February 13, 2012

Legal Drug Abuse: America's Prescription Pill Problem Spills Out

Lauren G. Wilkinson, California Western School of Law

Available at: https://works.bepress.com/lauren_wilkinson/2/
Legal Drug Abuse:  
America’s Prescription Pill Problem Spills Out  

Lauren G. Wilkinson  
Fall 2011
Introduction

Classified as an “epidemic” by the Centers for Disease Control and Prevention,¹ and a “critical public health problem,”² by the Food and Drug Administration (FDA), the abuse of prescription drugs is sharply on the rise and, second to marijuana, these medications are the most abused category of drugs in the country.³ According to the Substance Abuse and Mental Health Administration (SAMHA), in 2008, 53 million people in the United States said that they had used prescription drugs non-medically at least once and 6.2 million people were current users, meaning they had used prescription drugs non-medically within the past month.⁴ The term “non-medical use” of a drug is defined by SAMHA’s Drug Abuse Warning Network (DAWN) as, “taking a higher-than-recommended dose, taking a drug prescribed for another person,… or documented misuse or abuse.”⁵ When the FDA declares a drug to be safe it “does not mean free of risk,”⁶ however FDA considers the injuries and deaths caused by drug abuse to be preventable harms that can be mitigated or avoided with better risk management.⁷

In addition, the financial and public health costs of this crisis are enormous.⁸ Rehab admissions and emergency room visits for prescription drug abuse have grown significantly over

---

³ Epidemic: Responding to America’s Prescription Drug Abuse Crisis, Executive Office of the President of the United States, 2011, at 1 [hereinafter Prescription Drug Abuse Crisis].
⁷ FDA’s Safe Use Initiative Collaborating to Reduce Preventable Harm from Medications, U.S. Dept. of Health and Human Services Food and Drug Admin., Nov. 4, 2009, at 4, 5 [hereinafter Safe Use Initiative].
⁸ Prescription Drug Abuse Crisis, supra note 3, at 1.
the last decade and drug abuse costs to the U.S. government are estimated at $300 billion dollars per year. Emergency department visits for prescription or over the counter drugs totaled 1 million visits in 2008. Those emergency department visits for opioid analgesics, a commonly abuse class of prescription pain relievers, alone increased 111% during 2004-2008. Opioid analgesics also caused more deaths from unintentional overdoses in 2007 than heroin and cocaine combined. Also, the United States consumes 80% of the global opioid supply and 99% of the world’s hydrocodone supply, yet accounts for only 4.6% of the world’s population.

Moreover, the escalation of prescription drug abuse has resulted in what physician and Georgetown Medical School professor Susan Okie, M.D., considers a “striking shift,” from the predominant instances of fatal overdoses occurring in urban areas into rural counties. The state with the most deaths caused by prescription drug overdose is West Virginia, and individuals with low levels of education were more at risk for abuse, including those that lived in the state’s poorest county. This shift has been attributed to the increase in marketing and distribution of opioid pain relievers in the 1990s which caused these powerful drugs to be available in rural areas that had previously lacked access to an illicit drug market. Increased availability as a result of the drugs being legally dispensed in pharmacies across America in addition to the usage

---

11 Emergency Department Visits, supra note 5, at 514.
12 Id.
14 Manchikanto, Fellows, Ailinani & Pampati, supra note 10, at 402.
15 Oakie, supra note 13, at 1982.
16 Id. at 1983.
17 Id. at 1982.
of other substances such as alcohol with the prescription drugs are contributing factors to this high death rate.\textsuperscript{18}

FDA contends that the amount of harm from non-medical use of prescription drugs is difficult to estimate but the one thing that is certain is that instances of abuse are increasing in the United States.\textsuperscript{19} These medications are being prescribed with greater frequency and with stronger potency.\textsuperscript{20} In fact, in 2009 there were 257 million prescriptions dispensed for opioid pain relievers; a 48% increase just from the year 2000.\textsuperscript{21} In recent years, patients have enjoyed advancements in the treatment of pain through the development and prescription of effective and highly potent medications.\textsuperscript{22} With the development and greater therapeutic use of powerful prescription drugs in recent years, instances of drug abuse and misuse have followed, and governmental agencies including the FDA are taking action to curb drug abuse.\textsuperscript{23}

As a public health agency, the FDA is committed to promoting and protecting the public health and it must ensure that products that reach the market are safe and effective pursuant to its authority to regulate the approval, labeling, manufacturing and marketing of prescription drugs under the Food, Drug and Cosmetic (FD&C) Act.\textsuperscript{24} The process by which the FDA ensures a product’s safety is through a risk-benefit analysis conducted prior to approval of a drug.\textsuperscript{25} When the benefits of a drug outweigh the risks, FDA will consider approval and marketing in accordance with the drug’s labeling.\textsuperscript{26} After approval, FDA engages in an ongoing risk-

\begin{thebibliography}{99}
\bibitem{18} Id.
\bibitem{19} \textit{Safe Use Initiative, supra} note 7, at 3.
\bibitem{21} Id.
\bibitem{22} Oakie, \textit{supra} note 13, at 1982.
\bibitem{23} Id.
\bibitem{24} \textit{FDA and DEA Hearing, supra} note 9, at 21, 26 (testimony of Robert J. Meyer, M.D.)
\bibitem{25} \textit{Prevention Hearing, supra} note 6 (testimony of Sandra L. Kweder, M.D.).
\bibitem{26} Id.
\end{thebibliography}
management process that aims to keep the risks of a drug, “in line with [the] benefits.”\textsuperscript{27} FDA’s post-market regulatory role has been expanded in recent years\textsuperscript{28} and ultimately FDA carries the power to revoke a drug’s approval after it has gone to market if it feels that is necessary to protect the public well-being.\textsuperscript{29}

