Watson

May 9, 2013

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BY FEDERAL EXPRESS

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061 (HFA-305)
Rockville, Maryland 20852

RE: Require Additional Bioequivalence Criterion to Approve ANDAs for Generic RAPAFLO®

Dear Sir or Madam:

CITIZEN PETITION

Watson Laboratories, Inc. ("Watson") submits this Citizen Petition under Sections 505 and 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDC Act") and in accordance with the Food and Drug Administration's ("FDA's" or the "Agency's") regulation set forth at 21 C.F.R. § 10.30 to request that the Commissioner of Food and Drugs take certain actions with respect to generic versions of RAPAFLO® (silodosin) Capsules, 4mg and 8mg, submitted under FDC Act § 505(j) in an Abbreviated New Drug Application ("ANDA"). As discussed below, available data strongly suggest that an active metabolite of silodosin, glucuronide conjugate ("KMD-3213G"), contributes materially to the overall benefit of Silodosin Capsules. As such, failure to demonstrate bioequivalence of KMD-3213G using strict statistical evaluation of the standard pharmacokinetic ("PK") measures of area under the plasma concentration-time curve ("AUC") and the maximum or peak drug concentration ("C_{max}") (80%-125%) raises the distinct possibility that FDA could approve a non-equivalent version of the drug to the detriment of the public health.

I. ACTION REQUESTED

Watson requests that FDA:

(1) Refuse to approve any ANDAs for generic versions of RAPAFLO® – and in particular ANDA No. 204726 submitted by Sandoz Inc. – unless and until such sponsor demonstrates bioequivalence with respect to both silodosin and KMD-3213G using strict statistical evaluation of the standard PK measures of AUC and C_{max}; and

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(2) Revise Draft Guidance on Silodosin issued in April 2013 to require that bioequivalence be demonstrated with respect to both silodosin and KMD-3213G using strict statistical evaluation of the standard PK measures of AUC and C_{max}.[1]

II. STATEMENT OF GROUNDS

A. Factual Background

Silodosin is a selective alpha-1-adrenergic receptor antagonist that FDA approved on October 8, 2008 under New Drug Application ("NDA") No. 022206 as RAPAFLO® for the treatment of the signs and symptoms of benign prostatic hyperplasia ("BPH"). As discussed in the approved labeling for RAPAFLO®:

> Silodosin undergoes extensive metabolism through glucuronidation, alcohol and aldehyde dehydrogenase, and cytochrome P450 3A4 (CYP3A4) pathways. The main metabolite of silodosin is a glucuronide conjugate (KMD-3213G) that is formed via direct conjugation of silodosin by UDP-glucuronosyltransferase 2B7 (UGT2B7). . . . KMD-3213G, which has been shown *in vitro* to be active, has an extended half-life (approximately 24 hours) and reaches plasma exposure (AUC) approximately four times greater than that of silodosin.

RAPAFLO® Prescribing Information, at § 12.3 (Pharmacokinetics).

Due in part to the unique PK profile of silodosin, in which silodosin has shown a short terminal elimination half-life vis-à-vis the terminal elimination half-life of KMD-3213G (***Figures 1*** and ***2***, and ***Table 1*** below), FDA recommended once-daily dosing of 8 mg silodosin with food in BPH patients without renal impairment or with mild renal impairment, and 4 mg silodosin daily dosing with food in BPH patients with moderate renal impairment. RAPAFLO® is contraindicated in patients with severe renal impairment.

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[1] On May 6, 2013, Watson submitted a comment to Docket No. FDA-2007-D-0369 (Draft Bioequivalence Guidance on Silodosin Capsules) concerning the same issues raised in this Citizen Petition.

Figure 1: Mean Silodosin (SEM) Plasma Concentration (ng/mL) Time Profile by Dose Level and Timepoint after Multiple Doses (Study SI07004)

