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CITIZENS' PETITION

To: Dockets Management Branch
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852
Telephone 301-827-6860

Date: OCTOBER 21, 2004

Re: CITIZEN'S PETITION regarding ANDA 76-258

Dear FDA Officer:

The undersigned submit this citizens' petition in quadruplicate in accordance with 21 CFR 10.30 under Section 505 (j)(2)(C) of the Federal Food, Drug and Cosmetic Act, based on the authority granted by 21 CFR 314.127 (a)(8)(i) or any other statutory provision for which authority has been delegated to the Commissioner of Food and Drugs under 21 CFR 5.10 to request that the Commissioner of Food and Drugs refuse to grant final approval to ANDA 76-258 under its proposed labeling.

SPECIFIC ACTION REQUESTED:

We request that the Commissioner refuse to grant final approval to ANDA 76-258 for a generic fentanyl transdermal system under its current proposed labeling.

004P-0472

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STATEMENT OF GROUNDS

Overview

We are petitioning to request that the Commissioner refuse final approval for ANDA 76-258 because the marketing of this product under its current proposed labeling will pose an imminent and unnecessary hazard to the public health. ANDA 76-258 describes a generic form of transdermal fentanyl (fentanyl skin patch). The designated reference-listed drug product upon which this application is based is manufactured by the Alza Corporation and is currently marketed by Janssen Pharmaceutica under the brand name Duragesic (NDA 19-813; Approved Drug Products with Therapeutic Equivalence Evaluations. 23rd Edition page 3-158).

Publicly-available correspondence from the FDA's Office of Generic Drugs referenced below indicates that ANDA 76-258 can be expected to receive full approval on or after January 23, 2005. Information contained in this petition documents that the generic product has a significantly higher potential for diversion and abuse than its branded equivalent due to a significant difference in their formulations. As further documented in this petition, the recent approval of another fentanyl-containing medication with a potential for abuse similar to that of the proposed generic product was delayed by FDA until a special risk management plan was put into place by the drug's manufacturer. Because ANDA 76-258 was approved solely on the basis of therapeutic bioequivalence with a branded product for which no risk management plan had been required, no risk management plan was either formulated or put into place for this generic product.

Treating chronic pain and preventing drug abuse: finding a balance

As physicians who have devoted years to caring for patients with chronic pain we are certainly aware that safe opioid medications are vital to the health of many Americans. Scientific surveys indicate that over a third of adult Americans will suffer with chronic pain at some point in their lives (1) and that many will require treatment with an opioid analgesic. Undertreatment of chronic pain can be associated with serious morbidity and even mortality (2).

However, we are also painfully aware that many opioid medications have the potential to be abused, giving rise to terrible morbidity and mortality among people for whom these medications are usually not medically prescribed. One of the most important functions of Federal regulation of opioid medications is to balance the need for making potent analgesic medications available for therapeutic use while minimizing the risk of diversion and drug abuse.

Determinants of abuse potential

The molecular identity of a drug is not the only feature of an opioid medication that determines its potential for abuse. There are other factors, including dosage form and combination with excipients that can make a major difference in abuse potential. Formulations that make it difficult to extract the psychoactive ingredient, compounds with a slow onset of effect that cannot easily be converted to "fast release" forms, formulations that limit bioavailability, and formulations that are difficult to reverse-engineer all serve to affect the abuse potential of an opioid medication (3,4). The fact that the Drug Enforcement Administration will sometimes place different formulations of the same opioid drug into different schedules supports this view. For example, various formulations containing hydrocodone can be found in different DEA schedules (5).

Safety record of transdermal fentanyl

For over twelve years, the Duragesic transdermal fentanyl system has been a mainstay for the treatment of moderate-to-severe chronic pain due to both cancer and to non-malignant causes. The introduction of this medication gave physicians their first opportunity to safely use this opioid medication in an outpatient setting. While fentanyl is certainly subject to abuse, information contained in this petition documents that certain specific characteristics of the formulation of Duragesic have served to significantly limit its abuse potential compared to other formulations of fentanyl. While there have been incidents of abuse of Duragesic during its time on the American market, these have occurred in isolated and self-limited episodes in contrast to the widespread epidemics of abuse that have been seen with some other recently introduced powerful opioid medications.

Development of a "generic equivalent"

Earlier this year, the FDA granted tentative approval to Mylan Technologies for the marketing of a product that will be considered the generic equivalent of Duragesic. The Mylan product uses a formulation that has not been previously approved for the delivery of fentanyl in the United States. A letter from the FDA to Mylan Technologies indicated that this product (ANDA 76-258) can be expected to receive final approval in January 2005. Though the Mylan product is bioequivalent to Duragesic when used as directed, information in this petition indicates that its unique formulation gives it a significantly higher potential for diversion and abuse.

Authority to refuse approval of a bioequivalent generic

The Commissioner of Food and Drugs may refuse to grant final approval to an abbreviated new drug application despite the demonstration of bioequivalence. The legal authority for this comes from 21 CFR section 314.27 (8) (ii) (A) which states that *" the FDA will consider the inactive ingredients or composition of a drug product unsafe and*

refuse to approve an abbreviated new drug application under paragraph (a)(8)(i) of this section if, on the basis of information available to the agency, there is reasonable basis to conclude that one or more of the inactive ingredients of the proposed drug or its composition raises serious questions of safety or efficacy." One specific example of a change that may raise serious questions of safety is "*the use of a delivery or modified release mechanism never before approved for the drug.*" (21 CFR section 314.27 (8)(ii)(A)(5)).

Planning to reduce diversion

As documented in this petition, the FDA has already established a precedent for the institution of special risk-management plans prior to the approval of an opioid medication with an unusually high potential for abuse. (see FDA "Guidance for Industry" document for risk minimization action plans at: http://www.fda.gov/cder/guidance/5766dft.htm). In that case, the medication in question also used a novel delivery system for fentanyl that was eventually marketed under the brand name Actiq. Information contained in this petition indicates that, because of its unique formulation, the generic transdermal fentanyl product under consideration has a potential for abuse that is equal to or greater than that of Actiq. Because of this, the generic transdermal fentanyl product will pose an imminent hazard to the public health unless special risk-management measures are taken or a safer formulation is developed prior to its release on the market.

Specific differences in formulation

On November 21, 2003 the Food and Drug Administration granted final approval to Mylan Technologies (ANDA 76-258) for the manufacture and marketing of a transdermal delivery system for fentanyl as a generic equivalent to Duragesic. Though they are both fentanyl-based skin patches, the design of the generic delivery system is significantly different from that of Duragesic and will likely make the generic version less safe for non-compliant patients and sought after by drug dealers and drug abusers. The generic formulation uses a "solid state monolith" delivery system while the Duragesic patch has a "form-fill seal" design (also commonly called a "reservoir patch").

"Solid state monolith" design skin patches are currently in use in the United States for the delivery of a wide variety of drugs, ranging from nicotine to estrogen. "Solid state monolith" patches are viewed as advantageous because they are less expensive to manufacture than reservoir patches and because they have the potential for more flexible administration than reservoir patches. For example, they can be safely partitioned for custom dosing (6). The FDA's November 21, 2003 action was the first time that a "solid state monolith" delivery system had been approved for the transdermal delivery of fentanyl.

Bioequivalence testing does not address abuse potential

The approval of the "solid state" formulation was based on clinical studies that showed that the generic product was "bioequivalent" to Duragesic when applied to intact skin (i.e. it produced similar blood levels of fentanyl). When used as directed, both Duragesic and the generic "solid state" system provided for the "slow-release" of fentanyl into the bloodstream in doses ranging from 25 to 100 micrograms per hour. For comparison purposes, the currently marketed "fast-release" system for fentanyl (Actiq transmucosal oralet) delivers 200 to 1600 micrograms of fentanyl per hour. Under the 1984 Hatch Waxman amendment to the Federal Food, Drugs and Cosmetics Act (21 USC sect 301 et seq), pharmaceutical products submitted for approval as "generic equivalents" do not necessarily have to undergo the same safety and efficacy testing to which the FDA subjects new pharmaceutical products. They sometimes can be approved solely on the basis of demonstrated bioequivalence (7).

Reversal of full approval

On June 22, 2004, pursuant to a decision entered in a federal patent infringement lawsuit (*Alza Corporation and Janssen Pharmaceuticals v. Mylan Laboratories,Mylan Technologies and Mylan Pharmaceuticals Inc, 2004 U.S. Dist LEXIS 4914 (D Vt. March 25, 2004),* the FDA rescinded final approval of Mylan's abbreviated new drug application. The application was granted tentative approval with the expectation that it would be reactivated and that the generic equivalent would be approved for manufacture and sale upon the expiration of Alza's extended patent on January 23, 2005. In a June 22, 2004 letter notifying Dr. William E. Brochu of Mylan Technologies of the change in the application's status, Dr. Gary Buehler, Director of the FDA's Office of Generic Drugs, noted that "based on information you have presented to date, the drug [i.e., Mylan generic transdermal fentanyl patch] is safe and effective for use as recommended in the submitted labeling."

The "solid state" product will not be safe under the submitted labeling

The information contained in this petition indicates that this product will not be safe under its proposed labeling. The design of the generic slow-release system will allow each dosage unit to be easily converted into multiple fast-release dosage forms which will have a high potential for patient misuse as well as non-patient abuse. Portions of the "solid state" patch, when applied to the inside of the cheek or other mucous membrane, can be expected to rapidly release their full drug content because they will not have a rate-limiting membrane. The design of the generic product will allow it to be partitioned into "manageable doses" that will allow for repeated use, an important feature which, according to regulatory experts, will promote widespread diversion and abuse.

