MYLAN TECHNOLOGIES INC.

July 24, 2007

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

Re: Petition for Stay of Action

Dear Sir/Madam:

Pursuant to FDA regulations governing administrative stays, 21 CFR § 10.35, Mylan Laboratories Inc. ("Mylan") submits this petition for stay of approval of all applications for fentanyl transdermal delivery systems until the Food and Drug Administration (FDA) reaches a decision on Mylan's petition requiring that all such applicants conduct a study to support the safe use of an overlay with their respective patches (Mylan's Petition).

Notably, during a 2006 face-to-face meeting with the Agency regarding Mylan's Petition in which Associate General Counsel, Sheldon Bradshaw, Director of Office of Generic Drugs, Gary Buehler, PhD., and former Deputy Commissioner of Medical and Scientific Affairs, Scott Gottlieb, MD were present amongst others, the Agency explained that petitions raising policy issues would not prevent approvals of pending applications; whereas petitions that raise safety issues do. Mylan's Petition raises a significant safety issue regarding fentanyl transdermal delivery systems.

A. Pending Action

It has come to Mylan's attention that one or more pending applications under § 505(j) for fentanyl transdermal systems may be imminently approved by the Office of Generic Drugs. While Mylan has not yet substantiated this information, the possibility, however remote, that a fentanyl transdermal system can enter the market without the proper overlay raises significant safety issues.

2006P-0123

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B. Action Requested

Mylan respectfully requests that the Commissioner stay approval of all applications for fentanyl transdermal systems until FDA reaches a decision on Mylan's Petition requiring all applicants and holders of approved applications for fentanyl transdermal systems (patches) to (1) conduct a study to support the safe use of an overlay with their patches and (2) include information in their labeling regarding the type of overlay(s) that may be used with their respective fentanyl patches.

Alternatively, Mylan respectfully requests that the Commissioner stay approval of all pending fentanyl applications until the FDA has concluded the review of the innovator's Ortho-McNeil[1] supplement labeling for the use of an overlay system in connection with their fentanyl transdermal system.

Mylan's position is not frivolous, is being pursued in good faith, and has demonstrated sound public grounds supporting its requests. Additionally, the stay is not outweighed by public health or other public interests, and Mylan will suffer irreparable harm if a stay is not granted, in that the integrity of the fentanyl transdermal systems will be severely compromised regardless of the sponsor marketing this important drug product.

C. Statement of Grounds

Mylan has developed and received approval for a generic fentanyl transdermal system that is bioequivalent to Duragesic® (fentanyl transdermal system) with respect to both rate and extent of absorption. On March 16, 2006, Mylan submitted a petition under § 505 of the Federal Food Drug and Cosmetic Act, and 21 C.F.R. § 10.30 to request that the FDA require all applicants and holders of approved applications for fentanyl transdermal systems conduct a study to support the safe use of an overlay with their patches ("Citizen Petition"). The FDA assigned Mylan's petition docket number 2006P-0123/CPI.

Mylan's Citizen Petition raises significant safety concerns about the use of an untested overlay system with fentanyl transdermal systems. In this Petition, Mylan highlighted the potential danger associated with the use of an untested overlay system and provided information on the types of untested devices patients were using to maintain adhesion (such as duct tape and other unsafe means of affixing the patch to the skin). Accordingly, Mylan urged the FDA to require all applicants and holders of approved applications for fentanyl transdermal systems to conduct a study to support the safe use of an overlay system.

The FDA clearly recognizes the potential for inadvertent delivery of higher-than-anticipated amounts of fentanyl. Indeed, the FDA Alert for Healthcare Professionals in July 2005 highlighted this concern. As evidenced by this Alert, the patch may have

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[1] The innovator's product, Duragesic® is manufactured by Alza. It is marketed by Pricara, a unit of Ortho-McNeil.

problems "sticking" to the skin. Some patients have taken this problem in their own hands by using some type of an overlay to help the patch stick to the skin. The use of an unapproved and untested overlay may cause adverse consequences. Therefore, Mylan believes that in order to assess potential risks associated with the use of an overlay with any fentanyl transdermal system, the Agency should require all applicants and holders of approved applications for fentanyl transdermal systems to conduct a study to support the safe and appropriate use of an overlay with their respective patch.

