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Division of Dockets Management  
Food and Drug Administration  
Room 1061  
5630 Fishers Lane  
Rockville, MD 20852

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**CITIZEN PETITION**

At the request of the Food and Drug Administration (FDA), ALZA Corporation (ALZA) submits this petition under section 505 of the Federal Food, Drug, and Cosmetic Act to request FDA to take certain actions with respect to fentanyl transdermal products. ALZA supports FDA approval of generic fentanyl transdermal products, and none of the actions requested in this petition would prevent FDA from approving such products. Rather, the requested actions would reduce the potential for abuse of certain types of these products and would permit prescribers to choose among products having different characteristics.

***ACTIONS REQUESTED***

ALZA requests that FDA take the following actions:

- (a) FDA should require manufacturers of fentanyl matrix systems to develop and implement comprehensive risk minimization programs that successfully address the specific issues presented by their products.
- (b) FDA should classify matrix and reservoir fentanyl transdermal systems, as well as products with and without rate-controlling membranes, as different dosage forms that are not pharmaceutical equivalents.

***STATEMENT OF GROUNDS***

Duragesic<sup>®</sup>, a fentanyl transdermal product, is manufactured by ALZA and distributed by Janssen Pharmaceutica Products, L.P., both of which are subsidiaries of Johnson & Johnson. Duragesic<sup>®</sup> is a reservoir (form-fill-seal) transdermal system that includes a rate-controlling membrane to regulate the rate of drug delivery. Some transdermal fentanyl products being developed, including the product described in ANDA 76-258, submitted by Mylan Technologies, Inc., use a different technology (a matrix rather than reservoir system). In addition, some transdermal fentanyl products being developed, including the Mylan product, are significantly different in composition (eg, lacking a rate-controlling membrane).

*2004P-0506*



Different types of transdermal fentanyl products (including reservoir, matrix, and those without rate-controlling membranes) can provide safe and effective treatment for pain, and matrix products do afford some advantages over reservoir products in terms of cosmetics, adhesion, and eliminating the possibility of gel leakage. However, this petition is intended to bring to the attention of FDA differences in these transdermal dosage forms that should require their classification as different transdermal dosage forms. These differences present the following issues, which are discussed in this petition:

- Because (1) matrix systems can be cut into small pieces and (2) fentanyl is more easily extracted under certain conditions from a matrix product than from a reservoir system, matrix systems present a different and possibly larger potential for abuse in the United States compared to the Duragesic<sup>®</sup> reservoir system. The societal problem of prescription drug abuse in the United States has received considerable media and regulatory attention, as exemplified by abuse of the opioid medication OxyContin<sup>®</sup>. In light of the greater ease with which fentanyl matrix systems may be diverted and abused for recreational use, FDA should require manufacturers of fentanyl matrix systems to develop and implement comprehensive risk minimization programs that successfully address the specific issues presented by their products.
- The difference in potential abuse liability and drug delivery warrants classifying matrix and reservoir systems, and systems with and without rate-controlling membranes, as different dosage forms that are not pharmaceutical equivalents so as to allow prescribers to select among products with different characteristics. Many physicians select an opioid product with a lower risk of abuse when they have concerns about potential abuse. In addition, systems that lack a rate-controlling membrane and instead rely largely on the skin to regulate the rate of drug delivery from the system may perform differently than those with a rate-controlling membrane under conditions of actual use, such as in the presence of heat or when applied to compromised skin. Some matrix and reservoir products lack a rate-controlling membrane. Pharmaceutical products that differ in design, and may perform differently from the innovator product in conditions of actual use, should not be considered pharmaceutical equivalents to the innovator product. This issue has been the consideration of at least two separate citizen petitions for transdermal products.

## **I. Background**

Fentanyl is a potent opioid analgesic, classified in Schedule II under the Controlled Substances Act. Duragesic<sup>®</sup> has been marketed in the US since 1991 and is indicated for the treatment of chronic pain in patients who require continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics, or short-acting opioids. Duragesic<sup>®</sup> has a relatively low rate of abuse, presumably related to physical features of this reservoir system, as discussed in more detail below. It is estimated that 1.4 to 1.7 million patients received Duragesic<sup>®</sup> in 2003.



