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VIA E-MAIL AND FEDERAL EXPRESS

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

Re: Citizen Petition Docket No. 2004P-0140/CP 1 /PSA 1
(Petition of King Pharmaceuticals, Inc. Regarding Generic Metaxalone)

INTRODUCTION

We submit these comments on behalf of Corepharma LLC ("Corepharma") regarding the above-referenced Citizen Petition and Petition for Stay (collectively, the "Petition" or "CP") submitted by King Pharmaceuticals, Inc. ("King"). King's Petition seeks to block FDA approval of generic versions of its metaxalone product, which a King subsidiary sells under the brand name Skelaxin®.

Corepharma received tentative FDA approval of a generic metaxalone product last June, and currently awaits final approval under 21 U.S.C. § 505(j). Corepharma recently submitted an amendment to its abbreviated new drug application ("ANDA") for metaxalone tablets, withdrawing its certification under 21 U.S.C. § 505(j)(2)(A)(vii)(IV) (a "Paragraph IV certification") with respect to King's U.S. Patent No. 6,407,128 (the "'128 patent"), and including instead a statement under 21 U.S.C. § 505(j)(2)(A)(viii) (a "section viii statement") with respect to the '128 patent. Corepharma took these actions following receipt of a letter dated March 1, 2004 from the Director of the Food and Drug Administration's Office of Generic Drugs (the "March 1 letter"), explaining that ANDA applicants may "carve out" of their metaxalone labeling certain pharmacokinetic information recently added to the labeling for Skelaxin® that King contends is patent protected. *See* Exhibit ("Ex.") 1. King now argues in its Petition that the FDA's decision to allow this carve out was "scientifically and medically unsound" and "contrary to law." CP at 11, 24. Neither is true.

As the FDA's March 1 letter correctly observes (and King does not dispute), metaxalone has been used safely and effectively in this country for over forty years since its initial FDA approval in 1962. Throughout that time, the published literature and the approved labeling have

listed the same indications for the drug for which Corepharma now seeks approval (as an adjunct in the treatment of musculoskeletal conditions) and the same dosing schedule (800 mg three-to-four times daily), regardless of whether the drug is administered with food. As the FDA also observed, until Elan Pharmaceuticals, Inc. ("Elan") sought to modify the labeling for Skelaxin® in 2002 – after the drug had been used safely for four full decades – the labeling included none of the food-effect data at issue (that the bioavailability of Skelaxin® is relatively higher when taken with a high-fat meal and that this effect diminishes with age); nor has the labeling ever included a food-related instruction or dosing adjustment. Indeed, even now King does not argue that the drug's dosing schedule or effectiveness depends upon whether it is taken with food.

These facts alone demonstrate that the pharmacokinetic information to be carved out of Corepharma's labeling reporting such a potential bioavailability increase has no bearing (demonstrated or suspected) on the clinical use of the drug. Indeed, King's labeling acknowledges on its face that "the clinical relevance of these effects is unknown." This conclusion is further buttressed by several additional facts which King does not (and cannot) dispute. As the FDA noted in its March 1 letter, no link has ever been drawn between the safety or efficacy of metaxalone and its bioavailability increase when administered with food, and that is not surprising. Ex. 1 at 4. As explained by one learned expert in pharmacology (Dr. Paul Bass, Professor Emeritus of Pharmacology at the University of Wisconsin, whose Declaration is submitted herewith as Exhibit 2), no such link can be drawn, since the drug's mechanism of action is unknown, as are the plasma concentrations required for its therapeutic or toxic effects.

Moreover, as Dr. Bass also explains, while the bioavailability of metaxalone may be relatively higher following a *single* administration with a *high-fat* meal (as compared to a single administration in a fasted state), a normal meal unquestionably produces a far smaller increase. Smaller still would be the differences between steady-state fed and fasted levels when patients are dosed on the recommended schedule of 800 mg three-to-four times daily. Thus, as Dr. Bass explains, the bioavailability difference cited by King is so small and artificial as to be clinically irrelevant. Any difference between fed and fasted bioavailability levels of metaxalone experienced in normal use of the drug (*i.e.*, with normal eating and recommended dosing) would be statistically insignificant, particularly in view of the fact that the standard dosing schedule (which has been followed for decades with a notable absence of serious side effects) expressly incorporates a 33% variation in dosage by specifying that an 800 mg dose can be given either three or four times a day. King nowhere suggests that such variation raises an issue of safety or efficacy. Nor could it, since daily doses as high as 4,000, 9,200, and even 9,600 mg have been reported safe and effective.[1]

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[1] *See, e.g.*, Ex. 2 at ¶ 54; Morey, "Metaxalone, a New Skeletal Muscle Relaxant," *The Journal of the American Osteopathic Ass'n*, at 578/62 (1963) (Ex. 3); Fathie, "Musculoskeletal Disorders and Their Management with a New Relaxant," *Clinical Medicine* 72: 679, 682 (1965) (Ex. 4); Carter, "A new muscle relaxant," Diseases of the Nervous System 1962; 23(2): 1-3 and Table III (Ex. 5).

The information that King lobbies to force into the labeling for generic metaxalone thus matters not to the drug's safe or effective use, but rather to the profitability of King's recent acquisition of rights in the drug and the patents associated with it. Seeking to protect those interests, King now attempts to mount a legal and procedural challenge to the FDA's March 1 letter, arguing that it conflicts with the Hatch-Waxman Amendments to the Food Drug and Cosmetic Act ("FDCA") codified at 21 U.S.C. §§ 355 and 360(cc) (the "Hatch-Waxman Amendments"). King also argues that the FDA's March 1 letter contravenes the Agency's regulations and Good Guidance practices, and violates the Administrative Procedure Act ("APA"). Each of these arguments is incorrect.

Even King concedes (as it must) that the FDA is fully authorized under the Hatch-Waxman Amendments to carve out from drug labeling allegedly patented information that is unnecessary for the drug's safe or effective use, in order to make a generic version of the drug available to the public. *See* CP at 24-25. As the FDA correctly concluded in this case, there is no evidence to suggest that the pharmacokinetic data at issue has any such clinical relevance, and forty years of experience demonstrates that, in fact, it has none. The FDA's exercise of its authority to carve out that information in order to facilitate public access to a more affordable generic version of metaxalone thus furthers, not thwarts, the explicit purposes that the Hatch-Waxman Amendments were intended to serve. Nor has King demonstrated that the FDA's exercise of that authority in this case was procedurally improper in any respect. Contrary to King's insistence, the FDA's Good Guidance practices do not apply to the type of fact-specific, individualized communication incidental to ANDA approval at issue here. Nor does the APA require safety determinations made in such a narrow context to be preceded by the public notice and comment procedures associated with formal rulemaking, which the FDA's March 1 letter certainly was not.

Thus, contrary to King's contentions, the FDA's March 1 letter conveyed a scientifically sound safety determination well within the Agency's unique expertise, and its legitimate authority under the Hatch-Waxman Amendments and the APA. Simply put, the FDA did the right thing, for the right reason, and in the right way. King's arguments to the contrary are scientifically and legally insupportable, and thus fueled instead by a transparent commercial incentive to forestall competition. Each of these points is discussed more fully below.

