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March 18, 2004

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Room 1061
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CITIZEN PETITION

On behalf of King Pharmaceuticals, Inc. ("King"), the undersigned submit this petition under Section 527 of the Federal Food, Drug, and Cosmetic Act ("Act") and Parts 10.30 and 316 of the Food and Drug Administration regulations to request that the Commissioner of Food and Drugs ("the Commissioner") take the actions described below.

Actions Requested

The Commissioner is requested to: (a) rescind the March 1, 2004 'Dear Applicant' Letter issued by the Director of the Office of Generic Drugs ("OGD") regarding metaxalone labeling; (b) require applicants seeking approval to market generic metaxalone products that rely on King's SKELAXIN® as the reference listed drug ("RLD") to submit a patent certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii) for U.S. Patent No. 6,407,128; and (c) prohibit the removal from generic metaxalone labeling of the pharmacokinetics information that appears in the SKELAXIN® labeling.

2004P-0140

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Statement of Grounds

I. Factual Background

SKELAXIN® (metaxalone) is marketed and distributed by Petitioner King Pharmaceuticals, Inc. and its subsidiary Jones Pharma Inc. Originally owned by A.H. Robins Co., all rights, title, and interest in and to SKELAXIN® and the SKELAXIN® NDA were eventually acquired by Elan Pharmaceuticals, Inc. (“Elan”) and subsequently transferred to King on June 12, 2003. SKELAXIN® is indicated as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions.

To date, at least three generic companies have filed Abbreviated New Drug Applications (“ANDA”) with the Food and Drug Administration (“FDA”) seeking approval to market generic metaxalone products. Those generic companies are Eon Labs, Inc. (“Eon”), CorePharma, LLC (“Core”), and Mutual Pharmaceutical Co., Inc. (“Mutual”). FDA has not yet finally approved any ANDAs for generic metaxalone products.

SKELAXIN® is currently protected by two patents – United States Patent Nos. 6,407,128 (“the ’128 patent”) and 6,683,102 (“the ’102 patent”). Both the ’128 patent and the ’102 patent relate to the unexpected discovery that the bioavailability of SKELAXIN® can be increased by administering it with food. By filing their ANDAs,

Eon, Core, and Mutual have infringed both the '128 patent and the '102 patent, and patent litigations are currently pending against Eon and Core in the District Court for the Eastern District of New York and against Mutual in the District Court for the Eastern District of Pennsylvania.

Although SKELAXIN® has been on the market for quite some time, its mode of action is not fully understood, and its pharmacokinetics have only been investigated relatively recently. Over the last few years, Elan and King have performed a series of studies to characterize the pharmacokinetics of SKELAXIN®. These studies were submitted to FDA in support of two supplements (one already approved and one approvable) for changes to the SKELAXIN® label. These changes are intended to provide doctors and other healthcare practitioners with all available information concerning the pharmacokinetics of SKELAXIN®. These studies and the resulting labeling supplements are described below.

A. Studies Showing The Absence Of A Correlation Between *In Vitro* And *In Vivo* Bioavailability

SKELAXIN® was originally approved prior to enactment of the Drug Amendments Act of 1963. The drug was determined to be effective, however, pursuant to the FDA's Drug Efficacy Study Implementation ("DESI") review. At that time, the drug was not considered to be a drug with known or potential bioequivalence problems and, therefore, sponsors of ANDAs for generic versions of the product would have been

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considered eligible for a waiver of *in vivo* bioequivalency study requirements. 21 C.F.R. § 320.22(c).

During investigations of the pharmacokinetics of metaxalone products, however, Elan and Mutual (one of the current ANDA applicants), discovered that there was no correlation between *in vitro* dissolution and *in vivo* bioequivalence of metaxalone drug products. Accordingly, Elan provided the FDA with two sets of data – the first relating to the solubility of metaxalone and the second relating to *in vitro* dissolution as compared to *in vivo* bioavailability. See Elan submission to the Office of Generic Drugs (Feb. 27, 2001). Around the same time, Mutual also concluded that there is no *in vitro/in vivo* correlation (“IVIVC”) with metaxalone¹ and submitted a Citizen Petition requesting the FDA to reclassify metaxalone as a drug product for which potential or actual bioequivalence problems exist (“bio-problem drug”) and to require all ANDA applicants to conduct *in vivo* fasting bioequivalence studies. See Mutual Citizen Petition, Docket No. 01P-0117 (March 6, 2001).

On January 30, 2002, FDA granted Mutual’s Citizen Petition. See Letter Granting Citizen Petition, Docket No. 01P-0117 (Jan. 30, 2002), attached hereto as Exhibit 1. As a

¹ Apparently, Mutual was not aware that SKELAXIN® was eligible for a DESI waiver and mistakenly conducted **both** *in vitro* and *in vivo* bioequivalence studies on its version of metaxalone. During the course of these studies, Mutual realized that there was no IVIVC because, although appearing to be bioequivalent in *in vitro* studies, its product failed bioequivalence criteria in *in vivo* studies. See Mutual Citizen Petition, Docket No. 01P-0117.

result, metaxalone is now classified as a bio-problem drug in the Orange Book, and all ANDA applicants are required to conduct both *in vitro* and *in vivo* bioavailability studies.

B. Studies Showing The Effect Of Food On The Bioavailability Of Metaxalone

During its initial investigation of the pharmacokinetics of SKELAXIN®, Elan conducted two studies to examine the effects of food on the bioavailability of SKELAXIN®. The first of these studies was a two-treatment, randomized crossover study in which 42 healthy volunteers were given a single 400 mg dose of SKELAXIN® under fasting and fed (standard high-fat meal) conditions (“Study 101”). The data from this study demonstrate that administration of metaxalone with a high fat meal significantly enhances drug absorption. Specifically, food statistically significantly increased the rate (C_{max}) and extent of absorption ($AUC_{(0-t)}$, AUC_{inf}) of metaxalone from SKELAXIN® tablets. Relative to the fasted treatment, the observed increases were 177.5%, 123.5%, and 115.4%, respectively. The data also showed that the 90% confidence intervals for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, were not within the equivalence limits of 80% to 125% for either $AUC_{(0-t)}$ or for C_{max} – thereby establishing a “food-effect.”

The mean T_{max} was also increased to 4.3 +/- 2.3 hours after dosing (compared to 3.3 +/- 1.2 hours under fasted conditions), and the mean terminal half-life ($t_{1/2}$) was decreased to 2.4 +/- 1.2 hours (compared to 9.2 +/- 4.8 hours under fasted conditions). The decrease in half-life (compared to fasted subjects) is believed to be due to more

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complete absorption of metaxalone in the presence of a meal, resulting in a better estimate of half-life.

