SPECIAL REPORT

A Proactive Response to Prescription Opioid Abuse

Robert M. Califf, M.D., Janet Woodcock, M.D., and Stephen Ostroff, M.D.

We at the Food and Drug Administration (FDA) continue to be deeply concerned about the growing epidemic of opioid abuse, addiction, and overdose — an epidemic directly related to the increasingly widespread misuse of powerful opioid pain medications. As the federal agency charged with ensuring that the drugs used by the U.S. public are both effective and safe, we are committed to working in partnership with other government agencies, health care providers, the medical products industry and, most important, patients and their families to deal proactively with this unfolding public health crisis, which has already profoundly affected individuals, families, and communities throughout our country. We will do so while also safeguarding appropriate access to vitally important pain medications for the patients who need them (Table 1).

BACKGROUND

Over the course of a given year, approximately 100 million people in the United States suffer from pain. Some 9 million to 12 million of them have chronic or persistent pain, while the remainder have short-term pain from injuries, illnesses, or medical procedures. All of them should benefit from skillful and appropriate pain management, which may include the judicious use of opioid medicines in conjunction with other methods of treatment or in circumstances in which nonaddictive therapies are insufficient to control pain.

As physicians, we have treated both the intense suffering caused by acute pain and chronic pain with all its exhausting and debilitating consequences. But we have also witnessed the devastating results of opioid misuse and abuse, such as the addiction of patients who have been prescribed opioids for pain treatment and, increasingly, diversion to people for whom the prescription was not written. Many Americans are now addicted to prescription opioids, and the number of deaths due to prescription opioid overdose is unacceptable. This past month, our sister agency, the Centers for Disease Control and Prevention (CDC), estimated that in 2014 there were almost 19,000 overdose deaths in the United States associated with prescription opioids (Rudd R, CDC: personal communication).

Because protecting the public by ensuring the safety, efficacy, and quality of drugs is an essential part of the FDA's mission, it is appropriate to examine the agency's actions in coping with the public health crisis of opioid misuse. As FDA leaders and as physicians, we believe that these efforts must be founded on two complementary principles: that the United States must deal aggressively with opioid misuse and addiction, and at the same time, that it must protect the well-being of people experiencing the devastating effects of acute or chronic pain. It is a difficult balancing act, but we believe that the continuing escalation of the negative consequences of opioid use compels us to comprehensively review our portfolio of activities, reassess our strategy, and take aggressive actions when there is good reason to believe that doing so will make a positive difference.

We are launching this renewed effort in the context of a broad national campaign that includes a major initiative led by the Department of Health and Human Services (HHS)[1] designed to attack the problem from every angle. The number of annual opioid prescriptions written in the United States is now roughly equal to the number of adults in the population[2]; given these numbers, simply reinforcing opioid-related activities that are within the FDA's traditional regulatory scope will not suffice to stem the tide. Instead, we must work more closely with key federal agencies (including many within HHS), the clinical and prescriber communities, and other stakeholders to ensure that all available effective tools are brought to bear on this epidemic and that the evidence base for proper

Table 1. Responding to Prescription Opioid Abuse.

