

Declaration of H. Brian Goldman, M.D.

I, H. Brian Goldman, M.D., hereby declare as follows:

1. I am employed as a staff emergency physician at Mount Sinai Hospital, Toronto, Ontario. I also serve as an assistant professor in the department of family and community medicine at the University of Toronto. A copy of my *curriculum vitae* is attached hereto at Tab A.
2. Since the late 1980s, I have been involved in writing and lecturing on pain management and related issues. I have developed a particular interest in the issue of abuse and diversion risks involved in the prescription of opioids, as well as the recognition and management of individuals who seek prescription opioids for non-medical and abuse purposes. A list of my articles on this topic is included in my *curriculum vitae*. In addition to maintaining an office practice in the management of chronic pain from 1991-99, I also chaired the Opioid Subcommittee of the Chronic Pain Section of the OMA for two years. I am a member of the Task Force of the Canadian Pain Society that developed guidelines on the use of opioid analgesics in the treatment of chronic non-cancer pain.
3. I have been asked by Mylan Technologies Inc. to evaluate the issues raised in the Citizens' Petition submitted by Drs. Brookoff and Voth based on my experience and expertise in the abuse and diversion risks associated with prescription opioids. I am being compensated by Mylan for my work on this matter at my normal hourly rate and have no financial interest in the outcome of the agency's decision

in this matter.

4. In forming my opinion, I have reviewed thoroughly the current medical literature on opioid non-medical use and abuse. In particular, I have made extensive use of a taskforce position statement and review of the literature on prescription opioid non-medical use and abuse by College on Problems of Drug Dependence (Zacny J, Bigelow G, Compton P, Foley K, Iguchi M, Sannerud C., College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. *Drug and Alcohol Dependence* 2003;69:215-232.). One of the key purposes of the position statement was to inform scientists, policy makers and the public of the state of the knowledge on the scope of the problem, including epidemiology and abuse liability of opioid prescription drugs. It is widely recognized in the pain management community that all opioids used in the management of pain carry with them some risk of abuse or diversion. Zacny J, Bigelow G, Compton P, Foley K, Iguchi M, Sannerud C. College on Problems of Drug Dependence taskforce on prescription opioid non-medical use and abuse: position statement. *Drug and Alcohol Dependence* 2003;69: page 224. The reason for this is both the analgesic and abuse effects of opioids are mediated through activation of the same opioid mu receptors in the brain. See Zacny, page 224. “This last point cannot be overemphasized – opioid drugs that are most efficacious in relieving pain also are the opioids with the highest potential for abuse. Consequently, society is forced to seek a compromise between the competing goals of effective, convenient pain relief and regulating the availability of opioid drugs to minimize the extent of their abuse.” Zacny, page 224. Further

evidence that all opioids used in the management of pain carry a risk of abuse and diversion comes from reports of abuse and diversion itself. A study of prescription drug abuse in downtown Vancouver revealed a street market for a wide range of prescription opioids. Sajan A, Corneil T, Grzybowski S. The street value of prescription drugs. CMAJ 1998;159:139-142, and Goldman B. The news on the street: prescription drugs on the black market. CMAJ. 1998 Jul 28;159(2):149-50.] The National Forensic Laboratory Information System (NFLIS), a program sponsored by the Drug Enforcement Administration's Office of Diversion Control, collects systematically drug analyses by state and local forensic laboratories. NFLIS is intended to offer "a valuable resource for monitoring and understanding illicit drug abuse and tracking, including diverted pharmaceuticals such as narcotic analgesics". According to a Special Report on Narcotic Analgesics by NFLIS, a wide variety of commonly prescribed opioid analgesics were identified. NFLIS Special Report. Narcotic Analgesics, 2001-2003, National Forensic Laboratory Information System, Office of Diversion Control, Drug Enforcement Administration, June, 2004.

5. According to a Consensus Statement by the American Academy of Pain Medicine, American Pain Society and American Society of Addiction Medicine, addiction is defined as "a primary, chronic, neurobiologic disease with genetic, psychological and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued used despite harm, and craving." Definitions Related to the Use of Opioids for the Treatment of Pain. A consensus

