

May 14, 2004

*2004P-0139*

James N. Czaban  
Shareholder  
JCzaban@hewm.com  
(202) 912-2720 (ph.)  
(202) 912-2020 (fax)

Division of Dockets Management  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061, HFA-305  
Rockville, MD 20857

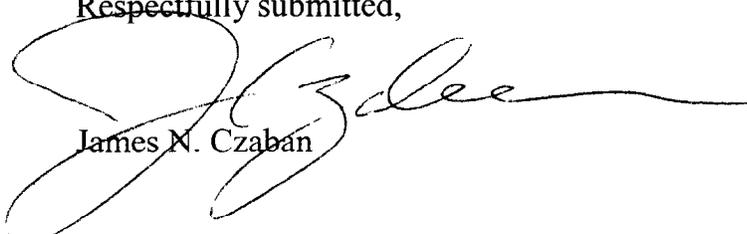
**Re: Docket No. 2004P-0139 -- Response to Citizen Petition**

Dear Sir or Madam:

On behalf of a client, we are herewith submitting comments to the March 19, 2004 Citizen Petition filed by McNeil Consumer & Specialty Pharmaceuticals (McNeil) in which McNeil requests that FDA apply additional bioequivalence metrics, other than the average bioequivalence parameters, as a condition for approval of generic versions of CONCERTA® (methylphenidate HC1) Extended-Release Tablets.

If you should have any questions regarding this submission, please contact the undersigned.

Respectfully submitted,

  
James N. Czaban

Enclosure

*2004P-0139*

*C 2*

May 14, 2004

Division of Dockets Management  
Food and Drug Administration  
Department of Health and Human Services  
Room 1061, HFA-305  
5630 Fishers Lane  
Rockville, MD 20857

**Docket No. 2004P-0139**  
**Response to Citizen Petition**

These comments are respectfully submitted in response to the citizen petition filed by McNeil Consumer & Specialty Pharmaceuticals (McNeil) dated March 19, 2004 regarding their proposal of an additional bioequivalence criteria in the evaluation and approval of generic versions of CONCERTA<sup>®</sup> (methylphenidate HCl) Extended-Release Tablets. These comments provide scientific justification and support for the Food and Drug Administration to affirm the currently accepted criteria for bioequivalence determination in the approval of generic versions of CONCERTA<sup>®</sup>.

**A. EXECUTIVE SUMMARY**

The FDA's currently accepted criteria for the approval of generic versions of methylphenidate immediate or extended release products is based on demonstrating statistical bioequivalence using the following three key pharmacokinetic (PK) parameters:  $AUC_{0-\infty}$ ,  $AUC_{0-t}$  and  $C_{max}$ . These criteria are stringent and legitimate from both a scientific and regulatory perspective. FDA should not adopt McNeil's proposal to require the additional PK parameter  $AUC_{pR}$  (area under the curve to the population median  $T_{max}$  of the reference formulation), because that parameter has not been proven scientifically valid or more sensitive in correlating clinical or therapeutic outcome, and has not been shown to be statistically feasible in establishing acceptable, unbiased criteria from a regulatory perspective for the approval of generic versions of CONCERTA<sup>®</sup>.

McNeil attempted to provide examples in proposing  $AUC_{pR}$  to be used as an additional PK parameter for the determination of bioequivalence of generic versions of CONCERTA<sup>®</sup>. They indicated that the currently accepted parameters, i.e.,  $AUC_{0-\infty}$ ,  $AUC_{0-t}$  and  $C_{max}$ , may not be adequate in predicting clinical effects for extended-release products (specifically CONCERTA<sup>®</sup>) in treating attention deficit hyperactivity disorder (ADHD). Based on the examples and comparisons provided in the citizen petition, McNeil considers that bioequivalence in  $AUC_{pR}$  would ensure therapeutic equivalence in the generic versions of CONCERTA<sup>®</sup> Extended-Release Tablets.

This response presents scientific justifications and evidence to disregard  $AUC_{pR}$  as a relevant or acceptable PK parameter for the determination of bioequivalence of generic versions of methylphenidate extended-release products, including CONCERTA<sup>®</sup>.