FACTUAL BACKGROUND

I. Longstanding Use of Metaxalone

The metaxalone compound was disclosed as early as 1962 in U.S. Patent No. 3,062,827, which was then assigned to A. H. Robins Company, Inc. ("Robins"). The FDA approved the drug also in 1962, and it has since been distributed under the brand name Skelaxin® by Robins, Carnrick Laboratories, Inc. (Robins' successor with respect to the drug), Elan (Carnrick's successor), and now King. Since its introduction in the 1960s, metaxalone has been indicated for use as an adjunct in the treatment of musculoskeletal conditions. While its particular mode of

action and the plasma concentrations required for its therapeutic and toxic effects remain unknown,[2] the drug has enjoyed a long history of safe and effective use with a minimum of adverse events and side effects throughout these many decades, particularly as compared to other muscle relaxants. *See* Ex. 1 at 4.[3] Moreover, as the FDA noted in its March 1 letter, the drug's safe use continued unabated for more than forty years without any food-related instruction, pharmacokinetic data, or dosing adjustment included in its labeling. *Id.*

Although daily doses as high as 4,000 mg to 9,600 mg have been reported safe and effective, the recommended dosing schedule for metaxalone has long been 800 mg three-to-four times daily for periods ranging up to 21 consecutive days and longer.[4] Consistent with this regimen, also since the early 1960's, the published literature has acknowledged that the drug may be administered safely and with a minimum of side effects with or after food or meals (as part of a routine, for ease of administration, or to prevent nausea or gastric upset), or in a fasted state.[5] In addition (and also since the 1960s), the literature has further confirmed (in reported studies conducted with Robins' participation) that the recommended daily dose of metaxalone remains 800 mg three-to-four times daily ***both*** when the drug is administered with food ***and*** when it is administered without food.[6]

The literature has also long recognized that metaxalone is practically insoluble in water, and that the bioavailability of such hydrophobic compounds is typically increased by their administration with high-fat foods.[7] As the FDA noted in its March 1 letter, however, to the

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[2] *See, e.g.* Albanese, *Nurses' Drug Reference* at 427 (2d ed. 1982) (Ex. 6); 1990 *Physicians' Desk Reference* at 831 (Ex. 7); *AHFS Drug Information* 12:20 at 1325 (2003) (Ex. 8).

[3] *See also* Harden, "A review of three commonly prescribed skeletal muscle relaxants," 15 *Journal of Back and Musculoskeletal Rehabilitation* 63-66 (2000) (comparing metaxalone, cyclobensaprine, and carisoprodol: "there are no reports in the literature of potentially dangerous side effects or safety concerns" relating to metaxalone; "Metaxalone has the fewest reported side effects of these three SMRs") (Ex. 9).

[4] *See, e.g.*, Ex. 3 at 521/65; Ex. 4 at 679; Ex. 5 at 99; Fathie, "A Second Look at a Skeletal Muscle Relaxant: a Double-Blind Study of Metaxalone," *Current Therapeutic research*, Vol. 6., No. 11 at 679 (1964) (Ex. 10); Abrams, *Clinical Drug Therapy* 146 (1995) (Ex. 11); *Drug Information for the Health Care Professional*, USPDI Vol. I at 2460 (15th ed 1995) (Ex. 12).

[5] *See* Ex. 3 at 578/62; Ex. 4 at 679, 682; Ex. 6 at 427; Ex. 10 at 679; Ex. 11 at 146-147, 149; Ex. 12 at 2460, 2465.

[6] *See, e.g.*, Ex. 3 at 578/62, 580/64; Ex. 4 at 679, 682; Ex. 10 at 679. *See also note* 5 *supra.*

[7] *See* Ex. 2 at ¶¶ 22, 25-27; *See also* Ex. 3 at 578/62; Carroll, "The pharmacology of a new oxazolidinone with anticonvulsant, analgetic and muscle relaxant properties," *Arch. Int. Pharmacodyn.*, Vol. 80, No. 3-4:280-98 at 280 (1962) (Ex. 13); Hamaguchi, "Effect of a high-fat meal on the bioavailability of phenytoin in a commercial powder with a large particle size," *Int'l. J. Clin. Pharmacol., Ther. Tox.*, Vol 31 No. 7:326-33 at 326, 329 (1993) (Ex. 14); Osol, *Remington's Pharmaceutical Sciences*

extent that the bioavailability of metaxalone is so increased, that has never warranted adjustment of the standard 2,400-3,200 mg daily dosing schedule or any other food-related instruction; nor has it ever been linked to any increase in adverse events associated with the drug. Ex. 1 at 4. Rather, as noted above, the optimal dosing schedule for metaxalone of 800 mg three-to-four times daily has long remained the same, and the drug has remained safe and non-toxic, regardless of whether it is administered with food. *See* notes 5-6 *supra*.

II. The Efforts of Elan and King to Patent the Information in Metaxalone Labeling.

Despite the longstanding practice of administering metaxalone both with and without food, the literature reporting both, and the complete silence in the approved labeling for Skelaxin® on any difference between the two for forty full years, in December of 2001 (with generic competition imminent) Elan attempted to co-opt the drug by applying for a patent on a "method of increasing the bioavailability of metaxalone by administration of an oral dosage form with food." *See* Ex. 17 at Abstract. To support this application, Elan cited a "single center, single dose, open-label, two-period, randomized, crossover trial" (*id.* at col. 2, lines 55-60), the protocol for which appears to have been derived from FDA Guidelines (although Elan failed to credit the FDA or its Guidelines in any respect).[8]

The first patent to issue from Elan's December 2001 application was the '128 patent, which issued on June 18, 2002. Each of its 22 claims requires a "method of increasing the oral bioavailability" (or "the rate and extent of absorption") of metaxalone, and the step of "administering" metaxalone to a patient "with food." *See* Ex. 17 at cols. 7-8. While the '128 patent was pending, Elan applied for a related patent, which issued as U.S. Patent No. 6,683,102 (the "'102 patent") on January 27, 2004. The '102 patent contains 15 claims, each of which requires "informing" a patient that the administration of metaxalone with food "results in an increase in at least one of C(max) and AUC(last)" as compared to administration without food. *See* Ex. 20 at cols. 7-8. And, while the '102 patent was pending, Elan filed yet another application for a patent on the purported effects of age on the oral bioavailability of metaxalone. This application (which presumably remains pending in the United States Patent Office) asserts

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at 867 (16th ed. 1980) (Ex. 15); Monograph No. 5838 of *The Merck Index* at 933 (11th ed., 1989) (Ex. 16).

[8] For instance, an October 2000 FDA Guidance for Industry states that "[c]oadministration of food with oral drug products may influence drug BA," and recommended "a single-dose, two period, two treatment, two-sequence crossover study" to demonstrate such an effect. *See* Ex. 18 at 18. A Draft Guidance for Industry distributed in December of 1997 similarly observed that "[t]he effects of coadministration of meals with drugs is maximal when the drug product is administered immediately after completion of a meal," and that "[m]eals that are high in calories, fat, and density are likely to provide the greatest effects on BA." *See* Ex. 19 at 1-2. This document therefore recommended use of the following "high-fat" test meal in such BA studies: "2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, 8 ounces of whole milk." *Id.* at 5. The study reported in Elan's December 2001 patent application utilized precisely the same test meal.

that fasted-state bioavailability levels of metaxalone increase with age by 10% over a fifty-year span, and seeks to patent methods of "reducing" this purported "age-effect" by administering the drug to all ages "with food," and of "informing" patients of the bioavailability effect of doing so. Ex. 15 at 18, 46-50; Ex. 2 at ¶¶ 64-67.

While Elan was pursuing these applications, it concurrently embarked on a campaign to include in the labeling for Skelaxin® (and, in turn, the labeling for any generic version thereof) information that it would later argue snared such products within the scope of whatever patents it could obtain. Thus, in mid-2002 (just one month after Corepharma filed its ANDA), Elan persuaded the FDA to modify the labeling for all metaxalone products to include Elan's *in vivo* bioavailability data demonstrating increases in Cmax and AUC when the drug is administered with a high-fat meal, as described in its applications for the '128 and '102 patents. *See* CP Ex. 3-4. And less than a year later, in April of 2003, Elan again sought to modify the labeling for the drug yet again, this time to include the data demonstrating the purported "age effect" on the bioavailability of metaxalone, which it similarly sought to patent. *See* CP Ex. 5. To date, this latter request remains pending. *See id.*

The initial labeling change implemented by the FDA in response to Elan's request included a discussion of Elan's data showing a relative bioavailability increase when metaxalone is administered with a high-fat meal, along with the following statement: "Given the magnitude of plasma level changes following a high-fat meal, Skelaxin tablets should be administered on an empty stomach." *See* Ex. 22. Apparently because such labeling would have insulated generic makers of metaxalone such as Corepharma from the soon-to-issue '128 patent (each claim of which requires administering the drug with food), Elan quickly petitioned the FDA to delete this "empty stomach" instruction from the labeling and instead include references to "statistically significant" increases in Cmax and AUC observed when administering the drug with a high-fat meal. CP Supplement ("Supp.") Ex. 14. The FDA approved Elan's request for these changes on June 20, 2002 (two days after the '128 patent issued), deleting the "empty stomach" instruction and substituting instead a statement explaining that "the clinical relevance of these effects is unknown." *See* CP Ex. 3.

