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

CITIZEN PETITION

At the request of the United States Food and Drug Administration, McNeil Consumer & Specialty Pharmaceuticals, a Division of McNeil-PPC, Inc. (McNeil), Fort Washington, PA, submits this petition under section 505 of the Federal Food, Drug, and Cosmetic Act, and 21 C.F.R. § 10.30. McNeil requests that the Commissioner of Food and Drugs apply additional bioequivalence metrics other than the average bioequivalence parameters, to ensure that the approval of generic versions of CONCERTA® (methylphenidate HCl) Extended-release Tablets are both bioequivalent and clinically equivalent to the innovator product.

A. ACTION REQUESTED

McNeil supports the FDA's Office of Generic Drugs in the approval of therapeutically equivalent drug products. McNeil has no objection to the consideration of a generic version of CONCERTA as long as FDA ensures that the generic version exhibits an overall pharmacokinetic profile comparable to CONCERTA, and can be found to be clinically equivalent. This petition presents scientific reasons to support the conclusion that a bioequivalence determination based solely on the average bioequivalence metrics (AUC_{0-t} , $AUC_{0-\infty}$, and C_{max}) for extended-release methylphenidate products for Attention Deficit Hyperactivity Disorder (ADHD) may not, in this particular instance, predict clinical effects. Therefore, McNeil requests that the metric, AUC_{pR} , or area under the curve to the population median T_{max} of the reference formulation in a single-dose study in healthy fasting volunteers, be used as an essential supplement to ensure bioequivalence and true therapeutic equivalence of extended-release methylphenidate products.

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In this petition, McNeil presents information demonstrating that two products that meet average bioequivalence metrics may, nevertheless, fail to provide the same clinical effects under their labeled conditions of use. Differences in early (and late) exposure to methylphenidate, result in detectable and important differences in clinical effects during the day.

Such clinical differences may include

- Acute tolerance
- Early magnitude of effect
- Duration of effect

These differences can be attributed to the overall pharmacokinetic profile of CONCERTA Extended-release Tablets. AUC_{pR} is a more sensitive measure of early absorption profiles, capturing differences due to both the immediate-release fraction of total methylphenidate and the extended-release technology. McNeil, therefore, requests that the AUC_{pR} metric be considered an essential supplement to ensure bioequivalence and, hence, therapeutic equivalence of extended-release methylphenidate products in ADHD.

B. STATEMENT OF GROUNDS

I. EXECUTIVE SUMMARY

Methylphenidate treatment has been proven to be highly effective in both managing the core symptoms of ADHD and mitigating many of the adverse outcomes of the disorder. Because the symptoms of ADHD are expressed over the course of a child's daily schedule, differences in methylphenidate clinical effectiveness over time may significantly affect a patient's ability to function well during critical periods of the day.

Different technologies for extending drug release and the varying fractions of total methylphenidate provided as immediate- (0 to 50%) and extended-release (50 to 100%) result in markedly dissimilar pharmacokinetic profiles among extended-release methylphenidate products. These profiles differ such that the early magnitude of effect, degree of acute tolerance, and duration of effect varies for similar total methylphenidate doses. Therefore, sufficient bioequivalence metrics that are sensitive to the overall pharmacokinetic profile and predictive of desired ADHD patient outcomes are essential in the evaluation of extended-release methylphenidate products.

- **For Extended-Release Methylphenidate Products, Bioequivalence Decisions Based on AUC_{0-t}, AUC_{0-∞}, and C_{max} Alone Are Insufficient**

Bioequivalence determinations are generally based on AUC_{0-t}, AUC_{0-∞}, and C_{max}. For this petition, only AUC_{0-∞} and C_{max} comparisons are discussed. AUC_{0-∞} is determined as the summation of area computed to the last observation and extrapolated area to infinity. For many drugs, the extrapolated area represents a significant amount of the total area represented by AUC_{0-∞}. However, for a drug with a short half-life drug, such as methylphenidate, plasma concentrations are close to the limit of detection by 24 hours. Hence, the AUC_{0-t}, determined at 24 hours, is very close in value to the AUC_{0-∞}.¹

If only AUC_{0-∞} and C_{max} are used, products that are not clinically equivalent could be inappropriately deemed therapeutically equivalent. To prevent this, in addition to AUC_{0-∞} and C_{max}, McNeil requests that AUC_{pR}, or area under the curve to the population median T_{max} of the reference formulation, be used as an essential supplement to establish bioequivalence of extended-release methylphenidate products in a single-dose study in healthy fasting volunteers. AUC_{pR} is a sensitive measure of early absorption profiles,

¹ Modi N, Noveck RJ and Gupta SK. Dose-proportional and stereospecific pharmacokinetics of methylphenidate delivered using an osmotic, controlled-release oral delivery system. J Clin Pharmacol. 2000;40:1141-1149.

because it captures the differences due to both the immediate-release fraction of total methylphenidate and the extended-release technology.

- **AUC_{pR} is Sensitive to Differences in the Absorption Profile and Clinical Effects Among Extended-Release Methylphenidate Products**

Collectively, study data show that comparable pharmacokinetic profiles are essential to ensure bioequivalence and clinical equivalence for extended-release methylphenidate formulations, in general, and for CONCERTA, in particular. These data show that products known to have significant clinical differences may, nevertheless, fall within the accepted confidence intervals for bioequivalence using only AUC_{0-∞} and C_{max}. These study data confirm the relationship between early exposure, AUC_{pR}, and clinical effects.

- **Low Intrasubject Variability Supports Use of AUC_{pR} For Methylphenidate**

FDA has previously expressed concern about use of partial areas as a reliable measure of bioequivalence, citing high variability (>30%) of AUC_{pR} shown in bioequivalence studies involving certain immediate- and extended-release products.² Analyses of CONCERTA methylphenidate plasma data show markedly low intrasubject variability ranging between 8.3 to 18.5% for AUC_{pR}. Moreover, the intra- and intersubject variabilities of AUC_{pR} were comparable to those for AUC_{0-∞} in the several studies evaluated. Adding AUC_{pR} to the conventional metrics of C_{max} and AUC_{0-∞} will have negligible impact on study size to determine bioequivalence.

² FDA response dated November 21, 2003 entered on December 10, 2003 to the citizen petition filed on behalf of Pharmacia Corporation and its affiliate G.D. Searle. Docket Number 01P-0546.

