



January 12, 2005

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

**Re: Docket No. 2004P-0506 (fentanyl transdermal products)**

These comments are submitted by ALZA Corporation (ALZA) in response to comments submitted by Mylan Technologies, Inc. (Mylan) on ALZA's citizen petition cited above and in response to comments submitted by Noven Pharmaceuticals, Inc. (Noven) to a different docket that nevertheless dealt with issues raised in our petition.<sup>1</sup> In our petition, we pointed out that fentanyl matrix transdermal products presented a different and potentially larger potential for diversion and abuse in the United States than the fentanyl reservoir transdermal product Duragesic<sup>®</sup>.

ALZA's petition requested that FDA require manufacturers of fentanyl matrix transdermal systems to develop and implement risk minimization programs to address the specific issues presented by their products. In addition, we requested FDA to classify matrix and reservoir fentanyl transdermal systems, as well as products with and without rate-controlling mechanisms, as different dosage forms.

We discuss below the various points raised by Mylan and Noven. First, however, ALZA wishes to refute any allegation that ALZA or any other Johnson & Johnson entity colluded with other parties who have recently filed citizen petitions pertaining to fentanyl transdermal patches, including petitions questioning whether a fentanyl matrix system may introduce safety risks or increase the potential for a fentanyl matrix patch to be abused or diverted. We did not initiate or help generate those citizen petitions, and we did not provide input, review, or advice to their

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<sup>1</sup> Noven submitted its comments to Docket No. 2004P-0472 in a letter dated December 10, 2004. In those comments, Noven stated that it would be separately commenting on the ALZA petition, but we have not yet seen those comments. We may file an additional response to Noven's comments on ALZA's petition.

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authors. The timing for submission of the other citizen petitions was the decision of their authors. Having recognized the potential for increased abuse and diversion of a fentanyl matrix patch in the United States, ALZA and Janssen Pharmaceutica conducted studies of fentanyl extraction and attractiveness early in 2004 and received further input on the potential for abuse and diversion from experts in the field of prescription drug abuse. ALZA filed a citizen petition with data suggesting that these risks are real, soon after these data were available and analyzed.

**I. Mylan and Noven Have Failed To Refute the Evidence That Fentanyl Matrix Systems Present a Larger Potential for Abuse**

In our citizen petition, we presented substantial evidence that fentanyl matrix systems present a different and possibly larger potential for abuse in the United States than Duragesic<sup>®</sup>. We showed that abusers are interested in fentanyl but that, based on databases such as DAWN, current abuse rates of Duragesic<sup>®</sup> are relatively low, presumably because of the difficulty of extracting fentanyl from a reservoir system combined with an inability to control the dose; abusers risk a fatal overdose if they abuse Duragesic<sup>®</sup>. By contrast, a matrix system permits abusers to accurately control the dose by cutting the system into a desired size, and a study on relative abuse liability submitted with our petition showed that a fentanyl matrix system would be significantly more attractive to abusers than Duragesic<sup>®</sup> in the United States.<sup>2</sup> Abusers could put a fragment of a fentanyl matrix system in their mouths for buccal or sublingual absorption, or they could extract the contents of a matrix system with common solvents for oral or intravenous administration or for smoking.

**A. Fentanyl Can Be Effectively Absorbed By Placing a Matrix System Fragment in the Mouth**

Mylan and Noven simply dismiss the possibility of buccal or sublingual absorption, arguing that their systems will not adhere to oral mucosal tissue and that, in any event, the controlled release mechanisms of their systems would prevent rapid release of fentanyl in the mouth just as they do when the systems are in contact with the skin. ALZA does not contend that a matrix system releases fentanyl faster in the mouth than on the skin. Rather, the body's absorption of the fentanyl is much faster through buccal tissue than through skin, which allows an abuser, by placing a piece of a matrix system in the mouth, to rapidly absorb an amount of fentanyl that can be controlled to avoid overdose and sufficient to create the effect desired by the abuser.

Attempted oral abuse of fentanyl transdermal systems can be expected. Indeed, oral abuse of Duragesic<sup>®</sup>, including chewing and sucking the product, is the most common type of abuse reported in our safety database.

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<sup>2</sup> Mylan's response to the concern about cutting a matrix system into pieces seems to assume, erroneously, that the issue is whether cutting the product into pieces would accelerate drug delivery. Cutting a matrix system would permit the abuser to control the fentanyl dose, thus preventing toxic or fatal amounts, whereas the inability to control the dose from a reservoir patch is apparently an important factor underlying the relatively low rate of abuse of Duragesic<sup>®</sup>.



