The National Center on
Addiction and Substance Abuse
at Columbia University

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May 15, 2009

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Division of Dockets Management
Food and Drug Administration
Room I-23
12420 Parklawn Drive
Rockville, MD 20857

***Re: Citizen Petition***

To Whom It May Concern:

Per FDA requirements, enclosed please find an original and three copies of the Citizen Petition by The National Center on Addiction and Substance Abuse (CASA) at Columbia University seeking the promulgation of new rules relevant to the content of Risk Evaluation and Mitigation Strategies (REMS) for opioid drugs.

Thank you for your attention to this matter.

Very truly yours,

Peter M. Jaensch, Esq.

Encl.

FDA.2009.P.0227

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Food and Drug Administration
Dockets Management Branch
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857

**CITIZEN PETITION**

The National Center on Addiction and Substance Abuse (CASA*) at Columbia University, a national organization that studies and seeks to combat the abuse of all substances in all sectors of society, submits this petition under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, 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 the Commissioner of Food and Drugs to take administrative action by issuing a new rule.

**Preliminary Statement**

Opioid medications are an important element in pain treatment, offering relief to patients. Unfortunately, as FDA has noted, abuse of these drugs is also on the rise[1], imposing significant costs on individuals and the community at large. FDA has begun to take action on this through consideration of classwide Risk Evaluation and Mitigation Strategies (REMS) for opioid drugs.

This petition is submitted in the interest of reducing the potential diversion and abuse of these drugs, while preserving their efficacy for legitimate treatment use. To that end, we propose that FDA require REMS for all opioid drugs, which, in addition to the minimal strategy elements detailed in 21 USC 355-

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* *The National Center on Addiction and Substance Abuse at Columbia University is neither affiliated with, nor sponsored by, the National Court Appointed Special Advocate Association (also known as "CASA") or any of its member organizations with the name of "CASA."*

1(d) would require medication guides, package inserts, elements to assure safe use, and certification of formulation to minimize the drug's abuse potential. Addressing these issues proactively is in the interests of both patients and industry, and may have substantial effect in preventing or minimizing abuse.

### A. Action Requested

CASA petitions the Commissioner of Food and Drugs to take action to strengthen FDA regulation of controlled prescription drugs, and help minimize the risks of diversion of controlled prescription drugs, by issuing a new rule mandating classwide Risk Evaulation and Mitigation Strategies (REMS) for all opioid drugs.

CASA proposes promulgation of a new regulation, based upon the language of 21 USC §355-1 to specify certain mandatory elements of classwide opioid drug REMS, providing:

> A risk evaluation and mitigation strategy shall be required for all opioid drugs, and shall include:
>
> > (1) A timetable for submission of assessments of the strategy at 18 months, 3 years and 7 years after the strategy is approved.
> >
> > (2) A medication guide, as provided for under part 208 of title 21, Code of Federal Regulations (or any successor regulations).
> >
> > (3) A patient package insert.
> >
> > (4) A communication plan, which may include:
> >
> > > (A) sending letters to health care providers;
> > >
> > > (B) disseminating information about the elements of the risk evaluation and mitigation strategy to encourage implementation by health care providers of components that apply to such health care providers, or to explain certain

safety protocols (such as medical monitoring by periodic laboratory tests); or

(C) disseminating information to health care providers through professional societies about any serious risks of the drug and any protocol to assure safe use.

(5) Elements to assure safe use. The Secretary may require that:

(A) health care providers who prescribe the drug have particular training or experience, or are specially certified;

(B) pharmacies, practitioners, or health care settings that dispense the drug are specially certified;

(C) the drug be dispensed to patients only in certain health care settings, such as hospitals;

(D) each patient using the drug be subject to certain monitoring;

(E) each patient using the drug be enrolled in a registry; or

(F) other measures be taken to minimize risk of abuse, diversion or harm while preserving patient access and therapeutic efficacy.

