



Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20852

SEP 15 2004

DOCKET NO. 2004P-0139: SUPPLEMENT
COMMENTS ON HELLEREHRMAN RESPONSE

On March 19, 2004, in response to the request of the United States Food and Drug Administration (FDA), McNeil Consumer & Specialty Pharmaceuticals, a Division of McNeil-PPC, Inc. (McNeil), Fort Washington, PA, submitted a Citizen Petition (Petition) under section 505 of the Federal Food, Drug, and Cosmetic Act, and 21 CFR § 10.30. The Petition requested that the Commissioner of Food and Drugs apply an additional bioequivalence metric, AUC_{pR} , to the two average bioequivalence parameters, C_{max} and $AUC_{0-\infty}$, because the current parameters will not ensure that the approval of generic versions of CONCERTA® (methylphenidate HCl) Extended-release Tablets are both bioequivalent and clinically equivalent to the innovator product. Collective evidence from well-controlled studies submitted with the Petition indicate that reliance upon the average bioequivalence parameters alone may result in inappropriate bioequivalence determinations for this type of product, suggestive of a potential bioequivalence problem that warrants assessments under 21 CFR § 320.33(a).

On May 14, 2004, a law firm, HellerEhrman, submitted to Docket No. 2004P-0139 comments in response to McNeil's Petition, which included a recommendation that FDA deny McNeil's Petition. In this Petition Supplement, submitted under 21 CFR § 10.30(g) to its above referenced Petition, McNeil addresses HellerEhrman's comments. McNeil plans to submit within the next several days, an additional supplement to our Citizen's Petition containing recently available data that raises important safety-related issues.

I. **BACKGROUND SUMMARY: INTENT AND SCIENTIFIC ISSUES OF MCNEIL'S ORIGINAL PETITION**

In our Petition of March 19, 2004, McNeil requested FDA action to address a bioequivalence issue with extended-release methylphenidate products that had only recently become apparent, with the availability of data from head-to-head clinical and pharmacokinetic studies and other analyses. These collective, well-controlled data provide strong evidence that a potential limitation exists with the current bioequivalence

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testing criteria, despite the fact that the clinical studies were not specifically designed to illustrate this limitation. At issue is the fact that differently formulated, branded extended-release methylphenidate products met the metrics for bioequivalence testing, and thus would allow a regulatory conclusion of therapeutic equivalence. However, in actual clinical practice, they were known to not be clinically equivalent. The principle demonstrated by these studies applies to potential generic versions of CONCERTA®.

The inability of the two current bioequivalence metrics, C_{max} and $AUC_{0-\infty}$, to adequately describe the complete drug exposure pattern of extended-release methylphenidate formulations allows products with relatively large differences in early and late exposure to be deemed bioequivalent. For extended-release methylphenidate products dosed once a day, differences in early or late exposure result in significant clinical differences. Although many clinicians have recognized these differences for some time, until now, there have not been data available to warrant assessment of this signal as requiring a third drug exposure metric, AUC_{pR} . However, the collective well-controlled data outlined by McNeil warrants use of AUC_{pR} in bioequivalence determinations of extended-release methylphenidate products.

Nothing in HellerEhrman's Response to McNeil's Petition negates the arguments presented by McNeil. Moreover, McNeil asserts the following:

- Collective evidence from well-controlled clinical trials, pharmacokinetic studies, and other analyses is a signal, highly suggestive of a potential bioequivalence problem for extended-release methylphenidate products when only C_{max} and $AUC_{0-\infty}$ are used. One would not expect different pharmaceutical alternatives at different molar doses and with different pharmacokinetic and clinical profiles to meet current criteria for bioequivalence.
- AUC_{pR} does not have to be validated and correlated with clinical endpoints for its appropriate use as a supplemental bioequivalence metric, given that neither C_{max} nor $AUC_{0-\infty}$ have been rigorously validated or correlated with clinical data.
- Data from four CONCERTA® bioequivalence studies submitted to NDA 21-121 showed that AUC_{pR} had similar estimates of intrasubject variability as that for $AUC_{0-\infty}$ within the same study, indicating no further increase in sample size needed. Moreover, individual response variability (multiple peaks in plasma methylphenidate concentration-time curves) is best addressed by using AUC_{pR} , because C_{max} is poorly estimated for products with multiple peaks.

I. COMMENTS ON HELLEREHRMAN'S RESPONSE

As stated in its Response's Executive Summary, HellerEhrman puts forward three objections to the McNeil Petition.

