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RESEARCH PAPER

Impact of Release Mechanism on the Pharmacokinetic Performance of PAUC Metrics for Three Methylphenidate Products with Complex Absorption

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ABSTRACT

Purpose Investigate the performance of partial area under the drug concentration-time curve (PAUC) metrics (0–3 h) and (3–24 h), for Concerta, Ritalin LA and Focalin XR (different Methylphenidate modified-release formulations). The metrics have been chosen as additional BE metrics for Ritalin LA by the FDA to establish BE for these products due to the early and late peak concentrations critical for treatment of morning and afternoon symptoms of attention deficit hyperactivity disorder (ADHD).

Methods Two-stage analysis was performed on plasma data for the methylphenidate modified-release products. Simulations using the fitted parameters determined how changes in fast absorption rate constant k0fast, and slow absorption rate constant KAslow affected curve shape and BE determination using Cmax, AUCINF and PAUC.

Results Sensitivity of the mean PAUC(test)/PAUC(reference) ratios to changes in k0fast and Kaslow were product dependent. Focalin XR mean PAUC(test)/PAUC(reference) ratios for PAUC0–3 h and PAUC3–24 h were most responsive to changes in k0Fast and Kaslow than Concerta and Ritalin LA. The PAUC(test)/PAUC(reference) ratios for (0–3 h) were not responsive to changes to Kaslow. Concerta PAUC (3–24 h) ratios were responsive to changes in Kaslow at ratios less than 1.

Conclusions Response to PAUC(0–3 h) in the formulations was greater for k0fast than was PAUC(3–24) to changes in KAslow.

KEY WORDS bioequivalence · curve shape · methylphenidate · partial AUC

ABBREVIATIONS

1-F1	relative bioavailability fraction of the administered, dose for the extended release compartment 2
ADHD	attention deficit hyperactive disorder
AUC_{ext}	extrapolated area
AUC_{inf}	area-under-the-curve to time infinity
AUC_T	area-under-the-curve to time T
AUC_{T-t}	area-under-the-curve from time T to time t with T defined as 3 h and t being 24 h
BE	bioequivalence
CI	confidence intervals
CL	clearance
D1	is duration of zero order absorption from the fast release compartment 1
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, describes the absorption of drug from the extended release compartment 2
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 extended release
PAUC	partial area under the curve

INTRODUCTION

A recent draft guidance discussing the bioequivalence (BE) requirements for methylphenidate hydrochloride, specifically Ritalin LA, was issued by the Office of Generic Drugs at

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the FDA to establish the metrics required to assess the BE for this drug (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281454.pdf). The unique nature of this guidance is that this drug and other currently marketed extended-release methylphenidate products are multi-phasic extended-release formulations. They were designed to release a bolus of methylphenidate followed by a slower drug delivery during the day. This creates a unique issue for BE since both peaks have been shown to be related to drug efficacy. Work by Swanson and colleagues has established that the early morning peak is needed to control morning hyperactivity while the later peak is required to control afternoon hyperactivity (1) during the school day. After school the ideal scenario is for plasma levels to decrease after 12 h so that there will be minimal stimulation. This is necessary since evening levels of methylphenidate have been shown to be associated with insomnia (2). The spirit of the current guidance addresses both the efficacy and safety issues by requiring that in addition to measuring AUC_{inf} and Cmax, that $AUC_{0\text{-}T}$ and $AUC_{T\text{-}t}$, defined as area-under-the-curve for time 0 to T and area-under-the-curve from time T to time t with T defined as 3 h and t being 24 h. Twenty-four hours defines the normal clinical response period. Functionally these two PAUC replace the traditional $AUC_{0\text{-}t}$. The intent is that during the course of the day, generic products will be therapeutically equivalent to the brand-name drug if both PAUC values match.

It is of pharmacokinetic interest to determine how do these metrics respond to the pharmacokinetic model parameters especially if one has a product that is non-BE to determine what is the likely reason. This is not straightforward as in the case of an immediate-release formulation since it has been shown that the model parameters are correlated (3). This information may help to better describe metric performance for this specific product and in general other extended-release methylphenidate formulations such as Concerta and Focalin XR.

The focus of this paper is to investigate the comparative performance of the proposed PAUC(0–3 h) and PAUC(3–24 h) metrics and their relationship to the determination of BE as additional metrics to AUC_{inf} and Cmax. Specifically, their performance was compared for the extended-release methylphenidate products Focalin XR, Concerta and Ritalin LA. Concerta which uses osmotic pressure as the mechanism of release has a distinctly different release mechanism than Focalin XR and Ritalin LA.