Issue	FDA Response
Balancing individual need and societal risk. Patients require access to safe and effective pain medication, but both individuals and society must be protected from the effects of opioid misuse.	The FDA will consult with partners including the National Academy of Medicine to craft a framework for opioid review, approval, and monitoring that balances individual needs for pain control with the risk of addiction, as well as the broader public health consequences of opioid abuse and misuse.
Meeting the need for timely action. The evolving threat of opioid abuse requires a flexible interim approach while the full policy framework is in development.	The FDA Science Board will convene in March to advise on the role of pharmaceuticals in pain management, development of alternative pain medications, and postmarketing surveillance activities. Multiple other actions will also occur over the next several months, including an evaluation of the existing Risk Evaluation and Mitigation Strategy (REMS) requirements for extended-release/long-acting (ER/LA) opioids. An advisory committee will consider this review and offer advice regarding possible expansion of the scope and content of prescriber education and whether to expand the REMS program to include immediate-release opioids, potentially increasing the number of prescribers receiving training on pain management and safe prescribing.
Reviewing labeling and postmarketing surveillance requirements. Current labeling requirements include detailed instructions, and manufacturers are required to conduct postmarketing safety surveillance and research studies, but these measures may need to be reevaluated.	The FDA will revise postmarketing requirements, expanding the requirements for drug companies to generate postmarketing data on long-term impact of ER/LA opioid use to provide better evidence on the serious risks of misuse and abuse associated with long-term opioid use, predictors of opioid addiction, and other important issues.
Prioritizing abuse-deterrent formulations and overdose treatments. Abuse-deterrent opioid formulations have the potential to reduce misuse of opioid medications, and broader access to naloxone may help mitigate harm from opioid overdose.	The FDA will continue to support abuse-deterrent formulations and, with guidance from an advisory committee, explore and encourage development of more effective abuse-deterrent features. The FDA will also prioritize issuance of draft guidance on generic abuse-deterrent opioids and will consider ways to make naloxone more widely available, including as an over-the-counter medication. In addition, new non–abuse-deterrent formulations submitted for FDA approval will also be reviewed by an advisory committee.
Addressing the lack of nonopioid alternatives for pain management. Although nonopioid medications for chronic pain have recently been approved for the market, more alternatives are needed, including nonpharmacologic treatments.	The FDA is working closely with industry and the National Institutes of Health to develop alternative medications without the addictive properties of opioids. Nonpharmacologic approaches to pain treatment have also been identified as an urgent priority.
Creating clear guidelines for opioid use. The current crisis in opioid misuse and abuse will continue unless prescribing physicians have a clear understanding of appropriate use and management.	The FDA is supporting the CDC's guideline for prescribing opioids for chronic pain control. The FDA also supports the Surgeon General's efforts to engage the clinical community in curbing inappropriate prescribing and proactively treating opioid addiction, while reinforcing evidence-based pain management approaches that spare the use of opioids.
Managing pain in children. Use of opioid medications in children with severe and chronic pain conditions requires special consideration, and physicians need information that helps them prescribe such medications safely and effectively, while protecting minors who lack mature decision-making capabilities.	An FDA Pediatric Advisory Committee will address the use of opioid medications in children, including the development of high-quality evidence to guide treatment, and provide input on the policies for adding new pediatric opioid labeling under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act before any new labeling is approved.
Developing a better evidence base. Despite ongoing efforts, the evidence base to guide the use of opioid medications, particularly in the setting of long-term use, is substantially lacking.	Health and Human Services agencies and the FDA program for mandated industry-funded studies are developing a coordinated plan for conducting research that will provide evidence to guide opioid use, elucidate the biologic phenomenon of pain, and consider new and alternative approaches to pain prevention and management.

pain management and appropriate opioid use is optimized and translated into practice.

BALANCING INDIVIDUAL AND SOCIETAL RISK

We will start by launching a broad reexamination of our approach, considering how best to apply existing policies to this problem, which policies need to be improved and updated, and whether new policies must be developed. Consideration of a range of risks that FDA-regulated products pose to their intended consumers and to others is important to our public health mission. In many cases, opioids can cause harm that goes beyond the risks to the person who has been prescribed the medicine, and inappropriate prescribing causes both direct and indirect harms that are difficult to track and measure but must be considered. We will therefore seek advice on how to more comprehensively take into account the risks of abuse for both patients and nonpatients when regulating these drugs.

We have asked the National Academy of Medicine (NAM) to help us develop a regulatory framework for opioid review, approval, and monitoring that balances individual need for pain control with considerations of the broader public health consequences of abuse and misuse. Assessing the long-term risks of addiction and hyperalgesia (in which the use of opioids results in excess pain rather than pain relief), as well as other toxic effects and societal harm caused by diversion and related addiction, will require extrapolation from imperfect data. The NAM brings an unbiased and highly respected perspective on these issues that can help us revise our framework.

