

DECLARATION OF LESLIE Z. BENET, PH.D.

1. I, LESLIE Z. BENET, PH.D, have been retained as an expert on behalf of King Pharmaceuticals, Inc. ("King"). In particular, I have been retained to assess the clinical relevance of the pharmacokinetic results of certain clinical studies conducted in connection with the muscle relaxant drug product, Skelaxin® (metaxalone). I have also been retained to assess the importance of describing such results in the labeling for generic versions of Skelaxin®.

I. STATEMENT OF QUALIFICATIONS

2. I was awarded the degree Bachelor of Science in Pharmacy in 1960 and the degree of Master of Science in Pharmaceutical Chemistry in 1962 from the University of Michigan. I was awarded the degree of Doctor of Philosophy in Pharmaceutical Chemistry from the University of California San Francisco in 1965.

3. I have received five honorary doctorates from: Uppsala University, Sweden; Leiden University, The Netherlands; University of Illinois, Chicago; Philadelphia College of Pharmacy and Science; and Long Island University.

4. I have been on the Faculty of the University of California San Francisco since 1969, and am presently Professor of Biopharmaceutical Sciences and Pharmaceutical Chemistry. My research interests include pharmacokinetics and pharmacodynamics, biopharmaceuticals and drug delivery, drug metabolism, and drug transporters.

5. I have been a member of the National Academy of Sciences, Institute of Medicine, since 1987. I have been or am currently on the editorial board of 10 scientific, peer reviewed journals. I have published more than 450 publications in scientific journals, and I have

received more than 20 international awards. In December 2003 I was listed as one of the 250 most cited pharmacologists in the world.

6. I am currently the Chairman of the Congressionally mandated IOM/NRC Committee on Accelerating The Research, Development, and Acquisition of Medical Countermeasures Against Biological Warfare Agents. I served as chairman of an FDA expert panel on Individual Bioequivalence (1998-2002) and have served as a consultant to the pharmaceutical industry through work with, among others, Allergan Inc. (1986-present), Eisai Co. (1987-present), Proctor & Gamble (1988-present), and Amgen (1996-present).

7. A copy of my Curriculum Vitae is attached as Exhibit A.

II. OVERVIEW OF OPINION

8. Based on my review of the March 1, 2004 letter from the Food and Drug Administration (“FDA”) Office of Generic Drugs to Abbreviated New Drug Application (“ANDA”) applicants for generic versions of metaxalone, it appears that the FDA may be planning to permit generic versions of Skelaxin® to omit from their labeling the results of human studies demonstrating the increase in the bioavailability of metaxalone when co-administered with food, despite the fact that this information properly appears in the labeling of Skelaxin®.

9. Based on my review of the current Skelaxin® labeling and the underlying studies that have been incorporated in the Clinical Pharmacology section of that labeling, I have been asked to assess whether the omission of this bioavailability information can pose safety and efficacy issues.

10. In my opinion, data demonstrating that bioavailability of Skelaxin® can vary under various conditions, including an increase in bioavailability under fed conditions as compared to fasted conditions, has clinical relevance. In my experience, such pharmacokinetic data, particularly in connection with a drug that has not been classified as a Biopharmaceutical Classification System (BCS) Class 1 drug, is an indication that safety and efficacy issues of clinical significance may exist. As such, the very omission of such data from the Skelaxin® labeling can pose safety and efficacy concerns.

IV. EXPERT OPINION

A. The Skelaxin® Drug Product

11. Skelaxin®, the active ingredient of which is a compound known as metaxalone, is used to treat discomforts associated with acute, painful, musculoskeletal conditions. Although Skelaxin® has been on the market for many years, its mode of action remains unknown. Only recently have studies been conducted to assess the pharmacokinetics of metaxalone. To date, these studies have been carried out to determine the effects of food, age, and gender on the bioavailability of the drug. The results of two of these studies are described in the approved package insert for Skelaxin®, and the remainder are the subject of an approvable labeling supplement pending with the FDA Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products.

12. To prove bioequivalence, the U.S. Food and Drug Administration (“FDA”) generally requires applicants seeking approval of generic versions of drugs to conduct *in vivo* bioequivalence studies comparing the proposed generic product to the approved, reference listed drug. (The requirement for *in vivo* bioequivalence studies may be waived for drug products

containing a highly soluble, highly permeable drug, when the drug product exhibits rapid dissolution (*i.e.*, Class 1 BCS drug products).

13. Metaxalone is not a Class 1 drug. On February 27, 2001, the documentation that metaxalone is a low solubility drug was provided to the FDA (both OGD and ODEV). I believe that metaxalone will be found to be a Class 2 compound, having low solubility and high permeability. As pointed out by Fleisher *et al.* (Clin Pharmacokinet. 36:233-245, 1999) Class 2 compounds typically exhibit an increase in the extent of bioavailability when administered with a high fat meal. This finding for Skelaxin® is consistent with my belief that metaxalone will be found to be a Class 2 compound. At present, Skelaxin® is a drug product for which *in vivo* bioequivalence studies are required for approval of a generic product. In addition, since Skelaxin® exhibits a food effect, a food effect bioequivalence study is required for approval of a generic equivalent to Skelaxin®.

