January 7, 2003

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

Re: Comments to Docket # 02P-0478/CP1

Dear Sir or Madam:

ALZA Corporation (ALZA), a wholly owned subsidiary of Johnson & Johnson, is the sponsor of the approved new drug application (NDA) for Duragesic® (fentanyl transdermal system) for the management of chronic pain in patients who require continuous opioid analgesic for pain that cannot be managed by lesser means, such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids. ALZA submits these comments in opposition to the citizen petition of Robert W. Pollock of Lachman Consultant Services, Inc., filed by FDA on November 5, 2002 (Docket # 02P-0478/CP1). The petitioner requested that FDA declare that fentanyl transdermal system 12.5 µg/h is suitable for submission in an ANDA.[1] The purported basis of the change is "providing the ability to titrate a patient to a required dose between two currently approved doses."

ALZA respectfully urges that FDA deny the petition for the following reasons:

- Current class labeling would be incomplete with the addition of a new "low-dose" fentanyl strength. The safe use of a new, lower-dose, strength would require significant changes to the label information and warnings. This alone requires the FDA to disapprove the ANDA.
- Prescriber confusion is likely with a new fentanyl dose, as is increased off-label use.
- Reformulations and new dosage strengths of Schedule II controlled drugs will likely result in new uses of the product in inappropriate populations and changes in abuse potential. The risk of these new uses and increased abuse should be investigated before a new dose strength is approved.

[1] Petitioner cites to 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), under which a person may submit a suitability petition requesting permission to file an ANDA for a drug with a different dosage strength from the reference listed drug. The FFDCA directs FDA to deny a suitability petition if it finds "that investigations must be conducted to show the safety and effectiveness of the drug or of any of its active ingredients, the route of administration, the dosage form, or strength which differ from the listed drug." 21 U.S.C. § 355(j)(2)(C)(i).

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I. Background

ALZA is the research-based pharmaceuticals company that manufactures Duragesic® in the United States to provide continuous systemic delivery of fentanyl. On 7 August 1990, FDA approved ALZA's Duragesic reservoir "patch" transdermal system in doses of 25, 50, 75, and 100 µg/h.

II. A new, "low-dose" fentanyl raises numerous potential problems.

As noted above, the FFDCA states that a suitability petition should be denied if FDA finds that investigations are necessary to show the safety and effectiveness of a generic drug candidate when its strength differs from that of the reference listed drug, 21 USC §355(j)(2)(C)(i); 21 CFR §314.93(e)(1)(i).

A. Current labeling would be incomplete with the addition of a new "low dose" transdermal fentanyl strength and would require significant changes to the label and warnings.

The current package insert for Duragesic does not include information pertaining to a 12.5 µg/h dosage strength. It states, "**BECAUSE SERIOUS OR LIFE-THREATENING HYPOVENTILATION COULD OCCUR, DURAGESIC® (FENTANYL TRANSDERMAL SYSTEM) IS CONTRAINDICATED:**

- **In the management of acute or post-operative pain, including use in out-patient surgeries because there is no opportunity for proper dose titration (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION),**
- **In the management of mild or intermittent pain that can otherwise be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or PRN dosing with short-acting opioids, and**
- **In doses exceeding 25 µg/h at the initiation of opioid therapy because of the need to individualize dosing by titrating to the desired analgesic effect."**

The boxed warning states, "**DURAGESIC® SHOULD NOT BE ADMINISTERED TO CHILDREN UNDER 12 YEARS OF AGE OR PATIENTS UNDER 18 YEARS OF AGE WHO WEIGH LESS THAN 50 KG (110 LBS) EXCEPT IN AN AUTHORIZED INVESTIGATIONAL RESEARCH SETTING."**

FDA regulations make clear that approval of a suitability petition may not occur if "[a]ny of the proposed changes from the listed drug would jeopardize the safe or effective use of the product so as to necessitate significant labeling changes to address the newly introduced safety or efficacy problem;" 21 CFR §314.93(e)(1)(iv).

Given the absence of relevant data/information in the package insert, the introduction of a new lower dosage strength of Duragesic poses a serious risk of off-label use in those patients

addressed in the boxed warning, and hence, a serious safety risk for those patients. For example, introduction of a new lower dosage strength would likely lead to its use for *initiation* of opioid therapy in opioid-naïve children or cachetic individuals weighing less than 50 kg. It would likely also lend a false sense of security to physicians and encourage its off-label use in the management of acute or post-operative pain. The introduction of a 12.5µg/h dosage strength of Duragesic that in all likelihood will be used for initiation of opioid therapy in these patients should be supported by relevant safety and dosing information in the package insert. As noted in the boxed warning for Duragesic, use in inappropriate patient populations may result in serious or life-threatening hypoventilation.

