

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”). I previously executed a declaration in support of King’s Citizen Petition dated March 18, 2004. Further to my original declaration, I have been asked to consider and comment on the comments submitted on behalf of Corepharma LLC (“Core”) regarding King’s Citizen Petition. In particular I have been asked to review and provide comments on the Declaration of Paul Bass, Ph.D., who has been retained as Core’s expert (“the Bass Declaration”). I have also been asked to consider and comment on the submissions made on behalf of Mutual Pharmaceutical Co., Inc. (“Mutual”).

I. STATEMENT OF QUALIFICATIONS

2. My statement of qualifications was submitted in my original declaration, dated March 18, 2004.

II. OVERVIEW OF OPINION

3. I understand that after King submitted its Citizen Petition, which included my original declaration, Core and Mutual each made submissions to the FDA regarding King’s Citizen Petition. I have reviewed these submissions, including the Bass Declaration accompanying Core’s comments. In my previous declaration, I was asked to assess the importance of describing the results of human studies demonstrating an increase in the bioavailability of metaxalone when co-administered with food in the labeling for generic versions of Skelaxin®. Based on my review of the submissions made by Core and Mutual, it

remains my opinion that permitting generic versions of Skelaxin® to omit from their labeling the results of human studies demonstrating an increase in the bioavailability of metaxalone when co-administered with food, despite the fact that this information properly appears in the labeling of Skelaxin®, would pose safety and efficacy concerns.

4. Core and Mutual both make a number of assertions to support their efforts to carve out certain information concerning the pharmacokinetics of metaxalone from their generic product labeling. Neither Core nor Mutual offers any actual data demonstrating that the omission of this information from the labeling for generic versions of Skelaxin® would not affect the safe and effective use of generic metaxalone. Core's expert purports to offer evidence in support of Core's comments; however, the Bass Declaration contains irrelevant and inconclusive information that cannot support Core's theories. At best, the opinions proffered by Core's expert are conjecture. Moreover, certain statements in the Bass Declaration are simply incorrect. Likewise, Mutual also relies on either incorrect or irrelevant statements to support its arguments. As such, Core and Mutual fail to provide any meaningful information regarding the impact of excluding pharmacokinetic data in the labeling for generic versions of Skelaxin® and fail to draw any credible conclusions regarding the same.

5. Nor do Core and Mutual provide any evidence or adequate arguments that refute my assertion that the pharmacokinetic data demonstrating that the fact that bioavailability of Skelaxin® can vary under various conditions - including an increase in bioavailability under fed conditions as compared to fasted conditions, 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, it remains

my opinion that the very omission of such data from the Skelaxin® labeling can pose safety and efficacy concerns.

III. EXPERT OPINION

A. Core's Reliance on the Longstanding Use of Skelaxin® To Support the Omission of Pharmacokinetic Data from Generic Labeling Is Misguided

6. No one denies that Skelaxin®, the active ingredient of which is a compound known as metaxalone, has been used for many years in the treatment of discomforts associated with acute, painful, musculoskeletal conditions. However, the historical use of Skelaxin® is irrelevant to the question of whether the omission from generic metaxalone labeling of pharmacokinetic data resulting from clinical studies designed to determine the effects of food, age, and gender can hinder the safe and effective use of generic metaxalone products.

7. Core's reliance on the fact that Skelaxin® had been marketed many years without labeling describing a food effect is misguided. I note that the history of Skelaxin® includes instances of similar misguided dependence on the predictability of Skelaxin®. For decades, as a DESI drug, Skelaxin® was presumed to be a drug with no known or potential bioequivalence problems. However, based on the results of bioequivalence studies, it was subsequently demonstrated that there is no correlation between *in vivo* dissolution and *in vivo* bioequivalence of metaxalone drug products.

8. As I stated in my original declaration: science progresses; we learn new facts that allow us to uncover problems that we previously had completely ignored. Based on the results of bioequivalence studies conducted in 2001 -- notwithstanding that *in vivo* studies had not been required in the past -- the FDA determined that the safety and efficacy of generic versions of Skelaxin® can only be adequately demonstrated by *in vivo* bioequivalence studies in addition to

in vitro studies. Similarly, based on the results of clinical studies designed to determine food-effects -- notwithstanding that fed studies had not been required in the past -- the FDA determined that the safety and efficacy of generic versions of Skelaxin® can only be adequately demonstrated by bioequivalence testing, which includes the demonstration of bioequivalence under both *fed* and fasted conditions. FDA also required that the labeling for Skelaxin® include the results of the clinical studies demonstrating the relative difference between administration of Skelaxin® in the fasted and fed conditions.