Since this intensive review will take time, we plan to pursue other activities and decisions in the interim. The evolving nature of the threat that opioid abuse poses to our country's health demands an approach in which we constantly consider available information, seek advice, and move forward, always ready to shift our actions as new information becomes available. Specifically, at its next meeting in March, the FDA's Science Board (comprising independent experts in regulatory science) will consider a series of relevant issues, aiming to advise the FDA on the role of pharmaceuticals in pain management, development of alternative pain medications, and postmarketing surveillance activities.

REVISITING OPIOID LABELING AND POSTMARKETING STUDY REQUIREMENTS

We will also reexamine how opioids should be labeled more generally. Current labeling for extended-release or long-acting (ER/LA) opioids, revised in September 2013, includes strict, detailed instructions requiring descriptions of their associated risks, the need for monitoring, and the facts that opioids should be used only when other measures are insufficient, the need to continue to use opioids should be reassessed regularly, and opioids should be dispensed in limited quantities.[3] In addition, manufacturers of ER/LA opioids will be required to conduct extensive postmarketing research (resulting in a total of 11 mandated studies), in order to study safety concerns that have been identified and evaluate methods to assess progress in mitigating them.

Manufacturers of ER/LA opioids are also subject to a Risk Evaluation and Mitigation Strategy (REMS)[4] program that requires them to fund continuing medical education (CME) providers to offer, at low or no cost, CME courses on the appropriate use of these products, subject to an online FDA curriculum. More than 38,000 prescribers have taken part in these voluntary educational programs, and an evaluation of these results is under way and will be considered by an advisory committee in the spring.

But although this voluntary training remains an important public health measure, the FDA continues to support mandatory education for prescribers, as called for in the 2011 Prescription Drug Abuse Prevention Plan[5] and reemphasized in the 2014 National Drug Control Strategy.[6] Together with other federal agencies and the clinical community, we should strive to overcome obstacles to enacting this measure. Along with improving prescriber education, we will assess whether broader measures should be instituted for labeling and postmarketing evaluation of the entire class of opioids.

DETERRING ABUSE AND MITIGATING HARM FROM OVERDOSE

In addition to the REMS approach to safety, the FDA has strongly supported the development and assessment of abuse-deterrent formulations

of opioids,[7] five of which the agency has already approved. The pharmaceutical industry has shown significant interest in developing abuse-deterrent opioid formulations and the field is progressing rapidly. The availability of abuse-deterrent formulations raises questions, including how to encourage their use in place of products without abuse-deterrent features and whether to modify criteria for the review and approval of oral opioid formulations that lack abuse-deterrent features or do not offer advantages in abuse deterrence relative to currently marketed products. We will continue to support abuse-deterrent formulations and encourage development of more effective abuse-deterrent features; we are also committed to convening advisory committees to consider new versions of non–abuse-deterrent opioids. In addition, draft FDA guidance on generic abuse-deterrent opioids will review many of the key issues; making this guidance available quickly is a high priority, since the availability of less costly generic products should accelerate prescribers' uptake of abuse-deterrent formulations. However, it is important to recognize that abuse-deterrent formulations by themselves when taken orally do not prevent the development of tolerance or addiction to opioids.

We have also strongly supported the development and marketing of countermeasures that can reverse overdose, such as the opioid antagonist naloxone. Rapid advances in the development and distribution of injectable and intranasal naloxone offer an example of an effort in which broad intersectoral collaboration has saved substantial numbers of people who would otherwise have died from overdose. The recent rapid approvals of intramuscular (via auto-injector)[8] and intranasal[9] naloxone were important steps in improving access to this lifesaving therapy. Are there ways to expand naloxone's availability? We will continue to explore expanding availability of naloxone in the coming year, including ways to make it available over the counter.

