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August 26, 2009

**VIA FEDERAL EXPRESS &
ELECTRONIC SUBMISSION**

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

Re: Petition for Stay of Action

Dear Sir or Madam:

Mylan Inc. ("Mylan") submits this petition pursuant to 21 C.F.R. § 10.35 and Section 505(q) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355(q)), requesting that the Commissioner of Food and Drugs stay the approval of a "new design" of Duragesic® with a substantially higher fentanyl content than currently approved products (hereinafter, the "High-Load, Matrix Design Duragesic®") or any other fentanyl transdermal product that contains a substantially higher drug load than what is currently on the market. This product presents a substantially increased risk of abuse and diversion of fentanyl, a dangerous and highly addictive drug when used inappropriately, without any corresponding patient benefit when compared with currently available fentanyl transdermal systems on the market. As a result, a stay is required to protect the public health.

A. Pending Action Involved

It has come to Mylan's attention that an application pending under 21 U.S.C. § 355(b)(2) for High-Load, Matrix Design Duragesic® has been or may imminently be approved by the Office of New Drugs.

On August 25, 2009, Ortho-McNeil-Janssen Pharmaceuticals, Inc.'s subsidiary PriCara announced that the Duragesic® fentanyl transdermal system has a "New Design" (Exhibit A) on their Internet site. This new design is shown in the prescribing information (Exhibit B), also made available on the same day.[1] The High-Load, Matrix Design Duragesic® has the same indications and dose strengths but replaces Duragesic's previous gel/liquid filled reservoir patch with a matrix design that has a substantially higher fentanyl content than the currently approved Duragesic® product and other commercially available fentanyl transdermal systems.

B. Action Requested

Based on a substantially increased risk of abuse and diversion without a corresponding increase in patient benefit, Mylan requests that the Commissioner stay approval of the application for High-Load, Matrix Design Duragesic® or any other fentanyl transdermal product that contains a substantially higher

[1] The prescribing information was first made available on or about August 21, 2009, but was then later withdrawn. It was again made available on August 25, 2009.

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drug load than what is currently on the market. Any delay resulting from a stay is not outweighed by public health or other public interests, because other fentanyl transdermal systems (with the same dose and indications, but with lower fentanyl content) are available to address the health needs of the public, without posing the same public health danger of abuse and diversion. The NDA holder notes that the matrix design of the High-Load, Matrix Design Duragesic® reduces certain disadvantages of the previous product, such as the "accidental exposure to gel" inherent in the reservoir design (Exhibit A). While replacing the reservoir patch with a matrix design is an important change due to the inherent leakage risk associated with a reservoir, the Agency should not exchange one risk for another by approving a product with higher drug load that increases the risk of abuse and diversion of fentanyl. As demonstrated by other commercially available approved products (*see, e.g.*, Exhibits D and E), it is possible to produce a matrix designed patch without the higher fentanyl content. Because the High-Load, Matrix Design Duragesic® introduces new risks without providing any commensurate benefit, FDA should stay approval of the application for High-Load, Matrix Design Duragesic® or any other fentanyl transdermal product that contains a substantially higher drug load than what is currently on the market.

C. Statement of Grounds

This petition raises significant public health issues concerning the potential approval of a product with a substantially higher fentanyl content than all other approved fentanyl transdermal systems available in the United States.

The FDA has mandated a Black Box Warning for all fentanyl transdermal systems, which in relevant part states:

> **Fentanyl can be abused and is subject to criminal diversion. The high content of fentanyl in the patches ... may be a particular target for abuse and diversion.**

To Mylan's knowledge, the FDA has never before approved a product that substantially increases the public health dangers recited in a Black Box Warning, when other equivalent products do not present the same dangers, and where there is no corresponding increase in patient benefit. As described in more detail below, no other fentanyl transdermal systems approved by the FDA contains the high amount of drug content contained in the High-Load, Matrix Design Duragesic®. While the High-Load, Matrix Design Duragesic® does mitigate the leakage risk associated with a gel/liquid-filled reservoir by replacing the patch with a matrix design, the proposed product unnecessarily introduces new concerns by substantially increasing the amount of drug load compared to other approved fentanyl transdermal systems.