As our petition showed, significant fentanyl can be extracted from a matrix system by water, and much higher amounts can be extracted by alcohol. Thus, it seems very likely that abusers could successfully extract fentanyl from a matrix system through its contact with saliva and common solvents.

Mylan and Noven have provided data supporting this expectation even while they deny the conclusion. Mylan states that only 15 percent of the fentanyl in its system was released in 30 minutes when soaking in water, and Noven claims that only 28 percent of the fentanyl in its system was released in an hour under stress conditions. By Mylan's admission, a matrix system that contains 10 milligrams of fentanyl could therefore release 1500 micrograms of fentanyl during a 30-minute exposure to water. Since 50 to 100 micrograms is an abusable dose, the rate of fentanyl release conceded by Mylan seems ample to allow for "party" use of pieces of a matrix system and, indeed, a matrix system could release a toxic or lethal dose. Although Mylan suggests that this release rate, which was measured in 500 ml of water, would not occur in the smaller liquid volume of saliva, Mylan does not take into account the likelihood that an abuser would chew the system fragment, potentially hastening drug release, or that an abuser could use alcohol to sharply increase drug release.

Mylan also minimizes the concern by pointing to the low oral bioavailability of fentanyl. However, although fentanyl has reduced bioavailability when swallowed, considerable drug will still enter the bloodstream. Additionally, and more importantly, fentanyl is rapidly absorbed buccally and is highly bioavailable through that route. These effects are illustrated by the following statement in the package insert for Actiq® (oral transdermal fentanyl citrate), which explains that about one-fourth of an oral fentanyl dose will be rapidly absorbed through the buccal mucosa and another fourth will be systemically absorbed more slowly after swallowing:

"The absorption pharmacokinetics of fentanyl from the oral transmucosal dosage form is a combination of an initial rapid absorption from the buccal mucosa and a more prolonged absorption of swallowed fentanyl from the GI tract. . . . Absolute bioavailability, as determined by area under the concentration-time curve, of 15 mcg/kg in 12 adult males was 50% compared to intravenous fentanyl. Normally, approximately 25% of the total dose of *Actiq* is rapidly absorbed from the buccal mucosa and becomes systemically available. The remaining 75% of the total dose is swallowed with the saliva and then is slowly absorbed from the GI tract. About 1/3 of this amount (25% of the total dose) escapes hepatic and intestinal first-pass elimination and becomes systemically available. Thus, the generally observed 50% bioavailability of *Actiq* is divided equally between rapid transmucosal and slower GI absorption."

In short, despite the incomplete oral bioavailability of fentanyl, the combination of buccal and gastrointestinal absorption would provide an ample and controllable amount of fentanyl to abusers from a piece of a matrix system held in the mouth. If sponsors of matrix fentanyl transdermal systems believe otherwise, they should be required to generate clinical data documenting the buccal absorption of fentanyl from their systems.



**B. The Extraction Study Submitted in ALZA's Petition Was Sound**

Apart from the ease with which abusers could extract a controlled dose of fentanyl through buccal or sublingual absorption from a piece of a matrix system, a study summarized in our petition showed that abusers who wanted fentanyl for injection or smoking could rapidly extract much more fentanyl from a matrix system than from a reservoir system by soaking the products in common solvents. Mylan objects to the validity of this study since it used Janssen's matrix system, which Mylan says has a different adhesive system and more fentanyl than the Mylan product.

Although the unavailability of the Mylan product required us to use the Janssen product in this study, there is no reason to believe that the different adhesive systems and fentanyl loads could be responsible for the very large differences in percentage yield between the matrix system and Duragesic<sup>®</sup>. For example, the use of rum as a solvent extracted over 90 percent of the fentanyl in the matrix system but less than 10 percent from Duragesic<sup>®</sup>.

**C. The Existence of Janssen Cilag's European Matrix System Does Not Refute the Need To Manage the Abuse Risk in the United States**

As stated in our petition, Janssen Cilag markets a matrix fentanyl system in parts of Europe. This fact, however, does not prove the lack of abuse potential of matrix systems in the United States, as Mylan argues.

