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DOCKET NO. 2004P-0139: SUPPLEMENT TO CITIZEN PETITION

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 average bioequivalence parameters, C_{max} and AUC_{0-∞}, because the current parameters do not ensure that 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 assessment under 21 CFR § 320.33 (a).

In this Petition Supplement, submitted under 21 CFR § 10.30(g), McNeil provides additional evidence from a clinical and pharmacokinetic-pharmacodynamic (PK-PD) study and from *in vitro* analytical experiments that signals the potential for differences in the risk of abuse, and as such, should be considered in approval of generic versions of CONCERTA:

- Recently available safety-related data from a clinical and PK-PD study relate differences in the early absorption rate of methylphenidate formulations with differences in drug "likability" or abuse potential. These data further support McNeil's original request to use early absorption exposure, AUC_{pR}, as a supplemental essential bioequivalence metric for extended-release methylphenidate products.
- Results from *in vitro* analytical tests show that CONCERTA's physicochemical properties — both the rigid cellulose acetate membrane of the osmotic-controlled delivery system and the hydrophilic polymers (polyethylene oxide) granulated

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with methylphenidate — impart abuse-resistant characteristics. McNeil also requests that FDA modify the approval criteria for generic versions of extended-release methylphenidate products to require additional *in vitro* analytical tests and/or evidence (e.g., extraction experiments) to ensure that a generic version of CONCERTA has similar abuse-resistant characteristics as CONCERTA and, hence, an equivalent safety profile.

I. SAFETY-RELATED DATA FURTHER ILLUSTRATES THE RELEVANCE OF AUC_{PR} AS A SUPPLEMENTAL ESSENTIAL BIOEQUIVALENCE METRIC

All approved methylphenidate products are currently regulated under Schedule II of the Controlled Substances Act, and the Federal Drug Enforcement Administration has expressed some concern over data in the 1990s regarding methylphenidate abuse, most notably RITALIN[®] abuse, which remains problematic.¹ The prevalence of Attention-Deficit/Hyperactivity Disorder (ADHD) in the young population, and hence the availability of stimulant drugs to treat the disorder, make abuse a significant safety concern. Because the symptoms of ADHD are expressed throughout the day, patients may be required to take medication at, or transport medication to, school² or other locations where there may be a higher risk of diversion to others who might abuse the medication.

Dr. Joseph Biederman and his colleagues have demonstrated in a longitudinal follow-up study that when ADHD is not effectively treated, adolescents will have a higher incidence of Substance Use Disorders (SUD) and that treatment with methylphenidate or other stimulants in young ADHD patients reduces, rather than increases, the risk of SUD.³

Extended-release methylphenidate products are expected to have differences in abuse potential because of differences in the

- amount of immediate-release methylphenidate (0% to 50%) in the formulations,
- early absorption rates,
- elimination rate over extended times, and
- extended-release drug delivery technologies and physicochemical properties.

¹ DEA Congressional Testimony, Terrance Woodworth, before the Committee on Education and the Workforce: Subcommittee on Early Childhood and Families. May 16, 2000.

<http://www.usdoj.gov/dea/pubs/cngrtest/ct051600.htm>. Accessed September 16, 2004.

² GAO Report to Congressional Requestors: Attention Disorder Drugs; Few Incidents of Diversion or Abuse Identified by Schools; Sept 2001.

³ Biederman J, Wilens T, Mick E, et al. Pharmacotherapy of attention-deficit/hyperactivity disorder reduces the risk for substance use disorder. *Pediatrics*. 1999;104:e20.

A. AUC_{pR} Provides More Information than C_{max} on Absorption Rates, Which Determine Methylphenidate-Induced Euphoric Effects

Differences in abuse liability between oral and intravenous methylphenidate are directly related to the difference in the rate at which each reaches peak brain concentrations (about 1.5 hours and less than ten minutes, respectively).⁴ Although the time to reach peak brain concentrations is the same for all oral immediate-release methylphenidate doses, the time for concentrations to reach a threshold value for dopamine transporter occupancy depends on the dose. Methylphenidate concentrations from low doses of oral immediate-release products will reach the threshold later than high doses of the same products and, thus, have fewer euphoric effects (i.e., drug likability).

The C_{max} bioequivalence metric is limited by the amount of information that it can provide on absorption rates, and as such, cannot adequately distinguish abuse potential among methylphenidate products. As shown with the bioequivalence data outlined in McNeil's original Petition, two extended-release products can have equivalent C_{max} values, but due to the formulation design, technology, and release rate, these maximum concentrations occur at different times (T_{max}).⁵ Therefore, the absorption rate, as depicted by the steepness (slope) of the initial portion of a pharmacokinetic curve, determines the intensity of methylphenidate's euphoric effects. Because AUC_{pR} can distinguish differences in early absorption rates among extended-release methylphenidate products, this metric is a more sensitive indicator of drug likability, and hence, of abuse potential.