As such, after weighing the benefits and risks, FDA approves the drug only for the medical uses specified on the label, thereby ensuring that benefits outweigh the risks only if the drug is taken as directed.\textsuperscript{30} Therefore, if a user takes the drug in a way that deviates from the specifications of the label, there is no guarantee that the drug is indeed safe and effective. This is relevant to drug abuse since non-medical use by definition\textsuperscript{31} involves taking a drug in a manner inconsistent with the medically approved usage of the substance. Also, when drugs are taken non-medically, there is no medical oversight of the risks since the drugs are not used in accordance with a prescription or directions from a health care professional.\textsuperscript{32} Since FDA’s risk-benefit assessment is based on patient usages stipulated on the drug’s label,\textsuperscript{33} that balance is upset when the drugs are used in a way that is contrary to those intended uses.

Thus, the abuse and misuse of prescription drugs circumvents FDA’s risk-benefit process for ensuring that drugs are safe and effective and creates a dangerous situation that calls for a unique regulatory process to assess drug abuse risks. Rather than assume for purposes of a safety evaluation that prescription drugs will be used according to the guidelines of the label, it may be necessary to use actual patterns of use in the population as a benchmark for determining the safety of a drug. Also, the individuals who abuse prescription drugs in the majority of cases

\textsuperscript{27} Id.
\textsuperscript{29} FDA and DEA Hearing, supra note 9.
\textsuperscript{30} Combating Misuse and Abuse of Prescription Drugs, supra note 4, at 1.
\textsuperscript{31} Emergency Department Visits, supra note 5, at 514.
\textsuperscript{32} Combating Misuse and Abuse of Prescription Drugs, supra note 4, at 1.
\textsuperscript{33} Prevention Hearing, supra note 6.
obtained the drug from a friend or relative with excess medication and did not interact with the health care community. For those users, there are no therapeutic benefits against which to weigh the risks of abuse, addiction, overdose and death. Therefore, regulatory measures would benefit from accounting for non-medical users that obtain the drugs through unregulated means and for whom the drugs carry an especially high risk in the absence of a therapeutic benefit. In any event, solving the prescription abuse crisis will call for “complicated [and] multifaceted solution[s],” and the FDA is heeding the call to action.

This paper will discuss: first, the current regulations and initiatives in place to mitigate the risks of prescription drug abuse, including FDA’s process for drug approval, assessment of abuse potential and scheduling; second, FDA’s recently enhanced regulatory role and the advent of Risk Evaluation Mitigation Strategies (REMS); and third, an evaluation of the existing and proposed risk management measures in light of the unique risks for non-medical users who take prescription drugs in an unintended manner and who may not experience a therapeutic benefit from the drugs.

FDA Drug Approval and Assessment of Abuse Potential

During the approval process and as part of the safety evaluation of a drug, FDA engages in an abuse liability assessment to determine a drug’s potential for abuse. Drugs with an abuse potential typically affect the central nervous system and are used non-medically, “repeatedly or sporadically, for the positive psychoactive effects they produce.” According to the FDA, this concept of abuse potential involves all aspects of the drug including: positive psychoactive

34 Manchikanto, Fellows, Ailinani & Pampati, supra note 10, at 414.
35 Oakie, supra note 13, at 1984.
36 Safe Use Initiative, supra note 7.
37 Combating Misuse and Abuse of Prescription Drugs, supra note 4, at 3.
effects of the drug such as sedation, euphoria or mood change, similarity to other drugs with known abuse potential and the drug’s effect on the central nervous system.\textsuperscript{39} When the above factors indicate that there is a potential for abuse, drug sponsors should include a section on the abuse potential assessment of the drug in the new drug application (NDA).\textsuperscript{40} FDA does not conduct the abuse potential assessment itself but drug sponsors are strongly encouraged to proactively involve FDA and consult about such matters as the, “design of the studies and the data to be included in an abuse potential assessment.”\textsuperscript{41}

Various approaches and methods used to assess a drug’s abuse potential are set forth in a recent FDA Guidance for Industry.\textsuperscript{42} One such approach involved conducting studies on animal behavior pharmacology.\textsuperscript{43} Pharmacology is the study of the sources, nature and properties of drugs and how the body reacts to those drugs.\textsuperscript{44} Animal abuse potential studies usually are conducted on rodents or primates and information gained during these studies can help the drug sponsor detect an indication of abuse potential early and decide what additional studies should be conducted in animals or in humans.\textsuperscript{45}

There are several types of abuse potential studies conducted in animals; one is the self-administration test which assesses the rewarding qualities of a drug based on whether the animal performs a behavioral task to receive a dose of the drug.\textsuperscript{46} Another study is conditioned place preference in which the drug is administered in only one of two environments and researchers

