Rehabilitating Opioid Regulation: A Prescription for the FDA's Next Proposal of an Opioid Risk Evaluation and Mitigation Strategy (REMS)

Hilary Homenko
REHABILITATING OPIOID REGULATION: A PRESCRIPTION FOR THE FDA’S NEXT PROPOSAL OF AN OPIOID RISK EVALUATION AND MITIGATION STRATEGY (REMS)

Hilary Homenko†

“We are going to need to find a balance between ensuring patients can achieve adequate pain control with access to opioid therapies while taking steps to protect against addiction and death.”¹

“FDA is not going to be able to do this alone.”²

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² J.D. Candidate, Case Western Reserve University School of Law, 2012; B.A., Stanford University, 2008. I would like to thank Professor Sharona Hoffman, Elizabeth Murphy, and Ruth Miller for their advice and support throughout the writing process. I would also like to acknowledge the editorial staff of Health Matrix, Volume 22, for its tremendous assistance in editing and publishing this Note. To my family and Joseph Bowman, thank you for your endless encouragement.
² Id.
INTRODUCTION

Abuse and dependence on prescription pain relievers has reached epidemic proportions in the United States. In 2010, a study published by the Substance Abuse and Mental Health Services Administration estimated that 5.1 million persons, aged twelve or older, use prescription pain relievers non-medically. Within this population, approximately 1.9 million persons have dependence on or abuse prescription pain relievers. While prescription pain relievers, commonly

3 See Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings, SAMHSA.GOV, 1 (Sept. 2011), http://oas.samhsa.gov/NSDUH/2k10NSDUH/2k10Results.pdf.
4 Id. at 12.
5 Id. at 70.

In 2007, Congress passed the Food and Drug Administration Amendment Act (FDAAA), which gave the U.S. Food and Drug Administration (FDA) greater authority to regulate prescription drugs, including opioids.\footnote{See Food and Drug Administration Amendments Act of 2007, 21 U.S.C. § 355-1 (2011) [hereinafter FDAAA].} Congress specifically granted the FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) as part of a drug approval application.\footnote{Id. \S 355-1(a)(1).} A REMS is a written plan developed by a drug manufacturer that identifies the risks associated with a particular prescription drug and describes the program(s) that a manufacturer will implement to help prevent the risks from materializing.\footnote{Id. \S 355-1(a)(2)(A).} Programs may include, but are not limited to, a medication guide or a special training program for health care providers prescribing the manufacturer’s drugs.\footnote{Having an opioid REMS would improve the FDA’s efficiency during the drug approval process. An opioid REMS would eliminate the need for the FDA to design a unique set of REMS requirements for each manufacturer seeking drug approval.} The FDA can require manufacturers to submit a REMS with a drug approval application.\footnote{Id. \S 355-1(e).} Alternatively, it can require a manufacturer to submit a REMS after drug approval, when newly discovered information brings into question whether the benefits of the drug outweigh its risks.\footnote{Id. \S 355-1(a)(2)(A).}
because they thought the regulations applying to doctor training were too weak.\textsuperscript{15} Going forward, the FDA should focus its efforts on strengthening the regulatory requirements under the next opioid REMS proposal. However, the FDA cannot single-handedly solve all of the opioid-related drug problems through REMS. The FDA should collaborate with regulatory agencies at the state level to achieve the proper balance between opioid regulation and medically necessary opioid use.

This Note will explore current opioid-related drug problems in the United States and will make recommendations for how the FDA should proceed with developing an opioid REMS. Part I of this Note will discuss the current problems associated with opioids, including (1) misuse and abuse, (2) drug diversion, and (3) undertreatment of chronic and acute pain. Part II will explain the FDA’s authority before and after Congress enacted the FDAAA, specifically describing the new three-tiered regulatory strategy that the FDA can employ to regulate drugs after the approval process. Part II will also explain the benefits of having a general opioid REMS, which include improved efficiency of the FDA’s drug approval process and increased manufacturer compliance with REMS requirements. Part III will identify why both the initial opioid REMS proposal and the FDAAA fell short of addressing the problems discussed in Part I. Finally, Part IV will recommend that the next opioid REMS proposal contain a mandatory training program, funded by manufacturers, for the purpose of educating doctors about the risks of prescribing opioids. Part IV will also outline an approach for improving opioid regulation outside of REMS by encouraging FDA collaboration with the states, since state medical boards have the authority to directly regulate doctors who prescribe opioids.\textsuperscript{16} Through greater collaboration with regulatory agencies at the state level, the FDA can successfully reduce opioid risks without sacrificing the availability of chronic and acute pain relief.

\textsuperscript{15} See Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee & Drug Safety and Risk Management Advisory Committee, FDA, 217 (July 23, 2010), http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndLifeSupportDrugsAdvisoryCommittee/UCM224671.pdf [hereinafter Joint Meeting Transcript].

I. PROBLEMS ENDEMIC TO OPIOID USE

A. Abuse and Misuse by Chronic and Acute Pain Patients

1. Early Opioid Regulation

Opium has been used around the world for centuries to alleviate pain. In 1806, a German pharmacist isolated a pure substance from the opium poppy plant, which he called morphine. His work inspired scientists several years later to create synthetic versions of the chemicals extracted from the opium poppy plants. Medications containing these synthetic chemicals are known as opioids.

In the nineteenth century, nonmedical use of opioids and other drugs such as heroine became increasingly popular. Due to the health risks posed by these drugs when used inappropriately, opioids became strictly regulated by some local and state laws by the end of the century. For example, San Francisco passed a local law in 1875 that prohibited people from smoking opium in places other than an opium den, while other cities passed laws that prohibited opium use altogether. In the cities that adopted stricter policies, opioids became unavailable to many people legitimately seeking pain relief.

Fortunately, in the twentieth century, opioids became accepted again as a mainstream medical treatment for acute and chronic pain. In 1996, the American Society of Anesthesiology adopted guidelines for treating chronic pain, which made recommendations about evaluating patients for drug therapies involving opioids.
lievers commonly used today include morphine, hydrocodone, and oxycodone.  

2. Illustrations of Opioid Abuse and Misuse

One of the prevailing problems associated with treating chronic and acute pain is opioid abuse and misuse. While the terms “abuse” and “misuse” are often defined as different drug-related behaviors, it is hard to clearly distinguish between them in practical terms.  

Suppose a doctor writes a prescription for patient A. It is for a high dose of oxycodone to be taken over the course of several weeks, while the patient recovers from a serious knee surgery.  

Patient A’s chart indicates that he has a history of substance abuse. After finishing the prescription, patient A’s knee pain is gone, but he experiences withdrawal symptoms after being without oxycodone for several hours. Patient A returns to his doctor and falsely reports severe knee pain. During the office visit, patient A also exhibits signs of withdrawal including goose bumps and dilated pupils.  

Nonetheless, patient A successfully receives another prescription of oxycodone and repeats this behavior several more times. Patient A likely falls into the category of abuse because he knowingly misrepresented his medical condition to the doctor for the purpose of obtaining a medically unnecessary prescription. The doctor is likely at fault for prescribing

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27 The World Health Organization adopted the following definitions from the Diagnostic and Statistical Manual (DSM-III-R), which is a manual that assists clinicians in diagnosing psychiatric disorders. “Abuse” means “a maladaptive pattern of use...despite knowledge of having a persistent or recurrent social, occupational, psychological or physical problem that is caused...[by] recurrent use....” Similarly, “misuse” means “[u]se of a substance for a purpose not consistent with legal or medical guidelines, as in the non-medical use of prescription medications.” Reference to the WHO definitions is necessary because FDA definitions for “abuse” and “misuse” do not yet exist. Furthermore, while “abuse” and “misuse” are often used colloquially to describe individuals who intentionally use or deal illicit drugs, such an inference should not be made when reading this Note. See Lexicon of Alcohol and Drug Terms by the World Health Organization, WHO, http://www.who.int/substance_abuse/terminology/who_lexicon/en/ (last visited Oct. 4, 2011).


29 Id. at 16.
high doses of opioids to a patient with a history of substance abuse. The doctor may be subject to liability for failing to perform a thorough physical examination at the follow-up visit, which likely would have detected the patient’s withdrawal symptoms and underlying addiction.

Now suppose the doctor writes the same oxycodone prescription for patient B, who has also recently undergone serious knee surgery. After a few days of taking the prescription, patient B is still experiencing persistent knee pain. To try and alleviate the pain, patient B decides to take the dose twice as frequently as the doctor prescribed. Patient B returns to the doctor two weeks early to refill his prescription. He honestly reports knee pain and does not exhibit any obvious signs of withdrawal. Patient B may fall into the category of misuse for taking his prescription against medical instructions. If this behavior persists, however, patient B may also fall into the category of abuse. Due to the overlap of terminology, in this Note the terms “abuse and misuse” will be used collectively to describe both (1) a physician administering opioids contrary to the practices of a reasonable physician, and (2) a patient taking opioids contrary to the instructions of a reasonable physician.