B. Clinical Study Shows Drug Likability Depends on Early Absorption Rates of Methylphenidate

Early absorption rate with subsequent uptake into the brain is the major determinant of the occurrence and intensity of methylphenidate's euphoric effects, factors strongly tied to abuse behaviors. A clinical and pharmacokinetic-pharmacodynamic (PK-PD) study⁶ to assess the kinetics of dopamine transporter (DAT) receptor occupancy in the brain and the degree of methylphenidate likability (subjective effects) was recently completed. The slow absorbing CONCERTA tablet (test formulation) was compared with a faster absorbing methylphenidate product (reference formulation) at doses that would provide similar maximum plasma concentrations (C_{max} values). This study was conducted in parallel groups of healthy adults by independent researchers, Thomas J. Spencer MD and Alan J. Fischman MD, PhD of Massachusetts General Hospital (MGH). It is entitled,

⁴ Volkow ND, Swanson JM. Variables that affect the clinical use and abuse of methylphenidate in treatment of ADHD. *Am J Psychiatry* 2003; 160:1909-1918.

⁵ RITALIN LA[®] prescribing information July 2003; CONCERTA[®] prescribing information April 2004.

⁶ Massachusetts General Hospital (MGH) Study Report Synopsis - A PET study examining pharmacokinetics, detection, and likeability, and dopamine transporter receptor occupancy of short and long-acting orally administered formulations of methylphenidate in adults. May 24, 2004.

A PET Study Examining Pharmacokinetics, Detection and Likeability, and Dopamine Transporter Receptor Occupancy Of Short and Long-Acting Orally Administered Formulations of Methylphenidate in Adults (see Synopsis in Attachment 1).

Because the main target of methylphenidate in the brain is the dopamine transporter (DAT),⁷ measuring central DAT activity can elucidate central pharmacokinetic effects. A highly sensitive methodology using the radioligand C-11 Altopane and Positron Emission Tomography (PET) was developed to measure central DAT occupancy.⁸ The time course of decay of the C-11 isotope permits repeated imaging, thus allowing documentation of the kinetics of DAT receptor occupancy in the brain. This methodology has been previously used to document the central pharmacokinetics of psychiatric drugs.^{9,10,11}

The study hypothesis was that the time to maximal receptor occupancy of methylphenidate after dosing with immediate-release tablets (40 mg) would be shorter than that after dosing with CONCERTA (90 mg). Moreover, it was hypothesized that subjective effects, including drug liking as measured by the Subject Drug Rating Questionnaire [DRQS], would be greater for immediate-release methylphenidate than CONCERTA, despite being less than one-half the total methylphenidate dose and having a similar maximum plasma concentration, C_{max}.

The study results demonstrate that the healthy adults reported significantly less pronounced subjective effects for 90-mg CONCERTA (five 18-mg tablets) compared with 40-mg immediate-release methylphenidate one to three hours post-dose and virtually no liking effects with CONCERTA at the times of its maximum plasma concentrations and dopamine transporter receptor occupancy (five to eight hours after oral dosing). Even with more than twice the total dose, Dr. Spencer's PET scan findings indicate that CONCERTA had a slower velocity of association as well as dissociation on target brain receptors. The increase in dopamine transporter occupancy with increasing plasma methylphenidate concentrations was greater in the immediate-release methylphenidate group than in the CONCERTA group.

⁷ 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.

⁸ Fischman AJ, Bonab AA, Babich JW, et al. [(11)C, (127)I] Altopane: a highly selective ligand for PET imaging of dopamine transporter sites. *Synapse* 2001; 39:332-342.

⁹ Fischman AJ, Bonab AA, Babich JW, et al. Positron emission tomographic analysis of central 5-hydroxytryptamine₂ receptor occupancy in healthy volunteers treated with the novel antipsychotic agent, ziprasidone. *J Pharmacol Exp Ther* 1996; 279:939-47.

¹⁰ Fischman AJ, Alpert NM, Rubin RH. Pharmacokinetic imaging: a noninvasive method for determining drug distribution and action. *Clin Pharmacokinet* 2002; 41:581-602.

¹¹ Christian BT, Livni E, Babich JW, et al. Evaluation of cerebral pharmacokinetics of the novel antidepressant drug, BMS-181101, by positron emission tomography. *J Pharmacol Exp Ther* 1996; 279:325-331.

Most importantly, the likability questionnaires indicated a greater subjective response to immediate-release methylphenidate than to CONCERTA, despite similar C_{max} and maximum dopamine transporter occupancies. As expected by the different release patterns, AUC_{pR} was about 80% greater for immediate-release methylphenidate at early times (median T_{max} was two hours). Plasma concentrations were greater for CONCERTA at times later than four hours, which reflect both the total dose difference (40 mg versus 90 mg) and the slower apparent elimination. The higher methylphenidate plasma exposure at later times is consistent with the slower velocity of dissociation on target brain receptors for CONCERTA.