- A. HellerEhrman claims the use of "invalid comparisons and examples" in McNeil's case for using AUC_{pR}, an additional essential metric for bioequivalence determinations in extended-release methylphenidate products.
- B. HellerEhrman claims a "lack of scientific evidence" to demonstrate AUC_{pR} relevance for these products.
- C. HellerEhrman claims a "lack of statistical justification and feasibility in establishing acceptance criteria for AUC_{pR}" for these products.

These issues are addressed, sequentially, as "A," "B," and "C," below.

A. COMPARISONS AND EXAMPLES: MCNEIL'S METHYLPHENIDATE PRODUCT COMPARISONS ARE SCIENTIFICALLY VALID AND SHOW CLINICALLY SIGNIFICANT EFFICACY DIFFERENCES OVER A COURSE OF A DAY

First, HellerEhrman states that its major criticism of McNeil's position is based on the fact that the McNeil Petition utilized extended-release comparisons and examples that are not generic versions of CONCERTA[®], but instead are NDA-approved products. HellerEhrman would insist on head-to-head comparisons between the innovator and bioequivalent generic products.

Because the head-to-head clinical and pharmacokinetic comparisons of different extended-release methylphenidate products were only conducted recently, HellerEhrman's references and comments to previously approved Summary Bases of Approvals (SBAs) of branded methylphenidate, are without relevance. In effect, HellerEhrman argues that only after generic versions of extended-release methylphenidate have been approved and marketed should FDA consider the implications of the recent and important peer-reviewed published data.^{1,2,3,4} This

¹ Swanson JM, Wigal SB, Wigal T, et al. 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.

² Lopez F, Silva R, Pestreich L, et al. Comparative efficacy of two once daily methylphenidate formulations (RITALIN LA and CONCERTA) and placebo in children with attention deficit hyperactivity disorder across the school day. *Pediatr Drugs*. 2003; 5: 545-555.

approach would not protect the public health and would undermine credibility in generic drug approvals.

Analysis of the *Pediatrics* (Swanson, et al.)¹ data in conjunction with other data submitted by McNeil, adequately demonstrates the limitation of the current bioequivalence metrics to assure therapeutic equivalence among extended-release methylphenidate products, a shortcoming that is remedied with the addition of the AUC_{pR} metric in these bioequivalence determinations. The fact that the drug products at issue in the *Pediatrics* (Swanson, et al.)¹ head-to-head comparison have submitted full safety and efficacy data to FDA in NDAs only provides a greater basis for FDA's ability to confirm their different clinical profiles even though they met the current metrics for bioequivalence.

Because the core argument HellerEhrman makes throughout its Petition is that the *Pediatrics* (Swanson, et al.)¹ study in the McNeil Petition should be discounted, McNeil wishes to address HellerEhrman's argument on this important point.

The scientific validity of the study rests on the quality of its design and analysis and the qualifications of the investigators. The scientific validity and clinical relevance of the *Pediatrics* study (Swanson, et al.)¹ was accepted by the peer reviewers of *Pediatrics*, the official journal of the American Academy of Pediatrics. In this recently published laboratory school study by Swanson et al., the behavior and attention of 184 Attention-Deficit/Hyperactivity Disorder (ADHD) children were evaluated over a 12-hour day using a randomized, double-blind, three-treatment crossover design.¹ The effectiveness of 20mg-, 40mg-, and 60mg- METADATE CD[®] was compared with that of 18mg-, 36mg-, and 54mg- CONCERTA[®] and with placebo. Subjects were assessed during each classroom session on the Swanson, Kotkin, Atkins, M/Flynn, Pelham Scale (SKAMP).

McNeil acknowledges that the *Pediatrics* (Swanson, et al.)¹ comparison is between two differently formulated branded extended-release methylphenidate products. However, it is important to note that one would not expect, as occurred in this study, two different pharmaceutical alternatives at different molar doses and with different pharmacokinetic and clinical profiles to meet the two current criteria for bioequivalence. This is a signal, highly suggestive of a potential bioequivalence problem in extended-release methylphenidate products using only C_{max} and AUC_{0-∞}. Moreover, the signal is equally

³ Gonzalez MA, Pentikis HS, Anderl N, et al. Methylphenidate bioavailability from two extended-release formulations. *Inter J Clin Pharm Ther.* 2002;40:175-184.

⁴ Markowitz JS, Straughn AB, Patrick KS, et al. Pharmacokinetics of Methylphenidate after oral administration of two modified-release formulations in healthy adults. *Clin Pharmacokinet.* 2003;42:393-401.

valid in the context of determining generic equivalence or the equivalence of a manufacturer's two extended-release methylphenidate products after a manufacturing site or process change.