\textsuperscript{40} Id. at 6.
\textsuperscript{41} Id. at 5, 10.
\textsuperscript{42} Id.
\textsuperscript{43} Id. at 7.
\textsuperscript{45} Abuse Potential Guidance, supra note 39, at 7.
\textsuperscript{46} Id. at 8.
observe whether the animal exhibits a preference for the environment containing the drug.⁴⁷ If there is a negative result in either of these two studies however, it does not necessarily mean that the drug lacks abuse potential because certain classes of drugs including hallucinogens, cannaboids, and other drugs with a “psychedelic” effect did not produce an addictive response in animals but have done so in humans.⁴⁸ Some drugs may have an abuse potential for humans but not in animals because the reasons for certain human behaviors, including why a person takes a particular drug, can be much more complex and while animal studies are useful they are not conclusory. In human studies, the subjects can clearly communicate to the researchers the effects of the drug and why a particular drug is desirable.⁴⁹

Further, human laboratory studies are also recommended by the FDA Guidance for drugs with abuse potential.⁵⁰ These studies are conducted on a population of experienced recreational drug users in a controlled laboratory setting⁵¹ after adequate data on safety and efficacy is gathered.⁵² The primary method of assessing the subjective effects of the drugs on humans is to give the participants various doses of the drug and administer standardized questionnaires.⁵³ Participants rate their subjective responses to the drug and are administered placebo and multiple doses of the new drug.⁵⁴ These human abuse potential studies are important because if the studies do not indicate the presence of abuse related behaviors such as rewarding effects then it is not likely that the drug will be deemed to have an abuse potential⁵⁵ and the sponsor can avoid increased control and regulation.

---

⁴⁷ Id. at 8.
⁴⁸ Id.
⁴⁹ Id. at 12.
⁵⁰ Id. at 8.
⁵¹ Id. at 10, 11.
⁵² Messplay & Heisey, supra note 38, at 20.
⁵³ Abuse Potential Guidance, supra note 39, at 11.
⁵⁴ Id. at 10, 11.
⁵⁵ Id. at 9.
Regulation of Controlled Substances, Efforts of FDA and DEA

If a drug is found to have an abuse potential, the sponsor is required to provide FDA with all the abuse-related data, a proposal for scheduling under the Controlled Substances Act (CSA), and data on drug overdose.  

FDA recommends the drug for scheduling under the CSA and forwards the recommendation to the Drug Enforcement Agency (DEA). The DEA is the lead agency charged with enforcement of the CSA and regulation of controlled substances; however FDA and DEA meet regularly to discuss prescription drug abuse prevention measures and are collaborating on several risk management initiatives. 

Also, FDA’s Office of Criminal Investigations participates and assists the DEA in criminal investigations, including state and federal joint task forces focused on curbing the illegal sale of controlled prescription drugs.

Under the CSA, the Department of Health and Human Services (DHHS) is required to notify the Attorney General, by way of the DEA, if a new drug has an abuse potential. DHHS has delegated this duty to FDA and the organization charged with this role within the FDA is the Controlled Substance Staff (CSS). The FDA’s Controlled Substance Staff is a division of FDA’s Center for Drug Evaluation and Research (CDER), Office of the Center Director and the organization is responsible for evaluating the abuse potential of a drug. The mission of the

---

56 21 CFR §314.50(viii).
57 FDA and DEA Hearing, supra note 9, at 30 (testimony of Robert J. Meyer, M.D.).
58 Id. at 30, 31.
59 Prevention Hearing, supra note 6, (testimony of Sandra L. Kweder, M.D.).
61 21 USC §5.10.
62 Consulting the Controlled Substance Staff, supra note 60, at 1.
63 Abuse Potential Guidance, supra note 39, at 3.
Controlled Substance Staff is to, “promote the public health through the medical science-based assessment and management of drug abuse risks.”

After FDA submits its scheduling recommendation, the DEA classifies the drug into one of five schedules based on the drug’s medicinal value and potential for abuse and dependence. Scheduling has an enormous impact on how the drug is tracked, sold and regulated and all registered handlers of controlled substances are required to register with DEA and provide the agency with data on the prescription of controlled substances. If a registered controlled substance handler violates the requirements of the CSA they can be subject to criminal liability or civil monetary liability. Schedule I drugs, which include heroin, marijuana, and LSD, have no currently accepted medical use and a high potential for abuse. Drugs that are classified as schedule II include opioids such as morphine and oxycodone, and while these drugs have a medically accepted use and are legally available with a prescription they may lead to, “severe psychological or physical dependence,” according to the United States General Accounting Office. Given this heightened risk, the annual quantity of schedule II controlled substances that may be manufactured is limited and an in-person consultation with a physician is required for a prescription. Schedule III – V drugs have less potential for safety or abuse liability than those in schedule II and many are available without a prescription.

---

64 Controlled Substance Staff- Mission, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180753.htm.
66 Id. at 13.
67 Id. at 13, 14.
68 OxyContin Abuse and Diversion Efforts, supra note 65, at 11.
69 Id.
70 Id. at 13, 14.
71 Id. at 11.
In addition, thirty-seven individual states including California\textsuperscript{72} have adopted Prescription Monitoring Programs (PMPs) through which the prescription of controlled substances can be tracked.\textsuperscript{73} These programs allow the state to collect information regarding the prescription, dispensing and use of controlled prescription drugs and are considered effective in reducing instances of abuse and misuse of controlled drugs.\textsuperscript{74} The data is analyzed by state agencies and used to identify individuals who are considered “doctor shoppers” because they get multiple prescriptions from various doctors, sometimes across state lines.\textsuperscript{75} Also, physicians who over-prescribe these potent drugs can be located.\textsuperscript{76} In addition to being helpful to law enforcement, doctors can use the PMP data in their favor by determining a particular patient’s risk for abuse and whether there are alternative treatments the patient would benefit from.\textsuperscript{77} These programs could be a useful tool for doctors to treat the patient’s addiction by referring non-medical users to rehab facilities or addiction counseling programs.

