



William B. Schultz  
(202) 778-1820  
wschultz@zuckerman.com

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

Docket No. \_\_\_\_\_

**CITIZEN PETITION**

Petitioner Mutual Pharmaceutical Co. ("Mutual") hereby submits this Citizen Petition under 21 C.F.R. § 10.30. Petitioners request that the Food and Drug Administration ("FDA" or "the Agency") take the action described below.

**A. Action Requested**

Mutual requests that FDA require labeling changes for Skelaxin® (active ingredient metaxalone) as set forth in the proposed revised packaging insert included as Attachment A to this Petition. The proposed labeling changes – which are highlighted in Attachment A -- are based on important *in vitro* data developed by Mutual regarding the metabolism of metaxalone by members of the P450 liver enzyme group. This data reveals the potential for Skelaxin® to interact with drugs or foods that inhibit or induce the enzymes that metabolize metaxalone. This information, currently absent from the Skelaxin® label, is essential to the safe and effective administration of the product.

2007P-0296

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**B. Statement of Grounds**

**1. Background: Previous Submissions to FDA Regarding Skelaxin® Labeling and Safety**

The importance of proper labeling to ensure the safe and effective use of Skelaxin® has been the subject of numerous submissions to FDA over the past several years by both King Pharmaceuticals, Inc. (“King”), the holder of the approved New Drug Application (“NDA”) for Skelaxin®, and Mutual, which has had an Abbreviated New Drug Application (“ANDA”) for a generic metaxalone product pending before FDA (No. 40-536) since 2003. Indeed, Mutual was the first to raise important safety issues relating to Skelaxin®, requesting in a 2001 citizen petition that FDA (1) reclassify Skelaxin® as a product for which potential bioequivalence problems exist and (2) require ANDA applicants for generic metaxalone to perform *in vivo* fasted studies.<sup>1</sup> Thus, Mutual’s concerns regarding the safety of Skelaxin® are longstanding. FDA granted the 2001 Mutual citizen petition.

In addition to its 2001 petition to FDA, in December 2005 and May 2007, Mutual submitted data to FDA in support of a 2004 King citizen petition, which King later supplemented in February 2007.<sup>2</sup> King’s petition sought a determination that food effect information

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<sup>1</sup> See <http://www.fda.gov/ohrms/dockets/dailys/01/Mar01/030601/cp00001.pdf>.

<sup>2</sup> The 2004 King petition can be found at <http://www.fda.gov/ohrms/dockets/dailys/04/mar04/031904/04p-0140-cp00001-01-vol1.pdf>.

The 2007 King Supplement can be found at <http://www.fda.gov/ohrms/dockets/dockets/04p0140/04P-0140-sup0006-toc.htm>.

Mutual’s 2005 and 2007 submissions to FDA in response to the petition and supplemental can be found, respectively, at <http://www.fda.gov/ohrms/dockets/dockets/04p0140/04p-0140-sup0005-toc.htm> and <http://www.fda.gov/ohrms/dockets/dockets/04p0140/04p-0140-sup0007-toc.htm>. Mutual had initially opposed the King petition, but later withdrew its opposition in light of its own studies confirming the importance of the food effect.



contained on King's initially-approved (and later revised) labeling for Skelaxin® could not be carved out of the label for generic metaxalone products because that information was essential to the safe and effective use of the product. The data submitted by Mutual to FDA in support of the King petition and supplement demonstrates that "metaxalone is metabolized by, inhibits and/or induces activity in, liver P450 enzymes that also act on certain narrow therapeutic index [NTI] drugs" (December 8 Mutual submission at 2) that "whether metaxalone is administered with food may have an impact on whether it can be co-administered safely with NTI and related drugs," (*id.* at 6), and that, therefore, "the metaxalone food-effect may in fact have important, clinically significant consequences for the safe administration of metaxalone."<sup>3</sup> *Id.* at 4.

Mutual now seeks a determination from FDA that information discovered by Mutual in its 2007 study (hereafter, "the Mutual 2007 Study") relating to the metabolism of metaxalone by liver P450 enzymes must be included in the approved Skelaxin® label. A discussion of that study and its implications for the safe and effective use of Skelaxin® follows.