Because this signal is based on collective evidence from well-controlled clinical trials and pharmacokinetic studies, McNeil has submitted this information to FDA, pursuant to the agency's procedures for amending a bioequivalence requirement.⁵

1. Scientifically Valid Study Design

HellerEhrman suggests several specific design features that FDA should require to determine if AUC_{pR} is associated with early magnitude of effect, overall therapeutic effect or duration of effect. It claims that inferences about AUC_{pR} can only be derived from head-to-head comparisons of formulations designed for the same daily therapeutic effect. Such data would have scientific value but they could not contradict the fact, documented in McNeil's Petition, that standard FDA metrics for bioequivalence fail to detect clinically significant differences between medications known to be nonequivalent therapeutically. In contrast, AUC_{pR} can detect such differences.

2. Clinically Significant Efficacy Differences Over A Course of A Day

HellerEhrman notes that although the difference between CONCERTA[®] and METADATE CD[®] from the *Pediatrics* study (Swanson, et al.)¹ was statistically significant, "it has yet to be proven if this difference is clinically significant, especially when considering the strong response to placebo as measured by SKAMP scores at time zero." There is no apparent basis in fact for its comment about the placebo effect. The existence of a placebo effect would not be expected to bias estimates of either the mean or standard deviations of outcomes for the two active medications. Thus, a placebo effect would not bias the effect size of the CONCERTA[®] versus METADATE CD[®] comparison.

Regarding the question of clinical significance, the *Pediatrics* study (Swanson, et al.)¹ include the following in their study conclusions:

"...the results of this study suggest that the pharmacodynamic effects of these two formulations are not equivalent. Despite the similarity in overall and maximum exposure to methylphenidate, the differences in early and late exposure to methylphenidate with these two once-daily formulations result in detectable and potentially important differences in clinical efficacy during the day. This suggests

⁵ See 21 C.F.R. §§ 320.33(a) and 320.32(c).

that single-dose bioequivalence comparisons that are based only on AUC and C_{max} may be insensitive to clinically important differences in pharmacodynamic effects for this class of agents in this patient population (pg. e214).”

“...This finding is important because it suggests that, under the right conditions (a carefully controlled laboratory school setting), relatively small differences in the pattern of release of the total dose and the corresponding differences in plasma concentrations of MPH produce differences in the behavioral effects of MPH that can be detected and quantified (pg. e215).”

This shows that the authors clearly viewed and concluded the differences to be clinically important. Given that several of the authors are recognized experts in the stimulant treatment of ADHD and that *Pediatrics* is a highly respected journal, this statement provides strong support for the assertion that the statistically significant differences between CONCERTA[®] and METADATE CD[®] are clinically significant. The authors' conclusions are consistent with a summary of clinical efficacy findings from available published studies and FDA summaries of approvals from laboratory classroom studies of extended-release methylphenidate products in subjects with ADHD, which were included in McNeil's Petition.⁶

This same *Pediatrics* study (Swanson, et al.)¹ comparing the two extended-release methylphenidate products, CONCERTA[®] (CON) with METADATE CD[®] (MCD), demonstrated significant clinical differences in both early and late exposures over the course of a day. Both extended-release methylphenidate products separated from placebo, although METADATE CD[®] was ineffective at 12 hours. In addition, statistical differences in efficacy between the products were detected in the morning over the first four hours of the school day, and in the early evening measured at 12 hours. The estimated effect sizes obtained in the early morning were directly related to the absolute dose administered in the immediate-release component of each methylphenidate formulation. These early and late clinical differences are consistent with reported differences³ between the products' pharmacokinetic profiles early in the day, expressed as partial areas AUC_{4h} and AUC_{6h}, as well as late in the day.

The *Pediatrics* study (Swanson, et al.)¹ discusses such differences and includes the following in the study results and discussion:

“...These significant interactions suggest that the treatments differed but the pattern depended on the time of the assessment (i.e., the session)...this revealed

⁶ McNeil Citizen Petition of March 19, 2004 submitted to Docket 2004P-0139, pg. 6-8.

four general patterns (Figure 1) of treatment efficacy that were consistent across the three measures: (1) immediately after dosing, the placebo treatment was better than active treatment; (2) during the morning when MCD was better than CON and both active treatments were better than placebo; (3) during the afternoon when MCD and CON were, for the most part, similar in efficacy, but both active treatments were still superior to placebo; and (4) in the early evening when CON but not MCD was superior to placebo in some measures (pg. e210)."

