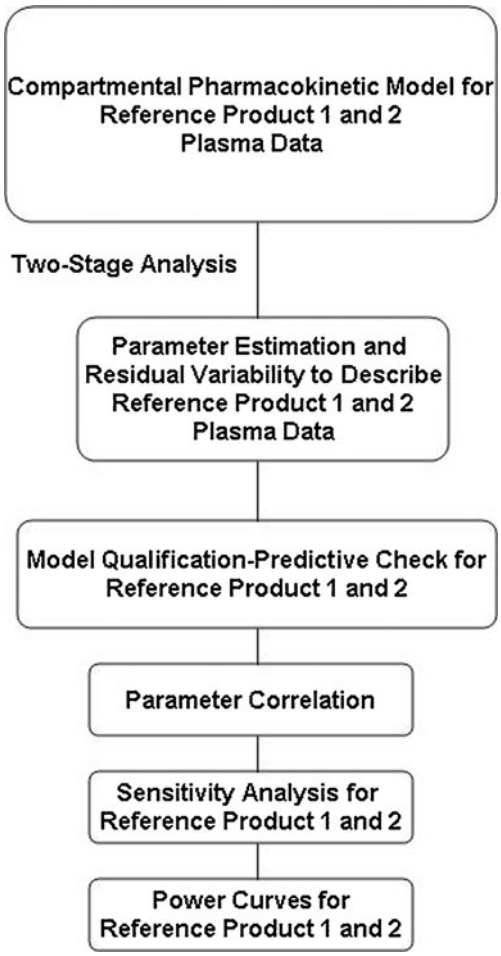

Fig. 2 Outline of the methods used to estimate parameter values for products 1 and 2, qualify the acceptability of the fits and for the subsequent simulation of bioequivalence studies for each product.

Simulated Sensitivity Analysis: Reference Product 1–K0Fast

Analysis of fitted individual subject K0Fast values indicated that there was a non-linear relationship between the fitted individual K0Fast values and PAUC for individual subjects which had been previously reported (1) for a simple first-order input.

Therefore, a simulation was done to determine the effect of changes in the mean [K0Fast(Test)/K0Fast(Reference)] ratio on the estimation of mean [PAUC0-4h (Test)/PAUC0-4h(Reference)] and mean [PAUC0-6h (Test)/PAUC0-6h(Reference)] ratio values. These PAUC values were chosen since they have been explored by the Office of Generic Drugs as an additional metric for product 1 and product 2. All simulations were conducted as reference vs. reference to determine the sensitivity of PAUC to changes in only the parameter of interest, K0Fast. The K0Fast(test) parameter for each subject was increased or decreased by a designated percentage. The same best fit reference parameters for N=34 subjects was used for both test and reference with the only variation in K0Fast(test) to represent the test formulation. The new test and best fit reference values were used to do a single N=34 subject simulation in Nonmem with the mean [PAUC0-4h(Test)/PAUC0-4h (Reference)] and mean [PAUC0-6h(Test)/PAUC0-6h (Reference)] ratio values calculated for the simulation. This was repeated for K0Fast(test)/K0Fast (reference) ratios from 0.5 to 3.0.

The aim was to determine the mean values of K0Fast (Test) that would result in mean [PAUC(Test)/PAUC(Reference)] values between 0.8 and 1.25 for PAUC0-4h and PAUC0-6h respectively.

Simulated Sensitivity Analysis: Reference Product 2–K0Fast

The same analysis was conducted for product 2 with N=19. The mean ratio values for K0Fast(Test)/K0Fast (Reference) that would result in mean PAUC(Test)/PAUC(Reference) values between 0.8 and 1.25 for PAUC 0-4h and PAUC 0-6h were determined for reference product 2.

Simulated Sensitivity Analysis (Lag, KAslow, Duration of Absorption)

The effect of an increase from 0 to 100% in lag time, KAslow, and duration of absorption for the test product on the mean of the ratios [PAUC(Test)/PAUC(Reference)] for PAUC 0-4h and PAUC 0-6h was investigated for product 1 and product 2.

Bootstrap Power Curves: Reference Product 1 and Reference Product 2

The best fit reference parameters for K0Fast were decreased or increased to give mean PAUC(Test)/mean PAUC(Reference) values between 0.8–1.25. The parameters at each PAUC ratio (i.e., as determined by K0Fast) were then bootstrapped 1000 x with replacement using SAS. For each of the 1000 (N=34 different combinations of subjects) studies the number of times the 90% confidence interval was between 80–125% of the reference was recorded and used to construct the power curve.

