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King & Spalding
Attention: Christina M. Markus
1730 Pennsylvania Avenue, N.W.
Washington, DC 20006-4706

JUL 30 2004

Docket No. 02P-0285/PRC

Dear Ms. Markus:

This is in response to your petition for reconsideration filed on March 12, 2003, requesting that the Food and Drug Administration (FDA) modify its decision denying the suitability of an abbreviated new drug application (ANDA) for the following products: Oxycodone Hydrochloride and Acetaminophen Tablets, 15 milligrams (mg)/325 mg and 20 mg/325 mg. That decision was dated February 12, 2003, and was a response to your citizen petition dated June 21, 2002 (Docket No. 02P-0285/CP1) submitted pursuant to § 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (Act). The listed drug product to which you refer in your petition is Percocet (Oxycodone Hydrochloride and Acetaminophen) Tablets, 10 mg/325 mg, ANDA 40-434, held by Endo Pharmaceuticals.

You do not believe that the FDA adequately considered the relevant information or views contained in the administrative record. You also state that your position is not frivolous and is being pursued in good faith, that sound public policy grounds support reconsideration, and that reconsideration is not outweighed by public health or other interests.

We have considered the information in your petition for reconsideration, as well as the information in the original citizen petition. This response incorporates by reference our previous response to the original citizen petition. We deny your petition for reconsideration for the reasons set forth below. In brief, there are safety and effectiveness concerns that preclude the submission of an ANDA for the requested products.

I. The safe use of the proposed products has not been demonstrated in the intended patient population.

The patient population for immediate-release oxycodone products containing 15 mg or 20 mg of oxycodone (with or without acetaminophen) is not the same patient population that would use Percocet, the *lower* dose combination product that you cite as your reference listed drug. Percocet is indicated for relief of moderate to *moderately severe* pain and is typically prescribed for patients for whom non-opioid analgesics (NSAIDs, for example) are either unable to control pain or not tolerated due to adverse events. Most commonly, these are patients undergoing surgical procedures who are in need of short-term opioid therapy on an as needed basis, and patients with more chronic conditions that require intermittent therapy with an analgesic.

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However, *higher* dose oxycodone products, such as the Roxicodone products you discuss in your petition, and the products you propose, are typically indicated for "management of moderate to *severe* pain where the use of an opioid analgesic is appropriate." The 15 mg and 20 mg oral doses of oxycodone, such as those you propose in your petition, are comparable to 30 mg and 40 mg oral doses of morphine sulfate, respectively. These doses would be considered appropriate for patients who might need to use opioids on a regular basis for moderate to severe pain and who can be expected to be less susceptible to sedation and respiratory depression by virtue of having more severe pain.

Given the difference in indications, it would not be appropriate to use the higher dose combination products, such as those that you propose, in the same manner as Percocet that you cite as your reference listed drug. Substantially different labeling would be required to adequately distinguish the products.

The dosing for the drug products you propose is based on the Percocet labeling, i.e., one tablet every 6 hours, with a maximum of 4 tablets per day for the 15 mg dose, and a maximum of 3 tablets per day for the 20 mg dose. This dosing schedule may be inadequate for patients who need high doses of oxycodone. These patients typically need greater dosing flexibility. This is reflected in the labeling for Roxicodone, which provides no upper limit with regard to dosing. Roxicodone contains oxycodone at the higher doses you propose.