3. Clinical Origins of Opioid Abuse and Misuse

While opioids have been used as pain relievers for hundreds of years, only recently has the medical field made recommendations on how they should be administered to patients.\(^{30}\) In 1998, the Federation of State Medical Boards published its first set of model guidelines for using opioids to treat pain.\(^{31}\) The guidelines apply to doctors treating both acute and chronic pain patients.\(^{32}\) Professional organizations, such as the American Society of Anesthesiology, have also developed guidelines that recommend quasi-objective methods for measuring a patient’s pain.\(^{33}\) For example, the guidelines suggest that doctors ask

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\(^{30}\) See Ballantyne & Mao, supra note 6, at 1943.


\(^{32}\) Trescot, supra note 28, at 2, 12, 14. Acute pain patients typically experience pain for a short, discrete period of time and the pain disappears when treatment resolves an underlying medical condition such as disease or infection. Chronic pain patients typically experience pain that persists for a long period of time and that does not respond to ordinary pain medication. See Acute v. Chronic Pain, CLEVELAND CLINIC, http://my.clevelandclinic.org/services/pain_management/hic_acute_vs_chronic_pain.aspx (last updated Sept. 12, 2008).

\(^{33}\) See Am. Soc’y of Anesthesiologists, supra note 25.
patients to rate their pain intensity on a numerical scale. Doctors are instructed to record the result at each visit in order to track the patient’s progress over time. Although the numerical measurement is based on the patient’s subjective pain experience, it is quasi-objective when compared to feedback from the same patient during previous visits.

Despite the medical field’s efforts to objectively measure pain, it remains a substantially subjective experience, which can only be conveyed through a patient’s self-report. Researchers have found that emotional, mental, physical, and spiritual factors influence a patient’s pain perception. For example, one study observed that the gender of the examiner influenced a patient’s feedback about pain. Patients tolerated pain for longer periods of time before expressing it when the examiner was the opposite gender. When pain reaches the threshold of evoking a response, patients generally communicate through words or expressions. However, language barriers due to national origin or disability may further diminish a patient’s ability to communicate. Pain reports by disabled patients may be limited to sounds, facial expressions, or translations of a guardian or interpreter.

Since doctors are limited by the information they can gather about a patient, a doctor’s diagnosis is only as accurate as her understanding of the patient’s pain experience. Sometimes a doctor may prescribe a dose that is too low, and the patient remains in pain—a situation commonly known as undertreatment. Undertreatment is estimated to occur in 43 percent of cancer patients seeking relief from acute pain. On the other hand, doctors may prescribe a dose that is too

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35 See id.
36 Some researchers have begun to experiment with functional MRI technology, which would enable medical professionals to observe the brain’s physical response to pain, but it is still doubtful that this technology would replace a patient’s subjective feedback. Adam Kolber, Pain Detection and the Privacy of Subjective Experience, 33 AM. J. L. & MED. 433, 447 (2007); see also Trescot, supra note 28, at 3.
37 Trescot, supra note 28, at 27.
38 Kolber, supra note 36, at 446-47.
39 Id.
40 Id. at 440.
41 See id.
42 See id.
44 The estimate was based on a review of twenty-six other studies. Id.
high or prescribe opioids for too long, resulting in addiction. In the past decade, the rate of opioid addiction in patients seeking relief from chronic pain was estimated to be 3.27 percent. Another study estimated, however, that abuse risk ranges between 0-50 percent for chronic pain patients. Patients fall at the higher end of the range, if they have a history of substance abuse or addiction. Due to the difficulty in properly prescribing opioids, patients may experience problems like opioid addiction at one end of the spectrum and undertreatment at the opposite end. Understanding the relationship between these two opioid-related problems is crucial to finding the proper balance between opioid regulation and medically necessary opioid use.

4. Potential Magnitude of Opioid Abuse and Misuse

The potential magnitude of opioid abuse is alarming considering that, in 2007, doctors wrote 21 million opioid prescriptions for 3.7 million individuals. The high volume of opioid prescriptions reflects a decade of escalating opioid prescribing habits. Between 1992 and 2002, the U.S. population increased by 13 percent, but prescriptions for noncontrolled substances increased by 57 percent, and prescriptions for controlled substances increased by 154 percent. During a similar time period, the number of people abusing controlled substances jumped 94 percent, which is twice the increase in marijuana abuse, five times the increase in cocaine abuse, and sixty times

45 The estimate was made from reviewing twenty-four studies involving a total of 2,507 subjects. David A. Fishbain et al., What Percentage of Chronic Non-malignant Pain Patients Exposed to Chronic Opioid Analgesic Therapy Develop Abuse/Addiction and/or Aberrant Drug-Related Behaviors? A Structured Evidence-Based Review, 9 PAIN MED. 444, 444 (2008).

46 An international literature review identifies the range in addiction prevalence for chronic non-malignant patients between 0 percent and 50 percent, while the prevalence of opioid addiction in cancer treatment between 0 percent and 7.7 percent. See Jette Højsted & Per Sjogren, Addiction to Opioids in Chronic Pain Patients: A Literature Review, 11 EUR. J. PAIN 490, 490 (2007).

47 Id. at 494.

48 Transcript for FDA’s Media Briefing on the Safe Use of Opioids, supra note 14, at 9.

the increase in heroin abuse. Although there are several types of opioids, the risks appear to be consistent across drug classes. Pain physicians agree that both extended-release and immediate-release opioids have a high potential for abuse.

Creating even greater concern is the possibility that various reporting systems actually underestimate the prevalence of opioid abuse. For example, the FDA’s Adverse Events Reporting System (AERS) tracks adverse drug experiences and errors in how drugs are prescribed. Health providers voluntarily participate in reporting data to this system, while manufacturers are required to participate when they become aware of an adverse drug event. Any system that attempts to collect information on drug abuse likely underestimates its prevalence because drug abuse is an inherently clandestine activity. People may not seek medical care for an adverse event arising out of drug abuse because they are ashamed of their addiction or afraid of getting in trouble. Subsequently, providers and manufacturers often never find out about the adverse event and never have an opportunity to report it. And even if providers treat a patient who experienced an adverse event, they may not report it to the data collection system, either because they do not know how to do so or they find it too burdensome. Consequently, the data reflects only what the patients and providers voluntarily report to the system and what the manufacturers are aware of and required to report.

The U.S. Department of Health and Human Services (DHHS) also collects data about drug abuse and misuse through the Drug Abuse Warning Network (DAWN). DAWN tracks drug-related emergency

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50 JOSEPH A. CALIFANO, NATIONAL CTR. ON ADDICTION & SUBSTANCE ABUSE AT COLUMBIA UNIV. (CASA), supra note 49, at i.
51 Joint Meeting Transcript, supra note 15, at 172.
53 See Records and Reports, 21 C.F.R. § 310.305(a) (2011); see also Adverse Event Reporting System, supra note 52.
54 See John J. Coleman, REMS for Opioids: A Review and Critique, 37 PHARMACY PRACTICE NEWS 42, 43 (2010). Many states also have their own data collection and reporting system; the systems provide limited value because they are often not capable of sharing data between states. See also Trescot, supra note 28, at 9.
55 See Coleman, supra note 54, at 43.
admissions and drug-related deaths at both a local and national level.\textsuperscript{56} The data is collected from emergency departments and coroners’ offices in thirteen metropolitan areas around the country.\textsuperscript{57} The extent of data collection, however, is dependent on the ability of DAWN’s staff to recruit and secure hospital participation in the program.\textsuperscript{58} Another limitation of DAWN’s data collection is that the areas where opioid abuse appears to be most prevalent are not necessarily the same places where DAWN collects data. Southeastern and western states are home to the teenagers most likely to abuse prescription pain relievers, but these states are not well-represented by the metropolitan areas targeted under DAWN.\textsuperscript{59} Realizing the limitations of national data collection systems is important for properly analyzing data, which will be used to develop the next general opioid REMS proposal.

5. **Financial Impact of Opioid Abuse and Misuse**

Without prompt changes to the current opioid regulatory scheme, opioid abuse will continue to place an enormous financial burden on society. Opioid abusers accrue medical expenses at a significantly higher rate than non-abusers.\textsuperscript{60} In 2003, the annual direct cost of health care for an opioid abuser was on average $15,884, compared to $1,830 for a non-abuser.\textsuperscript{61} This estimate does not account for indirect costs, such as the loss of productivity, caused by drug abuse and subsequent illness.\textsuperscript{62} When the researchers controlled for health care


\textsuperscript{58} See \textit{id.} at 1.

\textsuperscript{59} The states with the highest percentages of teenagers (12-17 years of age) using prescription pain relievers for non-medical purposes are: Arkansas (10.3 percent), Kentucky (9.8 percent), Montana (9.6 percent), Oregon (9.3 percent), Oklahoma (9.1 percent), Tennessee (8.9 percent), and West Virginia (8.9 percent). Manchikanti, \textit{supra} note 26, at 404.

\textsuperscript{60} See Alan G. White et al., \textit{Direct Costs of Opioid Abuse in an Insured Population in the United States}, 11 J. MANAGED CARE PHARMACY 469, 473 (2005) (finding that the average direct cost of health care for 740 opioid abusers was more than 8 times higher than those of non-abusers).

\textsuperscript{61} \textit{Id.}

\textsuperscript{62} \textit{Id.} at 475.
costs associated with the subjects’ comorbidities, they found that the direct cost of health care for drug abusers still exceeded non-abusers by at least 1.8 times. The escalated cost of health care for drug abusers is attributable to a higher frequency of hospitalizations and emergency room visits.