While state laws govern the regulation and monitoring of the prescription and dispensing of drugs by licensed health care providers,\textsuperscript{78} the FDA strongly supports the use of state-based PMPs\textsuperscript{79} and the White House Office of National Drug Control Policy plans to expand state-based PMPs.\textsuperscript{80} One law recently passed in Washington state, where deaths by drug overdoses surpassed motor vehicles as the leading cause of accidental death, is being closely watched by health

\textsuperscript{74} \textit{FDA’s Role in Preventing Prescription Drug Abuse}, http://www.fda.gov/NewsEvents/Testimony/ucm112718.htm.
\textsuperscript{75} \textit{FDA and DEA Hearing, supra} note 9, at 45 (testimony of Joseph T. Rannazzisi, Acting Deputy Assistant Administrator, Drug Enforcement Admin. Office of Diversion Control).
\textsuperscript{76} \textit{Id.} at 45.
\textsuperscript{77} \textit{Id.} at 45.
\textsuperscript{78} \textit{OxyContin Abuse and Diversion Efforts, supra} note 65, at 14.
\textsuperscript{80} \textit{FDA Acts, supra} note 2, at 1.
officials across the nation.\textsuperscript{81} This law is the first attempt to assess doctor’s performance at treating pain patients and requires physicians to track opioid patient’s pain level and functionality.\textsuperscript{82} The law would only apply to patients with non-cancer pain and physicians would be required to retain a pain specialist if they recommend a dosage of opioids above a certain threshold.\textsuperscript{83} In addition, the law requires the use of a mandatory prescription drug monitoring program and uniform pain management guidelines to be followed by opioid prescribers.\textsuperscript{84} While physician Perry Fine, M.D. acknowledges the concerns that doctors could be more hesitant to treat pain patients, he added that such a measure to monitor doctor’s success may lead to an opportunity for a measurable difference in how patients are treated and ultimately lead to results.\textsuperscript{85}

In addition, DEA, tasked with enforcing the Controlled Substance Act, continues to develop new strategies and examine new technologies to track controlled substances to reduce addiction and abuse.\textsuperscript{86} While not currently used, DEA is examining the usefulness of Radio Frequency Identification Technology (RFID) which is an emerging technology in which a detector wirelessly tracks a tagged object.\textsuperscript{87} This technology would identify any bottles of prescription controlled substances containing a chip that were diverted from the commercial containers.\textsuperscript{88} However, DEA recognizes that pills are often taken out of the commercial prescription container and the diverted controlled substances they find are in the form of loose tablets in unmarked bottles or plastic bags.\textsuperscript{89} DEA rarely encounters counterfeited versions of

\textsuperscript{81} Oakie, supra note 13, at 1984.
\textsuperscript{82} Id.
\textsuperscript{83} Id.
\textsuperscript{84} Id.
\textsuperscript{85} Id.
\textsuperscript{86} FDA and DEA Hearing, supra note 9, at 48, 50 (testimony of Joseph T. Rannazzisi).
\textsuperscript{87} Id. at 47.
\textsuperscript{88} Id.
\textsuperscript{89} Id.
controlled substances so the pills on the illegal market were legitimately manufactured.\textsuperscript{90} Therefore, DEA is looking to use this technology at the “dosage unit level,” perhaps to track individual pills when they leave the manufacturer to be more effective at collecting data on controlled substances.\textsuperscript{91}

In addition, in an effort to promote the safe disposal of controlled substances for those patients with excess medications, FDA and the Office of National Drug Control Policy have published guidelines for the appropriate disposal of medications.\textsuperscript{92} While this problem has not been exhaustively studied, it is particularly relevant to prescription drug abuse because the best documented consequence of leftover medications is the non-medical use of opiates.\textsuperscript{93} The American Society of Consultant Pharmacists found that each year, millions of pounds of prescription medications go unused in the United States.\textsuperscript{94} The availability of leftover medication contributes to the abuse and misuse of prescription drugs and is consistent with data that the majority of abused drugs are obtained from a friend or relative.\textsuperscript{95} Interestingly, some states have created programs that allow excess medication to be repackaged for use by patients who cannot afford treatment, thereby reducing harm from excess medication and making medications more affordable.\textsuperscript{96} This is an example of policymakers engaging in creative solutions that not only reduce harm but also benefit the overall public health.

\begin{itemize}
\item \textsuperscript{90} Id.
\item \textsuperscript{91} Id.
\item \textsuperscript{92} William H. Shrank, M.D., M.S.H.S., Our Bulging Medicine Cabinets- The Other Side of Medication Nonadherence, 364;17 New Eng. J. Med 1591, 1593 (2011).
\item \textsuperscript{93} Id. at 1592.
\item \textsuperscript{94} Id. at 1592.
\item \textsuperscript{95} Shrank, supra note 92, at 1593; Manchikanto, Fellows, Ailinani & Pampati, supra note 10, at 414.
\item \textsuperscript{96} Shrank, supra note 92, at 1593.
\end{itemize}
The Safe Use Initiative