II. THERAPEUTIC IMPLICATIONS FOR ATTENTION DEFICIT AND HYPERACTIVITY DISORDER (ADHD)

A. ADHD Prevalence and Impact on Society

ADHD is the most commonly diagnosed childhood behavioral disorder, affecting eight to ten percent of school-age children.³ Children with untreated ADHD have personal and social difficulties with far-reaching and long-term consequences.

The International Consensus Statement on ADHD concluded that ADHD patients are far more likely than their non-ADHD peers to have problems at school (32 to 40% drop out of school, five to ten percent complete college), at work (70 to 80% underperform at work), and in social interactions (50 to 70% have few or no friends, 40 to 50% engage in antisocial activities), and they use tobacco or illicit drugs more than those without ADHD. They are more likely to get pregnant at a young age (40%), suffer from sexually transmitted diseases (16%), be involved in multiple car accidents and suffer from depression (20 to 30%) and personality disorders (18 to 25%) as adults.⁴

B. Methylphenidate Benefits for ADHD

Both the American Academy of Pediatrics (AAP) Clinical Practice Guidelines and the American Academy of Child and Adolescent Psychiatry (AACAP) Practice Parameters recommend stimulants as first-line drug therapies for ADHD.⁵

Methylphenidate is a mild central nervous system stimulant that is used for treating ADHD core symptoms of hyperactivity, impulsivity and inattention. Research has shown methylphenidate's efficacy for improving cognitive processing,⁶ academic performance, social behavior, and aggression.⁷ Several studies have demonstrated that stimulant

³ American Academy of Pediatrics Committee on Quality Improvement and Subcommittee on Attention-Deficit/Hyperactivity Disorder. Diagnosis and Evaluation of the Child with Attention-Deficit/Hyperactivity Disorder. *Pediatrics*. 2000; 105: 1158-1170.

⁴ Barkley RA. International consensus statement on ADHD. *Clin Child Fam Psychol Rev*. 2002;5:89-111.

⁵ American Academy of Pediatrics Committee on Quality Improvement and Subcommittee on Attention-Deficit/Hyperactivity Disorder. Treatment of the school-aged child with attention deficit /hyperactivity disorder. *Pediatrics*. 2001;108:1033-1044. 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.

⁶ Berman T, Douglas VI, Barr RG. Effects of methylphenidate on complex cognitive processing in attention-deficit hyperactivity disorder. *J Abnorm Psychol*. 1999;108:90-105.

⁷ 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.

treatments, including methylphenidate, can lower the risk of developing substance use disorder in children with ADHD.⁸

C. ADHD Symptom Coverage Throughout the Day

It is clinically important that ADHD symptoms are managed in a predictable manner throughout the course of the day, with therapeutic goals in mind.⁹ CONCERTA is the only product that has been shown to provide therapeutic coverage for ADHD symptoms comparable to three times daily dosing of immediate-release methylphenidate. CONCERTA is the only once-daily methylphenidate product to have demonstrated clinical effectiveness through 12 hours after dosing.¹⁰

The other extended-release methylphenidate formulations were designed to provide coverage comparable to two times daily dosing of immediate-release methylphenidate resulting in shorter duration products. Table 1 provides a summary of clinical findings from available published studies and FDA summaries of approvals from laboratory classroom studies of extended-release methylphenidate products in subjects with ADHD.

⁸ Kramer JR, Loney J. Stimulant Medication, Childhood Symptoms, and Adult Substance Involvement Among Men with a History of ADHD. *Alcohol Clin Exp Res*. 2002; 27 (suppl 5): 182A; Katusic SK, Barbaresi WJ, Colligan RC, et al. The Impact of Psychostimulant Treatment on Drug/Alcohol Abuse Among Children with AD/HD. *J Dev Behav Pediatrics*. 2003; 24:396-397.

⁹ American Academy of Pediatrics Committee on Quality Improvement and Subcommittee on Attention-Deficit/Hyperactivity Disorder. Treatment of the School-Aged Child with Attention-Deficit/Hyperactivity Disorder. *Pediatrics*. 2001;108:1033-1044; 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.

¹⁰ CONCERTA prescribing information, October 2003.

Table 1. Efficacy and Duration Findings from Laboratory Classroom Studies of Extended-Release Methylphenidate (MPH)

Product, Dose and Study	Comparator	Measure	Reported Post-dose Efficacy and Duration Findings
CONCERTA 18-, 36-, 54-mg NDA 21-121 Protocol 98-003 ¹¹ Protocol 97-025 ¹²	Placebo tid MPH IR 5-, 10-, 15-mg tid	SKAMP attention	• CONCERTA > placebo through 12 hours
METADATE CD 20-, 40-mg NDA 21-259 Study 4 ¹³	Placebo MPH IR 10-mg bid	SKAMP attention; deportment PERMP	• METADATE CD > placebo through 9 hours SKAMP, PERM
METADATE CD 20-, 40-, 60-mg Greenhill LL, DeCroy HH, Hirshy-Dirksen SJ, et al ¹⁴ Hatch SJ, Swanson JM ¹⁵ Swanson JM, Wigal SB, Wigal T, et al ¹⁶	Placebo CONCERTA 18-, 36-, 54-mg once daily	SKAMP deportment, attention PERMP	<ul style="list-style-type: none"> • CONCERTA > METADATE CD and placebo at 12 hours for all three measures • CONCERTA and METADATE CD > placebo at hours 1.5 through 7.5 for all three measures • METADATE CD > CONCERTA at 1.5, 3.0 and 4.5 hours for SKAMP measures

SKAMP: Swanson, Kotkin, Atkins, M/Flynn; Pelham Scale; PERMP: permanent products math test; IR: immediate release

¹¹ Swanson J, Lerner M, Gupta S, 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.

¹² Pelham W, Gnagy E, Burrows-MacLean L, et al. Once-a-day CONCERTA methylphenidate versus three-times-daily methylphenidate in laboratory and natural settings. Pediatrics. 2001;107(6):e105.

¹³ Wigal SB, Sanchez DY, DeCory HH, et al. Selection of the optimal dose ration for a controlled-delivery formulation of methylphenidate. J Applied Research. 2003;3(1):46-63.

¹⁴ Greenhill LL, DeCroy HH, Hirshy-Dirksen SJ, et al. Comparisons of classroom deportment in 6–12 year olds with ADHD after administration of two once-daily extended release MPH formulations. American Psychiatric Association. May 21, 2003; San Francisco, CA.