Patient safety will be imperiled by the current "solid state" product

Because of its recognized efficacy and safety when used for treating severe chronic pain, transdermal fentanyl is often prescribed for patients with intractable pain due to cancer or other non-malignant illnesses for whom other drugs may not be suitable. Experience has shown that patient non-adherence with dosing regimens often complicates treatment plans. Patients experiencing constant severe pain with frequent episodes of exacerbation ("breakthrough pain") will often self-medicate or escalate dosing without proper medical supervision. This unsupervised dosing can result in unintentional drug overdose and death, especially among the elderly or persons suffering psychiatric comorbidities. Unlike the fentanyl transdermal reservoir patch that inhibits patient misuse for reasons explained below, the "solid state" fentanyl transdermal patch will actually facilitate drug "binging", unsupervised and unauthorized escalation of dosing and other non-compliant behaviors that will pose significant safety hazards for our patients. In effect, patients will be able to horde used or new "solid state" fentanyl patches for partition and transmucosal absorption of potentially dangerous quantities of fentanyl at will.

Duragesic's "reservoir" formulation has undermined abuse

The Duragesic patch has not been subject to widespread abuse or patient misuse despite the fact that it contains a large amount of a highly potent and abusable opioid drug. This is because its formulation makes it difficult to partition and repeatedly abuse. This has been the widespread impression of many pain specialists and hospice physicians who will often specifically prescribe Duragesic when they are concerned that a patient or a patient's family member is at risk of misusing or diverting medications (8). According to federal and state law enforcement sources, in its thirteen years on the U.S. market Duragesic has not been widely sought by drug abusers nor widely diverted or marketed by drug traffickers. This is documented in a report attached to this petition as "**Appendix 1** ". The lower incidence of abuse of Duragesic compared with other potent opioids such as OxyContin and methadone is due, in large part, to Duragesic's "reservoir" design. While the generic fentanyl patch may have pharmacokinetics similar to Duragesic's when used correctly, its "solid state" design will give it the abuse potential of a completely different fentanyl product, the transmucosal fentanyl oralet.

The example of the transmucosal fentanyl oralet

The transmucosal fentanyl oralet was introduced into the American market in 1998 under the brand name Actiq. Because of its high potential for abuse, final FDA approval for the marketing of Actiq was made contingent on the development and implementation of a stringent risk management plan (9). Actiq is a "fast release" formulation that delivers between 200-1600 micrograms per hour of fentanyl to the bloodstream when applied to the buccal mucosa inside of the cheek. Like the "solid state" transdermal product, the fentanyl oralet is a solid-state fentanyl delivery system that does not have a rate-limiting membrane to regulate drug outflow. Both the Actiq oralet and the "solid state"

transdermal patch can be cut into pieces and still be used to deliver fentanyl across mucous membranes. Because of its liquid gel "reservoir" design, the Duragesic patch is essentially rendered useless if an attempt is made to cut the patch (10).

Attempts to abuse Duragesic have generally met with failure

There have been anecdotal reports of drug abusers attempting to apply a Duragesic patch or its contents to a mucous membrane but these have been self-limited and isolated episodes which have quickly ended in catastrophe for the abusers (11,12,13,14,15). Attempts to remove and inject the fentanyl-containing gel, likewise, have been short-lived and disastrous (16, 17,18). There have also been reports of abusers trying to convert Duragesic into teabags (19) but the extremely low bioavailability of orally-ingested fentanyl would prevent this from becoming a preferred route of administration. There are even reports that some abusers have tried to convert Duragesic into a "solid state system" by freezing the patch and then cutting it up and "chewing it like Chiclets"(20). These reports have never been substantiated and are rendered rather unlikely by the fact that the freezing point of the contents of a Duragesic patch is somewhere below negative 50 degrees Celsius.

Duragesic has not been a preferred drug among abusers

Mr. John Coleman, a former assistant administrator of the Drug Enforcement Administration, has studied patterns of prescription drug abuse and has noted that *"other novel abuse methods involving Duragesic have been identified in the literature but most depict tragic consequences occasioned by the inability of the would-be abuser to regulate or measure the dosing of the exuded patch contents or to be able to extract and recover purified fentanyl from the hydroxyethylcellulose excipient. The presence of the latter, more so than anything else, appears to inhibit most forms of Duragesic abuse*"[quote used with Mr. Coleman's permission]

A large Regional Poison Information System study found infrequent reports of abuse exposure due to all transdermal medications over 5 years in the Western Pennsylvania area. There were 61 reports for all medications delivered in patch form and only two involved parenteral exposure (e.g., attempted injection). The preparations that resulted in the most intensive use of hospital resources were patches containing clonidine, a medication usually used to treat hypertension (21). This would appear to be confirmed by recent postings regarding Duragesic on Internet web sites that advocate for the diversion and abuse of prescription medications (22). A review of the medical literature using the National Library of Medicine's MedLine and ToxLine data bases from January 1993 through August 2004 showed fewer than fifty reports of abuse or overdose involving fentanyl transdermal systems, even though millions of units were prescribed and used in the United States in each of those years.

Minimization of abuse potential was designed into Duragesic

In 1981, the Alza Corporation responded to a call from a White House-created panel of scientists and physicians to develop more potent analgesics in alternative delivery systems for critically ill and dying patients who were suffering from intractable pain. Scientists from Alza wrote to the head of the Drug Abuse Unit of the FDA expressing interest in developing a transdermal dosage form for the delivery of an opioid analgesic for the relief of chronic pain. Concern about the potential for abuse was an important initial consideration for the scientists who developed Duragesic. This concern strongly influenced their design of the delivery system.

Work on the development of a fentanyl transdermal patch began in late 1982. A feasibility development team headed by Dr. Su Il Yum and Dr. Eun Soo Lee performed the initial research on the patch beginning in 1983. Late in 1983 the Alza feasibility team recommended continued development of the patch and transferred further work to a development team headed by scientists Robert Gale and Victor Goetz.

In early 1983, Alza representatives met with officials from the DEA to discuss the handling of fentanyl. Among other issues, the agency officials expressed concern that the dosage levels of fentanyl be kept to an absolute minimum, because of the potential for diversion and abuse of such a potent narcotic. Minimizing active and residual drug load accordingly became a main focus of Alza's fentanyl patch project.

In their initial development meetings, Alza scientists considered several delivery systems. Among them was a solid-state "monolith system" without a rate-controlling membrane much like the design that is currently proposed for the generic "solid state" fentanyl transdermal system. Another candidate system was a multilaminate patch in which the drug resided in a reservoir with ethanol to increase skin permeability and passed through a rate-controlling membrane. A third possibility was a form-fill seal, in which fentanyl was dissolved in an ethanol, aqueous solution with a large volume of hydroxyethylcelluose excipient. Even though the "solid-state" formulation would have been easier and cheaper to manufacture, only the latter two systems were forwarded to the development team because Alza concluded that systems with a rate-controlling membrane were preferable, given their concerns about potential overdosing and abuse of the delivery system.

Robert Gale's team took over development of the fentanyl patch in December 1983. The team members focused on the ethanol formed-fill seal design because it allowed them to reduce the size of the system and minimize its drug content. An internal company memo from Mr. Goetz noted that "[the] need to keep both residual drug and lag time to a minimum forced selection of an ethanol form-fill-seal design for [fentanyl] product development". Eventually, Alza was able to develop a patch that delivered 72% of its drug load to the patient (ratio of 1.38 = total drug/delivered drug). At a meeting with officials from FDA, DEA and the National Institute on Drug Abuse in 1990, Alza

scientists demonstrated that the amount of fentanyl that could be routinely extracted from its used patches would be non-euphoric doses for addicted users. A medical reviewer for the FDA concluded that Alza had successfully addressed potential abuse issues by minimizing the amount of drug in the patch (23).

On August 7,1990 Alza's ethanol form-fill-seal reservoir patch formulation of transdermal fentanyl was approved for the management of chronic pain in patients who required round-the-clock dosing that could not be managed by less potent analgesics. Alza subsequently entered into a licensing agreement with Janssen Pharmaceutica (a division of Johnson & Johnson) to market the patch under the brand name Duragesic. Duragesic gave physicians their first opportunity to safely prescribe fentanyl, a powerful medication that was specifically designed to treat pain, for long-term use in the outpatient setting. The designers of Duragesic made this possible by packaging the drug in a unique transdermal delivery system that steadily delivered fentanyl directly through the skin and into the blood stream. In its thirteen years on the American market, Duragesic has compiled an impressive record of safety and efficacy, with sizable increases in its medical utilization every year since its introduction.

Re-consideration of the "solid state" design

In 1998, Janssen Pharmaceutica considered changing the formulation of the Duragesic patch by replacing the reservoir design with a solid state delivery system that had been approved in Europe for the transdermal delivery of fentanyl. Switching to the solid state system would have saved the company substantial cost and likely would have resulted in increased sales. At a Janssen advisory board meeting of physicians and other advisors, John Coleman, retired assistant administrator of DEA, voiced concern that a solid state fentanyl formulation could easily be cut into multiple units that would greatly increase the abuse potential of this medication. He specifically warned Janssen executives that their proposed changes could turn Duragesic into "the next great party drug". Based on these concerns, the Janssen project was halted and was ultimately abandoned at considerable expense (John Coleman, personal communication). Experience over the past forty years has shown that fentanyl has an enormous potential for abuse when it is incorporated into a permissive formulation.