Once individuals begin to comprehend the direct health care costs associated with opioid abuse, they may impulsively blame the patients who abuse and misuse opioids. Media outlets often fuel this view, disparaging celebrity drug abusers as individuals intentionally deciding to use drugs in harmful and irresponsible ways. Yet, as our understanding of drug abuse develops, it appears that drug abuse problems in pain patients often develop unintentionally. For example, consider the testimony of Betty Tully, a patient who suffered from back pain.

I am a formerly diagnosed chronic pain patient who was misprescribed large amounts of opiates . . . . I went to the doctor for help with my back pain. I got little else than narcotics, along with a devastating addiction. I was also not aware that many doctors have as little as 12 hours of education in narcotic pharmacology, yet receive licenses to prescribe every scheduled drug manufactured and virtually no restrictions on practices.

Several factors may have contributed to this patient’s addiction, including the doctor’s limited training in prescribing opioids and the patient’s poor understanding of opioid risks. In 2007, these shortcomings likely encouraged Congress to pass the FDAAA. As the FDA works on developing the next opioid REMS proposal, it should continue to discuss issues such as physician training and patient education. Patients like Betty Tully are not drug addicts looking for an opportunity to get high. Regulatory solutions should encourage doctors to treat patients like Betty Tully with respect and help them access safe pain relief.

63 Id.
64 Id.
66 See Joint Meeting Transcript, supra note 15, at 45-47.
68 Joint Meeting Transcript, supra note 15, at 45-47.
B. Opioid Diversion

Another common problem associated with opioids is known as diversion, which in the drug context refers to “any criminal act that causes controlled prescription drugs to be sidetracked from their lawful (medical) purpose to illicit use.” Through diversion, third parties become subject to the same risks of abuse and misuse as patients receiving the drugs directly from doctors. In fact, third parties may be even more susceptible to the risks because they are not taking the drugs under the careful supervision of a health care professional.

Surprisingly, only a limited number of doctors are educated about the problem of drug diversion during their medical training. The National Center on Addiction and Substance Abuse at Columbia University (CASA) reported that only 19.1 percent of 979 doctors surveyed had training in medical school about prescription drug diversion and only 39.2 percent received training about it in their residency program. Experienced doctors, however, are often more aware of the problems that diversion creates. They encounter diversion in the form of “doctor shopping,” which means that a patient sees multiple doctors concurrently to obtain several prescriptions for pain medication. They also see patients who try to acquire pain prescriptions by lying or misleading doctors through dishonest claims of acute or chronic pain. Additionally, pharmacists encounter patients who attempt to fill prescriptions with forged or altered prescription forms.

While drug diversion is generally thought of as patient-initiated, a small segment of doctors help perpetuate the criminal activity. The U.S. Drug Enforcement Agency (DEA) has led several successful criminal investigations of doctors suspected of facilitating drug diversion. Courts have convicted doctors on charges such as “criminal conspiracy to commit delivery of or possession with the intent to deliver a controlled substance.” Since the DEA and a growing number of state licensure boards have jurisdiction over this issue, drug diversion facilitated by doctors was not likely a prominent regulatory goal.

69 JOSEPH A. CALIFANO, NATIONAL CTR. ON ADDICTION & SUBSTANCE ABUSE AT COLUMBIA UNIV. (CASA), supra note 49, at 45.
70 Id. at 6.
71 Id. at 45.
72 Id.
73 Id.
75 Id.
of the FDAAA. Nonetheless, diversion remains an important part of how patients and third parties gain access to opioids for nonmedical purposes. Thus, diversion should be a part of FDA discussions about interpreting the FDAAA and developing the next opioid REMS proposal.

C. Underreatment of Pain

Another major problem associated with opioids is undertreatment of pain. Undertreatment typically arises when a doctor either declines to write an opioid prescription or writes a prescription that is too weak to alleviate the patient’s pain.\textsuperscript{77} Undertreatment is common in acute pain patients, especially those with cancer.\textsuperscript{78} The underlying explanation for undertreatment is “opiophobia,” which is defined as “excessive concern about the addictive potential and side effects of narcotics.”\textsuperscript{79}

A doctor’s willingness to prescribe opioids may be subconsciously influenced by several factors. Some medical studies suggest that a patient’s race closely correlates with whether they will receive a prescription for opioids in the emergency room.\textsuperscript{80} For example, Hispanics who visit the emergency room for a broken bone are less likely to receive opioid pain relievers than non-Hispanic whites.\textsuperscript{81} One explanation for this racial bias is that doctors tend to perceive certain individuals as exaggerating their pain more than others.\textsuperscript{82} Age is another factor that appears to influence doctors when determining whether to prescribe opioids to an emergency room patient. One

\textsuperscript{77} See Deandrea, supra note 43, at 1987.
\textsuperscript{78} Id.
\textsuperscript{81} Pletcher, supra note 80, at 70.
\textsuperscript{82} Opioid prescribing is just one of several areas of medicine where a patient’s race has been found to influence a doctor’s treatment approach. See Pletcher, supra note 80, at 76.
study found that patients were significantly less likely to receive a prescription for opioids, if they were eighty years of age or older.83 The study suggested that this age bias is due to a lack of understanding about how to properly manage pain in elderly patients.84 Fears of legal liability for prescribing opioids may also influence a doctor’s medical decision making. Doctors likely consider the potential consequences of civil sanctions from the DEA85 or the potential loss of their medical license, if disciplined by the state medical board.86 Additionally, doctors may fear potential criminal sanctions imposed by local, state, or federal authorities for inappropriately prescribing opioids.87 Prescribing guidelines issued by organizations such as the Federation of State Medical Boards (FSMB) have tried to address these concerns by stating that “[p]hysicians should not fear disciplinary action from the Board for ordering, prescribing, dispensing or administering controlled substances, including opioid analgesics, for a legitimate medical purpose and in the course of professional practice.”88 Some courts have even held doctors liable for undertreating a patient’s pain. In the past decade, plaintiffs have brought successful cases against doctors who denied necessary pain medication to prison inmates and nursing home patients.89

The problem of undertreatment, however, is not a widely recognized problem. Critics argue that undertreatment is only a perception

83 Kevin M. Terrell et al., Analgesic Prescribing for Patients who are Discharged from an Emergency Department, 11 PAIN MED. 1072, 1076 (2010).
84 Id.
85 The DEA has authority to enforce civil penalties up to $25,000 for violating controlled substance registration requirements such as documentation. See e.g., 21 U.S.C. § 842(c) (2011).
86 See, e.g., Disciplinary Guidelines, Fla. ADMIN. CODE § 64B8-8.001(2) (2011).
87 For example, the DEA has authority to enforce criminal penalties of imprisonment not exceeding four years on individuals who try to use a fictitious or revoked DEA registration number to acquire or obtain controlled substances. See 21 U.S.C. § 843(d) (2011).
88 Model Guidelines for the Use of Controlled Substances for the Treatment of Pain, supra note 31, at 3.
89 See, e.g., Walker v. Benjamin, 293 F.3d 1030, 1040-41 (2002) (remanding the case to the district court because the court thought that a nurse and a doctor should not have refused to provide Walker pain medication); Sasser v. Ryder Truck Rental, No. 2:06cv593-CSC, 2008 U.S. Dist. LEXIS 160, at *23, 33 (M.D. Ala. Jan. 2, 2008) (finding plaintiff, who was not an inmate, failed to provide sufficient evidence showing that his employer was systematically trying to cut him off from necessary medical treatment, which included a pain prescription for oxycontin); Kathryn Tucker, Medico-Legal Case Report and Commentary: Inadequate Pain Management in the Context of Terminal Cancer. The Case of Lester Tomlinson, 5 PAIN MED. 214 (2004) (discussing Tomlinson v. Bayberry Care Ctr., No. C-02-00120 (Cal. Super. Ct. Contra Costa County 2003)).
and not a reality. They argue that the alleged racial bias actually results from doctors over-prescribing opioids to one racial group and prescribing appropriate levels of opioids to another. Their explanation is that emergency room doctors have less experience recognizing signs of abuse in white patients compared to other racial groups. Despite these criticisms, undertreatment is well-documented in research studies and litigation against doctors, both of which provide sufficient justification for addressing undertreatment of pain in the next opioid REMS proposal.

II. CHANGES TO FDA AUTHORITY

A. FDA Authority Prior to the FDAAA

The FDA has traditionally acted as the “gate keeper” for approving prescription drugs, including opioids. Congress specifically tasked the FDA with regulating the safety of food, human and veterinary drugs, medical devices, and cosmetics. With respect to drugs, the FDA controls over-the-counter and prescription drug approvals, labeling, and manufacturing standards. The FDA enforces these standards by regulating manufacturers because they are responsible for developing, packaging, and distributing the drugs. The FDA’s authority to regulate drugs does not extend to illegal substances such as cocaine and heroin because these substances are under the jurisdiction of the DEA.