¹⁵ Hatch SJ, Swanson JM. The COMACS study: Was it fair and does it matter? Am Acad Child Adolesc Psych. October 2003; Miami, FL;

¹⁶ 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:e206-216.

Table 1. Efficacy and Duration Findings from Laboratory Classroom Studies of Extended-Release Methylphenidate (MPH)

Product, Dose and Study	Comparator	Measure	Reported Post-dose Efficacy and Duration Findings
RITALIN LA 20-mg NDA 21-284 Protocol 02 ¹⁷	Placebo Other RITALIN MPH modified release	SKAMP attention	<ul style="list-style-type: none"> • RITALIN LA > placebo for AUC SKAMP attention 0-9 hours
RITALIN LA 20-mg Lopez F, Silva R et al. ¹⁸	Placebo CONCERTA 18-, 36-mg once daily	SKAMP attention, deportment combined	<ul style="list-style-type: none"> • CONCERTA and RITALIN LA > placebo for first 4 hours and over entire 8 hours • RITALIN LA > CONCERTA 18-, 36-mg for AUC 0-4 hours • RITALIN LA > CONCERTA 18-mg for AUC 0-8 hours
RITALIN-SR 20-mg Pelham WE, Sturges J, Hoza J, et al. ¹⁹ (structured daily schedule for 3 days at summer treatment program)	Placebo MPH IR 10-mg bid	Errors of omission in continuous performance tasks	<ul style="list-style-type: none"> • RITALIN-SR > placebo not until 3 hours and maintained through 8 hours

SKAMP: Swanson, Kotkin, Atkins, M/Flynn, Pelham Scale
 IR: immediate release

¹⁷ This study is cited in the discussion section of a published report of a different study: Biederman J, Quinn D, Weiss M, et al. Efficacy and safety of RITALIN LA in children with attention deficit hyperactivity disorder. *Pediatr Drugs*. 2003; 5(12): 833-841; NDA-21-284 Summary Basis of Approval.

¹⁸ Lopez F, Silva R, et al. Comparative efficacy of two once daily methylphenidate formulations (RITALIN LA and CONCERTA) and placebo in children with ADHD across the school day. *Pediatr Drugs*. 2003; 5:545-555.

¹⁹ Pelham WE, Sturges J, Hoza J, et al. Sustained release and standard methylphenidate effects on cognitive and social behavior in children with attention deficit disorder. *Pediatrics*. 1987;80(4):491-501.

III. VARYING DELIVERY FEATURES OF EXTENDED-RELEASE METHYLPHENIDATE PRODUCTS

Methylphenidate is a short-acting stimulant with a short half-life (3 to 4 hours). It requires multiple doses during the day to maintain improvements in behavioral symptoms of ADHD. Once-daily products generally improve patient compliance. In response to the need for improved patient compliance, methylphenidate products were formulated using various extended-release technologies (cellulose matrix, osmotic pump, and polymer-coated drug beads). In addition, these products also used different fractions of the total methylphenidate dose as immediate- (0 to 50%) and extended-release (50 to 100%). Currently available extended-release methylphenidate products are listed in Table 2. These design features result in markedly dissimilar pharmacokinetic profiles among these products, as discussed in Section IV of this petition.

Table 2. Comparison of Current Extended-Release (ER) Methylphenidate Products

ER Methylphenidate Product	Formulation Type; Percentage IR and ER	IR (mg)	ER (mg)	Total Dose (mg)
RITALIN-SR Tablet, ²⁰ 20-mg	Cellulose matrix 0% IR 100% ER Cellulose Matrix	0	20	= 20
CONCERTA Tablet, ²¹ 18-mg	OROS® Tri-layer 22% IR Coat 78% OROS	4	14	= 18
METADATE CD Capsule, ²² 20-mg	Beaded two-pulse system 30% IR Coated Beads 70% ER Coated Beads	6	14	= 20
RITALIN LA Capsule, ²³ 20-mg	SODAS™ beaded two-pulse system 50% IR Coated Beads 50% ER Coated Beads	10	10	= 20

IR – immediate release, ER – extended release

²⁰ RITALIN-SR prescribing information, January 2001.

²¹ CONCERTA prescribing information, October 2003.

²² METADATE CD prescribing information, July 2003.

²³ RITALIN LA prescribing information, February 2003.

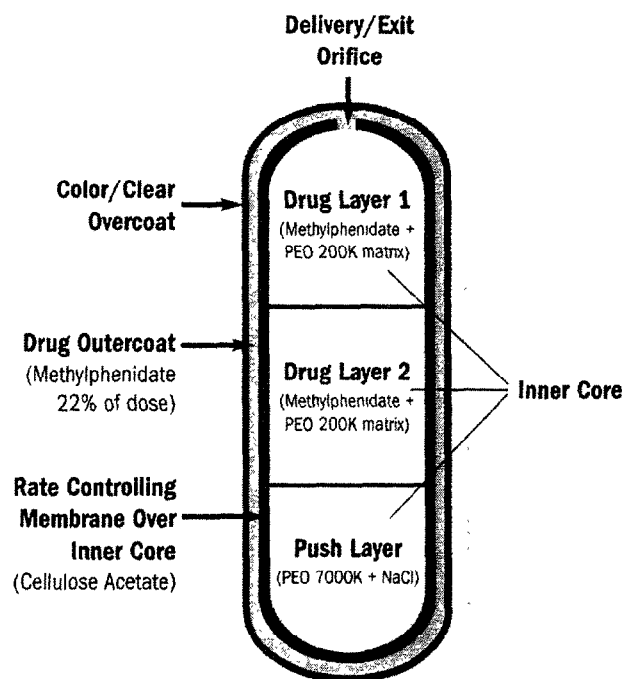
A study of ADHD children was conducted to examine the relationships between clinical effects and the drug delivery patterns. Compared with the bimodal methylphenidate concentration profile associated with twice daily dosing, a sustained flat profile lost about 40% full efficacy indicating acute tolerance.²⁴ The OROS methylphenidate delivery system of CONCERTA was designed to counteract acute tolerance by providing an initial immediate release of drug (22% of the dose in the outercoat) and an osmotic-controlled slow release of the remaining drug that results in an ascending absorption profile. CONCERTA was designed to approximate three times daily dosing of immediate-release methylphenidate, whereas the coated-bead formulations were designed to mimic two times daily dosing.