III. Factual Background Relating to Corepharma's ANDA

Corepharma filed its ANDA for generic metaxalone in April of 2002. In connection therewith, Corepharma proposed labeling for its generic metaxalone product consistent with the then FDA-approved labeling for Skelaxin®, which recited the same indication ("for the relief of discomforts associated with acute, painful, musculoskeletal conditions") and dosing schedule ("two tablets (800 mg) three to four times a day") that had long been included in the Skelaxin® labeling. Two months later, however, Elan's first labeling change was implemented, requiring metaxalone ANDA applicants to include a discussion of Elan's data reporting relative increases in Cmax and AUC following administration of the drug with the standard FDA high-fat meal compared to administration under fasted conditions.

As a result of this labeling change, ANDA applicants such as Corepharma were required to certify pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(III) or (IV) that their generic metaxalone products would not be sold prior to the expiration of Elan's '128 patent (a "Paragraph III certification") or that manufacture, use, or sale of the product would not infringe the '128 patent, or that the claims of such patent are invalid (a Paragraph IV certification). ANDA applicants were not permitted to provide, in lieu thereof, a section viii statement confirming that the patent does not claim a use for which approval is sought. This requirement in turn enabled Elan to sue Corepharma for infringement of the '128 patent under 35 U.S.C. § 271(e), and thereby delay FDA approval of Corepharma's ANDA pursuant to the thirty-month stay imposed by 21 U.S.C. § 355(j)(5)(B)(iii), whereas a section viii statement would have triggered no such stay. One other ANDA applicant, Eon Labs, Inc. ("Eon"), was similarly required to submit a Paragraph IV certification and sued for infringement of the '128 patent.

With the Hatch-Waxman stay in place and generic competition thwarted as a result, Elan managed to sell certain of its interests in Skelaxin® and the related patent rights, among other assets, to King in May of 2003. In addition to a substantial purchase price, this deal also provided for a $25 million bonus payment to Elan if neither a court nor Governmental or Regulatory Authority (including the FDA) issued an adverse decision regarding Elan's claims under the '128 patent (or the listing of that patent in the FDA's Orange Book) prior to January 1, 2004. King then assumed Elan's NDA for Skelaxin®, continued to pursue the age-effect labeling change that Elan had requested from the FDA, and continued to prosecute Elan's remaining metaxalone-related patent applications.

IV. The FDA's March 1 Letter

In February of 2003, Corepharma requested the FDA to waive the requirement of a Paragraph IV certification for its metaxalone ANDA and permit instead a section viii statement with respect to the '128 patent. Corepharma explained that a section viii statement was appropriate because Corepharma's ANDA seeks approval for only the same indication and conditions of use that the FDA long ago approved for metaxalone (as an adjunct in the relief of discomforts associated with acute, painful, musculoskeletal conditions), and does not seek approval for a method of use claimed in the '128 patent.

By letter dated March 1, 2004, the FDA advised Corepharma that a section viii statement would be accepted. The FDA concluded that the Elan data demonstrating increased bioavailability following administration of Skelaxin® with a high-fat meal is unnecessary for safe use of the drug, and that generic ANDA applicants therefore may carve that information out of their labeling. The FDA based this conclusion, in part, on the fact that metaxalone has been marketed safely for decades without dosing adjustment information related to fed-state administration, and Elan's own request to omit an "empty stomach" instruction in favor of a statement that the "clinical relevance of these effects is unknown." *See* Ex. 1 at 4. The FDA also observed that there is no data suggesting any link between increased plasma concentrations

of the drug and its efficacy or adverse events, and that the drug's labeling already addresses any concern over adverse events by advising that "Skelaxin may impair mental and/or physical abilities required for performance of hazardous tasks such as operating machinery or driving a motor vehicle, especially when used with alcohol or other CNS depressants." *Id.*

Having correctly determined that fed-state bioavailability data may be carved out of generic metaxalone labeling, the FDA further concluded that metaxalone ANDA applicants may submit a section viii statement with respect to the '128 patent (in lieu of a Paragraph IV certification), which would in turn lift the stay of the agency's approval of the ANDA under 21 U.S.C. § 355(j)(5)(B)(iii). King's Petition challenges that decision on two principal grounds: (1) that the food-effect data demonstrating a relative increase in the oral bioavailability of metaxalone when the drug is administered with a high-fat meal is "essential information" which the Food Drug and Cosmetic Act ("FDCA") and FDA regulations and Guidelines require in the labeling for generic metaxalone products, and (2) that the FDA's March 1 letter communicating its decision to allow ANDA applicants to carve out this information was contrary to its Good Guidance practices and the APA. As explained below, each argument is factually and legally insupportable. So too is King's companion request to stay approval of all generic metaxalone products while it presses these incorrect arguments before the FDA.

ANALYSIS

I. Neither the FDCA nor FDA Regulations or Guidelines Require Data Regarding the Effects of Food on Metaxalone to be Included in Generic Metaxalone Labeling.

A. The Food-Effect and Age-Effect Data Proffered by King Are Clinically Irrelevant.

Each of King's arguments hinges on a faulty factual premise – that the fed-state bioavailability data to be carved out of generic metaxalone labeling is "essential information for practitioners who prescribe the product." CP at 11. In fact, far from being "essential," this information is irrelevant both clinically and practically.

As the FDA observed in its March 1 letter, metaxalone has been used safely and effectively for more than four decades without dosing adjustment relating to fed-state administration, and with no mention of the food-effect data that Elan added to the pharmacokinetics section of the Skelaxin® labeling in 2002. Ex. 1 at 4. Nor did Elan's data demonstrating a relative increase in bioavailability when the drug is administered with a high-fat meal lead to any change in its recommended dosing schedule. Indeed, neither Elan nor King, nor King's experts have suggested such a change, for inclusion in the drug's labeling or in practice. Ex. 1 at 4. Rather, the optimal dose of metaxalone remains, as it has always been, 800 mg three-to-four times daily regardless of whether the drug is administered with food, just as King continues to advertise. *See* note 6 *supra*; Ex. 23.