The second study was a randomized four-period crossover study in which 59 healthy volunteers were given two 400 mg tablets of SKELAXIN® under fasting and fed (standardized high fat meal) conditions (“Study 103”). These data also demonstrate that administration of metaxalone with a high fat meal significantly enhances drug absorption. Specifically, food statistically significantly increased mean C_{max} and $AUC_{(0-inf)}$ of metaxalone from SKELAXIN® tablets by 194% and 142%, respectively. The mean T_{max} was also increased to 4.9 +/- 2.3 hours after dosing (compared to 3.0 +/- 1.2 hours under fasted conditions), and the mean terminal half-life ($t_{1/2}$) was decreased to 4.2 +/- 2.5 hours (compared to 8.0 +/- 4.6 hours under fasted conditions).

Elan submitted a supplement to the SKELAXIN® NDA seeking to incorporate the data from these studies into the labeling for SKELAXIN®. Simultaneously, based on data from Study 101, Elan filed a Citizen Petition with the FDA to require all ANDA applicants to conduct both fed and fasted *in vivo* bioequivalence studies. See Elan Citizen Petition, Docket No. 01P-0481 (Oct. 16, 2001). The FDA granted Elan’s Citizen Petition on March 21, 2002. See Letter Granting Citizen Petition, Docket No. 01P-0481 (March 21, 2002), attached hereto as Exhibit 2. Thereafter, FDA approved revised labeling reflecting data from Study 101 on June 20, 2002. See Letter to Elan approving

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S-044 (June 20, 2002), attached hereto as Exhibit 3. FDA approved a further revision to the SKELAXIN® labeling reflecting data from Study 103 in August 2002. *See* Letter to Elan approving S-036 (Aug. 20, 2002), attached hereto as Exhibit 4. Studies 101 and 103 were not intended to investigate, and did not determine, the specific clinical significance of the differences observed between fed and fasting administration of SKELAXIN®. Accordingly, the approved labeling describes the results of the studies but states that “the clinical relevance of these effects is unknown.”

Elan also submitted patent applications to the United States Patent and Trademark Office (“PTO”) based on the results of Study 101. The PTO issued the ’128 patent on June 18, 2002, and the ’102 patent on January 27, 2004. Both of these patents are listed in the Orange Book with Use Code U-189 – Enhancement of the Bioavailability of the Drug Substance.

C. Studies Showing The Effects Of Age And Gender On The Bioavailability Of Metaxalone

During its investigation of the pharmacokinetics of SKELAXIN®, Elan also conducted two studies to examine the effects of age and gender on the bioavailability of SKELAXIN®. The first study was designed to evaluate the effect of age on the pharmacokinetics of SKELAXIN®. Forty-four volunteers between the ages of 18-81 were administered two 400 mg SKELAXIN® tablets under both fasted and fed conditions (“Study 105”). The second study was designed to evaluate the effect of

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gender on the pharmacokinetics of SKELAXIN®. Forty-eight healthy male and female volunteers were administered two 400 mg SKELAXIN® tablets under fasted conditions (“Study 106”). Finally, a meta-analysis of the data from Studies 101, 103, 105, and 106 was performed to evaluate the effects of age and gender on the bioavailability of SKELAXIN® in both the fed and fasted states. The results of the meta-analysis revealed the following:

- (1) in the fed state, regardless of gender, age has little or no effect upon the bioavailability of SKELAXIN®;
- (2) in contrast, in the fasted state, regardless of gender, bioavailability is statistically significantly increased with an increase in age; and
- (3) in both the fed and fasted states, bioavailability is statistically significantly higher in females than in males.

The overall conclusion from all of the pharmacokinetic studies conducted by Elan was that age-related variations in the bioavailability of metaxalone are minimized when SKELAXIN® is administered with food. As a result of these findings, Elan once again supplemented its NDA with proposed labeling to reflect the data generated by Study 105, Study 106, and the meta-analysis and to recommend that SKELAXIN® be administered with food to ensure more consistent plasma levels of metaxalone. On March 15, 2004, King received a letter (dated March 12, 2004) from the FDA Division of Anti-

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Inflammatory, Analgesic and Ophthalmic Drug Products in the Office of Drug Evaluation (“ODE”) designating this labeling supplement as “approvable,” pending a change in format to comply with the general ADME (absorption, distribution, metabolism, elimination) layout currently used in new product labels. *See* Letter to King, S-046 (March 12, 2004), attached hereto as Exhibit 5. In that letter, the FDA reminded King that it would be required to include in its SKELAXIN® label “all previous revisions.” King is currently working with the FDA to incorporate the necessary format changes, and will formally respond with a proposed revised format shortly.

D. Generic Applicants And Recent FDA Action

As stated above, at least three generic companies have filed ANDAs seeking approval to market generic versions of SKELAXIN®. Initially, FDA took the position that pharmacokinetic information describing the relative bioavailability of metaxalone when taken with or without food, as reflected in the current approved SKELAXIN® label, must be included in the labeling for generic versions of SKELAXIN®, and required generic applicants to file patent certifications pursuant to 21 U.S.C. § 355(j)(2)(A)(vii) with respect to the listed ‘128 patent. *See* ‘Dear Applicant’ Letter from the Director, Office of Generic Drugs (March 1, 2004), attached hereto as Exhibit 6 (“March 1, 2004 Letter”). Because two of the ANDA applicants (Eon and Core) filed paragraph IV certifications to the listed ‘128 patent in 2002, Elan commenced patent

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litigation against them within 45 days of notice as provided by the Hatch-Waxman Amendments. As noted above, patent infringement cases against Eon, Core, and Mutual are currently pending.²

On March 9, 2004, King received the above-identified 'Dear Applicant' letter dated March 1, 2004, from the FDA explaining that it was reversing its position and inviting ANDA applicants to file section (viii) statements against the listed patents rather than paragraph IV certifications. FDA stated in its March 1, 2004 Letter that pharmacokinetic information describing the relative bioavailability of metaxalone when taken with or without food, as reflected in the current approved SKELAXIN® label, could be omitted from the labeling for generic metaxalone. As established in the balance of this Petition, this decision is arbitrary and capricious, a dramatic reversal in FDA policy, scientifically unsupported, contrary to law, and a violation of FDA's Good Guidance Practices and the Administrative Procedure Act.

² The Mutual ANDA, which was filed in 2004, included a Paragraph IV certification to the '102 patent.