(6) Formulation certification. Each opioid drug risk evaluation and mitigation strategy shall include a certification that the drug has been formulated to minimize potential for abuse, both intentional and unintentional, to the extent possible without compromising the drug's therapeutic effectiveness.

**B. Statement of Grounds**

In 2005, CASA published *Under the Counter: The Diversion and Abuse of Controlled Prescription Drugs in the U.S.*, the first comprehensive analysis of all aspects of controlled prescription drug abuse - how widely opioids, central nervous system depressants, stimulants and steroids are abused, and how these

drugs are diverted from their normal distribution channels. This petition is based on the findings from that study, a copy of which is attached hereto as Exhibit A.

***FDA Should Require REMS to be Completed for all Opioid Drugs.***

Under the new REMS regime established in 21 U.S.C. 355-1, FDA regulations already contemplate the inclusion of medication guides, package inserts, and elements to ensure safe use in the REMS. However, at present, these are additional elements the inclusion of which in any particular REMS is determined on a case-by-case basis. We propose instead that FDA mandate a REMS template for every opioid drug that requires inclusion of all these elements.

Opioid drugs are powerful tools for alleviating the suffering of patients. Unfortunately, their strength makes them attractive objects of abuse. That FDA has already recognized this is evident:

- Since 2001, FDA has required the use of boxed warnings, the agency's strongest type of warning, on labeling of long-acting opioid drugs.[2]
- Pursuant to FDAAA, FDA has begun to track and list drugs identified from the Adverse Event Reporting System (AERS) showing potential signals of serious risks or new safety information.[3] Those manufacturers are on notice that if, after further evaluation, FDA determines the drug is associated with the risk, development of a REMS may be required. [4] Opioid drugs are listed among the noticed drugs in 2008.[5]
- In February 2009, FDA advised fifteen drug manufacturers that REMS will be required for certain opioid drug products, primarily extended release versions of generic

and brand name formulations of fentanyl, hydromorphone, methadone, morphine, oxycodone and oxymorphone.[6]

Requiring REMS on a classwide basis for opioid drugs rather than piecemeal removes the uncertainty in the REMS process for industry and provides an efficient response to a known risk.

***FDA Should Require Pharmaceutical Companies to Certify in REMS for Opioid Drugs that the Drug is Formulated to Minimize the Drug's Potential for Abuse Insofar as Possible Without Compromising Therapeutic Value.***

Before a medication is released on the market, scientific tests are conducted by the manufacturer to assess the risk of abuse.[7] The manufacturer submits evidence to FDA demonstrating the safety and effectiveness of the drug, disclosing its abuse potential and comparing its effects (including potential for abuse) to existing drugs.[8] This assessment provides useful information to help guide physician education about the best use of a drug and how to reduce the risk of abuse. FDA and DEA, the federal agencies responsible for regulating drugs in the U.S., also use this information to determine how best to classify and regulate the drug.[9]

How pharmaceutical manufacturers formulate a particular drug can contribute to the drug's potential for abuse. The appeal of a prescription drug for abuse depends on the strength and immediacy of the high it can produce, as well as on how easily the medication can be altered for purposes of abuse.[10] For example, some controlled-release opioid formulations (e.g., Duragesic, MC Contin, OxyContin, and Dilaudid) can be altered through crushing or dissolving to release the full dose at once, producing an intense high.[11]

Adding an antagonist to an opioid drug - as was done with Talwin - can counteract its morphine-like effects in the event that the tablets are altered for abuse;[12] however, the addition of an antagonist is not routinely done in the manufacture of prescription drugs with potential for abuse.

In the case of OxyContin, FDA originally permitted Purdue Pharma to imply in its labeling that OxyContin had a lower abuse potential than other opioids because of its 12-hour release mechanism.[13] This was the first time such labeling had been allowed for a Schedule II drug.[14] Ironically, OxyContin appears to have greater, rather than lesser, abuse potential than other opioids, primarily because when crushed and then snorted or injected, OxyContin loses its time-release component and provides an immediate narcotic rush to the brain.[15] In addition, the original safety warning on the label instructed users not to crush the pills because when crushed, toxic levels of the drug could be released.[16] This labeling may have suggested to drug abusers how to abuse the drug. Although the label has since been rewritten in accordance with FDA requirements, the original labeling makes clear that the abuse-potential was known prior to release.