"...we related the size of the drug effects (ESs) to the initial bolus components of each formulation...the ESs (Figure 3) obtained in the early morning were directly related to the absolute dose administered in the IR MPH bolus for each formulation (i.e., the dose delivered by the IR beads for MCD and by the overcoat of CON) (pg. e211)."

"...Despite the similarity in overall and maximum exposure to methylphenidate, the differences in early and late exposure to methylphenidate with these two once-daily formulations result in detectable and potentially important differences in clinical efficacy during the day (pg. e214)."

In sum, the design and analysis of the study were of high quality, as were the qualifications of the investigators. The scientific validity and clinical relevance of the study were accepted by the peer reviewers of *Pediatrics*. This scientific evidence is highly credible and substantially more powerful than any "scientific justification and analysis" to the contrary, provided by HellerEhrman. It is precisely this type of information coupled with the other clinical and pharmacokinetics data brought forth in McNeil's Petition that signal a potential bioequivalence problem.

B. SCIENTIFIC EVIDENCE ADEQUATELY SUPPORTS THE RELEVANCE OF AUC_{pR} FOR EXTENDED-RELEASE METHYLPHENIDATE PRODUCTS' BIOEQUIVALENCE DETERMINATIONS

1. Issues on Acute Tolerance: Acute Tolerance Has Important Implications For the Rate of Delivery of Methylphenidate Treatment For ADHD

HellerEhrman states that the concept of acute tolerance⁷ is theoretical and that "the currently available clinical data and analysis results in the literature do not support the

⁷ "Acute tolerance" is defined as the rapid development of tachyphylaxis over the course of the day such that targeted delivery pattern of zero order sustained release does not maintain the full medication across the day.

existence of acute tolerance in the pharmacological effect of methylphenidate." This statement, a key aspect of its criticism of "lack of scientific evidence," is not correct.

Acute tolerance for methylphenidate has been empirically documented by demonstrating that methylphenidate concentrations measured soon after an initial dose cause a greater pharmacodynamic effect than concentrations occurring at a later time. This effect is seen graphically as a clockwise hysteresis in the plasma concentration-effect relationship. As reviewed below, several studies have documented biological hysteresis for methylphenidate's effects on brain dopamine and clinical hysteresis for methylphenidate's effects on ADHD outcomes.

Aoyama et al. studied the effects of methylphenidate on dopamine concentrations in rat striatum following intravenous administration of methylphenidate.^{8,9} Both studies reported clockwise hysteresis for methylphenidate's effects on dopamine release in striatum. At early time points, increasing methylphenidate in striatum led to higher dopamine levels but at later time points the same methylphenidate concentrations led to lower dopamine levels. These effects in striatum are relevant to the methylphenidate treatment of ADHD. As demonstrated by Volkow et al., *in vivo* neuroimaging studies showed that methylphenidate exerts its pharmacodynamic effects by binding to dopamine transporters, most of which are located in striatum.¹⁰ At doses used therapeutically for ADHD, methylphenidate may block more than 50% of the dopamine transporters. This increases dopamine levels^{10,11} and is believed to counteract the excess of dopamine transporter activity observed in neuroimaging studies of ADHD patients.^{12,13}

Volkow et al. used positron emission tomography to study the pharmacokinetics and pharmacodynamics of intravenous methylphenidate in the human brain.^{14,15} The

⁸ Aoyama T, Kotaki H, Sawada Y, et al. Pharmacokinetics and pharmacodynamics of methylphenidate enantiomers in rats. *Psychopharmacology (Berl)*. 1996; 127: 117-122.

⁹ Aoyama T, Yamamoto K, Kotaki H, et al. Pharmacodynamic modeling for change of locomotor activity by methylphenidate in rats. *Pharm Res*. 1997; 14: 1601-1606.

¹⁰ Volkow ND, Wang G-J, Fowler JS, et al. Dopamine transporter occupancies in the human brain induced by therapeutic doses of oral methylphenidate. *Am J Psychiatry*. 1998;155: 1325-1331.

¹¹ Volkow ND, Swanson JM. Variables that affect the clinical use and abuse of methylphenidate in the treatment of ADHD. *Am J Psychiatry*. 2003;160: 1909-18.

¹² Dougherty DD, Bonab AA, Spencer TJ, et al. Dopamine transporter density is elevated in patients with Attention-Deficit/Hyperactivity Disorder. *Lancet*. 1999; 354:2132-2133.