In 2009, FDA announced the launching of its “Safe Use Initiative” to reduce medication risks and harm caused by prescription drugs that have a high level of preventable harm.97 The goal of the initiative is to create, “collaborations among relevant stakeholders to identify specific, preventable problems related to medication use, develop cross-sector interventions to reduce harm, and identify metrics by which to measure the success of these interventions.”98 One of the broad sources of preventable injury from unsafe medication use identified in the Safe Use Initiative is intentional drug misuse, abuse and self-harm. FDA’s goal is to collaborate with other government agencies and stakeholders in the broader health care community such as health care providers, patients, pharmacists, health insurers, and others to address preventable medication harms.99

Some of these proposed collaborations are already being considered and the launching of medication risk reduction efforts are underway and others are ongoing.100 The Safe Use Initiative proposes harm reduction “interventions” that involve regulatory components, such as requiring risk mitigation strategies, discussed in the next section, before and after drug approval combined with non-regulatory measures undertaken by private stakeholders to compliment FDA’s efforts.101 In keeping with the collaborative spirit of the initiative, FDA seeks to get input in the development and design of interventions from those members of the health care community that would be affected by regulatory measures.102 This involvement is important given the strength of the health care lobbies and because the affected groups may be more likely

97 Safe Use Initiative, supra note 7, at 1, 4.
98 Id. at 4.
99 Id. at 1, 11.
100 Id. at 18
101 Id.
102 Id.
to support reform if they feel that their interests are represented and they have a say in the proposed policies and procedures.

Risk Evaluation Mitigation Strategies (REMS)

In recent years, FDA has increasingly focused on its role as a public health agency in addressing the rapidly growing increase in the abuse of prescription drugs. In the past, FDA has been reluctant to focus on regulation of drugs that are already on the market since it “does not regulate the practice of medicine,” but recent FDA initiatives and legislation indicate that FDA is increasing its regulatory role to address safe medication use. While post-market regulation and mitigating risks from the intentional misuse and abuse of medications have not been traditionally a focus of FDA’s regulation efforts, the recent passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA), which amended the FD&C Act, has increased FDA’s ability to deal with this growing problem. The FDAAA increased FDA’s overall responsibility and post-market safety authority, and in particular the agency was given the authority to develop a new process for ensuring that the benefits of a drug outweigh the risks, called Risk Evaluation Mitigation Strategies or “REMS.”

The purpose of the REMS program is consistent with FDA’s primary mission and is to ensure that the “benefits of a drug continue to outweigh certain risks.” REMS involve a risk mitigation plan and may be required for a drug before or after FDA approval if safety information indicates that a renewed risk-benefit assessment is necessary. Post approval, the FDAAA states that a drug company may be required to conduct studies or clinical trials based on

103 Qato & Alexander, supra note 28, at 1596.
104 Id. at 1595.
105 Safe Use Initiative, supra note 7, at 11.
106 Qato & Alexander, supra note 28, at 1595.
107 Safe Use Initiative, supra note 7, at 16.
new scientific data about the drug, or drugs that are chemically similar, the purposes of which are:

“…to assess a known serious risk related to the use of the drug involved, to assess signals of serious risk related to the use of the drug [and] to identify an unexpected serious risk when available data indicates the potential for a serious risk.”

An ongoing post-market safety evaluation is crucial because many risks are learned after a drug reaches the market as a much larger sample of the population is exposed and the drug is used in different settings. The need to keep the public safe from unnecessary and avoidable risks continues to be as important as during the drug approval process.

Further, the REMS submission should consist of a proposed REMS, which identifies the proposed goals and measures, and a REMS supporting document which expands on the proposal. The stated goals of a REMS proposal are important since the efficacy of the REMS is measured against its meeting of those goals. The description of the overall goals should identify the sponsor’s desired, “safety-related health outcome or the understanding by patients and/or health care providers of the serious risks targeted,” by the implementation of the REMS. In order to accomplish the stated goal, the sponsor must identify specific objectives and processes in order to eliminate known risks of the drug. In order to be sure that the measures in the REMS are effective in reducing harm, the strategy must outline procedures for tracking outcomes and

---

109 Qato & Alexander, supra note 28 at 1595.
112 Id.
113 Id.
efficacy. Since each drug is unique, FDAAA provides that an approved REMS must set forth a drug-specific timetable when the REMS assessment will be submitted to the FDA for evaluation of efficacy and progress toward stated goals.

Additionally, pursuant to the FDAAA, the FDA may require a REMS to include a Medication Guide or patient package insert, the information contained in such a guide however likely does not reach non-medical users who get the drugs through unregulated means. The Medication Guide, which is a paper handout that includes FDA approved information regarding the risks of a drug, is required if the FDA determines that a drug poses serious public health risks. The notion is that greater awareness of the risks can prevent adverse events. For example, the Medication Guide for the potent pain killer OxyContin states that the most important information the user should know about the drug is that it can, “cause serious side effects, including addiction or death.”

For those patients with serious pain such as cancer patients, they are willing to assume the serious risks associated with the drug. However, people abusing OxyContin and other addictive prescription opioids get the drug from for free from a friend or relative more than half of the time and never actually get a hold of the information that is intended to be disseminated along with the drug. When a drug is “diverted,” it is channeled away from its legal sources and redirected to the illegal marketplace. Therefore to the extent the drug is diverted, any value of the risk information contained in the Medication Guide is lost on non-medical users since those individuals do not get the drugs through legal and regulated means.