9. Because the results of clinical studies determining the effects of food, age, and gender on the pharmacokinetics of metaxalone are now known, there is no basis for Core to rely upon the use of Skelaxin® prior to the outcomes of such clinical studies, or on the text of former Skelaxin® labeling, to conclude that the results of such clinical studies are irrelevant or properly omitted from labeling. Indeed, absent a clinical study showing that the proposed differences in labeling do not affect safety or effectiveness, determining whether a generic metaxalone product would be equally safe and effective as Skelaxin® can only be based on bioequivalence and labeling equivalence to the Skelaxin® product as currently sold under the Skelaxin® NDA. The historic use and labeling of Skelaxin® are irrelevant in making that determination.

B. Core and Mutual Each Fail to Refute the Results of the Skelaxin® Bioavailability Studies and the Importance of Describing Such Results in Generic Labeling

10. Core and its expert, as well as Mutual, do not and cannot deny that the clinical studies conducted to examine the effects of food on the bioavailability of Skelaxin® (previously referred to as Study 101 and Study 103 in my original declaration) reveal that the administration of Skelaxin® with food statistically significantly increases its bioavailability as compared to its administration without food. Instead, Core and Mutual attempt to draw conclusions about the

data's clinical relevance. However, in the absence of any data, Core and Mutual cannot support their proffered conclusions.

1. Core and Mutual Fail to Draw Any Credible Conclusions Regarding the Clinical Import of Fed-State Bioavailability Data

11. Core relies on its expert's opinion that the lack of information correlating safety or efficacy of metaxalone with plasma concentration levels renders information relating to differences between fed and fasted blood levels of metaxalone clinically irrelevant. Such a conclusion suggests that Core's expert would thus logically argue that unless a correlation between plasma concentrations and safety and efficacy exists, there would be no basis for recommending a dose of a drug. When a food effect changes plasma concentrations, that result is equivalent to changing the dose. The listing of food effect data in the package insert is included to give clinicians information concerning the "available dose". This then gives the clinician relevant information that he/she chooses to use or not use based on his/her clinical experience with the drug.

12. It cannot be presumed that there is no relationship between the safety and/or efficacy of metaxalone and plasma concentration levels simply because the mechanism of action, the precise site of action, and plasma concentrations required for metaxalone's therapeutic and toxic effects are not known. As such, it also cannot be presumed that the differences in fed and fasted bioavailability do not correlate to any therapeutic effect and have no clinical significance. The lack of information about the relationship between the safety and/or efficacy of metaxalone and plasma concentration levels is not sufficient evidence to establish clinical insignificance.

13. That there is no known correlation between the safety and efficacy of other drugs and their plasma concentration levels is irrelevant to determining whether the omission of fed-

state bioavailability data for metaxalone poses safety and efficacy concerns. Absent data establishing that there is no relationship between plasma concentration levels and the safety and/or efficacy of metaxalone, any comparisons with other drugs are inapplicable. However, it is significant that the three examples singled out by Core's expert -- Nexium, Fosamax, and Prempro -- are all drugs that *include the results of food effect studies* in their labeling, notwithstanding the lack of a known correlation between their safety and efficacy and their plasma concentration levels.

14. Accordingly, Core fails to identify evidence regarding the relationship between plasma concentration levels and the safety and efficacy of metaxalone and/or evidence that the lack of an established relationship renders fed-state bioavailability data clinically irrelevant. Moreover, the only evidence that is provided by Core confirms my opinion that the omission of fed-state bioavailability data from the labeling for generic metaxalone would be inappropriate. Although there is no established correlation between safety or efficacy and plasma concentration levels for the three examples identified by Core's expert, FDA has required the labeling of all three drugs to include the results of food-effect studies.

15. Mutual attempts to argue that because the bioavailability studies conducted to assess the effects of food on the bioavailability of Skelaxin® did not measure safety or side effects and compare efficacy between the fed and fasted dosing regimens, it is inappropriate to presume a clinical effect based solely on the observed pharmacokinetic effect. It is not disputed that the bioavailability studies described in the current labeling for Skelaxin® -- like most other food effect studies -- did not measure clinical endpoints. However, this is simply irrelevant to the question of whether omission of such pharmacokinetic data from the labeling of generic

metaxalone would pose safety and efficacy concerns. Mutual fails to point to any studies or data to the contrary.