Abuse potential of the fentanyl molecule in a permissive formulation

Because fentanyl is such a potent opioid, most formulations of this drug have very high potentials for abuse. Since its first appearance in American operating rooms in 1965, fentanyl solution has been the drug of choice among physicians who are addicted to narcotics. Fentanyl overdose has been the leading cause of death among physician trainees in anesthesia residency programs in the United States for over twenty years (24, 25). In the years since these studies were done, education programs have been mandated for physicians at risk and controls over the transport and accounting procedures for injectable fentanyl in medical settings have been tightened. Unfortunately, a recent study

showed that these programs have had little impact on abuse and diversion by physicians and other medical personnel (26).

In addition to abuse by physicians, fentanyl has been abused for over thirty years by drug addicts on the street who administer it by injection. Nearly all of the fentanyl used in this fashion on the street comes from clandestine laboratories that are actually manufacturing an analogue molecule, 3-methylfentanyl, which is also known by its "street names" such as "China White" or "synthetic heroin" (27). In light of this, it is interesting to note that the introduction and rapid increase in the medical utilization of Duragesic in the United States throughout the decade of the 1990s did not lead to a significant increase in the "street use" of fentanyl (28).

Indirect evidence for low level of Duragesic diversion

Legally-manufactured fentanyl is currently not a significant component of the American street-drug market. In a recently published review of prescription-drug abuse, fentanyl was not listed among the commonly diverted drugs. A study reported in the Journal of the American Medical Association comparing data from the Drug Abuse Warning Network (DAWN) and the ARCOS (Automation of Reports and Consolidated Orders System) data bases found that the increased medical use of fentanyl in the United States between 1990 and 1996 was accompanied by a significant *decline* in DAWN mentions of fentanyl abuse during the same period (29). Of the five opioid drugs surveyed, fentanyl accounted for less than 1% of opioids mentioned in the DAWN survey in 1990. This was the year before Duragesic was introduced in the United States. By 1996, the number of mentions for fentanyl in DAWN had declined by 59% even though the overall manufactured supply of fentanyl reported to ARCOS had increased by 1168%. These data are subject to many interpretations. The Substance Abuse and Mental Health Services Administration that manages the DAWN database cautions that DAWN data cannot be used to measure the prevalence of drug abuse in society but only some of the medical consequences of such abuse (30,31). Nonetheleless, DAWN is often cited by state and federal regulatory officials as an important indicator of drug abuse trends.

The significance of prescription opioid abuse

Abuse of prescription opioid medications has long been an important concern for doctors, patients, regulators and the general public. This concern has accelerated since the onset of the current epidemic of prescription drug abuse, which started about six years ago. In some counties in the United States, deaths from narcotic overdoses have come to outnumber deaths attributed to traffic accidents (e.g. Allegheny County, PA). A growing proportion of these overdose deaths have been related to the diversion and abuse of prescription opioid medications. According to the March 2004 annual report of the Office of National Drug Control Policy, prescription drugs diverted for abuse have increased 163% since 1995, and today constitute a major share of the "street drug" trade, second only to marihuana and far outpacing cocaine and heroin. A report issued in May 2004 by the Florida State Medical Examiner indicated that, based on autopsy results from 6,767

death investigations in 2003, for the first time in history controlled prescription drugs were found to have caused more than half of all the drug-related deaths in the state (31a).

The role of formulation in determining the potential for diversion and abuse

The opioid medications that pose the greatest risk for diversion and abuse are those high-dose "slow-release" formulations that can easily be converted into "rapid-release" drugs. For the past twenty years, slow-release opioid medications have been the mainstay of treatment for moderate-to-severe chronic pain. Generally, the slow-release mechanism in these formulations makes them less susceptible to abuse than their fast-release counterparts. If, however, a slow-release product can be altered to allow fast release of the medication, then the opposite may be true – that is, the increased amount of drug in these formulations actually may increase their susceptibility to widespread abuse and heighten the risk of fatal overdose.

This certainly has been the case for OxyContin, an oral slow-release formulation of oxycodone that can be easily converted into a fast-release preparation by simply chewing or crushing the tablet. The current epidemic of OxyContin abuse has been characterized by a prominent commentator as " a uniquely horrifying case of a powerful drug wreaking havoc in American communities" (32). Because OxyContin tablets are available in dosage strengths that far exceed those in the immediate-release formulations of oxycodone such as Percocet or Percodan, the current outbreak of OxyContin abuse has been accompanied by considerably more overdose deaths than any of the previous outbreaks of oxycodone abuse recorded in the US (33).

Abuse potential of "solid state" fentanyl

Just as slow-release OxyContin can be easily converted to a dangerous fast-release form of the drug, the tentatively-approved "solid-state" generic transdermal fentanyl delivery system will be easily converted into a rapid-release drug by those who simply apply it whole or in part to a mucous membrane (e.g. the inside of the cheek) instead of to the skin. Unlike most drug forms, including the Duragesic reservoir fentanyl patch, the "solid state" generic fentanyl patch can be easily sliced into pieces for immediate misuse or abuse by one or more individuals.

A single 100mcg/hour "solid state" transdermal fentanyl delivery system can be expected to contain over 10,000mcg of fentanyl. A would-be abuser could partition the patch into 20 equal segments, each of which would contain 500mcg of instantly available fentanyl – enough to cause possible overdose and death for an opioid-naïve person. Given this very probable scenario, a single new or used "solid state" generic fentanyl patch could become the ultimate "party drug" for group drug-abuse gatherings in colleges and clubs and wherever else young people may congregate and experiment with psychoactive substances.

Comparing the "solid state" transdermal system to the fentanyl oralet

As mentioned previously, because of its formulation as a "solid-state" system, it is reasonable to expect that the generic fentanyl patch will be as easy to divert and abuse as the transmucosal fentanyl oralet, Actiq. Prior to its marketing, the FDA was aware of the increased abuse potential of the fentanyl oralet and, because of this, the agency delayed final approval until a specific risk management plan was formulated and submitted by the drug's sponsor, Abbott Laboratories. With a duration of delivery of fifteen minutes, a single oralet can rapidly deliver up to 400 micrograms of fentanyl into the bloodstream. (34). As a comparator, studies done with experienced narcotic addicts at Johns Hopkins Hospital showed that fentanyl gave rise to "pleasurable subjective effects" (e.g. a sustained "high") lasting one to two hours in doses of 125 to 250 micrograms (35). Actiq has been found to be better than oral morphine for the treatment of severe episodic pain in cancer patients (36) and better or equivalent to intravenous morphine for the treatment of postoperative pain (37).

In healthy volunteers, oral transmucosal fentanyl is pharmacokinetically similar to intravenous injections of fentanyl (38). In healthy volunteers, oral transmucosal fentanyl has been shown to produce "subjective pleasant sensations" (e.g. a "high") and at higher doses it can also produce sedation and respiratory depression (39). It is important to note that these studies were not undertaken in patients with chronic pain but in healthy volunteers. These healthy volunteers provide a good model for the population that is most at risk from the introduction of a highly abusable and potent prescription drug, the so-called "casual" rather than "hard core" abusers. This group includes many teenagers, for whom prescription analgesics are among the most widely abused drugs, second only to marijuana according to the 2003 National Survey on Drug Use and Health.

Pre-marketing risk planning for fentanyl oralets

In September 1997, at an FDA Advisory Committee hearing on the Actiq transmucosal delivery system, Dr. Laura McNicholas articulated the concern about the at-risk population of young people. She testified about her concerns about the abuse of this product, specifically among young people, despite the increased restrictions that the sponsor offered (unit-dose packaging, artificially elevated retail price, limited indication to the treatment of cancer pain). She made her comments in response to the testimony of Dr. George Bigelow, professor of behavioral biology at Johns Hopkins University School of Medicine (who had been a consultant with Anesta and helped to write the Abuse Liability Section of the original NDA application for Actiq). Dr. Bigelow testified that the heightened restrictions and limited availability of transmucosal fentanyl, along with some of its chemical features, would make it "relatively unattractive to serious drug abusers". In response to Dr. Bigelow's testimony before the FDA advisory committee, Dr. McNicholas stated:

"I don't think that it's going to be your established opioid addict that is going to be most at risk for abuse here. I think it's going to be your college-age kid, your young adult who wants a weekend party drug. And

I'll tell you, my nightmare is having 20 kids out there having a party all of them, so they can have a lollipop party. And 18 of them don't wake up the next morning. And my issue here is not that people are not going to do this. My issue is, what are the steps being taken? I've heard limited availability, limited availability, but I haven't heard exactly how that availability is going to be limited.

And my issue here is that for the first time in my professional career, we are finally getting to something approaching rationality in the treatment of pain and we are stopping this demonization of the appropriate use of opioids. And if something like this happens and it gets on "Good Morning America" and "Nightline" and everything else, I don't want us going back to where we were 20 years ago when we were treating cancer pain with aspirin. And I really see a danger that if something like this gets out we're going to have a horror story."

Actiq did not receive approval with its initial application. The FDA required that a risk management plan be developed that, among other things, included "restricted promotion, restricted indications, restricted distribution, restricted prescribing and restricted dispensing". The unique risk management plan recommended by the FDA advisory committee for Actiq featured a limited medical indication (restricted to cancer patients only), limited availability of the product and artificial elevation of the retail price in order to discourage third-party reimbursement.

Adherence to the Actiq risk management plan

As reported in the Wall Street Journal on May 17, 2004 (40), there have been features of the original Actiq risk management plan that have not been translated into clinical practice. A study done by NDCHealth, a healthcare information company, showed that this medication which was supposed to be limited to cancer patients was being prescribed to patients without cancer by a growing number of family doctors and internists. The article noted that the number of Actiq prescriptions has tripled in the last three years. This has been accompanied by an increase in the misuse and illicit trade of the fentanyl oralets which are being sold on the street under the nickname "perc-a-pops" and "crack sticks". An article carried by the Associated Press on April 28, 2004 (41) reported that the Attorney General of Pennsylvania had issued a public warning about Actiq, noting that there was " a growing trend in illegal street sales of this drug" in his state.

