MYLAN LABORATORIES INC.

March 16, 2006

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20857

CITIZEN PETITION

Mylan Technologies Inc. ("Mylan") submits this petition under section 505 of the Federal Food, Drug, and Cosmetic Act, and 21 C.F.R. § 10.30 to request that the Commissioner of the Food and Drug Administration (FDA) require that all applicants for fentanyl transdermal systems conduct a study to support the safe use of an overlay with their respective fentanyl transdermal product.

ACTION REQUESTED

Mylan has developed a generic fentanyl transdermal system that is bioequivalent to Duragesic® (fentanyl transdermal system) with respect to both rate and extent of absorption. In addition to a bioequivalence study, Mylan also conducted several studies of active and/or placebo systems to assess irritation and sensitization potential, which were found to be no greater than that of Duragesic. Based on the data analyzed from these studies, it was concluded that Mylan's fentanyl transdermal system and Placebo Transdermal Systems adhered as well as Duragesic.

However, as evidenced by the July 2005 FDA Alert for Healthcare Professionals, the patch may have 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, as Mylan is currently undertaking. The basis for this request is described in more detail below.

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STATEMENT OF GROUNDS

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").

A review of the summary basis of approval (SBOA) of Duragesic reveals that the vast majority of data submitted to FDA by the innovator was based on application of the patch for approximately twenty-four hours (24hr) and not seventy-two hours (72hr). *See* Medical Officer Review, NDA #19,813, TTS Fentanyl (Transdermal Therapeutic System), Volume I - Clinical Efficacy Studies. This seems to suggest that the initial design of Duragesic may have been to establish adhesion for limited duration. Apparently, during the later stages of development, there was a shift toward longer wear periods (up to 72hr) and thus the design of Duragesic was approved by FDA for a wear period longer than perhaps originally envisioned.

According to published IMS data, the use of fentanyl transdermal systems has steadily increased over the years. *See* IMS Health, National Sales Perspective Audit, Transdermals, December 2005 (Since 2001, the number of doses dispensed has increased from approximately 32 million to 67 million in 2005). Originally, Duragesic was used to manage severe chronic pain in cancer patients; however, the use of Duragesic has since increased to manage other types of severe chronic pain, such as lower back pain. *See* Ringe J.D. et al., *Transdermal Fentanyl for the Treatment of Back Pain Caused by Vertebral Osteoporosis*, Rheumatol Int. 22:199-203 (2002). Patient complaints about the "poor adhesion of the patches to the skin" continue to occur. *See* FDA Alert for Healthcare Professionals, *Fentanyl Transdermal Patch (marketed as Duragesic), Narcotic Overdose and* Death, July 2005. Well prior to this, however, the innovator[1] recognized "lack of adhesion" as a problem and as a potential solution offered (and continues to offer) directly to patients upon request, a Bioclusive® overlay to help the patch stick to the skin. *See HealthBoard.Com, Message Boards on Health Related Topics* (visited March 9, 2006), http://www.healthboards.com/boards/showthread.php?t=80663&page=1&pp=5 .

[1] Alza Corporation is the holder of the Approved New Drug Application for Duragesic; however, Duragesic is distributed by Janssen Pharmaceutica Product, L.P.

Mylan concurs with FDA that "poor adhesion" is a potential problem. However, Mylan is unaware of whether the innovator has conducted any studies to support its recommendation to patients for the use of an overlay. Mylan believes that in order for the innovator to supply an overlay, there must be a supporting study and corresponding FDA approval for the safe use of this extension of the formulation. Similarly, this would be an anticipated requirement for any approved generic formulation of a fentanyl transdermal system. Without such a requirement, the assessment of the potential risks associated with an overlay will remain an open topic.

Transdermal Delivery is Dependent on Adhesion

Transdermal drug delivery through a patch may offer significant clinical benefits over other dosage forms. *See* Ryan D. Gordon, PhD, and Tim A. Peterson, MS, *4 Myths About Transdermal Drug Delivery,* Drug Delivery Technology, www.drugdeliverytech.com/cgi-bin/articles.cgi. Some of these benefits include: controlled release of the drug into the patient, a steady blood-level profile, user-friendly, and multi-day dosing. *Id.* Although transdermal delivery may have its benefits, misuse of a fentanyl transdermal system has its own risks. "Fentanyl transdermal patches are potent opioid analgesics that should only be used by opioid tolerant patients who are already taking other narcotic analgesics, and who have chronic pain that is not well controlled with shorter-acting analgesics." FDA Alert for Healthcare Professionals, July 2005.

What seems to be recently recognized by the innovator is that the adhesive matrix dosage form (currently marketed in Europe) may represent an advance in technology, being inferred to be superior to their reservoir technology. *See* Gayatri Sathyan, Cindy Guo, et al., *Evaluation of the Bioequivalence of Two Transdermal Systems Following Single and Repeat Applications*, Current Medical Research and Opinions, 21(12):1961-1968 (2005). While the innovator appears to have developed a matrix and has reported bioequivalence to its reservoir formulation, they also report that the matrix system may have advantages such as consistent delivery, smaller and thinner, more flexible, and lays flatter to the skin. *Id.* The innovator's matrix formulation shares many of the same attributes as Mylan's FDA approved generic fentanyl transdermal system[2].