Power curves were constructed to report the proportion of the 1000 simulated studies that met the 80–125% BE criterion for AUCINF, area-under-the-curve to time T (AUCT), Cmax, PAUC0-4h, PAUC0-6h. Dependent on sample size, the power curve should have 100% of the simulated results meeting the BE criterion of 80%–125% of the reference when the true Test/Reference (T/R) ratio for PAUC 0-4h and PAUC0-6h are equal to 1 and only 5% meeting the criterion when the true T/R ratio for the partial area metrics is 1.25. All calculations for power used Cp_{ij}.

The procedures used for reference product 2 were the same, but the calculated changes in K0Fast required to produce mean PAUC(Test)/mean PAUC(Reference) values between 0.8–1.25 were different and product specific.

AUCINF was determined by regressing the time points near the limit-of-quantitation (loq) to obtain k30 (elimination rate constant) based upon the highest R-square value with k30 being positive, and calculated from at least 3 data points. The extrapolated area (AUCext) from the last measured concentration above loq (i.e., Cp_{ij}.loq) was calculated based upon AUCext=Cp_{ij}.loq/k30. An analysis of variance was performed using the natural logarithm (ln) of the truncated areas. The ANOVA model included only treatment and was analyzed as a parallel designed study. The ratio of geometric mean and its 90% confidence intervals (CI) were calculated using the least square means and the standard error of the estimate obtained from the ANOVA. The root mean square error (RMSE) from the ANOVA was used as the estimate of inter-subject variability.

RESULTS

Experimental Data and Model Evaluation via Bootstrapping

Best fit model parameters are presented in Table I for product 1 and product 2.

The median plasma-time concentration graphs for each of the resulting 200 bootstrapped (N=34) subject studies was compared with the median experimental plasma data for

Table I Summary of Fitted Parameters for Reference Product 1 and Reference Product 2. Values are Mean (±SD)

Parameter	Product 1	Product 2
K0fast(hr^{-1})	1.11(0.75)	3.14(2.25)
KAslow(hr^{-1})	0.40(0.26)	3.07(2.23)
CL (L/hr)	564.5(210.6)	451.8(157.8)
V (L)	1827.3(983.24)	1577(378.5)
D1 (hr)	0.91(0.28)	1.02(0.35)
LAG (hr)	2.89(0.37)	3.49(0.71)
F1	0.32(0.09)	0.53(0.07)
ε_1	0.05(0.04)	0.09(0.88)
ε_2	0.31(0.18)	0.16(0.14)

reference product 1 (N=34) from time 0 to time 24 h. The simulated curves in Fig. 3 (Product 1) on the left were similar in shape and equally distributed about the experimental median. For product 2 the results for 200 simulations (N=19) are presented in Fig. 3 (Product 2) on the right.

Simulated Sensitivity Analysis: K0Fast

Results for the relationships between the mean percent K0Fast (Test)/K0Fast(Reference) ratio and the mean PAUC(Test)/PAUC(Reference) ratio for product 1(left graph) and product 2 (right graph) are presented in Fig. 4. For product 1 the mean RATIO_04 is more responsive to changes in the mean K0Fast (Test)/K0Fast(Reference) ratio than is mean RATIO_06 which is reflected by the decrease in the mean RATIO_06 values when K0Fast(Test) becomes larger than K0Fast (Reference). Similar results are seen for product 2. However, for both products RATIO_06 was less responsive than RATIO_04 when K0Fast(Reference) is greater than K0Fast(Test).

Product 1 K0Fast is negatively correlated with duration and lag2 while KAslow shows negative and positive correlations with duration and lag2 as did product 2. On the other hand, a positive correlation existed between K0Fast, duration and lag for product 2 and negative correlations for KAslow and duration but a positive correlation for lag2 and KAslow. However, in contrast product 1 KAslow shows a much higher level of correlation to duration and lag2 than does product 2 KAslow. This clearly shows how the formulation factors influence release since product 2 is a 50:50 mixture of fast and slow beads and less formulation influenced, whereas product 1 is a 30:60 mixture of fast release outer core to extended release inner core. Product 1 correlations greater than 0.5 were observed for: additive error and K0Fast; KAslow and V3; KAslow and lag; KAslow and F; CL and additive error. Correlations for product 2 greater than 0.5 were: CL and V; F and proportional residual error (proerr).

