March 21, 2009.
Division of Dockets Management (HFA-305),
Food and Drug Administration,
Department of Health and Human Services,
5630 Fishers Lane, Room 1061,
Rockville, Maryland 20852.

CITIZEN PETITION

A. ACTION REQUESTED

The undersigned hereby submit this Citizen Petition under section 21 CFR § 10.30 of the Federal Food, Drug and Cosmetic Act, the Public Health Service Act to request that the Commissioner of the U.S. Food and Drug Administration use the FDA's statutory and regulatory authority to take the following specific steps in an effort to reduce the risk of prescription opioid drug products in the general population, while ensuring continued access to these products for patients in pain:

1. Publish a Guidance for Industry that will outline the approval requirements for safe and effective tamper-deterrent or abuse-deterrent formulations of opioid analgesics.
2. Grant fast track status to INDs for abuse-deterrent formulations (ADFs) of opioid analgesics.
3. Assign priority review timelines to NDAs for ADFs of opioid analgesics.
4. Develop and publish guidelines for clear meaningful labeling for these products.
5. Devote sufficient and appropriate budgetary, personnel and management resources to accomplish the above.
6. Propose legislative remedies to provide incentives for the pharmaceutical industry to develop ADFs for opioid analgesics; such remedies may include, but are not limited to, exclusivity and/or tax credits.

It is further requested that FDA initiate these steps within six months of the date of this petition, in view of the serious public health consequences of prescription opioid drug abuse, including addiction, overdose, and death.

B. STATEMENT OF GROUNDS

I. Opioid analgesics are important in pain management

Pain is the most common reason that patients give for seeking medical care. As stakeholders in the area of pain management and drug abuse, the petitioners feel a strong sense of responsibility for ensuring that adequate treatment is available to patients in pain. According to a recent bulletin of the American Pain Society, 87% of physician members support long-term treatment of chronic, non-cancer pain with opioid analgesics[1]. Opioid analgesics are a cornerstone of modern pain management[2]. As the result of efforts by cancer patient advocates, patients' rights groups, professional societies, and other stakeholders, and with FDA approval of new opioid drug products, access to opioids has markedly increased in the past several decades. This has resulted in more effective pain management and an improved quality of life for many patients with cancer, AIDS, and other acute and chronic painful disorders.

II. Prescription opioid abuse has become a serious public health concern

Opioids are among the most widely prescribed drugs in the United States[3], with 186,652,540 prescriptions dispensed in 2004[4]. The availability of prescription opioid drug products to patients with pain, however, comes at an enormous societal cost: the widespread diversion and abuse of prescription pain medication. In 2002, almost 30 million persons aged 12 or older (13 percent of the general population) reported having used prescription opioids non-medically at least once in their lifetime. In the ten years from 1990 to 2000 the number of first time abusers increased from 573,000 to 2 million

[1] Katz N, Fanciullo GJ. Role of urine toxicology testing in the management of chronic opioid therapy. Clin J Pain 2002; 18 (4 Suppl): S76-82.

[2] Trescot AM, Boswell MV, Atluri SL et al. Opioid guidelines in the management of chronic non-cancer pain. Pain Physician 2006; 9:1-40.

[3] Top 300 prescriptions for 2005. Available at: http://www.rxlist.com/script/main/art.asp?articlekey=79509 Accessed March 21, 2009.

[4] The top 300 prescriptions for 2004 by number of US prescriptions dispensed. NDCHealth Pharmaceutical Audit Suite (PHAST) Prescription Monthly. Available at http://www.rxlist.com/script/main/art.asp?articlekey=79509. Accessed on October 8, 2007.

persons[5]. In 2004, the number of past year new initiates that consumed psychotherapeutics non-medically was 2.8 million; of these 2.4 million used prescription pain relievers (more than the estimated number of new users of marijuana), 1.2 million used tranquilizers, and 793,000 used stimulants[6]. An estimated 19.4 percent of past-year users of prescription drugs were new users—a statistically significant increase of 13 percent over the 17.2 percent new initiates recorded in 2003[6,7]. The NSDUH reported that in 2005, opioids were the most common new illicit drug class consumed in the United States, for the first time surpassing marijuana use[8].

Dr. Bertha Madras, ONDCP's Deputy Director of Demand Reduction, points out in her Congressional Testimony on July 26, 2006, that "Among young adults (aged 18 to 25), non-medical use of prescription drugs was significantly higher in 2004 compared with 2002 for lifetime use (an increase from 27.7% to 29.2%) and for past month use (an increase from 5.4% to 6.1%)"[6]. Especially susceptible among users are America's young: the trend of prescription drug abuse in high school-age children escalated in the 1990's, and annual prevalence of current use remains "unacceptably high" (up to 9.7 percent among high school seniors, depending on the specific opioid)[6,9]. Dr. Nora Volkow, Director of the National Institute of Drug Abuse (NIDA), makes the point that abuse-related neurological changes in adolescents may have behavioral consequences

[5] Substance Abuse and Mental Health Services Administration. 2004. *Results from the 2003 National Survey on Drug Use and Health: National Findings* (Office of Applied Studies, NSDUH Series H-25, DHHS Publication No. SMAA 04-3964). Rockville MD.

