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**VIA HAND DELIVERY**

Division of Dockets Management  
U.S. Food and Drug Administration  
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**Comments of Mutual Pharmaceutical Co., Inc. to the Supplemental Submission of King Pharmaceuticals, Inc. in Support of Citizen Petition and Petition for Stay  
Docket Nos. 2004P-0140/CP1 and 2004P-0140/PSA1**

Mutual Pharmaceutical Co., Inc. (“Mutual”) respectfully submits these comments to the supplemental submission filed by King Pharmaceuticals, Inc. (“King”) in connection with King’s pending Citizen Petition and Petition for Stay regarding Skelaxin® (active ingredient: metaxalone) (“the King petitions”).<sup>1</sup>

Mutual supports King’s position in its supplement that the food effect information contained in King’s revised labeling for Skelaxin® cannot be “carved out” of the labeling for generic versions of metaxalone. At the same time, Mutual would like to take this opportunity to bring to FDA’s attention important updated information in Mutual’s possession that relates to (1) the food effect issues raised in King’s supplement and (2) the general safety profile and labeling requirements for metaxalone.

<sup>1</sup> The King petitions can be found at <http://www.fda.gov/ohrms/dockets/dailys/04/mar04/031904/04p-0140-cp00001-01-vo11.pdf> and <http://www.fda.gov/ohrms/dockets/dailys/04/mar04/031904/04p-0140-psa0001-vo11.pdf>.

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**I. Background**

**a. King's Submissions**

The original King petitions were filed on March 18, 2004, and sought from FDA a determination that (1) food effect information contained on King's approved labeling for Skelaxin® (metaxalone) could not be "carved out" of the labeling for generic versions of metaxalone, and that (2) generic companies seeking FDA approval for generic metaxalone must submit with their applications patent certifications to a King patent for metaxalone, United States Patent No. 6,407,128 ("the '128 patent"), pursuant to the Hatch-Waxman Act (21 U.S.C. § 355(j)(2)(A)(vii)). The King petitions argued in essence that the food effect information contained in Skelaxin® labeling was essential to the safe and effective use of Skelaxin® and its generic counterparts and that because this information could not be carved out of the generic label, it remained patent-protected and subject to the certification requirements of the Hatch-Waxman Act.

King filed its supplemental submission on February 13, 2007. This submission followed FDA's approval on November 24, 2006, of revised labeling for Skelaxin® and, similar to the original King petitions, sought from FDA a determination that (1) food effect information contained in King's revised Skelaxin® labeling could not be "carved out" of the labeling for generic metaxalone and that (2) generic companies seeking FDA approval for generic metaxalone must submit with their applications Hatch-Waxman patent certifications both to the



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'128 patent and to an additional King patent for Skelaxin®, U.S. Patent No. 6,683,102 (“the ‘102 patent”). It is evident from FDA’s decision to approve King’s addition of this new food effect information to the Skelaxin® package insert that the Agency believed this information to be important to the safety profile of Skelaxin®.

**b. Mutual’s Submissions**

Mutual has an Abbreviated New Drug Application (“ANDA”) for a generic version of Skelaxin® pending before FDA (No. 40-536).

In March 2001, Mutual, on the basis of studies it had performed showing lack of correlation between *in vivo* and *in vitro* dissolution, requested that FDA reclassify metaxalone as a product for which potential bioequivalence problems exist and require all ANDA applicants for generic versions of Skelaxin® to perform *in vivo* fasted studies.<sup>2</sup> Thus, Mutual’s concerns regarding safety issues with metaxalone are longstanding.

Subsequently, in filings with FDA dated April 5, 2004, May 17, 2004, and February 15, 2005 (the “2004-2005 submissions”),<sup>3</sup> Mutual took the position that King had failed to demonstrate that the food effect information contained in the Skelaxin® label had any clinical significance. Mutual argued, therefore, that this information *could* be carved out of generic metaxalone labeling and exempted from treatment under the Hatch-Waxman patent certification provisions.

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<sup>2</sup> See <http://www.fda.gov/ohrms/dockets/dailys/01/Mar01/030601/cp00001.pdf>.