B. Skelaxin® Bioavailability Clinical Studies

14. When investigating the pharmacokinetics of Skelaxin®, two clinical studies were initially conducted to examine the effects of food on the bioavailability of Skelaxin®. The first of these studies was conducted in 42 healthy volunteers in which a single 400mg Skelaxin® tablet was administered under both fasted and fed conditions -- Clinical Study AN151607-101 (“Study 101”) entitled “Bioavailability Study of Skelaxin® (Metaxalone) 400mg Administered With and Without Food to Healthy Volunteers.” The results of Study 101 revealed that the administration of Skelaxin® with food statistically significantly increases its bioavailability as compared to its administration without food.

15. The second study was conducted in 59 healthy volunteers in which two 400mg Skelaxin® tablets were administered under both fasted and fed conditions -- Clinical Study AN151607-103 (“Study 103”) entitled “Bioequivalence and Safety Study of Skelaxin® (Metaxalone) 1 x 800mg Tablet and 2 x 400mg Tablets Under Fasted and Fed Conditions in Healthy Volunteers.” The results of Study 103 also demonstrated that the bioavailability of Skelaxin® is statistically significantly increased when administered with food as compared to when administered without food and confirmed the results of Study 101.

16. As a result of Studies 101 and 103, labeling to reflect the data generated by those studies and to inform doctors and other healthcare practitioners that the bioavailability of Skelaxin® would be increased if the drug is administered with food was approved by the FDA. The language reflecting the results of Study 101 and Study 103 is included in the current Skelaxin® labeling.

C. Skelaxin® Bioequivalence Under Fed and Fasted Conditions Is Based on the Skelaxin® Bioavailability Clinical Studies

17. *In vivo* bioequivalence studies in both the fed and fasted states are routinely required for the approval of drug products when the drug is known to have a food effect or when the drug is in a modified release dosage form. These requirements are imposed by the FDA to eliminate the concerns related to the potential for different safety and/or efficacy profiles. This is based on the rationale that bioequivalent drug products are considered to have the same therapeutic effect, and thus have the same clinical effect and safety profile when administered to patients according to the approved labeling.

18. Based on current FDA guidance, if a generic drug product subject to these requirements fails to demonstrate bioequivalence under both the fed and fasted conditions, the FDA simply will not grant approval.

19. The safety and efficacy of generic versions of Skelaxin® can only be adequately demonstrated by appropriate bioequivalence testing, which necessarily includes the results of a food-effect study. Demonstration of bioequivalence under the appropriate conditions, *i.e.*, fed and fasted, assures that the generic version of Skelaxin® will have the same safety and efficacy profile.

20. As such, the FDA has already acknowledged the import of the determination that food has an effect on the bioavailability of Skelaxin®. Indeed, after completing Study 101, two separate submissions were made to the FDA -- the submission to incorporate the results of Study 101 in the labeling as well as a submission pointing out the significance of these studies such that any approval of a generic metaxalone drug product would be dependent on a demonstration of *in vivo* bioequivalence in the fed as well as the fasted states.

21. In sum, the FDA approved both the labeling submission *and*, based on the significance of the fed and fasted studies, the FDA also determined that a generic version of Skelaxin® must not only demonstrate *in vivo* bioequivalence in the fasted state, but also *in vivo* bioequivalence in the *fed* state.

D. Additional Skelaxin® Bioavailability Clinical Studies and Meta-Analysis

22. Two additional studies were conducted to investigate the pharmacokinetics of Skelaxin® -- studies designed to examine the effects of age and gender on the bioavailability of

Skelaxin®. The first study was conducted in young volunteers between the ages of 18-55 and elderly volunteers, age 65 and older, in which two 400mg Skelaxin® tablets were administered under both fasted and fed conditions -- Clinical Study ELN 151607-105 (“Study 105”) entitled “A Study to Evaluate the Pharmacokinetics of Skelaxin® (Metaxalone) 2 x 400mg Tablet Administered to Young and Elderly Volunteers Under Fed and Fasted Conditions”. The second study was conducted in healthy male and female volunteers in which two 400mg Skelaxin® tablets were administered under fasted conditions -- Clinical Study AN151607-106 (“Study 106”) entitled “A Study to Evaluate the Effect of Gender on the Pharmacokinetics of Skelaxin® (Metaxalone) 2 x 400mg Administered to Healthy Volunteers.” Finally, a meta-analysis of Study 105 and Study 106 was conducted in combination with Study 101 and Study 103 to investigate the effect of age and gender on the bioavailability of Skelaxin® in both the fed and fasted states.