[6] Congressional Testimony, Committee on House Government Reform Subcommittee on Criminal Justice, Drug Policy, and Human Resources. Statement of Bertha K. Madras, Deputy Director of Demand Reduction, Office of National Drug Control Policy. Prescription Drug Abuse: What is Being Done to Address this New Drug Epidemic?. July 26th, 2006. Available at: http://drugstrategies.com/internetdrugs/state02.html#1. Accessed March 21, 2009.

[7] Monitoring the Future. Full Press release on drug use from the University of Michigan. [University of Michigan webpage]. 2004. Available at: http://www.drugabuse.gov/Newsroom/04/2004MTFDrug.pdf. Accessed March 21, 2009.

[8] SAMHSA National Prevalence Data with Correlates of Substance Abuse: SAMHSA's National Survey of Drug Use & Health: Office of Applied Studies (OAS); Department of Health and Human Services (DHHS); 2006.

[9] NIDA-Sponsored Survey Shows Decrease in Illicit Drug Use among Nation's Teens but Prescription Drug Abuse Remains High. NIDA News Release, December 21, 2006. Available at http://www.nida.nih.gov/newsroom/06/NR12-21.html. Accessed on March 21, 2009.

that are different from those seen in adults[10]: "We also now know that addiction is a developmental disorder that begins in adolescence, and sometimes as early as childhood"; she reiterates that many important facets of cognition, decision-making, emotional regulation, and risk perception are not fully understood in individuals less than 20 years of age: because adolescents continue to undergo neuropsychobiologic maturation into adulthood, they may be particularly vulnerable to drugs of abuse that affect the nervous system. "Since drugs of abuse interact with some neurotransmitter systems that are essential for brain development (e.g., serotonin, acetylcholine), drug exposure during adolescence may be particularly harmful to the still developing brain"[11]; such exposure has the potential to produce irreversible changes in the nervous system.

Widespread availability and abuse of prescription opioid drug products clearly impact public health. According to the Centers for Disease Control, more than 9% of high school students (1.3 million adolescents) tried to kill themselves in 2003; records from the 15,000 hospital Emergency Department visits by 12-17-year-olds (registered by the Drug Abuse Warning Network - DAWN) document the use of at least one pain medication in half of such attempts, with 36% involving opioids[12]. These statistics place prescription analgesics at the forefront of drugs used in suicide attempts by teenagers. Furthermore, in a sample of 740 opioid abusers aged 12 to 64 years, a significantly higher prevalence of serious comorbidities was noted in comparison to non-abusers; these comorbid conditions include hepatitis, pancreatitis, and HIV-AIDS[13] - diseases that are likely spread via the intravenous route. In fact, injection drug use accounts for a large portion of AIDS cases in the United States: 11,635 (28%) of the 42,156 new cases of

[10] Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: concerns and strategies. Drug Alcohol Depend 2006; 81(2):103-7.

[11] Volkow ND. What do we know about drug addiction? (Editorial) Am J Psychiatry 2005; 162:1401-1402.

[12] New DAWN Report: Disposition of emergency department visits for drug-related suicide attempts by adolescents: 2004. Drug Abuse Warning Network, Issue 6, 2006.

[13] White AG, Birnbaum HG, Mareva MN, Daher M, Vallow S, Schein J, Katz N. Direct costs of opioid abuse in an insured population in the United States. J Manag Care Pharm 2005; 11(6):469-79.

AIDS reported in 2000 were associated with injection drug use[14]. One third of prescription opioid abusers in methadone maintenance treatment programs have a history of injecting their primary drug[15].

For decades, physicians have been consoled by assertions that opioids, when prescribed for pain, are rarely if ever associated with addiction; they have believed rather, that the problem of addiction occurs mostly in individuals outside the context of medical practice, not in patients with pain; this has proven to be incorrect. An estimated 30-45% of prescription opioid abusers claim that their first opioid was obtained by a doctor's prescription to treat their pain[16,17]; in contrast to the notion that only individuals at clear risk for developing addiction are susceptible to abusing opioids, recent evidence documents that a significant minority of individuals who develop addiction were not at apparent high risk for abuse prior to their first exposure[17].

Addiction and pain commonly co-exist. Approximately one tenth of the adult population suffers from chronic pain[18]. Given a 10% background rate of substance abuse, two to nine million individuals in the US may suffer from *both* chronic pain and substance use disorder. From another perspective, 1.5-2 million adults have opioid addiction, and as many as 40-60% (0.6 to 1.2 million) of opioid addicts are estimated to have chronic pain[16]. The only prospective study on the incidence of opioid abuse among patients prescribed opioids for the treatment of chronic pain found that 32% developed signs of

[14] CDC webpage: Drug-Associated HIV transmission continues in the United States. Available at: http://www.cdc.gov/hiv/resources/factsheets/idu.htm. Accessed on March 21, 2009.

