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May 13, 2009

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

Re: Citizen Petition
Correct Skelaxin® 800 mg (metaxalone) Tablet Labeling To Reflect
That It Is A Delayed Release Dosage Form

CITIZEN PETITION

A. Specific Regulatory Actions Requested

Mutual Pharmaceutical Co. ("Mutual") submits this citizen petition under 21 C.F.R. §10.30 to request that the FDA take the following 5 actions to correct the current inaccurate dosage form identification for Skelaxin®:

1. Declare Skelaxin® 800 mg (metaxalone) tablets to be misbranded unless King Pharmaceuticals, Inc. ("King") updates its labeling to reflect that Skelaxin® is a delayed release dosage form, including immediately labeling with precautionary language against crushing the tablets.
2. Update the dosage form listing of Skelaxin® in Approved Drug Products with Therapeutic Equivalence Evaluations to read "TABLET, DELAYED RELEASE."
3. Require King to develop a dissolution method that discriminates between immediate release and delayed release formulations of Skelaxin® and change the FDA-recommended dissolution methods to reflect the same distinction.
4. Apply the SUPAC-MR guidance for scale up and post approval changes to the manufacture of Skelaxin® and ANDAs relying upon Skelaxin® as their reference listed drug.
5. Require King to perform a pharmacokinetic study on crushed versus whole Skelaxin® tablets, to discern the effects of crushing on the delayed release characteristics of this product, and to label this product consistent with the results.

FDA-2009-P-0223-0001

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B. Statement of Factual and Legal Grounds Supporting Requested Actions

I. Background: Skelaxin®'s labeling and FDA's regulatory guidance must be updated to reflect new data regarding this drug.

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, 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 report the discovery that there was not an in vivo/in vitro dissolution correlation, as was previously believed, by way of a 2001 citizen petition regarding Skelaxin®. FDA granted the 2001 Mutual citizen petition¹ thereafter requiring a fasted bioequivalency study for ANDA approvals.

Recently, Mutual conducted bioequivalence studies on various metaxalone formulations that provide confirmatory in vivo data for earlier published in vitro dissolution studies that suggested Skelaxin® was a delayed release dosage form.² Because Mutual's data now reveals that Skelaxin® is a delayed release drug formulation, and because this fact has many regulatory and medical-use implications, Skelaxin® must be labeled as a delayed release dosage form. For example, immediate release metaxalone has a 390% higher C_{max} than the currently approved Skelaxin® product which is delayed release and current FDA approved labeling, and associated guidance, do not account for this and other differences.

The details of these issues are presented below.

II. Skelaxin®'s formulation contains a known pH dependent binder used to achieve delayed release profiles.

The Skelaxin® package insert discloses that the product formulation contains alginic acid as an inactive ingredient.³ Alginic acid is a well known pH dependent binder that is used with insoluble drug substances such as metaxalone.⁴ Alginic acid is insoluble at acidic pH levels and becomes soluble at higher pH levels. Therefore, due to the presence of alginic acid, Skelaxin® is insoluble at the acidic pH levels of gastric fluid and only becomes soluble at the higher pH levels achieved in intestinal fluid, resulting in

¹ FDA Docket No. 01P-0117/CP1, FDA response of January 30, 2002.

² Cacace J, Reilly EE, Amann A. Comparison of the dissolution of metaxalone tablets (Skelaxin) using USP Apparatus 2 and 3. AAPS PharmSciTech, 2004 Feb 6; 5(1):E6. Attached hereto at Tab A.

³ See "DESCRIPTION" section of Skelaxin® package insert attached at Tab B.

⁴ Handbook of Pharmaceutical Excipients, 5th Ed. (2006) (Alginic Acid monograph), identifying Functional Category both a "sustained release adjuvant" and "tablet binder". Attached at Tab C.

delayed release of metaxalone from Skelaxin®, especially under fasting conditions.⁵ The metaxalone drug substance and alginic acid are critical components of the delayed release tablet matrix in Skelaxin®.

While the tablet formulation mechanism of Skelaxin®'s delayed release can be identified, the delayed release characteristics of Skelaxin® have been masked by the higher pH dissolution method and medium (0.5% SLS in water) that has been recommended by the Agency for metaxalone since at least February 2004.⁶ The current FDA-recommended dissolution method for metaxalone would only be appropriate for true immediate release dosage forms of the drug. As described in section V below, Mutual therefore requests that the Agency change its dissolution method guidance to assure correct discrimination between immediate release and delayed release formulations of metaxalone.