Medicinally equivalent to Duragesic, more abuseable than Actiq

Under its current labeling, the generic "solid state" fentanyl transdermal system will be considered the equivalent of Duragesic even though its potential for abuse is expected to equal or exceed that of Actiq. If marketed under these conditions and without an effective risk-management plan, the generic "solid-state" fentanyl patch will certainly be much more available than the fentanyl oralet. Each "solid-state" patch will also contain hundreds of times more drug per dosing unit than the single-dose oralet. As one of our medical colleagues recently remarked, "if the Actiq oralet is being called a fentanyl lollipop, then this new product will soon be known as the fentanyl pizza". It is reasonable to expect that, without a change in the formulation or the implementation of an effective

risk management plan, the diversion and abuse of the generic "solid state" fentanyl transdermal system will quickly and surely exceed that of OxyContin.

Developing risk management plans for all new C-II products

In a recent review of the diversion and abuse of OxyContin, the General Accounting Office (GAO) recommended that risk management plans be developed for all new potent opioid products prior to their approval for marketing (42). In the report, GAO investigators stated that "to improve efforts to prevent or identify abuse and diversion of controlled substances such as OxyContin, FDA's risk management plan guidance should encourage pharmaceutical manufacturers with new drug applications to submit plans that contain a strategy for identifying potential problems with abuse and diversion." As the report documents, the FDA concurred with GAO's recommendation and issued proposed industry guidelines for "RiskMAPs" (risk minimization action plans) in 2004. Following a period of public comment, the FDA planned to provide guidance to the pharmaceutical industry by September 2004 on risk management plans (expected to be an "optional feature" of new drug applications for psychoactive substances). Consultants from the Drug Enforcement Administration interviewed for the report noted that "it is essential that risk management plans be put into place **prior** to the introduction of controlled substances into the marketplace."

The Federal Food, Drug and Cosmetic Act (FFDCA) and the Controlled Substances Act (CSA) were intended by Congress to be carried out in a collaborative fashion by the FDA and DEA. In practice, the FDA holds a superior role by virtue of its statutory authority to approve all new drugs. Once a new drug is approved by FDA for medical use, the DEA is obliged to schedule it if the FDA so recommends. The Controlled Substances Act does not permit DEA to deny scheduling for an approved drug, even if there should be a potential for excessive abuse, or to remove an FDA-approved drug from the market because of excessive abuse. Thus, if the FDA is to have superior authority over the scheduling of drugs, as the FFDCA and CSA now provide, then it should be required to give equal weight to abuse potential, along with efficacy and safety issues, when evaluating a new drug for approval. This weakness in the present law was compounded by the failure of the 1984 Hatch-Waxman Amendments to address abuse potential in generic versions of branded drugs. If abuse potential were given equal standing with efficacy and safety in the NDA and ANDA processes, the public would be better served by its federal drug regulatory agencies.

The population at risk for prescription drug abuse

The increase in the abuse of prescription opioids is a growing public health concern and should be addressed by identifying the causes and sources of diversion without interfering with legitimate medical treatment and proper patient care. Most patients with chronic pain do not escalate their dosages or abuse their medications (43, 44). There is little overlap between the population taking prescribed psychotropic medications and the

drug-abusing population (45). While claims of overutilization are often made, research suggests that underutilization occurs much more frequently, particularly with regard to the use of medications to treat patients with chronic pain (46).

Special safety considerations in evaluating opioid medications

The approval process for opioid medications deserves special consideration because concerns about the safety of these medications have to extend beyond the intended users. Knowing the relative magnitude of the various sources of diversion and weighing the risks and benefits of each diversion control method are essential in developing effective prescription drug abuse prevention strategies that do not have an adverse impact on medical practice or on the quality of patient care.

The FDA has already publicly endorsed the GAO recommendation that pharmaceutical manufacturers submitting new drug applications for schedule II controlled substances include strategies to address concerns about abuse and diversion. There is nothing in the 1984 Hatch-Waxman Amendments to the FFDCA that would compel the FDA to abrogate this obligation to safety in the case of products that are submitted under abbreviated applications. If adequate Federal regulation turns out to be lacking, then the states will be put in a position of having to impose additional restrictions.

In conclusion

Based on the information that we have presented in this petition, we think that it is reasonable to assume that once an A-B rated generic "solid state" fentanyl transdermal system enters the American market, the branded reservoir formulation that has been so useful for so many patients for so many years will soon disappear. Granting full approval to ANDA 76-258 in its present form will undermine our efforts to promote safe pain relief while preventing diversion by essentially replacing a safe and useful analgesic medication with a highly abusable and dangerous drug. As the Commissioner and the other experts at the FDA consider the question of final approval, we hope that they will be thinking of our patients who suffer with chronic pain, keeping in mind our young people who are at risk to abuse drugs and remembering the words of the spokesman for the American Medical Association who stated that "the war on drug abuse can and must be fought alongside the war on disease, pain and suffering; one must not be allowed to impede the other." (47)

DISCLOSURE/ IDENTIFYING INFORMATION

Dr. Daniel Brookoff is a full-time physician with specialty certifications in Internal Medicine and Medical Oncology in Memphis, Tennessee whose practice is focused on the continuing care of adults with chronic pain. He has been a full time employee of

Methodist Healthcare of Memphis since 1993 where he is currently Associate Medical Director of the Methodist-University of Tennessee Pain Institute. He has received honoraria and fees from pharmaceutical companies for lectures and consultation in the field of pain management and drug abuse within the past five years. These companies include Janssen Pharmaceutica, the marketers of Duragesic, as well as Pfizer, Purdue Frederick, Ortho-McNeil, Cephalon and others. His research interests and academic activities have focused on the treatment of chronic pain and the prevention of drug abuse. (see curriculum vitae attached to this petition as **Appendix 2**). Neither Dr. Brookoff nor any member of his immediate family have any other financial interests that would be influenced by the requested action.

Dr. Eric Voth is a full-time physician with specialty certifications in Internal Medicine and additional training in Addiction Medicine in Topeka, Kansas whose practice is focused on General Internal Medicine and Addiction Medicine. He has been affiliated with Stormont-Vail Health Care since 1995 where he is currently Assistant Medical Director. He has received honoraria for lectures from pharmaceutical companies within the past five years. These companies include Ortho-McNeil, a division of Johnson and Johnson which is also the parent corporation of Janssen Pharmaceutica, the marketers of Duragesic. His research interests and academic activities have focused on the prevention of drug abuse and the appropriate use of controlled medications (see curriculum vitae attached to this petition as **Appendix 3**). Neither Dr. Voth nor any member of his immediate family have any other financial interests that would be influenced by the requested action.

This petition was prepared in its entirety by Drs. Brookoff and Voth without any outside assistance or support or the offer thereof. They take full responsibility for its contents. No employees or agents of any of the involved pharmaceutical manufacturers or government agencies were consulted or even informed as to the preparation of this petition.

ENVIRONMENTAL IMPACT

Not applicable

CERTIFICATION

The undersigned certify that, to the best knowledge and belief of the undersigned, 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,

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http://www.deadiversion.usdoj.gov/drugs_concern/fentanyl.htm

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The patch is "too dangerous" to abuse:
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Abuser compares abuse utility of a solid matrix formulation to the reservoir patch:
http://www.erowid.org/experiences/exp.php?ID=36010
Dangers of abuse due to difficulty apportioning the contents:
http://www.erowid.org/experiences/exp.php?ID=28861
A five-year heroin user thinks that the reservoir patch is "too dangerous" to use:
http://www.erowid.org/experiences/exp.php?ID=29958
Difficulty abrogating the structure of the patch:
http://www.erowid.org/experiences/exp.php?ID=23983

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APPENDIX 1 *this manuscript was written by Mr. John Coleman and Dr. Daniel Brookoff and submitted for publication to the Journal of Pain and Symptom Management with the support of Jannsen Pharmaceutica. The authors later withdrew this manuscript from consideration at the request of Janssen executives who felt that it might serve to promote generic products at the expense of a new product that Janssen was anticipating bringing to market.*

TITLE: Assessment of the Abuse of Transdermal Fentanyl

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ABSTRACT

Background: In the wake of reports of abuse and overdose deaths related to precription opioids, several states are considering imposing additional restrictions on all Schedule II opioid medications.

Objective: To determine whether transdermal fentanyl has been subject to widespread abuse and trafficking.

Design: We reviewed Federal databases and surveyed large police departments for reports of unlawful activity related to this medication.

Results: In 8 of the last 10 years, fentanyl did not receive enough mentions in the Drug Abuse Warning Network (DAWN) emergency department survey to be included in the list of abused drugs. In the survey of medical examiners, fentanyl was mentioned in 53 of 11,651 (0.45%) drug-related deaths. The database of subjects admitted to federally-funded drug treatment programs contained no mention of admissions for treatment due to the use of transdermal fentanyl. Reviews of DEA's STRIDE II and NFLIS databases showed rare mentions of fentanyl . None of the databases surveyed distinguished among different formulations of specific drugs. Of 38 police departments responding to the survey, 33 specifically reported no criminal activity in their cities related to transdermal fentanyl. The five departments with positive responses reported either isolated cases or unsubstantiated reports of abuse.

Conclusions: Fentanyl in a sustained-release transdermal formulation has not been widely sought by drug abusers nor widely diverted or sold by drug traffickers in the U.S. in the ten years since its introduction.