[15] Rosenblum A, Parrino M, Schnoll SH et al. Prescription opioid abuse among enrollees into methadone maintenance treatment. Drug Alcohol Depend 2007; 90 (1):64-71.

[16] Jamison RN, Kauffman J, Katz NP. Characteristics of methadone maintenance patients with chronic pain. J Pain Symptom Manage. 2000; 19(1):53-62.

[17] Potter JS, Hennessy G, Borrow JA, Greenfield SF, Weiss RD. Substance use histories in patients seeking treatment for controlled-release oxycodone dependence. Drug Alcohol Depend 2004; 76(2):213-215.

[18] Roper Starch Worldwide, Inc. Chronic Pain in America: Roadblocks to Relief. Study conducted for American Academy of Pain Medicine, American Pain Society and Janssen Pharmaceuticals. [APS website]. 1999. Available at: http://www.ampainsoc.org/links/roadblocks/. Accessed March 21, 2009.

abuse during the one year follow-up period [19,20]. Studies of urine toxicology among patients who are *legitimately prescribed opioids* reveal that 20-40% of these have results suggesting co-morbid active substance abuse problems[1], and are at high risk for abusing the drugs that are provided to them for treating their pain. Physicians have been slow to accept these facts; but even those who are aware that an effective therapy for relieving a patient's pain also has potential to feed an addictive disorder nevertheless face a profound ethical dilemma when having to let patients go untreated for one or the other condition.

The steep rise in abuse of diverted prescription opioids is accompanied by an immense economic burden which includes health care costs, criminal justice, and workplace expenses marked by lost wages and productivity. Conservative analyses estimate societal costs of prescription drug abuse at $8.6 billion[21]. In a managed care setting, the cost for an average patient's care is approximately $1800 per year, while the equivalent amount for a patient with an opioid abuse diagnosis is nearly $16,000[13]. These amounts translate into average healthcare expenses that are *more than eight times higher for abusers of prescription opioids* than for non-abusers. A primary factor contributing to the disproportionately higher costs is the greater prevalence in abusers of comorbid conditions such as non-opioid poisoning, hepatitis A, B, and C, psychiatric illness, trauma, burns, pancreatitis and chronic pain; as a consequence, abusing individuals make significantly greater use of services like mental health and physician outpatient facilities, hospital inpatient stays, Emergency Room visits, and also of prescription medications, both opioid and non-opioid. When indirect expenses associated with loss of productivity in the workplace are factored in, the cost differential climbs much higher.

---

[19] Ives TJ, Chelminski PR, Hammett-Stabler CA, Malone RM, Perhac JS, Potisek NM, Shilliday BB, DeWalt DA, Pignone MP. Predictors of opioid misuse in patients with chronic pain: a prospective cohort study. BMC Health Serv Res 2006; 6:46.

[20] Adams EH, Brenier C, Cicero TJ, Geller a, Inciardi JA, Schnoll SH, Senay EC, Woody GE. A comparison of the abuse liability of Tramadol, NSAIDs and Hydrocodone in patients with chronic pain. J Pain and Symptom Manage 2006; 31 (5): 465- 476.

[21] Birnbaum HG, White AG, Reynolds JL, Greenberg PE, Zhang M, Vallow S, Schein JR, Katz NP. Estimated costs of prescription opioid analgesic abuse in the United States in 2001: a societal perspective. Clin J Pain. 2006; 22(8):667-76.

Numerous surveillance and information systems are in place for tracking abuse, but the full extent of criminal diversion of opioids remains unknown, and few surveillance systems are capable of identifying the *sources* of diversion. Despite their best efforts to provide opioids to legitimate patients within the context of medical treatment for pain, physicians unknowingly have become the source of many of the prescription opioids that are diverted through friends and family[22]. Sometimes patients engage in doctor-shopping or prescription forgeries to obtain opioids, and then sell their medications. Data from the Massachusetts prescription monitoring program suggest that approximately 2.5 million dosage units of prescription opioids are dispensed annually to individuals that meet the criteria for doctor-shopping, i.e., obtaining Schedule II drugs from ≥4 pharmacies and ≥4 physicians during the year[23]. Overall, close to 60% of users report obtaining pain relievers from friends or relatives, 16.8% receive them from doctors, 4.3% from dealers, and 0.8% use internet sources[22]; and among enrollees in opioid treatment programs, higher numbers of younger abusers (<21 years) claim to buy from dealers, friends, or family, whereas older abusers (>51 years) get their opioids most often from doctors' prescriptions[24]. Controlled substances may also be diverted by prescribers or pharmacists from inventory, or via loss, theft, and armed robberies at places where the drugs are distributed or dispensed: DEA statistics indicate that diversion of OxyContin due to theft and loss doubled (from 218,339 dosage units to 506,711) between 2000 and 2002[25].