The CONCERTA (methylphenidate HCl) extended-release tablet is unique among approved extended-release methylphenidate products in that it employs the OROS Tri-Layer osmotic technology, an advanced drug delivery system. This osmotic controlled-rate feature distinguishes CONCERTA from among all other currently marketed extended-release methylphenidate formulations, which employ drug-coated beads or a cellulose matrix.

Resembling a conventional tablet, CONCERTA is comprised of an osmotically active, tri-layer inner core coated with a rigid semipermeable cellulose membrane and an outercoat of immediate-release drug. The inner core contains two layers of a matrix of methylphenidate-polyethylene oxide and a push layer matrix of polyethylene oxide (PEO) plus other osmotic agents. A precision laser-drilled orifice allows delivery of the drug from within the inner core (see Figure 1).

²⁴ Swanson J, Gupta S, Gupta D, et al. Acute tolerance to methylphenidate in the treatment of attention deficit hyperactivity disorder in children. Clin Pharmacol Ther. 1999;66: 295-305; Swanson J, Lerner M, Gupta S, 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.

Figure 1. Schematic, Longitudinal Cross Section of the CONCERTA OROS Tablet



IV. REQUEST FOR AN ESSENTIAL SUPPLEMENTAL BIOEQUIVALENCE METRIC TO ENSURE THERAPEUTIC EQUIVALENCE

A. Statement of the Issue and Requested Action

FDA regulations define bioequivalence as the "absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study."²⁵ Preferably, the rate and extent of drug absorption is measured by means of an *in vivo* study in humans in which drug concentration in blood, plasma, or another appropriate biological fluid is measured as a function of time.²⁶ According to regulatory guidelines, blood should be sampled with sufficient frequency to estimate (i) the maximum drug concentration (C_{max}) and (ii) the total area under the curve for a time period at least three times the half-life of the drug (AUC).²⁷

Different technologies for extending drug release and the varying fractions of total methylphenidate provided as immediate- (0 to 50%) and extended-release (50 to 100%) result in markedly dissimilar pharmacokinetic profiles among extended-release methylphenidate products. The absorption part of the profiles differs as well as the early magnitude of effect and the degree of acute tolerance. Variations in the early part of the pharmacokinetic profile will result in subsequent variations in the late part for the same total methylphenidate dose. CONCERTA is the only once-daily methylphenidate product to have demonstrated clinical effectiveness through 12 hours after dosing.

If only $AUC_{0-\infty}$ and C_{max} are used, products that are not clinically equivalent could be inappropriately deemed therapeutically equivalent. The rate of absorption is determined indirectly by observations of maximum plasma concentrations (C_{max}) or peak exposure. However, C_{max} does not fully describe the absorption rate process of a drug, and more importantly, it is poorly estimated for products with multiple peaks.²⁸ As the sole rate metric, C_{max} does not adequately capture clinically meaningful differences in the absorption part of pharmacokinetic profiles, so two extended-release methylphenidate formulations that meet the conventional criteria ($AUC_{0-\infty}$ and C_{max}) for bioequivalence may not be therapeutically equivalent. However, products that employ the matrix-tablet technology with no immediate-release component, such that their pharmacokinetic profiles exhibit a

²⁵ 21 CFR § 320.1(e).

²⁶ 21 CFR § 320.24(b)(1)(i).

²⁷ 21 CFR § 320.26(c).

²⁸ Chen ML, Lesko L, Williams R. Measures of exposure versus measures of rate and extent of absorption. Clin Pharmacokinet. 2001;40: 565-572.

simplistic single-dose shape with one peak, may be sufficiently defined by average bioequivalence metrics (ie, $AUC_{0-\infty}$ and C_{max}).

For the last decade, leaders in academia, the pharmaceutical industry, and FDA have debated, simulated, and researched several other metrics that may measure the rate of absorption more accurately.²⁹ None were deemed clearly superior to C_{max} , although early drug exposure, expressed as the partial area under the curve (AUC_{pR}) to the population median peak time (T_{max}), was recognized to have value for certain therapeutic classes of drugs.³⁰ Various absorption patterns (a reflection of multiple peaks, troughs, peak sizes, and ascending sections) of the extended-release methylphenidate formulations are produced by the immediate- and extended-release fractions of the total dose and the release technologies. Therefore, in addition to $AUC_{0-\infty}$ and C_{max} , the use of AUC_{pR} will capture these differences in the absorption pattern and provide the necessary link to the overall pharmacokinetic profile.

FDA has previously expressed concern about the use of partial areas as a reliable measure of bioequivalence, citing high variability (>30%) of AUC_{pR} shown in bioequivalence studies involving certain immediate- and extended-release products. FDA has concluded that high variability would require large sample sizes and that AUC_{pR} is an insensitive measure of absorption rate.³¹ In the assessments, drugs were reported to be from a variety of therapeutic classes with no specific reference to methylphenidate. The assessment that AUC_{pR} is a highly variable and insensitive measure should not be broadly applied to all therapeutic classes and extended-release products without considering drug-, product-, and disease-specific data. The examples cited in FDA's correspondence did not assess the relationship between AUC_{pR} and clinical effects.³²

Scientific data from comparative bioequivalence and clinical efficacy studies of available extended-release methylphenidate products that support McNeil's request to supplement conventional bioequivalence metrics with AUC_{pR} are summarized in the following sections.

²⁹ Chen ML. An alternative approach for assessment of rate of absorption in bioequivalence studies. *Pharm Res.* 1992;9:1380-1385; Macheras P, Symillides, Reppas C. The cutoff point of the partial area method for assessment of rate of absorption in bioequivalence studies. *Pharm Res.* 1994; 11:831-834; Endrenyi L, Csizmadia F, et al. Metrics comparing simulated early concentration profiles for determination of bioequivalence. *Pharm Res.* 1998;15:1292-1299. Endrenyi L, Csizmadia F, et al. The duration of measuring partial AUCs for the assessment of bioequivalence *Pharm Res.* 1998;15:399-404.

³⁰ Chen ML, Lesko L, Williams R. Measures of exposure versus measures of rate and extent of absorption. *Clin Pharmacokinet.* 2001;40: 565-572.

³¹ FDA response dated November 21, 2003 entered on December 10, 2003 to the citizen petition filed on behalf of Pharmacia Corporation and its affiliate G.D. Searle. Docket Number 01P-0546.

³² FDA response dated November 21, 2003 entered on December 10, 2003 to the citizen petition filed on behalf of Pharmacia Corporation and its affiliate G.D. Searle. Docket Number 01P-0546.

