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October 16, 2001

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

**Citizen Petition**

Dear Sir or Madam,

The undersigned submits this petition in accordance with 21 CFR 10.30 to request the Commissioner of Food and Drugs to require an acceptable *in vivo* bioequivalence study conducted under fasting and fed conditions as a requirement for approval of an abbreviated new drug application (ANDA) for a generic version of Skelaxin (metaxalone) Tablets, 400 mg.

## A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration require, as a condition of approval an abbreviated new drug application for a generic version of Skelaxin (metaxalone) Tablets, 400 mg, an acceptable bioequivalence study that demonstrates the generic product is bioequivalent to the reference product when administered under both fasting and fed conditions. [Please note that Elan recognizes that the FDA, as described below, has initiated a process whereby they propose to notify industry of the need for an *in vivo* fasting study as a condition of ANDA approval. Should and when that decision become final and FDA publishes final notice in the Orange Book, and responds to the URL petition that an *in vivo* fasting study will be required for ANDA approvals for this drug product, the portion of this petition relating to the *in vivo* fasting study should be considered as withdrawn by Elan. However, the portion of the petition requesting a food effect study as a condition of ANDA approval shall remain active.]

## B. Statement of Grounds

The petitioner is aware of the March 6, 2001 petition filed by URL Mutual Pharmaceutical Co. Inc. (Docket No. 01P-0117/CP1) requesting the Food and Drug Administration require an acceptable *in vivo* fasting bioequivalence study demonstrating that the generic product and the reference product are



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bioequivalent as a condition of approval generic version of Skelaxin (metaxalone) Tablets, 400 mg. In support of their request, URL Mutual included the results of two *in vivo* bioequivalence fasting studies and three separate *in vitro* dissolution tests.

As a result of the data presented in the URL petition, the Division of Bioequivalence, Office of Generic Drugs, has published a proposal to change the designation for metaxalone tablets from a "non bioproblem" to a "bioproblem" drug. This change in designation recognizes that there is no defined *in vivo/in vitro* correlation and will thus require the submission of an *in vivo* bioequivalence study demonstrating that any generic metaxalone product is bioequivalent to Skelaxin. We agree that metaxalone should be designated as a bioproblem drug.

In addition, based on the results of a pharmacokinetics study showing a marked food effect on metaxalone, we are requesting that the abbreviated new drug application approval requirements be further modified to include acceptable bioequivalence to the reference product when administered under both the fed and fasting conditions.

Upon review of the data contained in the URL petition Elan concluded that an *in vivo* fasting study should be required as a subject of approval for a generic product. Based on this realization and a desire to further characterize the pharmacokinetic performance of its product, in July 2001 Elan initiated a study to determine if food has an effect on Skelaxin absorption. A single 400 mg dose of Skelaxin was administered under fasting (10 hour overnight fast) and fed (standard high fat breakfast) conditions in a two treatment, randomized, crossover study in 42 healthy volunteers (31 males, 11 females). The results indicate that the bioavailability was significantly increased when Skelaxin was administered with food in that both the rate ($C_{max}$) and extent of absorption ($AUC_{0-t}$) were increased. There was no significant difference noted for $AUC_{0-8}$. A copy of the final report, conducted in accordance with Protocol No. AN121607 is attached for your review.

In addition, concurrently with the filing of this petition Elan has submitted a labeling supplement to the Skelaxin NDA to revise the labeling to reflect the results of this study.

## C. Environmental Impact

Categorical exclusion is claimed under 21 CFR 25.31.

## D. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis if requested by the agency.

## 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 petitioner, which are unfavorable to the petition.

Sincerely,

Linda Ballai Fischer

Linda Ballai Fischer
Director, Regulatory Affairs

Cc: Gary Buehler
Director, Office of Generic Drugs (HFD-600)

Jonca Bull, M.D. – Cover letter only
Acting Director, Division of Anti-Inflammatory, Analgesic
And Opthalmic Drug Products (HFD-550)

# Elan Pharmaceuticals
# Petition to
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# October 16, 2001
# Clinical Documentation

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