III. Skelaxin® demonstrates a delayed release profile in dissolution testing.

In 2004, Dr. Janice Cacace and colleagues at Nova Southeastern University published the results of a laboratory study funded by Andrx Pharmaceuticals that evaluated the effect of pH on the dissolution behavior of metaxalone in Skelaxin® 400 mg. tablets (publication attached at Tab A). Results demonstrated that the release of metaxalone from Skelaxin®'s formulation is pH dependent and concluded that "Skelaxin Tablets should be considered a delayed release dosage form."⁷

The Cacace et. al. studies utilized USP dissolution Apparatus 2 and 3 and pH levels ranging from 1.5 to 7.4. At low pH (USP simulated gastric fluid without pepsin, pH 1.5), the dissolution of metaxalone from Skelaxin® tablets was less than 10% over 75 minutes. At pH 4.5, greater than 90% of drug was dissolved over 75 minutes. The authors concluded that the release profile of metaxalone "is highly pH dependent" and that in the Skelaxin® formulation "metaxalone presents itself as a delayed-release dosage form."⁸ These dissolution results are also consistent with the USP <724> requirements for a delayed release dosage form.⁹

⁵ The USP <1151> Pharmaceutical Dosage Forms defines Delayed Release as "Where the drug may be destroyed or inactivated by the gastric juice or where it may irritate the gastric mucosa, the use of "enteric" coatings is indicated. Such coatings are intended to delay the release of the medication until the tablet has passed through the stomach." (emphasis added). Attached at Tab D. In addition to formulations employing enteric coating to achieve delayed release, the addition of a pH-dependent binder, such as alginic acid, to an insoluble drug substance like metaxalone will also result in a delayed release profile.

⁶ "FDA-Recommended Dissolution Methods" database, available at <http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm?c=1>

⁷ Cacace at 3.

⁸ Id at 3.

⁹ There were some minor differences between the Cacace et al. testing methods and those of USP <724> for Delayed Release (Enteric Coated Articles)-General Use and Standard. The results clearly demonstrate that Skelaxin® is a delayed release tablet.

Mutual also conducted disintegration testing of Skelaxin®, the results of which are attached at Tab E. Consistent with the Cacace et. al. results, Mutual's disintegration testing showed that the Skelaxin® tablets remained intact after 1 hour in acidic media and disintegrated in about 1 hour in simulated intestinal fluid. These disintegration results are consistent with the USP <701> requirements for delayed release tablets.¹⁰ Only after the pH was raised to solubilize the alginate-based delayed release tablet matrix did the tablets disintegrate.

IV. Skelaxin® demonstrates a delayed release profile in bioequivalence testing.

Mutual conducted three bioequivalence studies comparing 800 mg Skelaxin® tablets to both immediate release and delayed release dosage forms of metaxalone. The combined summary data tables for these studies are attached at Tab F and described below. Mutual's bioequivalence studies demonstrate that immediate release (IR) metaxalone is extensively bioinequivalent to Skelaxin®, while delayed release (DR) metaxalone is nearly bioequivalent to Skelaxin®.¹¹

The first study (R06-0559) was a fasting 3 way crossover study comparing Skelaxin® (lot ES805379A) to an IR powder filled capsule formulation of metaxalone without a pH dependent binding system. The C_{max} of the IR formulation was 390% higher than Skelaxin®'s and the AUC_{0-inf} was 106% higher than Skelaxin®'s. The terminal half life of the IR formulation was 2.5 hours compared to the apparent terminal half life of 11.5 hours for Skelaxin®. The longer apparent half life of Skelaxin®, with measurable blood levels up to 35 hours after a single dose, reflects continued drug absorption from the delayed release dosage formulation.

The second study (R08-0136) was also a fasting 3 way crossover study that compared Skelaxin® (lot ES807221A) to an IR mini tablet formulation of metaxalone in a capsule without a pH dependent binding system. When corrected for dose, the results demonstrated a 129% increase in C_{max} and a 51% increase in AUC_{0-inf} for the IR mini tablet formulation as compared to Skelaxin®. Consistent with R06-0559, the terminal half life of the IR mini tablet formulation was 2.8 hours versus an apparent elimination half-life of 8.9 hours for Skelaxin® indicating drug absorption from the dosage form well beyond the dosing interval of every 6-8 hours.

The third study (R08-0135) was also a fasting 3 way crossover study but compared Skelaxin® (lot ES807221A) to a delayed release mini tablet formulation of metaxalone in a capsule with a pH dependent binding system. When corrected for dose, the results nearly demonstrated bioequivalence to Skelaxin®, with C_{max} ratio of 79.6% and AUC_{0-inf}

¹⁰ Testing was performed using USP <701> for Delayed Release (Enteric Coated) Tablets. The results clearly demonstrate that Skelaxin® meets the requirements for a delayed release tablet.