II. Substantial labeling changes would be required for the safe and effective use of the proposed product.

The change in strength that you propose raises both safety and effectiveness concerns that would require new labeling of a kind that could not be approved under an ANDA. The purpose of § 505(j) of the Act is to permit the marketing of generic drugs based on the FDA's prior conclusion of safety and effectiveness of the listed drug referenced in the generic drug application. The Act specifically requires that the labeling of a drug approved under an ANDA be the "same" as the labeling of the reference listed drug, "except for changes required because of differences approved under a petition filed under paragraph (2)(C) or because the drug and the listed drug are produced or distributed by different manufacturers;" See § 505(j)(4)(G) of the Act. It would not be consistent with the intent of § 505(j) to interpret the "difference due to difference in manufacturer" exception described in § 505(j)(4)(G) so broadly as to authorize significant changes to the labeling made necessary in order to address newly introduced safety or effectiveness problems presented by a change in the generic drug. Section 505(j)(4)(G) does not authorize the labeling changes necessary to address the safety and effectiveness concerns raised by the change requested in your petition. See also 21 CFR 314.93(e)(1)(iv).

Similarly, the suitability petition process described in § 505(j)(2)(C) of the Act does not permit the approval of ANDAs that differ so substantially from the reference listed drugs that new

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labeling is needed in an effort to assure the safe and effective use of that product. Like § 505(j)(4)(G), § 505(j)(2)(C) must be interpreted in a manner that is consistent with the purpose of § 505(j), which is to permit marketing of generic drugs that are as safe and effective as their brand-name counterparts. It would be inconsistent with this purpose to approve a petition for a change that would create a product for which the FDA has safety and effectiveness concerns that can not be addressed through the ANDA process. See § 505(j)(2)(C)(ii) of the Act (prohibiting approval of a drug with a different active ingredient if that drug cannot be adequately evaluated for safety and effectiveness based on the information permitted to be submitted in an ANDA).

III. The efficacy of the combination of the two components in the proposed ratio has not been demonstrated.

The combination of acetaminophen and oxycodone has been approved for the lower dose oxycodone combinations. There is no evidence, however, that 325 mg of acetaminophen in combination with *higher* doses of oxycodone (i.e., 15 mg or 20 mg of oxycodone, as you propose) offers any therapeutic advantage over 15 or 20 mg of oxycodone alone. See 21 CFR 300.50 (permitting fixed dose combinations only when each component contributes to the claimed effect).

It is by no means clear that both ingredients in Percocet will continue to show a contribution if the ratio of the two ingredients is substantially changed. This question is not purely theoretical, for it is not common medical practice to continue to prescribe acetaminophen to patients who transition from low dose opioid/non-opioid combination products to single agent, higher dose, around-the-clock opioid products. Once the opioid requirement reaches a certain level, it may be that acetaminophen no longer offers any advantage and so is discontinued. In any event, before a 15 mg/325 mg or 20 mg/325 mg combination oxycodone/acetaminophen product can be approved, clinical trials are required to establish that at 15 mg and 20 mg levels of oxycodone, 325 mg acetaminophen continues to contribute to the therapeutic effect of the combination product. If clinical trials are required to establish effectiveness, approval of an ANDA under a petition is not appropriate. See 505(j)(2)(C)(i) (prohibiting approval of a petition where FDA determines that investigations must be conducted to show the safety or effectiveness of the drug product or any of its active ingredients).

IV. The proposed products do not fill a currently unmet therapeutic need.

The therapeutic need for a product to titrate beyond the 10 mg of oxycodone currently available in the oxycodone/acetaminophen combination is already met by marketed single agent oxycodone products which are available in a wide range of doses, including the Roxicodone Tablets, 15 mg and 30 mg, which you discuss in your petition.

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V. Conclusion

After review of the administrative record, we find that your petition seeking a determination of ANDA suitability for Oxycodone Hydrochloride and Acetaminophen Tablets, 15 mg/325 mg and 20 mg/325 mg was appropriately denied. We do not find your petition for reconsideration to be frivolous or pursued in bad faith, but we also do not find sound public policy grounds supporting reconsideration. Public health interests outweigh reconsideration; namely, safety and effectiveness concerns preclude the submission of an ANDA for the requested products. For these reasons, your petition for reconsideration is denied.

Sincerely yours,

A handwritten signature in black ink, appearing to read "William K. Hubbard", written over a horizontal line.

William K. Hubbard
Associate Commissioner
for Policy and Planning