16. In making its point, Mutual argues that blood level measurements may not be a measure of clinical effect. What Mutual fails to mention is that the very same reference it relies on to make this assertion also concludes that bioavailability and clinical effect of most drugs do correlate. *See* Schmidt, Lars E. and Dalhoff, Kim, *Food-Drug Interactions*, *Drugs*, Vol. 62, No. 10, 1481-1502 (2002), at 1485, Mutual Exhibit C. Mutual also fails to mention that an asserted lack of correlation between blood levels and clinical effect would undercut the basic assumptions that underlay the approval of generic drugs that have been tested only for bioequivalence to a reference listed drug and have never been tested – other than in blood level comparisons – for clinical efficacy and safety.

3. Core and Mutual Each Fail to Draw any Credible Conclusions Regarding the Potential Effect of Different Meals on the Difference Between Fed and Fasted Bioavailability of Metaxalone

17. Core and its expert attempt to argue that when metaxalone is administered as recommended under what Core defines (without data) as normal eating conditions, any differences between fed and fasted bioavailability would become negligible. In particular, without providing any data, Core's expert opines that the significant increase in bioavailability of metaxalone when administered in the fed state as compared to the fasted state would become insignificant or negligible if metaxalone is co-administered with a meal other than the standardized high fat meal used in the clinical studies. Along similar lines, Mutual attempts to argue that the food-effect studies are unreliable because they failed to account for potentially significant differences in the type of meals consumed by patients taking metaxalone.

18. However, both Core and Mutual fail to identify any evidence from clinical studies demonstrating that the fed-state bioavailability of metaxalone would be affected by different types of food. Absent any such data, it is impossible to conclude that composition of the meal administered would affect the bioavailability of metaxalone in the fed state.

19. Instead, the assumptions made by both Core and Mutual are based on irrelevant references reporting the effects of different types of meals on the bioavailability of drugs other than Skelaxin®. Such studies provide no information on the bioavailability of metaxalone. Moreover, the evidence presented by these references is inconclusive. Core provides examples of drugs other than Skelaxin® whose bioavailability in the fasted state can vary upon administration with different types of food. However, even these cited studies do not support Core's assertions. In fact, Core cites at least one study demonstrating that co-administration with a low-fat meal can also significantly increase the oral bioavailability of certain drugs. *See Hamaguchi, T. et al., Effect of a high-fat meal on the bioavailability of phenytoin in a commercial powder with a large particle size, Internat. J. Clin. Pharmacol. Ther. Toxicol., Vo. 31, No. 7, 326-30 (1993), Core Exhibit 14 (reporting that the administration of phenytoin with a low-fat meal results in a significant increase in bioavailability).* Here, there is no evidence demonstrating that the food-effect is negligible or non-existent when metaxalone is co-administered with a low fat meal, and, indeed, as Core's reference demonstrates, there is no basis for Core's assumption that the food effect would be insignificant with a lower fat meal.

20. Mutual relies on similar references to support its arguments. Ironically, in contrast to Core, Mutual relies on evidence that co-administration with the standardized high fat diet may *not* optimize the bioavailability of all drugs. Mutual's submission includes studies demonstrating that for certain drugs, the co-administration with a low fat meal can result in a

greater increase in bioavailability than co-administration with a standard high fat meal. *See e.g.,* Martinez, M.N., *et al., Effect of Dietary Fat Content on the Bioavailability of a Sustained Release Quinidine Gluconate Tablet*, *Biopharm. Drug Dispos.*, Vol. 11, 17-29 (1990), Mutual Exhibit D.

21. Even though Mutual has no actual data to support its arguments that co-administration with various types of meals would affect the blood levels of metaxalone differently, Mutual relies on its presumption that there will be variation in fed-state bioavailability based on food constitution to make yet another presumption: Mutual suggests that dosing on an empty stomach would remove any effect of meal-to-meal variation and the purported resulting variation in bioavailability. As discussed above, there is no basis for Mutual to conclude that co-administration with meals other than the standardized high-fat meal used in the Skelaxin® bioavailability studies would result in variability in plasma concentration levels, much less to conclude that dosing on an empty stomach would prevent the theorized variations in blood levels of metaxalone.

22. In sum, unless and until studies are actually conducted, there is no evidence supporting Core and Mutual's conclusion that the results of King's clinical studies are irrelevant or unreliable simply because the studies utilized the standardized high fat meal required by the FDA for such studies.