**2. The Mutual Data and Its Implications for the Safe and Effective Use of Skelaxin®**

The Mutual 2007 Study (No. SP046306) was attached to Mutual's May 2007 submission to FDA regarding the food effect issues raised by King in its 2004 petition and 2007 supplement.<sup>4</sup> For convenience, it is appended as Attachment B. The key conclusion set forth in the Mutual 2007 Study is that Metaxalone is metabolized by the P450 enzyme group, and that

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<sup>3</sup> King's petition is still pending with FDA.

<sup>4</sup> As noted in that submission, this data has been licensed to King.



the particular enzymes that metabolize metaxalone are CYP1A2, CYP2D6, CYP2E1, and CYP3A4 (hereafter, “the P450 enzymes”).<sup>5</sup>

These data have significant implications for the safe and effective use of Skelaxin® -- in particular, when Skelaxin® is taken with other drugs or foods that are known inhibitors or inducers of the enzymes that metabolize it. A list of the drugs and foods that are recognized to inhibit or induce the P450 enzymes is included in Attachment C.

Put simply, on one hand, the effect of taking Skelaxin® with an *inhibitor* of one or more of P450 enzymes will likely be to *increase* blood concentrations of metaxalone. *See* 2006 Draft Guidance at 31 (Appendix C-2) (“A drug that inhibits a specific drug-metabolizing enzyme can decrease the metabolic clearance of a co-administered drug that is a substrate of the inhibited pathway . . . . A consequence of decreased metabolic clearance is elevated blood concentrations of the co-administered drug . . .”). And increased blood concentrations of metaxalone will, in turn, potentially impact the safety profile of Skelaxin® by causing an increase in CNS adverse events associated with the use of metaxalone – *e.g.*, drowsiness, dizziness, headaches, nervousness or irritability – and in digestive adverse events associated with the use of metaxalone – as nausea, vomiting, and gastrointestinal irritation. *Id.* (noting that elevated blood concentrations of drug that is coadministered with inhibitor of the enzymes that metabolize the co-administered drug “may cause adverse events . . .”)

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<sup>5</sup> The Mutual study employed two complementary study methods -- (i) incubations with single cDNA expressed CYP450s and (ii) pooled human liver microsomes and specific chemical inhibitors. These are two of the three “well-characterized methods for identifying the individual CYP enzymes responsible for a drug’s metabolism.” FDA Draft Guidance for Industry, “Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling,” September 2006 (“2006 Draft Guidance”), at 27. FDA has recommended that at least two of these three well-characterized methods be used to identify the specific enzyme(s) responsible for a drug’s metabolism. *Id.* Thus, Mutual’s study meets FDA’s guidelines as set forth in the 2006 Draft Guidance.



On the other hand, the effect of taking Skelaxin® with an *inducer* of one or more of the P450 enzymes will likely be to *decrease* blood concentrations of metaxalone, thereby potentially causing sub-therapeutic blood concentrations of Skelaxin®. *Id.* at 35 (Appendix C-3) (“A drug that induces a drug-metabolizing enzyme can increase the rate of metabolic clearance of a co-administered drug that is a substrate of the induced pathway. A potential consequence of this type of drug-drug interaction is sub-therapeutic blood concentrations.”)

Thus, the finding that metaxalone is metabolized by the P450 enzymes bears heavily on the safe and effective use of Skelaxin® and leads to important consequences for the administration of that product by a patient and his or her physician.

### 3. The Proposed Revised Label for Skelaxin®

Mutual’s proposed revisions to the current Skelaxin® label occur in two places. First, Mutual proposes that the “Distribution, Metabolism, and Excretion” portion of the label be revised to strike the sentence “Metaxalone is metabolized by the liver and excreted in the urine as unidentified metabolites” and to include the following, expanded discussion of metaxalone’s metabolism and related drug interactions:

Metaxalone is metabolized by the liver via hepatic cytochrome P450 isoforms CYP1A2, CYP2D6, CYP2E1, and CYP3A4 and excreted in the urine as unidentified metabolites. Therefore, co-administration of drugs that inhibit CYP1A2, CYP2D6, CYP2E1, and CYP3A4 may result in an increase in metaxalone plasma concentrations, whereas co-administration of drugs that induce CYP1A2, CYP2E1, and CYP3A4 may decrease metaxalone plasma concentrations (See **Drug Interactions**).

