



December 8, 2005

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

Re: Metaxalone: Citizen Petition filed by King Pharmaceuticals, Inc. (2004P-0140/CP1); Petition for Stay (2004P-0140/PSA2) filed by Mutual Pharmaceutical Co., Inc.

On March 12, 2004, FDA issued a letter to King Pharmaceuticals, Inc. ("King"), the holder of an approved New Drug Application ("NDA") for Skelaxin® (metaxalone) tablets, conditionally approving King's request to change the labeling of Skelaxin® to indicate that it should be taken with food. Subsequently, on March 18, 2004, King submitted a Citizen Petition requesting that FDA require that information regarding the effect of food on the drug's bioavailability be included in the labeling for *generic* versions of Skelaxin®.

Mutual Pharmaceutical Co., Inc. ("Mutual") has pending before FDA an Abbreviated New Drug Application ("ANDA") for generic Skelaxin® (No. 40-536). On April 5, 2004, Mutual petitioned FDA to stay the effect of the Agency's March 12, 2004 conditional approval letter to King and to delay any decision on other requests by King for labeling changes to Skelaxin® until the Agency had fully considered and resolved issues concerning the food effect on the drug. Mutual also filed a supplement to its Petition for Stay on May 17, 2004, and an opposition to the underlying King Citizen Petition on February 15, 2005. In these filings, Mutual argued that King had not demonstrated that the food effect on metaxalone's bioavailability had any clinical significance.

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Since making these representations, Mutual has sponsored three studies on metaxalone that indicate the drug is metabolized by, inhibits, and/or induces activity in liver P450 subenzymes that also act on certain narrow therapeutic index drugs and other drugs that raise significant safety issues.

These findings appear to have an important bearing on the issues raised in King's Citizen Petition and Mutual's Petition for a Stay of Action. The purpose of this letter is to submit these studies to FDA so that the Agency may take them into account in determining the labeling requirements for metaxalone. Since Mutual's Petition for Stay, supplement thereto, and opposition to the King Petition were submitted without the benefit of this new information, Mutual is also withdrawing those filings.

I. Background

Mutual has been studying the characteristics of metaxalone, the active ingredient in Skelaxin®, since before 2001, more than two years before it filed its ANDA, and it has submitted relevant findings to the FDA. In March 2001, Mutual filed a Citizen Petition (No. 01P-0117) requesting that FDA reclassify metaxalone as a drug product for which potential or actual bioequivalence problems exist and require all ANDA applicants to conduct *in vivo* fasting bioequivalence studies. FDA granted Mutual's petition on January 30, 2002.

Subsequently, King conducted food effect studies on metaxalone and obtained patents on those studies. King concluded that the food effect posed important safety issues relating to metaxalone and filed supplements to its NDA seeking to have the new information incorporated into the approved labeling for brand-name Skelaxin®. The Agency initially permitted King to describe



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the food effect studies in the labeling of Skelaxin®, and on March 12, 2004, it issued an “approvable” letter granting King’s request that the labeling “recommend that Skelaxin be administered with food to ensure more consistent plasma levels of metaxalone.” However, on March 1, 2004, FDA had issued a “Dear Applicant” letter in which it had announced that *generic* metaxalone applicants would be permitted to exclude the food-effect information from *their* labeling.

On March 18, 2004, King filed a Citizen Petition requesting that FDA reverse the position it took in its March 1, 2004 “Dear Applicant” letter and require the food-effect information to be included in the labeling for *generic* metaxalone. At the same time, King also filed with FDA a Petition for Stay requesting that the Agency withhold all ANDA approvals for generic metaxalone until it had ruled on the King Citizen Petition. Mutual responded by filing its own Petition for Stay, in which Mutual requested that FDA stay the March 12, 2004 approvable letter, and withhold approval of King’s proposed changes to the approved labeling for brand-name Skelaxin® until the Agency had ruled on King’s Citizen Petition. In its submissions to FDA, Mutual took the position that the metaxalone food-effect was of unknown clinical significance – *i.e.*, there were no data to support a determination that this food-effect had any impact on the safety of metaxalone – and therefore that the food-effect information could be excluded from the labeling of generic versions of metaxalone.



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In recent months, Mutual has commissioned, and received the results from, three studies that suggest that the metaxalone food-effect may in fact have important, clinically significant consequences for the safe administration of metaxalone.¹

II. The New Data

The new studies shed light on the manner in which the administration of Skelaxin® (and its generic counterpart) could affect the bioavailability, and therefore the safety, of certain highly sensitive “narrow therapeutic range” drugs (also known as “narrow therapeutic index” or “NTI” drugs)² and other drugs that raise significant safety concerns, in cases where such drugs are co-administered with Skelaxin®/metaxalone. The studies also are relevant to the issue of whether the food-effect of Skelaxin® is significant in terms of patient safety.

Specifically, the new studies indicate that:

- metaxalone is *metabolized* by two members of the cytochrome P450 (CYP) liver enzyme group: CYP1A2 and CYP2C19;

¹ Mutual has licensed this new safety data to the NDA holder, King.