The Duragesic<sup>®</sup> system utilizes a form-fill-seal design: a drug reservoir of fentanyl and alcohol gelled with hydroxyethyl cellulose that delivers fentanyl to the skin across a rate-controlling membrane, ensuring continuous controlled release of drug over the application period. Matrix designed products consist of an entirely solid material in which fentanyl is embedded in a layer of adhesive.

Matrix products do afford some advantages over reservoir products in terms of cosmetics, adhesion, and in the elimination of possible gel leakage. Janssen Cilag markets a fentanyl reservoir system (Durogesic<sup>®</sup>) outside of North America and has recently introduced a fentanyl matrix system in some European markets. As this new product is approved by local health authorities and is introduced in each new market, the reservoir product is being removed from each market. Our development of the reservoir and matrix products for ex-US markets has provided us extensive insight into the characteristics of the different types of systems. Differences in abuse or diversion potential between dosage forms are a consideration, particularly in societies such as the United States, where opioid abuse is considered to be a more substantial issue. Prior to submission of a regulatory application and subsequent marketing of Janssen Cilag's transdermal fentanyl matrix system in Europe, an assessment of local abuse potential was made. Additionally, a comprehensive set of studies was agreed with European health authorities beyond strict bioequivalence, which provided data on system performance/variability, including behavior on different skin types, to ensure that the product met regulatory requirements for safe and efficacious use, and could replace the original reservoir formulation. Specifically, these studies were: (1) single dose bioequivalence; (2) repeat dose bioequivalence and assessment/justification of PK variability; (3) PK in different skin types; (4) PK in different age groups, and (5) skin sensitization/phototoxicity.

## **II. Because of the Greater Relative Abuse Potential Associated with a Matrix Formulation, FDA Should Require a Specially Tailored Risk Minimization Plan for Matrix Systems and Should Consider Them a Different Dosage Form Than Reservoir Systems and Not Rate Them As AB Equivalent**

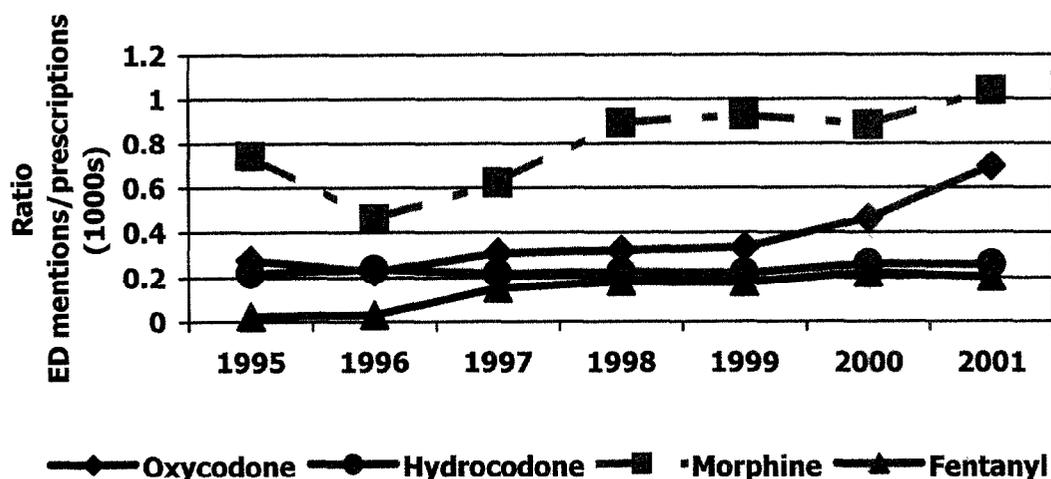
### **A. Attractiveness of Fentanyl to Abusers**

Fentanyl is an attractive target of abuse and diversion to substance abusers in the United States. Internet sites include discussions of methods and effects of fentanyl abuse. The medical literature contains reports of fentanyl abuse. Print and television news media have reported on fentanyl abuse.

Notwithstanding widespread knowledge among abusers about the potential of fentanyl and the broad (albeit strictly controlled) availability and use of Duragesic<sup>®</sup> in the United States since 1991, other opioids (such as Vicodin<sup>®</sup> and OxyContin<sup>®</sup>) have more commonly been reported as being the target of abuse in recent years. For example, an analysis of prescription opioid abuse in the US used Drug Abuse Warning Network (DAWN) emergency department mentions as a



measure of abuse, and the number of prescriptions dispensed as a measure of legitimate use.<sup>1</sup> As illustrated in the accompanying figure, the ratio of emergency room reports to prescription volume was lower for fentanyl than for other opioids, such as morphine and oxycodone.