The scope of the FDA’s authority to regulate drugs is expansive when compared to the narrow scope of the DEA’s authority to regulate drug diversion. While the FDA regulates drug approval, labeling, marketing, and use, the DEA focuses on prescription and distribu-

90 See Pletcher, supra note 80, at 76.
91 Id.
92 Id.
95 See id. § 355.
96 The laws regarding the FDA’s authority, specifically the drug approval process, allows the FDA to regulate manufacturers. See FDAAA, 21 U.S.C. § 355-1 (2011).
The roles of these agencies, however, have created some overlap of authority. When the DEA is deciding how to schedule a certain drug, the FDA makes scientific recommendations to the DEA about the drug’s abuse potential, which the FDA discovers through clinical studies required during the drug approval process.

The FDA’s scope of authority has gradually expanded during the last two decades. In 1992, Congress gave the FDA the authority to charge drug manufacturers fees for seeking drug approval through the Prescription Drug User Fee Act (PDUFA). Congress wanted the FDA to use the fees to hire more staff and expedite the drug approval process. Every five years PDUFA is eligible for reauthorization, and each time, Congress has reauthorized it.

In 2006, Congress authorized the FDA to require RiskMAPs as part of the drug approval process. A RiskMAP consisted of a written risk evaluation of a proposed drug, completed by the manufacturer. The authorization from Congress came after the FDA stated in its guidance to the pharmaceutical industry that there was a need to assess and minimize risks associated with prescription drugs. The

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99 Scheduling refers to the level of regulation DEA applies to the distribution and prescription of a certain drug. There are five drug schedules where Schedule I contains the most dangerous and highly-regulated drugs and Schedule V contains the least dangerous and minimally-regulated drugs. See id. at 5-6.

100 When deciding how to schedule a drug, the DEA considers the drug’s potential for abuse, patterns of actual abuse including scope and duration, scientific evidence, risks to public health, psychological or physiological effect of addiction, and relation to drugs already controlled by the DEA. See 21 U.S.C. § 811(c) (2011).


102 See Rhudy, supra note 101, at 99-100.

103 Id. at 100.

104 The most recent PDUFA reauthorization occurred in 2007 under the Food and Drug Administration Act, which granted $29.3 million towards improving the drug approval process. Id. at 103.


FDA described risk management as a process of steps by which a manufacturer (1) assesses the risk-benefit of a product, (2) develops and implements tools to minimize risk, (3) evaluates the effectiveness of the tools, and (4) makes adjustments to further assess the risk-benefit balance.\(^\text{107}\) The tools that the FDA allowed under RiskMAPs to reduce abuse included a process to screen patients for drug appropriateness, a higher standard of documentation, patient education requirements, patient and provider registration requirements, and mandatory lab tests.\(^\text{108}\) Despite criticisms that RiskMAPs sacrificed efficiency in the drug approval process, RiskMAPs became the precursor for Risk Evaluation Mitigation Strategies, otherwise known as REMS.\(^\text{109}\)

**B. FDA Authority After the FDAAA**

In 2007, Congress passed the Food and Drug Administration Amendment Act (FDAAA), which gave the FDA greater authority to regulate prescription drugs, including prescription pain relievers known as opioids.\(^\text{110}\) The FDAAA is considered to be “the most profound reworking of the U.S. drug regulatory framework in half a century.”\(^\text{111}\) For the first time, the FDA had the authority to extensively regulate drugs after the drug approval process.\(^\text{112}\)

1. **General Overview of REMS Content**

In Title IX of the FDAAA, Congress gave the FDA the authority to require Risk Evaluation Mitigation Strategies (REMS) as part of every drug application.\(^\text{113}\) It also gave the FDA the discretion to de-
cide what types of risk mitigation strategies drug manufacturers should incorporate into their REMS.\textsuperscript{114} The FDAAA organized REMS strategies into three tiers so that the FDA could apply less burdensome strategies to drugs with the least severe health risks and more burdensome strategies to drugs associated with the most severe health risks.

The least burdensome mitigation strategy consists of a series of assessments by which the manufacturer evaluates its drug’s risks at eighteen months, three years, and seven years after receiving drug approval from the FDA.\textsuperscript{115} The Secretary of DHHS can waive the assessment at seven years, if she believes that the drug’s risks were adequately assessed at three years.\textsuperscript{116} However, if the FDA feels that the minimal strategy is insufficient based on the potential risks associated with the drug, it can require the manufacturer to comply with additional strategies.

The middle-tier mitigation strategy consists of programs developed by the manufacturers for the purpose of educating providers and patients about a drug’s risks through medication guides, package inserts, and/or a communication plan.\textsuperscript{117} Since 2007, the FDA has required medication guides in all REMS and has required communication plans in some.\textsuperscript{118} A medication guide identifies important information about a drug’s known and potential risks.\textsuperscript{119} The guides are given to each patient who receives the drug.\textsuperscript{120} They are also available to patients and health care providers on the internet.\textsuperscript{121} Similarly, a communication plan is a packet of information that manufacturers send to health care providers within sixty days of drug approval and includes a “Dear Healthcare Provider Letter” explaining that the purpose of the information is to make them aware of the drug’s potential used in REMS, except REMS expands the scope of potential strategies that the FDA can require to mitigate risk. \textit{Id.} at 3-4.

\textsuperscript{114} \textit{Id.} at 2-3.
\textsuperscript{115} \textit{See} FDAAA § 355-1(d).
\textsuperscript{116} \textit{Id.}
\textsuperscript{117} \textit{Id.} § 355-1(e).
\textsuperscript{120} \textit{See Content and Format of a Medication Guide}, supra note 119.
\textsuperscript{121} \textit{See generally Approved Risk Evaluation and Mitigation Strategies (REMS), supra} note 118.
The packet contains copies of the medication guide and the professional label that will accompany the drug after approval.123

For drugs that the FDA finds inherently dangerous, it may require manufacturers to comply with the highest tier of risk management. This mitigation strategy, which is the most burdensome, is known as Elements to Assure Safe Use (ETASU).124 The Secretary determines that manufacturers should comply with ETASUs when (1) their drug has been associated with adverse drug experiences, (2) the FDA would deny or withdraw the drug’s approval without ETASUs, and (3) the risks of the drug are not adequately mitigated by the basic strategies.125 Under ETASUs, the FDA may require manufacturers to develop drug training and special certification examinations, designate specific drug dispensing locations, increase documentation of safe use, implement patient monitoring, and encourage patient enrollment in a drug-specific registry.126

Since 2007, the FDA has required some combination of ETASUs in 20 of the 146 approved REMS.127 For example, the FDA approved Butrans (buprenorphine), an opioid administered through a patch placed on the patient’s skin for managing moderate to severe chronic pain.128 Before granting drug approval, the FDA required the manufacturer, Purdue Pharma L.P., to create a REMS with the ETASU of special training for health care providers.129 The manufacturer developed a training program that provided general guidance on opioid use

122 See FDAAA § 355-1(e)(3); see Acterma, supra note 119, at 2.
123 See Acterma, supra note 119, at 10.
124 See FDAAA § 355-1(f)(3).
125 See id. § 355-1(f)(1)(A)-(B).
126 Id. § 355-1(f)(1)(A)-(F); see infra Part III.B.
127 See Approved Risk Evaluation and Mitigation Strategies (REMS), supra note 118.
129 Since the FDA has not decided on a standard opioid REMS, the FDA has required REMS with ETASUs on an ad hoc basis as manufacturers have presented opioids for drug approval. See PURDUE PHARMA L.P., Butrans: Risk Evaluation and Mitigation Strategy (REMS), 2 (June 30, 2010), http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM220880.pdf.
and specific advice about appropriate patient selection and abuse risks associated with Butrans.\(^{130}\)

Because opioids are associated with adverse drug events that the FDA believes cannot be mitigated by less burdensome strategies, the FDA has approved opioids such as Butrans with a REMS containing ETASUs.\(^{131}\) However, each time an opioid has come up for approval since 2007, the FDA has developed a new REMS by modifying the required ETASUs. Under the current opioid approval process, the FDA reviews an application, decides what combination of ETASUs to require, and notifies the manufacturer of its decision. This process is labor intensive for FDA employees and makes the drug approval process very inefficient. For manufacturers, the current process significantly delays their ability to put the drug on the market. Delays cause lost revenue that could have been used to fund further research and development of new drugs.\(^{132}\)

If the FDA used the same REMS for all opioid drug applications, it would not only improve the efficiency of the FDA’s drug approval process, it would improve manufacturer compliance with the requirements. Under a general opioid REMS process, manufacturers would be able to better anticipate the FDA’s expectations.\(^{133}\) If manufacturers knew what type of REMS they had to complete in order to acquire drug approval for an opioid, they could contact the individuals necessary to help them complete the REMS in advance of drug approval.\(^{134}\) These individuals may be scattered across the organization, so having advance notice would prevent delays caused by tracking them down and coordinating their participation.\(^{135}\) Furthermore, a general opioid REMS would allow manufacturers to ask for clarification of any requirement. Recognizing the benefits to manufacturers and the drug approval process, the FDA began drafting a general opioid REMS proposal. Unfortunately, the FDA has encountered difficulty developing a widely-accepted proposal.\(^{136}\)

\(^{130}\) Id.

\(^{131}\) Id.

\(^{132}\) See id. at 3.


\(^{134}\) Id. at 2.

\(^{135}\) Id. at 2-3.