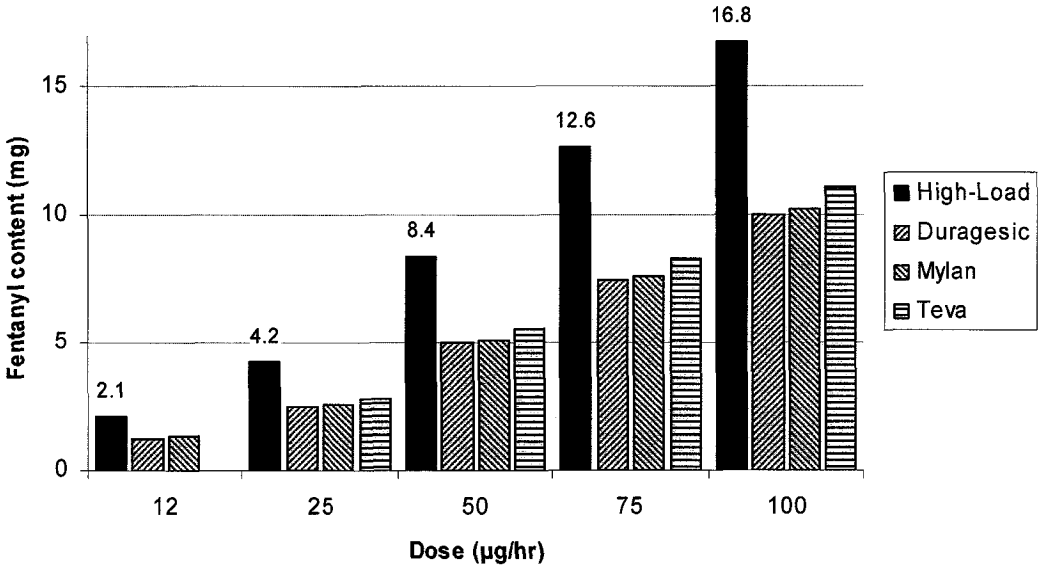
1. High-Load, Matrix Design Duragesic®

High-Load, Matrix Design Duragesic® does not offer any patient benefit over currently available products. It provides the same fentanyl doses (100, 75, 50, 25, and 12 µg/hr) over the same period of time (72 hours) for the same indications.[2]

[2] *Compare* Exhibit B *with* Exhibits C-E.

High-Load, Matrix Design Duragesic® does differ in one important respect, however. A side-by-side comparison reveals that High-Load, Matrix Design Duragesic® has a substantially higher fentanyl content before patient use:[3]

Table 1. Initial Fentanyl Load.[4]



The theoretical amount of residual fentanyl remaining after patient use (hereinafter, the "residual fentanyl content") can be calculated by subtracting the dose delivered over a 72-hour period from the initial fentanyl content.[5] The differences between High-Load, Matrix Design Duragesic® and currently available products are even more stark, with an ***over three-fold increase*** in residual fentanyl content[6] that is available for abuse and diversion:

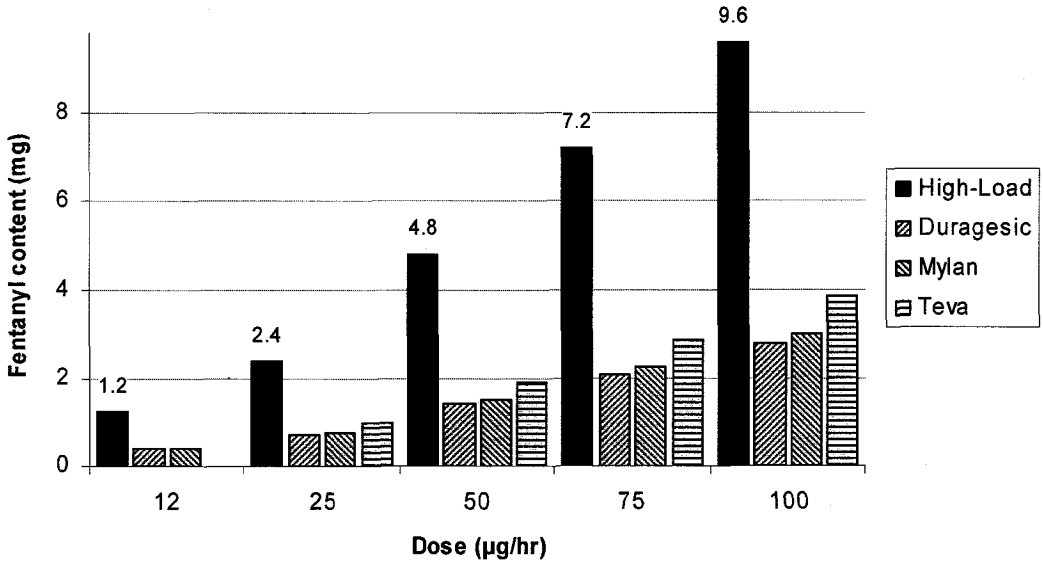
[3] For example, as shown in Table 1, the 100 µg/hr High-Load, Matrix Design Duragesic® has an initial fentanyl load of 16.8 mg, as compared to 10.0 mg for the previously available 100 µg/hr Duragesic® product.