INTRODUCTION

Since the mid-1980's there has been a steady increase in the abuse of prescription opioid medications in the United States. The latest Federal household survey found that more than 8% of respondents over the age of 12 years reported non-medical use of prescription opioids. 1.6 million Americans abused prescription opioids for the first time in the year 2000, representing a greater than three-fold increase in the number of new users over the past ten years (2). Data from the Federal Drug Abuse Warning Network (DAWN) showed that in the period between 1998 and 2000 medical emergencies attributed to the illicit use of the two most commonly-abused prescription opioids, hydrocodone and oxycodone, rose 53% and 108% respectively (3). A DAWN survey of 139 medical examiners reported a 53% increase in drug-abuse related deaths involving oxycodone between 1998 and 1999 (the latest year for which complete medical examiner results are available). Because of the way the data were reported, these findings could not be attributed to any specific formulations of the drugs.

News reports have linked the recent increase in medical emergencies related to oxycodone to a sustained-release formulation that was introduced into the American market in 1996 for the treatment of chronic pain (4,5). An official of the Drug Enforcement Administration (DEA) was quoted as saying that "no other prescription drug in the last 20 years has been illegally abused by so many people so soon after it appeared."(6). In response to these reports of abuse, legislation has been introduced in

several states that would place new restrictions on sustained-release opioid medications, including limiting their use to terminally ill patients (7).

Not all sustained-release opioids that are available for the treatment of chronic pain have shown recent increases in indices of abuse. One example is fentanyl, a potent opioid that has been available in a sustained-release transdermal patch formulation since 1991 (8). While fentanyl has a high potential for abuse when formulated as a liquid for intravenous injection (9,10), reports of abuse of the transdermal formulation have been rare (11). In order to assess the level of abuse of transdermal fentanyl, we examined existing drug-abuse related databases and surveyed law enforcement organizations for information concerning abuse and unlawful activities related to the diversion or trafficking of this medication.

METHODS

DAWN Databases

The federal Drug Abuse Warning Network (DAWN) is a national probability survey of hospital emergency departments (ED) conducted annually by the Substance Abuse and Mental Health Services Administration (SAMHSA). As such, the survey is designed to capture data on ED episodes that are induced by, or related to, the use of an illegal drug or the nonmedical use of a legal drug (3). DAWN does not include accidental ingestions or inhalations of substances with no intent of abuse nor does it monitor adverse reactions to prescription or over-the-counter medications taken as prescribed (3). In calendar year

2000, DAWN estimated that there was a total of 601,776 drug overdose episodes involving 1,100,539 individual drugs (3). In a separate survey, DAWN collects data from medical examiners (ME) on the frequency of mentions of drugs in drug-related or drug-induced deaths (12). In 1999, the last year for which complete statistics are published, there was a total of 11,651 drug abuse deaths involving 29,106 drug mentions reported to DAWN by 139 participating MEs in 40 metropolitan areas (12).

TEDS Database

The Treatment Episode Data Set (TEDS) collects information on approximately 1.6 million substance abuse treatment admissions reported annually by States receiving federal assistance for substance abuse treatment. Nearly 10 percent of patients seeking entry into drug treatment facilities are principally abusing "prescription drugs". The published records do not report the specific drugs or formulations for which treatment is being sought (13). Because of this, the SAMHSA program manager for TEDS was queried directly for mentions of fentanyl in the TEDS database.

Federal Law Enforcement Databases

The major database on arrests in the United States, the FBI's Uniform Crime Reports, does not identify drugs related to crimes or arrests. To obtain forensic data on criminal cases involving the diversion of transdermal fentanyl, an inquiry was made via the Freedom of Information Act to query the Drug Enforcement Administration's (DEA) STRIDE II database. STRIDE is an acronym for "System To Retrieve Information from Drug Evidence". STRIDE II provides information on drugs analyzed in DEA laboratories

and outside laboratories in cases in which DEA participated in the seizures. Besides processing tens of thousands of DEA drug exhibits each year, the DEA laboratory also performs forensic analyses for drug exhibits acquired by the FBI and other federal and some local law enforcement agencies throughout the United States.

The National Forensic Laboratory Information System (NFLIS) is a database maintained by DEA of drug samples presented to state and local crime laboratories. Of the 276 individual facilities in the United States that operate as state or regional laboratories processing drug evidence from law enforcement agencies, 105 participate as reporters to this system.

Police Department Survey

Because there is no national database on prescription medications involved in arrests processed entirely by state and local law enforcement agencies, we conducted a survey of local police agencies. Between January and October 2000, letters were sent to 51 police departments throughout the United States representing the largest cities by population, according to a list furnished by the International Association of Chiefs of Police. The letters requested information regarding reports of incidents in which the police departments encountered unlawful activity involving fentanyl patches.

RESULTS

DAWN

Each year, as part of its published findings, the DAWN Emergency Department survey ranks drugs by numbers of mentions and percent of total episodes. Substances receiving fewer than 200 weighted mentions in a given year are excluded from the published results ("weighted mentions" means that the actual number of reports are multiplied by a factor to come up with a nationwide estimate). In 1999, for example, the DAWN survey listed 108 "drugs mentioned most frequently by emergency departments". Fentanyl, receiving fewer than 200 weighted mentions out of an estimated 1,015,206 ED drug mentions in the contiguous US during 1999, was not listed. In reviewing DAWN ED data for the decade of 1991 through 2000, fentanyl has been included only twice in the annual list of most frequently mentioned drugs. In 1998, fentanyl was ranked #115 out of 123 drugs on the list with 223 out of 982,856 mentions and in 2000 fentanyl was ranked #92 of 102 drugs, with 291 out of 1,100,539 mentions (3).

In order to characterize subjects cited for fentanyl abuse, a special request was made to DEA to obtain the actual clinical reports to DAWN for fentanyl abuse during the 1996-1998 period (the most recent period for which this type of unweighted data was available). These are the raw data upon which DAWN's nationwide estimates are based. According to the DEA response, from January 1996 through June 1998, fentanyl was

mentioned in 52 of more than a million tabulated drug abuse-related ED visits. Of these 52 episodes, 23 (44%) involved fentanyl alone while the remainder involved fentanyl in combination with another substance (usually alcohol). According to DEA analysts familiar with these data, it was unlikely that these episodes involved the transdermal formulation of fentanyl. They indicated that it was more probable that the episodes involved injectible forms of fentanyl, which may include the formulations usually restricted to operating rooms as well as a more commonly encountered illicit, clandestinely manufactured analogue, alpha-methylfentanyl, known on the street as "China White" or "synthetic heroin"(14).

Analysis of these individual reports of fentanyl abuse in the special DEA query showed that fentanyl users differed from users of other opioids mentioned in DAWN in several important ways. Other opioids were generally abused for "recreational purposes," usually by subjects under the age of 30. When the 52 episodes involving fentanyl were reviewed, only 7% of the patients ascribed use of the drug to "recreational use". In more than 70% of the cases, the drug was used to support dependence or used to attempt suicide. Sixty-five percent of the fentanyl abusers in the DAWN sample were over the age of 35 and only 6% were under 24 years. By comparison, overall DAWN estimates for the age of abusers of prescription analgesics indicate that 75% of recreational abusers of these substances are between 12 and 34 years of age (3).

A review of the DAWN Medical Examiner database showed that in 1999 the opioids for which there had been a significant increase in the frequency of mentions over the

previous year were meperidine (59%) and oxycodone (53%). The relative frequency of reports of the various opioids linked to drug-abuse related deaths is listed in Table 1. As in the DAWN ED reports, the data furnished by the medical examiners did not identify the specific formulations of the drugs identified in their reports. For 1999, 139 participating medical examiners from 40 metropolitan areas reported a total of 11,651 drug-abuse related deaths involving 29,106 individual drug mentions. In the published list of "drugs mentioned most frequently" in the ME reports, fentanyl ranked forty-ninth with 53 mentions. During the period under review, 1991 through 1999, the DAWN ME annual survey listed fentanyl in less than one-half of one percent of all cases per year.

Treatment Episode Data Set (TEDS)

In 1998, the last year for which data have been published, TEDS recorded 1.6 million admissions for substance-abuse treatment. Heroin accounted for 13.8% and other opiates accounted for 1.1% of admissions. The TEDS data included drug-specific information from only 157,000 admissions, which is less than 10% of the total. Opiates that were specifically named in the data set included morphine, non-prescribed methadone, codeine, oxycodone, hydromorphone, D-propoxyphene, meperidine, and pentazocine. Fentanyl was not specifically mentioned. There was a category of "other opiates" which accounted for less than 0.3 percent of primary drugs of abuse reported to the database.

Federal Law Enforcement Databases

According to the STRIDE II database, from January 1,1991 until November 2, 2000, there were only two cases in which transdermal fentanyl was submitted to the DEA laboratory system. One was a case initiated by the FBI in 1993 in Tennessee in which 8 transdermal fentanyl patches were acquired as evidence. The second was a recent DEA case in Miami, Florida involving a total of 17 patches. In that case undercover police bought 8 of these patches for $100 each and the seller, a patient with AIDS, was arrested in possession of an additional 9 patches. This is the only case of street sale of the patches in the forensic database and it therefore set the unofficial "street price" of the patches at $100.

NFLIS data for drugs submitted to state and local crime laboratories for 2001 (Table 2) show that the two most frequently mentioned prescription opioids were hydrocodone and oxycodone. Fentanyl was mentioned in 23 of 7,680 reports involving prescription opioids analyzed by respondent laboratories during this period. According to DEA diversion specialists who assisted in the retrieval of these data, fentanyl patches are not a popular target for thieves nor a desirable drug of choice for addicts. Similarly, these specialists reported that fentanyl in its liquid form is a sought-after product for pharmacy thieves. There were only one or two cases in the past ten years, these experts report, where pharmacy burglaries involved thefts of transdermal fentanyl alone (*personal communication:* John J. Crowley, DEA Supervisory Diversion Investigator).