Figure 5 presents the concentration time profiles for product 1 (top graphs) and product 2 (lower graphs). The top left graph shows the result of increasing F1 for the test product 1 by 25%, while the lower left graph gives the results for a 25% increase in F1 for test product 2. Both graphs indicate a proportional increase in the AUC when F1 test is increased.

The graphs located on the top right-product 1 and bottom right-product 2 show the concentration time profiles when the mean K0Fast(Test)/K0Fast(Reference) ratio is increased to 170%. The resulting test graph for product 1 shows an increase in Cmax 1 (i.e., the first and lower Cmax value) and an increase in Tmax and lower levels for Cmax 2 (i.e., the second and higher Cmax value). On the other hand, for product 2 Cmax 1 shows a smaller response which results in a small decrease in Cmax 2 for product 2. These results are consistent with Fig. 4 results which indicated that product 1 PAUC values were more responsive to changes in K0Fast(Test) while product 2 was far less responsive. This ultimately reflects in the observed changes in Cmax 1 for both products to changes in K0Fast(Test).

Simulated Sensitivity Analysis: KAslow, Duration of absorption

Supplementary Material Figures S1 and S2 show the impact of an increase in the test model parameters (i.e., lag time, KAslow and absorption duration) on the mean PAUC (Test)/PAUC(Reference) ratios. For product 1, Figure S1, an increase in test lag time has the greatest effect on RATIO_06 since the time for the start of the slow release in the formulation is controlled by the lag time. As test lag is increased, there is a decrease in the resulting PAUC0-6h and a decrease in the value of the mean of the ratio with the increase in test lag time. The PAUC0-6h ratio reaches a minimum when the test lag time is increased 30%. An increase in KAslow would have the greatest effect on slow release thus as the value increases the PAUC0-6h would increase. Since the larger impact would be on PAUC0-6h, the ratio for PAUC0-6h increases faster than does the ratio for PAUC0-4h.

Effects of an increase in the duration of absorption for the test would allow PAUC0-4h to have drug available for a longer period of absorption resulting in higher RATIO_04 values as seen in Figure S1 for product 1. Product 2, Figure S2, results showed a trend similar to product 1 but the magnitude of changes were quite different. An increase in the test lag time seemed to only impact the RATIO_06 values with a plateau when the test lag time was increased by 50% for product 2 Figure S2. An increase in KAslow had almost no effect on the RATIO_04 values. RATIO_06 values increased as Test KAslow increased but the rate of increase was much lower than for product 1. Increasing the duration of absorption of the test fast release component did result in larger RATIO_04 values compared to RATIO_06 values for product 2 with the absorption duration increase

