



MAR 1 2004

ANDA for Metaxalone Tablets

Dear Applicant:

This letter is to inform you that the FDA has determined that labeling corresponding to the use (U-189) listed in *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) for U. S. Patent number 6,407,128 (the '128 patent) may be carved out of the metaxalone labeling. Previously, the FDA may have informed you that such omission would not be permitted. A preliminary decision not to permit omission of this labeling was challenged by an ANDA applicant. The applicant has submitted information and analysis that has persuaded FDA 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. Therefore, FDA has concluded that you may submit proposed labeling that omits the use (U-189) described in the Orange Book. Should you adopt this approach, you must accompany this submission with a "section viii statement" to the '128 patent, pursuant to section 505(j)(2)(A)(viii) of the Federal Food, Drug, and Cosmetic Act (Act)

The listed drug at issue is Elan's Skelaxin (metaxalone) Tablets, NDA 13-217.¹ Metaxalone is approved by FDA for use "as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful, musculoskeletal conditions." The '128 patent is listed for Skelaxin in the Orange Book. It is identified as a use patent. The use claimed by the patent is listed in the Orange Book as "enhancement of the bioavailability of the drug substance" (U-189). The question presented to the agency was whether a section viii statement with respect to the '128 patent would be permitted. A section viii statement asserts that the labeling in the ANDA does not include any use claimed by the use patent. Section 505(j)(2)(A)(viii); 21 CFR 314.94(a)(12)(iii). A section viii statement is only appropriate when an applicant can carve information protected by the use patent out of the labeling for the product proposed in the ANDA.

ANDA Applicants May Omit from Labeling Method of Use Information Claimed by a Patent if the Omission Will Not Render the Drug Less Safe and Effective

The regulatory principles governing FDA's decision on this matter are well established. FDA has authority to approve ANDAs that omit labeling carried by the listed drug, when such labeling is protected by patent or exclusivity. The Act requires that an ANDA contain "information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a [listed drug]." Section 505(j)(2)(A)(i). The Act also requires that an ANDA contain "information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug" Section

¹ This NDA is now owned by Jones Pharma, Inc., a subsidiary of King Pharmaceuticals, Inc.

505(j)(2)(A)(v). The Act specifies two exceptions to this requirement. ANDA labeling may differ from that of the listed drug because changes from the listed drug were approved pursuant to an ANDA suitability petition, or because the drugs are produced or distributed by different manufacturers. Section 505(j)(2)(A)(v).

The Act specifically contemplates that an innovator company may submit to FDA patents claiming an approved method of using a drug and that ANDA applicants may omit from proposed labeling methods of use covered by those patents. Sections 505(b)(1) and (c)(2) of the Act state that innovators may submit patents to FDA that claim the approved drug "or method of using such drug." If a method-of-use patent listed by the innovator does not claim a use for which an ANDA applicant is seeking approval (because it is omitted from the proposed ANDA labeling), the ANDA applicant may submit a "section viii statement" to FDA that it is not seeking approval for a use claimed by a listed patent. Section 505(j)(2)(A)(viii). The statutory provisions addressing patent listing and section viii statements use the same "method of use" terminology, and effectively mirror one another; a method of use claimed by a patent is also a method of use that an ANDA applicant may propose to carve out of labeling.

FDA regulations further describe the differences that are permitted between the proposed labeling in the ANDA and the listed drug. 21 CFR 314.94, "Content and format of an abbreviated application," provides:

Labeling (including the container label and package insert) proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required because of differences approved under a petition filed under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, 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 CFR 314.94(a)(8)(iv)(emphasis added). The courts have upheld FDA's authority to approve generic drugs with labeling that omits information protected by exclusivity, *Bristol-Myers v. Shalala*, 91 F.3d 1493, 1500 (D.C. Cir. 1996), and information protected by patent, *Purepac Pharm. Co. v. Thompson*, 238 F. Supp. 2d 191 (D.D.C. 2002); *aff'd Purepac Pharm. Co. v. Thompson*, Nos. 02-5410 & 03-5121, 2004 WL 76594 (D.C. Cir. Jan. 20, 2004).

The regulations further provide that to approve an ANDA that omits an aspect of labeling protected by patent or exclusivity, 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 CFR 314.127(a)(7). Whether a particular ANDA proposing labeling that

omits protected information may be approved depends upon the specific drug product and the labeling at issue. Therefore, whether FDA could approve a metaxalone ANDA that omits certain method of use information from the labeling depends upon whether the agency concludes that the drug will remain safe and effective for all the conditions of use that would remain in the label.

ANDA Applicants May Omit Labeling Related to Fed-State Bioavailability from Metaxalone Labeling

The agency has reviewed the labeling for Skelaxin, and determined that information related to the "enhancement of the bioavailability of the drug substance," may be omitted from the labeling for metaxalone products proposed in ANDAs, without rendering those drug products less safe or effective for the conditions of use that would remain in the label.

