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

Re: Petition of King Pharmaceuticals, Inc. Regarding Generic Metaxalone
(Docket No. 2004P-01-0140/CP 1/PSA/1) and Petition of Mutual
Pharmaceutical Co., Inc. for Stay of Action (Docket No. 2004P-
0140/PSA/CP1/PSA2)

SUPPLEMENTAL SUBMISSION

Mutual Pharmaceutical Co., Inc. ("Mutual") hereby submits the Affidavit of Dr. Daniel L. Azarnoff in opposition to the Petition of King Pharmaceuticals, Inc., and in support of Mutual's Petition for Stay of Action. Both petitions concern the significance of labeling that King has proposed regarding the possible food effects of King's drug Skelaxin (metaxalone). In his declaration, Dr. Azarnoff concludes that "there are no data or other information that would support a determination that metaxalone tablets sold with labeling that omits the information about food effects is either less safe or less effective than a product sold with labeling containing such information." Azarnoff Declaration ¶ 7. Dr. Azarnoff further concludes that "the omission of the food effects information from the labeling for generic metaxalone tablets is not clinically

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relevant and the omission of that information from generic metaxalone labeling would not render prescribing of the drug less safe or less effective than the brand product.” *Id.*

Respectfully submitted,

A handwritten signature in black ink that reads "William B. Schultz".

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DECLARATION OF DANIEL L. AZARNOFF, M.D.

I, Daniel L. Azarnoff, declare as follows:

QUALIFICATIONS

1. I received my M.D. from University of Kansas Medical School in 1955. Between 1955 and 1958, I was a medical intern and resident at the University of Kansas. Following post doctoral training in pharmacology at Washington University School of Medicine (1958-1960), between 1960 and 1978, (except during 1968 when I was a Fulbright Scholar at the Karolinska Institute in Stockholm, Sweden) I worked as a professor in the schools of medicine at St. Louis University School of Medicine and at University of Kansas Medical School where I rose to the rank of KUMC Distinguished Professor of Medicine and Pharmacology. From 1979-87, I was a Professor of Pharmacology at Northwestern University Medical School, and from 1979-87 I was Professorial Lecturer in Pharmacology at the University of Chicago Medical School. I was Clinical Professor of Medicine at Stanford University Medical School (1998-2002) and am currently Professor of Medicine at University of Kansas Medical School.

2. From 1978 to 1985, I held a number of senior executive positions at G.D. Searle & Co., the last position being President, Searle Research and Development & Chief Scientific and Medical Officer (Corporate). I have also held senior executive positions at three other, small pharmaceutical companies. Since 1986 I have been President of D.L. Azarnoff Associates, a company I founded that consults with domestic and foreign pharmaceutical companies.

3. I am a member or fellow of 17 professional associations, including the Institute of Medicine of the National Academy of Sciences, New York Academy of Sciences, American Association of Pharmaceutical Scientists and American Society Clinical Pharmacology and Therapeutics. I have held a position in 10 professional committees, councils or organizations and have served on committees of the National Academy of Sciences, the Institute of Medicine, the American College of Physicians, National Institutes of Health (Institute of General Medical Sciences), the Food and Drug Administration, US Pharmacopeia (chairman committee on bioavailability) and the World Health Organization.

4. I have served on the editorial or advisory boards of more than 19 journals and have published more than 175 articles in the medical and scientific literature. A copy of my curriculum vitae and a list of the articles that I have published are attached to this declaration.

SUMMARY OF OPINION

5. I have reviewed the March 1, 2004 letter from the Food and Drug Administration (“FDA”) to applicants who have filed abbreviated new drug applications (ANDAs) for metaxalone tablets, and the labeling for metaxalone, which is attached to the letter. I have also reviewed the March 18, 2004, Citizen Petition submitted by King Pharmaceuticals and the declarations of Leslie Z. Benet, Ph.D. and Michael F. Elia, M.D., submitted with the petition.

6. In the FDA’s March 1, 2004, letter, the FDA informs the metaxalone tablet ANDA applicants that information about the food effects of metaxalone may be carved out of the metaxalone labeling. I understand this to include all the pharmacokinetics information in the

Clinical Pharmacology section of the labeling. I have been asked to provide an opinion on whether labeling without such information renders metaxalone less safe or less effective than the brand product, Skelaxin®, containing such labeling.

7. In my opinion, there are no data or other information that would support a determination that metaxalone tablets sold with labeling that omits the information about food effects is either less safe or less effective than a product sold with labeling containing such information. In fact, there are no data or information that even suggests that omission of the information on pharmacokinetics would pose a safety or efficacy problem. In my opinion, the omission of the food effects information from the labeling for generic metaxalone tablets is not clinically relevant, and the omission of that information from generic metaxalone labeling would not render prescribing of the drug less safe or less effective than the brand product.