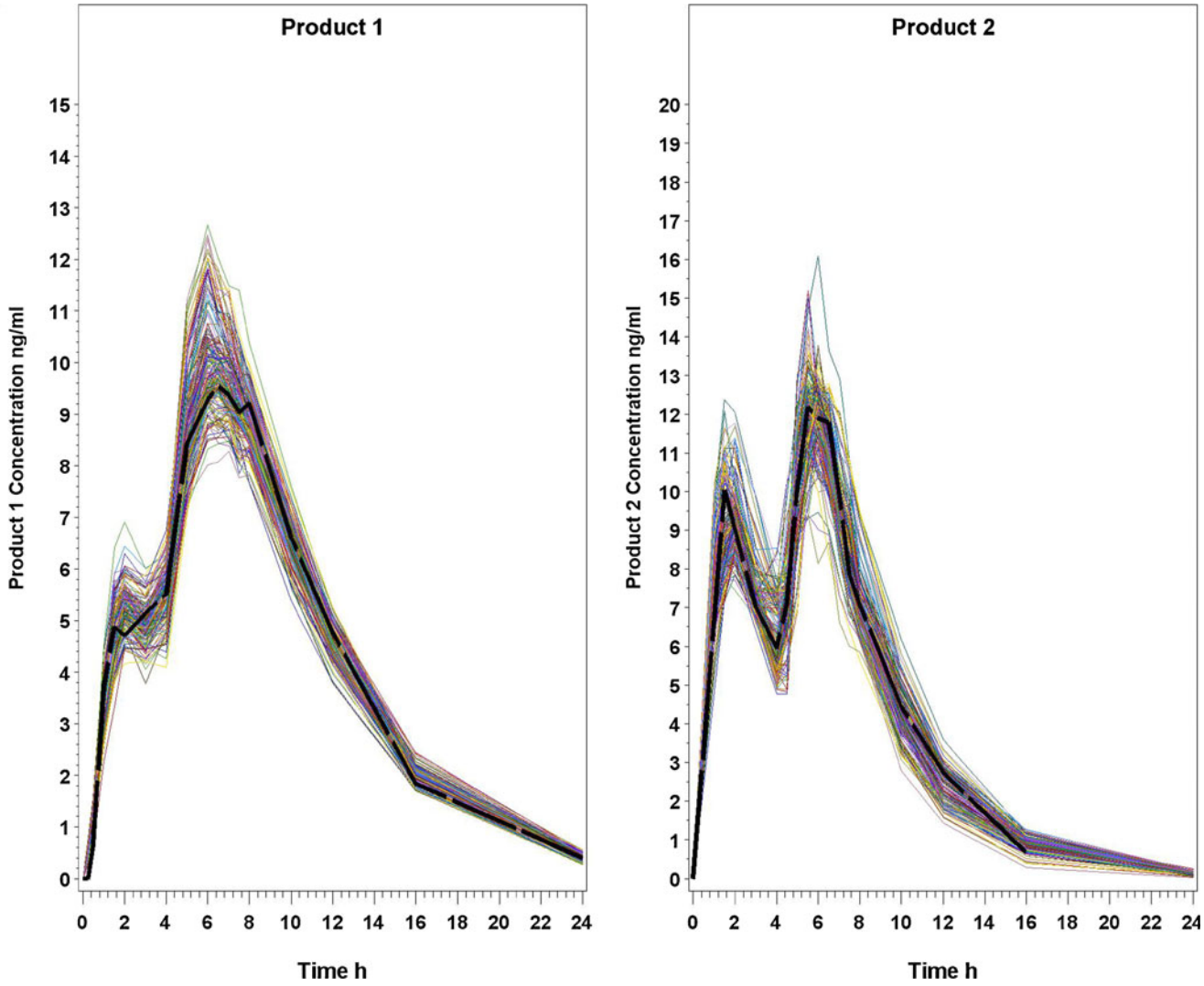

Fig. 3 Model qualification based upon the comparison of the median experimental value for product 1 and product 2 with the respective median values for $N=200$ simulations for each product. Product 1 is represented on the left while product 2 is on the right.

allowing more time for absorption of the rapid release component of the respective products.

Power Curves 1000 Bootstrapped Best Fit Data Sets

Power curves for product 1 and product 2 are shown in Fig. 6.

For product 1 (left graph) PAUC0-4h was most responsive to changes in K0Fast if the value was increased or decreased. The probability of rejecting BE was much lower for PAUC0-6h than PAUC0-4h especially as K0Fast was increased. At a ratio of 1.25, PAUC0-6h had a much higher probability of BE 87% compared to 15% for PAUC0-4h.

For product 2 the PAUC0-4h metric had a higher probability of failure than did PAUC0-6h at all K0Fast(Test)/K0Fast(Reference) ratio values for product 2. Cmax also showed a high probability of rejecting BE as K0Fast(Test) was increased. This may be related to the similarity of the peak sizes with peak 1 and peak 2 both possibly reflecting Cmax depending on parameter values. As anticipated, the probability of rejecting BE for AUCT and AUCINF was not influenced by changes in K0Fast.

The probability of being declared not to be BE was 0% for Cmax, AUCT, AUCINF, PAUC0-4h, and PAUC0-6h when the F1(Test)/F1(Reference) ratio was equal to 1.0 for both product 1 and product 2.

Variance

Results from comparison of the observed vs. simulated data is presented in Table II. Mean RMSE values for product 1 were all within 5% for Cmax, AUCT and AUCINF.

Meanwhile, for product 2 AUCT and AUCINF, mean values were within 8% while for Cmax there was a 16%