II. FDA Must Not Permit ANDA Applicants To Omit From The Labeling For Their Products The Information In The Approved Labeling Of The Reference Listed Drug Describing The Different Pharmacokinetic Profiles Of The Active Ingredient Metaxalone Under Fed And Fasted Conditions Applicable To The Conditions Of Use Covered By The ANDA

A. The Conclusion In FDA's March 1, 2004 Letter About The Significance Of The Pharmacokinetics Information In The SKELAXIN® Labeling Is Scientifically And Medically Unsound

1. The Dramatic Effect Of Food On The Bioavailability Of Metaxalone Is Essential Information For Practitioners Who Prescribe The Product

FDA's March 1, 2004 Letter is premised on the assumption that information in the labeling for SKELAXIN® which describes the relative bioavailability of metaxalone when taken with and without food, may be omitted from the labeling for generic versions of SKELAXIN® without rendering such generic drug products less safe or effective for their remaining conditions of use. In fact, as established below, this pharmacokinetic information is important to the safe and effective use of the drug, with or without food, for any indication. Therefore, omission of this information would render generic versions of SKELAXIN® less safe and effective. As the Agency's March 1, 2004 Letter acknowledges, under these circumstances, FDA regulations prohibit omission of the information. *See* 21 C.F.R. § 314.127(a)(7); March 1, 2004 Letter, p. 2.

King has consulted with Dr. Michael E. Elia, M.D., an orthopedic surgeon who regularly prescribes SKELAXIN®, as well as other drugs for pain management. As

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described in Dr. Elia's attached declaration, omission of bioavailability information from labeling of generic metalaxone products, including the information in the current SKELAXIN® Package Insert describing the relative bioavailability of metalaxone when taken with and without food, is potentially misleading. *See* Exhibit 7 ("Elia Decl."), ¶ 28. Omitting this information from the labeling of generic versions of SKELAXIN® raises serious safety and efficacy concerns. Elia Decl., ¶ 8.

As Dr. Elia explains, when prescribing drugs to patients, physicians need to be aware of conditions that may affect bioavailability. This information is critical to predicting drug plasma levels, which, in turn, is critical in deciding how a drug should be administered to a specific patient. Lack of information about the variables that might affect drug bioavailability can lead to problems with patient safety and/or treatment efficacy. Elia Decl., ¶ 10. For example, unexpected or unpredictable changes in a drug's bioavailability can lead to complications involving both the treatment of a patient and the patient's overall health. Elia Decl., ¶¶ 12, 14. In particular, when bioavailability of a drug is greater than expected under specific conditions, a potential safety risk can be created for the patient, unless the dosage is adjusted accordingly. Moreover, fluctuations in bioavailability can hinder a physician's determination of the most effective dose for a particular patient under certain conditions, unless sufficient information is provided to characterize those fluctuations. Elia Decl., ¶ 12.

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In Dr. Elia's opinion, the section of the current labeling for SKELAXIN® describing the relative bioavailability of metaxalone when taken with or without food is critical to physicians who prescribe SKELAXIN®, and would likewise be critical to physicians who would prescribe generic metaxalone products. This information aids in the safe and effective prescribing and use of SKELAXIN®. Elia Decl., ¶ 8.

If the information on food-effects were omitted from metaxalone labeling (whether brand or generic), Dr. Elia believes that a physician reading that incomplete labeling would conclude either that the bioavailability of metaxalone was unchanged when co-administered with food relative to administration without food or, alternately, that the effects of food on the bioavailability of the drug were unknown. The physician would therefore most likely conclude that it is not necessary to adjust the dosage or administration of SKELAXIN® to account for changes in bioavailability due to food-effects. Such an erroneous assumption could lead to sub-optimal dosing strategies and could negatively impact the outcome of drug therapy. Alternately, the physician might consider the possibility that there could be food-effects, but would be unable to make an informed choice of dosage and administration strategies because he or she would have no information about what those effects would be. Elia Decl., ¶ 18.

Dr. Elia uses the food-effect information in the current SKELAXIN® labeling to adjust dosage and administration and select proper dosage regimens for his patients. Elia

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Decl., ¶ 19. Moreover, because Dr. Elia often prescribes SKELAXIN® with other drugs, understanding that co-administration with food can increase its bioavailability is particularly important. This information can potentially lead to safer, more effective dosage regimens, with a decrease in the volume and frequency of the dosage of metaxalone needed for effectiveness. Elia Decl., ¶ 20.

In sum, as Dr. Elia explains, the pharmacokinetic information describing the relative bioavailability of metaxalone when taken with and without food is important to the safe and effective prescribing and use of the drug. Accordingly, this information should appear in labeling for SKELAXIN® as well as labeling for any generic versions of SKELAXIN® marketed in the future. Elia Decl., ¶ 29.

King has also consulted with Leslie Z. Benet, Ph.D., a recognized expert in clinical pharmacology. As Dr. Benet explains in his attached declaration, omission of the pharmacokinetic information describing the relative bioavailability of metaxalone when taken with and without food from labeling for generic versions of SKELAXIN® can pose safety and efficacy concerns and should not be permitted. *See* Declaration of Leslie Z. Benet, Ph.D., attached hereto as Exhibit 10, ¶¶ 10, 29, 31. Dr. Benet believes that there is no reliable evidence supporting OGD's conclusion that fed-state bioavailability information may be carved out of generic metaxalone labeling without rendering the drug less safe or effective for the remaining conditions of use. Benet Decl., ¶¶ 26, 30.

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Metaxalone's history of safe use and its marketing without dosing adjustment information related to fed-state administration provide no reliable evidence in support of OGD's conclusion, as evidenced by other instances in which new information uncovered problems not previously recognized with marketed products (*e.g.*, phen-fen, terfenadine, quinidine/digoxin, and fexofenadine/ketoconazole). Benet Decl., ¶ 28.

Finally, the Citizen Petition filed by Eon Labs, Inc. on January 28, 2003 strongly supports the view that prescribers need to be made fully aware of the dramatic difference in absorption when metaxalone is taken with or without food. Eon argues, for instance, that it is "clinically unwise, contravenes longstanding FDA policy, and represents a risk to the public health," even to allow physicians the choice to recommend that their patients take metaxalone with food. Eon Citizen Petition, Docket No. 03-0027, attached hereto as Exhibit 11, p. 10. While Eon over-reaches when it self-servingly suggests that taking metaxalone with food is unsafe, it certainly cannot consistently argue that information about the food-effect of metaxalone can properly be omitted from labeling altogether. Omitting this information from labeling would provide no guidance at all to physicians regarding the impact of food on the bioavailability of the product and the potential safety and efficacy implications for their patients. From both a policy and medical perspective, this should not be permitted.