\(^{136}\) See infra Part II.B.2.
2. **Initial Opioid REMS Proposal**

The FDA did not present a proposal for a general opioid REMS until July 22, 2010, at the Joint Meeting between the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee (Joint Meeting). The delay between approval of the FDAAA and the FDA’s first opioid REMS proposal is likely explained by the medical complexity of opioids and the widespread disagreement about how to design an opioid REMS. Also, the FDA likely wanted to proceed cautiously because of the potentially high financial burden an opioid REMS would place on key stakeholders in the pharmaceutical and health care industries. Manufacturers will experience financial burdens when the FDA requires them to create and offer training programs to health care providers prescribing their drugs. This is in addition to the financial burden manufacturers have already had to incur because of REMS requirements associated with nonopioids. Similarly, health care providers will experience financial burdens when they attend the training programs rather than spend time with patients.

The FDA first announced its plan to create an opioid REMS on February 6, 2009, with a letter to opioid manufacturers. During the first six months of 2009, the FDA created an Industry Working Group comprised of pharmaceutical industry representatives to discuss and develop an opioid REMS. In the following months, the FDA granted drug approval to two new opioids, indicating that when the FDA finalizes an opioid REMS, the manufacturers may have to revise their current REMS in order to comply with future policy changes. In December 2009, the FDA invited key stakeholders to work on de-

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137 See generally Joint Meeting Transcript, supra note 15, at 1.
138 Id.
139 Id.
140 See Transcript for FDA’s Media Briefing on the Safe Use of Opioids, supra note 14, at 2.
141 See, e.g., Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs; Notice of Public Meeting, 74 Fed. Reg. 59,568, 59,568 (Nov. 18, 2009). A special exception was made to antitrust laws to enable many significant stakeholders of the pharmaceutical industry to meet with each other. See Coleman, supra note 54, at 42.
veloping the first opioid REMS proposal. Six months later, however, at the Joint Meeting, the advisory committees voted to reject the initial opioid REMS proposal because it required “more teeth.”

The initial proposal for opioid REMS consisted of a medication guide, communication plan, and the ETASU of additional voluntary training for health care providers. The medication guide was intended as the primary form of education for health care providers who prescribe the opioid, and patients who receive the prescription. Before this proposal, there were several medication guides used by drug manufacturers of opioids. The initial opioid REMS proposal recommended that manufacturers and the FDA work to consolidate some of the preexisting medication guides. After the consolidation effort, manufacturers would have at their disposal a standard medication guide for each of the following: oral long-acting opioids, transdermal patch long-acting opioids, and tablet and oral solutions of methadone hydrochloride.

In addition to the medication guide, the initial opioid REMS proposal required a communication plan. No specific alterations were made to this strategy. Communication plans under the initial proposal followed the recommendation in the FDAAA, which requires drug manufacturers to send letters to key stakeholders, including prescribers, dispensers, state licensing authorities, professional associations, and all other DEA registrants, informing them of the known and potential risks of the drug.

Finally, the initial proposal recommended that the FDA exercise its authority to require an ETASU, specifically voluntary training for health care providers, developed by the manufacturers. The train-

143 See Risk Evaluation and Mitigation Strategies for Certain Opioid Drugs; Meeting Notice, 74 Fed. Reg. at 59,568.
144 See Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee; Meeting Notice, 75 Fed. Reg. at 32,188; see also Joint Meeting Transcript, supra note 15, at 232.
146 Id. at 14.
147 See id.
148 Id. at 14-15.
149 Id. at 17.
150 Id.
151 Id. at 23, 25.
ing would improve prescribers’ ability to select suitable patients and counsel them on the associated risks. The training would also serve as a reminder that the patient and the prescriber should carefully read the medication guide. The FDA would conduct an ongoing assessment of whether the training was successful. The tools used for detecting changes in opioid prescribing patterns after the implementation of opioid REMS would be database studies and surveillance studies conducted by an external review board called the Sponsor Management Group (SMG). If the SMG found that doctors failed to participate in the training program and their overall prescribing patterns did not change significantly, the FDA would make a recommendation to the DEA about incorporating a training requirement into the doctors’ DEA registration process. Even though the advisory committees rejected the initial opioid REMS proposal, the FDA should continue to work towards implementing an opioid-specific REMS because opioids are a unique class of drugs with a high risk for abuse. Through a general opioid REMS, the FDA can help ensure that the benefits of using opioids for pain relief always outweigh the risks.

III. OPIOID REMS: LEARNING FROM THE PAST AND IDENTIFYING FUTURE OPPORTUNITIES

A. Lessons From the Initial Opioid REMS Proposal

1. Voluntary Prescriber Training

In the initial proposal, the FDA relied on the ETASU of training to reduce opioid risks. The FDA included a training program that would educate prescribers on appropriate patient selection, dosing,
and patient monitoring.\textsuperscript{159} While the information conveyed in the training program is unquestionably valuable, the FDA’s suggestion of voluntary training is insufficient to improve prescribing habits.\textsuperscript{160} Doctors will likely decide against voluntary training, not because they fail to appreciate the importance of training, but simply because their demanding schedules do not allow it. If many doctors choose not to attend the training program, then prescribing habits for opioids will not improve in a way that reduces opioid abuse, diversion, and undertreatment.

At the Joint Meeting, several speakers suggested that a simple solution to improving the next opioid REMS proposal is to make training mandatory.\textsuperscript{161} While this seems logical, it is not necessarily feasible, at least for the FDA. The FDA controls drug approval, labeling, and manufacturing standards by regulating the manufacturers.\textsuperscript{162} It does not have regulatory authority over doctors and cannot enforce a training requirement.\textsuperscript{163} Since the FDA is unable to single-handedly improve opioid prescribing habits, it needs help from other regulatory agencies.

At the federal level, the DEA may be able to assist the FDA by requiring doctors to complete an opioid training program prior to receiving a DEA registration number.\textsuperscript{164} A DEA registration number permits doctors, pharmacists, and distributors to lawfully handle controlled substances.\textsuperscript{165} The current process requires an applicant to complete a written application and mail it to the nearest DEA field office, along with payment for a processing fee.\textsuperscript{166} In the future, the DEA could require doctors to show proof that they attended an approved opioid training course as part of the application process. Although this is not an immediate solution to increasing regulation of prescribers, it has the potential to provide long-term support to the FDA’s efforts.\textsuperscript{167}

\textsuperscript{159} See Joint Meeting Transcript, supra note 15, at 44.
\textsuperscript{160} See id. at 29.
\textsuperscript{161} Id. at 29-30.
\textsuperscript{162} See FDAAA, 21 U.S.C. § 355-1 (2011); see supra Part II.A.
\textsuperscript{163} See FDAAA § 355-1.
\textsuperscript{164} Registration Procedures, supra note 156.
\textsuperscript{166} Registration Procedures, supra note 156.
\textsuperscript{167} DEA involvement in requiring training for doctors prescribing opioids is not an immediate solution because it would require Congress to pass a law authorizing the DEA to require doctors to attend training before prescribing opioids to patients for pain. Buprenorphine, which is an opioid used to treat people addicted to drugs, illustrates this process. Congress passed the Drug Addiction Treatment Act of
At the state level, medical boards may be able to assist the FDA by requiring doctors to complete continuing medical education on opioids. The Federation of State Medical Boards (FSMB) plays an influential role in medical practice at the state level. It represents seventy professional medical organizations and 750,000 practicing physicians. The FSMB has already released professional guidelines for prescribing opioids, indicating that it recognizes the seriousness of opioid problems. The FSMB has the ability to persuade state legislatures to include opioid training as part of the medical licensure requirements. Since the manufacturers are responsible for the development and cost of the training programs, changing the state laws to include an opioid training program would not be a significant financial burden on the states. With the help of state-level regulatory agencies, opioid regulation would extend beyond manufacturers.

While changes may take place in the form of increased FDA collaboration with the DEA and state medical boards, manufacturers should continue to develop and offer the requisite training programs. Manufacturers understand their drugs the best. They conduct extensive clinical trials and complete a thorough application process in order to earn drug approval from the FDA. Manufacturers can use information they gathered prior to drug approval to design the training and can use information they gather postapproval to revise the training from time to time. Additionally, manufacturers are likely to have the financial resources to fund ongoing training efforts.

Prescriber training programs developed and implemented by the manufacturer, however, raise concerns about conflict of interest, specifically that a drug manufacturer will promote its own drug through information presented in the training program. Critics should realize that the FDA still has the authority to approve or reject the manufacturer’s proposed training program. In other words, if the FDA finds that the training is biased towards the manufacturer’s drug, the FDA

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2000 (DATA 2000), which gave the DEA the authority to require doctors prescribing buprenorphine for drug addictions to obtain a special registration number. In order to get the special registration number, doctors have to meet one of seven requirements to be a “qualified physician.” See infra Part III.B.1. Once doctors meet the requirements and obtain a registration number, they cannot write a valid opioid prescription as part of a patient’s addiction treatment unless they include their special registration number. Congress would have to pass a new law, if the DEA were to apply similar registration requirements on doctors who prescribe opioids for pain treatment. See Substance Abuse and Mental Health Servs. Admin., Buprenorphine: Physician Waiver Qualifications, BUPRENORPHINE.SAMHSA.GOV, http://buprenorphine.samhsa.gov/waiver_qualifications.html (last visited Oct. 4, 2011).