Focalin XR is an extended-release formulation of dexmethylphenidate with a bi-modal release profile. Focalin XR uses the proprietary SODAS (Spheroidal Oral Drug Absorption System) technology. Each bead-filled Focalin XR capsule contains half the dose as immediate-release beads and half as enteric-coated, delayed-release beads, thus providing an immediate release of dexmethylphenidate and a second delayed release of dexmethylphenidate (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021802s024lbl.pdf). Concerta® uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The tri-layer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components (http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021121s026s027lbl.pdf). Ritalin LA also exhibits a bimodal release profile with each bead-filled capsule containing 50% immediate-release beads and 50% enteric coated delayed-release beads (http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021284s018lbl.pdf).

MATERIALS AND METHODS

Experimental study data for reference products 1, 2 and 3 were submitted to the FDA. Studies were designed as single-dose, open-label, randomized, two-period crossover studies conducted under fasted conditions. The dose for Concerta was 54 mg ($N=34$) and for Ritalin LA dose was 40 mg ($N=19$), while for Focalin XR ($N=31$) the dose was 40 mg. Sampling times for all 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 24 h. Methylphenidate was assayed by a validated high performance liquid chromatography mass spectroscopy assay in all studies with a limit of quantitation of 0.25 ng/ml.

Model and Parameter Estimation

The structural model for the methylphenidate reference products is described by two parallel inputs. The first input is for the fast-release component which mimics the products immediate-release drug component which is fast dissolving and represented in the model with a rapid zero-order (k0fast) input into plasma. This is followed by the second input which is for the slow first order release of drug (KAslow). This may be due to water permeation into the product's core and extended drug delivery/release through a membrane as for Concerta or the release of enteric coated beads as for Focalin and Ritalin LA. The structural model, Fig. 1, for these methylphenidate products has been described in detail in a previous publication (3). The standard two-stage analysis (STS) methodology employed for estimation has also been described in that reference.

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.

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

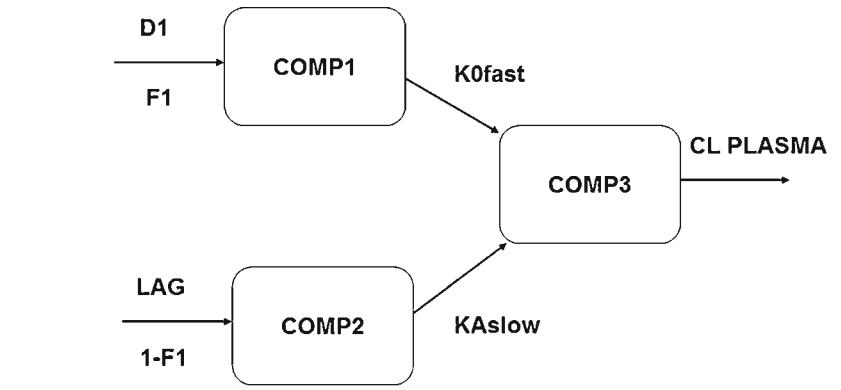

Fig. 1 Structural model for methylphenidate.

D1-duration of zero-order absorption from the fast release compartment 1
F1-relative bioavailability fraction of the administered dose for the fast release compartment 1
1-F1- process which was lagged to accommodate the duration of absorption for the fast release relative bioavailability fraction of the administered dose
Lag-time for absorption delay for slow release
k0fast-a zero-order absorption rate constant
KAslow -first-order absorption process
CL - clearance from plasma

Cpij 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 dependent on 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 σ_1^2 while for ε_{ij2} the variance is σ_2^2.

Model Qualification

The model qualification for Concerta previously referred to as reference product 1and Ritalin LA prior reference as product 2 has been presented in a prior publication (3). Model qualification for Focalin XR was done using a visual predictive check (4). Model generated simulated plasma data was compared to the original experimental data. The visual inspection allowed shape to be the most important aspect of the analysis. Cpij 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 31 subject dataset ($N=31$) were randomly re-sampled (*i.e.*, bootstrapped using SAS, version 9.1) with replacement. This produced 200 parameter data sets of the same size ($N=31$) with a different combination of subjects. The concentration profiles were simulated in NONMEM based on the 200 ($N=31$) bootstrapped PK parameters. Evaluation was done by calculating the 95th, 5th, and median for the observed data ($N=31$). The 95th, 5th and median 90% confidence intervals (CI) were calculated based on the 200 simulated ($N=31$) studies and were superimposed on the observed data.

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.

Sensitivity of PAUC(0–3 h) and PAUC(3–24 h) to k0fast

Each individual k0fastTest value was increased or decreased to give individual k0fast(Test)/k0fast(Reference) ratios between 0.5 and 2.5 for Concerta, Ritalin LA, and Focalin XR. These individual values were then used to simulate plasma curves from which mean values for PAUC(0–3 h)(Test)/PAUC(0–3 h)(Reference) and PAUC(3–24 h)(Test)/PAUC(3–24 h)(Reference) were estimated. The range of the individual k0fast(Test)/k0fast(Reference) ratios was changed until the mean range of PAUC(0–3 h)(Test)/PAUC(0–3 h)(Reference) ratios was between 0.5 and 2.5.