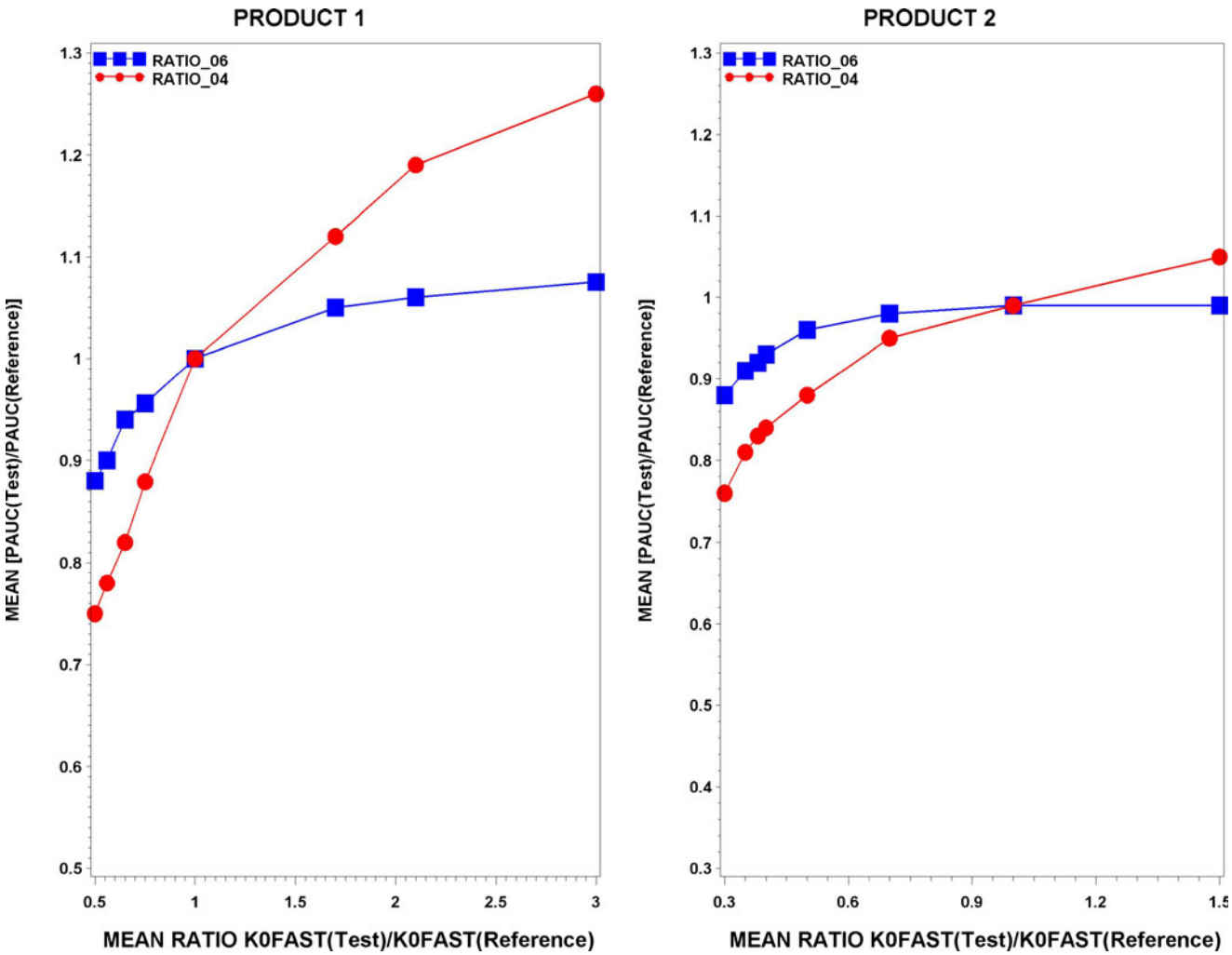

Fig. 4 Effect of mean percent change in the K0Fast(Test)/K0Fast(Reference) ratio on the mean change in the PAUC(Test)/PAUC(Reference) ratio.

difference between observed and simulated values. This may be related to the fact that peak 2 is always the highest peak for product 1 but not for product 2, Fig. 3, the peaks for product 2 are very similar in size which increases the likelihood that either peak 1 or peak 2 could be the Cmax for a given subject.

DISCUSSION

The standard metrics of AUC and Cmax have seemed to work quite well in defining BE products when curve shape is not important. However, as pointed out by a recent author (19), "it is not difficult to contrive a situation in which two different profiles yield identical AUC, Cmax or Tmax parameters. Therefore, an analysis based on any one of these pharmacokinetic parameters may result in a determination that two drug formulations are bioequivalent when they are not in fact clinically equivalent." This is because these pharmacokinetic parameters do not take the profile shape in consideration. New metrics such as the Rescigno index and Chinchilli metric attempt to take profile shape into consideration, through determiniation of the distance between curves (20–22).

PAUC was one of the original metrics proposed to evaluate early exposure, (11) especially when an early onset of clinical effect is important. Literature results indicate that the "PAUC method" may serve as an alternative technique for the assessment of relative absorption rates in BE trials (1,3). The FDA Guidance entitled "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products" has recognized that an assessment of early exposure may be appropriate for some immediate-release products where a better control of drug input rate is important for therapy (10).