168 See Joint Meeting Transcript, supra note 15, at 88.
can deny the manufacturer’s drug approval. If the FDA has already granted drug approval and discovers the manufacturer is presenting biased information, the FDA can rescind the approval and remove the manufacturer’s drug from the market.

The FDA could also extend the investigatory framework it applies to food and drugs to the training programs, which would allow the FDA to continuously monitor the quality and content of the training programs offered by manufacturers. The FDA could also extend the investigatory framework it applies to food and drugs to the training programs offered by manufacturers.

Through cooperation between regulatory agencies at the state and federal level, the FDA can improve oversight of information presented to doctors about opioids and ensure that a manufacturer’s bias does not interfere with a doctor’s training experience. Monitoring training programs across the country might be difficult and expensive, if the format of the program is face-to-face instruction. However, if the FDA allows manufacturers to fulfill the training ETASU by creating an educational platform such as an interactive website with tutorials and an on-line certification examination, continuous monitoring of a website would be less costly for the FDA and state officials commissioned to conduct the investigations. In addition, a web-based training program would be more cost effective for manufacturers than a program based on face-to-face instruction.

2. Public Education

The FDA properly included opioid training for prescribers in the initial proposal, but it failed to address educational opportunities for

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170 For continuous regulation of approved foods and drugs, the FDA relies on help from the states because the states share jurisdiction over the products located within their boundaries. Individuals who conduct examinations, inspections and investigations for the FDA are either: (1) FDA employees recognized by the state as an agent or special representative; or (2) a state regulatory officials commissioned by the FDA. See FDA, CHAPTER 3: FEDERAL AND STATE COOPERATION, INVESTIGATIONS OPERATIONS MANUAL 92-93 (2011), available at http://www.fda.gov/ICECI/Inspections/IOM/default.htm. Commissioned officials conduct inspections, collect samples, copy and verify records, and review official FDA documents. The FDA believes that this system enhances cooperation between state and federal agencies on regulatory matters and “increas[es] the amount of public health protection afforded to the American consumer.” FDA, CHAPTER 3: COMMISSIONING AND WORK SHARING, REGULATORY PROCEDURES MANUAL 2, 6 (Aug. 2011), available at http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074334.pdf.

171 See infra Part IV.A.

172 See infra Part IV.A.
the general public. Speakers at the Joint Meeting described the difference between training and education by explaining that training focuses on helping health care providers properly diagnose patients, dispense drugs, and monitor patients, whereas education focuses on communicating drug risks to doctors, patients, and the general public.

The FDA should not initially require manufacturers to fund public education campaigns about opioids. Manufacturers have limited resources and must maintain adequate funds for drug research, development, and manufacturing. The FDA should only ask manufacturers to spend money on developing mandatory training for prescribers. Training has the greatest chance of improving opioid prescribing patterns and reducing opioid-related problems of abuse, diversion, and undertreatment. Public education campaigns should be left to non-profit organizations, such as the American Pain Foundation (APF), at least until manufacturers have absorbed the start-up cost associated with developing training programs for prescribers.

The American Pain Foundation has the ability to educate the general public on the risks of opioid treatment. The APF communicates safety alerts to consumers and serves as a liaison to policymakers about drug-related issues. It recently called its members to take action against irresponsible, biased reports on opioid abuse within the population of wounded American soldiers. Since the APF already conveys messages about drug risks and calls people to take action against issues such as drug abuse, it can play an important role in educating the public about safe opioid use.

3. Drug Diversion

The initial proposal fell short of providing strategies to reduce drug diversion. While drug diversion falls under the jurisdiction of

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173 See Joint Meeting Transcript, supra note 15, at 30-32.
174 See id. at 27-28 (regarding training); see also id. at 30 (regarding education).
175 See id. at 43.
177 The APF pointed to an article published in USA Today saying that the newspaper misrepresented the prevalence of opioid abuse in soldiers by indicating up to 35 percent of wounded soldiers have become addicted to drugs. Action Requested, AM. PAIN FOUND., http://action.painfoundation.org/site/MessageViewer?em_id=12681.0&printer_friendly=1 (last visited Oct. 4, 2011).
178 Id.
the DEA, the FDA could have required a strategy within the opioid REMS proposal to help the DEA reduce the availability of drugs to third parties seeking to misuse and abuse opioids. One recommendation that came out of the Joint Meeting was to create a program for collecting unused opioids.\textsuperscript{179} Unused or improperly disposed opioids increase the risk that a third party will misuse or even abuse the drugs. The FDA could designate places in hospitals to collect unused drugs as part of the REMS.\textsuperscript{180} Including more robust strategies such as this may help persuade the FDA advisory committees to approve a future opioid REMS proposal.

4. \textit{Data Collection}

While the initial proposal provided that ongoing assessments by the SMG will evaluate the efficacy of an opioid REMS, especially the impact of training, the initial proposal did not explain how the SMG will function.\textsuperscript{181} The FDA left the areas of data collection, assessments, and information sharing undeveloped. Some of the unanswered questions related to data collection and assessments include (1) what type of data will the SMG collect, (2) will the SMG publicly report the data, and (3) if not, who will see the reports?

In determining the role of the SMG, the FDA should look to several states that gather data in prescription drug monitoring programs (PMPs). PMPs are electronic databases that store information about what drugs doctors and pharmacists dispense to patients.\textsuperscript{182} Forty-three states have laws creating PMPs, and thirty-four states have operational programs.\textsuperscript{183} Most programs are managed by state health departments.\textsuperscript{184} Individuals who can request data from PMPs include (1) licensed physicians; (2) pharmacists; (3) federal, state, and local law enforcement; (4) professional organizations; (5) regulatory boards; and (6) anyone whose prescription has been recorded in the database.\textsuperscript{185}

Massachusetts is representative of most PMPs because it allows monitoring of drugs that fall into Schedules II, III, and IV of the

\begin{footnotes}
\footnote{179 See Joint Meeting Transcript, supra note 15, at 138.}
\footnote{180 See id.}
\footnote{181 See Industry Working Group, supra note 145; see supra Part II.B.2.}
\footnote{183 Id.}
\footnote{184 Id. at 2.}
\footnote{185 Id. at 4.}
\end{footnotes}
DEA’s classification for controlled substances.\textsuperscript{186} Massachusetts’ PMP is funded in part by grants from the U.S. Department of Justice.\textsuperscript{187} It requires that pharmacies report to a data collection agency each week and no later than ten days after filling a prescription.\textsuperscript{188} Data points that must be sent to the agency include customer identification numbers, locations where customers filled prescriptions, the customer’s relation to the patient if they are not the same individual, and quantities of the drugs dispensed.\textsuperscript{189} Since most state laws permit PMPs to share data with law enforcement and regulatory agencies,\textsuperscript{190} the FDA and the SMG should strongly consider using PMP data to monitor changes in opioid prescribing habits.

5. **Pilot Study**

The FDA should also consider conducting a pilot study for the next opioid REMS proposal prior to its approval. The goal of the study would be to simulate the implementation of opioid REMS using one manufacturer seeking drug approval for a new opioid drug. The study would allow the FDA to work out any unanticipated difficulties in having the manufacturer offer prescriber training programs. It would also allow the FDA to receive feedback from doctors who attend the opioid training programs. Doctors would be able to critique whether the information was valuable and whether it was presented in an appropriate manner. A pilot study would help the FDA work out any glitches before requiring a large-scale implementation of the opioid REMS.

\textsuperscript{186} Id. at 3. Effective January 1, 2011 the record keeping for prescriptions expanded to drugs regulated by Schedule II-V. See Massachusetts Department of Public Health Prescription Monitoring Program Fact Sheet for Pharmacy, MASS.GOV (Oct. 13, 2010), http://www.mass.gov/Eeohhs2/docs/dph/quality/drugcontrol/pmp_pharmacy_factsheet.pdf.

\textsuperscript{187} Prescription Monitoring Program (PMP), MASS.GOV (Oct. 30, 2010), http://www.mass.gov, (click on link for “State Government,” then “Alphabetical List, All Branches,” then “Executive Office of Health and Human Services,” then tab called “For Providers,” then “Certification, Licensure, and Registration,” then “Compliance and Enforcement,” then “Drug Control,” then “Prescription Monitoring Program”).

\textsuperscript{188} See Massachusetts Department of Public Health Prescription Monitoring Program Fact Sheet for Pharmacy, supra note 186.

\textsuperscript{189} Additional data points include information about whether prescription partially filled, method of payment, electronic prescription reference number, whether patient is resident of the U.S., and whether prescription is compounded. Id. at 2-4.

\textsuperscript{190} See Nat’l Alliance for Model State Drug Laws, supra note 182, at 4.
Congress did not give express authority to the FDA through the FDAAA to conduct a pilot study of an opioid REMS before implementing it across the entire class of opioids. At the Joint Meeting, an FDA representative pointed out that conducting a pilot study for opioid REMS would be difficult without explicit statutory authority. Rather than proposing new legislation, the FDA should reallocate money within its budget to fund the pilot study and seek voluntary participation by one or more drug manufacturers. If attempts to do this are unsuccessful, the FDA should consider looking at risk management programs created by the states. However, one drawback to looking at state programs is that the FDA may not have the opportunity to observe the efficacy of specific ETASUs, if the states observed have not taken an approach modeled after ETASUs.