Sensitivity of PAUC(0–3 h) and PAUC(3–24 h) to KAslow

The same procedure was used for kaslow to obtain PAUC(0–3 h)(Test)/PAUC(0–3 h)(Reference) ratios and PAUC(3–24 h)(Test)/PAUC(3–24 h)(Reference) ratios between 0.5 and 2.5.

Power

The best fit reference parameters for k0fast were decreased or increased to give mean PAUC(Test)/mean PAUC(Reference) values between 0.5 and 1.25. The parameters at each PAUC

ratio (*i.e.*, as determined by k0fast) were then bootstrapped 1000 × with replacement using SAS. For each of the 1000 (Concerta for 34 different combinations of subjects; Ritalin LA-19 different combination of subjects; Focalin- 31 different combination of subjects) studies the number of times the 90% confidence interval was between 80% and 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 AUC_{inf}, area-under-the-curve to time T(AUC_T), Cmax, PAUC(0–3 h), and PAUC(3–24 h). 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(0–3 h) and PAUC(3–24 h) 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 Cpij. The procedures used for reference product 2 and 3 were the same, but the calculated changes in k0fast required to produce mean PAUC(Test)/mean PAUC(Reference) values between 0.8 and 1.25 were different and product specific. AUC_{inf} 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 (AUC_{ext}) from the last measured concentration above loq (*i.e.*, Cpij.loq) was calculated based upon AUC_{ext}=Cpij.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

Model Parameters and Qualification

Model parameters for Focalin XR, Concerta and Ritalin LA are presented in Table I (3). Ritalin LA and Focalin which have similar mechanisms of release have almost identical ratios for k0fast(Reference)/k0slow(Reference), Focalin (1.04), and Ritalin LA (1.02). Although the Ritalin parameter values are larger the ratios are almost identical.

The 95th, 5th and median 90% CI based on the 200 bootstrapped (N=31) studies were compared with the 95th, 5th, and median percentiles for experimental plasma data for Focalin XR. The percentiles for the observed data were within their corresponding 90% CIs for most points, Fig. 2.

Table I Fitted Parameters for Focalin XR, Concerta[a] and Ritalin LA[a]

Parameter	Focalin XR	Concerta	Ritalin LA
K0fast(hr-1)	1.27(1.00))	1.11(0.75)	3.14(2.25)
KAslow(hr-1)	1.20(1.21)	0.40(0.26)	3.07(2.23)
CL(L/hr)	190.64(61.37))	564.5(210.6)	451.8(157.8)
V(L)	526.90(403.17))	1827.3(983.24)	1577(378.5)
D1 (hr)	0.94(0.39)	0.9(0.28)	1.02(0.35)
LAG (hr)	3.41(1.70)68)	2.89(0.37)	3.49(0.7)
F1	0.47(0.18))	0.32(0.09)	0.53(0.07)
e_1	0.08(0.11)	0.05(0.04)	0.09(0.88)
e_2	1.27(1.24)	0.31(0.18)	0.16(0.14)

[a] Values from previous publication (3)

Values are Mean(±SD)

Simulated Sensitivity of PAUC to k0fast

Figure 3 left panel shows the effect of changes in k0fast(Test) values on the PAUC(0–3 h)(Test)/PAUC(0–3 h)(Reference) ratio and on the PAUC(3–24 h)(Test)/AUC(3–24 h) (Reference) ratio for Concerta, Focalin XR and Ritalin LA. The mean PAUC(0–3 h)(Test)/PAUC(0–3 h)(Reference) ratio for Concerta and Focalin XR increases as the mean ratio k0fast (Test)/k0fast (Reference) increases between 0.5 and 2.5 to a value of near 1.3 for Focalin XR and 1.25 for Concerta. Although Ritalin LA exhibits a similar increase in PAUC(0–3 h)(Test)/PAUC(0–3 h) (Reference) ratio as the mean ratio k0fast (Test)/k0fast (Reference) increases between 0.5 and 1;