¹³ Krause K, Dresel SH, Krause J, et al. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. *Neurosci Lett*. 2000;285:107-110.

¹⁴ Volkow ND, Wang GJ, Gatley SJ, et al. Temporal relationships between the pharmacokinetics of methylphenidate in the human brain and its behavioral and cardiovascular effects. *Psychopharmacology (Berl)*. 1996;123:26-33.

¹⁵ Swanson J, Volkow N. Pharmacokinetic and pharmacodynamic properties of methylphenidate in humans. *Stimulant Drugs and ADHD: Basic and Clinical Neuroscience*. 2001; 259-282.

distribution of radioactively labeled [^{11}C]methylphenidate in the brain was tracked over time. The uptake of [^{11}C]methylphenidate in striatum was very rapid, reaching peak concentrations within ten minutes. Clearance was relatively slow ($t_{1/2} = 90$ minutes). While being imaged, the subjects rated the degree to which they felt "high", "a rush", or "restlessness." These ratings were positively correlated with the initial uptake in striatum but consistent with acute tolerance, these ratings subsequently returned to baseline even though striatum showed the presence of substantial concentrations of methylphenidate.¹⁴ The authors concluded that there was acute tolerance to the behavioral effects of intravenous methylphenidate.

A study of the relationship between methylphenidate plasma concentrations and measures of attention showed that the medicine's pharmacodynamic effects were predominant in the early part of the absorption phase and were weaker after methylphenidate had reached its peak concentration.¹⁶ Different methylphenidate dosing strategies were studied in a double-crossover design.¹⁷ The best efficacy was achieved by an ascending profile of methylphenidate plasma concentration over time. A flat profile lost about 40% of full efficacy. The poor efficacy of the flat profile further supported the acute tolerance hypothesis. Swanson and colleagues confirmed the existence of acute tolerance in the methylphenidate treatment of ADHD youth.^{15,18,19,20} These findings are now well accepted as indicated by the American Academy of Child and Adolescent Psychiatry (AACAP) guidelines for the use of stimulant medication which state,

"The concentration-enhancing and activity-reducing effects of methylphenidate can disappear well before the medication leaves the plasma, a phenomenon termed 'clockwise hysteresis'" and "More recent pharmacodynamic studies suggest that stimulant plasma levels need to increase throughout the day to maintain constant efficacy. This is because short-term tolerance to methylphenidate develops by the second dose given in the same day".²¹

¹⁶ Perel JM, Greenhill LL, Curran S, et al. Correlates of pharmacokinetics and attentional measures in methylphenidate treated hyperactive children. *Clin Pharmacol Ther.* 1991; 49:160-161.

¹⁷ Swanson J, Gupta S, Guinta D, et al. Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. *Clin Pharmacol Ther.* 1999; 66:295-305.

¹⁸ Swanson J, Gupta S, Williams L, et al. Efficacy of a new pattern of delivery of methylphenidate in the treatment of ADHD: Effects on activity level in the classroom and on the playground. *J Am Acad Child Adolesc Psychiatry.* 2002;41: 1306-1314.

¹⁹ Swanson J, Gupta S, Lam A, et al. Development of a new once-a-day formulation of methylphenidate for the treatment of ADHD: Proof of concept and proof of product studies. *Arch Gen Psychiatry.* 2003; 60: 204-211.

²⁰ Swanson JM, Volkow N. Pharmacokinetic and pharmacodynamic properties of stimulants: Implications for the design of new treatments for ADHD. *Beh Brain Res.* 2002;130:73-78.

²¹ Greenhill LL, Pliszka S, Dulcan MK, et al. Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. *J Am Acad Child Adolesc Psychiatry.* 2002;41: 26S-49S.

2. Issues on Correlation of Early Plasma Exposure or AUC_{pR} with Therapeutic Effects: Time Course Impacts the Effects of Methylphenidate Treatment

HellerEhrman attempts to dismiss McNeil's claim that measuring drug exposure over a certain time interval is critical by stating that, for methylphenidate, "the relationship between early exposure (and/or rate of absorption) and response (for efficacy or acute tolerance) has not been critically established."

Attending to the time course of methylphenidate's action is essential for the therapeutic management of ADHD. Although the symptoms of the disorder can occur throughout the day leading to clinically significant impairments in a variety of life settings, the nature and timing of symptom expression varies greatly from one patient to the next. From a clinical perspective, it is well accepted by physicians that the treatment of ADHD must consider the clinical implications of the time course of methylphenidate's action throughout the day.

