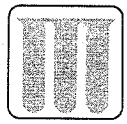

MYLAN LABORATORIES INC.

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July 21, 2006

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

Re: CITIZEN PETITION: Risk Management Program for Fentanyl Products

Dear FDA Officer:

Mylan Laboratories Inc. ("Mylan" or the "Petitioner") submits this citizen petition in accordance with 21 C.F.R. § 10.30 and the Federal Food, Drug & Cosmetic Act, 21 U.S.C. § 355.

I. SPECIFIC ACTION REQUESTED

The Petitioner requests the Agency determine the necessity for a Risk Management Program for transdermally administered fentanyl drug products. If the Agency determines a Risk Management Program is necessary, the petitioner requests the Agency to develop and adopt a single, unified Risk Management Program for all transdermal fentanyl drug products based on input provided by all sponsors of approved marketing applications for transdermal fentanyl products.

As with other marketed opioid products, Mylan believes that a Risk Management Program for prescription fentanyl transdermal patches, may provide additional safeguards for assuring that this form of pain medication is used safely and in accordance with FDA-approved labeling. As currently in place for Actiq® (oral transmucosal fentanyl citrate), Mylan further believes that a more active program of education and communication to healthcare providers and patients about risks, beyond the current FDA-approved labeling for Duragesic® and its generic equivalent fentanyl transdermal patch, could benefit healthcare providers and patients, reduce abuse risks and enhance proper use and overall safety.

At FDA's request, Mylan provided a conceptual outline of a Risk Management Program pertaining to transdermally administered fentanyl products during a September

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7, 2005 meeting with the FDA and is still awaiting feedback from the Agency on that proposal. Should FDA determine that a Risk Management Program, above and beyond the existing labeling, patient information and pharmacovigilance, is needed, the petitioner submits that any such Risk Management Program for fentanyl should be developed with the participation of all approved product sponsors and be implemented as a single, unified, comprehensive program. As discussed in detail below, the history of Risk Management Programs has demonstrated that when such programs are conducted on an individual basis with each drug company developing its own program, there is a substantial risk of customer confusion and the process of establishing any necessary monitoring or evaluation components of the program becomes more difficult. Moreover, as discussed in detail below, if the distribution of fentanyl is deemed to require the implementation of a Risk Management Program, that program should extend to all of the various dosage forms in which fentanyl is distributed, rather than focusing solely on the oral transmucosal and transdermal patch dosage forms. Recognizing that each dosage form may have unique attributes that require special attention, there should be a general overall Risk Management Program for fentanyl plus a component that is specific to each dosage form which includes product specific attributes relative to the individual dosage form (e.g., transdermal system, oral transmucosal dosage form, injectable dosage form, etc.) At a minimum, all fentanyl transdermal systems should have a single, unified Risk Management Program.

II. STATEMENT OF GROUNDS

1. Additional Education and Communication to Healthcare Providers and Patients Regarding the Proper Use of Fentanyl Drug Products Would Enhance the Safety of All Fentanyl Drug Products.

Fentanyl is a Schedule II opioid drug with a high medical risk of death or serious adverse events, and a high risk of abuse. As stated in FDA's July 15, 2005 Public Health Advisory, notwithstanding the existing product label and patient package insert, "[s]ome patients and health care providers may not be fully aware of the dangers of this very strong narcotic painkiller." A single, unified Risk Management Program for fentanyl drug products that incorporates a component of additional, active communication to prescribers and patients should help increase awareness of the potency and general abuse potential of these drug products.

Mylan has taken steps to try to enhance patient and prescriber awareness of the risks of fentanyl, beyond providing the FDA-approved patient package insert ("PPI") and prescribing information. For example, in July 2005, Mylan developed a patient brochure (not a formal PPI) entitled, "A Clear Choice – A Guide to Proper Application and Use." A copy is attached as **Exhibit 1**. Mylan has mailed a total of approximately 475,000 brochures to drug wholesalers, retail pharmacies and individual patients. In addition, Mylan provides on its distributing subsidiary's internet website, *www.mylanpharms.com*, links to the full prescribing information, FDA's safety advisory and patient application instructions. Further, Mylan proposed revised labeling to FDA for its Fentanyl Transdermal System product that would have further highlighted existing risk

information but, because Mylan's application is an ANDA and its product labeling is required to correspond with that of the NDA product, FDA would not permit the change absent a corresponding change initiated by the NDA holder. Additionally, at a September 7, 2005 meeting with Agency representatives from the Office of Generic Drugs, Office of Drug Safety, and others, Mylan provided, at FDA's request, a conceptual outline of a Risk Management Program pertaining to fentanyl transdermal patches. While Mylan is awaiting the Agency's feedback on that proposal, Mylan wishes to highlight through this citizen petition additional issues the Agency should consider in developing an appropriate plan.