Results from this clinical and PK-PD study are relevant to the consideration of AUC_{pR} as a supplemental essential bioequivalence metric for extended-release methylphenidate products. For example, the drug exposure patterns are consistent with the different times at which each formulation reaches its maximum concentration and further support the basic contention of McNeil's petition – that extended-release methylphenidate products present important and complex considerations related to their early absorption rates. AUC_{pR} provides more sensitive data in terms of early absorption. Although these clinical and PK-PD results are from a comparison of two pharmaceutical alternatives (immediate-release tablets versus CONCERTA extended-release tablets) at different molar doses (40 and 90 mg), they are highly suggestive of the potential for a bioequivalence problem if only C_{max} and $AUC_{0-\infty}$ are used to determine bioequivalence of extended-release methylphenidate products.

C. AUC_{pR} Differentiates the Immediate-Release Components of Extended-Release Methylphenidate Products Which Contribute to Abuse Potential

1. *Threshold Oral Dose for Abuse of Immediate-Release Methylphenidate*

Compared with oral immediate-release and intravenous formulations, the overall absorption rate of methylphenidate from CONCERTA extended release tablets is much slower. Brain concentrations of methylphenidate follow similar patterns to those in the plasma, so for CONCERTA, they will parallel the ascending absorption profile over time. Slowly increasing and persistent brain concentrations of methylphenidate are not conducive to producing the desirable *high* or reinforcement behavior of repeated self-administration.¹²

¹² Volkow ND, Ding YS, Fowler JS, et al. Is methylphenidate like cocaine? *Arch Gen Psychiatry*. 1995, 52:456-463.

Research data from published abuse liability studies¹³ using various doses of immediate-release methylphenidate tablets indicate that the *threshold oral dose*, above which subjective effects¹⁴ are associated with abuse behaviors in polysubstance abusers, is approximately 40-mg. Subjective effects measured on validated tools are specific to a drug and are dose dependent, so they strongly correlate with a drug's abuse potential.¹⁵ Further scientific evidence of this threshold oral dose for methylphenidate is provided by neuropharmacological data. In a study by Volkow et al.,¹⁶ using positron emission tomography to measure labeled methylphenidate in the human brain after oral doses of 10-, 20-, 40-, and 60-mg methylphenidate, the threshold level of dopamine transporter occupancy (about 70%) was reached starting with the 40-mg dose. This percent occupancy is consistent with data from the same research group that shows cocaine needs to block at least 60% of dopamine transporters in the human brain for intravenous cocaine to consistently induce a *high*.¹⁷

2. Comparison of Immediate-Release Components of the Extended-Release Methylphenidate Products

The immediate-release overcoat of CONCERTA contains 22% of the total dose; the remainder is contained within the osmotic core. Other available extended-release methylphenidate products with an immediate-release component contain greater fractions than CONCERTA. In addition to an abuse-resistant osmotic core¹⁸, the lower amount of immediate-release methylphenidate in the overcoat limits the likelihood of CONCERTA as the choice product for oral abuse. In order to experience *minimal euphoric effects*¹⁹ associated with the threshold 40-mg dose, more CONCERTA units are needed, which results in significantly more drug consumed overall. The excess amount is not expected to have reinforcing effects, because dopamine transporter

¹³ See Attachment 2, Summary Table of Published Abuse Liability Studies of Oral Immediate-Release Methylphenidate by Dose. Abuse liability studies of methylphenidate are summarized in a table included in the reference section.

¹⁴ Subjective effects were measured in polysubstance abusers with questionnaires and visual analog scales. Generally, scores for "Feel the drug now?", "Like the effects you feel?", and "How high are you?" were low in magnitude but separated from placebo at 40-mg methylphenidate.

¹⁵ Jaffe JH, Jaffe FK. Historical perspectives on the use of subjective effects measures in assessing the abuse potential of drugs. Also Jasinski DR, Henningfield JE. Human abuse liability assessment by measurement of subjective and physiological effects. In: Fischman MW, Mello NY, editors. Testing for abuse liability of drugs in humans. National Institute on Drug Abuse Research Monograph Series 92. Washington, DC: US Government Printing Office, 1989. pp. 43-100 (Department of Health and Human Services Publication No. (ADM) 89-1613).

¹⁶ Volkow ND, Wang G-J, Fowler JS, et al. Dopamine transporter occupancies in human brain induced by therapeutic doses of oral methylphenidate. *Am J Psychiatry* 1998; 155: 1325-1331.

¹⁷ Volkow ND, Wang GJ, Fischman MW, et al. Relationship between subjective effects of cocaine and dopamine transporter occupancy. *Nature* 1997; 386: 827-830.

¹⁸ See Section IIB for a discussion of the abuse resistance of the OROS osmotic device.

¹⁹ Minimal euphoric effects associated with the threshold oral dose of 40-mg immediate-releasing methylphenidate in abuse liability studies with polysubstance abusers are generally positive, but low, scores for "Feel Drug Effects" and "Like Drug Effects", and very low scores, if any, for the reinforcing *high* that is typically reported with intravenous administration.

receptors would be occupied for several hours after a dose due to the low brain clearance of methylphenidate.²⁰

Table 1 summarizes the number of product units (tablets, capsules, or OROS units) needed for different products to add up to the threshold oral dose of 40-mg immediate-release methylphenidate. If an abuser attempts to achieve a *high* by consuming multiples of an oral product, the total body load of methylphenidate increases substantially for CONCERTA. For example, only two 20-mg immediate-release tablets provide 40-mg methylphenidate; whereas, ten 18-mg CONCERTA OROS units are required to provide the equivalent amount in the overcoat. However, the total dose or body load of methylphenidate is 180 mg for this number of units consumed. Excess drug dose can lead to unfavorable effects that are well known in methylphenidate overdose²¹, including vomiting, hypertension, palpitation, tachycardia, and tremors. Such unfavorable effects are sufficient to deter repeated self-administration.