2. Approvable Labeling Changes Incorporating Additional Pharmacokinetic Information In The SKELAXIN® Labeling Confirm The Importance Of This Information To The Safe And Effective Use Of Metaxalone

As noted above, FDA has recently determined that King's pending labeling supplement incorporating information from Studies 105 and 106, and a meta-analysis of all four pharmacokinetic studies, is "approvable." Specifically, these additional data show that there is a gender effect in that bioavailability of the drug is higher in females than in males, and an age effect in that bioavailability of the drug increases with the age of the patient. The data, including the meta-analysis of all four studies, also show that the gender effect is observed regardless of whether the drug is administered with or without food, but the age effect is observed only when the drug is administered without food. On this basis, the approvable supplement includes a recommendation that the drug be administered with food so as to minimize age-related variability.

The approvable letter requested that King provide a reformatted version of the entire "Clinical Pharmacology" section of the labeling for SKELAXIN®, incorporating both the existing and the new information, based on current label format recommendations. King has informed the Division that it intends to amend its filing to address the Agency's request.

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The response to this labeling supplement by the ODE Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products provides further confirmation that the types of information which the March 1, 2004 Letter would permit generic manufacturers to omit from their labeling continue to be considered important and, indeed, necessary by those parts of FDA that are responsible for devising and approving the substantive content of prescription drug labeling. Through the “same labeling” provisions of Hatch-Waxman, it is this process – scientific review and approval through a consultative procedure between the RLD sponsor and ODE – which was to govern the substantive content of generic drug labeling. The approach outlined in the March 1, 2004 Letter would substantially and unjustifiably undercut that process. Moreover, practitioners would also consider this additional information important to the safe and effective prescribing and use of metaxalone. As explained in the attached declaration of Dr. Elia, information in the proposed revised labeling for SKELAXIN® about gender and age effects, and their interrelation with the food-effects, is important, and he would use this information to adjust dosage and administration to ensure more consistent drug plasma levels. Elia Decl., ¶¶ 21-25. Relatedly, Dr. Elia believes that the additional data on age and gender effects on bioavailability underscore the need to include all available information on the bioavailability of SKELAXIN® in labeling. Elia Decl., ¶ 26.

B. Permitting Generic Drug Applicants To Omit Information Contained In Approved RLD Labeling Regarding Metaxalone's Dramatic Food-Effect Is Inconsistent With The Agency's Position On The Need For Information To Be Included In Drug Labeling, Whether Or Not Its Specific Clinical Relevance Is Known

1. FDA Regulations and Guidance Generally Require Available Pharmacokinetic Information, Including Food-Effect Information, To Be Included In Prescription Drug Labeling, Whether Or Not The Specific Clinical Relevance Of The Information Has Been Determined

According to long-standing FDA regulations defining the proper content of the "Clinical Pharmacology" section of prescription drug labeling, "[p]harmacokinetic information that is important to safe and effective use of the drug is required, if known, e.g., degree and rate of absorption Inclusion of pharmacokinetic information is restricted to that which relates to clinical use of the drug." 21 C.F.R. § 201.57(b)(1).

Recent FDA Guidance further elaborates on this requirement with specific regard to the effect of food on the bioavailability of prescription drug products. As FDA's December 2002 *Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies* states: "Food effects on BA [bioavailability] can have clinically significant consequences." See Guidance, attached hereto as Exhibit 8, p. 2. As a result, the December 2002 Guidance recommends that food-effect bioavailability studies be conducted for *all* new chemical entities. Guidance, p. 3. It further provides: "The effect of food on the absorption and BA of a drug product should be described in the

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CLINICAL PHARMACOLOGY section of the labeling.” Guidance, p. 7. Importantly, this requirement is independent of the establishment of the clinical significance of the information. Thus, the presentation of pharmacokinetic data relating to food-effects in the “Clinical Pharmacology” section of labeling is required in all cases where the information is available, while the December 2002 Guidance separately provides: “In addition, the DOSAGE AND ADMINISTRATION section of the labeling should provide instructions for drug administration in relation to food based on clinical relevance” Guidance, p. 7. FDA in its Guidance thus requires information on food-effect bioavailability to appear in the Clinical Pharmacology section when the specific clinical relevance is unknown and in the Dosage and Administration section when what is known about the clinical effect warrants additional recommendations. FDA therefore clearly acknowledges the importance of including this information in the labeling even where, as here, the specific clinical significance of the information is not known.

Pursuant to this specific guidance, FDA has required and continues to require the labeling of SKELAXIN® to include data on the relative bioavailability of the drug when administered with and without food. This information, as discussed above, is pertinent to any use of the drug. The fact that studies have not been conducted to determine the specific clinical significance of the information does not mean that the information is

insignificant. Nor does this fact permit the omission of the information in violation of the regulations and guidance cited above.

2. FDA Regulations And Guidance Generally Require A Wide Range Of Information To Be Included In Prescription Drug Labeling, Even When The Specific Clinical Relevance of the Information Has Not Been Established

In its March 1, 2004 Letter, FDA repeatedly states that, because the clinical relevance of the food-effect is unknown, omission of information on the relative bioavailability of metaxalone when taken with and without food will not impact the safe and effective use of generic versions of SKELAXIN®. Underlying this conclusion is the unstated assumption that *only* information of demonstrated specific clinical relevance can impact the safe and effective use of a drug product and is of importance to practitioners. Relatedly, the Agency appears to assume, at least in the case of metaxalone, that *unknown* clinical relevance means *nonexistent* clinical relevance.

In fact, the Agency has long required information in prescription drug labeling that has no proven clinical relevance. For example, labeling generally includes a discussion of animal data of no proven clinical relevance. Presumably, this information is required because it may impact the safe and effective use of the drug and is relevant to practitioners, despite the lack of data specifically demonstrating its clinical relevance to the use of the drug in humans. Similarly, FDA's November 1999 *Guidance for Industry: In Vivo Drug Metabolism/Drug Interaction Studies – Study Design, Data Analysis, and*

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Recommendations for Dosing and Labeling provides that various types of metabolism and drug interaction information should be provided in labeling, even when the clinical significance of the data has not been evaluated. *See, e.g.*, Exhibit 9, p. 15. Thus, like the Food-Effect Guidance, this Guidance requires information of unknown clinical significance to appear in labeling.