B. Opportunities Under the FDAAA

The FDA advisory committee rejected the initial opioid REMS proposal because it only included voluntary training for prescribers, which is one of six ETASUs available to the FDA under the highest risk mitigation strategy. At first glance, it looks as though the FDA could have included more ETASUs in the first opioid REMS proposal. However, the following subsections describe the extent to which the FDA can incorporate ETASUs in the next opioid REMS proposal.

1. Certification

Under the FDAAA, the FDA can ask manufacturers to create certification programs for pharmacists, doctors, and health care facilities. If the FDA required manufacturers to develop a certification examination as part of an opioid REMS, health care professionals would have to complete the examination before prescribing and dis-

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191 See Joint Meeting Transcript, supra note 15, at 206.
192 Id.
193 Id. at 39.
pensing opioids. Certification is a tool, similar to training, which can improve the competency of health care professionals regarding the risks of opioid use. However, if the FDA exercises its authority to implement a special drug certification program, it would duplicate some preexisting DEA requirements for doctors who treat patients with drug addictions.

Under DEA regulations, doctors who wish to treat patients addicted to opioids must first meet the standards of a “qualifying physician.” They can meet that standard by completing one of the following: (1) state board certification in the addiction psychiatry subspecialty, (2) addiction certification from the Society of Addiction Medicine, (3) American Osteopathic Association board certification in the addiction medicine subspecialty, (4) eight or more hours of training from a professional medical organization, (5) participation in a clinical trial that led to drug approval, (6) sufficient training as specified by a state medical licensing board, or (7) any other training that the Secretary of DHHS finds sufficient to show that a physician is competent to prescribe opioids to patients.

Given the similarity between the DEA’s requirements for qualifying physicians and the FDA’s potential authority under the certification ETASU, the FDA would duplicate some of the DEA’s efforts. The overlap would occur in the case of doctors who treat patients currently addicted to opioids. While this would not affect all doctors, duplication in this subset of health care providers would force some doctors to spend twice as much time and money on certification. Over the long-term, this could deter some doctors from prescribing opioids, which would limit patient access to pain relief and cause widespread undertreatment of acute and chronic pain. It might also deter some doctors from treating patients addicted to opioids, which would be equally problematic.

Duplication could be avoided if the Secretary of DHHS recognizes that the FDA certification program satisfies the DEA requirements under subsection (7) of the qualifying physician standard. However, the Secretary has not yet addressed whether opioid training developed by a manufacturer for a REMS would fall within the scope of subsection (7). Conversely, the Secretary has also not addressed whether the DEA’s qualifying physician standard could satisfy the

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197 Id.
198 Id. The DEA requires doctors to have special certification to treat patients addicted to opioids because typical treatment involves drugs like methadone and buprenorphine, which carry their own health risks. 21 U.S.C. § 823(g)(2)(G)(ii)(I)-(VII) (2011).
199 Id.
certification ETASU and save manufacturers from developing a new system of certification.

2. **Dispensing Locations**

The FDA can also impose limitations on drug dispensing locations.\(^{200}\) The FDA has not addressed this ETASU in great detail during public meetings on opioid REMS.\(^{201}\) Without more information, it is difficult to know how the FDA would implement this ETASU to reduce the risks of abuse, undertreatment, and diversion. Limiting opioid dispensing locations has the potential to mitigate the risk of diversion by further controlling who receives opioids. Since the DEA’s primary concern is regulating the diversion of drugs for illicit use, this ETASU is more relevant to the DEA’s mission than the FDA’s objectives. Thus, the FDA should focus its efforts on incorporating other ETASUs into the next opioid REMS proposal.

3. **Patient Monitoring**

The FDA can also require the ETASU of patient monitoring in the next opioid REMS proposal,\(^{202}\) which includes techniques such as drug testing and pill counting.\(^{203}\) Patient monitoring helps doctors track whether patients are following their recommended treatment course. However, if the FDA required doctors to conduct drug testing or pill counts, it would overstep its authority by regulating the practice of medicine.

On several occasions courts have considered whether the federal government has the authority to regulate medical practice or whether that is an area of law reserved for the states.\(^{204}\) Most recently, the Supreme Court addressed the issue in *Gonzales v. Oregon*.\(^{205}\) In this case, the Attorney General argued that the Controlled Substances Act (CSA) gave him the authority to prohibit doctors from using con-

\(^{200}\) FDAAA § 355-1(f)(3)(C).

\(^{201}\) See, e.g., Transcript for FDA’s Media Briefing on the Safe Use of Opioids, supra note 14.


\(^{204}\) Parties defending the rights of the states to regulate medicine look to the 10th Amendment of the U.S. Constitution, which states “[t]he powers not delegated to the United States by the Constitution, nor prohibited by it to the States, are reserved to the States respectively…” U.S. CONST. amend. X.

trolled substances for physician-assisted suicide. The Supreme Court explained that even though Congress has the authority to regulate medical practice in order to prevent doctors from promoting illicit drug trafficking, Congress lacks the authority to regulate medical practice generally. Furthermore, while Congress delegated some of its authority to the Attorney General under the CSA, the Attorney General’s authority was specifically limited to promulgating and enforcing rules that (1) relate to manufacturing, distributing, and dispensing controlled substances; and (2) are necessary to his functions under the CSA’s subchapter “Control and Enforcement.” The Supreme Court rejected the argument that Congress granted the Attorney General broad implied authority that would include regulation of physician-assisted suicide. The Supreme Court, instead, reasoned that interpreting the Attorney General’s power more broadly to cover an area of medical practice, such as physician-assisted suicide, would “transform the carefully described limits on the Attorney General’s authority over registration and scheduling into mere suggestions.”

The Supreme Court’s decision in *Gonzales v. Oregon* was consistent with prior cases concerning the authority of federal regulatory agencies and the practice of medicine. Two decades before *Gonzales*, the Fifth Circuit considered the limits of the FDA’s authority in *U.S. v. Evers*. A doctor, who was accused of violating the Federal Food, Drug, and Cosmetic Act, produced an FDA notice from the Federal Register as evidence that the FDA should not be regulating his practice of medicine. In the FDA’s own words, “Congress did not intend the Food and Drug Administration to interfere with medical practice.” As a result, the *Evers* court declined to reconsider the district court’s decision that the federal government was prohibited from interfering with a doctor’s prescription practices. The court explained that medical practice is not an area generally regulated by the federal government or one of its agencies.

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206 *Id.* at 248-49.
207 *Id.* at 269-70.
208 *Id.* at 259.
209 *Id.* at 260.
210 *Id.* at 260-61.
212 *Id.* at 1048.
213 FDA Actions Against Unapproved Uses of Approved Prescription Drugs, 37 Fed. Reg. 16,503, 16,503 (proposed Aug. 15, 1972). The notice that the doctor submitted as evidence was to announce proposed legislation, but it never became law. *Id.* The FDA repeated the quote again in a notice about drug labeling in 2003. Labeling Requirements for Systemic Antibacterial Drug Products Intended for Human Use, 68 Fed. Reg. 6,062, 6,071 (to be codified at 21 C.F.R. pt. 201).
214 *Evers*, 643 F.2d at 1049.
If the FDA decides to require the patient monitoring ETASU as part of an opioid REMS in the future, it should expect to face challenges from doctors and state medical boards on the theory that the federal government is not authorized to regulate the practice of medicine. This potential challenge may explain why the FDAAA proposed several ETASUs and made them optional strategies. It may also explain why the FDA did not include the patient monitoring ETASU in the initial opioid REMS proposal. The FDA may believe that patient monitoring is an indispensable component of opioid regulation, but it should be careful not to overstep its authority and should leave enforcement of this ETASU to state medical boards instead.

4. Drug Registries

The FDAAA also gives the FDA authority to include a drug registry in the next opioid REMS proposal. However, as discussed in the previous section, the FDA likely lacks the authority to require prescribers to record patient data in a drug registry. Therefore, the success of this ETASU will depend on the voluntary participation of pharmacists, doctors, and nurses.

If the FDA seriously considers incorporating a drug registry into the next opioid REMS proposal, it should look to the states. Using information gathered by the states would cut down on the cost of implementation and prevent duplication in data collection. The FDA should also consider looking at registries used in other areas of medicine. Registries are frequently used in obstetrics to estimate the risks of prenatal prescription drugs by recording data from pregnant mothers. Health care providers report data on birth defects and fetal losses associated with prescription drugs to a registry using a toll-free number.

With any database, however, there are privacy concerns. The more patient-identifying information a database contains, the greater the privacy concerns. If the FDA considers moving forward with its own drug registry, it should carefully weigh the benefit of a national drug registry created by the FDA, against the costs, which include the financial burden of developing and maintaining the registry, as well as the risks to patient privacy.

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216 See supra Part III.A.4.
218 Id. at 357.
IV. **RECOMMENDED STRATEGY FOR THE FDA AND STATE MEDICAL BOARDS**

Considering the lessons learned from the initial opioid REMS proposal and the limitations of the FDAAA, the FDA should employ a three-fold strategy going forward. It should involve (1) the FDA developing an opioid REMS proposal with a web-based training program funded by manufacturers, (2) the state legislatures enforcing opioid training requirements and issuing opioid registration numbers to doctors, and (3) the FDA collaborating with the states on data collection.