Recognizing these safety risks concerning fentanyl transdermal delivery systems, Mylan initiated and completed its own study and submitted a supplement to its Petition. In this Petition Supplement, submitted under 21 C.F.R. § 10.30(g), Mylan provided evidence from its clinical study that demonstrates that an application of a Bioclusive™ overlay system with the Mylan fentanyl transdermal system does not alter the rate and extent of absorption of fentanyl from the patch. In addition, the study concludes that the use of a Bioclusive overlay system is an effective mechanism to ensure continuous contact between the patch and the skin. Further, in this supplement, Mylan also provided specific examples of proposed labeling to properly inform healthcare professionals and patients on the appropriate and safe use of an overlay system with Mylan's fentanyl transdermal system.

Importantly, the results of Mylan's clinical study clearly indicate that the Mylan fentanyl transdermal system with a Bioclusive overlay system is bioequivalent to the Mylan fentanyl transdermal system without a Bioclusive overlay. Moreover, the study indicates that continuous adhesion is maintained with the use of a Bioclusive overlay system. By requiring applicants and holders of approved applications to conduct similar clinical studies, FDA will be assured that use of a specifically identified and tested overlay system with their respective patch does not alter drug delivery and can be used as an intervention to overcome "lack of adhesion".

In addition, with the data generated from a study to support the use of an overlay system, FDA should require all applicants and holders of approved applications to provide information in their respective labeling that identifies which overlay system was tested and, therefore, considered appropriate for use. This will ensure that the public, including, physicians prescribing the product, pharmacists dispensing the product, and patients using the product, have sufficient information to make an informed decision on the appropriate overlay to be used if a patch does not stick to the skin. In its Petition, Mylan provided the FDA examples of the type of language that should be added to the labeling to appropriately inform the public on the correct use of an overlay system for a specific fentanyl transdermal system.

Subsequently, on July 20, 2006, the innovator, Ortho-McNeil, submitted a comment to Mylan's petition concurring with our request that FDA require applicants for fentanyl transdermal systems to conduct a study determining the effect of an overlay system with their respective patches. (See Comment 1). Here, the innovator emphasized that "mandating such data will enhance patient safety and reduce the potential for serious adverse consequences should a patient use a product capable of releasing higher rates of

fentanyl when an overlay dressing is applied to support adhesion in situations where occlusive overlay is needed."

Following Ortho-McNeil's comment to FDA, Mylan promptly filed another supplement to its petition reiterating its request to require all applicants and holders of approved applications for fentanyl transdermal systems to conduct a study[2]. (See Supplement 3 filed August 9, 2006). With the innovator concurring with Mylan, we believed that the resolution of the Citizen Petition was imminent. However, on September 12, 2006, to Mylan's complete surprise and disappointment, FDA provided only a tentative response indicating that it has been unable to reach a decision on Mylan's petition.

In light of the lack of a decision by the Agency on the Citizen Petition, Mylan requested the Agency to schedule a meeting with all stakeholders to discuss the resolution of the Petition. On March 22, 2007, the Agency held a meeting with the sponsors, but no resolution was provided by the Agency.

It is now our understanding that the innovator has submitted a labeling supplement that includes information on the safe use of an overlay system. Accordingly, once the innovator's labeling supplement is approved, all pending and approved applications for a fentanyl transdermal system must have the same labeling, thereby requiring a study to be conducted for purposes of determining the effect of an overlay system prior to approval.

We have recently heard from various sources in the market place that another fentanyl transdermal system may be imminently approved by the Office of Generic Drugs. Although we have not yet substantiated this information, the possibility, however remote, that a fentanyl transdermal system enters the market place without the proper overlay testing raises safety concerns that outweigh any delay resulting from the stay requested herein.