Additionally, consistent with FDA regulations and guidance, prescription drug labeling often contains other pharmacokinetic information, even when its clinical relevance has not been determined. For example, the labeling for Valcyte™ (valganciclovir hydrochloride tablets) discusses differences in pharmacokinetic parameters for ganciclovir resulting from three delivery systems, but also states that the clinical significance of the differences is unknown. Similarly, the Accutane® (isotretinoin) Package Insert includes information on metabolite activity in *in vitro* models, but also states that the clinical significance of the models is unknown. Another example is the labeling for Topamax® Sprinkle Capsules (topiramate), which provides information on an increase in renal clearance of topiramate in rats when probenecide is also given. The labeling states that this interaction has not been evaluated in humans. Finally, the “Clinical Pharmacology” section of the labeling for antibiotics often contains *in vitro* data on the susceptibility of various microorganisms to the effects of the drugs. Presentation of this information is typically accompanied by a statement that its clinical

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significance is unknown. *See, e.g.*, labeling for Ceclor® (cefactor), Zithromax® (azithromycin), Biaxin® (clarithromycin); *see* 21 C.F.R. § 201.57(b)(2).

Were FDA consistently to adopt the approach advocated in the March 1, 2004 Letter, manufacturers – brand and generic alike – could omit from their labeling any and all information of unknown clinical relevance. This could include, for example, drug interaction data, animal toxicity studies and carcinogenicity studies, as well as virtually all pharmacokinetic information. Treating such information, as well as other information of unproven clinical relevance, as merely optional for inclusion in labeling would constitute a significant departure from past Agency practice and would be inconsistent with existing prescription drug labeling regulations at 21 C.F.R. § 201.57.

3. The Position Taken In The March 1, 2004 Letter Injects Confusion Into The Status Of FDA's Bioequivalence Requirements

Allowing generic applicants to omit information about the food-effect from the labeling of their metaxalone products also has the potential to confuse the status of FDA's bioequivalence requirements for the drug. Even without pharmacokinetic information in their labeling, products approved under ANDA applications can themselves become reference listed drugs and can then, in turn, be cited as the basis for further ANDA applications. Sponsors of those subsequent applications could point to the absence of food-effect information in the labeling of the original ANDA products and reasonably claim that they are entitled to approval without having to conduct

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bioequivalence studies under fed conditions. This is because the December 2002 Guidance on Fed Bioequivalence exempts from this requirement immediate-release drug products: “When the RLD label does not make any statements about the effect of food on absorption or administration.” Exhibit 8, p. 4. We recognize that FDA may believe it has the authority to prevent the approval of any generic metaxalone products that do not demonstrate bioequivalence under fed conditions.³ However, the fact that this scenario creates a potential loophole in the FDA’s bioequivalence guidance dramatically underscores our concern that the position taken in the March 1, 2004 Letter has been poorly considered and indeed contradicts the prior consistent understanding, both within and outside of the Agency, that substantive information approved for inclusion in the labeling of innovator drug products is not “optional” or otherwise subject to second-guessing by ANDA sponsors or by OGD as to whether it is important enough to require ANDA sponsors to copy.

³ It could be pointed out, for instance, that FDA informally designates a single product, usually the innovator’s product, as a RLD by placing an asterisk next to it in the Orange Book. However, the Act itself does not prevent an ANDA applicant from choosing to refer to any approved drug as the RLD for their particular application. 21 U.S.C. § 355(j)(2)(A)(i). In light of this, FDA regulations state only that the listed drug referenced in an ANDA will “[o]rdinarily . . . be the drug product selected by the agency as the reference standard for conducting bioequivalence testing.” 21 C.F.R. § 314.94(a)(3). Furthermore, FDA policy acknowledges that sponsors can request designation of additional RLDs in the Orange Book. Moreover, if FDA truly believed that there were no clinical significance to the food-effect information at issue here, it would be possible for King to omit this information from its own SKELAXIN® labeling, with the same result as that described above – FDA’s December 2002 Guidance would no longer require ANDA sponsors to demonstrate bioequivalence of their products to SKELAXIN® under fed conditions. While King obviously has no intention to omit this information from its labeling, it could do so, and other firms in similar or different situations might choose to do so with respect to other “optional” labeling information, with similar, inappropriate and unintended consequences for generic product bioequivalence requirements.

C. Permitting Generic Drug Applicants To Omit Information Contained In Approved RLD Labeling Regarding Metaxalone's Dramatic Food-Effect Is Contrary To Law

1. The Federal Food, Drug, And Cosmetic Act And FDA Regulations Require That Generic Drug Products Have The Same Labeling As The Reference Listed Drug, With Very Limited Exceptions, None Of Which Are Applicable Here

In order to obtain ANDA approval, the labeling proposed for a generic drug must be the same as the labeling approved for the reference listed drug ("RLD") "except for changes required . . . because the new drug and the listed drug are produced or distributed by different manufacturers." 21 U.S.C. § 355(j)(2)(A)(v); *see also id.* § 355(j)(4)(G). FDA regulations more broadly define the potentially permitted differences between an ANDA applicant's proposed labeling and the corresponding approved RLD labeling to include "differences in expiration date, formulation, bioavailability, or pharmacokinetics,"⁴ labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act." 21 C.F.R. § 314.94(a)(8)(iv).

⁴ The reference in this regulation to differences in "bioavailability or pharmacokinetics" between the RLD and generic labeling applies only when the generic product has different bioavailability or pharmacokinetics than the RLD. *See, e.g.*, 21 C.F.R. § 320.1(e) (if generic has intentionally different rate of bioavailability than the RLD, but this difference is medically significant, the differences must be reflected in the labeling). The reference to "pharmacokinetics" in the regulation does not contemplate omission of truthful information about the pharmacokinetics of the generic product where they are identical to the RLD.

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FDA has repeatedly emphasized that “the exceptions to the requirement of ‘same labeling’ are limited.” Abbreviated New Drug Application Regulations, Proposed Rule, 54 Fed. Reg. 28872, 28879, 28884 (July 10, 1989); *see also id.* at 28881 (“Consistent labeling for duplicate versions of a drug product, insofar as this is possible, will avoid differences that might confuse health care professionals who prescribe and dispense prescription drug products or might create omissions of significant information”). Importantly, FDA regulations provide that, in order to approve an ANDA that omits an “aspect of labeling protected by patent,” FDA must find that the “differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use.” 21 C.F.R. § 314.127(a)(7).

In its March 1, 2004 Letter, FDA appears to conclude that it would be permissible under these regulations to omit, from generic product labeling, information in approved RLD labeling about the pharmacokinetics of metaxalone, specifically including information about the dramatically increased bioavailability of the drug when taken with food. Because this information relates to the safe and effective prescribing and use of the drug for *any* indication, we believe that the FDA position violates both the Act and FDA’s own regulations.