**A. Training Program**

When the FDA drafts the next opioid REMS proposal, it should require an opioid training program with content covering all types of opioids, including immediate-release and extended-release opioids. The program should advise doctors on how to distinguish between patients who are less likely to abuse opioids and those who are more likely. Recognizing the latter category of patients requires the skills to identify withdrawal symptoms and uncover a patient’s history of substance abuse. In order to help improve drug abuse detection, the program should include multimedia, such as videos and pictures, to help illustrate drug abuse behaviors in patients of all age cohorts and racial groups.

Doctors not only have to identify patients who are good candidates for opioids, they also have to write a prescription for an appropriate dose based on the patient’s age, weight, and health condition. The training program should discuss the appropriate types of opioids and corresponding doses for treating both chronic and acute pain patients. It would be helpful if the program presented a checklist of considerations, which doctors could routinely review when making decisions about opioid prescriptions.

The FDA should develop and maintain the training program or hire a third party, such as a professional organization of pain physicians, to do so. Development and maintenance of the training program should be funded by manufacturers based on the market share they hold in the opioid industry. The market share calculations should be based on each pharmaceutical company’s gross earnings from

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219 *See Joint Meeting Transcript, supra* note 15, at 192-93.
220 *See supra* Part I.A.3.
opioids during the previous calendar year. Under this system, smaller pharmaceutical companies introducing just one or two opioid products into the market would not be burdened by a significant training program expense.

The FDA should ensure that there is one uniform training program for opioids rather than individual programs developed by each manufacturer. If every manufacturer had to create a program, it would be unnecessarily duplicative and would place a very heavy financial burden on manufacturers. The burden would be especially heavy if the training programs involved face-to-face instruction because the manufacturers would have to hire individuals each year to teach the courses at various locations across the country. Furthermore, placing a heavy financial burden on manufacturers would likely have the unintended consequence of discouraging some manufacturers from seeking opioid drug approval. If fewer manufacturers entered the market, pharmaceutical development would slow and patient access to safe pain relief would be hindered. Thus, the FDA, or a third party hired by the FDA, should develop a web-based training program because, among other reasons, it is a more cost-effective approach.

A web-based training program would be better than face-to-face instruction for several reasons. First, a web-based program allows doctors to take the course at a time and place of their choice. Doctors would not have to pay to travel to a training program or rearrange their schedule in order to attend. Secondly, the information would be easy to access from either a personal or public computer. A doctor would register for a username and password, which they could use to save their progress on the training program each time they logged out of the website. Finally, a web-based training program would make it easier for the FDA or a third party to update the training information as new data becomes available.

A web-based training program would have its limitations. Doctors who do not have a strong internet connection for viewing multimedia might have difficulty completing the course. Technical support would be required to resolve these types of problems. A web-based program would also require the doctors to take more personal initiative to complete all of the lessons and read all of the material. In order to ensure that the doctors complete the program with a certain

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222 Id.
223 Id.
224 Id. at 19.
225 Id.
level of competence, the FDA should consider including a certification examination as the last step of the training program.

The certification examination should consist of fifty or so multiple-choice questions randomly generated from a database of several hundred multiple-choice questions. The certification exam at the end of the training program would not be as rigorous as the board certification requirement applied to doctors prescribing opioids to patients for addiction treatment. Nonetheless, doctors might be tempted to skip over material or have another individual take the certification exam on their behalf. The FDA should require doctors to complete a signature form, which states that they completed the exam without the assistance of another person and that the exam reflects their level of competency in the area of opioid prescribing. The doctors would then send the signature form to the medical board in the state where they practice medicine. The state medical boards should complete the remaining administrative steps for this recommended strategy.

B. State-Enforced Training Requirement

The states should assume the responsibility of enforcing doctor participation in the opioid training program. However, rather than requiring all doctors to complete opioid training, the states should only require doctors writing opioid prescriptions for pain to pass the certification examination. While this policy would still require many doctors to complete the training program, including surgeons, general practitioners, and even dentists, it would allow doctors who do not want to prescribe opioids to opt out of the training program and certification process.

If participating doctors finish the training and take the certification examination, they should complete the process by sending the signature form to their state medical board. Staff at the medical board should check the name of the doctor on the form with the examination results on the training course website, confirming that the doctor achieved a passing score. In addition, the staff should verify that the signature on the opioid training form matches the documents signed by the doctor when she applied for a medical license in the state. If the doctor meets both requirements, the state medical board should issue the doctor an opioid registration number. Thereafter, each time the doctor writes an opioid prescription for pain, she must put her opioid registration number on the prescription in order for it to be

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226 See supra Part III.B.1.
Pharmacists will play an important role in enforcing this process, since they will have to reject opioid prescriptions if doctors fail to include their opioid registration number on the prescription form. While the financial burden on state medical boards would be minimal under this system, states could nonetheless impose a nominal fee on doctors seeking an opioid registration number to offset the administrative costs associated with this process.

This recommended strategy requires the states to pass a new law so that opioid prescriptions written for pain relief would be invalid unless doctors include their opioid registration number on the prescription form. If states decline to implement this strategy, the Federation of State Medical Boards (FSMB) should talk with state representatives and persuade them to pass laws that revise the prescription requirements. Given that the FSMB represents seventy professional medical organizations and 750,000 practicing physicians, it likely has the resources and support to influence state action.

While critics may argue that one new federal law would be more efficient to pass than fifty state laws, a federal law takes years to navigate the legislative process and requires the support of Congress, which has been polarized on health care issues in recent years. Additionally, the state governments are a better place to modify the laws of opioid prescribing than the federal government because enforcing participation in opioid training programs through the states reduces the risk that the FDA will overstep its authority by regulating the practice of medicine.

C. Data Sharing

The FDA should collaborate with states that use prescription drug monitoring programs (PMPs). The FDA should request data from these programs on a quarterly basis and assess whether drug abuse and drug diversion problems decrease after the implementation of opioid REMS. While the FDA has authority under the FDAAA to establish new drug registries, resources may not be available for this purpose. Additionally, creation of an FDA drug registry would duplicate preexisting databases at the state level. Therefore, the key focus of FDA and state collaboration should be sharing data and tracking

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227 This is a similar system used for regulating doctors who are administering addiction treatments to patients using buprenorphine. The recommended strategy proposes expanding this to prescriptions for all opioids. Cf. Substance Abuse and Mental Health Servs. Admin., supra note 167.
228 See Joint Meeting Transcript, supra note 15, at 86.
229 See supra Part III.B.3.
the impact of opioid REMS on prescription drug abuse, diversion, and undertreatment.

There should not be any legal barriers to sharing data since most state laws concerning PMPs allow regulatory agencies, such as the FDA, to access their data.\(^{230}\) Although, as the states share data with more individuals or organizations, there is an increased risk that confidential information about a patient’s health condition will fall into the wrong hands. The states should consider removing from the data any primary identifying information, such as patients’ names or social security numbers, before transferring the data to the FDA. Removing this information would not decrease the value of the data, since the FDA is primarily focused on the prevalence and trends of opioid prescribing at the population level, rather than the patient level. Additionally, the states might consider using computer software to encrypt the data before passing it to the FDA for analysis, but the details of this would require further investigation and development.

D. Other Recommendations

Although the recommendation for a three-fold approach would likely improve opioid prescribing habits, there are several issues, such as public education campaigns and drug collection programs, which are not mentioned in the strategy above. Their omission from the strategy does not mean that they are any less important. Rather, they are strategies that should be considered by other regulatory agencies and the FDA at some point in the future. The FDA and state medical boards should use the recommended strategy as a short-term plan and reserve the other suggestions for long-term goals. In fact, some of the short-term plans may help achieve the long-term goals because improving doctor competency today will lead to safer opioid pain relief in the future. Over the years, information about health risks associated with opioids will trickle down from health care providers to the general public, even without formal interventions.

CONCLUSION

A common misconception is that people who abuse and misuse drugs do so intentionally. Over the past decade, testimonies by patients like Betty Tully have shed light on the truth.\(^{231}\) Many patients seeking pain relief receive not only a prescription for opioids, but a

\(^{230}\) See supra Part III.A.4.

\(^{231}\) See supra Part I.A.5.
devastating addiction through no fault of their own. As opioid use becomes more prevalent, the magnitude of risk for abuse, diversion, and undertreatment will continue to increase. The FDA and state medical boards should take advantage of the present opportunities to improve prescriber competence and work towards making opioids a safer option for pain relief.

In 2007, Congress passed the FDAAA and significantly transformed the FDA’s authority to regulate drug manufacturers. Through a three-tiered system of regulation called REMS, the FDA gained the authority to regulate drugs after the approval process by requiring manufacturers to engage in risk-mitigating activities such as distributing medication guides and communication plans to doctors prescribing their drugs. Since the advisory committees rejected the FDA’s initial opioid REMS proposal for being too weak, the FDA should strengthen the training requirements for doctors prescribing opioids to patients for chronic and acute pain relief. However, the FDA cannot single-handedly enforce stronger regulatory requirements against doctors. State medical boards should become more involved in opioid regulation by requiring doctors to successfully complete an opioid training program and certification examination before allowing doctors to write opioid prescriptions. With the help of state medical boards, the FDA can achieve a proper balance between opioid regulation and medically necessary opioid use.