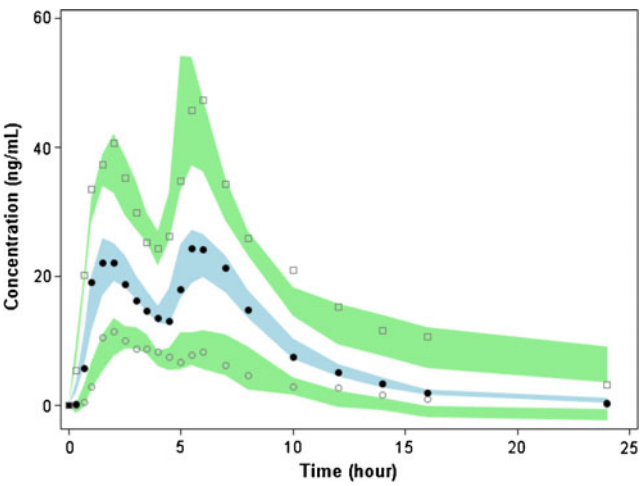

Fig. 2 Focalin model qualification plot based on 200 simulations (N=31 per simulation). The *upper light green bands* represents the 90% CI for the 95th Percentiles based on simulated data (*squares* are the observed 95th percentiles) while the *lower light green bands* are the 90% CI for the 5th Percentiles based on simulated data (*circles* are the observed 5th percentiles). The *light blue bands* are the 90% CI of the mean based on simulated data while the *black circles* are the observed median at each time point.

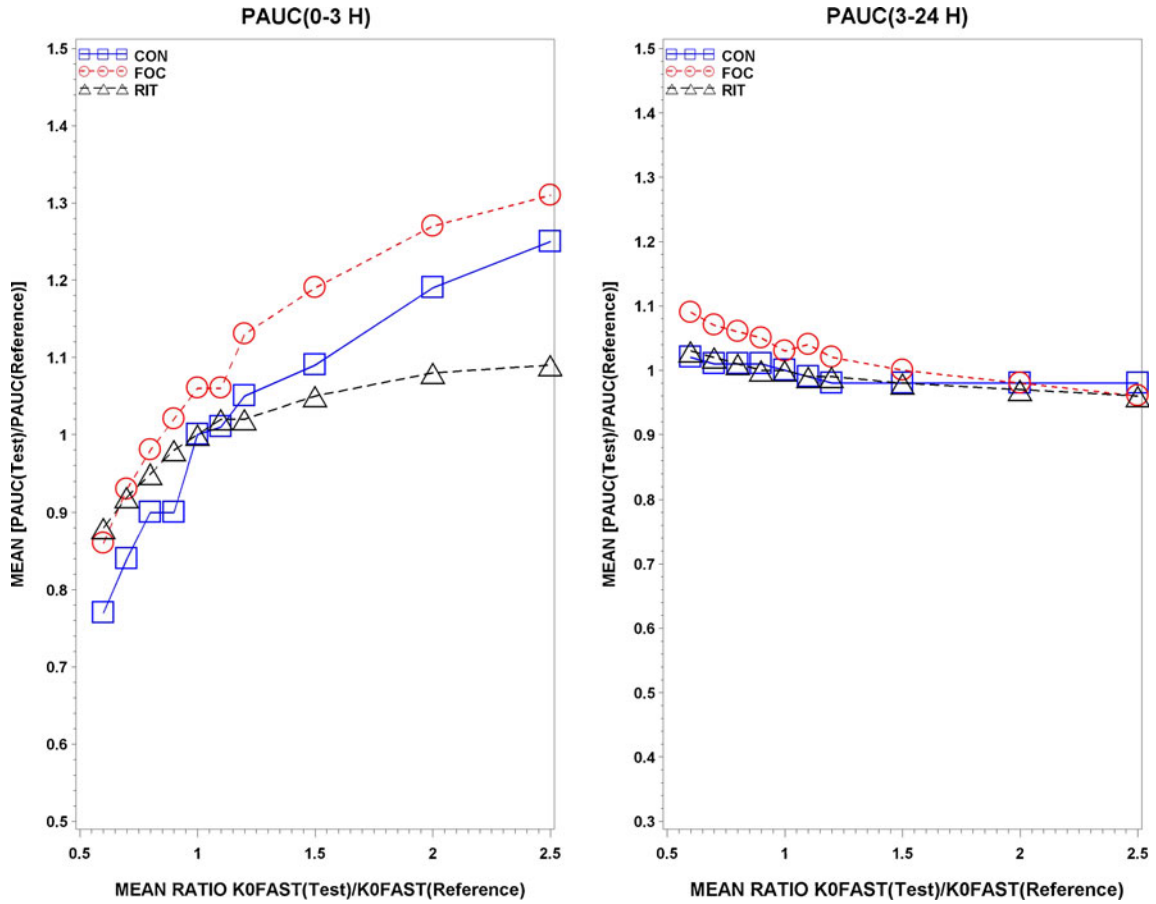

Fig. 3 Effect of mean percent change in the K0Fast(Test)/K0Fast(Reference) ratio on the mean change in the PAUC(Test)/PAUC(Reference) ratios for PAUC(0–3 h) and PAUC(3–24 h).

however, after the value of 1 the mean PAUC(0–3 h)(Test)/PAUC(0–3 h) (Reference) ratio becomes a constant at 1.05.