Table 1. Number of Brand Units Consumed Orally to Provide 40-mg Immediate-Release (IR) Methylphenidate

Product Brand	Formulation Type ^a	Brand Units	IR (mg)	ER (mg)	Total Dose (mg)
MPH, 20 mg	100% IR	2 Tablets	40	0	= 40
RITALIN LA, 40 mg	50% IR Beads; 50% ER Beads	2 Capsules	40	40	= 80
RITALIN LA, 20 mg	50% IR Beads; 50% ER Beads	4 Capsules	40	40	= 80
METADATE CD, 40 mg	30% IR Beads; 70% ER Beads	3 Capsules	36	84	= 120
METADATE CD, 20 mg	30% IR Beads; 70% ER Beads	6 Capsules	36	84	= 120
CONCERTA, 54 mg	22% IR Coat; 78% OROS	3 OROS	36	126	= 162
CONCERTA, 36 mg	22% IR Coat; 78% OROS	5 OROS	40	140	= 180
CONCERTA, 18 mg	22% IR Coat; 78% OROS	10 OROS	40	140	= 180

Abbreviations: IR – immediate release, ER – extended release, MPH – methylphenidate

a. Source – Physicians' Desk Reference 58th Edition, 2004

D. Important Safety Implications for the Use of AUC_{pR} as a Supplemental Essential Bioequivalence Metric

The inability of the two current bioequivalence metrics, C_{max} and AUC_{0-∞}, 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. (See Attachment 3 for pharmacokinetic profiles comparing

²⁰ Volkow ND, Ding YS, Fowler JS, et al. Is methylphenidate like cocaine? *Arch Gen Psychiatry*. 1995, 52:456-463.

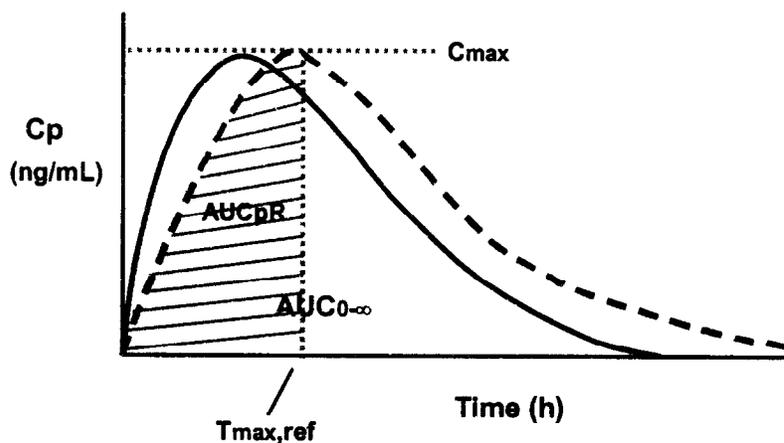
²¹ American Hospital Formulary Service (AHFS) Drug Information 2004;28:20, pg. 2347.

CONCERTA, RITALIN-SR[®], and METADATE CD[®]). For those extended-release methylphenidate products dosed once a day, differences in early and late exposure are expected to have differences in clinical and safety effects, including abuse potential.

Abuse potential is related to drug absorption rates and rate of uptake into the brain. FDA has 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 bioequivalence (21CFR § 320.1). McNeil's request to include AUC_{pR} as an essential supplement to ensure bioequivalence of extended-release methylphenidate products is based upon the collective well-controlled clinical and scientific evidence in the original and this supplemental Petition. Measures of low and high AUC_{pR} are consistent with less and more ADHD efficacy, and to less and more abuse potential (likability of any euphoric effects), respectively.

Although the comparisons were among pharmaceutical alternatives at different molar doses with different pharmacokinetics profiles, these data serve to signal potential bioequivalence problems. AUC_{pR} provides a reliable unbiased solution, when used together with C_{max} and $AUC_{0-\infty}$, to the situation where early and late parts of two comparative pharmacokinetic profiles are not sufficiently superimposable (Figure 1).