By filing this petition, Mylan should not be understood to suggest that fentanyl transdermal patches have a relatively high risk of potential abuse compared with other fentanyl drug products or other opioid drug products or that existing labeling is inadequate. To the contrary, transdermal fentanyl patches, particularly when the transdermal patch incorporates fentanyl in a matrix (as opposed to a reservoir) design, do not pose a significant risk of abuse, as FDA previously determined in rejecting citizen petitions on January 28, 2005. *See* **Exhibit 2**, January 28, 2005 FDA Consolidated Response to Four Citizen Petitions at FDA Docket Nos. 2004P-0506/CP1; 2004P-0472/CP1 & SUP1; 2004P-0540/CP1; and 2004P-0340/CP1, at 6 ("the matrix system does not raise product-specific abuse concerns."). Fentanyl transdermal patches (principally Alza Corporation's Duragesic®) have been marketed since the early 1990's without the necessity of a Risk Management Program, other than the passive education and communication program encompassed in the FDA-approved product labeling and prescriber and patient information. Further, Mylan is submitting a Controlled Correspondence to the Agency regarding its approved Abbreviated New Drug Application No. 76-258, summarizing all case reports of death associated with the use of Mylan's Fentanyl Transdermal System. The data summarized in Mylan's submission demonstrates "no new risk signals or adverse event trends associated with Mylan FTS." *Id.* Mylan also notes that, in adopting a new Risk Management Program, FDA should of course be cognizant of the potential burdens associated with such plans *See* **Exhibit 3** Speech before the American Medical Association, Remarks by Scott Gottlieb, M.D., Deputy Commissioner for Medical and Scientific Affairs, dated June 12, 2006 (describing the cumulative burden imposed by possible overuse of risk management plans); **Exhibit 4** (Guidance for Industry: Development and Use of Risk Minimization Action Plans) at 5 (RiskMAPs should "be used judiciously to minimize risks without encumbering drug availability or otherwise interfering with the delivery of product benefits to patients").

2. Any Fentanyl Risk Management Progam Should Be Developed as a Single, Unified Program Involving All Sponsors of Applications.

Fentanyl drug products are currently approved in multiple dosage forms. Fentanyl transdermal patches are currently being manufactured by two holders of approved applications, Alza Corporation and Mylan. Alza's NDA product is currently distributed under the trade name Duragesic®, as well as in an un-branded, "authorized generic" version by Sandoz. Mylan's ANDA product is currently distributed by Mylan

Pharmaceuticals Inc. Additional market entry by other manufacturers of fentanyl transdermal patches is certainly possible, if not likely. Therefore, in the absence of a single, unified Risk Management Program, individual fentanyl users and prescribing physicians would be exposed to multiple separate educational messages if each manufacturer developed and adopted its own Risk Management Program for fentanyl transdermal patches. This exposure to multiple messages from manufacturers is particularly salient when there is the potential for multiple generic producers of the product. In those circumstances, a particular patient may change from system to system as the pharmacy's purchasing patterns change, and as patients choose to fill prescriptions from different pharmacies over the course of treatment.

In its Guidance to Industry, FDA has indicated the importance of including all involved parties from the beginning of the development of Risk Management Programs. As FDA states:

> Involving all stakeholders during the initial phases of considering whether a RiskMAP is appropriate allows input and buy-in by all parties who will later have roles in implementing the RiskMAP. If a RiskMAP is appropriate, stakeholders can help shape the RiskMAP to foster its success in the healthcare delivery environment.

Exhibit 4, at 7.

