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Dockets Management Branch
Food and Drug Administration (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

PETITION FOR RECONSIDERATION --
DOCKET NO. 02P-0285/CP1

Pursuant to 21 C.F.R. § 10.33, the undersigned submits this petition for reconsideration of the February 12, 2003 decision of the Commissioner of Food and Drugs (hereafter "FDA") concerning Docket No. 02P-0285/CP1.

A. Decision Involved

King & Spalding LLP respectfully requests that FDA reconsider its denial of the Citizen Petition assigned Docket No. 02P-0285/CP1.[1]

B. Action Requested

We request that FDA declare abbreviated new drug applications ("ANDAs") may be submitted for the following two, separate products:

- Oxycodone hydrochloride and acetaminophen tablets, 15 mg/325 mg.
- Oxycodone hydrochloride and acetaminophen tablets, 20 mg/325 mg.

[1] This Petition for Reconsideration is timely: FDA's letter denying the referenced citizen petition is dated February 12, 2003, and this Petition for Reconsideration is submitted within 30 days after that date. 21 C.F.R. § 10.33(b).

02P-0285 PRC1

C. Statement of Grounds

1. Relevant information or views contained in the administrative record were not adequately considered.

We do not believe that relevant information in the administrative record was adequately addressed by FDA in reaching its original decision. The suitability petition at issue proposed 15 mg/325 mg and 20 mg/325 mg combinations of oxycodone hydrochloride/acetaminophen to enhance the ability of medical professionals to upwardly titrate opioid dosage for patients who require higher levels of oxycodone, in addition to acetaminophen, to control pain.

The prior approval of Roxicodone™ Tablets (oxycodone hydrochloride 15 mg and 30 mg) affirms the analgesic safety and effectiveness of relevant product strengths in immediate-release formulation.[2] Likewise, FDA has approved other applications for 325 mg of acetaminophen in combination with oxycodone. Therefore, the proposed combination products (15 mg/325 mg and 20 mg/325 mg oxycodone/acetaminophen) outlined in the petition should not present any need for animal or clinical studies to demonstrate their analgesic safety and effectiveness, as the proposed strengths and dosing fall within acceptable limits established by FDA.

A. 15 mg/325 mg Oxycodone Hydrochloride/Acetaminophen Combination

FDA identified a single concern with regard to the proposed oxycodone/acetaminophen 15 mg/325 mg combination product, namely:

> FDA has safety concerns regarding the possible exposure of opioid naïve patients to the higher doses of oxycodone hydrochloride in the proposed products, as Oxycodone Hydrochloride and Acetaminophen Tablets are often prescribed to patients seeking medical attention for acute pain conditions. These patients are often opioid naïve and may be harmed from the administration of higher oxycodone hydrochloride doses.

Letter from Gary J. Buehler to King & Spalding (Feb. 12, 2003) ("Buehler Letter") at p. 1.

While legitimate, this concern does not provide basis for FDA to conclude that animal or clinical trials must be conducted to establish the safety and effectiveness of the product at issue. *See* 21 U.S.C. § 355(j)(2)(C) (FDA "shall approve" an ANDA suitability petition unless the agency finds "that investigations must be conducted to show the safety and effectiveness of the drug or ... strength which differ[s] from the listed drug"); 21 C.F.R. § 314.93(e)(2) ("'investigations must be conducted' means that information derived from animal or clinical studies is necessary to show that the drug product is safe or effective").

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[2] This product was discussed in the original suitability petition at page 2.

Instead, the agency can address its concern through labeling that (i) clearly identifies the product strength[3] and (ii) reminds physicians that low starting doses and subsequent titration of opioid medications are appropriate for most patients. Strength-specific cautionary labeling can be added, if necessary, pursuant to a suitability petition-based ANDA, even if comparable language does not appear in labeling for the reference listed drug. A product approved under an ANDA generally must bear labeling identical to the reference listed drug. However, specific labeling differences may be required because of product differences approved under a suitability petition. 21 U.S.C. § 355(j)(2)(A)(v) and (j)(4)(G); 21 C.F.R. § 314.127(a)(7).

If included, the proposed labeling change would *not* be "significant labeling changes to address [a] newly introduced safety or effectiveness problem." 21 C.F.R. § 314.93(e)(1)(iv). The issue of opioid titration is already inherent in the reference listed drug labeling. *See, e.g.*, Dosage and Administration section of prescribing information for Percocet® (Oxycodone and Acetaminophen Tablets, USP), 7.5 mg/325 mg and 10 mg/325 mg (Attachment 3 to original suitability petition at p. 8) ("Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended ... in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of opioids.") An additional cautionary statement would simply highlight that element of current prescribing information.

Clinical studies are *not* reasonably necessary to determine appropriate labeling to protect opioid naïve patients, as several class examples already have been approved. For example, the Dosage and Administration section of the prescribing labeling for Roxicodone™ Tablets (oxycodone hydrochloride 15 mg and 30 mg) states:

> Patients who have not been receiving opioid analgesics should be started on ROXICODONE™ in a dosing range of 5 to 15 mg every 4 to 6 hours as needed for pain.