PRIORITIZING DEVELOPMENT OF NONOPIOID ALTERNATIVES FOR PAIN RELIEF

We are also working closely with industry and the National Institutes of Health to develop additional alternative medications that alleviate pain but do not have the addictive properties of opioids. Nonpharmacologic approaches to pain treatment are also an urgent priority. The FDA has approved nonopioid medications for treatment of various chronic-pain syndromes, including gabapentin (Neurontin), pregabalin (Lyrica), milnacipran (Savella), duloxetine (Cymbalta), and others, and a number of promising development programs are in the pipeline. But we need more. The FDA will use all the tools at its disposal to move these alternatives along as expeditiously as possible, while remaining mindful that all medicines have risks. For example, although nonsteroidal antiinflammatory drugs do not carry a risk of addiction, we now know that they carry increased risks of myocardial infarction, stroke, and serious gastrointestinal bleeding.

REFINING GUIDELINES FOR OPIOID USE

A comprehensive solution to the current opioid crisis goes well beyond the FDA's remit. However, thanks to our access to rich data sources and the broader federal effort to define the issues, we are in a position to see the problems that medical practice and public health must confront and to provide guidance in addressing them. Accordingly, we are supporting the CDC's Guideline for Prescribing Opioids for Chronic Pain. The draft guideline[10] received extensive public comment, and we look forward to participating in the process when the CDC finalizes it soon. We are also supporting the Surgeon General's efforts[11] to engage the clinical community in a concerted approach to curbing inappropriate prescribing and proactively treating opioid addiction, while reinforcing evidence-based approaches to treating pain in a manner that spares the use of opioids. Until clinicians stop prescribing opioids far in excess of clinical need, this crisis will continue unabated.

MANAGING PAIN IN CHILDREN

The care of children with debilitating pain for whom other measures do not bring comfort deserves particular consideration. Recent labeling changes for oxycodone (OxyContin) that provided evidence-based dosing information for pediatric use created substantial controversy. Children who are prescribed oxycodone or other opioids have severe conditions that include cancer, multisys-

tem trauma, and serious chronic diseases such as sickle cell anemia or have undergone multiple surgical procedures. We must care for our most vulnerable patients, but we must also do everything possible to avoid both the inappropriate prescribing of powerful opioid medications and the misuse of these prescriptions.

When Congress enacted the Pediatric Research Equity Act, it enabled the FDA to require industry to conduct studies to determine the appropriate dosing of medications in children; the Best Pharmaceuticals for Children Act provided incentives for performing these studies for products that were already approved.[12] For children whose circumstances require treatment with opioids, we will consider how best to ensure that doctors get the information they need to prescribe such medications safely and effectively, while protecting minors who lack mature decision-making capabilities.

As physicians and regulators — and as parents — we know that we must treat pain in a suffering child. But in some cases, children with serious conditions are being treated with opioids in the absence of adequate knowledge about correct indications and dosing. We must all work together to ensure that all appropriate therapeutic options for pain are available to children, but it is equally important that when opioids are used, they are prescribed and handled in an impeccably judicious manner, guided by the best and most current scientific evidence. To this end, we are convening the Pediatric Advisory Committee on two upcoming occasions in order to specifically address issues related to the use of opioid medications in children, including the development of high-quality evidence to guide treatment, pediatric labeling for opioids, and improving practice to reduce addiction, misuse, and diversion.

The committee will consider appropriate approaches for ensuring that clinicians have ready access to reliable dosing information and will recommend methods for ensuring that clinicians scrupulously follow the regulations and best practices governing the use of such medications.

DEVELOPING A BETTER EVIDENCE BASE FOR CHRONIC PAIN TREATMENT

The FDA does its best work when high-quality scientific evidence is available to assess the risks and benefits of intended uses of medical products. Unfortunately, the field of chronic pain treatment is strikingly deficient in such evidence. A key lesson learned during the development of the CDC guideline is that there is very little research on the long-term benefits of opioids for treating chronic pain. There is, however, growing evidence of harms associated with such use, and of the benefits of other nonopioid treatment alternatives. As with all clinical guidelines, continued research is needed to inform clinical practice. But given the severity of the crisis, the draft CDC guideline provides a highly reasonable set of recommendations for primary care providers to use in their clinical practices, allowing physicians and patients together to determine treatment plans on the basis of the best current understanding of risks and benefits.