Second, Mutual proposes that the “Drug Interactions” section be amended to include the following:



### Effects of Drugs on SKELAXIN Pharmacokinetics

In vitro studies using recombinant & pooled human microsomes have shown that CYP1A2, CYP2D6, CYP2E1, and CYP3A4 are responsible for the metabolism of metaxalone. Inhibitors of CYP1A2 (e.g., fluoroquinolone antibiotics, cimetidine, ticlopidine or fluvoxamine), CYP2D6, CYP2E1, and CYP3A4 may inhibit the metabolism of metaxalone resulting in higher metaxalone blood concentrations. Therefore when metaxalone is co-administered with CYP1A2, CYP2D6, CYP2E1, and CYP3A4 inhibitors, clinicians should monitor for increases in metaxalone related adverse events (e.g., CNS toxicities and gastrointestinal disturbances). Drugs that induce CYP1A2 (e.g., omeprazole), CYP2E1, and CYP3A4 may increase the metabolism of metaxalone resulting in lower metaxalone blood concentrations. Therefore when metaxalone is co-administered with CYP1A2, CYP2E1, and CYP3A4 inducers, clinicians should monitor for signs and symptoms associated with decreased efficacy.

These revisions serve three purposes. First, they add to the existing label the basic information concerning metaxalone's metabolism by the P450 enzyme group. As discussed below, this is the kind of basic pharmacokinetic information that FDA in its regulations and guidances has indicated belongs in product labeling and that is absent from the current label.

Second, the revisions explain the potential health and safety consequences of co-administering metaxalone with inhibitors or inducers of P450 enzymes. Once again, as discussed below, this is the kind of important drug interaction information that FDA has indicated belongs in product labeling.

Third, the revisions provide physicians and other health professionals with specific guidance in connection with the co-administration of Skelaxin® and inhibitors or inducers of the P450 enzymes, advising (1) increased monitoring for adverse events associated with Skelaxin® (CNS toxicities and certain gastrointestinal disturbances) in



connection with co-administration with P450 inhibitors, and (2) increased monitoring for signs of decreased efficacy or failure of expected pharmacological action of Skelaxin® in connection with co-administration with P450 inducers.

**4. Mutual's Proposed Labeling Revisions Are Essential to the Safe and Effective Use of Skelaxin®, and Are, in Fact, Precisely the Kinds of Labeling Changes FDA Has Requested in Its Regulations and Guidances.**

Taken together, Mutual's proposed labeling revisions provide important information that permits physicians to safely and effectively administer Skelaxin®, particularly with known P450 inducers/inhibitors. It also advises that particular attention be given to signs of adverse events and decreased efficacy under those circumstances. These revisions are precisely the kind of information that FDA has deemed essential to safety and effectiveness where, as here, clinically significant information regarding metabolism and pharmacokinetic interactions becomes available.

First, FDA regulations require that a prescription label include "clinically significant" pharmacokinetic information, including "mechanisms of clearance (*e.g.*, specific enzyme systems)" and "drug/drug . . . pharmacokinetic interactions (including inhibition, induction, and genetic characteristics)." 21 C.F.R. § 201.57(c)(13)(i)(C). This is exactly the kind of information implicated by the Mutual 2007 Study and set forth in the proposed labeling revisions.

Second, FDA's guidance documents confirm the importance of the metabolism/interaction data contained in the Mutual 2007 Study and explain the need to include this information in Skelaxin® labeling in order to ensure the safe and effective use of the



product. Most recently, in its 2006 Draft Guidance, “Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling,” FDA has noted that “adequate assessment of the safety and effectiveness of a drug includes a description of its metabolism and the contribution of metabolism to overall elimination” (2006 Draft Guidance at 1) and states that:

It is important that *all relevant information* on the metabolic pathways and metabolites and pharmacokinetic interactions be included in the PHARMACOKINETICS subsection of the CLINICAL PHARMACOLOGY section of the labeling. The clinical consequences of metabolism and interactions should be placed in DRUG INTERACTIONS, WARNINGS AND PRECAUTIONS, BOXED WARNINGS, CONTRAINDICATIONS, or DOSAGE AND ADMINISTRATION sections, as appropriate. When the metabolic pathway or interaction data results in recommendations for dosage adjustments, contraindications, or warnings (e.g., co-administration should be avoided) that are included in the BOXED WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, OR DOSAGE AND ADMINISTRATION sections, these recommendations should also be included in HIGHLIGHTS.