In the March 1, 2004 Letter, FDA cites two court decisions as support for the proposition that FDA has the authority to approve generic drugs with labeling that omits

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certain aspects of labeling protected by patent or nonpatent exclusivity: Bristol-Myers v. Shalala, 91 F.3d 1493 (D.C. Cir. 1996), and Purepac Pharm. Co. v. Thompson, 238 F.Supp.2d 191 (D.D.C. 2002), *aff'd*, 354 F.3d 877 (D.C. Cir. 2004). We do not here dispute the general proposition that certain aspects of RLD labeling, *i.e.*, information relating to patented or exclusive indications for use, may be omitted. However, neither of the cited cases involved the type of omission that is proposed in the March 1, 2004 Letter: the omission of RLD labeling information relating to the labeled indication for use proposed for the generic product.

The Purepac case did not involve a proposed omission of RLD labeling information at all. The issue in Purepac was whether a section (viii) statement was appropriate with respect to a listed use patent that did not cover *any* approved indication for use of the RLD. In that case, the proposed generic drug product labeling was essentially identical to the RLD labeling, and omitted no RLD labeling information at all about the approved use of the product. Thus, the Purepac case does not bear on FDA's authority to allow ANDA applicants to omit any RLD labeling information from the labeling for their products.

The Bristol-Myers case involved a drug that had been approved for three distinct indications – two of which were protected by three-year non-patent exclusivity at the time of the litigation. ANDA applicants requested approval of generic versions of the

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drug based on labeling that included information only on the one non-exclusive indication for use. The court concluded that approval of labeling on this basis was consistent with FDA's legal authority. The court did not rule or suggest, however, that the ANDA applicants could legally have been permitted to omit information appearing in approved RLD labeling that pertained to the indication for use that *did* appear in the proposed generic labeling. Accordingly, neither of the cases cited by FDA in its March 1, 2004 Letter support the conclusions stated therein.

In FDA's March 1, 2004 Letter, the Agency concludes that "the 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." As described in Section II.A., *supra*, however, this information is in fact essential for the safe and effective administration of the product. Thus, under 21 C.F.R. § 314.127(a)(7), this information may not be omitted from the generic labeling.

2. The Generic Applicants Have the Burden to Demonstrate that the Significant Food-Effect on the Bioavailability of Metaxalone Has No Clinical Significance

FDA appears to rest its conclusion that omission of the fed-state bioavailability information from the generic metaxalone labeling does not render the product less safe or effective solely on the fact that the specific clinical effect of the increased bioavailability of metaxalone is currently unknown. As explained above, this reasoning is both

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inconsistent with FDA's historical position regarding bioavailability information in drug labeling and scientifically and medically faulty.

In the case of metaxalone, the clinical significance of the difference between fed-state and fasted-state bioavailability is "unknown," as stated in the current SKELAXIN® labeling, only in the sense that definitive understanding of the precise clinical impact of the bioavailability differences on particular patient populations would require the conduct of extraordinary additional clinical trials that have not been designed and conducted. This does not in any way indicate that the available information about bioavailability does not have clinical significance or that the information that is known can or should be ignored in making prescribing decisions. Indeed, as reflected in Dr. Benet's declaration, the information has clinical relevance, though the specific nature of the clinical significance has not been established. Benet Decl., ¶¶ 10, 26-27, 29. Stated simply, lack of proof of clinical significance does not constitute proof of insignificance.

The March 1, 2004 Letter seems to be based on the unstated view that labeling information may be assumed to be superfluous unless its clinical significance is fully understood. As shown above, this view is completely inconsistent with FDA's long-standing labeling regulations and guidance. Importantly, it also reverses the established burden of proof under which all sponsors of NDAs and ANDAs are required to establish their eligibility for approval. Contrary to the position in the March 1, 2004 Letter, in

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order to justify omitting the information in the SKELAXIN® labeling regarding the dramatic differences in metaxalone bioavailability when the drug is taken with food as compared to without food, generic applicants have the burden of proof to demonstrate that this food-effect does *not* have clinical significance. See 21 C.F.R. § 12.87(d) (“At a hearing involving issuing, amending, or revoking a regulation or order relating to the safety or effectiveness of a drug, device, food additive, or color additive, the participant who is contending that the product is safe or effective or both and who is requesting approval or contesting withdrawal of approval has the burden of proof in establishing safety or effectiveness or both and thus the right to approval”); Section 7(c) of the APA, 5 U.S.C. § 556(d) (1996) (“Except as otherwise provided by statute, the proponent of a rule or order has the burden of proof.”). Until the generic drug applicants meet this burden, it is contrary to law for FDA to permit them to omit this information from the labeling for generic versions of SKELAXIN®.⁵

⁵ In this regard, the requirements of the Hatch-Waxman Amendments are in full accord. Under 21 U.S.C. § 355(j)(2)(A)(v), ANDA applicants have the burden of establishing that they propose to use the same labeling as was approved for the RLD and, thus, also to prove that any deviations therefrom fall within the limited exceptions to that requirement. This would necessarily include proof that the deviations they propose do not compromise the safety and efficacy of the drug.

D. Summary Reversal Of The Agency's Prior Guidance, Under Which Generic Metaxalone Products Were Not Permitted To Omit The Bioavailability Information At Issue, Violates The APA And The Agency's Good Guidance Practices Regulations

1. FDA Acknowledged The Importance Of Both Fed And Fasting Bioavailability Data When It Granted Mutual's And Elan's Citizen Petitions

As noted above, FDA granted both Mutual's and Elan's Citizen Petitions, resulting in a requirement that ANDA applicants submit acceptable *in vivo* studies demonstrating the bioequivalence of their metaxalone tablets to SKELAXIN® under both fed and fasting conditions. This requirement was based on data from *in vivo* studies conducted by Mutual that demonstrated that *in vitro* dissolution data alone were not sufficient to establish bioequivalence between different tablet formulations of metaxalone. The requirement was also based on *in vivo* studies conducted by Elan that showed that there was a significant effect on the bioavailability of metaxalone when taken with food.

Based on Elan's data, FDA concluded: "because food has a significant effect on the bioavailability of SKELAXIN®, an ANDA for a generic version of SKELAXIN® must include an acceptable fed bioequivalence study comparing the generic product with SKELAXIN®." Exhibit 2, p. 2. FDA in 2002 therefore clearly acknowledged the significance of the effect of food on the bioavailability of metaxalone. *See also* Benet

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Decl., ¶ 20. Shortly thereafter, FDA approved a revision of the SKELAXIN® labeling that described the relative bioavailability of the drug when administered with and without food. Letter to Elan approving S-044 (June 20, 2002), attached hereto as Exhibit 3.