[4] Source (Tables 1 and 2): High-Load: High-Load, Matrix Design Duragesic® (Exhibit B, p. 1, col. 2); Duragesic: Duragesic®, Ortho-McNeil Janssen Pharmaceuticals, Inc. (Exhibit C, p. 1, col. 1); Mylan: Fentanyl Transdermal System, Mylan Pharmaceuticals Inc. (Exhibit D, p. 1, col. 1); Teva: Fentanyl Transdermal System, Teva Pharmaceuticals USA (Exhibit E, p. 2).

[5] Residual (mg) = Initial (mg) – [Dose (µg/hr) x 0.001 (mg/µg) x 72 (hr)]. *See* Kathy A. Marquardt and R. Steven Tharratt, *Inhalation Abuse of Fentanyl Patch*, Clinical Toxicology, 32(1):75-78 (1994) (Exhibit F).

[6] For example, as shown in Table 2, the 100 µg/hr High-Load Duragesic® has a residual content of 9.6 mg fentanyl, as compared to 2.8 mg for the previously available 100 µg/hr Duragesic® product.

Table 2. Residual Fentanyl Content.



As shown by Tables 1 and 2, the difference between High-Load, Matrix Design Duragesic® and currently available products is not merely one of degree. Rather, High-Load, Matrix Design Duragesic® has a substantially higher fentanyl content. The higher content makes more drug available for illicit uses and possible overdose when used inappropriately or diverted. As recognized by the Black Box Warning for fentanyl transdermal systems, this fentanyl "may be a particular target for abuse and diversion."

2. Fentanyl Is a Highly Addictive Drug Subject to Abuse and Diversion

From the 1980s through 1990, when the first fentanyl transdermal system was approved, the FDA and other interested government agencies expressed acute concern about the risk of abuse and diversion of residual fentanyl found in transdermal products. A portion of this history was summarized in findings made by Chief Judge William Sessions III of the United States District Court for the District of Vermont:

> In early 1983 Alza[7] representatives met with agents from the United States Drug Enforcement Administration to discuss the handling of fentanyl. Among other issues, the agency expressed concern that the dosage be kept to an absolute minimum, because of the potential for diversion and abuse of such a potent narcotic. Before the advent of the transdermal patch, fentanyl had only been administered in hospital settings, where the opportunities for abuse were largely limited to hospital personnel with access to the drug. Large excesses of fentanyl

[7] Alza is the manufacturer of both High-Load Duragesic® and the previous Duragesic® product, and is a subsidiary of Johnson & Johnson, the parent of NDA holder Ortho-McNeil-Janssen Pharmaceuticals, Inc.

remaining in discarded patches would substantially increase the risk of abuse.[8]

The broader availability of fentanyl transdermal systems has been accompanied by an increase in fentanyl abuse.[9] "Fentanyl drug patches, even those previously used, contain a potentially lethal amount of this potent narcotic analgesic and provide a source of fentanyl for drug abusers."[10]

3. Increased Fentanyl Content Poses an Unacceptable Public Health Risk

High-Load, Matrix Design Duragesic® would more than triple the residual fentanyl content that is available for illicit uses and diversion to the black market. *See* Table 2, *supra*. This raises a significant public health issue that justifies a stay of approval.

The manufacturer of High-Load, Matrix Design Duragesic® previously emphasized that a "***critical design parameter***" for the product is "***minimizing the amount of fentanyl in the patch***" because "unused patches would be available to patients in their homes and used patches would be available in refuse."[11] Likewise, the patent for Duragesic® explains that a key design consideration for the fentanyl transdermal system is "keeping the amount of drug within both the unused and depleted systems to a minimum."[12] "Since fentanyl is a restricted drug, significant amounts of residual fentanyl pose regulatory (DEA) problems and potential safety risks."[13] Therefore, it is essential to limit the fentanyl content. "If a potential abuser finds that only a relatively small amount of drug is available from a single patch, the potential abuser may be less likely to abuse the patch. Therefore, a patch having a relatively smaller reservoir volume and drug load may work to reduce or deter abuse."[14]

Relying on arguments by the manufacturer, the courts have likewise recognized the dangers posed by high residual fentanyl content. Chief Judge Sessions concluded that "[l]arge excesses of fentanyl remaining in discarded patches would substantially increase the risk of abuse."[15] On appellate review, the United States Court of Appeals agreed that "large excesses of a controlled substance that remained in discarded patches ... could then be abused."[16]

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[8] *Alza Corp. v. Mylan Labs., Inc.*, 310 F. Supp. 2d 610, 614-15 (D. Vt. 2004).