B. Prescribing confusion is likely with a new fentanyl dose, as is increased off-label use.

The successful use of Duragesic over many years, with minimal problems related to drug misuse, can fairly be attributed to practitioners being guided by definitive product labeling based on rigorous clinical data. This has led to clearly defined parameters for product use regarding indications, patient selection, pharmacokinetic parameter tables, tables on conversion from other analgesics, titration information, dose selection, duration of use, precautions, and adverse event monitoring.

To introduce a "new" dose of a scheduled drug is likely to introduce new prescriber confusion and misuse. Without clinical data, physician prescribing of a new dose would itself constitute uncontrolled experimentation in a drug poorly suited for such use. Physicians will very likely prescribe a lower strength of the product for painful conditions that can be managed by NSAIDs and acetaminophen-opioid combinations. Accordingly, a new dose will, intended or not[2], result in an expansion of the market for fentanyl. For example, some of the patient selection criteria (such as the warnings against use in children, in adolescent patients weighing less than 110 pounds, and, for certain dosages, patients who are not opioid tolerant), warnings and precautions, contraindications, or other use instructions in the current labeling may mistakenly be taken less seriously for a lower dose—which could result in an abrupt change in the drug's adverse event profile.

C. Schedule II controlled drugs require additional investigation to evaluate their potential use in inappropriate populations and any changes in abuse potential.

As the recent Oxycontin® (sustained release oral oxycodone hydrochloride) experience demonstrated, even a small change in a controlled drug can tip the balance toward significantly increased drug abuse and misuse. Oxycontin became a dramatically abused drug only after a seemingly innocuous change in dosage form. Clearly great caution must be exercised in approving changes to controlled drugs that may affect their abuse potential. The Duragesic labeling describes the product as "a potent opioid analgesic" and states that "60 mg/day IM morphine was considered to provide analgesia approximately equivalent to Duragesic® 100 µg/h

[2] Although ALZA hopes that the petition is not intended to obtain a "low-dose" fentanyl that can be aimed at expanding the fentanyl market, the claimed need for intermediate dosing is sufficiently thin as to cause serious questions in this regard.

in an acute pain model." Fentanyl is a strong opioid controlled drug with special abuse liability concerns.

Duragesic was clinically studied in more than 500 patients at the approved 25, 50, 75, and 100 µg/h dose strengths. The clinical data from those studies support the safety and efficacy of the current dose strengths of Duragesic, but in no way ensure the safety or efficacy of different doses—even a new "low dose." Not only does the basic safety of a 12.5 µg/h dose remain unproven, but drug misuse and drug abuse liability testing for such a dose have not been conducted. Additionally, there is the potential for prescribing errors between a 12.5 µg/h system and a prescription for 125 µg/h of Duragesic (fentanyl transdermal system), with only a decimal to differentiate the 12.5 strength from a medical order for 10 times that dose.

As the petitioner notes, there are "potentially fatal side effects with Fentanyl (sic)." Given the current abuse environment in the US, we believe that there is a potential to increase the risk to public health through the introduction of alternative controlled-release dosage forms of opioids, such as the matrix-type dosage form proposed by the petitioner. The risk comes from the unknown increase in abuse liability of alternative dosage forms of opioids that are not accompanied by data assessing their abuse liability. For these reasons, the sponsor of a new formulation or dosage strength of an approved Schedule II drug product should be required to assess the potential for misuse and abuse of that new product.

III. Conclusion

Several issues, including concerns about public safety, argue against the citizen petition (Docket # 02P-0478/CP1. First, adding a new lower dose of Duragesic would require significant changes in the labeling of the reference drug, which are not allowed in ANDAs. Second, the petitioned new dose will create new prescriber confusion and misuse as well as off-label use. Finally, Duragesic, a potent opioid product, is a Schedule II controlled substance. As such, it is not a product for which data or experience should be extrapolated in order to introduce new dose strengths. The special safety concerns for controlled drugs (ie, abuse liability potential) warrant definitive clinical data support for product changes. For all these reasons, the petition should be denied.

Thank you for your timely consideration of these comments. I would be happy to discuss further the issues raised in this docket submission. Please contact me at 650-564-4282.

Sincerely,

Janne Wissel
Senior Vice President, Operations
ALZA Corporation