The conclusion in FDA's March 1, 2004 Letter that the significant difference in bioavailability when metaxalone is administered with and without food may be omitted from generic metaxalone labeling, then, directly contradicts its previous position on the importance of the *in vivo* bioavailability of this product.

2. FDA Consistently Required Patent Certifications From Metaxalone ANDA Applicants And Patent Litigation Triggered By Those Certifications Has Been Underway For Over A Year

The March 1, 2004 Letter indicates that a number of ANDA applicants have consistently been informed by FDA of the need to provide labeling that duplicates the approved labeling for SKELAXIN® and the need to make certifications to the '128 SKELAXIN® patent. It also appears that a number of those applicants have sought to change FDA policy in order to avoid either these labeling requirements or the certification requirements and thereby, perhaps, to expedite the effective approval of their applications. Until the March 1, 2004 Letter was issued, however, FDA had consistently required generic metaxalone ANDA applicants to file patent certifications to the '128 patent, acknowledging that the use of metaxalone protected by that patent cannot appropriately be removed from the labeling for the generic products.

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FDA's requirement that ANDA applicants for generic versions of metaxalone file patent certifications resulted in patent litigation that has been ongoing for almost 15 months. The sequence of those filings has also resulted in first-to-file status for one ANDA applicant, which would potentially result in a period of exclusivity for that applicant as the sole generic marketer of metaxalone. Therefore, a change in FDA policy at this time, applied retroactively to existing applications for metaxalone, would result in a substantial upheaval in the expectations and rights of virtually all of the interested parties.

3. Under FDA's Good Guidance Practices Regulations, FDA May Adopt Such A Dramatic Reversal Of Policy Only After The Agency Announces A Contemplated Change, Affords A Full, Public Opportunity For All Affected Parties To Express Their Views On The Proposed Change, And Formulates A Final Agency Position In Light Of The Comments Received

The position stated in FDA's March 1, 2004 Letter constitutes a Level 1 guidance document under FDA's Good Guidance Practices ("GGP") Regulations. 21 C.F.R. §§ 10.115(b)(2), (c). The Agency's conclusion to suddenly permit ANDA applicants to omit information about significant food-effects contained in approved RLD labeling relates to "[t]he design, . . . [and] labeling, . . . of regulated products; [and] the processing, content, and evaluation or approval of submissions" 21 C.F.R. § 10.115(b)(2). It also sets forth "changes in interpretation or policy that are of more than a minor nature;" raises "complex scientific issues;" and "cover[s] highly controversial issues." 21 C.F.R. §

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10.115(c)(1). As such, FDA must follow the procedural requirements set forth in the GGP regulations for a Level 1 guidance, including publishing a notice in the Federal Register announcing the availability of a draft guidance document, inviting comments on the draft guidance document, and reviewing the comments received. 21 C.F.R. §§ 10.115(g)(1)(ii), (iv).

FDA has clearly acknowledged that the Agency “may not use documents or other means of communication that are excluded from the definition of a guidance document to informally communicate new or different regulatory expectations to a broad public audience for the first time [and that] GGPs must be followed whenever regulatory expectations that are not readily apparent from the statute or regulations are first communicated to a broad public audience.” 21 C.F.R. § 10.115(e); *see also* 21 U.S.C. § 371(h)(1)(C) (“For guidance documents that set forth initial interpretations of a statute or regulation, changes in interpretation or policy that are of more than a minor nature, complex scientific issues, or highly controversial issues, the Secretary shall ensure public participation prior to implementation...”); CDRH Manual for the Good Guidance Practices (GGP) Regulations; Final Guidance for FDA Staff at 3 (stating that FDA may not use means other than a guidance document to communicate new policy or new regulatory approaches). Because FDA did not follow the procedural requirements set forth in its GGP regulations, the position set forth in FDA’s March 1, 2004 Letter should

be stayed – at least until it can be reconsidered in light of the comments of all interested parties.

4. By Announcing What Appears To Be A Final Agency Determination, Despite The Lack Of Any Indication By The Agency That It Was Considering Such A Dramatic Reversal Of Policy, The March 1, 2004 Letter Violates The APA

FDA's dramatic reversal in Agency policy set forth in the March 1, 2004 Letter violates the Administrative Procedure Act for at least two reasons: (1) it was issued without notice or comment and (2) it is a change of policy that is not supported by reasoned analysis.

FDA's March 1, 2004 Letter is a substantive rule that requires notice and comment under the APA. The letter, however, was issued without any prior notice to the affected parties. Moreover, none of the public filings, such as Citizen Petitions and comments thereto, pertaining to metaxalone to date suggested that the pharmacokinetic information contained in the SKELAXIN® labeling be omitted from the labeling of generic versions. FDA's March 1, 2004 action was thus both completely unprecedented and unexpected by at least some of the parties directly affected by it.

The APA defines a "rule" as "an agency statement of general or particular applicability and future effect designed to implement, interpret, or prescribe law or policy or describing the organization, procedure, or practice requirements of an agency and includes . . . practices bearing on any of the foregoing." 5 U.S.C. § 551(4). In contrast,

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the APA defines an “adjudication” as “an agency process for the formulation of an order,” and defines “order” as “the whole or part of a final disposition ... of an agency in a matter other than rule making but including licensing.” *Id.* at § 551(6), (7). Agency adjudications and “interpretive rules” are exempt from notice and comment requirements. *Id.* at §§ 554, 553(d)(2).

FDA’s conclusion in the March 1, 2004 Letter does not meet the definition of adjudication or interpretative rule because the March 1, 2004 Letter established a new Agency policy regarding the importance of pharmacokinetic and bioavailability information in drug labeling and the need to include information in labeling that lacks a definitive demonstration of clinical significance, and then applied that new policy to affect the individual rights and obligations of several parties. “If a new agency policy represents a significant departure from long established and consistent practice that substantially affects the regulated industry, the new policy is a new substantive rule and the agency is obliged, under the APA, to submit the change for notice and comment.” Shell Offshore Inc. v. Babbitt, 238 F.3d 622, 630 (5th Cir. 2001); *see also, e.g., Alaska Professional Hunters Ass'n v. FAA*, 177 F.3d 1030, 1034 (D.C.Cir.1999) (“When an agency has given its regulation a definitive interpretation, and later significantly revises that interpretation, the agency has in effect amended its rule, something it may not accomplish without notice and comment”).

