



CELLTECH

May 6, 2004

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Re: McNeil-PPC, Inc. Citizen Petition 2004P-0139

Dear Sir/Madam:

We respectfully submit this letter in support of the above-referenced Citizen Petition, dated March 19, 2004. McNeil-Consumer & Specialty Pharmaceuticals, a division of McNeil PPC, Inc. (McNeil)'s Citizen Petition requests that the Commissioner of Food and Drugs apply an additional bioequivalence metric to the review of abbreviated new drug applications (ANDAs) for methylphenidate HCl extended-release tablets. McNeil's petition presents scientific rationale and data to support the conclusion that average bioequivalence metrics are insufficient to ensure that generic methylphenidate HCl extended release tablets are both bioequivalent **and** clinically equivalent to their innovator product. Celltech Pharmaceuticals Inc. (Celltech) joins McNeil in supporting the use of this additional bioequivalence metric for certain extended release methylphenidate HCl formulations, and is submitting its own petition today requesting that FDA apply this additional measure when reviewing abbreviated new drug applications (ANDAs) for its product, Metadate® CD Capsules.

Celltech markets Metadate® CD, which is an extended release form of methylphenidate HCl. Methylphenidate has been used effectively in the treatment and management of attention deficit hyperactivity disorder (ADHD) in children. Because methylphenidate is a short-acting stimulant with a short half-life, it typically requires multiple doses to maintain its treatment effects during the course of a day. Extended release formulations that allow for once daily doses provide for greater patient compliance, especially in a patient population consisting largely of children. Not all extended release formulations of methylphenidate HCl are alike, however. Different extended release methylphenidate HCl products have different pharmacokinetic profiles, affecting both drug tolerance and its onset and magnitude of effect.

The conventional bioequivalent metrics currently employed to determine bioequivalence are not sufficient to ensure that certain extended release methylphenidate HCl products are actually therapeutically equivalent. For example, one capsule of Metadate® CD, is designed to replace twice-a-day dose regimens of methylphenidate and medication administered in the school setting. One Concerta® tablet is designed to replace two or three times-a-day regimens of methylphenidate. Despite these differences, Gonzalez, et al.¹, determined that using

¹ Gonzalez MA, Pentikis HS, Anderl N, et al. Methylphenidate bioavailability from two extended-release formulations. *Inter J Clin Pharm Ther* 2002;40:175-184.

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conventional bioequivalence metrics (AUC and C_{max}), Concerta® and Metadate® CD were found to be bioequivalent. However, the study also showed that the plasma concentration profiles produced over time by these two formulations were clearly different. Plasma concentrations of methylphenidate were significantly higher for Metadate® CD than for Concerta® for the first 6 hours after dosing, however, plasma concentrations were higher for Concerta® at 8, 10, and 12 hours after dosing. Because of this, physicians using Concerta® sometimes add immediate release methylphenidate to compensate for these lower morning plasma methylphenidate concentrations that occur with Concerta®. This is further evidence that clinical response is not predicted by typical bioequivalent metrics.

Gonzalez applied an additional metric, AUCpR (area under the curve to the population median Tmax of the reference formulation).² When AUCpR was included as a basis for analysis, the results clearly indicated that doses of Concerta® and Metadate® CD that meet conventional pharmacokinetic criteria for bioequivalence are unlikely to be clinically equivalent. The finding of Swanson supported this conclusion and showed that these dose pairs do not produce clinically equivalent effects on ADHD symptoms when compared prospectively under double-blind conditions in a laboratory classroom³.

AUCpR is sensitive to differences in absorption profiles and clinical effects among extended-release methylphenidate products. The data described in the Gonzalez study demonstrates low intra-subject variability and reinforces the use of AUCpR as an additional bioequivalence metric to ensure therapeutic equivalence. FDA should therefore require that AUCpR be an additional bioequivalence metric when analyzing whether a generic version of extended release methylphenidate HCl is therapeutically equivalent to the innovator product.

Sincerely,



Norman D. LaFrance, MD, FACP, FACNP
Senior Vice President,
Medical & Regulatory Affairs

² The Gonzalez study did not report AUCpR, but partial areas up to four, six and eight hours. AUC4th, used by McNeil, most closely approximates AUCpR as the mean Tmax for Metadate CD is about 4 hours.

³ 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, Pediatrics March 2004; 113: No. 3 206-216