This issue of early onset and clinical impact have become more prevalent and troublesome when Cmax and AUC estimates often result in no statistical difference and a declaration of BE is made in spite of the different absorption kinetics especially for modified release products (23,24).

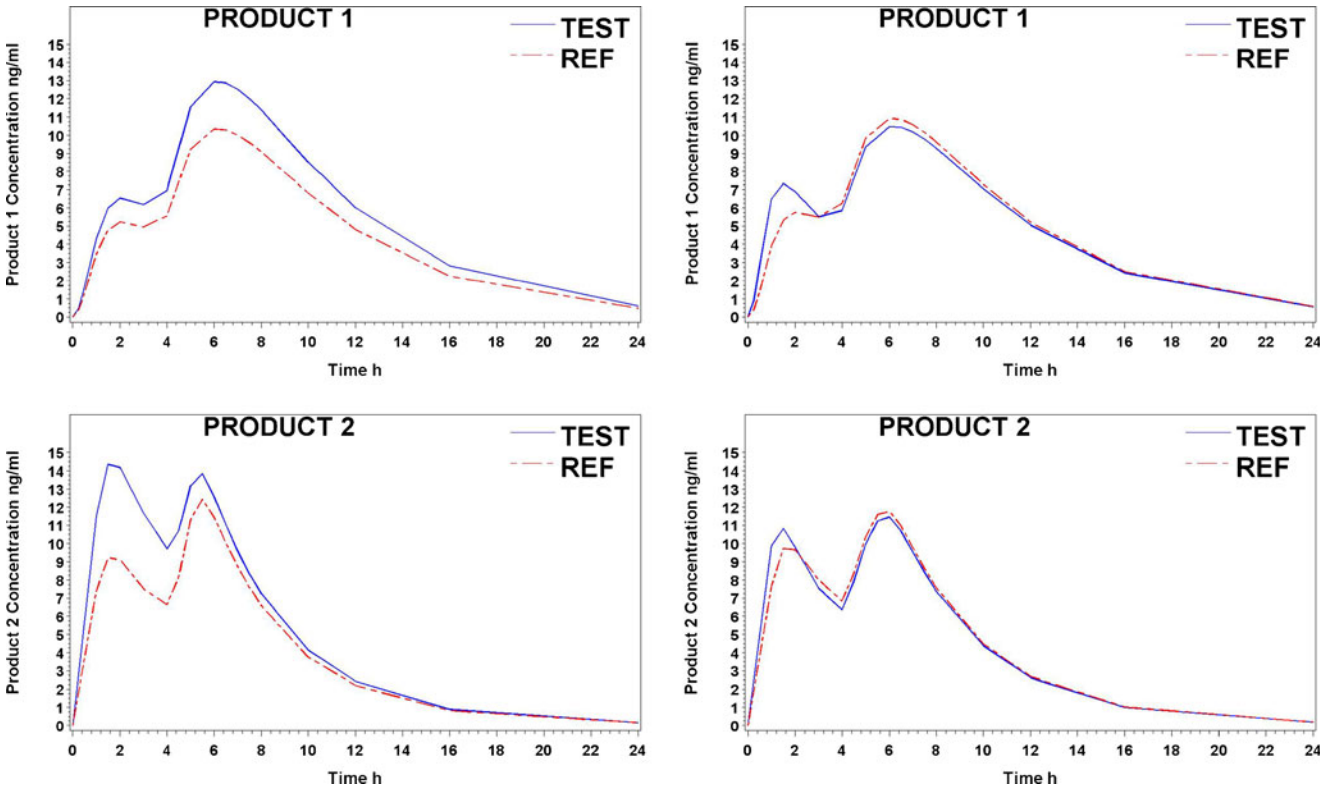

Fig. 5 Mean concentration time profiles for product 1 (top right) and product 2 (*bottom left*) when F1 of the test is increased 25%. Top right graph and bottom right graphs show the mean concentration time profiles when mean per cent change in the K0Fast(Test)/K0Fast(Reference) ratio was 170% for product 1 and product 2 respectively.