The impact of changes in the k0fast (Test)/k0fast (Reference) ratio (right panel) on the mean PAUC(3–24 h)(Test)/PAUC(3–24 h)(Reference) ratio for Concerta, Focalin XR and Ritalin LA are only seen for ratios less than 1 and mainly for Focalin XR. The PAUC(3–24 h)(Test)/PAUC(3–24 h)(Reference) ratio for Focalin XR decreases from 1.1 to 1 at the ratio of 1.5 for k0fast (Test)/k0fast (Reference) . After the k0fast (Test)/k0fast (Reference) ratio exceeds 1 the PAUC(3–24 h)(Test)/PAUC(3–24 h)(Reference) ratio equals 1 for all three products.

Simulated Sensitivity of PAUC to KAslow

Figure 4 shows the effect of changes in the mean KAslow (Test)/KAslow (Reference) ratio on the PAUC(0–3 h)(Test)/PAUC(0–3 h) (Reference) ratio left panel and on the PAUC(3–24 h)(Test)/PAUC(3–24 h) (Reference) ratio right panel. Changes in KAslow(Test)/KAslow (Reference) ratio had no effect on the PAUC values for PAUC 0–3 h. However, when the KAslow(Test)/KAslow (Reference) ratio was increased from 0.5 to 1.1 there was an increase in the PAUC(3–24 h)(Test)/PAUC(3–24 h)(Reference) ratios for Concerta. Focalin XR and Ritalin LA PAUC(3–24 h)(Test)/PAUC(3–24 h)(Reference) ratios were constant at 1.0 for all K0slow (Test)/K0slow (Reference) ratio investigated between 0.5 and 2.5.

Bootstrapped Power Curves from Best Fit Data

The power curves for the effect of changes in the k0fast (Test)/k0fast (Reference) on the power for Concerta, Ritalin LA and Focalin XR are presented in Fig. 5. For Concerta, PAUC(0–3 h) was most responsive to changes in k0fast while PAUC(3–24 h) was less responsive as indicated by the probability of rejecting BE never going below 80% for all k0fast (Test)/k0fast (Reference) ratios investigated. Focalin XR also exhibited a similar pattern except that PAUC(3–24 h) was even less responsive and had a 0% probability of rejecting BE. On the other hand, Ritalin LA showed a response for both PAUC(0–3 h) and PAUC(3–24 h) to changes in the k0fast (Test)/k0fast (Reference) ratios. PAUC(0–3 h) had a probability of rejecting BE of greater than 95% at k0fast (Test)/