As the FDA also observed, there is no suggestion that an increase in plasma levels of metaxalone caused by administration with food leads to an increase in adverse events. Ex. 1 at 4; note 6 *supra*. And, again, neither King nor its experts have identified such a link. That is not surprising, since, as even King acknowledges, the drug's mechanism of action remains unknown (CP at 3), as do the plasma concentrations required for its therapeutic and toxic effects. *See* Ex. 8 at 1325. Thus, contrary to the unsubstantiated contentions of King and its experts, the food-effect data that King would require in generic metaxalone labeling could not enable a clinician "to adjust the dosage or administration" of metaxalone, since there are no known effective or toxic plasma concentrations for a clinician to seek to achieve or avoid. Rather, as Dr. Bass explains, clinicians should adhere to the recommended dosing of 800 mg three-to-four times daily – with food or without – which has been established to be safe, effective, and non-toxic through forty years of experience.[9]

Moreover, even if the fed-state data cited by King were of any clinical import (which it is not), it is utterly lacking in practical significance. At most, the data suggests a potential relative increase in the bioavailability of metaxalone when a single dose is administered with a high-calorie, high-fat breakfast which was designed to produce the greatest bioavailability increase possible.[10] As Dr. Bass explains, far smaller relative increases (if any increase at all) would be experienced if the drug were administered with a lower fat meal, or if the drug were taken at a later point in time with respect to a meal, or both. Ex. 2 at ¶ 40-45. The fed-state levels cited by King are thus artificially high. Equally important, any difference between fed and fasted levels of metaxalone will substantially decrease as the drug is administered three to four times daily, as recommended. As Dr. Bass explains, this is due to the longer half-life of metaxalone, and the greater residual amount of each dose retained in the body over time, in the fasted state. *Id.* at ¶ 42. Given that the drug is administered three-to-four times daily for numerous consecutive days, the fasted-state levels cited by King are thus artificially low. As Dr. Bass explains, normal use of the drug (as opposed to the exaggerated conditions assumed by King) leads to a relative increase in oral bioavailability in a fed state that is either statistically insignificant or non-existent.[11]

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[9] Metaxalone is not unusual in this respect. As Dr. Bass explains, the therapeutic effects of many drugs are unrelated to plasma concentrations and elimination over time (half life). Like metaxalone, such drugs are properly dosed, not according to the pharmacokinetic factors that King identifies (Cmax, AUC, and half-life), but according to a schedule that has been determined safe and effective for their intended indication. Ex. 2 at ¶ 38.

[10] Contrary to King's suggestion, this effect was hardly "unexpected." *See* CP at 2. As noted above, it has long been known that metaxalone is practically insoluble in water (indeed, that property is apparent from the compound's structure alone), and that the bioavailability of such hydrophobic substances is increased by their administration with fatty foods. *See* note 7 *supra*; Ex. 2 at ¶ 22, 25-27.

[11] Indeed, as Elan's data confirms, fasted-state administration of metaxalone can produce plasma levels exceeding those in a fed-state, even when a high-fat meal is ingested. That is because the body naturally performs the same enhanced digestive functions that are attendant to digestion of a high-fat meal

The purported "age" and "gender" effects cited by King are even less relevant. According to King, a "meta-analysis" of four pharmacokinetic studies demonstrates "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." CP at 16. And, while this "gender effect" is purportedly observed regardless of whether the drug is administered with food, the age effect occurs only in a fasted state. *Id.* Based on this data (which King chose not to submit with its Petition), King has requested a further change to the labeling for its Skelaxin® product which includes a recommendation that the drug be administered with food "so as to minimize age-related variability" (though it seeks no comparable change to minimize gender-related variability). *Id.* Conveniently for King, if forced upon ANDA applicants, this change would improve King's position with respect to the patent rights it just purchased from Elan for a substantial sum. But that is all it would improve.

Even if King's "meta-analysis" is to be fully credited,[12] it demonstrates, at most, a mere 10% increase in fasted bioavailability levels over a fifty-year age span. *See* Ex. 21 at 18. As Dr. Bass explains, such a trivial increase is well within the range of variability expected in the population at large, and therefore statistically insignificant. Ex. 2 at ¶¶ 65-67. Thus, even accepting King's age-effect data at face value, there is no true "age-related variability" to "minimize." Indeed, the very data on which King relies to demonstrate its age effect acknowledges that the drug "was safe and well tolerated by the subjects." *See* Ex. 25 at 34; Ex. 2 at ¶ 31. King's argument grows even weaker when it is considered that steady-state fasted bioavailability levels will be insignificantly different from fed-state levels in normal use of the drug in any event, and neither plasma level (fed or fasted) requires any dosing adjustment, as explained above. And even King concedes the clinical irrelevance of such variability in plasma levels among patients, when it opts to tolerate "significantly higher" bioavailability levels in women than in men. *See* CP at 8; CP Ex. 7 at ¶ 24.[13]

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every ninety minutes, even absent a high-fat meal or any food at all. *See* Ex. 2 at ¶ 23; Bass, "Gastric Emptying: Differences Among Liquid, Fiber, Polymer and Solid Dosage Forms of Medications" (1993) (Ex. 24). Thus, as Dr. Bass explains (and Elan's data confirms), fasted-state bioavailability levels can equal or exceed those experienced when metaxalone is administered with a high-fat meal. Ex. 2 at ¶ 28; Ex. 17 at Table 1.

[12] As the patent application directed at this "age effect" demonstrates, King's "meta-analysis" was necessary because none of the referenced studies individually demonstrated the age effect that King now proffers. *See* Ex. 2 at ¶¶ 70-72. And even that analysis identified an effect too small to be informative in a population too small to support any meaningful conclusions. *Id.*

[13] Corepharma notes that Mutual Pharmaceuticals, Inc. ("Mutual") has filed a Petition to Stay King's pending request to include this purported age-effect and gender-effect data and a corresponding food instruction in its Skelaxin® labeling. Corepharma supports Mutual's Petition, and further notes that this information is similarly excludable from generic metaxalone labeling for the same reasons and on the same grounds discussed in the FDA's March 1 letter and herein in connection with the food-effect data that Elan added to the Skelaxin® labeling in 2002.

King's experts create no controversy on these points. While King's Dr. Elia faithfully repeats King's assertion that fed-state data is necessary to "make an informed choice of dosage and administration strategies" (CP Ex. 10 at ¶¶ 18-19), he carefully avoids stating whether he has ever, in fact, adjusted a dose of metaxalone based on this information, or how he might do so. That is undoubtedly because data pertaining to the administration of a single dose of metaxalone with a high-fat meal has no practical application to steady-state dosing under normal eating conditions. Nor does such data support a dosing adjustment absent an understanding of the drug's mode of action and effective plasma levels, both of which are unknown.

Similarly, while Dr. Elia also insists that he "would follow the recommendation to administer Skelaxin® with food in order to ensure more consistent plasma levels" among various age groups (a variability that apparently does not concern him when it occurs between gender groups), he makes no attempt to explain what type of food instruction he would give, whether he would adjust dosing as a result, or what either measure would accomplish. *See* CP Ex. 7 at ¶ 23. Again, that is because the optimal dosing of metaxalone continues to be 800 mg three-to-four times a day, regardless of whether the drug is administered with food, and regardless of plasma levels.

Likewise, while King's Dr. Benet warns that omission of food-effect and age-effect data from metaxalone labeling "*can* pose safety and efficacy concerns," he too fails to identify what those issues might be. *See* CP Ex. 10 at ¶ 31 (emphasis added). At most, he argues that "safety and efficacy issues of clinical significance *may* exist," and that the information might "assist" scientists and practitioners in "characterizing metaxalone's disposition and the relevance of pharmacokinetic changes." *Id.* at ¶ 29, 31 (emphasis added). As the FDA recently concluded in connection with a labeling carve-out pertaining to generic ribavirin capsules, such "speculative and conclusory statements" are a wholly insufficient basis to conclude that a carve-out of allegedly patent-protected information would render use of a generic drug less safe or effective than the branded drug. *See* Letter dated April 6, 2004 from Steven K. Galson, M.D., M.P.H., Acting Director, Center for Drug Evaluation and Research, to David M. Fox, in Docket No. 2003P-0321/CP1 (hereinafter, the "Ribavirin Decision") at 19.