Police Department Survey

Thirty-eight police departments representing jurisdictions with an aggregate population of over fifty million responded to the mailed survey. Five of the of the 38 respondents reported unlawful activity involving fentanyl patches. All of these responses described either isolated cases or unsubstantiated reports (see Table 3). The remaining police departments specifically reported no incidents of unlawful activity related to the fentanyl patch . These include the police departments of New York City, Los Angeles, Chicago, Houston, Philadelphia, Boston, Dallas and Metro-Dade Miami (Table 4).

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DISCUSSION

Our findings indicate that transdermal fentanyl has not been widely sought by drug abusers nor widely diverted or sold by traffickers. In the course of carrying out this study, reviews of cases with DEA diversion specialists did not turn up any evidence of widespread diversion, abuse or thefts of transdermal fentanyl. For example, the Boston DEA Diversion Group reported one mention of fentanyl patches in the six-state New England region over the past five years and this was an isolated overdose death related to transmucosal abuse of the patch (*personal communication:* John Crowley, DEA Supervisory Diversion Investigator).

Reports of abuse of transdermal fentanyl in the medical literature have also been rare (10,15). A large study of fentanyl-related deaths done by the Office of the Coroner for

Los Angeles County found little evidence of recreational abuse of the transdermal formulation (16). In a review of cases between 1997 and 2000 occurring in Los Angeles County (population of 9.9 million), the coroner recorded 25 deaths in which the transdermal formulation of fentanyl was a factor. Most of the subjects had cancer, AIDS or other chronic pain conditions and were using transdermal fentanyl prescribed to them by a physician. Two of the deaths were related to recreational use of the fentanyl patch, one of them by a teenager who used patches prescribed for his father, a cancer patient.

Transdermal fentanyl is probably less subject to abuse than other potent opioids because of its chemical formulation. Serum levels of transdermally-administered fentanyl can take up to 72 hours to reach peak levels (8). The complete first-pass metabolism of fentanyl to inactive metabolites makes its oral bioavailability "essentially zero"(17) and has subverted abuse by oral ingestion (18,19). The excipients used in the transdermal formulation appear to limit intravenous abuse. In published reports, intravenous injection of the contents of the fentanyl patch is quickly followed by massive pulmonary embolism (20,21) due to the hydroxyethyl cellulose in the patch reservoir from which the fentanyl is difficult to separate. Attempts at heating and inhaling the contents of the patch likewise have resulted in immediate respiratory arrest (12) as have attempts to apply the contents of the patch transmucosally (22). A recent study of prescription opioid abuse among patients in a large pain clinic over a three year period showed that transdermal fentanyl had the lowest potential for misuse of the commonly-prescribed opioids (23). When formulated in an injectable liquid form, however, fentanyl has been related to large outbreaks of lethal overdoses (14,24-26).

When deciding to prescribe opioid medications, physicians often will choose a drug based on their perception of its abuse potential (27), relying on government classifications of abuse potential for guidance (28). In classifying drugs, regulators recognize that the chemical identity of a drug is not the only determinant of its abuse potential. For example, some opioids, which in their pure form are listed in Schedule II (licit drugs with the highest potential for abuse) such as hydrocodone, codeine, and diphenoxylate, are listed in less restricted categories when formulated within specific dosage limits in combination with other medications (e.g. acetaminophen) or in low-dose elixirs. To inhibit abuse without reducing dosage strength, opioid antagonists can be incorporated into analgesic medications to specifically prevent abuse by alternate routes of administration (29).

The abuse potential of an analgesic medication may also be reduced due to characterististics of a drug's delivery system or by its combination with inactive excipients. This is evident in the case of dronabinol, which was re-classified from Schedule II to Schedule III in 1999 (30). Dronabinol is a synthetic isomer of delta-9-tetrahydrocannabinol, one of the active ingredients in herbal marijuana, (which remains in Schedule I). In its decision to loosen restrictions on dronabinol, the DEA took into account the specific nature of the formulation, finding that "despite dronabinol's THC-like abuse liability, there are several factors that deterred its actual abuse and trafficking." These factors included dronabinol's formulation in sesame oil, the improbability that the

THC would be extracted from the product and abused by another route of administration and its delayed onset of effects (31). In light of the DEA's decision, our findings could support a reconsideration of the scheduling of transdermal fentanyl.

The federal government's task of assessing the abuse potential of controlled medications depends upon the individual discretion exercised by its experts in the fields of public health and public safety, supported by available data on drug abuse. Because some of these medications are vital for the treatment of chronic pain, unnecessarily restrictive scheduling may inhibit appropriate pain management and thus compromise good patient care. One disturbing finding of our review of government databases, was the lack of a single source of data on the prevalence of abuse of specific drug formulations. This concern about the lack of data on prescription drug abuse and diversion is not new, having been expressed in the pages of JAMA over ten years ago (32). In order to prevent the abuse of pain medications while promoting pain relief it will be necessary to gather accurate and accessible information on prescription drug abuse.

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TABLE 1. DAWN Medical Examiner data on opioids reported in drug-abuse related deaths excludes data on homicides and deaths in which AIDS was reported. (12)

Overall Rank*	Drug	# of Mentions	% of Total Deaths**
2	Heroin/Morphine	4,820	41.37
4	Codeine	1,395	11.97
8	Methadone	643	5.52
11	d-Propoxyphene	466	4.00
13	Hydrocodone	447	3.84
19	Oxycodone	262	2.25
32	Meperidine	103	0.88
49	Fentanyl	53	0.45
53	Hydromorphone	46	0.39

*among all drugs mentioned

** most deaths had more than one drug mentioned

TABLE 2. NFLIS reports for prescription analgesics in order of frequency January 1-March 31, 2001 (33)

DRUG	Number of Mentions	Percentage
Oxycodone	**740**	**35.12%**
Hydrocodone	729	34.60%
Codeine	244	11.58%
Propoxyphene	147	6.98%
Morphine	119	5.65%
Hydromorphone	54	2.56%
Meperidine	32	1.52%
Tramadol	18	0.85%
Nalbuphine	15	0.71%
Fentanyl	6	0.28%
Pentazocine	2	0.09%
Butorphanol tartrate	1	0.05%

TABLE 3. The responses of the five police departments that reported unlawful activity involving transdermal fentanyl.

Virginia Beach Police Department: August 3, 2000

Detective S. L. Wichtendahl with Special Investigations, formerly with the diversion squad, has informed me of one case involving Duragesic. In October 1998, a female subject fraudulently obtained a prescription for five (5) patches of Duragesic, indicating it was for personal use. At the time of this incident, she was the designated caretaker for her elderly father who had a legitimate need and prescription for this drug. This subject, who had a long history of prescription drug abuse, was subsequently charged with an overwhelming number of other felony prescription violations involving Vicodin, but none for the Duragesic violation.

— Alfred M. Jacocks, Jr., Chief of Police

Montgomery County, MD, Police Department August 10, 2000

The Montgomery County Police, Special Investigations Division, Pharmaceutical Unit, is aware of one case of abuse which resulted in the death of an individual. In January 2000 the individual placed several Duragesic patches on his body and died as the result of an opioid overdose. The Homicide and Sex Unit investigated the case and his death was classified as an accidental overdose. No other cases of abuse or diversion have been brought to the attention of this Department.

— Captain Brian McManus, Special Investigations Division

Milwaukee Police Department: September 15, 2000

To date, the Milwaukee Police Department has no record of unlawful activity involving Duragesic. However, upon contact with the Wisconsin Regional Crime Laboratory (1578 S. 11th Street, Milwaukee, WI, (414-382-7500) a spokesman, John Motquin reported two cases of Duragesic sent to the crime lab to date. Mr. Motquin stated that the cases were from Wisconsin's Walworth County and Barron County.

— Arthur L. Jones, Chief of Police

Pittsburgh Police Department:August 4, 2000

The Pittsburgh narcotics unit in the four years under my command has never had a seizure of Duragesic, nor conducted any investigations regarding the diversion of this drug. I have learned from one of our task force officers that one local location caught someone going through the trash looking for patches that were discarded and this organization was developing a policy to tighten up within their organization better methods of disposing of Duragesic.

— William J. Joyce, Commander, Narcotics and Vice Division

Indianapolis Police Department August 8, 2000
Detective Conder, in charge of prescription crimes and diversion for the City of Indianapolis Police Department, advised by phone that there have been no reported incidents involving Duragesic on file with the Indianapolis Police Department. In an effort to obtain more information, Det. Conder contacted other departments throughout the state. One unnamed investigator in a location near the Ohio border reported hearing about someone who was trying to sell a single used patch. This was never confirmed and Det. Conder advised that the individual in question was never identified.

— Det. Conder, Indianapolis Police Department Drug Squad

Table 4. Overall results of the police departments survey.