Figure 1. Example of Two Drug Products (Solid Versus Dashed Lines) That Could Meet Regulatory Criteria for Bioequivalence Using Only C_{max} and $AUC_{0-\infty}$, Even Though the Whole Drug Exposure Pattern is Not Sufficiently Superimposable



II. REQUEST FOR *IN VITRO* ANALYTICAL AND OTHER PHYSICOCHEMICAL TESTS TO ASSESS ABUSE-RESISTANCE AS PART OF GENERIC PRODUCT APPROVAL

A. Statement of the Issue

The relative abuse resistance of products scheduled under the Controlled Substances Act (CSA) is another issue that FDA should consider in assessing the approval requirements for a generic version of CONCERTA. It has been increasingly noted that the relative ease or difficulty of compromising a product's physical form can contribute to its potential for abuse. For example, the DEA has expressed its concerns over the possible abuse of methylphenidate by adolescents or young adults crushing the tablets for inhalation or dissolving the tablets in water for injection of the mixture.²² FDA has described situations in which the time-release formula of a prescription pain reliever has been disrupted by abusers to speed up the drug's absorption, through chewing the tablets, crushing them and snorting the powder, or dissolving them in water and injecting the drug.²³

Extended-release methylphenidate products are expected to have different abuse potentials, in part, because of differences in the:

- amounts of immediate-release methylphenidate (e.g., 0% to 50%) in the formulation
- early absorption rates
- elimination rate over extended times
- extended-release technologies (cellulose matrix, osmotic pump, and polymer-coated drug beads)
- formulation physicochemical characteristics and excipients.

CONCERTA extended-release tablet uses an osmotic-controlled system (OROS), which resembles a conventional tablet in appearance but is comprised of an osmotically active tri-layer inner core coated with an inert rigid semipermeable cellulose acetate membrane and an immediate-release drug outer coat. CONCERTA's specific design features, in addition to the relatively low amount of methylphenidate (22% of dose) in the immediate-release outer coat, a slow absorption rate, and extended residence time in the body, reduce its abuse potential compared with other forms of methylphenidate, especially

²² The Drug Enforcement Administration (DEA), Office of Diversion Control. *Stimulant Abuse by School Age Children: A Guide for School Officials*, June 2001.

www.deadiversion.usdoj.gov/pubs/brochures/stimulant/stimulant_abuse.htm Accessed September 15, 2004.

²³ The Food and Drug Administration. *Prescription Drug Use and Abuse*, FDA Consumer Magazine, 35 (5) September-October 2001. www.fda.gov/fdac/501_toc.html Accessed September 15, 2004.

immediate-release oral products that can be converted for intranasal and intravenous use.²⁴

Both CONCERTA's early absorption pattern and the potential dose-related unfavorable effects associated with methylphenidate overdose would not make CONCERTA an attractive drug if oral abuse or repeated self-administration were attempted. Given the contribution of absorption rate to methylphenidate's abuse potential, it is important to require the early exposure metric, AUC_{pR}, as a link of early absorption profile to the overall pharmacokinetic profile for extended-release methylphenidate products. AUC_{pR} relates directly to early magnitude of effect and drug "liking" effects and indirectly to duration of clinical effects and reinforcing behaviors of drug abuse.²⁴

B. Requested Action

In this Supplement, McNeil provides scientific evidence from *in vitro* analytical experiments showing that CONCERTA's physicochemical characteristics and excipients make this tablet formulation resistant to physical compromise and drug extraction. Even if attempts were made to crush and extract methylphenidate from the OROS delivery system by using solvents, the extract would be undesirable for abuse. Moreover, crushed CONCERTA is unlikely to provide a material form that abusers would seek for intranasal abuse.

Specifically, the CONCERTA tablet characteristics that render it abuse-resistant include:

- a rigid, inert nondisintegrating cellulose acetate membrane; it remains intact during gastrointestinal transit and is eliminated in the stool as a tablet shell.
- methylphenidate granulated with polyethylene oxide 200K, which is contained in an osmotic delivery system including polyethylene oxide 7000K. Both polyethylene oxide 200K and 7000K are hydrophilic polymers that quickly form soluble viscous hydrogels when exposed to water, which slow drug release from the expanding matrix.

Based on the evidence provided herein, McNeil requests that FDA modify the approval criteria for generic versions of extended-release methylphenidate products to require additional *in vitro* analytical tests and/or evidence to ensure that a generic version of CONCERTA has similar abuse-resistant characteristics as CONCERTA.

²⁴ McNeil Citizen Petition of March 19, 2004 submitted to Docket 2004P-0139.

FDA currently considers all tablets as the same dosage form for purposes of AB ratings. However, as data in this supplement show, not all tablet versions of methylphenidate have the same abuse-resistant characteristics and, therefore, it cannot simply be assumed that all tablet forms of methylphenidate are interchangeable. If a generic version of CONCERTA is "AB" rated and it lacks the abuse resistant formulation characteristics of CONCERTA, then the generic version will not have the same safety profile. Generic versions of CONCERTA should have no appreciably different risk of abuse potential, especially since generic versions will be substituted for prescriptions of CONCERTA. This would allow the prescribing health care practitioner to substitute products with the confidence that the abuse potential of the generic version will be no greater than that of the innovator product.