Prior to a decision whether to market a matrix system, independent experts consulted by Janssen Cilag advised that the environment for prescription drug diversion and abuse in major European countries differs substantially from that in the United States and that the introduction of a fentanyl matrix system in those countries would not lead to significant increases in diversion and abuse. On that basis, Janssen Cilag concluded that a fentanyl matrix system is appropriate for Europe. Janssen Cilag is monitoring for evidence of abuse in Europe and would take appropriate action if developments warrant. By contrast to expert opinion in Europe, experts on United States drug abuse whom we consulted about our matrix product expressed substantial concern about the introduction of a fentanyl matrix system in the United States.

**D. Classifying Matrix and Reservoir Products As Different Dosage Forms Is Warranted**

In our petition, we requested FDA to classify fentanyl transdermal systems into multiple dosage forms depending on whether they use a reservoir or matrix technology and whether they have a rate-controlling mechanism. As we showed in our petition, in the case of fentanyl products, some physicians may want to select a product based on its potential for abuse, and various forms of the products may have different delivery characteristics when applied to compromised skin or in the presence of heat, even if they have been determined to be bioequivalent under normal conditions. Differentiation based on dosage form would permit clinicians to select a product with certain characteristics. Mylan asserts that FDA has already rejected this proposal by treating all nitroglycerin and nicotine transdermal products as the same dosage form.



In the case of nitroglycerin and nicotine transdermal products, there may have been no reason to distinguish among types of systems for purposes of dosage form classification, as these other types of products do not have the known potential for abuse and diversion characteristic of scheduled narcotics. As our petition showed, however, there is a different potential for abuse and diversion between matrix and reservoir fentanyl systems, and clinicians may want to select a reservoir system for some patients, for that reason.

In addition, products that lack a rate-controlling membrane may perform differently than products that have one under certain conditions, such as on compromised skin or in the presence of heat. Mylan argues that skin integrity is difficult to compromise and visible when it exists, but this argument does not exclude the real possibility that, in actual clinical use, a matrix system could be applied to compromised skin and deliver more fentanyl than a reservoir system would. Similarly, we have determined that heat applied to the Duragesic<sup>®</sup> reservoir system and the ALZA matrix system does substantially enhance fentanyl delivery, but this effect is similar for both systems; however, other products lacking a rate-controlling membrane may release significantly more fentanyl than those that have one. Furthermore, we have shown that this is not just a hypothetical consideration; the safety database contains reports of serious adverse events related to intentional or accidental heat exposure. These potential differences should be signaled to clinicians by treating the products as different dosage forms.

## **II. FDA Can and Should Require the Manufacturers of Generic Fentanyl Matrix Systems To Have Risk Minimization Programs**

Our petition requested that FDA require manufacturers of fentanyl matrix systems to adopt risk minimization programs to address the new abuse potential raised by their products. Mylan objects to ALZA's request on the ground that Duragesic<sup>®</sup> does not have such a program. Moreover, although Mylan does not contest FDA's authority to impose a risk minimization program on generic products, Noven does. These arguments do not withstand analysis.

Although there is not a formal risk management in place for Duragesic<sup>®</sup>, Janssen has consistently supported all efforts to prevent the misuse of opioid analgesics, with education as the cornerstone of the risk management programs for health care professionals, patients, and caregivers.

Examples of Janssen's education and risk management programs in the United States include:

- The National Pain Education Council (NPEC), a comprehensive online resource, educates clinicians about chronic pain management, including state-of-the-art information on appropriate usage, dosing, instructions, conversion, functionality measures, and patient types for opioid analgesics.
- Pain Chronicles Program, a series of video case studies, teaches physicians about Duragesic<sup>®</sup> patch adhesion, disposal, dosing, and appropriate patient types.



- Patient Pak, which physician office staff distribute to new patients at the onset of using Duragesic<sup>®</sup>, teaches patients about appropriate patch adhesion, disposal, and potential side effects.

Janssen also works closely with the American Pain Society, the American Academy of Pain Medicine, and the National Pain Foundation to help teach clinicians to assess and treat chronic pain appropriately.

Mylan's position that a risk minimization program is appropriate only if imposed on all fentanyl transdermal systems fails to account for the predictable difference in potential abuse liability between reservoir systems and matrix systems. As we showed in our petition, a fentanyl matrix system has a different and larger potential for abuse than a fentanyl reservoir system. This difference warrants treating the systems as different dosage forms and requiring risk minimization programs appropriate to the risks presented by each type of system.

Noven's claims about FDA's alleged lack of authority serve to highlight the value of treating matrix and reservoir systems as different dosage forms. If the innovator product and its generic copies share the same risk factors, the generics can be required to adopt risk minimization programs like the innovator's because those programs can be described in the innovator's labeling, which the generic versions are required by law to copy.