B. Scientific Evidence Supports Use of the AUC_{pR} Metric for Extended-Release Methylphenidate Products

1. Low Intrasubject Variability Supports Use of AUC_{pR} For Methylphenidate

AUC_{pR} was calculated *post-hoc* using CONCERTA methylphenidate plasma data from studies in NDA 21-121. Both the intra- and intersubject variabilities of AUC_{pR} were estimated from data in bioequivalence studies where two treatments of CONCERTA were administered to the same subjects after fasting. In one study,³³ the intrasubject variabilities of the C_{max} and AUC_{0-∞} metrics were assessed *a priori* by employing the replicate crossover design. This design provides the best estimate of intrasubject variability on which sample size is based, because each subject receives both the test and reference formulations twice.

Results of the analyses to estimate the intra- and intersubject variabilities of AUC_{pR} for CONCERTA are provided in Table 3, along with those of AUC_{0-∞} for comparison. The intrasubject variabilities of AUC_{pR} range between 8.3 and 18.5%, which is lower than estimates³⁴ (>30%) provided for other immediate- and extended-release products. Moreover, the intra- and intersubject variabilities of AUC_{pR} were comparable to those for AUC_{0-∞} in each of the studies. Adding AUC_{pR} to the conventional metrics of C_{max} and AUC_{0-∞} will have negligible impact on study size to determine bioequivalence.

³³ ALZA Study C-2001-018. Bioequivalence of two 27-mg and three 18-mg OROS (methylphenidate HCl) extended-release tablets and assessment of the intra- and intersubject variability in the pharmacokinetics (January 2002). Located in NDA 21-121.

³⁴ FDA response dated November 21, 2003 entered on December 10, 2003 to the citizen petition filed on behalf of Pharmacia Corporation and its affiliate G.D. Searle. Docket Number 01P-0546; Gokhale M et al. Feasibility of application of early exposure measures in bioequivalence studies of extended-release oral formulations. AAPS PharmSci. 2000; 2; Wahba Z et al. Feasibility of application of early exposure measures in bioequivalence studies of immediate-release oral formulations. AAPS PharmSci. 2000; 2.

Table 3. Intra- and Intersubject Variabilities of Methylphenidate AUC_{pR} and AUC_{0-∞} After Fasted Administration of CONCERTA Extended-Release Tablets

Study Number	CONCERTA Treatments	N	AUC _{pR}		AUC _{0-∞}	
			Intrasub Var%	Intersub Var%	Intrasub Var%	Intersub Var%
C98-002	CONCERTA 18-mg Formulation 1	24	18.5	38.2	12.7	39.3
	CONCERTA 18-mg Formulation 2					
C99-001	CONCERTA 18-mg Site 1	36	10.8	22.6	10.1	20.9
	CONCERTA 18-mg Site 2					
C99-005	CONCERTA 36-mg Lot 1	33	13.5	23.2	9.8	25.4
	CONCERTA 36-mg Lot 2					
C01-018	CONCERTA 18-mg (Three Tablets)	34	8.3	32.3	8.8	30.9
	CONCERTA 27-mg (Two Tablets)					

N – number of subjects in the study; Var – variability

2. AUC_{pR} is Sensitive to Differences in the Absorption Profile and Clinical Effects Among Extended-Release Methylphenidate Products

When assessing the bioequivalence of two extended-release methylphenidate formulations, it is essential to consider the clinical implications of the pharmacokinetic profile throughout the day. The overall absorption pattern of a product (a reflection of multiple peaks, troughs, peak sizes, and ascending sections) is created by the immediate- and extended-release fractions of the total dose and the release technology. Both the early magnitude of effect and the degree of acute tolerance to methylphenidate are related to the early absorption profile. Early exposure, AUC_{pR}, provides the necessary link to the overall pharmacokinetic profile upon which to make accurate bioequivalence decisions.

Table 4 provides a summary of pharmacokinetics data from three bioequivalence studies that compare CONCERTA with other extended-release methylphenidate products. In practice, bioequivalence studies are designed to compare formulations with the same molar dose. However, CONCERTA has a lower molar dose (18-mg) than the comparative dose (20-mg) for all other extended-release methylphenidate products. To account for this difference, data were normalized in these studies to the reference product's dose. This adjustment is a recognized limitation, because a true pass or fail bioequivalence conclusion would be based on the regulatory definition of equal molar doses.³⁵ However, recognizing this limitation, bioequivalence and clinical studies collectively support supplementing the conventional metrics with AUC_{pR} to determine therapeutic equivalence of extended-release

³⁵ 21 CFR § 320.1(e).

methylphenidate products. For example, even though the commercially available strengths of CONCERTA are each 90% of the available strengths of RITALIN-SR, METADATE CD, and RITALIN LA, only CONCERTA demonstrates clinical effectiveness through 12 hours after dosing.

An ALZA pharmacokinetics study summarized in Table 4 is Study C98-024, which was submitted in NDA 21-121.³⁶ It is a crossover study that originally compared the pharmacokinetics of CONCERTA 18-mg, RITALIN-SR 20-mg, and IR RITALIN 5-mg tid. The study was reanalyzed after removing the RITALIN 5-mg data to construct a bioequivalence test of the two extended-release methylphenidate products. CONCERTA was selected as the reference product, so AUC_{pR} was calculated to the median T_{max} of six hours and data for RITALIN-SR were dose normalized to 18-mg to provide an equimolar dose comparison.

The shortest 90% confidence intervals for log-transformed AUC_{0-∞} and C_{max} fell within the limits of 80 to 125%, such that CONCERTA and RITALIN-SR would be declared bioequivalent in this constructed test. However, the labeling for the products documents that these two extended-release methylphenidate products are not clinically equivalent; CONCERTA is effective through 12 hours after dosing, whereas RITALIN-SR has a duration of action of approximately eight hours.³⁷

Methylphenidate concentrations for CONCERTA continue to ascend for about three hours after the peak concentration of RITALIN-SR in ALZA Study 98-024. The AUC_{pR} metric accounts for this difference between the absorption profiles, such that if AUC_{pR} were included as an essential bioequivalence criterion, these extended-release methylphenidate products would not be declared bioequivalent.

³⁶ ALZA is a wholly owned subsidiary of Johnson & Johnson. ALZA is the registered NDA holder for NDA 21-121 and manufactures CONCERTA for distribution by McNeil. ALZA transferred agent rights for NDA 21-121 to McNeil on May 1, 2003.