Requiring FDA approval criteria to assess abuse-resistant formulation characteristics should also be applied to other drug products scheduled under the CSA that are deemed by FDA as pharmaceutically equivalent and bioequivalent. Any difference in abuse potential of an innovator and generic product would result in a product with a potentially different safety profile and would, therefore, not permit the agency to find that the two products were indeed therapeutically equivalent. Considering such additional approval criteria for generic versions of innovator products is entirely consistent with FDA risk management concepts, which include planning to minimize risks throughout a product's lifecycle, to optimize its benefit/risk balance and for product sponsors to consider how to minimize risks from the product's use.²⁵

C. In Vitro Analytical Test Results Show CONCERTA Tablet (OROS System) Has Abuse-Resistant Physicochemical Characteristics

Results of crushability and extraction experiments²⁶ demonstrate that the physicochemical characteristics and excipients of the OROS delivery system render a CONCERTA tablet resistant to physical compromise and methylphenidate extraction and, hence, undesirable for abuse. Even if attempts are made to crush and extract methylphenidate by using solvents, CONCERTA still releases methylphenidate slowly over several hours, and the resulting extract is of high viscosity and turbidity due to the presence of polyethylene oxide and other excipients. Both a physically compromised CONCERTA tablet and its extracted excipients would be extremely difficult to abuse intranasally and largely unsuitable for intravenous use.

²⁵ Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for Industry. Development and use of risk minimization action plans. DRAFT Guidance. May 2004. <http://www.fda.gov/cder/guidance/5766dft.htm>. Accessed September 16, 2004.

²⁶ Such experiments are sometimes referred to as "kitchen chemistry" because they include common steps and methods taken by drug abusers in their attempt to prepare a more abusible drug form.

1. Rigid Cellulose Acetate Membrane and Excipients Make Crushed Form Undesirable for Abuse

A crushability test²⁷ was designed to assess the “crushing” characteristics of various methylphenidate formulations, because crushing is a common step taken by drug abusers in their attempt to prepare a more abusable form. Five commercially available methylphenidate products were tested: CONCERTA tablets (osmotic delivery formulation), RITALIN tablets (immediate-release formulation), RITALIN-SR tablets (extended-release matrix formulation), RITALIN-LA[®] capsules (extended-release coated-bead formulation) and METADATE CD capsules (extended-release coated-bead formulation). Product samples were wrapped in wax paper and struck a maximum of three times with a hammer.

The appearances of each methylphenidate product, both intact and crushed forms from the crushability test are provided in Attachment 4. The immediate-release tablet yielded a fine powder in appearance. The coated-bead formulations yielded a fine material similar in appearance to the immediate-release tablet. The RITALIN-SR tablet yielded a coarser material when compared to that of the immediate-release and coated bead formulations (RITALIN-LA and METADATE CD). Compared with other methylphenidate formulations, the “crushed” CONCERTA tablet (OROS delivery system) yielded the coarsest material containing large, thick chunks. This is a result of the rigid, insoluble cellulose acetate membrane, which renders the CONCERTA tablets difficult to crush. Even with crushing, the OROS system does not yield a fine powder because of its granulated polyethylene oxide-methylphenidate physical complex.

Intranasal abuse of a crushed and ground CONCERTA tablet containing methylphenidate is unlikely to provide a material form abusers would seek.²⁸ Some likely reasons for this are:

- the polyethylene oxide-methylphenidate granulation that comprises both drug layers of the inner core, along with the push layer, forms a viscous, gel-like material when it comes in contact with very humid air or small volumes of water. This hydrogel is likely to form within the larger nasal passages and prevent movement of the solids into the nasal sinuses.
- even if the cellulose acetate membrane is disrupted and the inner core is crushed into granules, the physical complex of polyethylene oxide with methylphenidate maintains a slow, extended-release of the drug.

²⁷ Images of intact and crushed products provided in Attachment 4.

²⁸ Jaffe, SL. Letters to the Editor: Failed attempts at intranasal abuse of CONCERTA. *J Am Acad Child Adolesc Psychiatry* 2002; 41(1): 5.

2. Slow, Inefficient and Laborious Extraction To Recover Active Ingredient From Compromised Drug Product

Several extraction experiments²⁹ were conducted to evaluate the extractability of methylphenidate using readily available solvents and procedures that one would expect typical abusers to use when wishing to subvert the delivery system and immediately access the bulk of its active ingredient. CONCERTA 27- and 54-mg tablets were tested in a controlled laboratory setting and under conditions including, "As Is" (intact), "Crushed" (hit repeatedly with a hammer), and "Ground" using a mortar and pestle. These samples were either soaked in a 50-mL solution (~10 teaspoons) or placed in a 50-mL solution with continuous stirring. Common household solvents were used including water, vinegar, vodka and acetone. At fixed time intervals, aliquots were removed and assayed by high performance liquid chromatography to determine methylphenidate recovery. For comparison, methylphenidate recovery from RITALIN (an immediate-release tablet formulation) 20 mg, was studied under "As Is" and "Crushed" conditions.³⁰

Results from these extraction experiments demonstrate that substantially longer times (several hours), and greater effort and sophistication were required to recover similar percentages of methylphenidate from CONCERTA when compared to recovery from an immediate-release tablet. Maximum recovery of methylphenidate from either the 27- or 54-mg "As Is" CONCERTA was not observed until ten hours for the stirred tablets and more than 24 hours for the soaked tablets versus maximum recovery observed at one hour for the stirred "As Is" RITALIN tablet.