There is concern that fentanyl abuse may be increasing in the US, and the introduction of more easily abusable dosage forms could accelerate this trend. Possible factors limiting the attractiveness of Duragesic<sup>®</sup> for abuse include (1) the relative difficulty of extracting an abusable dose of fentanyl from the Duragesic<sup>®</sup> reservoir system, (2) the recognized danger to abusers presented by their inability to control the amount of fentanyl extracted from the reservoir system, and (3) the reservoir technology, which limits the abuser to one exposure or event per system.

### B. Increased Abuse Liability of Matrix Systems

The societal problem of prescription drug abuse in the US is an important consideration in evaluating differences in abuse potential for a matrix system compared to a reservoir system. Matrix systems allow potential abusers to maintain control over the amount extracted, thus avoiding the danger of unintended overdose. Unlike a reservoir system, a matrix product can be easily cut into small discrete units, each containing a known quantity of pharmaceutical grade fentanyl, thereby permitting abusers to maintain control over the dose and avoiding highly variable and potentially fatal doses that can result when extracting fentanyl from a reservoir system.

This characteristic of the matrix technology may facilitate illicit distribution and increase the likelihood that matrix systems could achieve widespread popularity, eg, by cutting systems into “unit doses” for use as a “party drug” to be placed in the mouth and absorbed through the

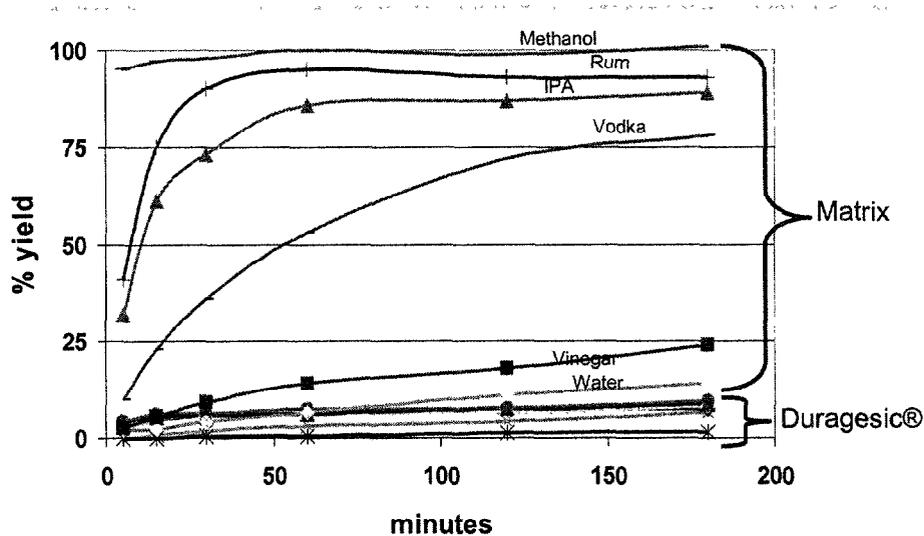
<sup>1</sup> Zacny J, Bigelow G, Compton P, Foley K, Iguchi M, Sannerud C. College on Problems of Drug Dependence task force on prescription opioid non-medical use and abuse: position statement. *Drug and Alcohol Dependence* 69:215-232 (2003).



sublingual or buccal mucosa. These small segments could also be easily hidden and saved for use at a later time. The division of matrix systems into small units for sublingual or buccal absorption could become commonplace and thus lead to a major new risk for prescription drug abuse in the U.S. Moreover, even used systems could be diverted and abused in a manner similar to fresh systems.

In addition, fentanyl for smoking or intravenous injection may be more rapidly and completely extracted from a matrix system than from a reservoir system. For example, as shown in the following figure, when Duragesic<sup>®</sup> and our own matrix system were soaked at room temperature in various common solvents, there was a much larger percentage yield of fentanyl from the matrix system than from Duragesic<sup>®</sup>.