³⁷ RITALIN-SR prescribing information, January 2001; CONCERTA prescribing information, October 2003.

Table 4. Comparative Bioequivalence Data Among Extended-Release Methylphenidate Products

Product Comparisons	IR (mg)	ER (mg)	AUC _{0-∞} (ng h/mL) mean (SD)	90% CI	C _{max} (ng/mL) mean (SD)	90% CI	BE 2 Metrics ^a	AUC _{pR} (ng h/mL) mean (SD)	90% CI	BE 3 Metrics ^b
ALZA Study C98-024³⁸										
RITALIN-SR Tablet, 20-mg (dose normalized)	0	20	41.8 (14.3)	96.8 to 102.9	4.32 (1.43)	107.9 to 121.8	YES	19.0 (6.0)	142.2 to 152.3	NO
CONCERTA Tablet, 18-mg	4	14	41.8 (13.9)		3.73 (1.01)			12.9 (4.1)		
Gonzalez et al. (2002)³⁹										
CONCERTA Tablet, 18-mg (dose normalized)	4	14	40.5 (15.0)	100.1 to 107.6	3.81 (1.32)	93.8 to 105.3	YES	6.98 (2.95)	66.2 to 73.8	NO
METADATE CD Capsule, 20-mg	6	14	39.7 (11.8)		3.89 (0.99)			10.0 (3.06)		
Markowitz et al. (2003)⁴⁰										
CONCERTA Tablet, 18-mg (dose not normalized)	4	14	66.9 (32.8)	80 to 96	5.9 (2.18)	56 to 66	NO	9.3 (4.74)	45 to 54	NO
RITALIN LA Capsule, 20-mg	10	10	78.7 (42.5)		9.9 (4.06)			18.5 (8.14)		

BE – bioequivalent; CI – confidence interval; IR – immediate release, ER – extended release

a: 2 Metrics are AUC_{0-∞} and C_{max}

b: 3 Metrics are AUC_{0-∞}, C_{max}, and AUC_{pR}

³⁸ ALZA Study C-98-024. Methylphenidate HCl pharmacokinetics when administered as OROS (methylphenidate HCl), RITALIN-SR, and RITALIN. May 1999. Results for RITALIN-SR are dose-normalized to 18-mg, because CONCERTA is the reference product in the calculation of AUC_{pR}. Located in NDA 21-121. AUC_{pR} (AUC_{6h}) is listed in Table 4.

³⁹ Gonzalez MA, Pentikis HS, Anderl N, et al. Methylphenidate bioavailability from two extended-release formulations. Inter J Clin Pharm Ther. 2002;40:175-184. Results for CONCERTA are dose-normalized to 20-mg, because METADATE CD is the reference product. AUC_{pR} is not reported, but rather partial areas up to four, six, and eight hours. AUC_{4h} is listed in Table 4 because it closely approximates AUC_{pR}. The mean T_{max} for METADATE CD is about four hours.

⁴⁰ 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. Results for CONCERTA are not dose-normalized to 20-mg. However, the mean value for CONCERTA C_{max} is significantly lower than that for RITALIN LA such that dose-normalization would not change the overall conclusion of not bioequivalent. AUC_{4h} is listed in Table 4 for AUC_{pR}.

The second pharmacokinetics study summarized in Table 4 is by Gonzalez et al, and compares single doses of CONCERTA 18-mg with METADATE CD 20-mg in a crossover design.⁴¹ The data for CONCERTA are dose-normalized to 20-mg because METADATE CD is the reference product. AUC_{pR} was not reported, but rather partial areas up to four, six, and eight hours. AUC_{4h} is considered in this discussion because it closely approximates AUC_{pR}. The mean T_{MAX} for METADATE CD is about four hours.

Based on data from Gonzalez et al, CONCERTA and METADATE CD would be declared bioequivalent. The 90% confidence intervals for log-transformed AUC_{0-∞} and C_{max} fell within the limits of 80 to 125%. The data indicate bioequivalence for normalized and not normalized doses of CONCERTA. Other CONCERTA doses were evaluated in this study, and results of the 90% confidence interval tests, both normalized and not normalized, indicate bioequivalence with AUC_{0-∞} and C_{max-2}. However, the product labeling,⁴² placebo-controlled clinical studies,⁴³ and a recently published direct head-to-head pharmacodynamic comparison using the laboratory school model⁴⁴ demonstrate that these two products are not clinically equivalent.

In this recently published laboratory school study by Swanson et al, the behavior and attention of 184 ADHD children were evaluated over a 12-hour day using a randomized, double-blind, three-treatment crossover design.⁴⁵ The effectiveness of 20-, 40-, and 60-mg METADATE CD was compared with that of 18-, 36-, and 54-mg CONCERTA and with placebo. Both extended-release methylphenidate products separated from placebo,

⁴¹ Gonzalez MA, Pentikis HS, Anderl N, et al. Methylphenidate bioavailability from two extended-release formulations. *Inter J Clin Pharm Ther*. 2002;40:175-184. Other doses were evaluated in this study, and results of the 90% CI tests, both normalized and not normalized, indicate bioequivalence with AUC_{0-∞} and C_{max-2}. In all comparisons, the partial areas at four and six hours were not equivalent.

⁴² METADATE CD prescribing information, July 2003; CONCERTA prescribing information, October 2003.

⁴³ Greenhill LL, Findling RL, Swanson JM. A double-blind, placebo-controlled study of modified-release methylphenidate in children with attention-deficit/hyperactivity disorder. *Pediatrics*. 2002;109:E39; Swanson J, Lerner M, Gupta S, 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; Wolraich M, Greenhill LL, Pelham W, et al. Randomized controlled trial of OROS methylphenidate qd in children with Attention Deficit/Hyperactivity Disorder. *Pediatrics*. 2001;108:883-892.

⁴⁴ 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: 206-216.

⁴⁵ Greenhill LL, DeCory HH, Hirshey SJ, et al. Comparison of classroom deportment in 6-12 year olds with ADHD after administration of two once-daily extended release methylphenidate (MPH) formulations. *Am Psych Assoc*. 2003, San Francisco, CA. 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: 206-216.

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 differences⁴⁶ 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. When the AUC_{pR} measure of the absorption profile is included as an essential bioequivalence criterion, the products would not be declared bioequivalent. This conclusion is consistent with the documented differences in clinical ADHD effects reported in the above laboratory school study.