[9] Nabarun Dasgupta et al., *Association Between Non-Medical and Prescriptive Usage of Opioids*, Drug and Alcohol Dependence, 82:135-142 (2006) (Exhibit G).

[10] Lisa M. Flannagan et al., *Fentanyl Patches Left on Dead Bodies: Potential Source of Drug for Abusers*, Journal of Forensic Sciences, 41(2):320-321 (1996) (Exhibit H); *see also* Kathy A. Marquardt and R. Steven Tharratt, *Inhalation Abuse of Fentanyl Patch*, Clinical Toxicology, 32(1):75-78 (1994) (Exhibit F); Kathy A. Marquardt et al., *Fentanyl Remaining in a Transdermal System Following Three Days of Continuous Use*, Annals of Pharmacotherapy, 29:969-971 (1995) (Exhibit I).

[11] Plaintiffs' Pre-Trial Memorandum in Civil Action No. 2:02-CV-20, at 4-5 (Aug. 19, 2003) (Exhibit J) (emphasis added).

[12] U.S. Patent No. 4,588,580, at 1:58:60 (Exhibit K).

[13] U.S. Patent No. 5,186,939, at 2:32-35 (Exhibit L).

[14] Int'l Pub. No. WO 2009/052204 A1, at 19 ¶ 65 (Exhibit M).

[15] *Alza Corp. v. Mylan Labs., Inc.*, 310 F. Supp. 2d 610, 615 (D. Vt. 2004).

[16] *Alza Corp. v. Mylan Labs., Inc.*, 391 F.3d 1365, 1367 (Fed. Cir. 2004).

High-Load, Matrix Design Duragesic® multiplies the amount of fentanyl available for abuse and diversion. The FDA has recognized that this public health risk is unacceptable. Thus, for example, the FDA refused to approve Noven Pharmaceuticals, Inc.'s ANDA No. 76-804 because, like High-Load, Matrix Design Duragesic®, its "higher [fentanyl] drug content" raises "safety concerns."[17]

Indeed, FDA recently reiterated the dangers of high residual drug content of transdermal products in response to a recent citizen petition. In considering a clonidine transdermal system, the FDA stated that it "is aware of certain circumstances (involving other transdermal products) where we might not allow a higher drug content (i.e., circumstances in which significantly greater residual drug content would not be permitted)."[18] A residual fentanyl content that is over three times that of other commercially available fentanyl transdermal systems presents the dangerous situation of a "higher drug content" that should not be permitted. As FDA noted, "if there is evidence that the amount of drug contained in the reservoir could cause serious adverse events . . ., residual drug content significantly in excess of that in the reference product might not be permitted." Likewise, as a potent opioid analgesic that can be potentially fatal if abused, misused or diverted, fentanyl transdermal systems that contain excess, residual drug content should not be approved regardless of whether the patch is a matrix design or a liquid/gel filled reservoir.

Moreover, when the FDA originally approved Duragesic®, it never contemplated the heightened fentanyl content found in High-Load, Matrix Design Duragesic®. Rather, when considering the issue of diversion of products that contain residual fentanyl after patient use, the NDA sponsor assumed that only 3.0 mg of fentanyl would remain in the 75 µg/hr product – an amount that FDA concluded was unlikely to be attractive to an individual addict.[19] As Mary Southam, the Vice President of Technology Assessment of Alza testified, "Alza successfully addressed the abuse issue" by "minimizing the amount of drug in each patch."[20] The manufacturer of High-Load, Matrix Design Duragesic® now seeks to reverse course and substantially increase the residual fentanyl content, presenting new dangers not previously approved by the FDA. Approval of High-Load, Matrix Design Duragesic® without further review of this serious issue of abuse and diversion would endanger the public health.

As noted in the prescribing information made available by Duragesic®'s manufacturer, High-Load, Matrix Design Duragesic® will be available in a matrix designed patch different than the manufacturer's current reservoir design delivery system. As a series of recalls have confirmed over several years, liquid/gel filled reservoir patches have inherent safety risks due to the design of the system which has the potential of accidental leaks that can result in accidental overdose of the patient or an accidental exposure to a healthcare provider or family member of the patient.[21] While replacing the

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[17] *Noven Provides Update on Developmental Fentanyl Patch* (Sept. 28, 2005) (Exhibit N).