Dr. Benet's warning of potential drug-drug interactions is no more persuasive. For one thing, the approved labeling for metaxalone has long advised (and continues to do so) of known therapeutic interactions, by explaining that the drug "may enhance the effects of alcohol, barbiturates and other CNS depressants." CP Ex. 4 at 5. Dr. Benet fails to explain how the food-effect and/or age-effect data that King seeks to include in generic metaxalone labeling would supplement this information, or help practitioners determine whether any unknown drug-drug interactions exist or what they are. On the contrary, Dr. Benet admits that such determinations would require in the first instance "information as to the metabolic profile of metaxalone, or its potential to be a substrate for transporters," none of which is known. CP Ex. 10 at ¶ 27. The pharmacokinetic data at issue therefore could not help determine any unknown drug-drug

interactions, nor does Dr. Benet contend that it would help determine the unknowns necessary to do so.[14]

Dr. Elia's observation that he frequently prescribes metaxalone with other medications (CP Ex. 7 at ¶ 20) does not alter this analysis. While information regarding the metabolic profile of metaxalone is lacking, what is known is that the drug has long been recommended as an "adjunct" with other therapies (*i.e.*, rest, physical therapy, and other agents, including analgesics and anti-inflammatories), and that daily doses of 3,200 mg (and up to ***triple*** that amount) are effective, safe, and non-toxic. *See* notes 1-3 *supra*. After forty years of such reliable and safe use as an adjunctive measure, King's stated concern over the drug's use in combination with other agents rings particularly hollow.

B. The FDA's Decision to Allow Metaxalone ANDA Applicants to Carve Out Food-Effect Data is Consistent with the Hatch-Waxman Amendments and their Underlying Purpose.

"King does not dispute that FDA has the authority to permit ANDA applicants to carve out labeling pertaining to patented or exclusive uses of pioneer products, as long as the omitted labeling does not bear on the safe and effective use of the generic products for the indications and conditions of use that remain in the generic labeling." CP Supp. at 3. While this concession confuses the standard required for a labeling carve-out, it is dispositive here nonetheless.[15] As shown above, the food-effect data that Elan included in the labeling for Skelaxin® in 2002, and the age-effect and gender-effect data that King would include in the labeling now, have no bearing on the safe or effective use of metaxalone, since none of this information requires a dosing adjustment. Nor could it be used to fashion a dosing adjustment, because the drug's mechanism of action and its therapeutically effective plasma levels remain unknown. Nor is the data needed to avoid any side-effects or adverse events (to which the information has no known relationship, in any event), since far higher levels have long been determined safe and non-toxic. Nor would it allow for the determination of additional drug-interactions, or assist in the avoidance of any known therapeutic interactions (which are already addressed in the labeling, in any case).

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[14] To the extent Dr. Benet believes that this data might assist with further research regarding the drug (CP Ex. 10 at ¶ 29), its omission from generic labeling certainly would not prevent such research. Indeed, its omission from Corepharma's labeling would not even affect a prescribing physician's use of the drug, since Corepharma does not market its drugs or distribute its labeling to physicians, in any event.

[15] As the FDA observed in its March 1 letter, FDA regulations authorize a carve-out of an indication or other aspect of drug labeling protected by patent or exclusivity where the omission of that information would "not render the proposed drug less safe or effective than the listed drug for all remaining, non-protected conditions of use." Ex. 1 at 2 (quoting 21 C.F.R. §314.127(a)(7)). The regulation is not restricted, as King suggests, to information that "does not bear on the safe and effective use of the generic product" whatsoever. *See* CP Supp. at 3.

Thus, the evidence is entirely one-sided that omission of the data that Elan has added and that King would add to the labeling for Skelaxin® would not render generic versions of Skelaxin® less safe or effective than Skelaxin® for its approved indications and for all remaining, non-protected conditions of use. Instead, such data bears only on Elan's and King's patent positions. Seeking to protect that pecuniary interest, King attempts to avoid a carve-out of this information on three purported grounds. Each is unavailing.

First King suggests that the authority to carve out information from approved reference drug labeling is limited to "patented or exclusive indications for use," and does not authorize the omission of information that pertains to a remaining indication or condition of use. CP at 26-27. Not so. The FDCA permits differences in generic labeling required "because the new drug and the listed drug are produced or distributed by different manufacturers," 21 U.S.C. § 505(j)(2)(A)(v), and the FDA regulation implemented under this section permits "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) (emphasis added).

On its face, this regulation (which King does not challenge) permits a carve-out of not only "patented or exclusive indications for use" as King would suggest (CP at 26), but also any "other aspect of labeling," including one that pertains to a remaining approved indication or condition of use. Indeed, the FDA adopted this language, in part, to address concerns over "a possible claim of inducement or infringement where a *nonapproved*, but patented, *method of administration* is *discussed* in the innovator's label" (57 Fed. Reg. 17962, emphasis added), just as King and Elan seek to use the information they would include in the pharmacology section of the labeling for metaxalone, though Corepharma seeks approval for only the same indication that has long been recited in the indications and usage portion of the labeling for Skelaxin® for decades. As the FDA observed in its March 1 letter and its recent Ribavirin Decision, this regulation has been repeatedly upheld by the courts. *See* Ex. 1 at 2 (citing cases); Ribavirin Decision at 12-13 (citing cases).[16] And it has been repeatedly relied upon by the FDA to carve out information that relates to a remaining indication or condition of use, where its omission does

[16] King pays these decisions short shrift, arguing that they do not address the specific fact pattern presented here, in which the information to be carved out allegedly pertains to a remaining indication or condition of use. CP at 26-27. But that argument misses the point. These decisions uphold the regulation, *see, e.g., Bristol-Meyers Squibb Co. v. Shalala*, 91 F.3d 1493, 1496, 1500 (D.C. Cir. 1996), and the plain language of the regulation provides for such a carve-out on its face. Moreover, King challenges neither the propriety of the regulation nor the FDA's interpretation of it; nor could King mount such a challenge. *See Zeneca, Inc. v. Shalala*, 213 F.3d 161, 170 (4th Cir. 2000) (upholding the FDA's interpretation of 21 C.F.R. 314.94(a)(8)(iv) and noting that such interpretation is entitled to "substantial deference").

not render the proposed drug less safe or effective. *See* Ribavirin Decision at 20 (citing, *inter alia*, Docket Nos. 01P-0495, 02P-0191, and 02P-0252).[17]

King next argues that the FDA's mere addition to the Skelaxin® labeling of the food-effect data proffered by Elan in 2002 stands, by itself, as a determination of "the importance" of that information (CP at 30), and that Elan's concession in the labeling that the "clinical relevance of these effects is unknown" merely reflected "the belief, held by both Elan and FDA, that the available clinical data did not, at that time, warrant a specific dosing recommendation with respect to food." Supp at 2. Notably, King's suggestion that the FDA must have regarded the data as clinically relevant to have included it in the labeling in the first place sharply contradicts its alternative contention that "the Agency has long required information in prescription drug labeling that has no proven clinical relevance," and that it should continue that practice here. CP at 20. But contradictory or not, both arguments are incorrect.

Contrary to King's attempt to recharacterize history (and the labeling), the contemporaneous correspondence makes clear that the FDA questioned whether Elan's food-effect data had any clinical relevance, and Elan answered that "the clinical relevance of these effects is unknown." CP Supp. Ex. 12. If anything, by including this statement in the labeling, Elan and the FDA "mutually acknowledged" that there was nothing to suggest that the data had any bearing on the drug's safe or effective use. And there still is not. While King would now recast these exchanges as a mutual acknowledgment "that the available clinical data did not, at that time, warrant a specific dosing adjustment" (Supp. at 2), the argument proves too much. If Elan's data did not warrant a dosing adjustment or a food instruction then, nor does King's data now. And if the information warrants no such adjustment or instruction, there is nothing to prevent safe and effective use of the drug without it.