### Room Temperature Soak

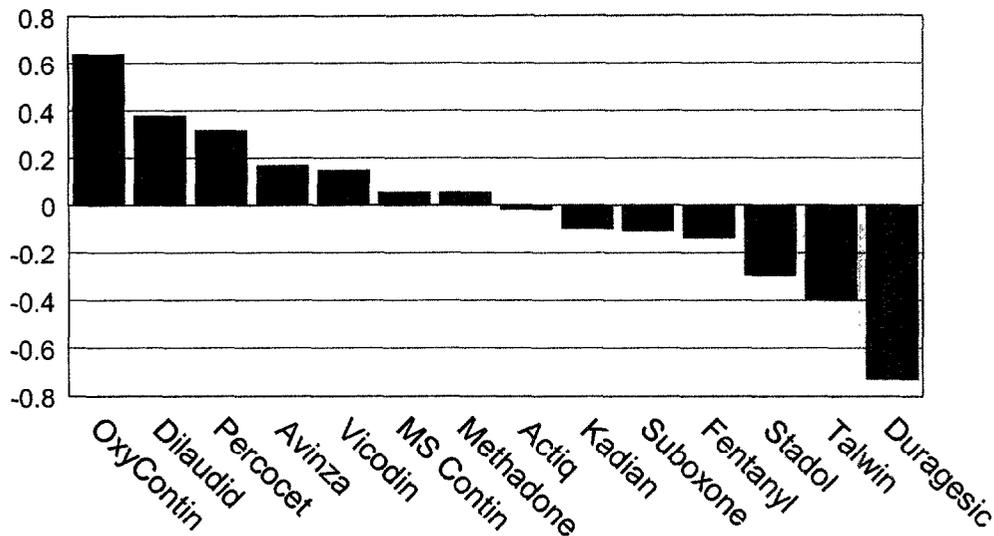


Because there was no rigorous method for comparing the attractiveness of particular prescription opioid products to potential abusers, Janssen Medical Affairs, LLC commissioned a study to develop such a scale.<sup>2</sup> Using state-of-the-art psychometric procedures, the researchers developed an index that they demonstrated was valid and reliable. Fourteen products were rated using the scale; OxyContin<sup>®</sup> was rated most attractive while Duragesic<sup>®</sup> was least attractive. As illustrated in the following figure, a fentanyl matrix system (labeled “fentanyl” in the graph) was rated as more attractive than Duragesic<sup>®</sup>. The degree of difference in attractiveness between the ratings for Duragesic<sup>®</sup> and the fentanyl matrix system was considered to be clinically significant. This measurement, by a novel and validated technique, supports the conclusion that fentanyl matrix systems may present significant new and unique abuse risks not present in Duragesic<sup>®</sup>.

<sup>2</sup> Butler SF, Budman SH, Katz N. Development and validation of a scale to measure attractiveness of prescription opioid products to potential opioid abusers. 2004.



## Average Effect Size for Each Drug with All Other Drugs



Effect Size = Cohen's D for each drug averaged across all other drugs

### C. Need for Tailored Risk Minimization Plan

Over the last few years, FDA has increasingly indicated that scheduling under the Controlled Substances Act and product labeling are by themselves inadequate to control the abuse and diversion of prescription opioid drugs. On May 5, 2004, FDA released several related draft guidance documents, including one on the development and use of comprehensive risk minimization action plans (RiskMAPs).<sup>3</sup> The draft specifically recommends development of RiskMAPs for schedule II controlled substances. A RiskMAP should include efforts to minimize overdose, abuse, addiction, and diversion.

In patent litigation involving Mylan's fentanyl matrix system, Mylan's president testified that FDA had no questions for Mylan about the abuse potential of its system and that the company conducted no studies of its abuse potential.<sup>4</sup> In light of the apparent difference between the abuse potential of Duragesic<sup>®</sup> and a matrix system, FDA should reconsider this issue and determine that appropriate data on abuse potential as well as a risk minimization action plan should be required.

This situation is somewhat similar to FDA's approval of generic versions of OxyContin<sup>®</sup>. In that case, the generic manufacturers agreed to implement risk minimization programs similar to that for OxyContin<sup>®</sup>.<sup>5</sup> Here, however, the situation is different and more concerning since fentanyl matrix products present substantial new abuse and diversion liability risks that are not applicable to Duragesic<sup>®</sup>. Based on the special attributes of fentanyl matrix products and their potential for

<sup>3</sup> Guidance for Industry: Development and use of risk minimization action plans (draft), May 2004.

<sup>4</sup> *ALZA Corp. v. Mylan Laboratories, Inc.*, Civ. File No. 02-20 (D. Vt.).