[22] The NSDUH Report: How Young Adults Obtain Prescription Pain Relievers for Nonmedical Use. National Survey on Drug Use and Health, Issue 39, 2006.

[23] Katz NP, Audet A, Bilansky A, et al. Prescription Monitoring of Medical and Non-Medical Schedule II Opioid Use in Massachusetts: 1996-2006. Abstract, Annual Meeting of College on Problems of Drug Dependence, June 19, 2007.

[24] Postmarketing surveillance of abuse of prescription drugs. Presentation at NASCSA Conference, October 20, 2006. Theodore J. Cicero, PhD, Vice Chairman for Research, Washington University School of Medicine. Available at http://www.nascsa.org/2006%20Conference/Presentations/Cicero.AbuseTrends.pdf. Accessed October 3, 2007.

[25] Gilson, AM, Ryan KM, Joranson DE, Dahl JL. A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control: 1992-2002. J Pain & Symptom Management 2004; 28(2):176-188.

The other side of this dilemma is the fact that many health care professionals are inadequately prepared for administering treatments for pain management[26], and some may not have the training to identify which of their patients on opioid analgesics benefit from the medications, and which might abuse or divert them. This results in *prescription opioid abuse* or *under-treatment of pain*[27]. Doctors' fears of criminal action taken against them by the DEA deter them from prescribing opioid analgesics for patients that experience chronic pain on the basis of regulatory concerns rather than medical issues[28]. Other physicians operate under the misconception that "drug-seeking" patients can be readily discriminated from legitimate pain patients, and deny the reality that such identification is possible only for the most obvious cases of patients who are abusing[1]; these caregivers tend to *underplay* the potential for abuse. Physicians are thus faced with the conflicting realities of an imperative to make medical treatment accessible to patients in pain, along with considerable reluctance to provide what in many cases is the most effective medication. *The petitioners argue that achieving a reduction in the risk of abuse and diversion of prescribed opioids would impact both of these issues.*

III. Current approaches to addressing pain and the abuse of prescription pain medication

Within a regulatory context, FDA has been promoting the concept of Risk Management, which refers to efforts aimed at maximizing the medical value of a therapeutic agent, while minimizing the risks associated with the use of that agent. However, the extent to which such management approaches mitigate the risks of abuse without compromising legitimate access to pain relief remains unknown. "Balanced approaches" that simultaneously address the twin concerns of managing abuse risk and providing efficacious treatment, are preferred since they have the potential to impact both sides of

[26] Hampton T. Physicians Advised on How to Offer Pain Relief While Preventing Opioid Abuse JAMA 2004; 292:1164-1166.

[27] Kuehn, BM. Opioid Prescriptions Soar. Increase in Legitimate Use as Well as Abuse JAMA. 2007; 297:249-251.

[28] Jung B, Reidenberg MM. The risk of action by the Drug Enforcement Administration against physicians prescribing opioids for pain. Pain Med. 2006; 7(4):353-7.

the pain-abuse axis[29]; in other words, a *balanced treatment approach* is targeted at decreasing opioid abuse, while concurrently increasing pain relief. Such approaches are embodied in the principles of universal precautions[29,33].

Tools developed for making risk assessments have been used with varying degrees of success. Historically used assessments, such as medical interviews, depend on self-reporting by patients, a process which is likely to be unreliable: chronic pain patients often provide inaccurate information about their drug use (prescribed and illicit)[30], perhaps for fear of being denied medical care. Evaluations based on aberrant behaviors miss many abusers[1, 30], and urine toxicology tests only detect opioids in a fraction of patients that are actively abusing[31]. Validated screening tests, such as the Screener and Opioid Assessment for Patients with Pain (SOAPP)[32], are most useful in estimating a patient's risk for opioid abuse. An undeniable caveat, however, is that all assessment tools have gaps, and evaluations with 100% capture rates are difficult to design.

These considerations have led to the recommendation that doctors providing long-term opioid treatment be trained in the practice of *Universal Precautions*. A keystone of these precautionary guidelines is that visual inspection is not adequate for determining an individual's risk for opioid therapy, or his/her outcome status with regard to abuse; thus, initiation of opioid therapy should be administered in combination with *universal*

[29] Katz NP, Adams EH, Benneyan JC, Birnbaum HG, Budman SH, Buzzeo RW, Carr DB, Cicero TJ, Gourlay D, Inciardi JA, Joranson DE, Kesslick J, Lande SD. Foundations of opioid risk management. Clin J Pain 2007; 23(2):103-118.