document from the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine, 2001. Opioid drugs are generally associated with the risk of addiction because they can produce pleasure or euphoria in individuals at genetic risk by increasing dopamine levels in several areas of the brain. Addiction is believed to occur in patients who are at risk of the disorder when repeated use of an opioid (causing repeated experiences of pleasure – also known as ‘reward’) triggers a change in the brain that leads to a continuous desire to use the drug. Gardner E. The neurobiology and genetics of addiction: implications of the rewards deficiency syndrome for therapeutic strategies in chemical dependency. *Addiction: Entries and Exits*. New York: Russell Sage Foundation, 1999, 57-119. The risks of abuse and diversion vary between opioid products depending in large part on the desirability of the product to abusers. There is a wealth of scientific data on the methods used to assess the abuse risk of various drugs. Data from these assessments have provided guidance to the DEA and FDA in discharging their regulatory responsibilities. Zacny, page 224, and Brady JV, Lucas SE (Eds), 1984. *Testing Drugs for Abuse Liability and Dependence Potential: Methods used in Animals and Man*. US Government Printing Office. NIDA Research Monograph No. 52, DHHS Publication No. (ADM) 84-1332 Washington, DC. An important factor in the desirability (and therefore the abuse and diversion risk) of an opioid product is the ability of the user to obtain a rapid increase in the levels of the drug inside the brain. The rate of drug onset in the brain is believed to influence the ability of the drug to trigger abuse and addiction. Zacny, page 224, and Roset PN, Farre M, dela Torre R, Mas

M, Menoyo E, Hernandez C, Cami J. Modulation of the rate of onset and intensity of drug effects reduces abuse potential in healthy males. *Drug Alcohol Depend* 2001;64:285-298, and Savage, SR, Joranson DE, Covington EC, Schnoll SH, Heit HA, Gilson AM. Definitions Related to the Medical Use of Opioids: Evolution Towards Universal Agreement. *J Pain Symptom Manage* 2003;26:655-667, and Koob GF. Drug addiction, dysregulation of reward and allostasis. *Neuropharmacology* 2001;24:97-129. A rapid increase in opioid levels in the brain will trigger a rapid increase in dopamine in the brain, producing euphoria or pleasure of rapid onset. Following the rapid rise in dopamine, there is a consequent rapid fall, which produces intense dysphoria or sadness, which triggers those users at risk of addiction to attempt to obtain and use more opioids.

6. It follows that slowing down the rate and extent of delivery of the opioid into the blood stream (as well as the brain) would reduce the risk of opioid abuse. This is the rationale behind transdermal opioid delivery systems such as Duragesic® as well as controlled-release oral opioid drugs such as OxyContin®. Used as directed, these drugs provide a gradual onset and sustained delivery of medication. Zacny, page 224.

7. However, the problem with this approach is that users may tamper with the formulation in order to circumvent its gradual release properties. OxyContin® provides a good example of this problem. OxyContin® is a controlled-release version of the opioid oxycodone. When taken as directed, OxyContin® provides a slow and sustained release of oxycodone over a 12 hour period into the blood stream and the brain. OxyContin® has been prone to abuse. Sharpe Potter J,

Hennessy G, Barrow JA, Greenfield SF, Weiss RD. Substance use histories in patients seeking treatment for controlled-release oxycodone dependence. *Drug and Alcohol Depend* 2004;76:213-215 by circumventing its gradual release properties. By crushing or dissolving an OxyContin® tablet, the entire dose of oxycodone is converted to a form that can be absorbed rapidly. Thus, a dose that was intended to be absorbed over a 12 hour period can be made available immediately for use by the oral, nasal or intravenous routes. Zacny, page 224, and Prescription Drugs. OxyContin Abuse and Diversion and Efforts to Address the Problem. GAO-04-110, Report to Congressional Requesters, United States General Accounting Office, December, 2003, page 34.

8. I have reviewed information about the Mylan fentanyl transdermal system, including the Declaration of Dr. Gordon Flynn to determine whether there is evidence that this fentanyl transdermal system would be prone to abuse or diversion issues.
9. Based on that information, it is my conclusion that the Mylan fentanyl transdermal system would not be an attractive opioid product for abusers and, therefore, would not be at a high risk for abuse and diversion problems. In particular, Dr. Flynn's analysis indicates that, unlike the OxyContin® and Actiq® examples given in the Petition, the Mylan fentanyl transdermal system retains its slow release character even if it is cut into pieces and placed in the mouth. The possible abuse of the Mylan fentanyl transdermal system by placing it in the mouth, even if tried, would not provide the kind of quick release of drug that is desirable for opioid abusers.
10. In the absence of a quick release of drug and the accompanying physiological

effects in the user, the Mylan fentanyl transdermal system would be unlikely to become a drug product of choice among opioid abusers. Therefore, the Mylan fentanyl transdermal system cannot be characterized as having a high abuse potential.

11. I have also looked at the experience with the solid-state matrix fentanyl patch, Durogesic® SMAT introduced by Janssen Pharmaceutica in Germany. The literature does not reflect any abuse problems relating to the introduction of the solid-state matrix fentanyl transdermal system in Germany.
12. I have also reviewed the literature concerning abuse of Duragesic® patches. The literature reflects examples of abuse attempts (sometimes with deadly consequences) using syringes to withdraw fentanyl gel from the Duragesic® reservoir. That particular form of abuse would not be possible for Mylan's fentanyl transdermal system.

I declare under the penalty of perjury under the laws of the United States of America that
the foregoing is true and correct.

Executed on November 12, 2004.

Toronto, Canada


H. Brian Goldman, M.D.