---

114 Id.
116 Safe Use Initiative, supra note 7, at 16.
119 FDA Acts, supra note 2, at 1.
120 Manchikanto, Fellows, Ailinani & Pampati, supra note 10, at 420.
Other potential REMS requirement includes a Communication Plan or Elements of Safe Use.\textsuperscript{121} A communication plan is targeted at health care providers and may involve sending letters to health care professionals about the REMS to encourage implementation and to inform the medical community about safety protocols and any serious risks of a drug.\textsuperscript{122} The elements to assure safe use are safety measures designed to mitigate a specific serious risk of a prescription drug listed on the drug’s labeling and to ensure safe access to the drug which would otherwise be unavailable to patients.\textsuperscript{123} These measures may include special monitoring, patient enrollment in a registry or enhanced certification for pharmacies or prescribers.\textsuperscript{124} Almost half of the 139 REMS in place as of August 2011 combined more than one of the approaches or elements whether it was a medication guide, communication plan or elements of safe use.\textsuperscript{125} If the requirements of an approved REMS are not complied with, the person or entity in violation is subject to civil monetary penalties up to $250,000 per violation under the enforcement provisions in FDAAA.\textsuperscript{126}

**Opioid Risk Evaluation Mitigation Strategy (REMS)**

The FDA has taken full advantage of its expanded regulatory role under the FDAAA and has been active in developing risk mitigation strategies. In connection with a White House plan to reduce the prescription drug abuse epidemic, FDA has been working over the past few years to develop a REMS to manage the risks associated with the prescribing and use of extended-release and long acting opioids.\textsuperscript{127} In the correspondence sent to the opioid manufacturers, FDA states that the grounds for determining that a REMS is necessary is that FDA has become aware

\textsuperscript{121} Qato & Alexander, supra note 28 at 1595.  
\textsuperscript{122} REMS Guidance, supra note 110, at 11.  
\textsuperscript{123} Id.  
\textsuperscript{124} Qato & Alexander, supra note 28 at 1595.  
\textsuperscript{125} Id.  
\textsuperscript{126} REMS Guidance, supra note 110, at 7.  
\textsuperscript{127} Oakie, supra note 13, at 1981; FDA Acts, supra note 2, at 1.
of, “substantial numbers of postmarketing reports of abuse, misuse, addiction, and overdose resulting in fatalities,” associated with the drug.\textsuperscript{128} While some argue that the REMS should include all opioids, the proposal focuses on extended-release and long acting opioids because the unique way in which the medication is delivered makes those formulations more risky than immediate-release opioids.\textsuperscript{129}

Given that millions of patients are prescribed these opioids annually, FDA’s opioid REMS will “affect far more people than any existing REMS for high-risk medications.”\textsuperscript{130} Aside from those 4 million patients with prescriptions for medical use, more than 33 million Americans misused extended- release and long-acting opioids in 2007.\textsuperscript{131} Given the dangers to public health and the staggering fatalities from overdose,\textsuperscript{132} targeting opioids is an attempt to combat the larger prescription drug abuse problem by focusing on an area where the need for action is clear. The risk management measures proposed in the REMS, a central feature of which is education and training of health care professionals, will become effective in 2012 and FDA has notified opioid drug manufacturers that they must propose a REMS within 120 days after receiving notice of FDA’s REMS requirements.\textsuperscript{133} Since notifying the opioid sponsors of the need for REMS, FDA has worked with those drug representatives on the required REMS and developed a final blueprint completed in October 2011 for public comment prior to implementation next year.\textsuperscript{134}

\textsuperscript{129} Oakie, supra note 13, at 1983.
\textsuperscript{130} Id. at 1981.
\textsuperscript{131} FDA Acts, supra note 2, at 2; Oakie, supra note 13, at 1981.
\textsuperscript{132} Oakie, supra note 13, at 1981.
\textsuperscript{133} FDA Acts, supra note 2, at 2; Oakie, supra note 13, at 1983.
\textsuperscript{134} Opioid Drugs and Risk Evaluation Mitigation Strategies, http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm.
Under the proposed opioid REMS, there is a health care provider education component and a parent, youth and patient education component. The REMS would include a voluntary Prescriber Continuing Education Program designed to ensure that drugs are being prescribed properly and are only given to appropriate patients and that patients are adequately counseled on how best to properly dispose of any excess medication. The proposal indicates that prescribers of opioids should be knowledgeable about various aspects of opioid treatment including: assessing patients for abuse risk, managing ongoing therapy and how to counsel patients on safe use. The draft opioid REMS discusses the importance of the role of health care professionals who prescribe opioids since they are in a unique position to balance the benefits of the drug against, “risks of serious adverse outcomes including addiction, unintentional overdose and death.” Also, as members of the health care community, prescribers of these potent drugs share in the responsibility to ensure the safe and effective use of opioids. In order to educate health care professionals and reduce the risks of abuse, the opioid REMS would call for drug marketers to develop training materials, prescribers would voluntarily participate in the program and the company would assess the efficacy of the program in the process. Further, as part of managing the treatment process, the proposed REMS would require prescribers to monitor opioid patients for misuse and abuse by doing the following: “recognizing aberrant behavior, utilizing [prescription drug monitoring programs] to identify potential abuse where available, understanding the role of drug testing and performing drug screens as indicated [and] screening and referring for substance abuse treatment when