[30] Katz NP, Sherburne S, Beach M, Rose RJ, Vielguth J, Bradley J, Fanciullo GJ. Behavioral monitoring and urine toxicology testing in patients receiving long-term opioid therapy. Anesth Analg. 2003; 97(4):1097-1102.

[31] Michna E, Jamison RN, Pham LD, Ross EL, Janfaza D, Nedeljkovic SS, Naran S, Palombi D, Wasan AD. Urine Toxicology Screening Among Chronic Pain Patients on Opioid Therapy: Frequency and Predictability of Abnormal Findings. Clin J Pain 2007; 23(2):173-179.

[32] Butler SF, Benoit CM, Budman SH, Fernandez KC, McCormick C, Wing Venuti S, Katz N. Development and validation of an opioid attractiveness scale: a novel measure of the attractiveness of opioid products to potential abusers. Harm Reduct J. 2006; 3(1):5.

screening[33], a multi-faceted screening system that includes validated screening tests, monitoring of prescription drug data, review of medical records, family member interviews, and urine or serum toxicology tests. All medications must be securely stored, and every patient should be educated in the use and potential misuse of the drugs, and made signatory to a contract that outlines objectives, goals and expectations of the patient for the duration of the treatment. Universal precautions provide fuller coverage of patient assessments and increased capture rates for identifying at-risk patients. Yet even these are not totally secure.

Many physicians also view prescription monitoring as a necessary tool to supplement clinical practice, and as a way to address issues of abuse as well as diversion[23,34,35.] But even when red flag behaviors are targeted in patients that are at high risk of opioid abuse, disqualifying those with a legitimate need from having their pain addressed medically may be counterproductive: individuals that are left with unresolved pain on account of their risk for opioid addiction may be compelled to self-treat using diverted drugs, thus perpetuating the addictive cycle.

IV. Reducing the potential for abuse of opioid analgesics

ADFs offer a balanced approach to risk management: they have intrinsic features that decrease the likelihood or consequences of one or more forms of abuse; by the same token, they also may improve access to pain relievers. The petitioners believe that *the development of abuse-deterrent products is a public health priority*.

[33] Gourlay DL, Heit, HA, Almahrezi A. Universal precautions in pain medicine: a rational approach to the treatment of chronic pain. Pain Medicine 2005; 6(2): 107-112.

[34] GAO-040524T Statement of Marcia Crosse, Director, Health Care – Public Health and military Health Care Issues. State monitoring programs may help reduce illegal diversion. Testimony before the Subcommittee on Health, Committee on Energy and Commerce, House of Representatives. March 4, 2004. http://www.gao.gov/new.items/d04524t.pdf. Accessed March 21, 2009.

[35] GAO-02-634; 2002. Prescription Drugs. State monitoring programs provide useful tool to reduce diversion. US General Accounting Office, Report to the Subcommittee on oversight and Investigations, Committee on Energy and Commerce, House of Representatives. May, 2002; http://www.gao.gov/new.items/d02634.pdf. Accessed March 21, 2009.

Limited data support the notion that the addition of formulation barriers to prescription opioid products has the potential to limit abuse. Talwin-NX, a combination of pentazocine and naloxone, was introduced with the aim of decreasing abuse of Talwin, the parent product. Subsequent data indicate that abuse of pentazocine decreased significantly after the introduction of Talwin-NX[36], although there is some question whether this decrease may have resulted from other causes[36]. Buprenorphine, approved for the treatment of opioid addiction, has already been approved in two forms: Subutex, which contains buprenorphine alone, and Suboxone, which contains buprenorphine and naloxone, and which appears to limit the abuse potential of the parent compound in specific populations of abusers[37, 36]. Overall, experience with these and other ADFs shows that prescription opioid abusers are less interested in products with tamper-deterrent features[32.]

The task of developing effective ADFs is formidable, and producers need to overcome technical, scientific, regulatory as well as economic hurdles. The science and technology applied to the design of tamper-resistant formulations must be solidly rooted in a comprehensive understanding of the types of abuse, and the main methods and routes of administration that individuals use to self-administer their drugs. Current thinking identifies discrete types of prescription opioid abuse[38]. *Intravenous abuse* occurs when individuals extract the active ingredient from prescription opioids, typically by crushing, dissolving and injecting. Such abuse is a major public health problem in its own right: 12-60% of addicts in treatment programs nationwide indicate use of the intravenous use of

[36] Fudala PJ, Johnson RE Development of opioid formulations with limited diversion and abuse potential. Drug Alcohol Depend 2006; 83S: S40-S47.

[37] Comer SD, Collins ED. Self-administration of intravenous buprenorphine and the buprenorphine/naloxone combination by recently detoxified heroin abusers. J Pharmacol Exp Ther 2002; 303: 695-703.