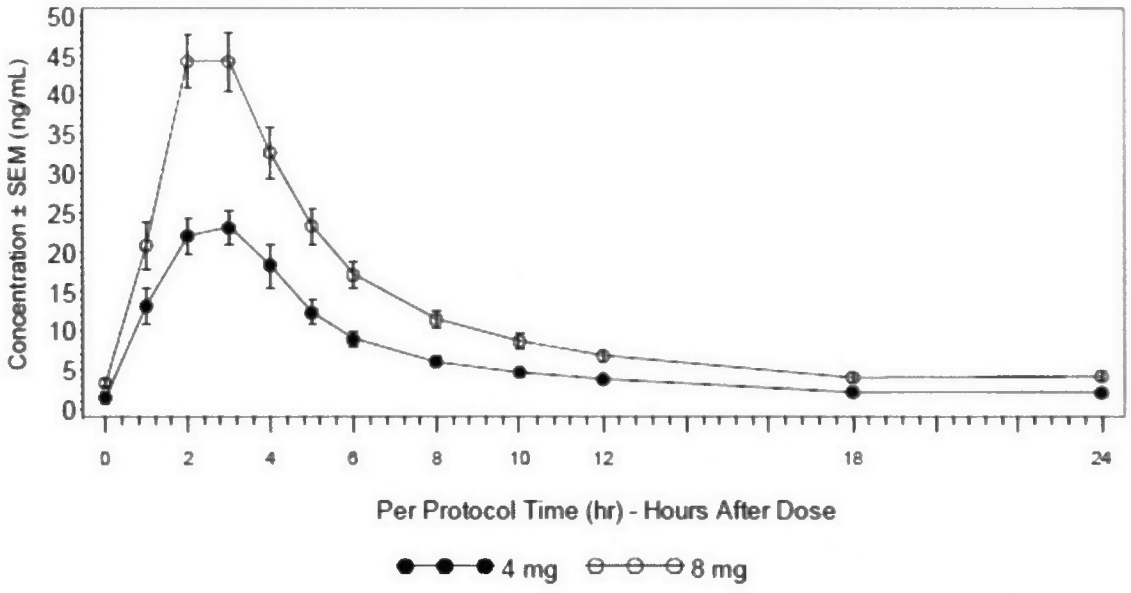

Figure 2: Mean KMD-3213G (SEM) Plasma Concentration (ng/mL) Time Profile by Dose Level and Timepoint after Multiple Doses (Study SI07004)

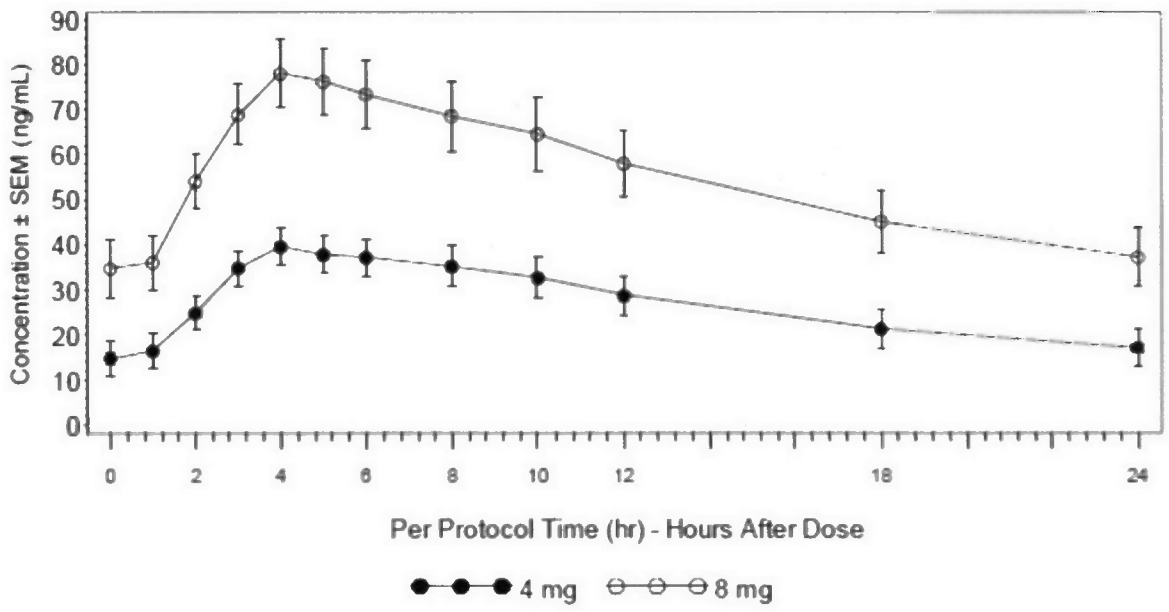

Table 1: Mean (SD) PK Parameters Following Silodosin 8 mg Once-Daily for 7 Days in Target Age Population (Study SI06004) (n=19, except *n=18)

	AUC_{0-24}, ng*hr.mL	AUC Ratio to Silodosin	C_{max}, ng/mL	T_{max}, hr	$T_{½}$, hr
Silodosin	373.4 (164.94)	--	61.6 (27.54)	2.6 (0.90)	13.3 (8.07)
KMD-3213G	1660.5 (647.23)	4.45	102.4 (36.51)	5.5 (2.29)	24.1 (16.62)*