Furthermore, if CONCERTA were the reference product in the pharmacokinetic study by Gonzalez et al,⁴⁷ the conclusion that the products are not bioequivalent would be identical when AUC_{6h} is considered. Because the median T_{max} for CONCERTA is about six hours, AUC_{6h} closely approximates the expected AUC_{pR} in this scenario. The fact that the identical conclusion is obtained using either CONCERTA or METADATE CD as the reference product, demonstrates internal consistency and reliability of the AUC_{pR} metric for extended-release methylphenidate products.

The third pharmacokinetics study summarized in Table 4 is by Markowitz et al, and compares single doses of CONCERTA 18-mg with RITALIN LA 20-mg in a crossover design.⁴⁸ The shortest 90% confidence intervals for log-transformed AUC_{0-∞} fell within the equivalence limits, but those for log-transformed C_{max} did not. Therefore, CONCERTA and RITALIN-LA would not be declared bioequivalent. Although results for CONCERTA were not dose-normalized to 20-mg, the mean value for CONCERTA C_{max} is significantly lower than that for RITALIN LA. Accordingly, dose-normalization would not change the overall conclusion that the products are not bioequivalent. The partial area to four hours for RITALIN LA is two-fold higher than that for CONCERTA, which reflects the higher amount of methylphenidate in the immediate-release component (10-mg versus 4-mg, respectively). The inclusion of the AUC_{pR} metric would account for these differences.

⁴⁶ Gonzalez MA, Pentikis HS, Anderl N, et al. Methylphenidate bioavailability from two extended-release formulations. *Inter J Clin Pharm Ther*. 2002;40:175-184.

⁴⁷ Gonzalez MA, Pentikis HS, Anderl N, et al. Methylphenidate bioavailability from two extended-release formulations. *Inter J Clin Pharm Ther*. 2002;40:175-184.

⁴⁸ 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.

In a head-to-head pharmacodynamic study in 36 ADHD children, RITALIN LA 20-mg was compared with CONCERTA 18- and 36-mg, and with placebo for nine hours.⁴⁹ Clinical differences in efficacy over four and eight hours were demonstrated between RITALIN LA 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.

3. *For Extended-Release Methylphenidate Products, Bioequivalence Decisions Based on $AUC_{0-\infty}$ and C_{max} Alone Are Insufficient*

Collectively, these study data demonstrate that fully comparable pharmacokinetic profiles are essential to ensure bioequivalence and therapeutic equivalence for extended-release methylphenidate formulations, in general, and for CONCERTA, in particular. The absorption parts of the profiles differ as well as the early magnitude of effect and the degree of acute tolerance. Variations in the early part of the pharmacokinetic profile will result in subsequent variations in the late part for the same total methylphenidate dose.

McNeil requests that AUC_{pR} be a supplemental metric to compare absorption profiles because it captures the differences due to both the immediate-release fractions of total methylphenidate and the extended-release technologies. Therefore, AUC_{pR} becomes the necessary link to the overall pharmacokinetic profile. If only $AUC_{0-\infty}$ and C_{max} are used, products that are not clinically equivalent could be inappropriately deemed therapeutically equivalent (see Figure 2).

AUC_{pR} is a more sensitive absorption metric that can distinguish the absorption profile differences among extended-release methylphenidate formulations. Extended-release methylphenidate products, having immediate-release fractions within a closer range of doses, could be considered bioequivalent (eg, CONCERTA versus RITALIN-SR or METADATE CD) even though they have documented clinical differences.⁵⁰ By contrast, those extended-release products that have immediate-release fractions over a wider range of doses are appropriately declared not bioequivalent (eg, CONCERTA versus RITALIN LA, and METADATE CD⁵¹ versus RITALIN-SR). Figures 3 and 4 show the pharmacokinetic

⁴⁹ 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.

⁵⁰ 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: 206-216; RITALIN-SR prescribing information, January 2001; CONCERTA prescribing information, October 2003.

⁵¹ Bioequivalence data comparing METADATE CD with RITALIN-SR are reported in the Summary Basis of Approval for NDA 21-259. Although $AUC_{0-\infty}$ fell within the 80% to 125% confidence interval limits, C_{max} did not.

profiles in the comparisons of products A with B and products B with C, respectively. Use of the supplemental metric, AUC_{pR}, accounts for the absorption patterns and would, therefore, lead to data-reliable decisions.

In summary, it is essential to consider the clinical implications of the overall pharmacokinetic profile throughout the day when assessing the bioequivalence of two extended-release methylphenidate formulations. Current exposure metrics, C_{max} and AUC_{0-∞}, do not sufficiently distinguish between the clinically important differences in the absorption profile. Therefore, AUC_{pR} should be used as an essential supplemental metric to establish bioequivalence in single-dose studies that compare extended-release methylphenidate formulations in fasting healthy volunteers. This metric is sensitive to early absorption differences and provides the necessary link to the overall pharmacokinetic profile upon which to base bioequivalence decisions. Bioequivalence and clinical study data support the relationship between AUC_{pR} and clinical effectiveness in treating ADHD symptoms in the morning with once daily products.

Figure 2. For Extended-Release Methylphenidate Products, Bioequivalence Decisions Based on AUC_{0-∞} and C_{max} (2 Metrics) Are Insufficient

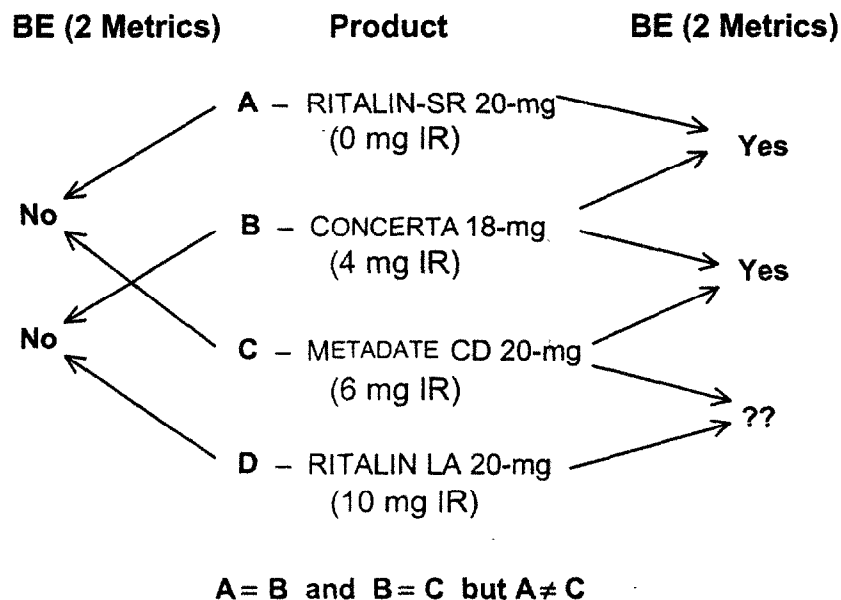


Figure 3. Pharmacokinetic Profiles for RITALIN-SR and CONCERTA that Illustrate Similar $AUC_{0-\infty}$ and C_{max} , and the Need for AUC_{pR} (Adapted from ALZA Study C98-024)