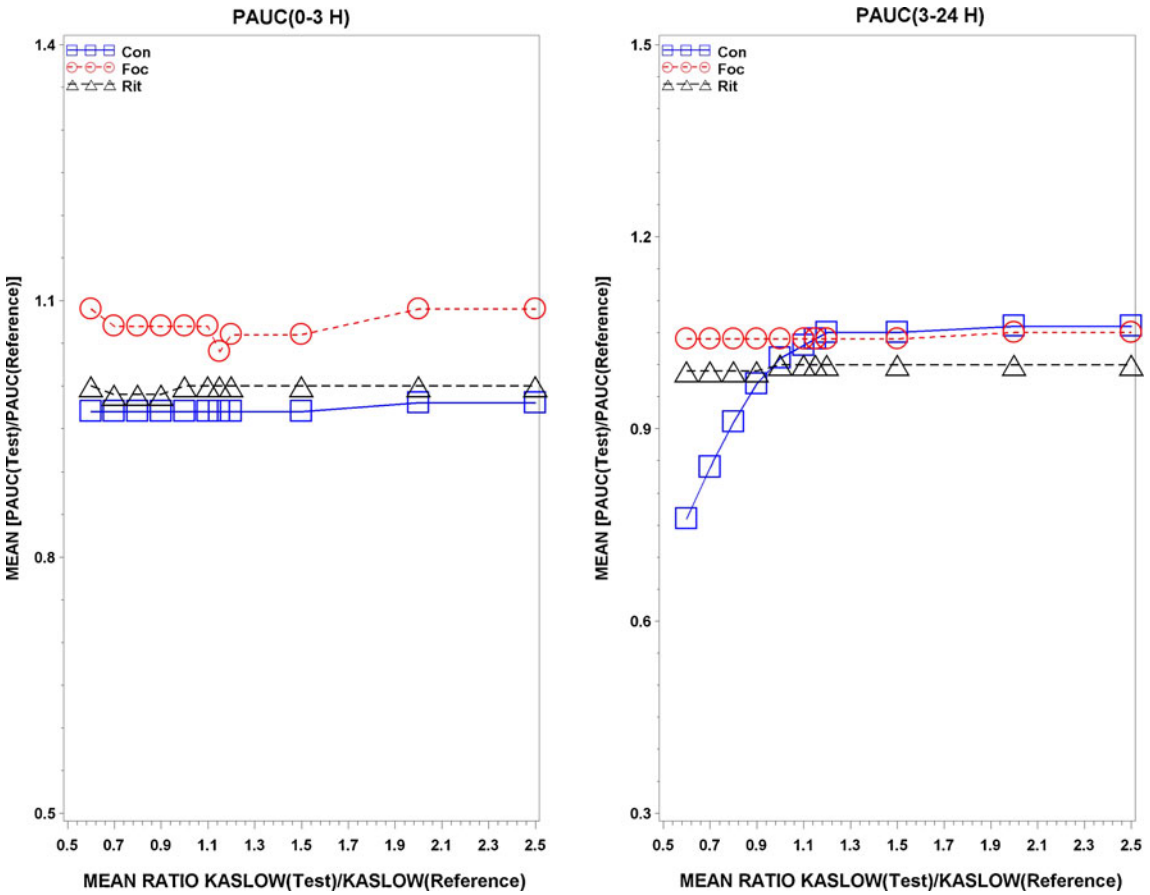

Fig. 4 Effect of mean percent change in the KAslow(Test)/KAslow(Reference) ratio on the mean change in the PAUC(Test)/PAUC(Reference) ratios for PAUC(0–3 h) and PAUC(3–24 h).

k0fast (Reference) ratios of 0.8 and 1.25. For PAUC(3–24 h) the probability of rejecting BE was approximately 40% at these same k0fast (Test)/k0fast (Reference) ratios for Ritalin LA.

The main effect of KAslow was seen on Concerta for PAUC(3–24 h) KAslow(Test)/KAslow(Reference) ratios less than 1.0. There was no effect on Focalin XR or Ritalin LA. This minimal effect of KAslow on PAUC is to be expected since ka values have less influence on area-under-the curve as time increases.

Power curves for the impact of changes in the KAslow(Test)/KAslow(Reference) ratios on the probability of being declared BE for Concerta, Ritalin LA and Focalin XR are presented in Fig. 6. For Concerta, when KA slow(Test)/KAslow(Reference) ratios were between 0.5 and 0.8 all BE measures had less than an 80% probability of being BE with the greatest impact on Cmax and PAUC(0–3 h). The probability of rejecting BE increased for Cmax and PAUC(0–3 h) as KAslow(Test)/KAslow(Reference) ratio increased beyond 1. For Ritalin LA only the power for PAUC (3–24 h) was impacted by changes in the KAslow(Test)/KAslow(Reference) ratio. For Focalin XR only PAUC(0–3 h) was responsive to changes in the KAslow(Test)/KAslow (Reference) ratio with the probability of rejection being approximately 95% at 0.8 and 80% at 1.25.

DISCUSSION

The additional comments section of the recent guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281454.pdf) on methylphenidate products recommends the following metrics for Ritalin LA, "reference product. Thus, for Ritalin LA® the following two PAUC metrics are proposed in addition to the traditional (AUC_{inf} and Cmax) metrics:

- $AUC_{0\text{-}T}$ should compare test & reference systemic exposure responsible for early onset of response during the early part of the once-daily dosing interval; and
- $AUC_{T\text{-}t}$ should compare test & reference systemic exposure responsible for sustaining the response later during the once-daily dosing interval."

