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April 19, 2006

SUITABILITY PETITION

VIA FEDERAL EXPRESS

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, Maryland 20852

Dear Sir or Madam:

The undersigned submits this petition in quadruplicate, pursuant to section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FDC Act), 21 U.S.C. § 355(j)(2)(C), and 21 C.F.R. §§ 10.20, 10.30 and 314.93, to request that the Acting Commissioner of Food and Drugs permit the submission of an Abbreviated New Drug Application (ANDA) for an Oxycodone and Acetaminophen drug product in an orally disintegrating tablet (ODT) form, in strengths of 7.5mg/325mg and 10mg/325mg.

A. Action Requested

The petitioner requests that the Acting Commissioner of Food and Drugs and the Food and Drug Administration (FDA) permit the submission of an ANDA for an oxycodone and acetaminophen drug product in an orally disintegrating tablet (ODT) form, in strengths of 7.5mg/325mg and 10mg/325mg. The Reference Listed Drug (RLD) product upon which this petition is based is Percocet® (oxycodone/acetaminophen) in a tablet form, in strengths of 7.5mg/325mg and 10mg/325mg. FDA approved Percocet in these strengths in ANDA #40-434. The petitioner requests a change from the RLD only in dosage form (from tablet to ODT form).

B. Statement of Grounds

The FDC Act provides for the submission of an ANDA for a drug product that differs in dosage form from that of the listed drug product (as the product is identified by FDA in its "Approved Drug Products with Therapeutic Equivalence Evaluations," commonly referred to as "the Orange Book") provided FDA has approved a petition that permits such a submission.

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21 U.S.C. § 355(j)(2)(C). According to the Orange Book, the RLD for oxycodone/ acetaminophen in strengths of 7.5mg/325mg and 10mg/325mg is Percocet tablets. (See Attachment 1.) Percocet is indicated for the relief of moderate to moderately severe pain.

The proposed drug product is an ODT form of the tablet. It contains the same active ingredients in the same strengths as the RLD and is intended for the same route of administration. The proposed product will be labeled with the same conditions of use as the RLD and is expected to have the same therapeutic effect when used as indicated in the labeling. (A copy of the proposed package insert is Attachment 2.) In fact, the labeling of the proposed product is expected to be the same as that for the RLD, with the exception of the section denoting the change in dosage form, which will instruct the user to place the ODT on the tongue, allowing it to disintegrate rapidly and be swallowed.

The petitioner is aware that, according to the Pediatric Research Equity Act (PREA) of 2003, which amended the FDC Act, a pediatric assessment is required for a new proposed product with a new dosage form, unless the applicant has obtained a waiver. 21 U.S.C. § 355c; 21 C.F.R. § 314.55. FDA will grant a full waiver of the requirement to submit pediatric assessments for new drugs if the applicant certifies and FDA finds one or more of the following:

> (a) Necessary studies are impossible or highly impracticable ([e.g.], the number of patients is so small or the patients are geographically dispersed) [, or]
>
> ... [The indication] has extremely limited applicability to pediatric patients, because the pathophysiology of these diseases occurs for the most part in the adult population.
>
> (b) There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups.
>
> (c) The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and (2) is not likely to be used in a substantial number of pediatric patients.

21 U.S.C. § 355c(a)(4)(A); see also C.F.R. § 314.55(c)(2)(i).[1]

It should be noted that the FDA previously granted a requested pediatric waiver and approved a suitability petition allowing the submittal of an ANDA for an opioid analgesic drug product in an ODT dosage form when the RLD approved dosage form was a tablet. Specifically, FDA approved a suitability petition for the drug product hydrocodone

[1] While Percocet is a marketed drug product, we believe that FDA will consider the product at issue, in an ODT form, to be a "new drug" for purposes of PREA evaluation. See 21 U.S.C. § 355c(a)(1)(A).

bitartrate/acetaminophen 5mg/500mg (Docket 02P-0233; included as Attachment 4) to permit an ANDA submission for a change from a tablet to an ODT dosage form. FDA also granted the applicant's request for a pediatric waiver for the change in dosage form.

Similarly, the petitioner of this action is requesting a pediatric waiver for the ODT dosage form of oxycodone/acetaminophen. This dosage form is intended for individuals who may have difficulty in swallowing an intact tablet or who prefer the proposed dosage form.

The petitioner believes that the FDA should grant a full waiver for all pediatric age groups because:

1. The proposed product is not likely to be used in a substantial number of pediatric patients because it does not provide any meaningful therapeutic benefit over existing products available to pediatric patients.

2. There is evidence strongly suggesting that the drug would be unsafe in pediatric patients younger than 12 years of age.