But even assuming that the FDA's addition of Elan's food-effect data to the labeling for Skelaxin® could be viewed as a preliminary conclusion that it may have some possible clinical relevance (though the labeling states outright that its clinical relevance is "unknown"), nothing prevents the FDA from carving out that information pursuant to the Hatch-Waxman Amendments and the implementing regulations, where doing so would not render the generic drug less safe or effective. Indeed, in response to concerns that such "insignificant labeling

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[17] King attempts to distinguish the FDA's Ribavirin Decision as one in which the carve-out "related solely" to a potential use "that was proposed to be carved out of the labeling." CP Supp. at 4. But, in fact, the Ribavirin Decision considered whether the carve-out would have rendered the generic drug less safe or effective for "the remaining, non-protected conditions of use," in view of a challenge by the innovator that the absence of such information presented "a high risk of medication error," particularly a "potential for erroneous dosing." Ribavirin Decision at 18. After satisfying itself that the carve-out created no such risk, the FDA correctly concluded that the generic drug would be no less safe or effective. So too here. Since the pharmacokinetic information to be carved out of generic metaxalone labeling has no bearing on proper dosing (because the recommended dosing of metaxalone remains unchanged regardless of that information) a carve-out is equally justified in this case.

changes otherwise could become a tool to impede the ability of generics to compete" (particularly changes requiring pharmacokinetic data to be submitted by ANDA applicants), the FDA stressed that it "reserves the right to examine such labeling changes on a case-by-case basis to determine whether additional pharmacokinetic data are necessary before the ANDA holder changes labeling." 57 Fed. Reg. 17961-62. That is precisely the discretion that the FDA properly (and correctly) exercised in its March 1 letter.

Finally, King attempts to divert attention from the dearth of evidence to support its position by seeking to reallocate the burden of proof. According to King, where an innovator like itself proffers pharmacokinetic data regarding a brand name drug with no proof of its clinical relevance whatsoever, "it is the burden of those who would omit that information from their labels to provide data proving that the information is truly irrelevant to the safety and effectiveness of their products for their labeled uses." CP Supp. at 5-6. Putting aside the undisputed fact that there is already forty years of data demonstrating that the pharmacokinetic data proffered by King is "truly irrelevant to the safety and effectiveness of metaxalone," this argument fails also for a panoply of additional reasons.

As an initial matter, King's purported statutory and regulatory support for this argument is plainly inapposite. On its face, 5 U.S.C. § 556 applies only to hearings required under 5 U.S.C. §§ 553 (which governs rulemaking) and 554 (which governs statutorily required hearings), and states only that "the proponent of a rule or order has the burden of proof." 5 U.S.C. § 556(d). Corepharma is the proponent of neither. Moreover, as explained below, the FDA's March 1 letter involved no rulemaking, and even King makes no attempt to argue that a hearing was required under § 554 before the FDA could send it. Similarly, 21 C.F.R. 12.87(d) applies only to hearings "issuing, amending, or revoking a regulation or order," which, again, Corepharma does not seek to do. Finally, 21 U.S.C. § 355(j)(2)(A)(v) merely requires an ANDA to show that its proposed label is the same as that for the reference drug, except for differences required "because the new drug and the listed drug are produced or distributed by different manufacturers." The section contains no language indicating which party bears the burden of proof on questions raised under it. And, to the extent the FDA's implementing regulations shed any light on the question, they suggest that the party opposing a carve-out should shoulder the burden of proving that it would jeopardize safety or efficacy, since the regulations allow a carve-out ***unless*** it would "render the proposed drug product less safe or effective." *See* 21 C.F.R. § 314.127(a)(7).

The Hatch-Waxman Amendments and their legislative history support the same conclusion, particularly here, where the carve-out concerns information that the innovator's successors – not the ANDA filer – sought to add to the reference drug's labeling ***after*** the ANDA was filed and ***after*** the drug was used safely and effectively without that information for over forty years. Indeed, a central purpose of the Hatch-Waxman Amendments was to simplify and hasten the approval of generic drugs by allowing ANDA applicants to dispense with safety and efficacy data in lieu of establishing the bioequivalence of the ANDA filer's generic drug and the

reference drug.[18] That is the very sense in which an ANDA is "abbreviated." *Id.* Thus, as the FDA's Advisory Committee on Pharmaceutical Science has observed, once an ANDA applicant establishes the bioequivalence of its proposed generic product, the burden of demonstrating that the generic drug should not be approved (for instance, an assertion of bio-inequivalence) should be imposed upon the party challenging approval (*i.e.*, the innovator), not the ANDA applicant.[19] The same should hold true in a case such as this, where the ANDA applicant (Corepharma) has already established the bioequivalence of its product and the reference drug, and seeks approval only for the same indications and usage of the reference drug that have been used safely and effectively for the last four decades.

Accordingly, the burden of proving that a carve-out of food-effect data from generic metaxalone labeling would render the drug less safe or effective should fall on King, not Corepharma. And King has resoundingly failed to shoulder that burden. As noted above, King's Dr. Benet merely speculates that unidentified "safety and efficacy issues of clinical significance *may* exist" (CP Ex. 10 at ¶ 31 (emphasis added)), which is precisely the sort of "speculative and conclusory statement" that the FDA correctly rejected in its Ribavirin Decision. And the alleged prescription practices of King's Dr. Elia amount to no more than one physician's unsubstantiated views, which the FDA has also observed is "an improper ground upon which to base statements in prescription drug labeling."[20] But even assuming that Corepharma were instead required to prove that its generic metaxalone product would be no less safe or effective without fed-state pharmacokinetic data in its labeling, Corepharma has met that burden handily, and with far more evidence than metaxalone's history of safe use without dosing adjustment information related to fed-state administration" (CP at 15), although that history is surely sufficient evidence by itself.[21] In addition, Corepharma has demonstrated that:

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[18] *See* 47 Fed. Reg. 46627: "Generally, under an abbreviated application, the agency waives the submission of preclinical and clinical studies regarding the safety and effectiveness of the active ingredient because the agency already has sufficient available data and information in its files to make appropriate conclusions on those elements of the drug approval decision. Thus, an abbreviated application provides a means to eliminate unnecessary animal and human experimentation, to reduce the burdens on manufacturers in attempting to market duplicates of established drugs, and to ease the workload of FDA in reviewing and processing applications."

[19] *Prescription Pharm. and Biotechnology* ("*The Pink Sheet*"), 66/016 (April 19, 2004) ("the burden of proof is on the challenger to have an adequately well-controlled study demonstrating beyond a reasonable doubt ... that they are truly bioinequivalent").

[20] *See* 44 Fed. Reg. 37443: "The impressions or beliefs of physicians, though they are honest and may prove to be valid, are an improper ground on which to base statements in prescription drug labeling."

[21] Ironically, King attempts to discredit the long and safe history of its own drug by pointing to "other instances in which new information uncovered problems not previously recognized with marketed products." CP at 15. But, as Dr. Bass explains, each of these "instances" is wholly inapplicable to metaxalone. *See* Ex. 2 at ¶¶ 57-61.

- Any relative increase in the bioavailability of metaxalone caused by administering it with food would be, at most, statistically insignificant under normal conditions (*i.e.*, normal eating and steady-state dosing). *See* Ex. 2 at ¶¶ 40-45.

- The optimal 2,400-3,200 mg daily dosing schedule for metaxalone remains unchanged when it is administered with food (and thus notwithstanding any such bioavailability increase). *See* Ex. 3 at 578/62, 580/64; Ex. 4 at 679, 683; Ex. 6 at 679, 682.

- Doses far in excess (and even triple) this standard dose have been demonstrated safe and effective (further demonstrating that the much smaller plasma levels cited by King have no safety or efficacy ramifications). *See* Ex. 3 at 578/62, 580/64; Ex. 4 at 679, 683; Ex. 5 at 1-3; Ex. 10 at 679, 682.

- The plasma levels cited by King cannot be linked to safety or efficacy, because metaxalone's mechanism of action, and the levels required for its therapeutic or toxic effects, are unknown. *See* Ex. 6 at 427; Ex. 7 at 831; Ex. 8 at 1325.

- The labeling for generic metaxalone already addresses overdose and drug interaction issues by advising that metaxalone "may enhance the effects of alcohol, barbiturates and other CNS depressants" and "may impair mental and/or physical abilities required for performance of hazardous tasks such as operating machinery or driving a motor vehicle, especially when used with alcohol or other CNS depressants." *See* CP Ex. 4 at 5.