<sup>3</sup> These filings can be found, respectively, at <http://www.fda.gov/ohrms/dockets/dailys/04/apr04/040604/04p-0140-psa00002-vo11.pdf>; <http://www.fda.gov/ohrms/dockets/dailys/04/may04/052504/04p-0140-sup0002-01-vol2.pdf>;



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On December 8, 2005, however, Mutual withdrew its 2004-2005 submissions regarding metaxalone and submitted to FDA data developed by Mutual (and licensed to King) that indicated that metaxalone is “metabolized by, inhibits or induces activity in liver P450 enzymes that also act on certain narrow therapeutic index [‘NTI’] drugs.” This data was initially generated in 2005 by incubations using single cDNA expressed CYP450s (and, as discussed below, was reconfirmed in early 2007 using the same methodology plus a separate study using pooled human liver microsomes and specific chemical inhibitors, as prescribed in the relevant FDA guidance). The data also indicated that the “inhibitory or induction effects of metaxalone on [these P450 subenzymes] could have a corresponding adverse effect [on] . . . the operation of these subenzymes on certain highly sensitive drugs that might be co-administered with metaxalone.” Therefore, as Mutual explained, “whether metaxalone is administered with food may have an impact on whether it can be co-administered safely with NTI and related drugs.”<sup>4</sup>

FDA has not acted on the original King petitions, which have been effectively superseded by King’s supplemental submission of February 13, 2007. Mutual submits these additional comments (1) in response to King’s contention that the food effect information in King’s *revised* Skelaxin® labeling cannot be “carved out” of generic metaxalone labeling, and (2) to further assist FDA in determining in general the significance of the metaxalone food effect in connection with labeling requirements for that product (whether it is taken in a fed *or* fasted state).

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and <http://www.fda.gov/ohrms/dockets/dailys/04p0140/04p-0140-sup0004-01-vol5.pdf>.

<sup>4</sup> Mutual Submission to FDA dated December 8, 2005, at pp. 2, 3-4, and 6. The Mutual December 8, 2005 submission is attached as Exhibit A hereto.

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## **II. Analysis**

### **a. King's Revised Labeling Contains Food Effect Information that Is Relevant to the Safe and Effective Use of Skelaxin®**

As set forth in Mutual's December 8, 2005 submission to FDA, Mutual's own studies relating to Skelaxin®'s metabolism by the P450 liver enzyme group, the potential drug-drug interactions that might ensue, and the relationship between these concentration-related activities and food consumption, indicate that food effect information is in fact relevant to the safe and effective use of Skelaxin® and its generic counterparts. The revised Skelaxin® labeling, as noted in King's supplement, identifies new clinical pharmacology information relating to the food, age, and gender effects, and the interrelationship of these effects, on Skelaxin® and also contains in the "Precautions" section of the revised labeling guidance that can help patients and physicians use Skelaxin® in a safe and effective manner given these potential effects. King Supplemental Submission at 13-15. This information, like the Mutual data previously submitted to FDA, clearly supports the clinical significance of the Skelaxin® food effect.

### **b. Additional Data Developed by Mutual Is Also Relevant to the Skelaxin® Food Effect**

The clinical significance of the Skelaxin® food effect, among other aspects of the drug interaction profile for metaxalone, is *further* supported by additional confirmatory data that Mutual has developed since its December 8, 2005 submission to FDA.<sup>5</sup> Mutual submits this

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<sup>5</sup> Overall, Mutual has performed studies using two methods recommended by FDA-- (i) incubations using single cDNA expressed CYP450s and (ii) incubations using pooled human liver microsomes and specific chemical inhibitors --, each of which supports the findings set forth below. Mutual performed the first of these studies in 2005 (the study was attached to Mutual's December 2005 submission to FDA), and then reconfirmed the study in early



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confirmatory data to FDA for the Agency's consideration in connection with its review of the labeling requirements for Skelaxin® and its generic counterparts.

Mutual's additional, confirmatory P450 data is consistent with the data previously submitted in December 2005 by Mutual to FDA and demonstrates that:

1. Metaxalone is metabolized by the P450 subenzyme group;
2. The particular subenzymes that metabolize metaxalone are CYP1A2, CYP2D6, CYP2E1, and CYP3A4;
3. These subenzymes also metabolize certain "narrow therapeutic index" drugs, such as R-warfarin (metabolized by CYP1A2), theophylline (metabolized by CYP2E1) and quinidine and quinine (metabolized by CYP3A4);<sup>6</sup>
4. These subenzymes are clinically significant<sup>7</sup> in the metabolism of many other FDA approved products including:
  - CYP1A2 - clozapine, cyclobenzaprine, imipramine, mexiletine, naproxen, riluzole and tacrine
  - CYP2D6 - S-metoprolol, propafenone, timolol, amitriptyline, clomipramine, desipramine, imipramine, paroxetine, haloperidol, risperidone, thioridazine, aripiprazole, codeine, dextromethorphan, duloxetine, flecainide, mexiletine, ondansetron, tamoxifen, tramadol and venlafaxine. The risk of increased blood levels of drugs primarily metabolized by CYP2D6 is even more pronounced in the population

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2007. Mutual performed the second of these studies for the first time in early 2007. This latter study-- Study SP046306: In Vitro Assessment of Reaction Phenotyping (Enzyme Identification) for Human Cytochrome P450 Enzymes by Metaxalone (2007)-- is Exhibit B hereto. Mutual has licensed this new data to the NDA holder, King.