For a significant period of time, there have been several alternative pain remedies approved and available for the entire age range of pediatric patients, including Lortab® Elixir, Tylenol® with Codeine Elixir, Ibuprofen Drops/Suspension, and Demerol® Syrup. These alternative therapies are more suitable for use in children than the oxycodone/acetaminophen ODT dosage form. Specifically, this dosage form may be inappropriate to meet the unique dosing requirements for pediatric patients owing to its variable pharmacokinetic profile and its safety risks compared with other opioids.

The pharmacokinetic profile of oxycodone is highly variable in younger children; this profile becomes similar to adults only as children approach 12 years of age. Pokela and colleagues (2005) studied the pharmacokinetics of a single intravenous (IV) dose of oxycodone (dose based on body weight) in infants aged 1 day to 6 months.[2] The authors concluded that clearance and half-life (t½) varied greatly between subjects and this variation was most pronounced in the patients who were younger than 2 months (range: <1 week to 2 months). Kokki and colleagues studied the pharmacokinetics of a single dose of oxycodone in generally healthy children aged 6 months to 93 months undergoing surgery. The authors concluded that the oxycodone pharmacokinetics after parenteral administration were similar to those reported in adults; however, buccal and gastric administration resulted in large interindividual variation in the rate and extent of absorption. As a result of this large interindividual variation, the authors suggested that oxycodone doses in pediatric patients should be administered intravenously and should be individually titrated to achieve an optimal clinical response. Recently, El-Tahtawy and colleagues (2006), using data from the investigations by Kokki *et al.* (2004), conducted a population pharmacokinetic analysis, which allowed for more clear

[2] All published supporting studies are included together in Attachment 5.

interpretation of the large interindividual variability. The analytical model used by El-Tahtawy *et al.* showed that using a weight-based approach for oxycodone dosing is valuable in patients between 6 months and 7 years of age.

The subpopulation of patients younger than 12 years of age is an important consideration for the petitioner because published pharmacokinetic data indicate that this group may be more susceptible to the effects of oxycodone, specifically respiratory depression, because of the temporal correlation with plasma concentrations (i.e., peak rapidly and recover quickly as plasma concentrations decline) shown after IV administration. Olkkola and colleagues (1994) investigated the pharmacokinetics and ventilatory effects of oxycodone in pediatric patients aged 2 to 10 years. Post-operatively, patients were administered a single IV dose of oxycodone (based on body weight). The authors reported that major decreases in ventilatory rate occurred in all patients; the mean ventilatory rates were lower than those observed with other opioids given in presumed equianalgesic doses to comparable patients.

USP DI® Vol. 1, Drug Information for the Health Care Professional (2002) (Attachment 6) provides information similar to Olkkola *et al.*'s research. In addition, Goodman & Gilman's The Pharmacological Basis of Therapeutics (2006) states that, for children 6 months of age, especially those who are ill or premature, the pharmacokinetics and potency of opioids can be substantially altered and, in some cases, there is a significant risk of apnea (Attachment 7).

In conclusion, the available published data suggest that the most appropriate oxycodone dosing regimen for pediatric patients is IV administration with dose based on body weight and individually titrated to achieve an optimal clinical response. Although this dosing regimen is believed to reduce the pharmacokinetic variability, there may still be an increased risk of ventilatory depression in the pediatric population. Based on this published research, the petitioner believes that this new proposed dosage form will not provide an appropriate treatment option for pediatric patients because the dosing regimen recommended by researchers cannot be attained with this fixed-dose oral formulation.

Thus, the petitioner requests a waiver based on the following conditions:

1. The proposed product is not likely to be used in a substantial number of pediatric patients because it does not provide any meaningful therapeutic benefit over existing products available to pediatric patients.

2. There is evidence strongly suggesting that the drug or biological product would be unsafe in pediatric patients younger than 12 years of age.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 C.F.R. § 25.31.

D. Economic Impact

The information will be provided upon request by FDA.

E. Certification

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which is unfavorable to the petition.

Respectfully submitted,

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Attachment 1	Listing in Approved Drug Products with Therapeutic Equivalence Evaluations (2006)
Attachment 2	Proposed Package Insert for ODT Dosage Form of Oxycodone/APAP
Attachment 3	Guidance for Industry (Draft): How to Comply with the Pediatric Research Equity Act (September 2005)
Attachment 4	Hydrocodone Bitartrate/Acetaminophen Petition (Docket 02P-0233)
Attachment 5	Published Supporting Studies
Attachment 6	USP DI® Vol. 1, Drug Information for the Health Care Professional (2002)
Attachment 7	Goodman and Gilman's The Pharmacological Basis of Therapeutics (2006)

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