In April 2013, FDA issued draft bioequivalence guidance recommending that companies seeking approval for a generic version of RAPAFLO® conduct two bioequivalence studies using the 4mg strength of the drug product, in addition to dissolution testing: two single-dose, two-way crossover *in vivo* studies, one under fasting conditions and another under fed condition. For each study, FDA recommends that companies measure both the amount of silodosin and KMD-3213G in an appropriate biological fluid. For purposes of demonstrating bioequivalence, however, FDA recommends that ANDA sponsors perform a strict statistical evaluation of the standard PK measures of AUC and C_{max} with respect to silodosin only. FDA proposes not to apply strict statistical criteria to KMD-3213G. Instead, with respect to KMD-3213G, the draft guidance states:

> Please submit the metabolite data as ***supportive evidence*** of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}.
>
> FDA, Draft Guidance on Silodosin, at 1 (Apr. 2013) (emphasis added).

B. Bioequivalence Standards

Under the FDC Act and FDA's implementing regulations, in order for FDA to receive and approve an ANDA for a proposed generic version of a brand-name drug product, the application must contain, among other things, information showing that the proposed generic drug product is "bioequivalent" to the drug identified in FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (i.e., the "Orange Book") as the Reference Listed Drug ("RLD"). See FDC Act §§ 505(j)(2)(A)(iv), 505(j)(4)(F); 21 C.F.R. §§ 314.94(a)(7), 314.127(a)(6)(l) (FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the listed drug referenced in the ANDA). A generic drug product is bioequivalent to the RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the [RLD] when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses." FDC Act § 505(j)(8)(B)(i).

The purpose of demonstrating bioequivalence is to determine whether changes in a proposed drug product's formulation or manufacturing affect the rate or extent to which the active ingredient reaches the primary site of action. It is presumed that a drug product containing the identical active ingredient will behave in the same way as the RLD if it reaches the primary site of action at the same rate and to the same extent as the RLD. See 21 C.F.R. § 320.1(e). FDA's regulations state that "bioequivalence may be demonstrated by several in vivo and in vitro methods," which are described at 21 C.F.R. § 320.24(b) in descending order of preference. In particular, FDA's regulations state that bioequivalence may be demonstrated by "[a]n in vivo test in humans in which the concentration of the active ingredient or active moiety, and, ***when appropriate, its active metabolite(s)***, in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time." 21 C.F.R. § 320.24(b)(1)(i) (emphasis added).

To establish bioequivalence, FDA generally requires that the 90% confidence intervals surrounding the mean ratios of the test drug to the reference drug for AUC and C_{max} – calculated to both the last measured concentration time and extrapolated to infinity – fit entirely within boundaries of 80% to 125% (i.e., the two one-sided test procedure).

C. Argument: FDA Should Require a Strict Statistical Evaluation of KMD-3213G

FDA's Draft Guidance on Silodosin requiring a statistical analysis of AUC and C_{max} with respect to silodosin, but not with respect to KMD-3213G, reflects the Agency's general policy articulated in a March 2003 guidance for industry, titled "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations" (hereinafter "BA/BE Guidance"), that for bioequivalence studies intended to support the approval of an ANDA, FDA recommends measurement of only the parent drug released from the product, rather than the metabolite. According to FDA, "[t]he rationale for this recommendation is that concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination." BA/BE Guidance at 18. But this recommendation is not absolute. The BA/BE Guidance identifies the following exceptions:

- Measurement of a metabolite may be preferred when parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time. We recommend that the metabolite data obtained from these studies be subject to a confidence interval approach for BE demonstration. If there is a clinical concern related to efficacy or safety for the parent drug, we also recommend that sponsors and/or applicants contact the appropriate review division to determine whether the parent drug should be measured and analyzed statistically.

- A metabolite may be formed as a result of gut wall or other presystemic metabolism. If the metabolite contributes meaningfully to safety and/or efficacy, we also recommend that the metabolite and the parent drug be measured. When the relative activity of the metabolite is low and does not contribute meaningfully to

safety and/or efficacy, it does not have to be measured. We recommend that the parent drug measured in these BE studies be analyzed using a confidence interval approach. The metabolite data can be used to provide supportive evidence of comparable therapeutic outcome.

Id. Silodosin fits neatly within the second exception – i.e., "If the metabolite contributes meaningfully to safety and/or efficacy, we also recommend that the metabolite and the parent drug be measured" – and, more broadly, within the Agency's overarching rationale preceding the two exceptions, because KMD-3213G functions as an active ingredient once in systemic circulation during the latter half of the concentration-time profile.