135 Prescription Drug Abuse Crisis, supra note 3, at 3, 4.
136 Oakie, supra note 13, at 1983.
138 Id.
139 Id.
140 Oakie, supra note 13, at 1983.
indicated…”141 By integrating the prescriber education component of the proposed REMS, FDA can ensure that those patients who need opioids for pain management will still have access but risks will be reduced at the provider level for those who are misusing or abusing the drugs.142

Initially, the FDA’s advisory committed to the proposed opioid REMS said that the proposed REMS requirements did not go far enough and one advisory committee member from New York University School of Medicine commented that, “we need to think about how we would construct a REMS if we were going to be marketing heroin.”143 The advisory committee recommended making pain-management training mandatory for being able to register with the DEA in order to legally dispense controlled prescription drugs.144 In the proposed opioid REMS, FDA does not mandate prescriber training and does not require individuals treated with long-acting opioids to register with the state or to sign “Patient Provider Agreements” or PPAs.145 While not required by FDA, doctors should be aware of PPAs, which are documents signed by both the patient and the prescriber when an opioid is prescribed that outlines the risks and goals of treatment and safe medication use.146 Since doctors are regulated on a state level, some have argued that any mandatory training or licensing requirements should be dealt with through state medical boards.147

Since FDA was granted the legislative authority to require REMS in 2007, a total of two REMS for opioids, distinct from the proposed long-acting opioid REMS, have been approved.148 One medication, Onsolis, is a short-acting opioid designed for cancer patients who are already

141 Draft Opioid REMS, supra note 137, at 3.
142 FDA Acts, supra note 2, at 2.
143 Oakie, supra note 13, at 1981.
144 Id. at 1983.
145 Id.
146 Draft Opioid REMS, supra note 137, at 3.
147 Oakie, supra note 13, at 1983.
taking pain medication and can safely use an additional dose of opioid medicine.\footnote{Id.} The REMS for this medication, which was approved in 2009, is specifically tailored to the unique qualities of that drug and does not apply more broadly to long-acting opioids.\footnote{Id.} Another newly approved opioid drug, Embeda, was approved with a REMS that includes a Medication Guide.\footnote{Id.} However, FDA is waiting to determine what the outcome of the proposed long-acting opioid REMS is and once those requirements are determined the REMS for this drug will be modified to incorporate other risk management measures.\footnote{Id.} Despite FDA’s clear efforts to reform its risk management criteria with the REMS program, there is little scientific data on the efficacy and success of the program including the success of specific REMS measures.\footnote{Id.} However, considering that the strategies are still being developed and the problem is multi-faceted, it will likely take more time to develop and analyze criterion by which to measure success.

In addition, FDA is careful not to infringe on the rights of pain management and patient’s rights interest groups who advocate for easy access to pain medication and fear stigmatization for people with chronic pain.\footnote{Id.} During the development of the opioid REMS requirements, FDA has held public meetings, met with pharmaceutical representatives, doctors, and patient advocates, to discuss the best methods to curb abuse while preserving the interests of pain patients to have easy medication access. Pain management advocates argue that despite the advancements in pain treatment and the efficacy of pain medications like opioids, there is still an under treatment of acute pain for some Americans.\footnote{Id.} The balance with regulations that FDA and

\begin{footnotes}
\item Id.
\item Id.
\item Id.
\item Id.
\item Id.
\item Qato & Alexander, supra note 28 at 1596.
\item Oakie, supra note 13, at 1983.
\end{footnotes}
other agencies must strike is to curb abuse without hindering legitimate patient’s access to pain treatment.\footnote{156 Bridget M. Kuehn, \textit{FDA Opioid Safety Plan Promotes Patient, Physician Education to Prevent Abuse}, 304 J. Amer. Med. Assoc. 845 (2010) [hereinafter \textit{FDA Opioid Safety Plan}].}

**Discussion**

Given the severity of the prescription drug abuse problem, it is clear that action is necessary\footnote{157 \textit{FDA Opioid Safety Plan}, supra note 156 at 845; Oakie, \textit{supra} note 13, at 1981.} to protect the public health and the recent efforts of the White House, Congress and FDA are laudable.\footnote{158 Qato & Alexander, \textit{supra} note 28 at 1596.} However, the regulatory challenges of this problem are unique since drug abuse circumvents FDA’s risk-benefit process for ensuring that drugs are safe and effective. In FDA’s initial drug approval process, a drug is safe and effective when the risks of an unwanted outcome are weighed against the potential therapeutic benefits of the drug \textit{when the drug is used optimally} according to its labeling instructions and the prescriber’s directions.\footnote{159 \textit{Safe Use Initiative}, \textit{supra} note 7, at 5; \textit{Combating Misuse and Abuse of Prescription Drugs}, \textit{supra} note 4, at 1.} Individuals who abuse drugs for which they do not have a prescription not only fail to take the drugs in accordance with the label, but use the medications purely for positive psychoactive effects and/or as a result of physical dependence. In theory, although non-medical users subjectively benefit from a “high” they feel, there is no therapeutic benefit against which to weigh the substantial risks of taking the potent prescription drugs. Thus, the non-medical user is left only with the risk of taking the drug without the benefit for which the prescription has been legally approved for.