There are two approved applications for fentanyl transdermal patches and the sponsors have each met independently with FDA to discuss risk management issues. However, there has been no request that the two sponsors work together on addressing risk management issues although the petitioner has suggested this approach to FDA, a suggestion that is consistent with FDA's own comments stated above.

FDA's recent experience with Risk Management Programs suggests that, where a product that is subject to such a plan is being distributed by multiple companies, there is the potential for consumer confusion, particularly in situations where they may switch brands during the course of ongoing therapy. This potential confusion was the subject of testimony on February 26, 2004 before the FDA Drug Safety and Risk Management Advisory Committee. *See* excerpt, **Exhibit 5,** at 44 (differences between plans "have caused marketplace confusion" and "mid-course changes by the patient's pharmacy provider in brand of isotretinoin dispensed can result in patient confusion") (complete transcript available at *www.fda.gov/ohrms/dockets/ac/04/transcripts/4017T1.pdf*). As a result of the experience with multiple Risk Management Programs, a centralized program for isotretinoin, which was required by FDA, has now been developed and implemented. *See* **Exhibit 6**, FDA White Paper dated July 8, 2004, "Isotretinoin Teratogenicity Risk Management Program."

Developing a unified Risk Management Program for fentanyl drug products would eliminate the potential patient confusion created by separate corporate educational programs and, therefore, avoid the risk that patients would be confused and possibly

endangered by changes in providers. Moreover, to the extent that FDA envisions the need either now or in the future for any sort of evaluation or monitoring program, establishing a single, unified Risk Management Program would facilitate the evaluation and monitoring process. Because the use of a single, unified Risk Management Program would provide these benefits and not impose a substantially greater burden on the companies selling fentanyl transdermal systems, FDA should work with sponsors towards the development of such a program.

3. Any Fentanyl Risk Management Program Should Be Comprehensive

As addressed in the earlier citizen's petitions concerning the issue of potential Risk Management Programs for fentanyl, there is no indication that the transdermal patch dosage form is particularly or uniquely vulnerable to abuse. In fact, there is significant abuse potential associated with the transmucosal form (Actiq®) and the injectable form of fentanyl and it is acknowledged that a Risk Management Program is currently in place for Actiq. Therefore, to the extent that FDA determines that fentanyl presents the need for the implementation of a Risk Management Program, that plan should encompass all of the dosage forms in which fentanyl is prescribed rather than focusing on just the oral transmucosal and transdermal dosage forms. *See* Exhibit 4 (Guidance for Industry), at 7 (indicating that opiate drug products generally are associated with significant risk of overdose, abuse and addiction and, therefore, FDA "recommends that sponsors" "consider developing RiskMAPs for these products"). Such a program could also provide dosage form specific attributes that address issues unique to each specific dosage form.

The development of a single, comprehensive, uniform Risk Management Program would be of particular utility for FDA to evaluate the effectiveness of such program in minimizing risk and to determine the factors that contribute to or create safety risk. Involving all fentanyl sponsors in a Risk Management Program permits the success of the program to be more easily measured and facilitates the identification of potential weaknesses or contributors to program failures by using data from all products. Such an approach would also allow FDA to more easily compare the risk between two products and determine whether there are any greater risks associated with a particular product or product design. For example, because of the differences in the formulations of the reservoir and matrix patches, there may be differences in risk that could be best evaluated in a comprehensive program. For example, the effect of total drug content in a fentanyl product on safety is currently unknown. While both the Mylan fentanyl matrix transdermal system and Duragesic have approximately the same total drug content, it is possible that future approvals for other transdermal products may have higher total drug content. At this time it is not known if a higher total drug content has the same safety profile as a product with a lower drug content. Because of these issues, a single, unified Risk Management Program for fentanyl transdermal systems would be the best approach to assess the contributions of different factors such as product design elements versus the risk associated with fentanyl itself thereby minimizing risk for these products.

III. ENVIRONMENTAL IMPACT

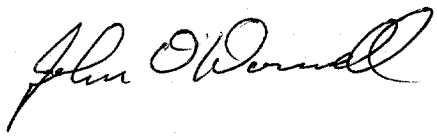
Not applicable.

CERTIFICATION

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

Sincerely,

MYLAN LABORATORIES INC.



John P. O'Donnell, Ph.D.,
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