Metaxalone is approved by FDA only for use "as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful, musculoskeletal conditions." The mode of action of metaxalone has not been clearly identified, but may be related to its sedative properties. The drug has been marketed for approximately 40 years, and is considered to have a favorable safety profile. Until recently, Skelaxin had no information in its labeling related to the effect of administration of the drug with food.

In 2001, Elan conducted a food effect study with metaxalone, and submitted the results to FDA in a labeling supplement. In June 2002, FDA approved changes to the Clinical Pharmacology section of the Skelaxin labeling to incorporate information from the food effect study.² It is this pharmacokinetic information that an applicant seeks to delete from its labeling as corresponding to the use claimed in the '128 patent. The bioavailability data submitted by Elan did not result in new Dosing and Administration labeling information for Skelaxin. Nor did it result in any changes to the warnings, precautions, or contraindications in the Skelaxin labeling

The pharmacokinetic information submitted by Elan and included in the labeling demonstrated that administration of metaxalone with a high fat meal enhances drug absorption. See attached Skelaxin labeling. The Skelaxin label includes pharmacokinetic information from dosing following a standardized high fat meal. The results from this study showed that food statistically significantly increased the rate (C_{max}), and extent of absorption (AUC_{0-12} , AUC_{inf}) of metaxalone. The approved Skelaxin labeling further acknowledges that "[t]he clinical relevance of these effects is unknown."³

The agency's assessment of whether pharmacokinetic information may be omitted from metaxalone labeling without rendering the drug less safe or effective for the remaining uses focused on whether information about enhanced fed-state bioavailability was necessary to the

² Elan did not receive three years of exclusivity for this labeling change under section 505(j)(5)(D)(iii) or (iv) because bioavailability studies are not clinical studies that qualify for exclusivity. 21 CFR 314.108(a).

³ If Elan had conducted clinical trials to demonstrate a clinical effect arising from the difference in fed- and non-fed-state bioavailability, the inclusion of such information in labeling might have been considered necessary for the safe and effective use of metaxalone. No such study has been submitted.

safe and effective use of the drug. The agency looked specifically at the relationships between bioavailability and efficacy, and bioavailability and the occurrence of known adverse events, particularly drowsiness.

FDA has concluded that omission of information regarding fed-state bioavailability will not negatively affect the safe use of metaxalone. On May 31, 2002, FDA approved an addition to the Skelaxin Clinical Pharmacology labeling that stated "Given the magnitude of the plasma level changes following a high fat meal, Skelaxin tablets should be administered on an empty stomach." The agency had approved this information because it was concerned about enhanced bioavailability and increased adverse events. However, no related changes were made to the Dosing and Administration portion of the labeling. After discussions with Elan and additional review of the available information, the agency later concluded that there were insufficient data to support a correlation between enhanced drug concentrations and increased adverse events. The label was further revised in June 2002, to remove information regarding dosing on an empty stomach, and to state that the clinical effect of the increased bioavailability is unknown.

Because the clinical effect of the increased bioavailability is unknown, omission of fed-state bioavailability information from the labeling will not render the drug less safe for its approved uses. There are no data to support an increase in adverse events related to increased drug concentrations. Even if it were reasonable to conclude that increased bioavailability relates to an increase in adverse events, the labeling already adequately addresses the primary CNS (central nervous system) adverse events by way of the caution 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." This caution applies to use of metaxalone without reference to the conditions of administration.

The Skelaxin labeling provides no information that links variations in bioavailability to the effectiveness of the drug. In fact, as noted above, the approved labeling specifically states that the clinical relevance of the food effect is unknown. Thus, because the clinical effect of increased bioavailability is unknown, omission of information on this characteristic of the drug will not affect the effective use of metaxalone.

Finally, FDA notes that metaxalone has a long history of safe use. It has been marketed for decades without dosing adjustment information related to fed-state administration. Few adverse event reports have been entered into the Adverse Event Reporting System. Based upon the data available to the agency, there is no reason to believe that metaxalone will not continue to be safe and effective for use as an adjunct to rest, physical therapy, and other measures for the relief of discomforts associated with acute, painful, musculoskeletal conditions.

For the reasons described above, FDA has concluded that an ANDA applicant may delete from its labeling information on fed-state bioavailability claimed by the '128 patent because metaxalone products with such labeling will be no less safe or effective for all of the remaining conditions of use.

If you have further questions regarding this issue, please contact Cecelia Parise, Regulatory Policy Advisor to the Director, Office of Generic Drugs, at (301) 827-5845.

Sincerely,

A handwritten signature in black ink that reads "Robert West / for". The signature is written in a cursive style.

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment: Skelaxin Labeling

cc: Jones Pharma, Inc.
Daniel E. Troy, OCC