- The food-effect data to be carved out could not assist practitioners in identifying any other potential drug interactions, because the metabolic profile of metaxalone also is unknown. *See* Ex. 2 at ¶¶ 51-55.

- The age-effect data proffered by King suggests at most a 10% increase in the fasted-state bioavailability of metaxalone over a fifty-year span, which is statistically insignificant. *See* Ex. 2 at ¶¶ 64-67; Ex. 17 at 18.

- The gender-effect data proffered by King admittedly requires no dosing adjustment or food instruction. *See* CP at 16.

On this record, there can be no serious dispute that a bioequivalent generic metaxalone product would be no less safe or effective than Skelaxin® without the pharmacokinetic data that King proffers included in its labeling.[22]

C. FDA Regulations and Guidance Documents Likewise Support Omission of Food-Effect Data From Generic Metaxalone Labeling.

With no evidence that its food-effect data has any clinical relevance whatsoever, King ultimately retreats to the position that FDA regulations and guidance documents nevertheless "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." CP at 20-21. But this argument, too, is a non-starter. The question is not what information is properly included in drug labeling, but rather, what information may be properly carved-out. Were the FDA precluded from carving out information merely because it was properly included in the labeling at issue to begin with, no carve-out would ever be permissible. And yet, as shown above, the FDA's authority to carve-out allegedly patent protected drug labeling that is not needed for the drug's safe or effective use is so well established that even King does not challenge it in principle. *See* CP Supp. at 3.

Thus, there can be no reasoned suggestion that general FDA regulations or guidance documents "trump" the FDA's specific authority under the Hatch-Waxman Amendments to carve out information that such regulations and guidance documents would otherwise operate to include in drug labeling. On the contrary, the guidance documents on which King relies (like all others) state on their face that they "do not create or confer any rights for or on any person and do not operate to bind FDA or the public," and that "[a]n alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations." CP Ex. 8 at 1; CP Ex. 9 at 1 n.1. The regulations are to the same effect. *See* 21 C.F.R. § 10.115(d)(3) ("guidance documents do not legally bind FDA. . . . Therefore, FDA employees may depart from guidance documents . . . with appropriate justification and supervisory concurrence"). In addition, the regulations implementing the Hatch-Waxman Amendments explicitly acknowledge the permissibility of deviations in generic drug labeling "made to comply with current FDA labeling guidelines or other guidance," 21 C.F.R. § 314.94(a)(8)(iv), which, if anything, support exclusion of the data at issue here.

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[22] King feigns concern that allowing a carve-out here might encourage future metaxalone ANDA applicants to cite the resulting generic products as reference drugs, "point to the absence of food effect information" in such generic products' labeling, and "claim that they are entitled to approval without having to conduct bioequivalence studies under fed conditions." CP at 22-23. But King forgets that its predecessor (Elan) and Mutual, through their Citizen Petitions, successfully lobbied the FDA to reclassify metaxalone as a bio-problem drug, and thereby imposed upon generic metaxalone applicants the requirement of conducting *in vivo* bioequivalence studies, as well as fed and fasted bioavailability studies, *before* the data from any such studies was included in Elan's own labeling. *See* CP Ex. 1-2. A carve-out of that data from King's or any other manufacturer's labeling will not unmake those requirements.

For instance, as even King acknowledges, FDA regulations state that the pharmacokinetic information to be included in drug labeling is restricted "to that which relates to clinical use of the drug." *See* CP at 18; 21 C.F.R. § 201.57(b). The legislative history similarly acknowledges "that any section or subsection of the labeling format may be omitted if it clearly does not apply to a particular drug; accordingly, pharmacological information that clearly lacks clinical applicability is not required by § 201.57(b) to be included in prescription drug labeling." 44 F.R. 374442 (citing 21 C.F.R. § 201.56(d)(3)). The FDA's Food-Effect Guidance document similarly suggests that a food instruction should be "based on clinical relevance," such as "whether or not the changes in systemic exposure caused by co-administration with food results in safety or efficacy concerns." CP Ex. 8 at 7. And again, the regulations are to the same effect. *See* 21 C.F.R. § 201.56(c) ("No implied claims or suggestions of drug use may be made if there is inadequate evidence of safety or a lack of substantial evidence of effectiveness."). If anything, these provisions favor exclusion of the food-effect data relating to metaxalone, since, as shown above, it has no bearing on safety, efficacy, adverse events, drug interactions, or any other clinical aspect. They would also militate against the food instruction that King proffers, King having presented no clinical evidence whatsoever suggesting the need for, or usefulness of, that instruction.

II. The FDA's March 1 Letter Complied Fully with its Good Guidance Practices and the APA.

Lastly, King attempts to mount a procedural challenge to the FDA's March 1 letter, complaining that it evidenced a "dramatic reversal of policy" that constituted a Level 1 guidance document requiring notice and comment under the FDA's Good Guidance Practices regulations, (CP at 32) or a substantive rule requiring notice and comment under the APA. *Id.* at 34. Once again, both arguments are incorrect. Contrary to both contentions, the March 1 letter evidenced no "reversal of policy," dramatic or otherwise, if for no other reason than the FDA's initial inclusion of Elan's pharmacokinetic data in the labeling for Skelaxin® did not rise to the level of a "policy" in the first place.[23] Nor did the March 1 letter constitute a "reversal" of any kind. On the contrary, the FDA's conclusion stated in its March 1 letter that removal of this data from generic metaxalone labeling will not render the drug less safe or effective – a fact-specific

[23] As King acknowledges, there are only three metaxalone ANDA applicants (Corepharma, Eon, and Mutual), which makes the universe of parties potentially affected by the FDA's March 1 "Dear Applicant" letter decidedly small. *See* CP at 10. Moreover, the safety and efficacy issues addressed in that letter relate to only one drug: metaxalone. Such an individualized, fact-specific safety determination affecting limited persons hardly constitutes an agency "policy." *See Alliance for Bio-Integrity v. Shalala*, 116 F. Supp. 2d 166, 172 (D.D.C. 2000) ("policy statements" are "statements issued to advise the public prospectively of the manner in which the agency proposes to exercise a discretionary power"). But even if it did, that would not require the notice and comment proceedings for which King now argues. *Id.* at 173 (holding that FDA statement published in Federal Register it would presume that genetically modified foods were "generally recognized as safe" and not subject to regulation was a statement of policy, not substantive rule, and therefore was not subject to notice and comment procedures).

question that had never before been addressed by the FDA – was entirely consistent with the caveat it previously included in the labeling for Skelaxin® that the "clinical relevance of these effects is unknown."