[38] Schnoll SH. The phenomenology of prescription opioid abuse: what types of abuse do products need to resist? Presentation at Tufts Health Care Institute on Opioid Abuse. October 27-28, 2005.

administration[38, 39]. *Snorting* is a common form of ingestion of prescription opioids, typically performed by crushing a tablet into powder and sniffing it. Snorting produces its own set of complications, including necrosis of the nasal septum[40]. *Crushing with a simple implement and swallowing, or chewing*, is used to defeat the extended release properties of various opioid formulations – this is a common and potentially dangerous method for misuse of Oxycontin and other products. And s*wallowing of intact formulation* remains the most frequently used approach for ingesting prescription opioid drugs. The extent to which an ADF will succeed in decreasing the public health consequences of prescription opioid abuse will depend on the extent to which the novel formulation can deter each of the above behaviors.

It is incumbent upon developers and marketers of abuse-deterrent opioids to understand the different types of abuse, and the types of abuse that can be realistically deterred by a specific ADF. Drug users are motivated to tamper with formulations in order to enhance the availability of active ingredients, accelerate onset of drug effects via alternate routes of administration, or separate undesirable ingredients and excipients from the active agents[32,41]. Thus for example, the manufacturer must know that products that resist conversion by tampering of oral dosage forms into forms that can be injected, would be useful for preventing intravenous injection, but would be futile for stemming diversion of drugs to individuals who consume their drugs orally, by swallowing or chewing.

The overarching challenge for manufacturers, then, is to develop formulations that are therapeutically effective for pain relief with no added risk to the target population, but are resistant to conversion for intravenous use, conversion of slow onset formulations to

[39] Butler SF, Budman SH, Licari A, Cassidy TA, Lioy K, Dickinson J, Brownstein JS, Benneyan JC, Green TC, Katz N. National addictions vigilance intervention and prevention program (NAVIPPRO™: a real-time, product-specific, public health surveillance system for monitoring prescription drug abuse. Pharmacoepidemiol Drug Saf 2008; 17(12):1142-1154

[40] Greene D Total necrosis of the intranasal structures and soft palate as a result of nasal inhalation of crushed OxyContin. Ear Nose and Throat Journal 2005; 84(8) 512, 514, 516.

[41] Cone E. Ephemeral profiles of prescription drug and formulation tampering: evolving pseudoscience on the Internet. Drug Alcohol Depend 2006; 83 Suppl 1:S31-9.

rapid onset ones, release of higher drug doses by physical manipulations (such as crushing), accelerated extraction with alcohol, and supra-therapeutic exposure (overdosing). The need to develop such technology is acknowledged by industry as "the right and responsible thing to do"[42].

Some approaches that are already under evaluation include the use of less euphorigenic analgesics, formulations that render drug extraction from the extended-release version more difficult, addition of aversive ingredients, inactive prodrugs that are converted into active opioid agents only after being ingested, non-injectable drugs, combinations of opioid agonists with antagonists that are activated by drug tampering, and smart patient dispensing devices[43,44]. Despite the fact that no product will be abuse-proof, and none will relieve the physician of responsibility to exercise universal precautions in treating patients with legitimate needs, it is widely accepted that successful tamper-deterrent formulations have the potential to decrease the diversion of prescription analgesics, reduce negative health consequences, lower the risk of pediatric ingestion and collateral patient damage, decrease hospital Emergency Department admissions, and in the final run, alleviate health care costs, while at the same time effectively addressing the therapeutic needs of legitimate pain patients[36].

A major challenge for developing these ADFs is the perception of a lack of validated methods to demonstrate that one formulation is in fact more abuse-resistant than another[29]. Indeed, few published studies have specifically addressed abuse deterrence. However, there is extensive experience with methods of evaluating abuse liability, and

---

[42] Pinizzotto M (Senior Director, Global Drug Safety and Pharmacovigilance at Endo Pharmaceuticals). Industry Perspective on Risk Management. Presentation at the Tufts Health Care Institute Meeting on Opioid Risk Management. March 2005. Available at: http://www.tmci.org/opioid/mar05docs/Pinizzotto%20March%2024.pdf. Accessed March 21, 2009.

[43] Katz NP, Adams EH, Chilcoat H et al. Challenges in the Development of Prescription Opioid Abuse-deterrent formulations. Clin J Pain 2007; 23:648-660.