Where the generic product presents risks that are different from the innovator, however, an approach based on identical labeling is not appropriate. Instead, by declaring the generic product to be a different dosage form, FDA can, as a condition of approval of the necessary suitability petition, require that the manufacturer of a generic product adopt an appropriate risk minimization program and reflect that program in the labeling of its product.<sup>3</sup> FDA should adopt this approach to address the novel abuse potential of fentanyl matrix systems. FDA may well have other legal authorities that it could also rely on to ensure that generic products presenting new risks for abuse and diversion are subject to adequate controls.

### **III. ALZA's Petition Is Not a Last Minute Attempt To Block Generic Competition**

Contrary to Mylan's allegation that ALZA timed its petition to block generic competition despite knowing "for years" that Mylan is developing a matrix system, the fact is that, although ALZA has been developing data and information on this issue for some time, it has only recently been in a position to present the information to FDA. As FDA knows, ALZA was developing a matrix fentanyl system for the U.S. market several years ago but discontinued that plan after receiving a consultant's report on the risk of diversion and abuse of such a product in this country. ALZA then began development of a matrix fentanyl system containing naltrexone to

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<sup>3</sup> Federal Food, Drug, and Cosmetic Act, § 505(j)(2)(A)(v), (C) (permitting differences between the labeling of the innovator product and a generic product based on differences approved in a suitability petition).



reduce the risk of abuse. As part of this development effort, ALZA continued to work with consultants on abuse liability and other issues.

Much of this additional work has only recently come to fruition. The consultant who previously advised us about our own product updated the analysis on the abuse potential of matrix fentanyl systems and issued a revised report to us in late September 2004. The Butler study to develop and validate a measurement of abuse attractiveness, which was included in our petition, was started on February 1, 2004, and reported on September 24, 2004. The extraction studies reported in our petition were completed only a few months ago. Mylan's claim that ALZA could have submitted its petition years ago but delayed for competitive reasons is baseless.

Mylan's assertion that ALZA's petition is anti-competitive under a previously expressed concern of the Federal Trade Commission because it is similar to three other petitions recently submitted is a misreading of the FTC's comments and is otherwise unwarranted. The FTC staff comments cited by Mylan noted the value of citizen petitions, like ALZA's, that bring important safety issues to FDA's attention:

"Citizen petitions often raise legitimate issues concerning matters within the agency's jurisdiction. In fact, issues raised in citizen petitions have played useful roles in ensuring the safety of various drug products."<sup>4</sup>

In the case of "cumulative or duplicative petitions," the FTC staff suggested only that FDA might want to require identification of similar petitions so that FDA could "potentially ease its burdens by allowing it to consolidate the petition with other pending petitions or to respond to the petition more quickly."<sup>5</sup> Mylan has identified the petitions for FDA, thus satisfying the FTC staff's recommendation.

Neither ALZA nor any other unit of Johnson & Johnson caused the submission to FDA of the other citizen petitions addressing the risks associated with fentanyl matrix systems. These petitioners acted independently out of concern for the issues they raised. There is no basis for Mylan's suggestion to the contrary.

#### **IV. Conclusion**

As stated in our petition, ALZA supports the approval of generic fentanyl transdermal products, but the approvals should be accompanied by suitable controls and information. Manufacturers of matrix systems should be required to adopt risk minimization programs that deal with the specific new abuse risks presented by their products. In addition, FDA should treat matrix and reservoir systems, and those with and without rate-controlling membranes, as different dosage forms to allow clinicians to select products with the characteristics they desire.

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<sup>4</sup> FTC comments at 3 (attached to the Mylan comments).

<sup>5</sup> FTC comments at 3, 7.



Mylan and Noven have presented no persuasive arguments against these requests. Their insistence that matrix products do not pose an increased abuse potential is not supported by any data and is refuted by the available information, including data submitted by Mylan and Noven on extracting fentanyl from their own systems. The information indicates that abusers can obtain controlled, i.e., abusable *and* nonlethal, doses of fentanyl if they place product pieces in their mouths, and that fentanyl is more easily extracted from matrix patches than from Duragesic<sup>®</sup>. This increased abuse potential is a serious risk that FDA should address by requiring risk minimization programs and treating the products as distinct dosage forms.

Sincerely,

A handwritten signature in black ink that reads "Susan P. Rinne".

Susan P. Rinne  
Vice President, Regulatory Affairs