The Commissioner Should Grant Mylan's Request For A Stay

The FDA has always recognized that fentanyl, and fentanyl transdermal systems, carry both substantial benefits and risks. Duragesic is an analgesic patch that is designed to control severe pain by releasing a strong opioid analgesic through the skin over a period of 72 hours. "Duragesic is indicated for management of persistent, moderate to severe chronic pain that: (i) requires continuous, around-the-clock opioid administration for an extended period of time; and (ii) cannot be managed by other means such as non-steroidal analgesics, opioid combination products, or immediate-release opioids". Duragesic Labeling ("Black Box Warnings").

With a potent narcotic such as fentanyl, any change in absorption of fentanyl may result in adverse consequences. A patient who seems to be tolerant on a fentanyl patch

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[2] In this Supplement Mylan also provided evidence from a clinical study using an overlay manufactured by its medical product division which it proposes to distribute to patients upon request.

(with poor adhesion) may suddenly not be tolerant because of the use of an overlay on a subsequent fentanyl patch. The chances of a patient receiving variable amounts of fentanyl from patch to patch, when intermittently using the same or different overlays, are significantly high because a fentanyl transdermal system is only prescribed for chronic pain and a patient will most likely use multiple patches throughout the course of therapy. This uncontrollable cycle of different amounts of absorption of fentanyl from patch to patch due to the use of an overlay may unjustifiably increase patient risk.

For these reasons among others, applicants and holders of approved applications for fentanyl transdermal systems should conduct a study to determine the effect of overlays with their respective patches. Furthermore, the approved labeling should include appropriate information on the type of overlay(s) which may be used with the respective fentanyl patch.

Without any studies to support the safe use of a specific overlay, patients using an untested overlay with fentanyl transdermal systems may be more prone to risks associated with variable performance of fentanyl patches. A product like fentanyl transdermal systems already require close monitoring of the amount of the drug delivered as well as strict adherence to the specific directions for use. By requiring applicants and holders of approved applications to conduct a study to support the use of an overlay with their respective fentanyl transdermal system, FDA will be assured not only that an overlay poses no safety or efficacy issues, but also that patients have an approved overlay which they can safely use.

The possibility of a fentanyl transdermal system entering the market which may be used with an untested overlay system raises significant safety concerns that far outweigh any stay of approval of a pending application for fentanyl transdermal system.

Further, Mylan would be disadvantaged if the FDA approved fentanyl transdermal patches without requiring the necessary studies on the use of an overlay, and then subsequently the FDA approves the innovators label supplement. In this situation, the applicant would not have conducted the necessary studies and would nevertheless be permitted in the market with a product that is less safe and that could potentially cause more confusion on which products and types of overlays can be used. These overlays should not be used interchangeably. In fact, there is a chance that patients or health care professionals may use an overlay tested by Mylan and/or the innovator with the interim approved product which could put Mylan at a disadvantage while compromising patient safety.

To date, the FDA's action and inaction on this important matter is troubling. On the one hand, at least one division of the Agency is currently reviewing a labeling supplement to enhance patient safety by mandating data from a clinical study, and on the other hand, another division is approving a product without requiring such data. These conflicting and competing scenarios within the Agency in no way comports with any plausible interpretation of FDA's regulatory scheme to facilitate patient safety.

D. Conclusion

For the reasons set forth herein, we request that the Commissioner not approve any fentanyl transdermal systems until that system has been properly tested with a proven overlay system which does not alter the release rates of fentanyl during administration. In the alternative, Mylan requests that the Commissioner stay the approval any fentanyl transdermal systems until the Agency has concluded the review of the innovator's supplement labeling for the use of an overlay system in connection with a fentanyl transdermal patch.

In the event that FDA fails to review or grant this petition for stay, or that it fails to communicate that fact in a timely fashion to Mylan, we would effectively be without the availability of an adequate administrative remedy. Accordingly, immediate judicial intervention would be justified.

Respectfully submitted,

Carolyn Myers, Ph.D.
President
Mylan Technologies Inc.

cc: Associate General Counsel, Sheldon Bradshaw
Director of Office of Generic Drugs, Gary Buehler, Ph.D.