¹¹ Mutual's DR metaxalone had 90% CI of (68.8, 92.3) on C_{max} and (80.9, 102.5) on AUC_{inf} when compared to Skelaxin®. Additionally, Mutual's IR metaxalone had 90% CI of (432.2, 566.7) on C_{max} and (182.0, 234.1) on AUC_{inf} .

of 88.5% compared to Skelaxin®. The apparent terminal half life of the DR formulation was 5.8 hours compared to 8.0 hours for Skelaxin®

The results from these three studies demonstrate that Skelaxin® is extensively bioinequivalent to immediate release metaxalone and nearly bioequivalent to Mutual's formulation of delayed-release metaxalone¹¹. The delayed release nature of Skelaxin® in retrospect should not have been a surprise since it is consistent with its labeled pharmacokinetic profile and higher bioavailability in the presence of food (which tends to raise pH and thereby dissolution of the drug). However, the food effect alone does not account for the degree of difference between immediate release metaxalone and Skelaxin®, as detailed above. The Skelaxin® label (attached at Tab B) reports an increase in C_{max} of 177.5% from a high fat meal whereas the data presented above demonstrates an increase in C_{max} of 389.6% from removal of the delayed release formulation mechanism. Skelaxin® is clearly a delayed release formulation and does not remotely resemble an immediate release product.

V. Skelaxin®'s delayed release profile necessitates five FDA actions requested by this petition.

Having established that the delayed release nature of Skelaxin® is evidenced by its formulation, dissolution studies, and bioequivalence profiles, it follows that the Agency should undertake the following 5 actions in order to correct the current inaccurate dosage form identification of Skelaxin®.

1. Declare Skelaxin® 800 mg (metaxalone) tablets to be misbranded unless King Pharmaceuticals updates its labeling to reflect that Skelaxin® is a delayed release dosage form.

Under the Federal Food, Drug and Cosmetic Act (FDCA), a drug is deemed misbranded "if its labeling is false or misleading in any particular." 21 U.S.C. §352(a). Since the Skelaxin® labeling has now been found to inaccurately describe the approved dosage form, the Skelaxin® labeling needs to be corrected.

Moreover, under 21 C.F.R. §201.56(a)(2), King Pharmaceuticals, the holder of the Skelaxin® NDA, is obligated to continue to update the Skelaxin® package insert to keep it truthfully labeled: "The labeling must be informative and accurate..." and "...must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading." Since the Agency requires numerous modified release products to be properly labeled in this regard, and since there are many regulatory, medical use, and safety implications of proper labeling as enumerated in this document, the Agency should require King to immediately correct the labeling of Skelaxin® in light of this new information.

The current inaccurate labeling of Skelaxin® could be remedied by King with as few as three edits:

- Skelaxin® should be identified as SKELAXIN (Metaxalone) Delayed-Release Tablets in the Description section of the package insert and on the package label.
- The following sentence should be added to the CLINICAL PHARMACOLOGY/Absorption section of the package insert: "Skelaxin is a delayed-release product."
- Add a warning against crushing the Skelaxin® tablets (WARNINGS: "Do not crush Skelaxin tablets before swallowing.") until King has conducted a pharmacokinetic study to determine if crushing Skelaxin® tablets does not have an adverse impact on clinical bioavailability. Since Skelaxin® is currently labeled similarly to many immediate release products, there are no labeled instructions to prevent a health care provider from administering crushed tablets, thereby exposing patients to the potential hazards of dose dumping. Until King performs crushed tablet studies, as described in 5 below, King should be required to immediately update the Skelaxin® label to include a warning against crushing Skelaxin® tablets.

The Agency should immediately require King to label Skelaxin® in accordance with these three edits.

2. Update the dosage form listing of Skelaxin® in Approved Drug Products with Therapeutic Equivalence Evaluations to read "TABLET, DELAYED RELEASE."

The Agency has independent authority as the publisher of Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") to change the dosage form identified for Skelaxin®.¹² Accurate identification of the Skelaxin® dosage form as "TABLET, DELAYED RELEASE" in the Orange Book will prevent therapeutic equivalence evaluation difficulties or confusion as subsequent metaxalone tablet products are approved.

3. Require King Pharmaceuticals to develop a dissolution method that discriminates between immediate release and delayed release formulations of Skelaxin® and change the FDA-recommended dissolution methods to reflect the same distinction.

In the absence of an established USP dissolution method for metaxalone, an appropriate dissolution method needs to be developed that reflects the delayed release profile of Skelaxin®. The current FDA-recommended dissolution method could result in approval of an AB rated equivalent to Skelaxin® and, even though the test batch passed bioequivalency, subsequent production batches could harbor unintended and unacceptable changes in product quality (e.g. immediate release or dose dumping) that

¹² 21 U.S.C. §355(j)(7); Orange Book, 29th ed., Preface at v.

the current dissolution method and release tests would not detect, with adverse patient safety consequences.