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In the Shell case, the court held that if the Department of Interior wanted to change its established practices and procedures in a manner that so significantly affected regulated parties, it was required to give them notice and an opportunity to comment on the proposed change. The court stated: "Interior's new practice may be a reasonable change in its oversight practices and procedures, but it places a new and substantial requirement on many OCS lessees, was a significant departure from long established and consistent past practice, and should have been submitted for notice and comment before adoption." 238 F.2d at 630. Under the APA, "a person may not in any manner be required to resort to, or be adversely affected by, a matter required to be published in the Federal Register and not so published." 5 U.S.C. § 552(a)(1). Accordingly, the March 1, 2004 Letter can be accorded no legal effect.

Furthermore, as explained above, the new policy announced in FDA's March 1, 2004 Letter "runs counter to the evidence before the agency," and therefore is arbitrary and capricious and must be overturned. Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983). In particular, courts have consistently held that an abrupt change in course by an agency must be supported by reasoned analysis. *See, e.g.,* Motor Vehicle Mfrs. Ass'n, 463 U.S. at 42 ("an agency changing its course by rescinding a rule is obligated to supply a reasoned analysis for the change"); National Black Media Coalition v. FCC, 775 F.2d 342, 355-56, 356 n.17 (D.C.Cir. 1985) (agency

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must offer sufficient explanation to ensure court that it is not “repudiat[ing] precedent simply to conform with a shifting political mood”) (citing cases); Brae Corp. v. United States, 740 F.2d 1023, 1038 (D.C.Cir. 1984) (agency must explain why the original reasons for adopting the rule or policy are no longer dispositive), *cert. denied*, 471 U.S. 1069 (1985); Delmarva Power & Light Co. v. FERC, 770 F.2d 1131, 1142, n. 9 (D.C.Cir. 1985) (“review of the reasonableness of an administrative adjudication includes consideration of the administrator’s consistency in deciding similar cases”) (quoting Dep’t of Treasury v. FLRA, 707 F.2d 574, 581 n. 25 (D.C.Cir.1983)); Greater Boston Television Corp. v. FCC, 444 F.2d 841, 851-52 (D.C.Cir.1970) (agency shifts in policy are “danger signals”), *cert. denied*, 403 U.S. 923 (1971). FDA has failed to provide a sufficient factual, legal and scientific basis for its significant departure from prior Agency policy in this case. Accordingly, the conclusions in its March 1, 2004 Letter are arbitrary and capricious in violation of the APA.

FDA’s violation of the APA in this instance is particularly egregious because the Agency’s policy change completely alters the rights and obligations created under FDA’s previous guidance. Indeed, FDA has previously acknowledged the potential implications of such an agency action in its preamble to the proposed rule on patent listing requirements and application of 30-month stays: “If we were to adopt an alternative implementation plan, we would risk upsetting legitimate expectations held by those who

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had relied on our earlier interpretation of the act.” 67 Fed. Reg. 65448, 65457 (Oct. 24, 2002); *see also* 68 Fed. Reg. 36676, 36696 (June 18, 2003).

Based on FDA’s prior interpretation of the statute and regulations in this case, in particular the requirement that generic applicants file paragraph IV certifications to the ‘128 patent, a number of parties have filed applications and certifications and have begun resolving the relevant patent issues in an orderly fashion as envisioned by Hatch-Waxman. We also point out that King purchased the SKELAXIN® product and NDA from Elan in 2003, when FDA’s position had been clearly stated and appeared to be entirely consistent with past FDA practice and applicable legal precedents, ANDA applicants had already made filings in accordance with that position, and the process of patent litigation had already begun.

As noted above, the implications of the change in policy described in the March 1, 2004 Letter extend far beyond the case of metaxalone. Seemingly settled Agency policy regarding the scope of required prescription drug labeling is now in doubt if, in the absence of proof of the specific “clinical relevance” of the information, many common categories of labeling information may now be considered “optional.” For this reason, this is an issue that potentially affects the pharmaceutical industry, physicians, and the public in ways that FDA may have failed entirely to consider.

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In these ways and others, the sudden reversal of FDA's prior position based on the March 1, 2004 Letter will significantly damage those parties who have relied upon it and may significantly affect the interests of the pharmaceutical industry, prescribers and the public at large.⁶ Under the APA, policy changes of such magnitude may not be implemented by an agency without providing prior notice and an appropriate opportunity for comment, and a reasoned analysis supporting any final decision to implement a change in course.

Conclusion

Based on the foregoing, the Commissioner is requested to; (a) rescind the March 1, 2004 Letter issued by the Director of OGD; (b) require applicants seeking approval to market generic metaxalone products that rely on King's SKELAXIN® as the RLD to submit a patent certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii) on U.S. Patent No. 6,407,128; and (c) prohibit the removal from generic metaxalone labeling of the pharmacokinetic information that appears in the SKELAXIN® labeling.

⁶ For these reasons, issuance of the March 1, 2004 Letter violated King's rights under the Due Process Clause and, if the policies announced in the Letter are implemented, will constitute a taking under the Fifth Amendment.

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Environmental Impact

According to 21 C.F.R. § 25.25(a)(8), this petition qualifies for a categorical exclusion from the requirement for submission of an environmental assessment.

Economic Impact

According to 21 C.F.R. § 10.30(b), information on economic impact is to be submitted only when requested by the Commissioner following review of the petition.

Certification

The undersigned certify 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 known to the Petitioner which are unfavorable to the Petition.

Respectfully submitted,



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EXHIBITS

Letter Granting Citizen Petition, Docket No. 01P-0117 (Jan. 30, 2002)	1
Letter Granting Citizen Petition, Docket No. 01P-0481 (March 21, 2002)	2
Letter to Elan approving S-044 (June 20, 2002)	3
Letter to Elan approving S-036 (Aug. 20, 2002)	4
Letter to King, S-046 (March 12, 2004)	5
'Dear Applicant' Letter from the Director, Office of Generic Drugs (March 1, 2004)	6
Declaration of Dr. Michael E. Elia, M.D.	7
<i>Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies</i> (Dec. 2002)	8
<i>Guidance for Industry: In Vivo Drug Metabolism/Drug Interaction Studies – Study Design, Data Analysis, and Recommendations for Dosing and Labeling</i> (Nov. 1999)	9
Declaration of Leslie Z. Benet, Ph.D.	10
Citizen Petition by Eon Labs, Inc. (January 28, 2003), FDA Docket No. 03P-0027 (petition only, without exhibits)	11