Reported criminal activity related to transdermal fentanyl.
Indianapolis IN
Milwaukee, WI
Montgomery County, MD
Pittsburgh, PA
Virginia Beach, VA

Reported no criminal activity related to transdermal fentanyl

Baltimore City Police Department (MD)
Baltimore County Police Department (MD)
Boston Police Department (MA)
Buffalo Police Department (NY)
Chicago Police Department (IL)
Columbus Police Department (OH)
Dallas Police Department (TX)
Denver Police Department (CO)
Detroit Police Department (MI)
El Paso Police Department (TX)
Ft. Worth Police Department (TX)
Honolulu Police Department (HI)
Houston Police Department (TX)
Kansas City Police Department (MO)
Las Vegas Police Department (NV)
Los Angeles Police Department (CA)
Los Angeles Sheriff's Department (CA)
Maryland State Police (MD)
Memphis Police Department (TN)
Metro-Dade Police Department (FL)
Minneapolis Police Department (MN)
Nashville Police Department (TN)
Nassau County Police Department (NY)
New York City Police Department (NY)
Newark Police Department (NJ)
Philadelphia Police Department (PA)
Portland Police Department (OR)
Prince Georges County Police Department (MD)
San Antonio Police Department (TX)
San Diego Police Department (CA)
Seattle Police Department (WA)
Tulsa Police Department (OK)
Washington D.C. Police Department (DC)

(Table 4 continued)

Did not respond to survey

Atlanta Police Department (GA)
Austin Police Department (TX)
Cincinnati Police Department (OH)
Cleveland Police Department (OH)
Charlotte-Mecklenberg Police Department (NC)
New Orleans Police Department (LA)
Oakland Police Department (CA)
Phoenix Police Department (AZ)
Salt Lake City Police Department (UT)
San Francisco Police Department (CA)
San Jose Police Department (CA)
St. Louis Police Department (MO)
Suffolk County Police Department (NY)

APPENDIX 2. Curriculum Vitae of Dr. Daniel Brookoff

Curriculum Vitae

May 3, 2004

Daniel Brookoff

Present Position:
Associate Medical Director, Methodist-University Comprehensive Pain Institute
Clinical Associate Professor (Medicine, Preventive Medicine, Urology)
University of Tennessee College of Medicine

Previous Positions at Methodist Healthcare
Associate Director, Medical Education,Methodist Healthcare System (1993-2001)
Site Director, Methodist Hospital; University of Tennessee Hematology-Oncology Fellowship Program (1995-2000)

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email: Brookofd@methodisthealth.org

Education:
1969-72Bronx High School of Science, Bronx NY
1972 Deep Springs College, Deep Springs, CA
1972-76 SUNY at Stony Brook Stony Brook, NY (B.S. in Applied Mathematics 1976)
1976-82University of Pennsylvania School of Medicine, Philadelphia PA (M.D. 1982, Ph.D (Pathology)1985

Postgraduate Training and Fellowship Appointments:

1974-76 Research Associate, Brookhaven National Laboratory, Upton NY
1982-85 Residency in Medicine, Hospital of the University of Pennsylvania
1985-87 Fellowship in Hematology-Oncology, Hospital of the University of Pennsylvania
1997 Havard- Macy Foundation Fellowship in Medical Education

Specialty Certification:

1985 American Board of Internal Medicine
1987 Subspecialty Certification in Medical Oncology

Other Certifications:
ACLS
ATLS
ATLS-Instructor

Faculty Appointments:

1987-88 Lecturer in Medicine, University of Pennsylvania
1988-91 Assistant Professor of Medicine, University of Pennsylvania
1991-93 Assistant Professor of Medicine, University of Tennessee College of Medicine at Memphis
1995- Clinical Associate Professor of Medicine, University of Tennessee College of Medicine at Memphis

Licensure: Tennessee, Pennsylvania

Awards and Honors
1972 National Merit Scholarship Finalist
1976-82 Scholar of the Pennsylvania Plan
1986 American Cancer Society Fellowship
1990 Research Prize, American Association of Family Physicians
1994 Memphis Area Health Industry Council Prize Award for Excellence in Research
1995,98 Miracles in Motion Award, Methodist Health System
1998 Meritorious Service Award THA-Tennessee Hospital Association
2000 Malcolm Grow Lectureship, Society of Air Force Physicians

Professional Societies:
American College of Physicians
American Medical Association
American College of Emergency Physicians
American Pain Society
American Public Health Association
College of Physicians of Philadelphia
Society for Academic Emergency Medicine
Southern Medical Association
Southern Association for Oncology
Tennessee Medical Association
Shelby County Medical Society
Southern Pain Society
Tennessee Pain Society
American Academy of Hospice and Palliative Medicine

Board Memberships and Other Appointments:

1990-91 Pennsylvania Medical Society Task Force on Drug Abuse
1990-3 National Association for a Drug-Free America (Board Member)
1991-2 Assistant Director, Office of Drug Policy, City of Memphis
1991-4 Advisory Board, "Baby Love" program for substance-abusing mothers
1991- Medical Advisory Board, Interstitial Cystitis Association
1991 Task Force on Drug Abuse, Memphis 2000

1992 Board Member, Project Advance (anti-drug program for junior high school
1992- TN Delegate, Drug Watch International
1996- International Drug Policy Institute
1994-7 Advisory Board, Methodist Home Care and Hospice
1994-99 Board member, Aloysius Home for People with HIV and AIDS, Vice-Chairman 1996; Chairman 1996-98
1995-2000 Shelby County Task Force on Domestic Violence, 1998 Executive Committee
1996- Tennessee Pain Society, Vice President 1996-7; President 1997-8
1998-9 Advisory Board, Friends For Life
1998-9 Working group on Alcohol and Domestic Violence. Office of Justice Program Dept of Justice. Washington
1999 Board member, Exchange Club Family Center
2000-2 National Advisory Council, Center for Substance Abuse Prevention; SAMHSA, HHS
2000- AGS Task Force on Pain Research Guidelines

Editorial Positions:
1988- Reviewer, Journal of General Internal Medicine
1991- Reviewer, Annals of Internal Medicine
1992- Reviewer, Southern Medical Journal
1993- Reviewer, Journal of Women's Health
1994- Reviewer, Annals of Emergency Medicine
1995-7 Editorial Board, Southern Medical Journal
1997-9 EditorialBoard, The Journal of AcutePain and Symptom Management: Index & Reviews

Original Papers:

1. Reincke U, Brookoff D, Burlington H, Cronkite EP, Gerard E. Differentiated cells in marrow and spleen of mice subjected to Fe-55 erythrocytocide. Exp Hemat 1976; 4:6-10

2. Reincke U, Brookoff D, Burlington H, Cronkite EP, Pappas N, Zanjani E. Susceptibility of hemopoietic stem cells to Fe-55 radiation damage. Radiat Res 1978; 74:66-73.

3. Reincke U, Brookoff D, Burlington H, Cronkite EP, Gerard E. Are stem cells regulated by late erythroid precursors? In: Baum SJ and Ledney GD (eds) Experimental Hematology Today. Springer-Verlag, New York 1978.

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21. Brookoff D, Cook CS, Williams C, Mann CS. Testing reckless drivers for cocaine and marijuana. New England J Med. 1994; 331:518-22.

22. Brookoff D. Compliance with doxycycline in the outpatient treatment of pelvic inflammatory disease. Southern Med J. 1994; 87:1088-1091

23. Brookoff D, Kellermann AL, Hackman BB, Somes G, Dobyns P. Do blacks get bystander CPR as often as whites? Ann Emerg Med. 1994; 24:1147-1150.

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Miller E et al Hypogonadism in patients on Opioids … (at AAPM 2003 – get entire ref)

Miller E et al Transdermal fentanyl without rescue….. (at APS 2003 – get entire reference)

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Brookoff D. review of Sickle Cell Disease. Ann Int Med 1994; 120:174.

Voth E, Brookoff D. review of Marihuana, the Forbidden Medicine. Ann Int Med 1994;120:348.

Committee Assignments at Methodist Hospital

Clinical Competencey Committee
Cancer Committee
Credentials Committee
Critical Care Committee
Emery House and Trauma Coverage Committee
Patient Education Committee

Lectures by Invitation:

1988 Cardiovascular Resucitation, Atlantic County Medical Center
1989 Cardiac Arrhythmias, Roxborough Hospital
1989 Cocaine Abuse, York Hospital, York, PA
1990 Pain Management, St. Luke's-Roosevelt Hospital, New York
1991 Emergency Pain Management, Strong Memorial Hospital, Rochester NY
1991 Pain Management, Mercer County Hospital, Trenton, NJ
1992 Treatment of Patients with Sickle Cell Disease, Howard University
1992 Approaches to Cocaine Abuse, Governor's Conference for a Drug-Free Tennessee
1992 Treatmen of Sickle Cell Pain-The Emergency Physician's Approach National Sickle Cell Center Meeting, Nashville TN
1992 Opioid Medications in Pain Management, Harbor-UCLA Medical Center, Los Angeles
1992 Emergency Management in Sickle Cell Disease, National Medical Association, Washington DC
1992 Pain Management, Emory University
1993 Pain Management, Nursing Pain Assoc, UCSF
nesthesia, Med Coll VA
1993 Sickle Cell Disease, American College of Emergency Physicians AnnualcMeeting, Chicago
1993 Oncologic Emergencies, American College of Emergency Physicians, Chicago
1993 Grand Rounds, Sickle Cell Crisis, Children's Hospital, Detroit, MI
1993 Pain Management, Interstitial Cystitis Association, Orlando FL
1994 Grand Rounds, Sickle Cell Disease, Cedar-Sinai Medical Center, Los Angeles
1994 Drugged Driving; International PRIDE Conference; Philadelphia PA
1994 Hematologic Emergencies, Amer College of Emergency Physicians, New Orleans