4. Core Errs in Relying on Statements that the Effects of a Single Dose Study Would Differ From the Standard Dosing Regimen for Metaxalone

23. Core also relies on its expert's opinion that when metaxalone is administered under what it contends are normal eating conditions at the recommended dose three to four times

a day, any differences between fed and fasted bioavailability would be clinically insignificant. Core's expert is simply wrong. Regardless of whether metaxalone is administered as a single dose or in multiple doses, if there is an increase in bioavailability in the fed state as compared to fasted state, that change in bioavailability will be present when multiple doses are taken. The increase in bioavailability will not diminish just because more than one dose is administered and steady-state is achieved.

24. By way of analogy, consider one patient who takes 800 mg of metaxalone three times a day and a second patient who takes 400 mg of metaxalone three times a day. The subject administered 800 mg will be exposed to twice the amount of metaxalone as compared to the subject that is administered a 400 mg dose. Similarly, a subject administered multiple doses of metaxalone with food will be exposed to a greater amount of metaxalone compared to a subject administered the same doses of metaxalone at the same intervals, but without food.

5. Core Fails to Draw Any Credible Conclusions From the Variability in the Data Resulting From the Bioavailability Studies

25. Core also relies on its expert's observation that there is variability in the fasted state bioavailability of metaxalone in certain individual patients. Core's expert theorizes that certain subjects exhibited an increase in plasma concentration levels in the fasted state versus the fed state because the fasted administration of metaxalone coincided with secretion of bile into the duodenum, which, according to Core's expert, occurs approximately every ninety minutes. Based on this, Core states that fasted-state bioavailability of metaxalone can equal or exceed fed-state bioavailability. However, it is irrelevant that administration of metaxalone that purportedly coincides with fasted state secretion of bile into the duodenum can lead to an increase in bioavailability. Core's expert fails to explain that the bioavailability of all drugs, not just

metaxalone, is impacted by such normal digestive functions. Despite this, food-effect information is routinely included in drug product labeling.

26. Regardless of any effects of these normal digestive functions, Studies 101 and 103 still demonstrate that in comparison to administration in the fasted state, the bioavailability of metaxalone is increased when administered in the fed state. Core's expert is unable to provide any data that suggest otherwise. The identification of gastric phenomena that can enhance the bioavailability of drugs administered in the fasted state is not evidence that the clinically established food-effect is somehow insignificant or non-existent.

C. Core and Mutual Fail to Identify Data Demonstrating that Drug-Drug Interactions Do Not Exist for Metaxalone

27. In addition to their failure to present data showing that the omission of the results of bioavailability studies from the labeling of generic metaxalone products would not render those products less safe or effective than Skelaxin®, neither Core nor Mutual offer any data to refute my statements in my original declaration that differences in the pharmacokinetic parameters of drugs that are not Class 1 drugs are a very strong indication that such changes may have clinical effect. In the absence of information, it cannot be presumed that metaxalone will not be a potential substrate for transporters. It also cannot be presumed that there will be no drug-drug interactions that can affect the safety and efficacy of metaxalone. The pharmacokinetic changes that are demonstrated by the results of Studies 101 and 103 cannot be presumed clinically irrelevant in the absence of any data.

28. Mutual attempts to argue that such a presumption is proper because it is well known that for many drugs with a known food effect, the effect is not associated with any major changes in clinical effect. However, it is significant that all of the examples that Mutual cites

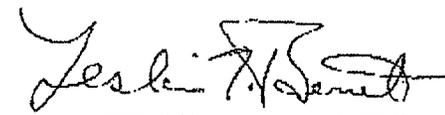
(pravastatin, phenoxymethylpenicillin and furosemide) are Class 3 drugs (i.e., high solubility, low permeability). As discussed in my original declaration, I believe that metaxalone will be found to be a Class 2 drug, and as such, its pharmacokinetic changes are a strong indication that the existence of a food effect is a harbinger of drug-drug interactions that can affect the safe and effective dosage of the drug. The evidence that Class 3 drugs with known food effects are not associated with major changes in clinical effect is irrelevant with respect to metaxalone.

IV. CONCLUSION

29. I confirm the statement of my previous declaration: 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. Core and Mutual have failed to provide any scientific evidence to the contrary or to refute my statements. Rather, both have relied on presumptions that are irrelevant to determining whether the omission of bioavailability data causes safety and efficacy concerns. As such, it remains my opinion that the very omission of the pharmacokinetic 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.

July 20, 2004
(Date)



Leslie Z. Benet, Ph.D.