If necessary, FDA could require an appropriate labeling statement as a condition of approving the proposed ANDA to highlight the intended patient population for the 15 mg/325 mg product. Acceptable language would be negotiated during the review process.

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[3] As discussed in the original petition, FDA has approved a range of oxycodone/acetaminophen combination products. Physicians and pharmacists are therefore already accustomed to having to identify these products by specific component strengths. Other risk management strategies also have been successfully implemented to distinguish strengths within single-entity and combination-ingredient product lines. These include, for example: labeling that highlights and color-codes strength information; labeling that highlights the fact a new strength is being offered or dispensed; dosage form imprinting with strength information; and dosage forms produced in varied shapes and colors.

B. 20 mg/325 mg Oxycodone Hydrochloride/Acetaminophen Combination

FDA raised two objections concerning the 20 mg/325 mg combination product, specifically:

- The safety concern about use in opioid naïve patients discussed in the preceding section; and

- "[T]he change in strength, when considering the proposed Oxycodone Hydrochloride and Acetaminophen Tablets, 20 mg/325 mg strength, is not supported by the approved labeling for the listed drug Percocet®. Specifically, the proposed ... 20 mg/325 mg strength can not conform to the dosing recommendations of one tablet every six hours as needed for pain as is recommended for the listed drug. The labeling that you propose recommends the usual adult dose of one tablet every six hours, but limits the maximum daily dose to three tablets, and is likely to lead to medication errors and increases the risk to opioid naïve patients."

Buehler Letter at p. 1.

The first FDA concern is addressed in Section C.1.*A.* of this petition for reconsideration.

With regard to the second concern, we believe the proposed labeling is, in fact, appropriate and supported by the reference listed drug labeling. FDA has noted correctly that the proposed product commonly would be prescribed as a "prn" or "as needed" analgesic for acute pain (*e.g.*, to relieve breakthrough pain during the daily activity of a patient who is on an around-the-clock opioid medication). It is therefore expected that the product will be prescribed in accordance with the proposed labeling -- *i.e.*, use of one, two, or three tablets per day.

Again, product labeling could clearly highlight proper administration parameters, such as by bolding the statement concerning maximum daily administration. FDA could require separate, strength-specific prescribing labeling for the 20 mg/325 mg product to further minimize any potential confusion with related products.

We certainly appreciate FDA's concern about medication errors, but believe that clear labeling can alleviate that concern. Concerning product safety, we note that, if (contrary to the labeling) the 20 mg/325 mg product were taken four times in a day, the total 80 mg of oxycodone a patient would ingest remains well within the level that FDA has found safe vis-à-vis other products. In fact, although the current reference drug labeling for the proposed product generally limits the maximum daily dose of oxycodone to 60 mg, the FDA-approved labeling contemplates certain patients may require higher doses:

> It may occasionally be necessary to exceed the usual dosage recommended ... in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of opioids.

See Percocet® Dosage and Administration section.[4]

2. Petitioner's position is not frivolous and is being pursued in good faith.

The medical community, FDA, and the pharmaceutical industry continue to strive toward effective pain management for the U.S. population, including through the use of opiate-containing pharmaceutical products, when appropriate. There is no significant dispute that opioid medications generally should be titrated according to individual patient needs and responses, nor is there significant dispute that some patients require periodic oxycodone doses at or above 15 mg to achieve effective pain relief. This ANDA suitability petition is being pursued to enable legitimate, new therapeutic options to be brought to market in an appropriate and efficient manner.

3. Sound public policy grounds support reconsideration.

FDA is charged to facilitate the marketing of safe and effective drug products, provided it can appropriately protect the public health (*e.g.*, through clear prescribing labeling). *See* 21 U.S.C. § 393(b). The proposed products will allow physicians and other health care providers to upwardly titrate the opioid dosage for a patient who benefits from oxycodone/acetaminophen combination, while maintaining an effective, yet low, daily dose of acetaminophen, if appropriate.

4. Reconsideration is not outweighed by public health or other interests.

No negative consequence will flow from FDA's reconsideration of the decision in Docket No. 02P-0285/CP1. The products at issue ultimately must undergo agency review and approval before they may be marketed (*i.e.*, there is no risk to the public health during the period of reconsideration). On the other hand, should FDA, upon further consideration, agree that it can review the products at issue under the streamlined ANDA regulatory regime, it will facilitate the entry of valuable new products into the health care marketplace.

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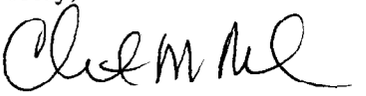
Thank you for your attention to this Petition for Reconsideration. Please contact me at 202-626-2926 should you wish to discuss the requested action.

Sincerely,



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[4] The only stated maximal daily dose in this context stems from the need to limit acetaminophen to 4000 mg per day. A patient would not exceed this limit by ingesting four oxycodone hydrochloride/acetaminophen 20 mg/325 mg tablets in one day (*i.e.*, the patient would ingest a total 1300 mg acetaminophen).