The grounds for rejecting McNeil's proposal of using  $AUC_{pR}$  as an additional key PK parameter for the approval of generic versions of CONCERTA<sup>®</sup> Extended-Release Tablet are as follows:

- Invalid comparisons and examples used by McNeil in addressing bioequivalence vs. therapeutic equivalence of various formulations of methylphenidate products.
- Lack of scientific evidence to demonstrate that  $AUC_{pR}$  is relevant in correlating the clinical outcome of methylphenidate products, especially in terms of acute tolerance and duration of effect
- Lack of statistical justification and feasibility in establishing acceptance criteria for  $AUC_{pR}$  as a key parameter in determining bioequivalence between extended-release methylphenidate products

## B. SCIENTIFIC JUSTIFICATIONS AND ANALYSES

After reviewing the examples and data presented by McNeil and the available, large body of scientific literature, and performing additional pharmacokinetic and statistical analyses of available data, there are strong scientific justifications and bases to reject the proposal of using  $AUC_{pR}$  as an additional key PK parameter for the approval of generic versions of CONCERTA<sup>®</sup> Extended-Release Tablet. These justifications and analyses are presented as follows.

- **Invalid comparisons and examples used by McNeil in addressing bioequivalence vs. therapeutic equivalence in the approval of generic versions of CONCERTA<sup>®</sup>**

The major criticism and scientific invalidity of McNeil's demonstration for its proposal is that all comparisons and examples used by McNeil have been for extended-release products that are not generic versions of CONCERTA<sup>®</sup>, but products that were approved under NDAs based on demonstrating clinical efficacy and safety. Specifically, CONCERTA<sup>®</sup> is designed to provide comparable drug coverage as the three-times-daily (tid) immediate-release methylphenidate (MPH) products (given every 4 hours); while the rest of the modified-release products used in McNeil's examples (i.e., METADATE<sup>®</sup> CD, RITALIN<sup>®</sup> LA and RITALIN<sup>®</sup> SR) are designed to mimic the twice-daily (bid) immediate-release MPH products (given every 4 hours).

McNeil's advocacy of using  $AUC_{pR}$  for generic versions of CONCERTA is based on presumptions and conjecture. To legitimately support the use of this parameter as correlating pharmacokinetics to variations in therapeutic effects (or clinical outcome) between CONCERTA<sup>®</sup> and its bioequivalent products (based on current criteria), McNeil would have to provide data from clinical end-point trials of a head-to-head comparison between the innovator and bioequivalent generic products. In these trials, acceptance criteria for determination of therapeutic equivalence using the agreed primary clinical end point(s) would need to be defined in advance based on statistical validity/justification. In addition, acceptable **clinically significant** difference(s) in the primary end point(s) would need(s) to be established in advance for sample size and confidence interval calculations. In the absence of rigorous clinical evidence, McNeil's proposal of using  $AUC_{pR}$  to address "predicted" therapeutic inequivalence between bioequivalent products and CONCERTA<sup>®</sup> is problematic and unjustified.

Based on review of the available pharmacokinetic and clinical efficacy/safety data in the literature and in the Summary Basis for Approval (SBAs) of several methylphenidate products, the currently accepted criteria for approval of generic versions of extended-release methylphenidate products such as CONCERTA<sup>®</sup>, i.e.,  $AUC_{0-\infty}$ ,  $AUC_{0-t}$  and  $C_{max}$ , are adequate and legitimate. In the following sections, data and rationale are provided to show that it is not scientifically relevant or justifiable to use an additional PK parameter,

i.e.,  $AUC_{pR}$  as proposed by McNeil, to establish bioequivalence between CONCERTA<sup>®</sup> and generic products.

- **Lack of scientific evidence to demonstrate that  $AUC_{pR}$  is correlated with clinical effect of methylphenidate, especially in terms of acute tolerance and duration of effect as presented by McNeil**

McNeil claims that using  $AUC_{0-\infty}$ ,  $AUC_{0-t}$  and  $C_{max}$  alone as the bioequivalence parameters may be inadequate to predict clinical effects and that  $AUC_{pR}$  is more sensitive in predicting clinical outcome. However, as stated above, the examples of products used by McNeil for making such comparisons and correlations are invalid and misleading. These products (i.e., CONCERTA<sup>®</sup>, METADATE<sup>®</sup> CD, RITALIN<sup>®</sup> LA and RITALIN<sup>®</sup>-SR) are all brand/NDA products and are not intended to be bioequivalent to each other.<sup>1,5,7</sup> Most importantly, McNeil cites no actual **individual** plasma concentration-time profile data from participants in the study to demonstrate if  $AUC_{pR}$  correlates better with therapeutic effects than  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , and  $C_{max}$  alone or together.<sup>8</sup> It is well known that modeling PK/PD data based on simulated plasma concentration data, assuming no variation, can result in misleading conclusions. Furthermore, the therapeutic effects as measured using surrogate markers such as the SKAMP scores appeared to show variations at some time points during a day between different products intended for bid or tid uses as exemplified by McNeil in the citizen petition or shown in the literature.<sup>9,10</sup> However, these studies did not assess whether the observed variations or differences in the surrogate pharmacological effects are clinically relevant.