[18] Letter of Janet Woodcock to William Vodra, Docket No. 2001-P-0563-0005, at 4 n.7 (Aug. 18, 2009) (Exhibit O).

[19] Curtis Wright, Medical Officer Review, NDA #: 19,813 (Volume 5 – Abuse and Diversion), at 4-5 (Apr. 10, 1990) (Exhibit P).

[20] Hearing transcript in Civil Action No. 2:02-CV-20, at 50 (Aug. 25, 2003) (Exhibit Q).

[21] See, for example Food and Drug Administration MedWatch. The FDA Safety Information and Adverse Event Reporting Program. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm166413.htm.Accessed Aug. 26, 2009; U.S. Food and Drug Administration. U.S. Department of Health and Human Services. Pricara™ Recalls 25 mcg/hr Duragesic® (fentanyl transdermal system) CII Pain Patches(Press release also covers Sandoz recall). February 12, 2008. Available at: http://www.fda.gov/Safety/Recalls/ArchiveRecalls/2008/ucm112374.htm. Accessed Aug. 26, 2009; U.S. Food and Drug Administration. U.S. Department of Health and Human Services. Actavis Recalls Certain Fentanyl Patches in the US as Precaution. February 17, 2008. Available at:

reservoir filled patch with a matrix patch reduces the risk of leakage concerns, additional risks are created if the non-leaking patch contains higher drug load. As the Agency has previously held, fentanyl 72-hour transdermal systems with a drug load greater than the currently approved and marketed Duragesic® gel filled reservoir should not be approved due to the safety concerns with abuse and increased risk of intentional and accidental exposure and overdose.[22] As has been demonstrated by at least two applicants to date, it is possible to formulate fentanyl into a drug in an adhesive matrix patch with essentially the same drug load as the Duragesic gel filled reservoir product.[23] Consequently, FDA should not replace one risk (ie, leaky patches) for another (higher drug load).

Drug load needs to be minimized in any reformulation of fentanyl transdermal drug system due to potential abuse and safety issues. Moreover, approving a fentanyl transdermal system with drug load higher than what is on the market would run counter to FDA's heightened efforts to minimize abuse, misuse, and intentional and unintentional overdose of certain opioid containing products. As announced in February 2009, FDA intends to require a Risk Evaluation and Mitigation Strategies ("REMS") on various opioid products, including fentanyl, in an effort to mitigate risks associated with (1) the use of certain opioid products in patients who are not opioid tolerant; (2) abuse; and (3) accidental and intentional overdose. As the FDA recognized, "Opioid drugs have serious risks when used improperly . .[and] the rates of misuse and abuse, and of accidental overdose of opioids, have risen over the past decade. The FDA believes that establishing a REMS for opioids will reduce these risks, while still ensuring that patients with legitimate need for these drugs will continue to have appropriate access." [24] High-Load, Matrix Design Duragesic® only raises additional safety concerns and potential for abuse and misuse and as a result, should not be approved by the FDA

D. Conclusion

For the reasons set forth above, Mylan requests that the Commissioner stay approval of any application for High-Load, Matrix Design Duragesic® or any other fentanyl transdermal product that contains a substantially higher drug load than what is currently on the market.

E. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became

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http://www.fda.gov/Safety/Recalls/ArchiveRecalls/2008/ucm112381.htm. Accessed Aug. 26, 2009; U.S. Food and Drug Administration. U.S. Department of Health and Human Services. 2008 Safety Alert: Fentanyl Transdermal System Patches. Watson Announces Limited Recall of Fentanyl. August 8, 2008. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm126727.htm.Accessed Aug. 26, 2009; Watson Announces Limited Recall Of Fentanyl Transdermal System. Aug. 7, 2009. Available at: http://ir.watson.com/phoenix.zhtml?c=65778&p=irol-newsArticle&ID=1318770&highlight=. Accessed Aug. 26, 2009. (Exhibit R)

[22] See attached Noven Press release, Exhibit N.

[23] See approval letter to Mylan Technologies Inc. for ANDA #76-258; approval letter to Teva Pharms, for ANDA # 77-449; and Exhibits D and E.

[24] See FDA Press Release available at http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm. (Exhibit S).

known to the party on whose behalf this petition is submitted on or about the following date: August 21, 2009, the date on which Mylan first learned of High-Load, Matrix Design Duragesic®. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: my employer Mylan Inc. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Brian S. Roman
Vice President and General Counsel, North America

cc: Deborah Autor, Esq., Director, Office of Compliance, FDA
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