The National Institute of Mental Health (NIMH) Multimodal Treatment Study of ADHD showed the clinical advantages of adjusting doses during chronic therapy. The methylphenidate treatment of ADHD led to better long-term outcome when closely managed by experts in comparison to management by physicians in the community.^{22,23} These differences have been attributed to the careful attention to dosing strategies used by the expert clinicians.^{23,24,25}

A survey of ADHD experts provides insights into the clinical significance of adjusting methylphenidate doses to fine tune the time course of therapeutic and adverse effects.²⁶ The clinical practice guidelines derived from the survey listed "time course" factors to be considered when choosing a dosing schedule for patients. The AACAP practice guidelines also recognize the complexity of dosing and timing stimulant medication, noting that these medications can require complex schedules of administration and that adjusting the timing of doses can sometimes alleviate side effects.²¹

²² The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for Attention-Deficit/Hyperactivity Disorder. *Arch Gen Psychiatry*. 1999;56: 1073-1086.

²³ Greenhill L, Beyer DH, Finkleson J, et al. Guidelines and algorithms for the use of methylphenidate in children with attention-deficit/hyperactivity disorder. *J Attent Disord*. 2002; 6: 89-100.

²⁴ Greenhill LL, Abikoff HB, Arnold LE, et al. Medication treatment strategies in the MTA Study: relevance to clinicians and researchers. *J Am Acad Child Adolesc Psychiatry*. 1996;35: 1304-1313.

²⁵ Vitiello B, Severe JB, Greenhill LL, et al. Methylphenidate dosage for children with ADHD over time under controlled conditions: lessons from the MTA. *J Am Acad Child Adolesc Psychiatry*. 2001; 40: 188-196.

²⁶ Conners CK, March J, Frances AJ, et al. Treatment of Attention-Deficit/Hyperactivity Disorder: Expert consensus guidelines. *J Attent Disord*. 2001;4(S1).

Physicians and patients rely on the FDA to ensure that an innovator and generic product version will have the same safety and efficacy profiles. Further, for patients with ADHD who have been stabilized on CONCERTA[®], these patients and their parents and doctors expect that any "AB" rated generic drug product has a similar coverage pattern as CONCERTA[®]. Currently, extended-release methylphenidate products (including a generic version of CONCERTA[®]) can be approved by applying only the two bioequivalence metrics of C_{max} and AUC_{0-∞}. However, the available data brought forward by McNeil in its Petition suggest an uncertainty in, and potentially unreliability of, expected daily clinical outcomes if one extended-release methylphenidate product were to be substituted for another. In the absence of clinical equivalence, such substitution would potentially disrupt ADHD treatment regimes, which are tailored to the specific daily schedules of children with ADHD.

3. Issues on Correlation between AUC_{pR} and Duration of Effect

Numerous studies utilized SKAMP scores, which HellerEhrman attacks as an "unvalidated surrogate marker." In fact, the SKAMP score has established reliability and validity and is widely used in ADHD research, and in clinical studies of ADHD medications approved by FDA.^{1,2,15,27,28,29,30,31}

HellerEhrman also criticized the *Pediatrics* study (Swanson et al.)¹ because it used a crossover study design, claiming that a crossover study is not valid because patients should have been stratified (based on their needs for methylphenidate coverage) to receive CONCERTA[®] versus METADATE CD[®]. This statement is made without providing any data or theoretical justification and it is not explained how a crossover design would have biased the results to be supportive of AUC_{pR}. The suggestion for assigning treatments based on subject characteristics is actually at variance with standard approaches for comparing two medications, which call for either randomized parallel designs or crossover designs.

²⁷ Swanson JM, Lerner M, Wigal T, et al. The use of a laboratory school protocol to evaluate concepts about efficacy and side effects of new formulations of stimulant medications. *J Atten Disord.* 2002;6: S73-88.

²⁸ Wigal S, Gupta S, Guinta D, et al. Reliability and validity of the SKAMP rating scale in a laboratory school setting. *Psychopharmacol Bull.* 1998;34:47-53.

²⁹ McCracken JT, Biederman J, Greenhill LL, et al. Analog classroom assessment of a once-daily mixed amphetamine formulation, SL1381 (ADDERALL XR), in children with ADHD. *J Am Acad Child Adolesc Psychiatry.* 2003;42: 673-683.

³⁰ Swanson J, Wigal S, Greenhill L, et al. Analog classroom assessment of Adderall in children with ADHD. *J Am Acad Child Adolesc Psychiatry.* 1998;37: 519-526.