Stated differently, high-risk medications such as opioids are approved in light of the benefits provided to a group of patients suffering from severe pain, often cancer related, and only for those individuals do the benefits of much needed pain relief outweigh the risks of abuse. In order to address the safety of a drug for non-medical users, it is necessary to concede that the benefits of the drug, a positive psychoactive effect, do not objectively outweigh the prevalent...
risks of dependency, overdose and death. FDA’s efforts to reduce harm from prescription drug abuse would benefit from a shift in the manner in which drugs are deemed safe and effective to account for actual use in the population as opposed to intended use, and by placing more emphasis on the risks of a drug for non-medical users for whom the drug has little or no therapeutic benefit.

Further, in FDA’s new REMS regime, the underlying risk-management paradigm remains the same post-approval, aiming to ensure that the benefits of the drug continue to outweigh the risks.\textsuperscript{160} Rather than premise the risk-benefit analysis on an assumption that the drug will be used in accordance with its approved uses, and thereby confer a clinical benefit, drug safety may be better measured by actual usages in the population. This could be ascertained by gathering post-market scientific data on usage, of the sort being collected with Prescription Drug Monitoring Programs. While it is vital that prescription medications, including opioids, remain easily available for legitimate patient’s needs, the overall safety and efficacy of a drug could be more accurately assessed by using a paradigm that includes non-medical users or weighs the risks of abuse more heavily.

In addition, the REMS measures make important changes to address drug abuse and misuse from a regulatory perspective that is relatively new for the FDA.\textsuperscript{161} However, measures that are predicated on the involvement of health care professionals may not be as effective for non-medical users who get the drugs without a prescription. A large majority of non-medical users, up to 70.2\%, obtain the prescription drug from a friend or relative whether the individuals get the drug for free, pay for it, or take the drug without asking.\textsuperscript{162} Medication Guides, which

\textsuperscript{160} Qato & Alexander, supra note 28 at 1595.
\textsuperscript{161} Id. at 1596.
\textsuperscript{162} Manchikanto, Fellows, Ailinani & Pampati, supra note 10, at 413.
have been the sole safety measure implemented in nearly half of the REMS,\textsuperscript{163} may accurately warn the reader of serious health risks associated with taking the drug but the person who receives that information is the individual who got the drug through legal and regulated means. The data on the source of prescription drugs that are being abused would indicate that the majority of non-medical users do not interface with a health care professional directly and would therefore not get the benefit of enhanced risk awareness.

Alternatively, a promising safety measure included in the new proposed opioid REMS is the requirement that drug manufacturers set goals and implement procedures for tracking the program’s efficacy.\textsuperscript{164} This requirement that the drug companies implement safety measures to reduce known risks and continually monitor the effectiveness of those measures at reducing harm is a distinct feature of the new REMS program established by FDAAA.\textsuperscript{165} This is an important measure that will hold drug manufacturers accountable for the safety of the drugs that they distribute. While the responsibility for reducing the public health costs of prescription drug abuse is spread amongst various federal and state agencies and stakeholders in the medical community,\textsuperscript{166} drug manufacturers are in the best position to reduce known risks. Drug companies not only have greater resources but the manufacturers arguably benefit more than any other stakeholder because they create and profit off of the drugs. The central role that drug manufacturers play and the benefits they enjoy should result in an assumption of the bulk of responsibility for mitigating the risks of abuse.

\textsuperscript{163} Qato & Alexander, \textit{supra} note 28 at 1595.
\textsuperscript{164} \textit{REMS Guidance}, \textit{supra} note 110, at 88.
\textsuperscript{165} Qato & Alexander, \textit{supra} note 28 at 1595.
\textsuperscript{166} See \textit{Safe Use Initiative}, \textit{supra} note 7.
Further, while drug manufacturers are accountable to FDA for submitting REMS assessments for efficacy and progress pursuant to a timetable, the program may benefit from providing incentives or assigning penalties if the risks are not adequately managed. The REMS assessment is intended to, “evaluat[e] the extent to which each of the REMS elements are meeting the goals and objectives of the REMS, and whether or not the goals, objectives or REMS elements should be modified.” Under the current REMS, FDA may initiate an enforcement action against drug manufacturers for monetary penalties if they fail to complete a REMS assessment since that would be a violation of the requirements. However, since drug manufacturers design and implement the REMS assessments for FDA review, providing some sort of incentive to ensure results may be necessary. This is particularly true in light of evidence that REMS have gained little support from drug manufacturers.

Conclusion

Ultimately, there are many interests at play and sweeping reform may not come without opposition from the entities that profit from the sale of high-risk pharmaceuticals. However, given the vast resources expended on combating the dangers of illegal drug use, the efforts to reduce the abuse of legal prescription drugs should be equally as great and the responsibility shared amongst stakeholders. Since drug abuse and misuse are an unintended result of the availability of legal prescription drugs, it makes the precise harm difficult to estimate, and likewise to regulate. Taking into account the unintended reality of abuse, misuse, addiction,

---

167 *REMS Guidance, supra* note 110, at 5.
168 *Id.* at 18.
169 *Id.* at 24.
171 *Id.* at 1596.
172 *Safe Use Initiative, supra* note 7, at 3.
overdose and death before and after drug approval, will highlight the risks of dangerous medications and encourage practical regulations that address the problem head-on.