McNeil argues that the specific clinical effects that may vary between products and could be more sensitively differentiated by  $AUC_{pR}$  include acute tolerance, early magnitude of effect and duration of effect. However, based on review of the literature data and data presented in the Summary Basis of Approval (SBA) for CONCERTA<sup>®</sup> (NDA 21-121), there is not sufficient scientific evidence to support that  $AUC_{pR}$  is a relevant or more sensitive parameter in correlating with these clinical effects, again primarily due to lack of rigorous and valid analysis as stated above, and for other reasons summarized below.

#### Issues on Acute Tolerance:

In its petition McNeil attempted to theorize that the lack of therapeutic effects of certain sustained-release MPH products (such as RITALIN<sup>®</sup>-SR) in some patients is due to the apparent "flat" plasma profile over an approximate 4-hour period which causes acute tolerance. This concept of acute tolerance remains a theoretical one<sup>1,8,11</sup> and was attempted by McNeil primarily with the use of a simulated pharmacokinetic profile in a pharmacokinetic-pharmacodynamic (PK-PD) analysis approach.<sup>11</sup> Given the known large intersubject variability in MPH pharmacokinetic profiles, the absence of actual clinical plasma concentration-time profile of MPH is problematic.<sup>11</sup> In addition, the simulated mean plasma MPH concentration vs. time data for the three-times-daily (every 4 hour) administration of immediate-release MPH presented by McNeil<sup>®</sup> are apparently

inconsistent with the actual data. The actual data show that the highest peak MPH concentration occurs after the second dose of IR MPH<sup>12,13</sup>, but the simulated data show a highest peak after the third dose of IR MPH.<sup>11</sup> This inconsistency between simulated and actual data discounts the validity of the PK-PD work through which McNeil attempted to document the presence of “acute tolerance” in MPH effect.

As shown in the SBA for CONCERTA<sup>®</sup> (NDA 21-121), the FDA reviewers did not accept the claim that acute tolerance is developed following a single dose of MPH based on data presented by the innovator, due to the lack of real plasma profile data, not incorporating variability in simulating PK data, and lack of validation of the PK-PD model. In addition, the clinical responses as measured by SKAMP scores at the “peak” and “trough” times following administration of an immediate-release product according to a dosing schedule guided by PK simulation intended to generate a “flat” plasma profile did not show evidence of development of acute tolerance<sup>11</sup>. Clinical literature indicates that there are substantial changes in ADHD children’s behavior over the course of a day, i.e., fatigue and deterioration in behavior (e.g. more disruptive, less on task, less likely to achieve target goals) over time. This situation can complicate clinical assessment of a true medication effect.<sup>9,14</sup> In several studies of ADHD children<sup>9,11,14,15</sup>, time-dependent changes in response to a placebo treatment as measured by the SKAMP scores were observed, which could have substantial impact on the interpretation and analysis of methylphenidate PK-PD data, and must be adequately accounted for. After accounting for time-dependent behavioral changes and responses to placebo treatment, the magnitude of the perceived “acute tolerance” effect, if it exists at all, is predicted to be insignificant. In order to validly support the existence and significance of “acute tolerance”, the quantitative relationship between the change in pharmacological effects and the changes (or lack of changes) in plasma MPH concentrations over time by including data from the placebo treatment must be established.

Overall, the currently available clinical data and analysis results in the literature do not support the existence of acute tolerance in the pharmacological effect of methylphenidate.

#### Issues on Correlation of Early Plasma Exposure or AUC<sub>pR</sub> with Therapeutic Effects:

In obtaining regulatory approval for CONCERTA<sup>®</sup>, the innovator conducted one double-blind, placebo-controlled, parallel-group, clinical end-point trial<sup>16</sup> along with two small double-blind, placebo-controlled, crossover clinical trials<sup>14,15</sup>, to support claims of demonstrating efficacy and safety. In these clinical trials, three products were compared, i.e., CONCERTA<sup>®</sup>, a placebo tablet, and an immediate-release MPH product for tid administration (MPH IR tid). These studies showed that the total plasma exposure to MPH as determined by AUC<sub>0-∞</sub> for CONCERTA<sup>®</sup> relative to that of MPH IR tid was 91% (i.e., comparable to each other) and that the early plasma exposure as characterized by C<sub>max</sub> at the first and second peak times for the MPH IR tid product were lower for CONCERTA<sup>®</sup> as compared to MPH IR tid.<sup>12,13</sup> Even though these trials were not planned statistically to prove therapeutic equivalence between CONCERTA<sup>®</sup> and MPH IR tid, the clinical efficacy parameters were comparable or similar<sup>14,16</sup> between the two