Recent publications, FDA Guidances, and a FDA workshop addressed the issues mainly related to modified release formulations which exhibit multiple components, and the ability to substitute one product for another with no concern for differences in efficacy and/or safety (i.e., interchangeability) (15,25–30). The confidence that this can be done may depend on the following two factors: (a) the sensitivity of some or all of the drug effects to acute differences in concentration and (b) the close similarity of pharmacokinetic profiles of the drug products. To determine if Tmax and/or the shape of a plasma concentration–time curve is important for assessment of interchangeability, one should address the question of what possible effect might arise as a result of such a difference in concentration. It has been suggested that other measures in addition to the current pharmacokinetic parameters (i.e., AUC and Cmax) may be needed for assuring BE. In this context, several measures have been recommended, in the literature including the use of PAUC at different times after dosing (15,24–30).

The current study based upon a pharmacokinetic model for methylphenidate in two different product formulations has determined how changes in the fast absorption rate constant, K0Fast, affect the other important model parameters which define curve shape for the two modified release products (12,13). Product 1 uses osmotic pressure to deliver methylphenidate HCl at a controlled rate with an early release of ~30% of the dose by 6 h with a small early peak. Product 2 has been formulated to contain half the dose as immediate-release beads and half as enteric-coated, delayed-release beads, thus providing an immediate-release of methylphenidate and a second delayed release of methylphenidate.

Results from this study has shown that the sensitivity of the mean PAUC(test)/PAUC(reference) ratios for PAUC0-4h and PAUC0-6h to changes in K0Fast are product dependent. Product 1 shows a greater response in the mean PAUC(test)/PAUC(reference) ratio for PAUC0-4h when the K0Fast(test) is decreased and increased. The product 1 mean PAUC(test)/PAUC(reference) ratios for PAUC0-6h is not very responsive to changes in K0Fast(test). On the other hand, product 2 mean PAUC(test)/PAUC(reference) ratios for PAUC0-4h and PAUC0-6h show little response to increases in K0Fast (test) but a greater response to decreases in the value. This is clearly reflected in the greater observed changes in curve shape for a 175% increase in test K0Fast(test) for product 1 presented in Fig. 5 compared to product 2. These results are also related to the observed differences in correlation between the model parameters for the two products.

A major problem with PAUC when applied to immediate-release formulations was cutoff point, as has