23. Based on the results of the meta-analysis, it was found that, in the fed state, regardless of gender, age has little or no effect upon the bioavailability of Skelaxin®. In contrast, in the fasted state, regardless of gender, bioavailability is statistically significantly increased with an increase in age. Moreover, in both the fed and fasted states, bioavailability is statistically significantly higher in females than in males.

24. The overall conclusion drawn from all of the pharmacokinetic studies was that age-related variations in the bioavailability of metaxalone are minimized when Skelaxin® is administered with food. As a result of these findings, proposed labeling to reflect the data generated by Study 105, Study 106, and the meta-analysis and a recommendation that that Skelaxin® be administered with food to ensure more consistent plasma levels of metaxalone was submitted to the FDA. The FDA has recently indicated that the labeling supplement is

approvable, pending a change in format to comply with the general ADME (absorption, distribution, metabolism, elimination) layout currently being used in new product labels.

E. The Label and its Relevance to Health Care Practitioners

25. Doctors, pharmacists and other healthcare practitioners rely on the label, as approved by the FDA, to provide them with factual information, preferably the results of well-conducted and approved studies, and the necessary background to safely and effectively administer drugs to patients. Skelaxin® exhibits an increase in drug exposure when the drug product is administered with a high fat meal. Approved generic equivalents of Skelaxin® will also exhibit such an increase in exposure. This is a fact that is presently included in the label of the approved drug product.

26. On May 31, 2002 FDA approved an addition to the Skelaxin® Clinical Pharmacology labeling that stated, “given the magnitude of the plasma level change following a high-fat meal, Skelaxin® tablets should be administered on an empty stomach.” However, as described in the March 1, 2004 letter to the ANDA Applicant for metaxalone tablets, the label was further revised in June 2002 to remove information regarding dosing on an empty stomach, and to state that the clinical effect of the increased bioavailability is unknown. I concur with this change and believe that it accurately reflects the information available to the FDA. I further believe that there is no reliable information upon which the FDA can judge that “the fed-state bioavailability information maybe carved out of the metaxalone labeling without rendering the drug less safe or effective for the remaining conditions of use.” I make this statement because there is no additional or previous reliable information that will support such a contention as described below.

27. I believe that metaxalone will be found to be a BCS Class 2 compound. As I presented in a seminar at the FDA on November 10, 2003 entitled "BCS and its Application to Predicting Drug Disposition: Transporter/Absorption/Elimination Interplay", transporter-enzyme interplay will be primarily important for Class 2 compounds. Drug-drug interactions are not limited to enzymatic processes, and since transporter interactions can frequently occur, and particularly transporter-enzyme interplay will particularly be observed for Class 2 compounds. At this time, I am aware of no information as to the metabolic profile of metaxalone, or its potential to be a substrate for transporters. However, if metaxalone is a substrate for the cytochrome P4503A enzyme and an intestinal efflux transporter, there will be significant drug interactions with this compound. There will also be drug-drug interactions if the compound is a substrate for metabolism by other hepatic enzymes and either uptake and efflux hepatic transporters. At present, none of this information is known.

28. The FDA is well aware that it cannot reasonably depend on "a long history of safe use" and the fact that a compound "has been marketed for decades without dosing adjustment information related to fed-state administration." Such information is highly suspect and cannot be reliably depended upon for regulatory judgments (*e.g.*, phen-fen; terfenadine being considered for over the counter status; the fact that it took 60 years to identify that there was a significant life-threatening pharmacokinetic drug interaction between quinidine and digoxin; the expectation that fexofenadine would not exhibit a drug interaction with ketoconazole.) Science progresses; we learn new facts that allow us to uncover problems that we previously had completely ignored.

29. I believe that studies to determine which enzyme(s) metabolize metaxalone and which transporters affect the drug would make obvious that there are, in fact, a number of drug-drug interactions with this pharmaceutical. Until the FDA has reviewed submitted experimental

or clinical prospective data and analysis that shows that changes in bioavailability due to the fed-state are immaterial, and more importantly that the drug is characterized so that reliable studies may be designed to test the potential for significant drug-drug interactions, the FDA would be misguided to remove from the labeling information that assists healthcare scientists and practitioners in truly characterizing metaxalone's disposition and the relevance of pharmacokinetic changes.

30. The FDA is a science based regulatory agency. There is no doubt that a food effect occurs with metaxalone. There is no reliable evidence, based on science, that "fed-state bioavailability information may be carved out of the metaxalone labeling without rendering the drug less safe or effective for the remaining conditions of use."

CONCLUSION

31. In sum, the bioavailability data should not be omitted from the labeling for generic versions of Skelaxin®. Based on my experience, it is my opinion that such pharmacokinetic data, particularly in connection with a drug that requires *in vivo* bioequivalence testing, is an indication that safety and efficacy issues of clinical significance may exist. As such, the very omission of such data from the Skelaxin® labeling can pose safety and efficacy concerns.

I declare under the penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

March 18, 2004
Date


Leslie Z. Benet, Ph.D.

**EXHIBIT A TO
EXHIBIT 10**