products despite the differences in their early plasma exposure profiles. Thus, the differences in early plasma exposure profiles between CONCERTA<sup>®</sup> and MPH IR tid apparently did not result in clinically significant (or relevant) differences in therapeutic effects, indicating a questionable correlation between AUC<sub>pR</sub> and therapeutic effects. This is an example where some differences in the early exposure profile of MPH do not directly translate into clinically relevant differences in therapeutic effects, and that comparable or equivalent clinical efficacy can be achieved between two products with comparable AUC<sub>0-∞</sub>. This is the longstanding position of the agency that has repeatedly withstood challenges of many kinds over the past twenty years.

#### Issues on Correlation between AUC<sub>pR</sub> and Duration of Effect:

As pointed out earlier, at present, there have been no adequate and valid studies to support the notion that AUC<sub>pR</sub> is a key PK parameter that correlates well with therapeutic effects of MPH and that can be used to predict the duration of therapeutic effects of MPH.

Nevertheless, the study<sup>9</sup> cited by McNeil comparing “therapeutic effects” between CONCERTA<sup>®</sup> and METADATE<sup>®</sup> CD using an unvalidated surrogate marker (SKAMP score) enrolled ADHD patients who previously required either bid or tid dosing of immediate-release MPH products. Since the trial was crossover in design, patients were not stratified (based on their needs for MPH coverage) to receive CONCERTA<sup>®</sup> vs. METADATE<sup>®</sup> CD. The results showed that SKAMP scores measured at 7.5 hours post dose were not statistically significantly different between CONCERTA<sup>®</sup> and METADATE<sup>®</sup> CD treatments in the overall patient population. At 12 hours post dose, there were “statistically” significant differences in SKAMP scores between CONCERTA<sup>®</sup> and METADATE<sup>®</sup> treatments in the overall population, with differences generally  $\leq 0.20$  in effect size. Even though the difference of 0.20 in effect size between treatments was statistically significant, it has yet to be proven if this difference is clinically significant, especially when considering the strong response to the placebo treatment as measured by SKAMP scores observed at time zero. As shown in Figure 1 of the publication by Swanson et al.<sup>9</sup>, the study using SKAMP scores showed a statistically significant placebo effect with an effect size ranging from 0.18 to 0.60 when comparing the placebo treatment with the active treatments. This indicates that a “clinically” significant difference in effect size using SKAMP scores would have to be much greater than 0.20 when comparing two active treatments in order to be meaningful. Therefore, this study by Swanson et al. lacks scientific validity and statistical rigor to serve as evidence to demonstrate differences in duration of effect between MPH products due to different PK profiles.

Interestingly, in another study<sup>17</sup> where METADATE<sup>®</sup> CD was compared to placebo in a randomized, parallel-group design with patients only requiring bid coverage of MPH, the therapeutic effects measured by parent ratings (Conners’ Global Index Scale) at home (usually in the evening, approximately 12 hours post dose) showed that METADATE<sup>®</sup> CD was effective (and superior to placebo) in reducing ADHD symptoms, suggesting a

long duration of effect (approximately 12 hours) for this extended-release product designed for bid coverage. Thus, in practice, any difference in duration of effect between CONCERTA<sup>®</sup> and METADATE<sup>®</sup> CD<sup>9</sup> as quoted by McNeil may have little clinical importance especially when concurrent behavioral treatment is implemented.<sup>14</sup>

Based on the above analysis, McNeil has failed to present scientifically valid or convincing evidence to demonstrate that AUC<sub>pR</sub> is a key pharmacokinetic parameter that correlates with the duration of MPH effects.

Issues on Correlation between AUC<sub>pR</sub> and Early Magnitude of Effect:

The utility and validity of AUC<sub>pR</sub> as a means of determining early magnitude of effect must be assessed by rigorous statistical analysis incorporating variability considerations<sup>8,12</sup> and appropriate clinical trial design. At the present time, there have been no valid or scientifically meaningful studies to demonstrate that AUC<sub>pR</sub> correlates with early magnitude of clinical effect. The study by Swanson et al.<sup>9</sup> utilized the SKAMP scores to differentiate early clinical effects between CONCERTA<sup>®</sup> and METADATE<sup>®</sup> CD. The studies showed differences in early plasma exposure profiles. "Statistically" significant differences in mean SKAMP scores between CONCERTA<sup>®</sup> and METADATE<sup>®</sup> CD in the magnitude of 0.06 to 0.39 in effect size were found at 1.5, 3, and 4.5 hours post dose. However, the significant placebo effect ranging from 0.18 to 0.60 in effect size (as mentioned above) confounded the assessment of any true "clinically" significant differences in therapeutic effects between the two active treatments. Furthermore, individual plasma concentration-time data were not available to establish that individual AUC<sub>pR</sub> values correlated with early magnitude of effects. Therefore, no conclusion can be made with regard to correlation between AUC<sub>pR</sub> and early magnitude of clinical effect based on this study.