³¹ Wigal SB, Swanson JM, Greenhill L, et al. Evaluation of individual subjects in the analog classroom setting: II. Effects of dose of amphetamine (Adderall). *Psychopharmacol Bull.* 1998; 34: 833-838.

4. Issues on Correlation between AUC_{pR} and Early Magnitude of Effect

HellerEhrman states that there have been no valid or scientifically meaningful studies to demonstrate that AUC_{pR} correlated with early magnitude of clinical effect. Such is irrelevant since neither C_{max} nor AUC_{0-∞} has been as rigorously validated and correlated with clinical endpoints. McNeil's Petition has presented a number of valid clinical and pharmacokinetic studies demonstrating that AUC_{pR} is consistent with the results and serves as an essential metric to make the appropriate decision in bioequivalence tests of extended-release methylphenidate products.³²

The *Pediatrics* study (Swanson, et al.)¹ specifically demonstrates that the size of the drug effects (ESs) obtained in the early morning was directly related to the absolute dose administered in the immediate-release methylphenidate bolus for each formulation (i.e., the dose delivered by the immediate-release beads for METADATE CD[®] and by the overcoat of CONCERTA[®]). Additionally, despite the similarity in overall and maximum exposure to methylphenidate, the differences in early and late exposure to methylphenidate with these two once daily formulations result in detectable and potentially important differences in clinical efficacy during the day. Further, in a head-to-head pharmacodynamic study in 36 ADHD children, clinical differences in efficacy over four and eight hours were demonstrated between RITALIN LA 20-mg and CONCERTA 18-mg, which coincide with the pharmacokinetic differences. The conclusion that these products are not bioequivalent accurately reflects the morning clinical differences demonstrated in this study.²

In its comments, HellerEhrman attempts simply to refocus attention from the need for an additional AUC_{pR} metric to that of validating the metric. McNeil's response on such validation, including that related to individual plasma concentration-time data, is detailed in the next section.

C. STATISTICAL JUSTIFICATION AND FEASIBILITY: BOTH EXIST FOR ESTABLISHING ACCEPTANCE CRITERIA FOR AUC_{pR} FOR EXTENDED-RELEASE METHYLPHENIDATE PRODUCTS

HellerEhrman criticizes the use of "mean" clinical effects and pharmacokinetic data to support McNeil's proposal of AUC_{pR} as an additional essential bioequivalence metric. However, mean data are used to make regulatory decisions, whether in safety and efficacy determinations in an NDA (difference in means between treatments and placebo) or in bioequivalence determinations (ratio of least square means for log-

³² McNeil Citizen Petition of March 19, 2004 submitted to Docket 2004P-0139, pg. 15-20.

transformed C_{max} and $AUC_{0-\infty}$). Per current FDA guidelines for a generic version of CONCERTA, mean pharmacokinetics data obtained in adults would be used to determine the bioequivalence of two extended-release methylphenidate products, which if equivalent, would lead to a regulatory conclusion of therapeutic equivalence in children. No individual C_{max} and $AUC_{0-\infty}$ data in adults have been correlated with the safety and efficacy of extended-release methylphenidate products in children. Rather the bioequivalence test is based on an understanding that some relationship exists between mean pharmacokinetic measures of drug exposure and safety/efficacy.³³

The individual response variability (multiple peaks in the plasma methylphenidate concentration-time curves of CONCERTA®) issue raised by HellerEhrman is best addressed by using precisely the AUC_{pR} metric McNeil proposes. As noted in McNeil's original Petition (pg. 12), C_{max} is poorly estimated for products with multiple peaks. Additionally, the overall absorption pattern of a product -- a reflection of multiple peaks, troughs, peak sizes, and ascending sections created by the immediate and extended-release fractions of the total dose and release technology -- is best obtained with the early exposure metric AUC_{pR} . This metric links the early absorption profile (which relates directly to early magnitude of effect and indirectly to duration of effect) to the overall pharmacokinetic profile, allowing accurate bioequivalence decisions (pg. 15).³⁴

Data from four CONCERTA bioequivalence studies submitted to NDA 21-121 and reanalyzed for McNeil's original Petition (Table 3, pg 15) showed that AUC_{pR} had similar low estimates of intrasubject variability as that for $AUC_{0-\infty}$ within the same study. No increase in study sample size would be needed with the addition of AUC_{pR} , and the statistical test criterion of the 90% confidence intervals being contained within the 80 to 125% limits for equivalence remains identical as that for C_{max} and $AUC_{0-\infty}$. The reanalyses of these study data demonstrate that all formulation and treatment comparisons readily met this statistical criterion, and that the mean pharmacokinetic curves were sufficiently superimposable.