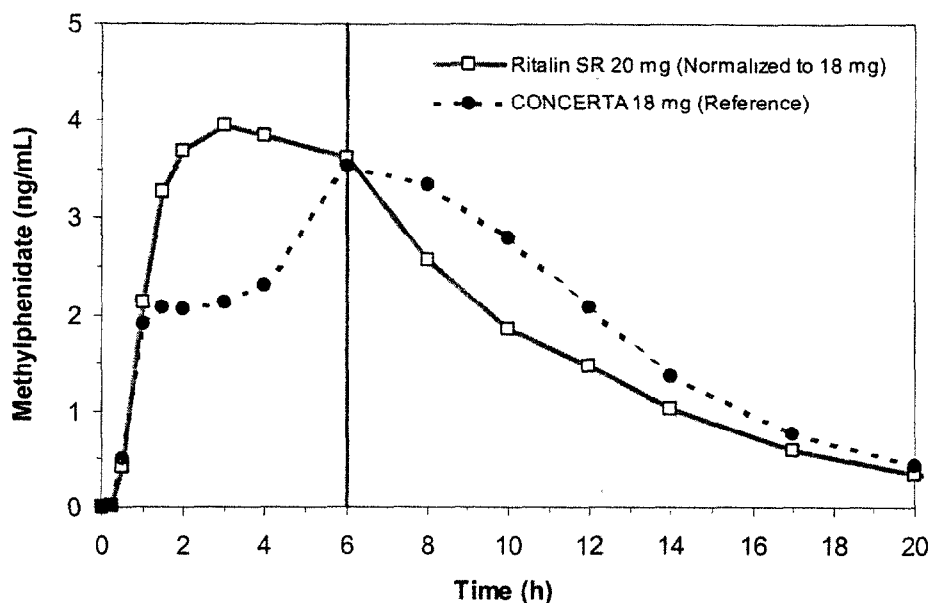
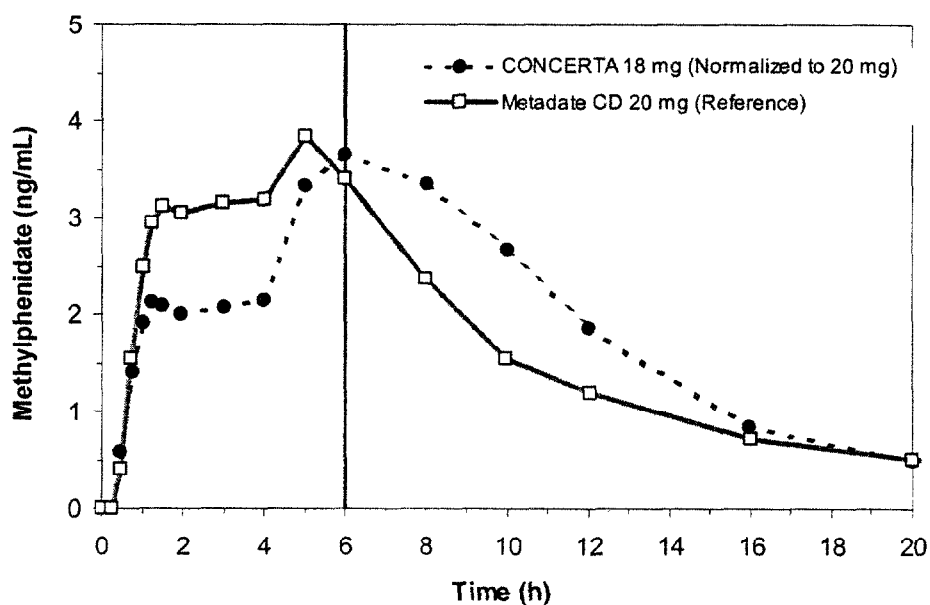


Figure 4. Pharmacokinetic Profiles for CONCERTA and METADATE CD That Illustrate Similar $AUC_{0-\infty}$ and C_{max} , and the Need for AUC_{pR} (Adapted from Gonzalez et al. 2002)⁵²



⁵² 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. Potential Safety Implication of AUCpR

Products with higher amounts of immediate-release methylphenidate are expected to have concentrations that cross the threshold value for dopamine transporter occupancy sooner than products with lower amounts. As a surrogate for these safety considerations among extended-release methylphenidate products, the C_{max} metric is limited by the amount of information that it can provide on absorption rates as a bioequivalence metric. Because AUCpR can distinguish the early absorption differences among extended-release methylphenidate products, this metric is a more sensitive measure of overall absorption rates.

V. CONCLUSIONS

- Recent published clinical and pharmacokinetic studies and data analyses demonstrate that if only $AUC_{0-\infty}$ and C_{max} are used, products that are not clinically equivalent could be inappropriately deemed therapeutically equivalent.
- In addition to $AUC_{0-\infty}$ and C_{max} , McNeil requests that the metric AUCpR, or area under the curve to the population median T_{max} of the reference formulation, be used as an essential supplement to ensure bioequivalence and therapeutic equivalence of extended-release methylphenidate products.
- Sufficient bioequivalence metrics that are sensitive to the overall pharmacokinetic profile and predictive of desired ADHD patient outcomes are essential.
- McNeil is conducting additional clinical studies and will provide results as they become available.

C. ENVIRONMENTAL IMPACT

The action requested is subject to a categorical exemption from environmental assessment under 21 C.F.R. §§ 25.22 and 25.31.

D. ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), McNeil will provide data concerning the economic impact of the relief requested should such information be requested by FDA.

E. CERTIFICATION

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petitioner.

Very truly yours,

MCNEIL CONSUMER & SPECIALITY PHARMACEUTICALS



Debra L. Bowen, MD

Vice-President, Research and Development