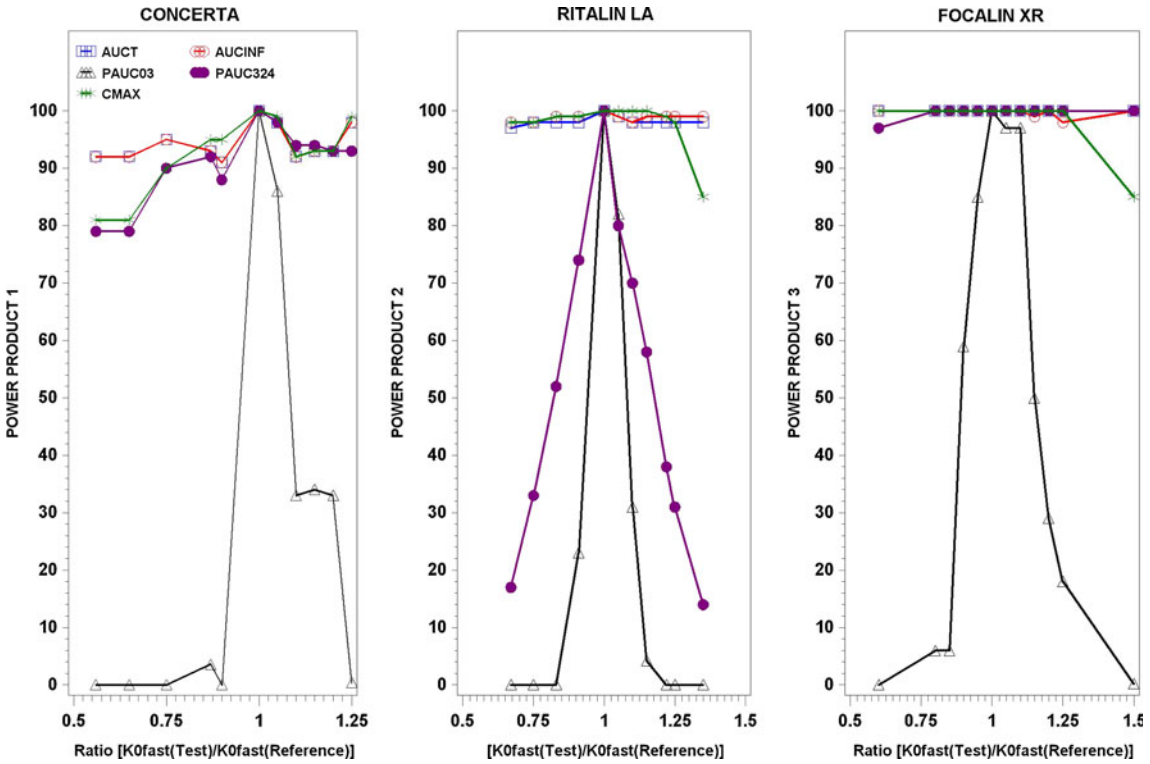

Fig. 5 Power curves showing the proportion of the 1000 simulated studies that meet the 80–125% bioequivalence criterion as a function of the mean per cent change in the K0Fast(Test)/K0Fast(Reference) ratio. Results are reported for PAUC(03 h) (Δ), PAUC(324 h) (●), Cmax (*), AUCinf (○), AUC0-t (□) for Concerta, Ritalin LA and Focalin XR.

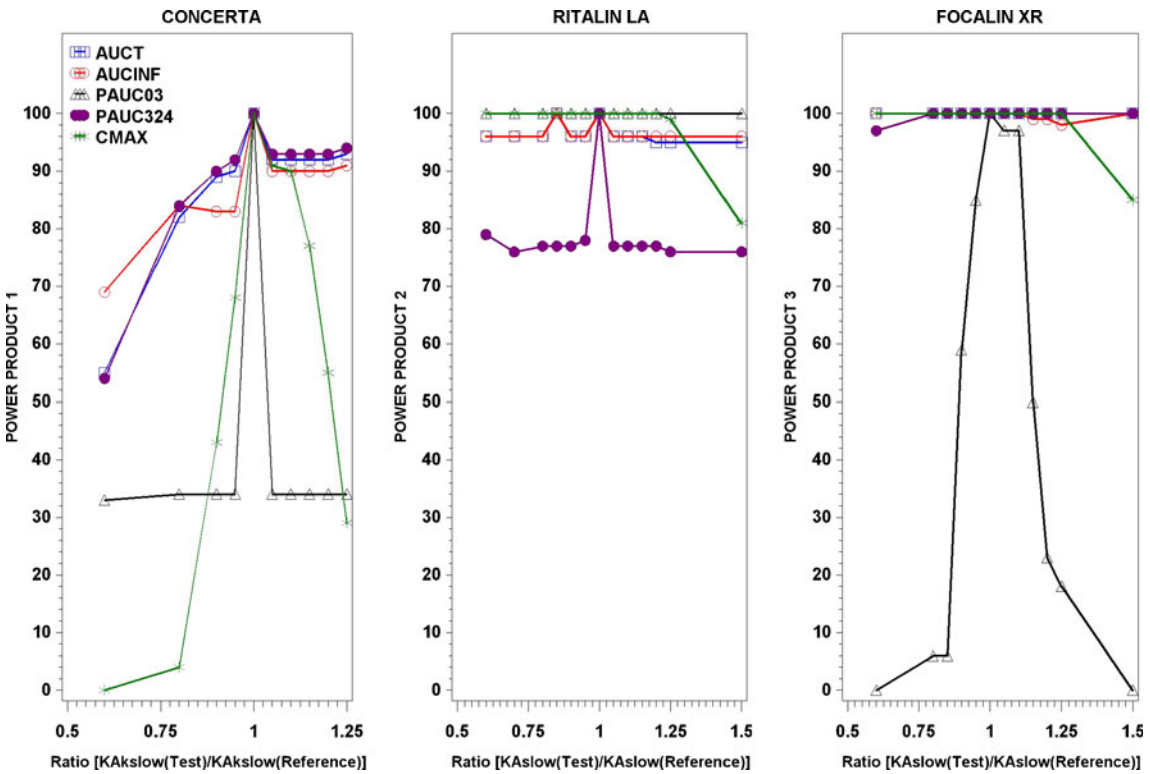

Fig. 6 Power curves showing the proportion of the 1000 simulated studies that meet the 80–125% bioequivalence criterion as a function of the mean per cent change in the KAslow(Test)/KAslow(Reference) ratio. Results are reported for PAUCT(03 h) (Δ), PAUC(324 h) (●), Cmax (*), AUCinf (○), AUC0-t (□) for Concerta, Ritalin LA and Focalin XR.