2006 Draft Guidance at 15 (*italics added, upper case lettering in original*).

Similarly, in the precursor to the 2006 Draft Guidance, a 1999 Guidance entitled “In Vivo Drug Metabolism/Drug Interaction Studies – Study Design, Data Analysis, and Recommendations for Dosage and Labeling” (“1999 Guidance”), FDA stated that:

Relevant in vitro and in vivo metabolic drug-drug interaction data describing the drug’s effects on substrates and inhibitors and inducers on the drug should be presented in the DRUG-DRUG INTERACTIONS section of the labeling in the CLINICAL PHARMACOLOGY section . . . . If findings indicate a known or potential interaction of clinical significance . . . , these should be mentioned briefly in the clinical pharmacology interactions section and described more fully in the interaction section under PRECAUTIONS, with advice on how to adjust treatment placed in WARNINGS/PRECAUTIONS, DOSAGE AND



ADMINISTRATION, and CONTRAINDICATIONS, as appropriate.

1999 Guidance at 13 (upper case lettering in original). *See also* FDA Guidance for Industry, “Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements,” January 2006, at 6 (noting that “[f]requently, there is a subset of [drug interaction] information that is clinically relevant and essential for prescribing decisions.”)

These Agency guidances, along with FDA’s regulations, make clear that information regarding Skelaxin®’s metabolism by P450 enzymes and the concomitant potential adverse drug-drug (or drug-food) interactions with known inhibitors or inducers of these enzymes should be included as an “important” part of Skelaxin’s® labeling. Indeed, consistent with FDA’s guidance, other drug products that are metabolized by P450 enzymes include similar labeling information to that proposed by Mutual for Skelaxin®. A representative sample of products with similar labeling as that proposed here by Mutual includes Lexiva®, Reyataz®, Prezista®, and Vfend®, the labels of which are Attachment D.<sup>6</sup>

C. **Conclusion**

For the foregoing reasons, Mutual requests that FDA require the attached proposed labeling revisions for Skelaxin®.

D. **Environmental Impact**

The action requested in this petition will have no impact on the environment.

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<sup>6</sup> The relevant information on the Lexiva® label is on pages 8 and 23. The relevant information on the Reyataz® label is on pages 10-11. The relevant information on the Prezista® label is on page 8. The relevant information on the Vfend® label is on page 7.



**ZUCKERMAN SPAEDER LLP**

1800 M STREET, NW WASHINGTON, DC 20036-5802  
202.778.1800 202.822.8106 fax www.zuckerman.com

Carlos T. Angulo  
Partner  
(202) 778-1811  
ctangulo@zuckerman.com

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VIA FACSIMILE

Ms. Jennie Butler  
Director  
Division of Dockets Management  
U.S. Food and Drug Management  
5630 Fishers Lane, Room 1061 (HFA-305)  
Rockville, MD 20857

Re: Citizen Petition Submitted by Mutual Pharmaceutical Company on  
July 27, 2007, Regarding Skelaxin® Labeling

Dear Ms. Butler:

This will confirm in writing that Mutual Pharmaceutical Co. understands that all the attachments submitted in connection with the above citizen petition 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,

*Carlos T. Angulo*  
Carlos T. Angulo

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E. Certification

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 the Petitioners that are unfavorable to the Petition.

*William B. Schultz*

William B. Schultz  
Carlos T. Angulo  
ZUCKERMAN SPAEDER LLP  
1800 M Street, N.W.  
Washington, D.C. 20036  
(202) 778-1800

ATTORNEYS FOR PETITIONER  
MUTUAL PHARMACEUTICAL CO.