<sup>5</sup> The Pink Sheet. "OxyContin generics from Endo and Teva will include risk management plans." 66:28 (Mar. 29, 2004).



illicit use, FDA should require development of a medication guide and a comprehensive risk minimization surveillance and intervention program that addresses the features of matrix systems.<sup>6</sup>

#### **D. Treating Matrix and Reservoir Systems As Different Dosage Forms Which Are Not Pharmaceutically Equivalent**

In consulting with physicians who prescribe pain medications, we have learned that many physicians prescribe Duragesic<sup>®</sup> rather than an alternative opioid medication when they have concerns about potential abuse. Feedback from healthcare providers and attendees at advisory meetings confirms this conclusion.

The lack of a rate-controlling membrane in a matrix product might especially affect the rate of fentanyl delivery in two situations common in clinical practice but not tested for in current bioequivalence studies – in patients with compromised skin and in situations where the system is exposed to heat.

A citizen petition recently filed with FDA included the results from testing a proposed fentanyl system that lacked a rate-controlling membrane.<sup>7</sup> When the system was tested on skin that had been stripped of the stratum corneum, as might occur, for example, through removal of an adhesive bandage, the patients experienced “rapid absorption of fentanyl delivery and concentration, potentially exposing patients to toxic levels of fentanyl” that could have led to “serious injury or death” in an uncontrolled situation. Although the system “generally performed well,” it occasionally “delivered a huge overdose,” that “was traced to the lack of a rate-controlling membrane” and the setting of “stripped” skin. This behavior was seen in about 5-10 percent of the subjects, according to the petition.

A separate issue is the effect of heat. It is well established that the application of heat to a fentanyl transdermal system enhances drug delivery. This is an issue of considerable practical importance, since patients using an analgesic system may use heat pads or other heating methods to treat the pain for which the system has been prescribed, despite a warning advising patients and their caregivers to avoid exposing the Duragesic<sup>®</sup> application site to direct external heat sources.<sup>8</sup> Examples of transdermal fentanyl overdose as a result of heat – either from an external

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<sup>6</sup> Based upon European expert opinion, we believe the environment regarding prescription drug abuse in Europe differs from that in the US and a significant problem with matrix systems would not be anticipated. Nonetheless, Janssen-Cilag, the marketing arm of J&J in Europe, intends to continue to monitor and evaluate the environment to detect any early signal, should one occur. Similarly, J&J intends to monitor and evaluate the environments in other regions of the world in order to detect any early signals.

<sup>7</sup> Docket No. 2004P-0340 (submitted by Steven L. Shafer, M.D., Professor of Anesthesia, Stanford University).

<sup>8</sup> “ALL PATIENTS AND THEIR CAREGIVERS SHOULD BE ADVISED TO AVOID EXPOSING THE DURAGESIC<sup>®</sup> APPLICATION SITE TO DIRECT EXTERNAL HEAT SOURCES, SUCH AS HEATING PADS OR ELECTRIC BLANKETS, HEAT LAMPS, SAUNAS, HOT TUBS, AND HEATED WATER BEDS, ETC. WHILE WEARING THE SYSTEM. THERE IS A POTENTIAL FOR TEMPERATURE-DEPENDENT INCREASES IN FENTANYL RELEASED FROM THE SYSTEM.”



source or from high body heat caused by fever or overexertion – are documented in the literature.<sup>9</sup> The capacity for heat to increase fentanyl delivery from systems is so profound that ZARS, Inc. is developing a product that would intentionally apply additional heat to a transdermal fentanyl system to treat breakthrough pain.<sup>10</sup>

The risk from heat is not limited to patients who ignore the label warning. Patients with fentanyl systems may be exposed to common heat sources such as excessively warm cars and fever. Examples of each of these potential exposures are documented in our safety database.

If the lack of a rate-controlling membrane alters performance and allows for delivery of yet higher doses of fentanyl under the influence of heat, this could increase the risk for patients to receive excessive and potentially harmful doses of fentanyl. We did not find that effect in our own matrix product, which lacks a rate-controlling membrane, but that result is not necessarily applicable to other transdermal matrix designs that may differ in composition (eg, differing in skin-permeation enhancers or a different fentanyl load).