The aim is to have more effective metrics for determining BE for this complex dosage form which has slow and fast release components. A follow-up publication (5) described how the PK data from the IR MPH formulation was used in an attempt to have an unbiased estimate of the Tmax of the IR component of the MER (mixed extended release) formulation which occurred at ~2 h. which is also the time at which the peak PD effect of the early portion of Ritalin LA® is observed (6). Based upon this result and the fact that 95% of observations fall within two standard deviations of the mean, PAUC (0–3 h) was determined to be best for fasting studies while PAUC(0–4 h) was chosen for fed studies. However, this empirical approach in the guidance was not supported by any experimental data. The current work looked in detail at the pharmacokinetic performance of the PAUC(0–3 h) and PAUC(3–24 h) metrics for Concerta, Focalin XR and Ritalin LA. The performance of the PAUC(0–4 h) metric was investigated in a prior publication (3).

The results from the previous and current work shows that these PAUC metrics are product dependent. The PAUC metrics have product related performance as evidenced by the sensitivity results from the current study. PAUC(0–3 h) is far more responsive to changes in k0fast than to changes in KAslow for all 3 formulations. Alternatively, PAUC(3–24 h) does not respond to changes in KAslow for all 3 compounds except for Concerta at KAslow(test)/KAslow(reference) ratios less than 1 Table II. This is due to the fact that the absorption controlled by k0fast is not lagged and thus effects the earlier portion of the absorption time curve. Kaslow is lagged for Focalin XR by 3.49 h and would have minimal impact on partial areas less than 3 h, Fig. 4. Changes in k0fast have a much greater effect on the Oros and SODAS technology for Concerta and Focalin XR respectively, than on the slow and fast beads formulation for Ritalin LA. For Ritalin LA the k0fast(Test)/k0fast(Reference) ratio has no effect on PAUC(0–3 h) as the ratio increased beyond 1.

Table II Sensitivity Comparison of the PAUC Metrics for Concerta, Focalin and Ritalin LA

Metric	Concerta	Focalin	Ritalin LA
	Drug Parameter K0Fast		
PAUC(0–3 h)	+++	++++	+
PAUC(3–24 h)	+	0	0
	Drug Parameter KAslow		
PAUC(0–3 h)	+	0	0
PAUC(3–24 h)	+	0	0

Power was also very different for each product with Ritalin LA showing the highest probability of rejecting BE for PAUC(0–3 h) and PAUC(3–24 h) compared to Concerta and Focalin XR as the k0fast(Test)/k0fast(reference) ratio was changed. Changes in the ratio k0fast(Test)/k0fast(reference) had more effect on Ritalin LA for both PAUC(0–3 h) and PAUC(3–24 h) than for Concerta or Focalin XR. This would indicate that the metric seems to have a higher probability of declaring this product not to be BE compared to Focalin XR and Concerta. Some of these observations are due to the observed correlations between the parameters for the formulations. The Oros and SODAS technologies had a much higher correlation between k0fast, KAslow and F by at least a 2 fold margin compared to the beaded Ritalin LA product which makes F a more important component of curve shape and BE for Concerta and Focalin XR. On the other hand, Ritalin LA had a much higher correlation between k0fast and Kaslow than did Concerta and Focalin XR which explains why changes in k0fast impacts the power for PAUC(3–24 h), Fig. 5 and not for the other formulations. In contrast Fig. 6 shows the effect of the more than the 2 fold larger correlation between Kaslow and F1 for Concerta and Focalin XR having an impact on PAUC(0–3 h).

The lack of sensitivity of the second peak to Kaslow is not an issue since in addition to Kaslow, F2 plays an important role. This is related to the fact that oftentimes generic formulations may have only one peak. Therefore if the first peak is present the product could be declared to be BE even if the second peak is absent. The impact of F2 and KAslow in defining the second peak would preclude the approval of these formulations. On the other hand, a formulation that was BE late and had only the second peak and not the first could have previously been declared to be BE, based only on the second peak. However the use of an early PAUC value (*e.g.*, PAUC(0–3 h) prevents this from occurring.

These PAUC metrics deal directly with the problem of when the test products are equivalent early, and then, based on this, might be found equivalent overall, since early equivalence might lead one to conclude that the products must also be equivalent late. Therefore, based on this study, and the issues of the product specificity and lack of sensitivity of the metrics, PAUC(0–3 h) and PAUC(3–24 h) at all k0fast(test/reference) and Kaslow(test/reference) ratios, both have favorable pharmacokinetic and statistical properties for determining Ritalin LA BE.

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The views expressed in this manuscript are those of the author and do not reflect the official policy of the FDA. No official

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