The issue of correlation between AUC<sub>pR</sub> and early magnitude of effect or overall therapeutic effect and duration may be addressed by future clinical trials with appropriate design, effect measures and analysis methods. These clinical trials need to be double-blind, clinical end-point trials with head-to-head comparisons between extended-release methylphenidate products that are designed for the same daily coverage (both for either tid or bid MPH coverage). In order to evaluate the significance of AUC<sub>pR</sub> in differentiating clinical effects, these two products should present statistically significant difference in AUC<sub>pR</sub> as determined by a statistically acceptable cutoff point (which is yet to be debated and determined with rigorous simulation work as discussed in the following section). To alleviate the concerns over response to placebo treatment (especially for those measured by a surrogate marker such as the SKAMP scores), a placebo arm should also be incorporated with any placebo response accounted for in the statistical analysis. A prospectively established primary clinical end-point(s) should be incorporated into the protocol. The primary end points should have been validated and clinically acceptable. In addition, what constitutes a "clinically" significant difference in the primary end point(s) need(s) to be determined in advance (and agreed with the regulatory agency) for calculation of sample size and the 90% confidence intervals for determination of

therapeutic equivalence or inequivalence. Clinical effects should be measured throughout the day (morning, afternoon and evening) to assess differences in early and late-day coverage as relevant to correlating differences in plasma profiles with therapeutic effects. To practically simulate “real-life” and most clinically relevant situations, the trial should also incorporate background behavioral treatments as recommended by Pelham et al.<sup>14</sup> In addition, to incorporate potential variability in the pharmacokinetics of MPH between patients in the correlation analysis, actual plasma concentration-time profiles of MPH should be collected in individual patients.

Therefore, only clinical trials designed with statistical and scientific rigor and clinical relevance can validly evaluate if  $AUC_{pR}$  correlates with clinical outcome and, further if  $AUC_{pR}$  should be used as an additional PK measure in determining bioequivalence between extended-release methylphenidate products.

- **Lack of statistical justification and feasibility in establishing acceptance criteria for  $AUC_{pR}$  to be used as a key parameter in determining bioequivalence between extended-release products of methylphenidate**

In addition to the inadequacy of the use of “mean” clinical effects to support its proposal of  $AUC_{pR}$  as an additional PK parameter, McNeil also falls short in its use of only “mean” MPH pharmacokinetic data of extended-release MPH products. ( Figures 3 and 4 of McNeil’s petition.) These figures appear to indicate that the plasma concentration-time curve of CONCERTA<sup>®</sup> is smooth with only one peak occurring at about 6 hours after dosing. In reality, the results of a bioavailability study with CONCERTA<sup>®</sup> showed that plasma MPH concentration-time curves of CONCERTA<sup>®</sup> in individual subjects have multiple peaks around the indicated population  $T_{max}$  region. Specifically, in the majority, 22/34 (65%), of the subjects in this study, at least two peaks appeared between 5 and 8 hours post dose. Furthermore, the peak MPH concentrations associated with CONCERTA<sup>®</sup>’s multiple peaks are very similar within each individual subject, with the median coefficient of variation in  $C_{max}$  of only 3.75% (range: 0.62% - 11.8%) among the 22 subjects. Since the concentrations of these multiple peaks are similar in magnitude, individual  $T_{max}$  can occur randomly between 5 and 8 hours post dose depending on variations in study conditions or bioanalytical methodology. A more appropriate description of the PK characteristics of CONCERTA<sup>®</sup> (and probably for other extended-release MPH products) is that CONCERTA<sup>®</sup> has a “ $T_{max}$  zone”, which may vary from 5 to 8 hours post dose for the majority of subjects. This variability casts doubt and technical challenges over the issue of whether the conventional  $AUC_{pR}$ , based on a single  $T_{max}$  value is an appropriate and sensitive parameter to further ensure the bioequivalence and therapeutic equivalence of extended-release methylphenidate products in addition to the currently accepted criteria.

$AUC_{pR}$  has been discussed by the FDA as a potential measure to differentiate early plasma exposure between immediate-release drug products in the categories of analgesics or antihypertensives where clear correlation of clinical efficacy and safety in relation to

the early plasma exposure has been established.<sup>18</sup> In the case of methylphenidate, the relationship between early exposure (and/or rate of absorption) and response (for efficacy or acute tolerance) has not been critically established. There has been no controlled, prospectively defined study which accounts for placebo effects, inter- and intra-subject variability in PK and in sensitivity to methylphenidate effect, and background behavioral treatment effect in clinical settings.