It has been observed that some patients may have negative physical reactions to the antagonist and may not be able to take the reformulated medication.[17] In requiring pharmaceutical companies to certify in their REMS for opioid drugs that they have formulated the drug to minimize the drug's potential for abuse, FDA should continue to take these considerations into account when reviewing new drug applications and should weigh drugs' potential for abuse together with matters of safety and efficacy.

***Background:***

While America has been congratulating itself in recent years on curbing increases in alcohol and illicit drug abuse and in the decline in teen smoking, abuse and addiction of controlled prescription drugs have been rising sharply. Controlled prescription drugs, such as OxyContin, are now the fourth most-abused class of substances in America, exceeded only by abuse of (1) marijuana, (2) alcohol and (3) tobacco. Particularly alarming is the 213 percent increase from 1992 to 2003 in the number of 12- to 17-year olds abusing controlled prescription drugs, and the increasing number of teens trying these drugs for the first time. New abuse of prescription opioids among teens is up an astounding 542 percent, more than five times the rate of increase among adults.[18]

The abuse of controlled prescription drugs was foreshadowed by dramatic increases in their manufacture and distribution and in the number of prescriptions written and filled. Between 1992 and 2002, while the U.S. population increased 13 percent and the number of prescriptions written for non-controlled drugs increased by 57 percent, the number of prescriptions filled for controlled drugs increased by 154 percent.[19] Between 1992 and 2003, there was a 93.8 percent increase (from 7.8 million to 15.1 million) in the number of people who admitted abusing controlled prescription drugs.[20] The explosion in OxyContin prescriptions written to treat non-cancer pain - from 670,000 in 1997 to some 6.2 million in 2002 - and the resulting rampant abuse and addiction related to the drug have drawn attention to gaps in prevention and control.

***Opioid Drugs:***

Also referred to as narcotics, analgesics, painkillers or pain relievers, opioids commonly are taken to relieve pain,[21] the most common complaint that physicians hear from their patients.[22] Opioids are prescribed for three types of pain: acute or short-lived pain, chronic malignant (cancer) pain and chronic nonmalignant pain.[23] Opioid medications include morphine, codeine, oxycodone (e.g., OxyContin, Percocet), hydrocodone (e.g., Lortab, Vicodin), hydromorphone (e.g., Dilaudid), propoxyphene (e.g., Darvocet, Darvon), and meperidine (e.g., Demerol).[24] Opioids attach to opioid receptors in the brain, block the transmission of pain signals to the brain and, like illicit opioids (e.g., heroin), produce a sense of heightened pleasure.[25] The use of opioids is an important component of pain management.[26]

***Abuse Potential of Opioid Drugs:***

Prescription opioids, like their illicit counterpart heroin, are addictive and usually classified as Schedules II and III drugs. Yet, determining the risk of addiction to opioids following prescribed use has stirred considerable debate among pain management and addiction specialists.[27] Pain management specialists tend to emphasize the risk of under-treating pain,[28] sometimes understating the risk of addiction;[29] addiction specialists tend to emphasize the risk of abuse and addiction,[30] sometimes understating the risk of under-treated pain.

Some physicians and patients fear that using opioids therapeutically can result in addiction;[31] such concern can affect physicians' prescribing practices. In addition to the fear of causing addiction, some physicians fear being scrutinized by regulatory agents for too liberally prescribing controlled substances.[32] Surveys of physicians, however, show that concerns

about addiction tend to outweigh concerns about regulatory scrutiny.[33] CASA's survey of physicians found that 63.5 percent do not worry much or at all about the possibility of review of their prescribing practices by regulatory or enforcement agencies. About a quarter (24.2 percent) say they worry somewhat and 9.5 percent say they worry a great deal about this possibility.