Irrespective of the design of the fentanyl patch, however, the patch must continuously "stick" to the skin in order to work as designed. *See* Amir Mehdizadeh and Tayabe Toliate, et al., *Design and In Vitro Evaluation of New Drug-In Adhesive Formulations of Fentanyl Transdermal Patches*, Acta Pharm. 54:301-317 (2004). The drug from the fentanyl patch is released to the upper layer of the skin, known as the stratum corneum, controlling the rate and amount of the drug which will be delivered into the bloodstream. Because the stratum corneum is the major barrier within the skin that

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[2] However, one of the key differences between the innovator's matrix formulation and Mylan's formulation is that the acrylic adhesive used by the innovator contains significantly greater amount of drug in the patch, which makes it more susceptible to other potential safety issues. Durogesic® DTrans® 25/50/75/100 Transdermal Patch Labeling ("Qualitative and Quantitative Composition") – "Each Durogesic DTrans 25/50/75/100 patch contains fentanyl 4.2/8.4/12.6/16.8mg." In contrast, Mylan's fentanyl patch contains 2.55/5.10/7.65/10.20mg of fentanyl, respectively.

controls the rate and amount of drug delivered, the structural integrity of the stratum corneum must be maintained. *See* Hongbo Zhai and Howard Maibach, *Occlusion vs. Skin Barrier Function*, Skin Research and Technology 8:1-6 (2002). "Transdermal absorption occurs through a slow process of diffusion driven by the gradient between the high concentration in the delivery system and the zero concentration prevailing in the skin". Stanley Scheindein, *Transdermal Drug Delivery: Past, Present, Future, Reflections*, Molecular Interventions, Science in the Culture Context, 4(6):308-312 (2004)[3].

A review of various postings on the internet (message boards) indicates that patients also realize the importance of adhesion and because there is no FDA approved device, patients are tackling the adhesion issue on their own. *See HealthBoards.Com, Message Boards on Health Related Topics* (visited March 9, 2006), http://www.healthboards.com/boards/shothread.php?t=8063&page=1&pp=5; *see also eHealth Forum, How to Keep Duragesic Patches Attached and Waterproofed* (visited March 9, 2006), http://www.ehealthforum.com/health/topic27226.html. Patients have tried everything from "athletic tape" to "waterproof band aids" in an attempt to make sure that the fentanyl patch continues to stick to the skin. *Id.* Some patients have even tried using tape to remove the hairs and oil from the application site in an effort to make the patch stick, which is clearly in contradiction to the approved labeling. *See Duragesic Patches Don't Stick* (visited March 9, 2006), http://www.usenet.derkeiler.com/Archive/Alt/alt.support.chronicpain/2005-11/msg02176.html. In theory, patients' actions may be justified; however, the use of an untested combination of a device with a patch poses potential risks such as the potential for irritation of the skin. The innovator seems to have recognized adhesion as a problem and therefore, has facilitated the availability of a Bioclusive overlay for patients to use to correct adhesion[4].

Occlusion, however, which typically refers to "skin covered directly or indirectly by impermeable films or substances such as diapers, tape…" is sometimes also used to enhance the delivery of drug into the bloodstream. Because of the permeation limitation provided by the stratum corneum, occlusion is widely utilized to enhance the penetration of applied drugs. *See* Zhai and Maibach, *Occlusion vs. Skin Barrier Function*. "The effects of occlusion on skin are complex, and may produce profound changes including altering epidermal lipids, DNA synthesis, epidermal turnover, pH, epidermal morphology, sweat glands…" *Id.*

As evidenced by the February 17, 2004 recall[5], due to its construction, a reservoir system may be subject to leakage either from the inherent relative fragility of the design or from manufacturing defect. Janssen Pharmaceutica Products, L.P., Urgent Class 1

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[3] Indicating that sink conditions exist within the skin.

[4] Patients can call the toll-free number identified on the innovator's package insert, and speak to a customer representative who after discussing the different devices used by the patient will send directly to the patient a supply of Bioclusive overlays. *See HealthBoards.Com*, http://www.healthboards.com/boards/shothread.php?t=8063&page=1&pp=5; *see also eHealth Forum*, http://www.ehealthforum.com/health/topic2726.html.

[5] This recall was followed by an expanded recall for multiple lots which were deemed to be defective due to a seal breach. *See* Janssen Pharmaceutica Products, L.P., Press Release April 5, 2004, Urgent: Expanded Product Recall, http://www.jnj.com/news/jnj_news/20040402_170309.htm.

Drug Recall Notification Patient Level, *Subject: Duragesic® (fentanyl transdermal system) CII 75 mcg/h, NDC #50458-035-05, Lot Control Number 0327192 (expiration October 2005)* ("A potential seal breach on one edge may allow drug to leak from the patch."). The application and use of an overlay on a reservoir system may magnify the possibility of fentanyl leakage. For example, the placement of an overlay over the reservoir may cause a stress in the seal of the reservoir, thus resulting in fentanyl leaking from the patch. The spread of fentanyl gel from a reservoir increases the effective skin surface area for absorption, which potentially could result in an increase in fentanyl absorbed into a patient's systemic circulation. The Duragesic Labeling clearly states that: "[i]f the Duragesic system is cut or damaged, controlled drug delivery will not be possible, which can lead to the rapid release and absorption of a potentially fatal dose of fentanyl." Duragesic Labeling ("Safety and Handling").

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 (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 transdermal fentanyl 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.

Accordingly, Mylan requests that applicants and holders of approved applications for fentanyl transdermal systems conduct a study to determine the effect of overlays with their respective patches. Furthermore, Mylan recommends that 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 transdermal fentanyl product may be more prone to risks associated with variable performance of fentanyl transdermal system patches. A product like transdermal fentanyl already requires 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.

ENVIRONMENTAL IMPACT

The action requested is subject to a categorical exemption from environmental assessment under 21 C.F.R. §§ 25.22 and 25.31.

ECONOMIC IMPACT

Pursuant to 21 C.F.R. § 10.30(b), MTI will provide data concerning the economic impact of the relief requested should such information be 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 it includes representative data and information known to the petitioner, which are unfavorable to the petitioner.

Sincerely,

John O'Donnell

John P. O'Donnell
Chief Scientific Officer