The National Center on
Addiction and Substance Abuse
at Columbia University

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October 25, 2007

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Re: Citizen Petition

Dear Dr. von Eschenbach:

Per FDA requirements, enclosed please find 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 new approvals of scheduled drugs.

In light of the subject matter concerned, we believe it may be appropriate and advantageous for this petition to be forwarded for consideration to the Drug Safety and Risk Management Advisory Committee.

Thank you for your attention to this matter.

Very truly yours,

Elizabeth Planet.

Elizabeth Planet, Esq.

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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.

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 new rules:

(1) requiring pharmaceutical companies manufacturing controlled drugs to demonstrate and certify in their application materials for FDA approval of new drugs that they have made every effort to formulate the drug in such a way that avoids or at least minimizes the drug's potential for both intentional and

unintentional abuse without compromising its therapeutic effectiveness; and

(2) requiring pharmaceutical companies to include proactive risk management plans in all new applications for controlled drugs, demonstrating strong evidence of a prescription drug's safety, as well as concrete steps that will be taken to prevent the abuse of the drug while maintaining its maximum 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.

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 - opioids, central nervous system depressants and stimulants - have been rising sharply. Controlled prescription drugs, such as OxyContin, Ritalin and Valium, 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.[i]

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.[ii] 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.[iii] 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.

Abuse Potential:

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 manage the risk of diversion and abuse required for all controlled drugs prior to their release.

Diversion:

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).[iv] 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.

FDA Action:

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

to industry requirements. Although FDA recommends that pharmaceutical manufacturers submit risk minimization action plans (RiskMAPs) with new drug applications for potentially abusable opiates[viii], FDA has not gone so far as to *require* pharmaceutical companies to prepare RiskMAPs prior to bringing such drugs to market. And 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 the drug's potential for abuse.

Consequently, CASA petitions FDA to require pharmaceutical companies to take these actions by (1) requiring the certification and demonstration that every effort has been made to formulate the drug in a way that will prevent or minimize abuse potential, and (2) requiring the submission of a RiskMAP, subject to FDA approval, in all applications for approval of new controlled prescription drugs.

FDA should require pharmaceutical companies to demonstrate in their application materials for FDA approval of new controlled drugs that they have made every effort to formulate the drug in such a way that avoids or at least minimizes the drug's potential for abuse.

Before a medication is released on the market, scientific tests are conducted by the manufacturer to assess the risk of abuse.[ix] 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.[x] 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.[xi]

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.[xii] 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.[xiii]

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;[xiv] 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.[xv] This was the first time such labeling had been allowed for a Schedule II drug.[xvi] 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.[xvii] 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.[xviii] 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.[xix] In requiring pharmaceutical companies to demonstrate in their application materials for FDA approval of new controlled drugs that they have made every effort to formulate the drug in such a way that avoids or at least minimizes 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.

FDA should require pharmaceutical companies to include proactive risk management plans in all new applications for controlled drugs.

Recognizing the widespread abuse of controlled prescription drugs, FDA recommends - but does not require - pre-market risk assessment and implementation of risk management plans for all new controlled prescription drugs.[xx] FDA currently offers guidance on the crafting of an appropriate RiskMAP in agency documents such as *Guidance for Industry; Development and Use of Risk Minimization Action Plans*, available at http://www.fda.gov/cber/gdlns/premarkrisk.htm.

Some pharmaceutical companies have initiated risk management plans to assess the risk associated with marketing a new drug. Recently, FDA's Anesthetic and Life Support Drugs Advisory Committee recommended that Purdue Pharma LP take such precautions in its release of Palladone, a controlled-release form of hydromorphone, in addition to requiring a black box warning about the medication's potential for abuse.[xxi] This plan included a statement in the package that the drug should not be crushed, dissolved or chewed, a hotline for information on adverse effects and a yearlong phased launch of the drug.[xxii] During the

introductory period, the company focused its sales on pain management specialists and began collecting data about the drug's abuse through its Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) system - a system designed to monitor the diversion and abuse of prescription opioid medications with recognized abuse potential.

This proactive approach, which can effectively preempt unexpected and widespread instances of abuse of new prescription drugs, is a recommended but not mandatory feature of new drug applications to FDA for controlled substances.[xxiii] However, the failure of FDA to require these plans to be made in advance leaves a potential gap between the identification of problems and a solution course to remediate, which there is no reason to permit when a corrective tool already exists. Given the potential for avoidance of abuse this approach offers, FDA should require pharmaceutical companies to include proactive risk management plans in all new applications for controlled drugs.

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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EXHIBIT A:

Under the Counter: The Diversion and Abuse of Controlled Prescription Drugs in the U.S.