Development of an appropriate dissolution method should be done by King in consultation with FDA. The dissolution method recommended by FDA needs to be adjusted to reflect that Skelaxin® is a delayed release product. Until an appropriate dissolution method is developed, FDA should remove the current inaccurate dissolution testing method from the Agency's list of recommended testing methods.

4. Apply the SUPAC-MR¹³ guidance for scale up and post-approval changes to the manufacture of Skelaxin® and ANDAs relying upon Skelaxin® as their reference listed drug.

Because Skelaxin® is a delayed release dosage form, SUPAC-MR should be applied to scale up and post-approval manufacturing changes to require an appropriate level of control over product quality assurance and quality control. These consequences include that sponsors should:

- provide justification for claiming that any excipients are non-release controlling excipients in the formulation;¹⁴
- when changing manufacturing sites, be required to pass cGMP inspection as well as provide Level 3 changes of three batches for stability, multipoint-drug release testing, and a single bioequivalence study if no established in vivo/ in vitro correlation exists.¹⁵

SUPAC-MR requirements should be applied immediately to the Skelaxin® NDA as well as any pending or approved ANDAs referencing Skelaxin®.

5. Require King Pharmaceuticals to perform a pharmacokinetic study on crushed versus whole Skelaxin® tablets to discern the effects of crushing on the delayed release characteristics of the product, and to label the product consistent with the results.

As presently labeled, Skelaxin® contains no information regarding the effect of crushing the delayed release matrix of the tablet on the product's release and clinical characteristics. As this delayed release tablet is the only dosage form commercially available, it is undoubtedly subject to being crushed for administration to certain

¹³ FDA Guidance for Industry: SUPAC-MR: Modified Release Solid Oral Dosage Forms, Scale Up and Post approval Changes: Chemistry, Manufacturing and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (September 1997).

¹⁴ Id. at 2.

¹⁵ Id. at 15 This is consistent with the Agency's Guidance *Changes to an Approved ANDA or NDA* (November 1999), which recommends re-performance of bioequivalence studies against the reference listed drug (p. 7) and preapproval inspection if the formulation modifies the rate and extent of availability of the drug. (p. 9).

patients, whether orally (mixed with food) or through tube feeding. Crushing the tablets would destroy the delayed release matrix causing a decrease in disintegration time and increasing the surface area thus promoting faster drug dissolution. Commercially available modified release products commonly have a warning to not crush the tablets. The pharmacokinetic effects of crushing Skelaxin® tablets are not currently known. King should be required to perform a pharmacokinetic study on crushed versus whole Skelaxin tablets, to discern the effects of crushing on the delayed release characteristics of the product, and to label the product in accordance with those results.

C. Environmental Impact

The actions requested are subject to a categorical exclusion from environmental assessment under 21 C.F.R. § 25.30(h).

D. Economic Impact

Pursuant to 21 C.F.R. § 10.30(b), we will provide data concerning the economic impact of the actions requested should such information be requested by the FDA.

E. Certification of Service

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 dates: (i) Mutual obtained the study report for R06-0559 on September 12, 2006; (ii) Mutual obtained the study reports for R08-0135 and R08-0136 on September 10, 2008; (iii) The combined impact of the various pharmacokinetic studies on the approved labeling of Skelaxin® was first noted by Mutual on March 27, 2009. 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: I am an employee of Mutual and am making these representations on behalf of Mutual as part of my responsibilities as an employee of Mutual and am not being separately compensated for submitting this petition. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.



Robert Dettery
Vice-President, Regulatory Affairs
Mutual Pharmaceutical Company, Inc.

Attachments

From: Origin ID: REDA (215) 807-1044
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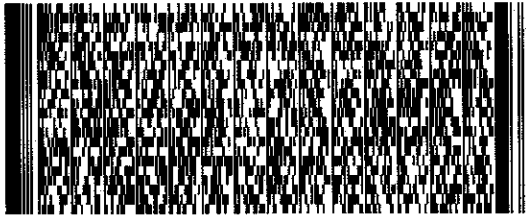


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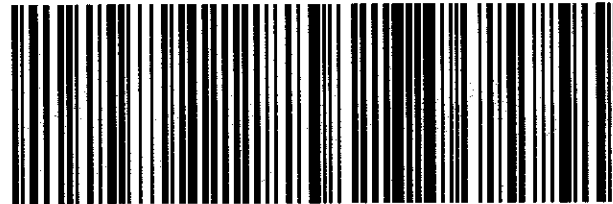
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