Even if CONCERTA is crushed and extraction is attempted with water or other common high methylphenidate-solubility solvents, the granulated chunky matter still slowly releases methylphenidate over many hours due to the polyethylene oxide-methylphenidate physical complex. Even with grinding of the granulated matter and stirring, maximum methylphenidate recovery was not observed until after five hours for both the 27- and 54-mg CONCERTA tablets. In comparison, more than 96% of methylphenidate was extracted within five minutes after crushing and stirring a 20-mg immediate-release tablet.

²⁹ Technical Report TR-1505 on file.

³⁰ According to the DEA, RITALIN® (i.e., immediate-release methylphenidate) is one stimulant that is abused. DEA, Office of Diversion Control. *Stimulant Abuse by School Age Children: A Guide for School Officials*, June 2001. www.deadiversion.usdoj.gov/pubs/brochures/stimulant/stimulant_abuse.htm Accessed September 15, 2004.

3. Polyethylene Oxide and Other Excipients Make the Extract Undesirable for Abuse

The extraction (kitchen chemistry) experiments demonstrate that, while it was possible to recover methylphenidate from the OROS system, it required long times (several hours) and substantial effort. If the CONCERTA formulation is compromised, the resulting extracts contain significant amounts of excipients and have a high viscosity due to the presence of the polyethylene oxide hydrogel and other osmotic agents. Additionally, they are highly turbid due to colorants and cellulose acetate membrane fragments. For example, the extract for the crushed 54-mg CONCERTA tablet was red because of the colorants in the overcoat and inner core, turbid because of cellulose acetate fragments, and viscous because of the polyethylene oxide that was extracted together with methylphenidate.

Such physical characteristics make the extract largely unsuitable for intravenous use. The high molecular weight polyethylene oxide present in the OROS system push layer substantially increases the viscosity of an aqueous solution. According to a supplier of these resins, a 1% solution (100 mg/mL) of polyethylene oxide 7000K has a viscosity of 7,500 to 10,000 centi-Poise (cP) at room temperature, a viscosity similar to that of blackstrap molasses. A 5% solution of the lower molecular weight, polyethylene oxide 200K, has a viscosity of 55 to 90 cP, comparable to that of corn oil.³¹

³¹ Viscosity. Transtronics, Inc. <http://xtronics.com/reference/viscosity.htm> Accessed September 15, 2004; POLYOX™ Water-Soluble Resins NF. Dow. http://www.dow.com/polyox/app/ap_phar.htm Accessed September 15, 2004.

III. CONCLUSIONS

- Recently available safety-related data on absorption rate differences between methylphenidate products and the link to the velocity of drug association to brain receptors, and hence drug likability, further signal a potential bioequivalence problem in assessing generic versions of CONCERTA based solely on the two current bioequivalence metrics. These data indicate that AUC_{pR} is more sensitive to absorption rate differences than C_{max}.
- Results from the *in vitro* analytical tests show that CONCERTA's physicochemical characteristics (rigid cellulose acetate membrane of the osmotic-controlled delivery system and the polyethylene oxide granulated with methylphenidate) render it abuse resistant. Moreover, FDA currently considers all tablets as the same dosage form for purposes of AB ratings. Not all tablet versions of methylphenidate have the same abuse-resistant characteristics. Therefore, generic versions of CONCERTA tablets should incorporate sufficient abuse-resistant properties to ensure that the risk of potential abuse is not appreciably different when interchanged for CONCERTA.

Based on the well-controlled clinical data and *in vitro* analytical tests provided herein:

- McNeil renews its original request that the early absorption metric AUC_{pR}, or area under the curve to the median T_{max} of the reference formulation, be used as an essential supplement to current bioequivalence metrics, AUC_{0-∞} and C_{max}, to ensure bioequivalence and therapeutic equivalence of extended-release methylphenidate products. In the absence of AUC_{pR}, the current metrics may not only fail to indicate clinical equivalence but also fail to highlight differences in abuse potential, which raise public health concerns.
- McNeil also requests that FDA modify the approval criteria for generic versions of extended-release methylphenidate products to require additional *in vitro* analytical tests and/or evidence (e.g., extraction experiments) to ensure that a generic version of CONCERTA has similar abuse-resistant characteristics as CONCERTA and, hence, an equivalent safety profile.