Regarding HellerEhrman's discussion of the need for establishing regulatory acceptance criteria for AUC_{pR} , it should be noted that establishing bioequivalence relies on pharmacokinetic measurements, such as C_{max} and $AUC_{0-\infty}$, which are reflective of systemic drug exposure.³³ The standard study design is conducted in healthy adults (not pediatric patients) and may be viewed as a simple controlled bioassay to ensure that different formulations of the same active moiety provide similar patterns of systemic

³³ FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (March 2003).

³⁴ McNeil Citizen Petition of March 19, 2004 submitted to Docket 2004P-0139.

exposure. As FDA states in its Guidance³³: “This approach rests on the understanding...that some relationship exists between efficacy/safety and concentration of active moiety and/or its important metabolite or metabolites in the systemic circulation”.

In effect, neither C_{max} nor $AUC_{0-\infty}$ has been as rigorously validated and correlated with clinical endpoints as that suggested be mandated for AUC_{pR} by the comments of HellerEhrman in order for this early exposure metric to be used in establishing bioequivalence. McNeil never set out to validate AUC_{pR} ; only to bring before FDA the best available scientific data on methylphenidate bioequivalence. Complete validation should not be required for FDA to consider AUC_{pR} 's utility as an additional metric as proposed in McNeil's Petition, given the troublesome signal of potential bioequivalence problems identified in collective well-controlled clinical and pharmacokinetics data.

FDA has itself acknowledged the limitations of both direct (e.g., rate constant, rate profile) and indirect (e.g., C_{max} , T_{max} , mean absorption time, mean residence time, C_{max} normalized to AUC) parameters in their ability to assess rate of absorption, one of the statutory definitions for bioequivalence³⁵ and an important consideration in establishing bioequivalence for extended-release methylphenidate products. Importantly, AUC_{pR} is the bioequivalence metric that is most consistent with the available data.

On the basis of the collective available scientific evidence from several extended-release methylphenidate products, McNeil's Petition requested that early exposure, AUC_{pR} , serve as an additional essential metric or anchor to the pharmacokinetic profile that more closely accounts for the whole drug exposure pattern. Other exposure metrics may be considered, but AUC_{pR} is most consistent with the available well-controlled data.

Although AUC_{pR} captures the early drug exposure pattern, differences in AUC_{pR} also indirectly reflect differences in late drug exposure or the latter part of the pharmacokinetic profile. For most drug products, the general shapes of comparative pharmacokinetic profiles are somewhat superimposable, so the two metrics (C_{max} and $AUC_{0-\infty}$) are adequate to establish bioequivalence. However, if the early and late profiles (times generally before and after T_{max}) differ markedly, then only one additional metric describing either side is needed. The reason that two additional metrics are not needed is that $AUC_{0-\infty}$ is equal to the sum of early AUC_{pR} and late AUC_{pR} . Therefore, adding late AUC_{pR} as the fourth metric to describe the complete drug exposure pattern would be redundant.

³⁵ 21 CFR § 320.1.

III. CONCLUSIONS

- Overall, HellerEhrman's comments do not succeed in challenging the scientific rationale supporting McNeil's conclusions and request as previously stated in our Petition. Moreover, their comments direct attention away from the central scientific issue, i.e., the need for an additional bioequivalence metric for extended-release methylphenidate products that is sensitive to the overall pharmacokinetic profile and consistent with desired ADHD patient outcomes. HellerEhrman inappropriately refocuses the debate to that of validation and correlation with clinical endpoints of the proposed metric (AUC_{pR}). HellerEhrman's demands, and approach for AUC_{pR} are not warranted, especially given that neither C_{max} nor $AUC_{0-\infty}$ has been as rigorously validated and correlated with clinical endpoints.
- Based on available well-controlled data brought forth, McNeil raises an important concern that current requirements for a regulatory conclusion of bioequivalence are not sufficient to ensure clinical equivalence for extended-release methylphenidate products and, as such, generic versions could be inappropriately deemed therapeutically equivalent. In the absence of clinical equivalence, extended-release methylphenidate substitution can disrupt ADHD treatment regimes, which are tailored to the specific daily schedules of children with ADHD.
- McNeil renews our request that the metric AUC_{pR} , or area under the curve to the population median T_{max} of the reference formulation, be used as a supplemental essential metric, in addition to $AUC_{0-\infty}$ and C_{max} , to ensure bioequivalence and, hence, therapeutic equivalence of extended-release methylphenidate products.

Respectfully yours,

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