BASES OF OPINION

8. The information that FDA has permitted to be carved out of labeling for generic metaxalone contains information from two studies. Both studies compare the plasma concentration levels and pharmacokinetics of Skelaxin in individuals given Skelaxin under fasting conditions and under fed conditions, which in both studies was a high fat meal. Under these conditions, there was a statistically significant increase in the absorption of Skelaxin when given with a high fat meal. The effect on absorption under these conditions is to approximately double the absorption rate of Skelaxin and increase the extent of absorption 15-50%. The results of these studies are the worst case food effect, a diet with little or no fat having a significantly lesser effect on the rate and extent of absorption.

9. The bioavailability studies described in the labeling do not identify any dose response relationship to safety or efficacy. Thus there is no evidence in these studies that safety decreases or efficacy increases if the peak plasma concentration increases approximately two fold or the extent increases approximately 50%. It is also significant that other factors may affect the plasma concentration of a drug such as Skelaxin, such as the weight of the patient, the dosing frequency of the drug (if it is q.i.d. one dose is typically take at bedtime and not after a meal), concomitant administration of other drugs, liver or kidney dysfunction, potential genetic differences in patient's drug metabolizing enzymes.

10. Based on the size of the maximal food effect identified, the absence of evidence of the slope of a dose response, and the other factors that may affect the absorption of metaxalone, it is my opinion that even if metaxalone were given under the "extreme" conditions of these studies, the food effect of Skelaxin should not have any clinical relevance.

11. The conditions under which the food effects of Skelaxin were studied bear little or no relationship to the conditions under which it is actually used by most patients. First, most patients do not regularly eat high fat meals. For patients who consume diets with little or modest amounts of fat, the increased rate and extent of absorption of Skelaxin will be considerably less. Therefore, the typical patient's plasma concentrations would not be significantly affected by whether he or she takes Skelaxin on an empty stomach or after eating. In my opinion, the difference in absorption of metaxalone between patients in a fasted and a fed (typical diet, not high fat) state is not clinically relevant.

12. The labeling of Skelaxin contains no directions or recommendations to the physician about how to take the food effects into account when treating patients. The labeling does not recommend that Skelaxin be taken on an empty stomach; nor does it recommend that the dose of Skelaxin be reduced if the drug is given with a high fat meal. By omitting any instructions as to how the food effect studies should be used in clinical practice, the labeling of Skelaxin supports my conclusion that the food effects information is not clinically relevant.

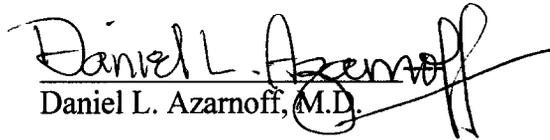
13. I have reviewed the Declaration of Dr. Leslie Z. Benet, submitted in connection with the King petition. Dr. Benet states that the pharmacokinetic data included on Skelaxin's labeling "is an indication that safety and efficacy issues of clinical significance *may exist*", and that "the very omission of such data from the Skelaxin labeling *can pose* safety and efficacy concerns." Benet Declaration ¶¶ 10, 31. These are very qualified statements. As I understand his declaration, Dr. Benet does not conclude that the absence of the food effects labeling would raise safety or efficacy issues, but only that there "may" be significance.

14. In my opinion, the two studies that would be carved out of the generic labeling for metaxalone are not a basis even for finding that safety and efficacy issues may exist and provide no indication that such issues may exist. But even if they did, as Dr. Benet agrees "the clinical effect of the increased bioavailability is unknown." Benet Declaration ¶ 26. In fact, in the Skelaxin labeling, there is a statement after the discussion of each bioavailability study "the clinical relevance of the[food] effects is unknown."

15. In other words, it does not matter if a high fat diet increases plasma metaxalone concentrations. At the current time, there is no evidence the increased concentrations attained when Skelaxin is taken with a high fat diet have any clinical relevance. Therefore, there is no supportable clinical decision that a physician could make based on these studies. Metaxalone has been prescribed by physicians for many years without knowledge of this food effect and without a high incidence of side effects. For these reasons, carving this information out of generic versions of Skelaxin should not affect the safety or effectiveness of generic metaxalone.

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Under the penalty of perjury, I declare that the foregoing is true and correct.


Daniel L. Azarnoff, M.D.

Date: JANUARY 26, 2005