[44] Grudzinskas C, Balster RL, Gorodetzky CW, Griffiths RR, Henningfield JE, Johanson CE, Mansbach RS, McCormick CG, Schnoll SH, Strain EC, Wright C. Impact of formulation on the abuse liability, safety and regulation of medications: the expert panel report. Drug Alcohol Depend. 2006; 83 Suppl 1: S77-82.

this can be readily applied to the evaluation of abuse-deterrent opioids. Techniques have been developed to assess the benchtop extractability (tamper-resistance) of opioid formulations[45], the preclinical abuse liability of prescription opioids[46], abuse potential in human clinical pharmacology experiments[47], diversion rates in clinical trials[48], incidence of abuse[19] and related adverse events in clinical trials, and abuse rates in registry studies[49] and in a variety of epidemiologic and surveillance studies[36]. A number of outcome measures are available to predict the risk of opioid abuse in a particular sample for the purpose of clinical trial design, or to measure abuse of, and addiction to, prescription opioids when they occur[49,50], including external measures such as urine toxicology testing[31] or prescription monitoring program data[34,35]. Although experience with many of these measures is limited, *it is the position of the petitioners that adequate methods exist for moving forward with scientifically evaluating new formulations for abuse deterrence.*

V. An FDA Guidance Document is needed to facilitate the efforts of drug companies in developing abuse-resistant formulations

Challenges in the development of ADFs include the absence of clear direction from the Agency on standards for chemical and physical integrity of a formulation, requirements for human abuse liability testing, identification of specific criteria that can result in specific labeling claims, and requirements for demonstrating abuse deterrence in the post

---

[45] Katz NP, Buse DC, Budman SH, Venuti SW, Fernandez KC, Benoit C, Bianchi R, Coper D, Jasinki DR, Smith DE, Butler SF. Development and preliminary experience with an ease of extractability rating system for prescription opioids. Drug Development & Industrial Pharmacy 2006; 32(6) 727-746.

[46] Balster RL, Bigelow GE. Guidelines and methodological reviews concerning drug abuse assessment. Drug Alcohol Depend. 2003; 70 (Suppl 3: 1), S13-S40.

[47] McColl F, Sellers M. Research design strategies to evaluate the impact of formulations on abuse liability. Drug and Alcohol Dependence 2006 83S:S52-S62.

[48] Wright C, IV, Zalman MA, Haddox JD, Kramer ED, Colucci RD, D'Ambrosio P. Systematic assessment of abuse or diversion in a clinical trial of analgesics. Abstract, College on Problems of Drug Dependence Annual meeting, June 2006.

[49] Adams LL, Gatchel RJ, Robinson RC et al. Development of a self-report screening instrument for assessing potential opioid medication misuse in chronic pain patients. J Pain Symptom Manage 2004; 27:440-449.

[50] Wu SM, Compton P, Bolus R, Schieffer B, Pham Q, Baria A, Van Vort W, Davis F, Shekelle P, Naliboff BD. The addiction behaviors checklist: validation of a new clinician-based measure of inappropriate opioid use in chronic pain. J Pain & Symptom Management. 2006; 32(4):342-51.

marketing environment, all of which could be put in place to develop the evidence for more explicit labeling claims of abuse deterrence. Pharmaceutical company representatives indicate that the inability to quantify the risks of attempting to develop tamper-resistant products impedes their ability to allocate resources to this area[42], and that *FDA guidance would have a significant impact in removing this barrier to development*.

In order to facilitate the translation of the above approaches into ADFs, we request that the FDA provide comprehensive and detailed Guidance for Industry in the following areas:

- CMC standards for classification of products based on extractability and degree of physical tamper-resistance.
- Preclinical studies if any that are required to support the safety of the ADFs by various routes of abuse.
- Human clinical pharmacology studies that are required for approval: specifically, requirements to assess the effects of ethanol on the safety and abuse deterrent claim for each active constituent of ADF.
- Human abuse liability studies that are required for all "abuse-deterrent" opioid formulations, and to support each specific claim related to abuse deterrents.
- The specific requirements for satisfying 21 CRF § 300.50 when an antagonist component is added to the opioid drug product to deter IV abuse.
- Clinical trials (efficacy) if and when they are required for a formulation whose active pharmaceutical ingredient (API) is "bioequivalent" to the reference listed drug
- Safety requirements if and when they are required for a formulation whose API is "bioequivalent" to the reference listed drug.
- Epidemiological studies if and when they are needed to address public health concerns related to maintaining benefit (analgesia/access), or reducing adverse consequences that could affect patients, non-patients (abusing populations) and

individuals subjected to inadvertent exposure (e.g., accidental use by children), monitoring direct Health Care costs (e.g., cost of addiction treatment) or indirect expenses (e.g., cost of abuse-related diseases).

We further assert that expediency in developing ADFs is of great importance for national public health. Dr. Sandra Kweder, Deputy Director of the FDA has stated before the Subcommittee on Criminal Justice, Drug Policy and Human Resources (Committee on Government Reform House of Representatives) that ADFs would be considered appropriate for priority review (July 2006).

While industry representatives agree in principle that designing tamper-deterrent formulations is necessary, it is clear that the absence of specific incentives coupled with regulatory uncertainty regarding approval, labeling and ultimately reimbursement, limits the ability of pharmaceutical companies to justify resource allocation for these complicated programs. Some incentives already exist at the Agency's discretion, such as use of Fast Track designation, Priority review assignment, and the development and publication of FDA Guidance for Industry.