<sup>6</sup> See <http://medicine.iupui.edu/flockhart/table.htm>.

<sup>7</sup> See <http://medicine.iupui.edu/flockhart/clinlist.htm>



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with a genetic polymorphism of CYP2D6. This includes 5-10 percent of the U.S. Caucasian population.

- CYP2E1 - acetaminophen and chlorzoxazone
  - CYP3A4 - Clarithromycin, erythromycin, telithromycin, alprazolam, diazepam, midazolam, triazolam, cyclosporine, tacrolimus, indinavir, ritonavir, saquinavir, astemizole, chlorpheniramine, amlodipine, diltiazem, felodipine, nifedipine, nisoldipine, nitrendipine, verapamil, atorvastatin, cerivastatin, lovastatin, simvastatin, aripiprazole, buspirone, Gleevec®, haloperidol (in part), methadone, pimozone, sildenafil, tamoxifen, trazodone and vincristine
5. Ingestion of a high-fat meal will result in higher blood levels of metaxalone;
  6. Ingestion of a high-fat meal will result in increased blood levels of metaxalone which will likely compete for CYP1A2, CYP2D6, CYP2E1, and CYP3A4 activity with NTI drugs (specifically theophylline, warfarin, quinidine and quinine) that are metabolized by the same subenzymes as metaxalone; and
  7. Ingestion of a high-fat meal will result in increased blood levels of metaxalone which will likely compete for CYP1A2, CYP2D6, CYP2E1, and CYP3A4 activity with other drugs that are metabolized at a clinically relevant level by the same subenzymes as metaxalone.

In addition, data from an April 2006 Mutual-sponsored study show that at the concentration of 40  $\mu$ M, metaxalone induced CYP1A2 activity ranging from about 2- to 3.3-fold. The data also show that induction of CYP1A2 is concentration dependent. As stated in the Skelaxin® package insert, compared to fasted conditions, the presence of a high fat meal at the time of metaxalone administration increased the concentration of metaxalone in the blood, specifically increasing C<sub>max</sub> by 177.5%. Because the induction of CYP1A2 by metaxalone is

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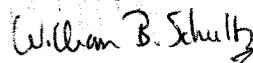
concentration dependent, the presence or absence of a high fat meal at the time of metaxalone administration may affect the induction of CYP1A2. Therefore, the cessation of metaxalone (taken with high fat meals) may cease the induction of CYP1A2 and concomitantly increase the blood levels of NTI drugs, like theophylline, that are metabolized by CYP1A2.<sup>8</sup>

In sum, therefore, the 2006 and 2007 Mutual studies confirm what the studies submitted by Mutual in December 2005 showed – *i.e.*, the potential for adverse drug-drug interactions between metaxalone and certain widely prescribed drugs which include NTI drugs, interactions which are made more likely when metaxalone is taken with certain foods.

### **III. Conclusion**

Accordingly, Mutual requests that FDA (1) grant King's petition supplement regarding the need to include the food effect information contained in the revised Skelaxin® labeling in the labeling for generic metaxalone, and (2) consider the attached Mutual data as part of its ongoing review of the labeling requirements for metaxalone.

Respectfully submitted,



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<sup>8</sup> Mutual's April 2006 study is Exhibit C hereto.



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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)**  
**Bob Rappaport, Director, Division of Anesthesia, Analgesia, and Rheumatology Products**  
**(w/attachments)**

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VIA FACSIMILE

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Re: Comments of Mutual Pharmaceutical Co., Inc. to the Supplemental Submission of  
King Pharmaceuticals, Inc. in Support of Citizen Petition and Petition for Stay  
Docket Nos. 2004P-0140/CPI and 2004P-0140/PSAI

Dear Ms. Butler:

As you requested, this will confirm in writing that Mutual Pharmaceutical Co. understands that all the attachments submitted in connection with the above submission will be available to the public once they are filed in the docket. Thank you for your assistance and please give me a call if you have any further questions.

Sincerely yours,

William B. Schultz