Although  $AUC_{pR}$  has been discussed by the FDA as a potential measure to differentiate early plasma exposure and clinical efficacy or safety, all simulation work and statistical considerations have utilized immediate-release drug products as examples.<sup>18,19</sup> With more straight-forward cases of immediate-release products where a single peak exists for each product, the simulation work showed that the test using  $AUC_{pR}$  (or early AUC) to differentiate early exposure is more sensitive if the cutoff point for calculating  $AUC_{pR}$  uses the early  $T_{max}$  of the two products (whether test or reference) within each individual subject. In the case of extended-release MPH products, where multiple peaks with similar magnitudes often occur over a wide range of time periods even within a subject (as discussed above), the most sensitive cutoff point determined by simulation work performed for the immediate-release products will not be applicable. Therefore, even if  $AUC_{pR}$  were rigorously proven to be a necessary and clinically relevant additional parameter for differentiating therapeutic inequivalence among bioequivalent extended-release MPH products, additional simulation and statistical work must be conducted to provide a robust and unbiased method for the calculation of  $AUC_{pR}$  with a statistically justifiable cutoff point. In addition, statistical and pharmacological justifications need to be provided to determine an acceptable and "clinically significant" difference (and associated 90% confidence interval) in  $AUC_{pR}$  between two products to declare bioequivalence. This clinically significant difference in  $AUC_{pR}$  is expected to be greater than the generally accepted difference (i.e., 20%) for  $AUC_{0-\infty}$  and  $C_{max}$ , if  $AUC_{pR}$  were to be used as an "additional" criterion for proving bioequivalence. This is because the relationship between plasma concentrations and pharmacological effect (or clinical efficacy) is generally not linear but follows a nonlinear relationship as characterized by an  $E_{max}$  model, where a 2-fold change in concentration (or exposure) may only correspond to a less than 10% difference in effect at the  $EC_{90}$  region (the targeted response area). Therefore, the establishment of regulatory acceptance criteria for  $AUC_{pR}$  must be based on the consideration of its relationship to clinical outcome (i.e., the concentration-response curve).

Based on the above discussions and analysis, McNeil has failed to establish that the use of  $AUC_{pR}$  as a key pharmacokinetic parameter in differentiating therapeutic inequivalence between CONCERTA<sup>®</sup> and potential generic products that meet current bioequivalence criteria is scientifically justified.

## C. CONCLUSIONS

- No valid evidence or comparisons have been presented in the March 19, 2004 citizen petition filed by McNeil Consumer & Specialty Pharmaceuticals to support the use of  $AUC_{pR}$  (area under the curve to the population median  $T_{max}$  of the reference formulation) in determining bioequivalence of generic versions of CONCERTA®.
- No data support that the currently accepted criteria for the approval of generic versions of methylphenidate products, i.e., based on bioequivalence determination using the established key pharmacokinetic parameters, i.e.,  $AUC_{0-\infty}$ ,  $AUC_{0-t}$  and  $C_{max}$ , are inadequate from both the scientific and regulatory perspectives.
- No additional pharmacokinetic parameter, such as  $AUC_{pR}$ , has been scientifically or clinically proven to be more sensitive in correlating or predicting clinical outcome (in terms of early response, acute tolerance and duration of effect) of methylphenidate.
- If  $AUC_{pR}$  were proven scientifically to be a critical and relevant parameter in determining bioequivalence of generic versions of CONCERTA (which, of course, is not the case), there is currently no statistically justifiable and feasible method for the calculation of  $AUC_{pR}$  with a sensitive and unbiased cutoff point nor are there meaningful acceptance criteria.

Lastly, as FDA stated in its November 21, 2003 response to a similar petition regarding Covera HS<sup>20</sup>, "it is neither reasonable nor in the interest of the public to impose such testing standards on generic applicants because (1) the approach has not been fully developed and (2) the current methods are effective in establishing bioequivalence between drug products." Therefore, for all of the above reasons, McNeil's petition should be denied.

## D. REFERENCES

1. Markowitz JS, Straughn AB, and Patrick KS. Advances in the pharmacotherapy of attention-deficit-hyperactivity disorder: focus on methylphenidate formulations. *Pharmacotherapy* 2003;23:1281-1299.
2. Pelham WE, Gnagy EM, Chronis AM, Burrows-MacLean L, Fabiano GA, Onyango AN, Meichenbaum DL, Williams A, Aronoff HR, and Steiner RL. A comparison of morning-only and morning/late afternoon adderall to morning-only, twice-daily, and three times-daily methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics* 1999;6:1300-1311.