Other physicians - particularly those who specialize in pain management - feel that opioids are under-utilized to treat pain.[34] They argue that the under-treatment of pain can lead to health problems such as increased risk of pneumonia or respiratory problems and also can cause acute pain to develop into chronic pain.[35]

FDA REMS for opioid drugs will help physicians provide appropriate pain management to their patients while avoiding over-prescribing, misuse and patient addiction.

***Consequences of Abuse:***

Long-term use of opioids can lead to physical dependence on the drugs. Physical dependence is characterized by tolerance to the drug and withdrawal symptoms when use of the drug is reduced or stopped. Opioid withdrawal symptoms include insomnia, bone and muscle pain, diarrhea and vomiting. These signs of physical dependence may occur even when opioids are used appropriately for medical purposes. Opioid abuse - particularly taking a large dose at one time - can lead to severe respiratory depression and death.[36]

***Opportunites for Industry:***

Diversion - any criminal act that causes controlled prescription drugs to be sidetracked from their lawful (medical) purpose to illicit use - can occur at any point in the manufacturing and

distribution chain (in which prescription drugs typically are sold by pharmaceutical manufacturers to wholesalers, who in turn sell them to pharmacies where they are purchased by patients with a valid prescription from a physician).[37] Diversion can occur through theft, fraudulent prescriptions, patient scams, dishonest healthcare practitioners, prescription sharing and through criminal operatives. The risks of diversion can be increased by the way that drugs are formulated and marketed. In an effort to manufacture and sell products that benefit those with physical or psychological illnesses while at the same time maximize company profits, pharmaceutical company practices at times have contributed to the problems of prescription drug diversion and abuse.

Pharmaceutical companies may contribute to abuse and diversion by the way they formulate controlled prescription drugs. As such, FDA regulation of drug formulation has the potential to effectively curtail at least some abuse of prescription drugs. The appeal of a prescription drug for abuse is largely dependent upon the strength and immediacy of the high it creates. Drugs like OxyContin and Dilaudid that can easily be altered to destroy their time-release mechanism are consequently at a premium on the drug abuse market. Adding an antagonist to an opioid drug can counteract its morphine-like effects in the event that the tablets are altered for abuse. However, pharmaceutical companies do not routinely include antagonists in the manufacture of abusable prescription drugs on the grounds that patients may have negative physical reactions to the antagonist or because it may reduce the drug's efficacy. In fact, formulation of a drug to reduce its abuse-potential is not a required consideration by either pharmaceutical companies or FDA in bringing a controlled drug to market. Nor are plans to mitigate the risk of diversion and abuse required for all controlled drugs prior to their release.

***FDA Action:***

FDA has taken action to address the abuse and diversion of controlled prescription drugs by, among other things, publishing consumer information,[38] publishing guidance for industry and reviewers on assessing abuse potential[39] and implementing risk management procedures on a pre-and post-market basis[40]. However, FDA's actions in this area with respect to pharmaceutical manufacturers have historically taken the form of non-binding recommendations, as opposed to industry requirements.

FDA has now begun implementation of the new REMS system, which may be required on a case-by-case basis, and is currently considering requiring REMS on a *classwide* basis for opioid drugs. While manufacturers submit evidence to FDA in new drug applications demonstrating the safety and effectiveness of the drug, disclosing its abuse potential and comparing its effects (including potential for abuse) to existing drugs, FDA does not *require* companies to demonstrate that they have made every effort to formulate potentially abusable drugs in such a way as to minimize or eliminate the drug's potential for abuse.

Consequently, CASA petitions FDA to require pharmaceutical companies to complete and submit REMS for *all* opioid drugs, and further, that these REMS should require inclusion of:

- Medication guides;
- Package inserts;
- Elements to assure safe use; and
- Formulation certification.

### C. Environmental Impact

Nothing requested in this petition will have an impact on the environment; we further claim categorical exclusion under 21 C.F.R. 25.31.

### D. Economic Impact

Economic impact will be addressed at the request of the Commissioner.

### E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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