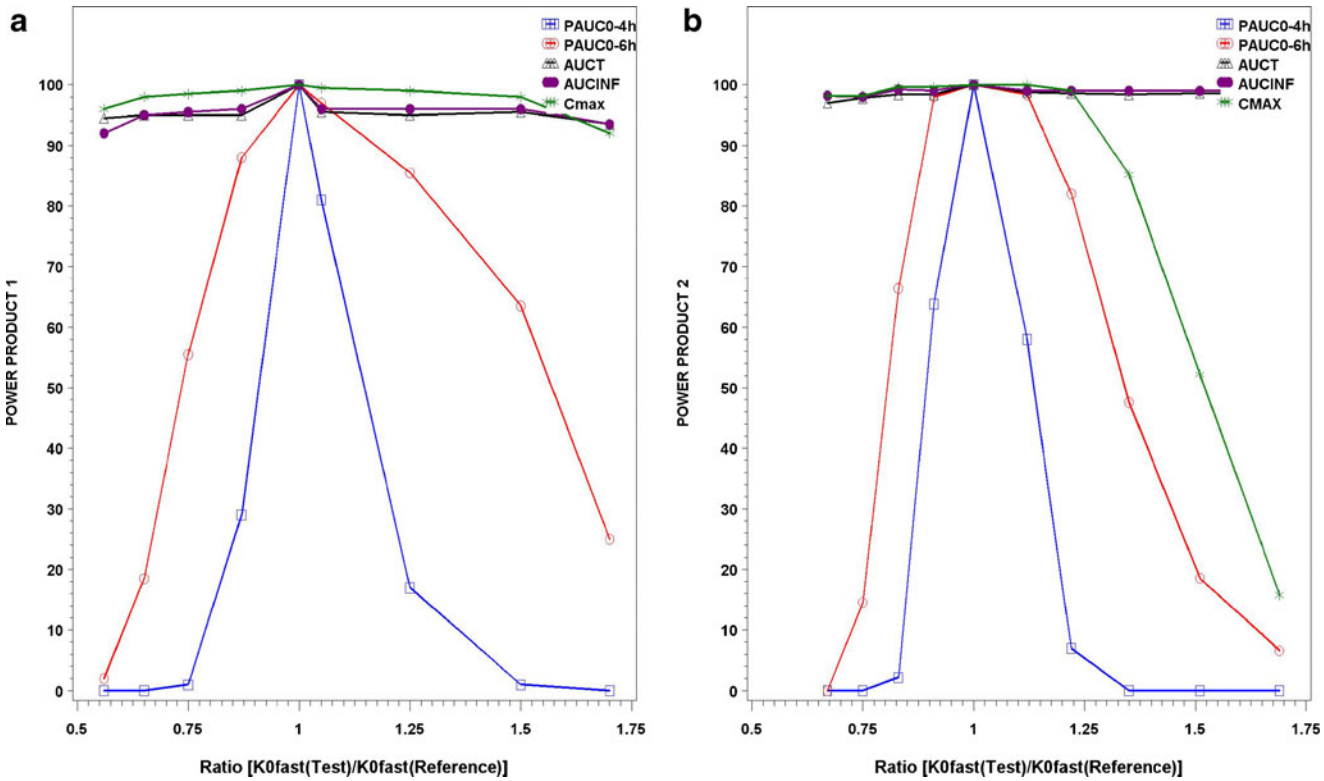

Fig. 6 Power curves showing the proportion of the 1000 simulated studies that meet the 80–125% bioequivalence criterion as a function of the mean per cent change in the K0Fast(Test)/K0Fast(Reference) ratio. Results are reported for PAUCT04h(□), PAUC0-6h (○), Cmax (*), AUCinf (●), AUC0-t (Δ). (**a**) product 1; (**b**) product 2.

been recently addressed based upon clinical implications for modified-release products. It has been suggested that for current modified-release formulations (e.g., Methylphenidate) the PAUC should be measured to Tmax+2 SD based upon onset of response (24).

Methylphenidate product 1 and product 2 have been characterized by multiple peaks which have been shown to be related to clinical effect (14). Within 1 to 2 h after oral administration of a clinical dose of methylphenidate, peak serum concentration is achieved and maximum clinical effects are manifested (i.e., decreases in the symptoms of ADHD: hyperactivity, inattention, and impulsivity). To achieve the same effect in the afternoon current products have a second release in the afternoon since the drug has a short half-life of 2 to 3 h. For methylphenidate, clearly drug effect is related to curve shape.

Table II Comparison of Observed and Simulated RMSE Values (i.e., as a Measure of Intersubject Variability) for Analysis as a Parallel Designed Study. Simulated Values are the Mean of 1000 Simulations

Parameter	Product 1		Product 2	
	Observed	Simulated	Observed	Simulated
Cmax	43%	39%	45%	29%
AUCT	46%	41%	32%	31%
AUCINF	46%	41%	39%	31%

Results of the current study indicate that metric sensitivity and correlation are very product specific, which means that a new PAUC may be needed for each drug and also for different conditions i.e., fasting, fed, sprinkle formulation etc.

The current work establishes the lack of uniform performance of PAUC across products and results in a different performance of PAUC for each product as shown by the power for PAUC0-4h and PAUC0-6h. An additional problem occurs when the products are equivalent early, and they are also found to be equivalent overall (i.e., AUCINF, 84–97%, and AUCT, 83–96%) since this would lead one to conclude that they must be equivalent late. This is not always a reliable conclusion (e.g., Figure S3). For this drug PAUC0-3h was 101–121% but when the PAUC3-24h is estimated its value was 75–88%. This finding would require estimation of an additional late metric, PAUC3-24h. A better suited metric would be one that would perform the same for all profiles. This may be a role for a direct curve approach which uses the entire profile and ideally would work the same for all generics as do the current Cmax and AUC whenever curve shape is a factor.

Several measures that assess curve shape have been described in the literature, such as the Kullback-Leibler information criterion, Chinchilli index, Rescigno Index, etc. (20–23). However,

they have not been systematically studied for statistical performance. Several authors have suggested that direct curve metrics may better detect curve shifts and also better detect differences in the case of multiple peaks, the topic of the current investigation, or flat profiles. This will require a systematic investigation of these proposed metrics. Until that is done PAUC is "useful" if the limitations are understood. This approach would appear to have utility although it does require multiple PAUC values to be calculated for each drug (15). One should realize that the utility of PAUC depends on the product's clinical pharmacology. For a drug with a quick onset it is quite useful, which would not be the case for a drug whose chronic effects are more important such as for antidepressants that require several days or weeks of dosing to achieve their effects.

ACKNOWLEDGMENTS AND DISCLOSURES

The authors thank the Office of Clinical Pharmacology Division 1 especially Mehul Mehta and Ramana Uppoor for their valuable discussions related to this manuscript.

The views expressed in this manuscript are those of the authors and do not reflect the official policy of the FDA. No official support or endorsement by the FDA is intended or should be inferred.

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