3. American Academy of Pediatrics Committee on Quality Improvement and Subcommittee on Attention-Deficit/Hyperactivity Disorder. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. *Pediatrics* 2001;108:1033-1044.
4. Stein MA, Sarampote CS, Waldman ID, Robb AS, Conlon C, Pearl PL, Black DO, Seymour KE and Newcorn JH. A dose-response study of OROS methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2003;112:e404-e413.
5. Gonzalez MA, Pentikis HS, Anderl N, Benedict MF, DeCory HH, Dirksen SJH, and Hatch SJ. Methylphenidate bioavailability from two extended-release formulations. *Int J Clin Pharmacol Ther* 2002;40:175-184.
6. Dirksen SJH, D'Imperio JM, Birdsall D and Hatch SJ. A postmarketing clinical experience study of Metadate<sup>®</sup> CD. *Curr Med Res Opin* 2002;18:371-380.
7. Markowitz JS, Straughn AB, Patrick KS, DeVane CL, Pestreich L, Lee J, Wang Y and Muntz F. Pharmacokinetics of methylphenidate after oral administration of two modified-release formulations in healthy adults. *Clin Pharmacokinet* 2003;42:393-401.
8. Wolraich ML and Doffing MA. Pharmacokinetic considerations in the treatment of attention-deficit hyperactivity disorder with methylphenidate. *CNS Drugs* 2004;18:243-250.
9. Swanson JM, Wigal SB, Wigal T, Sonuga-Barke E, Greenhill LL, Biederman J, Kollins S, Nguyen AS, DeCory HH, Dirksen SJH, Hatch SJ, and the COMACS Study Group. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (The Comacs Study). *Pediatrics* 2004;113:e206-e216.
10. Lopez F, Silva R, Pestreich L and Muniz R. Comparative efficacy of two once daily methylphenidate formulations (Ritalin<sup>®</sup> LA<sup>TM1</sup> and Concerta<sup>®</sup>) and placebo in children with attention deficit hyperactivity disorder across the school day. *Paediatr Drugs* 2003;55:545-555.
11. Swanson J, Gupta S, Guinta D, Flynn D, Agler D, Lerner M, Williams L, Shoulson I and Wigal S. Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. *Clin Pharmacol Ther* 1999;66:295-305.
12. Summary Basis of Approval for NDA 21-121: Concerta 18 mg&36 mg Extended-Release Tablets (Alza Corporation) 8/1/2000 Approval [Attention Deficit Disorder]

13. CONCERTA<sup>®</sup> Product Information in Physician Desk Reference 2004.
14. Pelham WE, Gnagy EM, Burrows-Maclean LB, Williams A, Fabiano GA, Morrisey SM, Chronis AM, Forehand GL, Nguyen CA, Hoffman MT, Lock TM, Fielbelkorn K, Coles EK, Panahon CJ, Steiner RL, Meichenbaum DL, Onyango AN and Morse GD. Once-a day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. *Pediatrics* 2001;107(6):e105.
15. Swanson J, Gupta S, Lam A, Shoulson I, Lerner M, Modi N, Lindemulder E, and Wigal S. Development of a new once-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 2003;60(2):204-211.
16. Wolraich ML, Greenhill LL, Pelham W, Swanson J, Wilens T, Palumbo D, Atkins M, McBurnett K, Bukstein O and August G, on behalf of the Concerta Study Group. Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2001;108(4):883-892.
17. Greenhill LL, Findling RL, Swanson JM and the MPH MR ADHD Study Group. A double-blind, placebo-controlled study of modified-release methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2002;109(3):e39.
18. Chen ML, Lesko L and Williams RL. Measures of exposure versus measures of rate and extent of absorption. *Clin Pharmacokinet* 2001;40:565-572.
19. Endrenyi L, Csizmadia F, Tothfalusi L, Balch AH and Chen M-L. The duration of measuring partial AUCs for the assessment of bioequivalence. *Pharm Res* 1998;15:399-404.
20. FDA Response dated November 21, 2003 to the Citizen Petition filed December 7, 2001 on behalf of Pharmacia Corporation and its affiliate G.D. Searle. Docket No. 01P-0546