Recognition of this problem led the FDA, several years ago, to require industry to perform a series of studies on questions that are critical for ensuring safe prescribing.[4] For example, until recently it was believed that opioids' pain-relieving properties would not be time-dependent, but new studies have raised the question of whether opioids continue to be effective or may even increase pain in some patients after several months of use. To explore this question, 1 of the 11 postmarketing studies the FDA is requiring industry to fund is a clinical trial in which participants are randomly assigned to continue opioid therapy or to be weaned from it on a schedule over the course of 1 year of follow-up.

As policies are implemented and new evidence is generated, we will continuously assess findings and ensure that the agency's proposed strategies are evaluated in the context of new data. By implementing a coordinated effort among public and private partners, we will be able to adapt our strategies as the evidence base improves. We are committed to this renewed effort and believe that by working together we can solve the opioid crisis, while gaining ground in the national effort to prevent and control short-term and chronic pain.

Nationally, the annual number of deaths from opioid overdoses now exceeds the number of deaths caused by motor vehicle accidents.[13] Regardless of whether we view these issues from the perspective of patients, physicians, or regulators, the status quo is clearly not acceptable. As the public health agency responsible for over-

sight of pharmaceutical safety and effectiveness, we recognize that this crisis demands solutions. We are committed to action, and we urge others to join us.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Food and Drug Administration, Silver Spring, MD.

This article was published on February 4, 2016, at NEJM.org.

1. Department of Health and Human Services. HHS takes strong steps to address opioid-drug related overdose, death and dependence. March 26, 2015 (http://www.hhs.gov/about/news/2015/03/26/hhs-takes-strong-steps-to-address-opioid-drug-related-overdose-death-and-dependence.html).
2. Centers for Disease Control and Prevention. Vital signs: opioid painkiller prescribing. July 2014 (http://www.cdc.gov/vitalsigns/opioid-prescribing).
3. Food and Drug Administration. Letter to application holders: ER/LA opioid analgesic class labeling changes and postmarketing requirements (http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf).
4. Food and Drug Administration. Risk evaluation and mitigation strategy (REMS) for extended-release and long-acting opioids (http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm).
5. Executive Office of the President of the United States. Epidemic: responding to America's prescription drug abuse crisis. 2011 (https://www.whitehouse.gov/sites/default/files/ondcp/policy-and-research/rx_abuse_plan.pdf).
6. Office of National Drug Control Policy. National Drug Control Strategy. 2014 (https://www.whitehouse.gov/sites/default/files/ondcp/policy-and-research/ndcs_2014.pdf).
7. Food and Drug Administration. Guidance for industry: abuse-deterrent opioids — evaluation and labeling. April 2015 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf).
8. Food and Drug Administration. FDA approves new hand-held auto-injector to reverse opioid overdose. April 3, 2014 (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm391465.htm).
9. Food and Drug Administration. FDA moves quickly to approve easy-to-use nasal spray to treat opioid overdose. November 18, 2015 (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm473505.htm).
10. Federal Register Notice. Proposed 2016 guideline for prescribing opioids for chronic pain (https://www.federalregister.gov/articles/2015/12/14/2015-31375/proposed-2016-guideline-for-prescribing-opioids-for-chronic-pain).
11. Office of the Surgeon General. National prevention strategy — America's plan for better health and wellness. 2011 (http://www.surgeongeneral.gov/priorities/prevention/strategy/report.pdf).
12. Eunice Kennedy Shriver National Institute of Child Health and Human Development. About the Best Pharmaceuticals for Children Act (http://bpca.nichd.nih.gov/about/Pages/Index.aspx).
13. Centers for Disease Control and Prevention. Web-based Injury Statistics Query and Reporting System (WISQARS). 2014 (http://www.cdc.gov/injury/wisqars/fatal.html).

DOI: 10.1056/NEJMsr1601307