Respectfully yours,

MCNEIL CONSUMER & SPECIALITY PHARMACEUTICALS

Minnie Baylor-Henry, RPh, JD
Vice-President, Medical and Regulatory Affairs

Figure 1. 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)¹

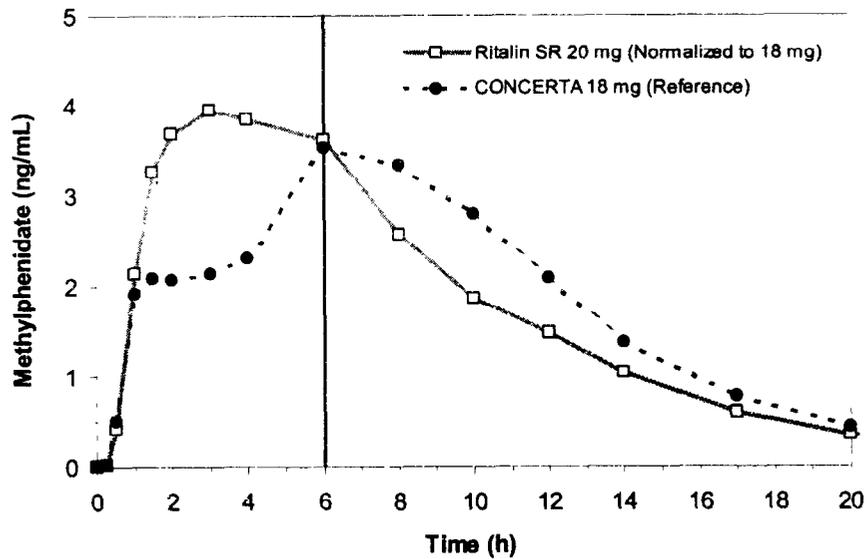
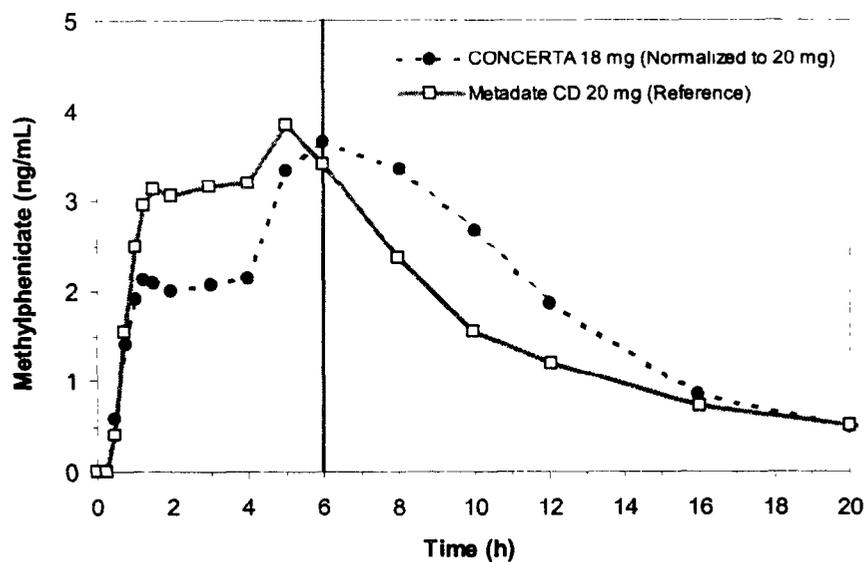


Figure 2. Pharmacokinetic Profiles for CONCERTA and METADATE CD That Illustrate Similar $AUC_{0-\infty}$ and C_{max} , and the Need for AUC_{Pr} (Adapted from Gonzalez et al. 2002)^{1,2}



¹ McNeil Citizen Petition of March 19, 2004 submitted to Docket 2004P-0139.

² Gonzalez MA, Pentikis HS, Anderl N, et al. Methylphenidate bioavailability from two extended-release formulations. In *J Clin Pharmacol Ther.* 2002;40:175-184.

III. CONCLUSIONS

- Recently available safety-related data on absorption rate differences between methylphenidate products and the link to the velocity of drug association to brain receptors, and hence drug likability, further signal a potential bioequivalence problem in assessing generic versions of CONCERTA based solely on the two current bioequivalence metrics. These data indicate that AUC_{pR} is more sensitive to absorption rate differences than C_{max}.
- Results from the *in vitro* analytical tests show that CONCERTA's physicochemical characteristics (rigid cellulose acetate membrane of the osmotic-controlled delivery system and the polyethylene oxide granulated with methylphenidate) render it abuse resistant. Moreover, FDA currently considers all tablets as the same dosage form for purposes of AB ratings. Not all tablet versions of methylphenidate have the same abuse-resistant characteristics. Therefore, generic versions of CONCERTA tablets should incorporate sufficient abuse-resistant properties to ensure that the risk of potential abuse is not appreciably different when interchanged for CONCERTA.

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- McNeil renews its original request that the early absorption metric AUC_{pR}, or area under the curve to the median T_{max} of the reference formulation, be used as an essential supplement to current bioequivalence metrics, AUC_{0-∞} and C_{max}, to ensure bioequivalence and therapeutic equivalence of extended-release methylphenidate products. In the absence of AUC_{pR}, the current metrics may not only fail to indicate clinical equivalence but also fail to highlight differences in abuse potential, which raise public health concerns.
- McNeil also requests that FDA modify the approval criteria for generic versions of extended-release methylphenidate products to require additional *in vitro* analytical tests and/or evidence (e.g., extraction experiments) to ensure that a generic version of CONCERTA has similar abuse-resistant characteristics as CONCERTA and, hence, an equivalent safety profile.

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