## INDEX

1. Markowitz JS, Straughn AB, and Patrick KS. Advances in the pharmacotherapy of attention-deficit-hyperactivity disorder: focus on methylphenidate formulations. *Pharmacotherapy* 2003;23:1281-1299.
2. Pelham WE, Gnagy EM, Chronis AM, Burrows-MacLean L, Fabiano GA, Onyango AN, Meichenbaum DL, Williams A, Aronoff HR, and Steiner RL. A comparison of morning-only and morning/late afternoon adderall to morning-only, twice-daily, and three times-daily methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics* 1999;6:1300-1311.
3. American Academy of Pediatrics Committee on Quality Improvement and Subcommittee on Attention-Deficit/Hyperactivity Disorder. Clinical practice guideline: treatment of the school-aged child with attention-deficit/hyperactivity disorder. *Pediatrics* 2001;108:1033-1044.
4. Stein MA, Sarampote CS, Waldman ID, Robb AS, Conlon C, Pearl PL, Black DO, Seymour KE and Newcorn JH. A dose-response study of OROS methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2003;112:e404-e413.
5. Gonzalez MA, Pentikis HS, Anderl N, Benedict MF, DeCory HH, Dirksen SJH, and Hatch SJ. Methylphenidate bioavailability from two extended-release formulations. *Int J Clin Pharmacol Ther* 2002;40:175-184.
6. Dirksen SJH, D'Imperio JM, Birdsall D and Hatch SJ. A postmarketing clinical experience study of Metadate<sup>®</sup> CD. *Curr Med Res Opin* 2002;18:371-380.
7. Markowitz JS, Straughn AB, Patrick KS, DeVane CL, Pestreich L, Lee J, Wang Y and Muntz F. Pharmacokinetics of methylphenidate after oral administration of two modified-release formulations in healthy adults. *Clin Pharmacokinet* 2003;42:393-401.
8. Wolraich ML and Doffing MA. Pharmacokinetic considerations in the treatment of attention-deficit hyperactivity disorder with methylphenidate. *CNS Drugs* 2004;18:243-250.
9. Swanson JM, Wigal SB, Wigal T, Sonuga-Barke E, Greenhill LL, Biederman J, Kollins S, Nguyen AS, DeCory HH, Dirksen SJH, Hatch SJ, and the COMACS Study Group. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (The Comacs Study). *Pediatrics* 2004;113:e206-e216.
10. Lopez F, Silva R, Pestreich L and Muniz R. Comparative efficacy of two once daily methylphenidate formulations (Ritalin<sup>®</sup> LA<sup>TM1</sup> and Concerta<sup>®</sup>) and placebo in children with attention deficit hyperactivity disorder across the school day. *Paediatr Drugs* 2003;55:545-555.

11. Swanson J, Gupta S, Guinta D, Flynn D, Agler D, Lerner M, Williams L, Shoulson I and Wigal S. Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. *Clin Pharmacol Ther* 1999;66:295-305.
12. Summary Basis of Approval for NDA 21-121: Concerta 18 mg&36 mg Extended-Release Tablets (Alza Corporation) 8/1/2000 Approval [Attention Deficit Disorder]
13. CONCERTA<sup>®</sup> Product Information in Physician Desk Reference 2004.
14. Pelham WE, Gnagy EM, Burrows-Maclean LB, Williams A, Fabiano GA, Morrisey SM, Chronis AM, Forehand GL, Nguyen CA, Hoffman MT, Lock TM, Fielbelkorn K, Coles EK, Panahon CJ, Steiner RL, Meichenbaum DL, Onyango AN and Morse GD. Once-a day Concerta methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. *Pediatrics* 2001;107(6):e105.
15. Swanson J, Gupta S, Lam A, Shoulson I, Lerner M, Modi N, Lindemulder E, and Wigal S. Development of a new once-a-day formulation of methylphenidate for the treatment of attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 2003;60(2):204-211.
16. Wolraich ML, Greenhill LL, Pelham W, Swanson J, Wilens T, Palumbo D, Atkins M, McBurnett K, Bukstein O and August G, on behalf of the Concerta Study Group. Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2001;108(4):883-892.
17. Greenhill LL, Findling RL, Swanson JM and the MPH MR ADHD Study Group. A double-blind, placebo-controlled study of modified-release methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics* 2002;109(3):e39.
18. Chen ML, Lesko L and Williams RL. Measures of exposure versus measures of rate and extent of absorption. *Clin Pharmacokinet* 2001;40:565-572.
19. Endrenyi L, Csizmadia F, Tothfalusi L, Balch AH and Chen M-L. The duration of measuring partial AUCs for the assessment of bioequivalence. *Pharm Res* 1998;15:399-404.
20. FDA Response dated November 21, 2003 to the Citizen Petition filed December 7, 2001 on behalf of Pharmacia Corporation and its affiliate G.D. Searle. Docket No. 01P-0546