1994 Pain Management, New York Academy of Family Physicians, New York City
1994 Sickle Cell Crisis, Howard University School of Medicine
1994 Interstitial Cystitis, American Pain Society, Miami FL
1994 Pain Management, Hospice of Southwestern Missouri, Branson MO
1994 Medical Grand Rounds, Pain Management, Medical College of Pennsylvania, Philadelphia, PA
1995 Management of Pain in Sickle Cell Disease, Division of Hematology; Vanderbilt University Medical School,
1995 Medical Grand Rounds; Pain and Suffering Vanderbilt University Medical School
1994 Combined Medicine/Family Medicine GrandRounds: The Use of Opiates in Chroni
1995 Non-malignant Pain; San Francisco General Hospital
1995 Grand Rounds: Pain and Its Management; U Tennessee Medical Center at Knoxville
1995 Grand Rounds; Sickle Cell Disease Howard University Hospital; Washington DC
1995 Pain Management in Interstitial Cystitis,NIH-NIDDK Conference on Interstitial Cystitis; San Diego CA
1995 Keynote Speaker, Statewide Conference; Michigan Communities in Action for Drug-Free Youth (MCADY); Lansing Michigan
1995 Treatment of Cancer Pain. University of Tennessee Medical Center at Knoxville
1995 Interstitial Cystitis: a Chronic Progressive Visceral Pain Syndrome; American Pain Society, Los Angeles
1995 Medical Grand Rounds, Pain Management, Muhlenberg Regional Medical Center, Plainfield, NJ
1995 Medical Grand Rounds, Pain Management, Tulane Medical School, New Orleans
1996 Hematology-Oncology Grand Rounds; Sickle Cell Disease; Presbyterian Hospital, Charlotte NC
1996 Profile of Families Who Call for Help; Shelby County Domestic Violence Council
1996 Pain Management; Frye Regional Hospital, Hickory NC
1996 Domestic Violence; Universities Prevention Center; Memphis TN
1996 The Science Of Pain; Arkansas Blood and Cancer Society; Little Rock Arkansas
1996 Pain Management, Wilford Hall Medical Center, San Antonio, TX
1996 Pain Management Strategies; Heme-Onc Conference; UTMB Galveston
1996 Care of the Dying Patient, Hospice of El Paso
1996 The Role of Drug Abuse in Domestic Violence, National Institute of Justice Seminar Series; Department of Justice; Washington, DC
1996 Pain Management in the Hospice Setting; Hospice of San Antonio, San Antonio,Texas
1996 Pain Management; Emergency Care of Patients with Sickle Cell Disease; Tulane Medical School, New Orleans
1996 Opioid Therapy for Chronic Pain: Balancing the Benefits and the Perils, Symposium Moderator; American Pain Society, Washington, D.C.
1996 Drug Testing, American Society of Criminology, Chicago, IL
1997 Medical Grand Rounds:The Science of Pain; Upstate Medical Center, Syracuse
1997 Pain Management, Hospice of San Antonio
1997 Total Pain Management,NPACE Nurse Practitioners Association; Orlando, FL
1997 Hospice Care for Patients with Non-Cancer Diagnoses; Trinity Hospice Palliative Care Symposium, Memphis TN
1997 Pain in AIDS, Assoc Nurses in AIDS Care Memphis, TN
1997 Treatment of Cancer Pain, Int'l Cancer Alliance Symposium; Georgetown Medical Center, Washington, D.C.
1997 Medical Grand Rounds: Nonmalignant Pain Memorial Regional Hospital, Hollywood, Fl
1997 Pain Management Issues In the Hospital and Office Practice, Swedish Medical Center, Seattle WA
1997 Medical Grand Rounds: Pain Management; Jackson-Madison County General Hospital
Jackson, Tennessee
1997 Medical Grand Rounds: Pain Management; Kaiser Hospital, Santa Rosa, California
1997 American Cancer Society Annual Update for Primary Care (Oschner MedicalFoundation): Pain Management for Cancer Patients; New Orleans, LA
1997 Pain Management in Interstitial Cystitis; NIH/NIDDK Symposium on Interstitial Cystitis, Washington, D.C.
1998 Non-malignant Pain. Memorial City Hospital. Houston TX
1998 Pain Management. Columbia-Northwest Hospital/ U of Ariz CME Program, Tuscon AZ
1998 Pain Management. St Jude's Children's Hospital, Memphis TN
1998 Sickle Cell Disease. Internal Medicine Conference. U of Mississippi MedicalCenter, Jackson MS
1998 Pain Workshop and Plenary Session on "Bringing Hope to Hospice" Joint meeting of the Louisiana and Mississippi Hospice Organizations; Biloxi MS
1998 Symposium on Alcohol and Crime, Department of Justice, Washington DC
1998 Managing Chronic Pain, Medical Grand Rounds, U of Kansas Medical Center, Kansas City
1998 Medicine Grand Rounds - Sickle Cell Disease, Medical College of Wisconsin
1998 Neurology Grand Rounds - Chronic Pain Medical College of Wisconsin
1998 The Appropriate Use of Pain Medication Texas Academy of Family Physicians Annual Meeting, Houston, Texas
1998 Adjuvant Medications for Pain; St. Tammany's Hospital, Covington, Louisiana
1998 Medical Grand Rounds, Pain Management; Jackson General Hospital, Jackson, TN
1998 Medical Grand Rounds, Chronic Non-Malignant Pain, Providence Hospital, Portland Ore
1998 Anesthesia Grand Rounds, Medical Pain Management,Oregon Health Sciences University, Portland, Ore
1998 Hematology-Oncology Grand Rounds: Sickle Cell Disease;LSU Medical Center, Shreveport, Louisiana
1999 Keynote Speaker, Pain and Chemical Dependecy in the USA
Third Conference on Pain and Chemical Dependency sponsored by NIDA, New York
1999 Sickle Cell Disease; Hematology-Oncology Program; Mayo Clinic Jacksonville, FL
1999 Optimizing Pain Management in the Long Term Care Setting; American Medical Directors Association; Orlando, FL
1999 Opioid Analgesics in Clinical Practice; Symposium on Chronic Pain sponsored by Johns Hopkins School of Medicine at the meeting of the American College of Physicians, New Orleans
1999 "The Science of Pain" and "The Legal Ramifications of Pain Treatment" Kaiser-Permanente Symposium on Pain; Newport Beach, CA
1999 Pain in the Public Eye, American Pain Society; Ft Lauderdale, FL Moffitt Cancer Center, Tampa Florida

2000 Society of Air Force Physicians, Malcolm Grow Memorial Lecture "Pain Control in the New Millenium" San Antonio,
2000 Pain Management for Homebound Patients; Academy of HomeCare Physicians Annual Meeting; Nashville TN
2000 "Opioids in Non-Cancer Pain" International Conference on Palliative Care, Irish Cancer Society, Dublin Ireland
2000 Palliative Care Grand Rounds: "Pain Management" Texas Medical Center, Houston, Texas
2000 "Opiology 202" presentation at American Pain Society, Atlanta, GA
2001 "Chronic Pain" Pain Awareness Week; University of Texas Southwestern Medical Center, Dallas Texas
2001"Patients as Partners in Pain Management" American Society of Pain Management Nurses; Houston,Texas
2001 "Pathways of Pelvic Pain" International Pelvic Pain Society; Phoenix AZ
2001 " Managing the Complex Patient with Psychiatric Comorbidity" American Pain Society; Phoenix AZ
2001 Keynote Address; Tennessee Hospice Association; Nashville, TN
2001 Keynote Address; Indiana Support Initiative to Improve End-of-Life Care; Christian Theological Seminary, Indianapolis, IN
2001 "Is Pain A Disease?" ACP-ASIM Regional Meeting St Louis, MO
2001 "Chronic Pain" Virigina Society of Rheumatology, Roanoke, VA
2001 Pain Grand Rounds, MD Anderson Cancer Hospital, Houston Texas
2001"BackPain" Northridge Hospital Pain Symposium,FortLauderdale,FL
2001 Medicine Grand Rounds"The Pathophysiology of Chronic Pain" Univ.of Texas, San Antonio Medical School
2001 "Treatment of Cancer Pain", Wilford Hall Medical Center, San Antonio TX
Center,San Antonio,TX
2001Chronic Pain" U.of Florida/Shands Medical Center,Gainesville FL
2001Surgery Grand Rounds "Pain Management in the Chronic Pain Patient" U. of Florida/Shands Medical Center,Gainesville FL
2002Treatment of Cancer Pain; Canadian Pain Society,Whistler B.C
2002Use of Opioids for Cancer Pain. Opioid Analgesic Forum, Tokyo Japan
2002 Optimizing Opioid Regimens in Chronic Pain; AAPM,San Francisco
2002 The Physiology of Chronic Pain, ASPMN, SaltLake City
2002Pain Management in Primary Care PriMed Conference, Long Beach,California
2002 Pain Management Issues Eleventh Pharmaceutical Drug Diversion Conference, US Drug Enforcement Administration, St Louis, MO
2002 Pain Management in the 21st Century, University of Kentucky, Lexington,KY
2002 "Pain Management and the Use of Opioids" State and Local Diversion School; Drug Enforcement Administration; Quantico, VA
2002 "Pathophysiology of Pain" Psychiatry and Medicine Conference; U of Kansas; Kansas City, KS
2002 "Pain Management, Safety, Science and Regulations" Intermountain Health Care, Salt Lake City, UT
2003 "The Science of Chronic Pain" Albequerque VA Medical Center, Alberquerque, New Mexico
2003 Keynote Address: "The Meaning of Cancer Pain" Arizona State Cancer Pain Initiative, Phoenix AZ
2003 "Cancer Pain" Creighton University Cancer Center, Omaha, Nebraska
2003"Professionalism and End of Life Care" Panelist; Federation of State Medcial Boards Annual Meeting; Chicago IL
2004 "Mechanisms and Treatment of Cancer Pain" Chinese Association for Clinical Oncology Annual Meeting, Kunmin PR China
2004"The Pathophysiology of Pain" Ontario Medical Association; Toronto Canada
2004"Chronic Pain" joint meeting of the Society of Anaesthetists of Hong Kong and the Hong Kong Society of Clinical Oncology, Kowloon, Hong Kong
2004 Treating Cancer Pain, chinese Society of Oncology, Kunming, PRC