In addition, the March 1 letter plainly does not constitute a guidance document. As the FDA recently observed in its Ribavirin Decision, FDA regulations provide for communications with ANDA applicants "about scientific, medical, and procedural issues that arise during the review process," and further allow for such communications to take the form of letters where "appropriate to discuss the particular issue at hand." *See* Ribavirin Decision at 32 (quoting 21 C.F.R. § 314.102). As the FDA also observed, guidance documents do not include such "communications directed to individual persons or firms." *Id.* (quoting 21 C.F.R. § 10.115(b)(3)). "Communicating with potential applicants for generic drugs is a routine part of FDA's business that is generally conducted by letter responses to questioners, and not by the issuance of guidance documents." *Id.* "Accordingly, it is entirely appropriate for the agency to communicate [labeling] review issues by letter to specific ANDA applicants." *Id.*

The fact that there are three metaxalone ANDA applicants potentially affected by the FDA's March 1 letter does not alter this analysis. "Because there are usually multiple generic applicants for the same reference listed drug, OGD often receives the same question from multiple sources." *Id.* "The fact that the conclusions reached about one applicant's ANDA labeling have relevance to other applicants who submit ANDAs for the same drug seems rather self-evident when viewed in the context of generic drugs, in which sameness of labeling is a fundamental concept." *Id.* Moreover, "it would be infeasible and inconsistent with an underlying goal of the Hatch-Waxman Amendments (i.e., to promote generic competition) to issue guidance documents in response to all of these requests for information, and neither the statute nor FDA's regulations requires [the FDA] to do so." *Id.*

It is equally clear that the March 1 letter did not constitute a substantive rule requiring notice and comment proceedings. Although King makes no attempt to address them, the factors to be considered in determining whether an agency communication constitutes such a substantive rule are well established. They include:

> (1) whether in the absence of the rule there would not be an adequate legislative basis for enforcement action or other agency action to confer benefits or ensure the performance of duties, (2) whether the agency has published the rule in the Code of Federal Regulations, (3) whether the agency has explicitly invoked its general legislative authority, or (4) whether the rule effectively amends a prior legislative rule.[24]

[24] *American Mining Congress v. Mine Safety & Health Admin.*, 995 F.2d 1106, 1112 (D.C. Cir. 1993). *See also Texas Food Indus. Ass'n v. Espy*, 870 F. Supp. 143, 147 (W.D. Tex. 1994) (quoting *American*

As suggested by King's failure even to discuss these factors, none of them applies to the FDA's March 1 letter. For instance, nothing in the March 1 letter remotely indicates that the FDA "invoked its general legislative authority" to promulgate a regulation; nor did the FDA publish it in the Code of Federal Regulations. A plain reading of the letter further demonstrates that it provides no "legislative basis for enforcement action or other agency action to confer benefits or ensure the performance of duties." Rather, as explained above, the letter merely conveyed a particular safety determination and answered a related labeling question during the course of an ANDA review, as is the FDA's practice to do through private correspondence. At most, such an interim step in the review process is "an 'informal adjudication' which is the administrative law term for agency action that is neither the product of formal adjudication or a rulemaking." *American Bioscience, Inc. v. Thompson*, 269 F.3d 1077, 1084 (D.C. Cir. 2001). Cases are legion in holding that such fact-specific determinations within an agency's unique expertise[25] are not substantive rules requiring formal notice and comment proceedings under the APA.[26]

Furthermore, as explained above, the FDA's March 1 letter neither reverses nor amends any prior legislative rule. On the contrary, it adheres to the FDA's original view expressed (as in the Skelaxin® labeling) that the "clinical relevance," if any, of the data to be carved out of generic metaxalone labeling "is unknown." Nor does the letter reverse or amend the FDA's earlier requirement of fed and fasted bioavailability studies to establish the bioequivalence of generic metaxalone products. And, while the letter states that "the FDA may have informed" the applicant that omission of the data from such studies from generic labeling "would not be permitted," that is only because the FDA had not yet addressed any ANDA applicant's request to carve-out that information and submit a section viii statement, which the March 1 letter has now

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Mining factors in determining whether FDA decision was not substantive rule subject to notice and comment requirements).

[25] *See Zeneca v. Shalala*, 213 F.3d at 169 (noting in the context of upholding an FDA labeling decision that "FDA's judgments as to what is required to ascertain the safety and efficacy of drugs falls squarely within the ambit of FDA's expertise").

[26] *See, e.g., Warder v. Shalala*, 149 F.3d 73, 75 (1st Cir. 1998) (holding that the classification of a bracing system for Medicare reimbursement purposes was an interpretive rule exempt from notice and comment procedures); *Truckers United for Safety v. Federal Highway Admin.*, 139 F.3d 934, 939 (D.C. Cir. 1998) (holding that regulatory guidance issued by agency in Q&A format was interpretive rule not subject to notice and comment requirements); *Virginia Dep't of Ed. v. Riley*, 86 F.3d 1337, 1347 (4th Cir. 1996) (holding that agency's enforcement of its interpretation of statute was not subject to notice and comment requirements), *overruled on other grounds*, 106 F.3d 559 (4th Cir. 1997); *American Mining*, 995 F.2d at 1107 (holding that "Program Policy Letters" issued by agency stating that certain x-ray readings qualified as "diagnoses" of lung disease within the meaning of agency reporting requirements were interpretive rules); *Berlex Labs., Inc. v. FDA*, 942 F. Supp. 19, 27 (D.D.C. 1996) (holding that FDA's guidance document, published in Federal Register, stating that regulations permit approval of biological products based on clinical data of another product if the products are shown to be comparable was not subject to notice and comment requirements); *Texas Food Indus.*, 870 F. Supp. at 147.

correctly done. Moreover, even if this carve-out could be considered a change of position (which it cannot), as courts have repeatedly recognized, such a product-specific determination does not rise to the level of a prior legislative rule, in any case. *See* notes 23-24 and 26 *supra.*

III. King's Petition for Stay Fails to Identify any Legitimate Private or Public Interest.

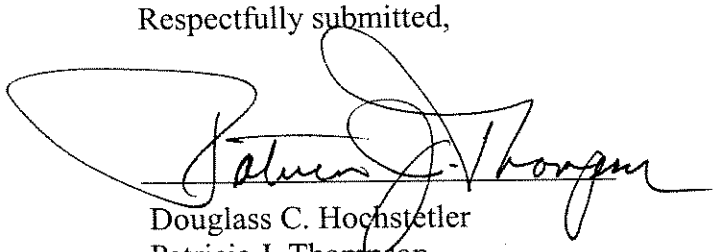
As shown above, King's substantive and procedural challenges to the FDA's March 1 letter raised in King's Petition are at odds with the facts and the law at every turn. King has identified no factual issue or substantive evidence suggesting that the safety or efficacy of generic metaxalone would be compromised by the omission of the pharmacokinetic data at issue from its labeling; indeed, King has failed even to substantiate inclusion of that data in the labeling for Skelaxin® in the first place. King has also failed to explain how or why the FDA's decision to allow a carve-out of that data would otherwise violate the FDCA, FDA regulations, or FDA Guidance. And King's procedural challenge is similarly empty, failing even to address the factors necessary to determine whether the FDA's March 1 letter is subject to notice and comment proceedings, which it clearly is not.

The circumstances surrounding King's Petition – the imminence of generic competition, the patents it recently purchased, and the need for this data to be included in generic metaxalone labeling to retain in place the stay of generic approval imposed under the Hatch-Waxman Amendments – reveal King's motives. But were there any doubt, King's Petition for Stay of all ANDA approval while the FDA is put to the task of resolving its less-than-serious Citizen Petition makes that purpose explicit. As King explains, it faces "immediate and substantial lost sales of SKELAXIN® and the revenue therefrom." Petition at 4. And, while King professes an unidentified concern for public safety, even that lip service runs a distant second to its worry over "a swift and irrecoverable erosion in the price of SKELAXIN® as King is forced to compete with generic competitors' prices." *Id.* The truth is that King's interest in the labeling for generic metaxalone products (which physicians and patients will likely never see) is purely pecuniary; and that is a decidedly insufficient interest to justify depriving a generic applicant of the right to compete and the public of a long-overdue, more affordable drug.

FDA regulations provide that "the Commissioner may grant a stay in any proceeding if it is in the public interest and in the interest of justice." 21 C.F.R. 10.35(e). It would serve no such interest to grant a stay here. On the contrary, a stay pending resolution of King's Petition would only further protract the delay that King and its predecessors have already imposed upon Corepharma, the FDA, and the public, absent any identified (let alone substantiated) safety concern. *See Zeneca v. Shalala*, 213 F.3d at 166 (upholding FDA denial of stay where alleged safety issues were unsubstantiated). To hold otherwise would only encourage the filing of baseless citizen petitions, such as King's, as a means of obtaining an additional automatic stay of ANDA approval.

For the foregoing reasons, Corepharma respectfully submits that its ANDA relating to generic metaxalone should be approved as submitted.

Respectfully submitted,



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