Conferees at the Office of Management Budget Formulation and Presentation (Office of Management; House Report 109-102) noted that "if CDER received a new drug application for a product for which there is reasonable evidence or scientific basis to conclude it would be safer and have a lower abuse potential in people other than the intended population, compared to an already marketed product, we would work with the company to achieve an expedited action". They also stated that "providers and patients alike will benefit from the expedited review of safer drugs, as well as the provision of information that accurately differentiates abuse-resistant formulations" (House Committee on Appropriations, HR 109-102).

The panel additionally recommended the development of "a conditional expedited review process for drugs to treat diseases in particular need of treatment", and that the government could consider providing additional financial incentives – such as longer patent lives for innovative drugs and shorter patent terms for "me-too" drugs – to shape the drug development process". Additional initiatives may require collaboration between FDA and Congress.

Provision of financial incentives to the pharmaceutical industry could have a meaningful impact in emphasizing the urgency with which this problem should be tackled.

In sum, incentives can take various forms:

a) Fast track designation with frequent meetings and protocol consultation particularly in the absence of articulated guidance.

b) Priority status granted for the review of ADFs.

c) Promulgation of standards for meaningful labeling that could result in reimbursement for approved formulations that are designed to reduce abuse, and thus more widespread adoption by the prescribing community.

d) Proposal of legislative remedies to provide incentives for development of ADFs such as, but not limited to:

   (i) Limits extended beyond the usual 3 years Waxman-Hatch exclusivity for an NDA submitted under 505(b) (2) for a reformulation. Such remedies as the Orphan Drug Act and the Pediatric Exclusivity first provided for in Section 505(A) of the FDA Modernization Act are examples of exclusivity provisions that have stimulated the development of new therapies to address an identified public health need.

   (ii) Tax credits for the conduct of specific studies required for approval, similar to the provisions in the Orphan Drug Act which provides for tax credits for clinical trials.

Failure to devote sufficient resources within the FDA will undermine public benefits of expediting these goals. Thus we urge the FDA to allocate internal FDA resources to accomplish the above. Conferees at the Office of Management Budget Formulation and Presentation[51] noted that "FDA may use available funds to support review and action on new drug applications and supplements seeking approval for replacement or alternative abuse resistant formulations of currently available drug products that include an active ingredient that is a listed chemical under the Controlled Substances Act." We also acknowledge, however, that to date there is minimal evidence to support the public health benefits of ADFs; thus, in order to validate such incentives provided to companies, the Agency will likely have to require companies to document the beneficial effects of ADFs in the post marketing phase.

The petitioners contend that the social, economic and law enforcement issues associated with the diversion and abuse of analgesics have led to a culture that interferes with the ability of physicians to care for their patients. The petitioners include pain management specialists and addiction specialists who, in the course of a many years of clinical experience, have evaluated and cared for thousands of patients who suffer from pain, or from prescription drug abuse. We underscore the urgent need to engage the focus and intense involvement of pharmaceutical companies in developing alternate, abuse-resistant formulations for opioid analgesics. We propose that the development of abuse-resistant opioid formulations will facilitate medically appropriate use of these potent analgesics, and thus improve the quality of life for millions of individuals that suffer from profoundly debilitating conditions, while minimizing the abuse potential of these drugs. We request that the FDA support such development by publishing a Guidance Document that specifies the approval requirements for developing safe, effective, and abuse-resistant opioid analgesics within an expeditious time frame.

[51] Office of Management; HR 109-102. Conference Report (House Report 109-255) – Making appropriations for agriculture, rural development, Food and Drug Administration, and related agencies programs for the Fiscal year ending September 30, 2006, and for other purposes - Significant Items. Item: Abuse-resistance Drugs, page 102. [FDA webpage]. 2007. Available at: http://www.fda.gov/oc/oms/ofm/budget/2007/HTML/5SignificantItems.htm. Accessed October 3, 2007.

DEFINITIONS OF TERMS USED

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the term "substance abuse disorder" refers to a "maladaptive pattern of substance use leading to clinically significant impairment or distress".

The term "non-medical use" is defined by the National Survey of Drug Use and Health (NSDUH) as use of drugs "that were not prescribed for you or that you took only for the experience or feeling they caused".

The Institute of Medicine defines "abuse" as any harmful use of a drug, whereas the DEA considers "abuse" to be any nonmedical use of a drug.

C. ENVIRONMENTAL IMPACT STATEMENT

As provided in 21 C.F.R. §25.30, the petitioners believe that this petition qualifies for a categorical exclusion from the requirement to submit an environmental assessment or an environmental impact statement.

D. ECONOMIC IMPACT STATEMENT

As provided in 21 C.F.R. § 10.30 (b) the petitioners will submit an economic impact statement if requested by the Commissioner.

E. CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

_____
(Signature)

_____
(Print name of petitioner)

_____
(Mailing Address)

_____

_____

_____
(Phone)