The issues presented by fentanyl systems that lack a rate-controlling membrane are similar to the issues currently under consideration by FDA in response to a citizen petition submitted by Boehringer Ingelheim Pharmaceuticals.<sup>11</sup> One of the concerns raised in that petition is that a proposed clonidine transdermal matrix system product, which did not contain a rate-controlling membrane, poses a safety risk because it may deliver excessive medication under certain circumstances, such as when skin temperature is elevated due to illness or exercising or when the patient's skin is abraded. FDA held a hearing on the issue in April 2003, and the concern apparently remains unresolved.

FDA recognizes differences between product types by designating them as different dosage forms. Even relatively minor differences can be the basis for regarding products as different dosage forms, eg, tablet versus capsule, cream versus lotion.<sup>12</sup> Distinctions in dosage form do not imply differences in safety or effectiveness but rather guide prescribers who seek a product with particular characteristics.

The difference in potential for abuse between the two types of transdermal systems, as well as the differentiation of systems with and without rate-controlling membranes, may be significant factors in a prescriber's selection of an opioid product. The medical community should be

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<sup>9</sup> K.A Carter, Heat-Associated Increase in Transdermal Fentanyl Absorption, *Am. J. Health-Syst. Pharm.* 60:191-192 (2003), G. Newshan, Heat-Related Toxicity with the Fentanyl Transdermal System, *J. Pain Symptom Mgmt.* 16: 277-78 (1998).

<sup>10</sup> <http://www.zars.com/titragesia.html>. Although the company initially conducted studies using its product in combination with Duragesic<sup>®</sup>, it now apparently plans to use a matrix system. FDA may have in its files information that compares the relative effect of heat on systems with and without a rate-controlling membrane, as the company states that it submitted an IND to FDA on February 6, 2003. The ANDAs submitted by Mylan and other applicants for fentanyl transdermal systems may also contain data on the effects of heat.

<sup>11</sup> FDA Docket 01P-0470.

<sup>12</sup> Dosage forms are listed at [www.fda.gov/cder/orange/uniterm.htm](http://www.fda.gov/cder/orange/uniterm.htm).



alerted to these differences through the FDA's appropriate categorization of different dosage forms that are not pharmaceutically equivalent.

#### **IV. Conclusion**

ALZA supports the approval of generic fentanyl transdermal products, and none of the actions requested in this petition would prevent FDA from approving such products. However, as discussed above, the differences between matrix and reservoir products, and products with or without a rate-controlling membrane, preclude characterizing these products as pharmaceutically equivalent dosage forms.

The potential for diversion and abuse is a concern for fentanyl products, including these different types of transdermal products. As discussed above, FDA should require tailored risk minimization programs for fentanyl matrix products, in light of their possibly greater potential for diversion and abuse in the US environment.

Public health must be considered when these products are developed and evaluated for approval. A determination that the different product types are not pharmaceutically equivalent will support the ability of prescribers to select the most appropriate type of product for their patients. Product specific risk minimization programs are needed to support the introduction of products, including fentanyl matrix products that may present a greater potential for diversion and abuse in the US environment.

#### ***ENVIRONMENTAL IMPACT***

ALZA believes that this petition is exempt under 21 C.F.R. § 25.31 from the requirement for an environmental assessment.

#### ***ECONOMIC IMPACT***

ALZA will submit information on the economic impact of the actions requested in this petition if requested by FDA.



***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 are unfavorable to the petition.

A handwritten signature in cursive script that reads "Susan P. Rinne".

Susan P. Rinne  
Vice President, Regulatory Affairs  
ALZA Corporation  
1900 Charleston Road  
P.O. Box 7210  
Mountain View, CA 94039  
650-564-3000



## ATTACHMENTS

1. Zacny J, Bigelow G, Compton P, Foley K, Iguchi M, Sannerud C. College on Problems of Drug Dependence task force on prescription opioid non-medical use and abuse: position statement. *Drug and Alcohol Dependence* 69:215-232 (2003).
2. Butler SF, Budman SH, Katz N. Development and validation of a scale to measure attractiveness of prescription opioid products to potential opioid abusers. 2004.
3. The Pink Sheet. "OxyContin generics from Endo and Teva will include risk management plans." 66:28 (Mar. 29, 2004).
4. K.A Carter, Heat-Associated Increase in Transdermal Fentanyl Absorption, *Am. J. Health-Syst. Pharm.* 60:191-192 (2003).
5. G. Newshan, Heat-Related Toxicity with the Fentanyl Transdermal System, *J. Pain Symptom Mgmt.* 16: 277-78 (1998).