Nonclinical and clinical data regarding KMD-3213G strongly suggest that the metabolite contributes meaningfully to the pharmacodynamics of RAPAFLO®, and subsequently, to the overall therapeutic benefit and safety/effectiveness profile of the drug product in treating the signs and symptoms of BPH. In particular:

(1) The effect of KMD-3213G on noradrenaline-induced contraction of isolated rat prostate specimens was shown to be approximately ½ the effect of silodosin (***Table 2***).

Table 2: The Effects of Silodosin and KMD-3213G on Noradrenaline-Induced Contraction in Isolated Rat Prostate (Study KMD-11004)

Test Article	pKb Value [a)]	Efficacy Ratio [b)]
Silodosin	10.15 ± 0.04	1.0
KMD-3213G	9.86 ± 0.05	1/1.9

pKb – negative logarithmic value of a dissociation constant of binding of a competitive antagonist and the receptor (- log Kb)

a) The efficacy ratio was obtained by assuming the value of silodosin as 1.0.

b) The efficacy ratio was calculated using 10M (M=pKi (glucuronide conjugate K of silodosin) – pKb (silodosin)).

(2) The distribution of KMD-3213G into rat prostate was approximately 1/10 the distribution of silodosin after a 4 hour infusion (***Table 3***).

Table 3: Prostatic/Plasma Concentration Ratio of Silodosin and KMD-3213G at 4 hours after Starting Continuous Intravenous Injections in Rats (Study KMD-11005)

Test Article	Prostate/Plasma Concentration Ratio [a)]	Relative Ratio [b)]
Silodosin	7.55 ± 2.57	1.0
KMD-3213G	0.73 ± 0.30	1/10.3

a) The prostate/plasma concentration ratio means the ratio in terms of the measured substance.
b) The relative ratio was calculated by assuming the prostate/plasma concentration ratio of silodosin as 1.0.

(3) As shown above, plasma exposure in humans of KMD-3213G at steady-state was 4.4 times the exposure of silodosin (AUC_{0-24} 1660.5 versus 373.4 ng*hr/mL, respectively (***Table 1***; Study SI06004)).

Available data show that approximately 22% of the pharmacologic activity of RAPAFLO® over the 24-hour dosing period could be attributed to the contribution made by KMD-3213G. Moreover, because of the large differences in half-life between silodosin and KMD-3213G – i.e., 13.3 hours for silodosin versus 24.1 hours for KMD-3213G; Study SI06004) – the shapes of their respective exposure profiles are dramatically different (***Figures 1*** and ***2*** above). This phenomenon suggests that during the latter half of the dosing period when silodosin concentrations are extremely low, KMD-3213G is responsible for ***virtually all*** of the pharmacologic activity of RAPAFLO®, and, therefore, the therapeutic effect of the drug.

D. Conclusion

For the reasons set forth above, FDA should not approve an ANDA for a generic version of RAPAFLO® unless and until the ANDA applicant demonstrates bioequivalence with respect to both silodosin and KMD-3213G using strict statistical evaluation of the standard PK measures of AUC and C_{max}. In addition, FDA should amend the Draft Guidance on Silodosin to reflect the requirement that ANDA sponsors demonstrate bioequivalence with respect to both silodosin and KMD-3213G using strict statistical evaluation of AUC and C_{max}.

Given the importance KMD-3213G plays in the overall therapeutic effect of RAPAFLO®, which importance increases as silodosin levels taper off due to silodosin's short terminal elimination half-life vis-à-vis the terminal elimination half-life of KMD-3213G, it is critical that FDA require ANDA sponsors to demonstrate bioequivalence of both silodosin and KMD-3213G using statistical analyses. Failure to demonstrate bioequivalence of silodosin and KMD-3213G increases the likelihood that FDA could approve a non-equivalent version of RAPAFLO® in which patients are over- or under-dosed with KMD-3213G, resulting in serious consequences to patient health. This is a particular concern with BPH patients with moderate renal impairment for whom 4 mg silodosin daily dosing with food is recommended.

III. ENVIRONMENTAL IMPACT

Watson claims a categorical exclusion under 21 C.F.R. § 25.31.

IV. ECONOMIC IMPACT STATEMENT

Watson will, upon request by the Commissioner, submit economic impact information, in accordance with 21 C.F.R. § 10.30(b).

V. CERTIFICATIONS

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 Watson which are unfavorable to the Petition.

Watson makes the following certification pursuant to FDC Act § 505(q)(1)(H): I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: April 8, 2013. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Watson. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Kevin Barber, Ph.D., R.A.C., P.M.P.
Vice President, Regulatory Affairs
U.S. Proprietary Products

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