² FDA has defined “narrow therapeutic range” drugs as “those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation.” FDA Guidance for Industry: Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (August 2000). *See also* 21 C.F.R. § 320.33(c) (defining “narrow therapeutic index” drug products as those for which (1) there is less than a 2-fold difference in median lethal dose and median effective dose values, *or* there is less than a 2-fold difference in the minimum toxic concentrations and minimum effective concentrations in the blood; *and* (2) safe and effective use of the drug products require careful titration and patient monitoring).



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- metaxalone *inhibits* the activity of the two subenzymes described above, as well as the activity of four other members of the CYP group, CYP2B6, CYP2D6, CYP2E1, and CYP3A4; and that
- metaxalone *induces* activity of CYP1A2, when administered at certain levels.

The relevant metabolism, inhibition, and induction studies are attached hereto as Attachments A, B, and C, respectively.³

The significance of these findings is that the same subenzymes that are affected by metaxalone are also known to act upon a range of NTI drugs, including Coumadin® (warfarin), Dilantin® (phenytoin), Cerebyx® (fosphenytoin), and Theo-Dur® (theophylline), as well as certain non-NTI drugs that also raise significant safety issues, such as Mexitil® (mexiletine) and Mellaril® (thioridazine).⁴ Thus, the data suggest that the inhibitory or induction effects of metaxalone on these subenzymes could have a corresponding adverse effect of interfering with or promoting, respectively, the operation of these subenzymes on certain highly sensitive drugs that might be co-administered

³ Attachment A includes the protocol and final report of the metabolism study. Attachments B and C include the protocol and the results and data portions of the final report for the inhibition and induction studies, respectively. Mutual will submit the completed final reports for the inhibition and induction studies once they become available.

⁴ See Cytochrome P450 Drug Interaction Table, <http://medicine.iupui.edu/flockhart/table.htm> (last visited December 1, 2005) (listing drugs that are metabolized by CYP 450 enzymes, with references).

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with metaxalone, with potentially serious consequences for the patient.⁵

These findings relate to the Skelaxin® food-effect because higher blood levels of Skelaxin®, which would result from administration of the drug under fed (as opposed to fasted) conditions, may cause greater effects on the blood levels of the corresponding NTI (and other) drugs, and, in such a case, would increase the potential for the adverse, drug-drug interactions. King's food-effect data demonstrate that the bioavailability of metaxalone correlates with its administration with food. In short, the new data suggest that whether metaxalone is administered with food may have an impact on whether it can be co-administered safely with NTI and related drugs.

* * *

The new studies appear to bear on the question of whether metaxalone's food effect is clinically significant. Accordingly, Mutual has determined that it should no longer adhere to the position taken in its Petition for Stay and related papers that the food effect *clearly* has no clinical significance, and it is providing the new data to FDA so that the Agency can engage in a full review of the data and its impact on the pending issues before the Agency regarding metaxalone. In the

⁵ Indeed, the CYP 450 enzyme group is generally known to metabolize many drugs and FDA has long recognized the need for greater examination and awareness of the potential inhibitory, induction, and competitive effect of certain drugs on these enzymes. *See* Badyal, D.K.; Dadhich, A.P., "Cytochrome P450 and drug interactions," *Indian J. Pharm.* 2001:33(4):248-259 (hereafter, "Badyal and Dadhich") (noting that the CYP enzyme family plays a dominant role in the biotransformation of a vast number of structurally diverse drugs); 59 Fed. Reg. 39398, 39400 (August 2, 1994) (Noting in the context of geriatric uses of certain drugs that "for drugs metabolized by cytochrome P-450 enzymes, it is critical to examine the effects of known inhibitors There is a rapidly growing list of drugs that can interfere with other drugs that metabolize, and sponsors should remain aware of it.")



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meantime, Mutual withdraws its Petition and supplement, as well as Mutual's opposition to the King petition, each of which to one degree or another argues the clinical insignificance of the metaxalone food-effect. Mutual also requests that FDA consider the studies accompanying this submission in assessing the significance of the metaxalone food-effect and whether these studies should be required as part of the labeling for Skelaxin® and generic metaxalone. Mutual will rely on FDA's expertise in evaluating the significance of the food effect of metaxalone.

Respectfully submitted,

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Attachments

cc: Gary Buehler, Director, Office of Generic Drugs (w/attachments)
Robert Meyer, M.D., Director, Office of Drug Evaluation II (w/attachments)
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January 23, 2006

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Attention: Jennie Butler

**Re: Metaxalone: Citizen Petition filed by King Pharmaceuticals, Inc.
(2004P-0140/CP1); Petition for Stay (2004P-0140/PSA2) filed by
Mutual Pharmaceutical Co., Inc.**

We are writing on behalf of Mutual Pharmaceutical Co. ("Mutual") to inform you that Mutual hereby waives any confidentiality claims with respect to the attachments to Mutual's December 8, 2005 letter to FDA, concerning the above-referenced Petitions to FDA. Please do not hesitate to contact us with any additional questions.

Sincerely,

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