JOINT MEETING OF THE ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

Marriott Inn and Conference Center
University of Maryland University College
3501 University Boulevard East
Adelphi, MD

July 22 and 23, 2010

Risk Evaluation and Mitigation Strategies (REMS) for Extended-Release and Long-Acting Opioid Analgesics

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought a proposed REMS for long-acting and extended-release opioids intended to reduce misuse and abuse, overdose and death to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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July 22 and 23, 2010

Background Package:
Risk Evaluation and Mitigation Strategies (REMS) for Extended-Release and Long-Acting Opioid Analgesics

Table of Contents

D. Summary of National Survey on Drug Use and Health (NSDUH)

E. Summary of Drug Abuse Warning Network (DAWN)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIA AND ANALGESIA PRODUCTS

MEMORANDUM

DATE: June 22, 2010

FROM: Bob A. Rappaport, MD
Director
Division of Anesthesia and Analgesia Products
Office of Drug Evaluation II, CDER, FDA

TO: Chair, Members and Invited Guests
Anesthetic and Life Support Drugs Advisory Committee (ALSDAC)
Drug Safety and Risk Management Advisory Committee (DSaRM)

RE: Overview of the July 22 and 23, 2010, ALSDAC/DSaRM Meeting to Discuss FDA's Proposed REMS for Long-Acting and Extended-Release Opioid Drug Products

At this joint meeting of the ALSDAC and DSaRM, we will be discussing FDA's current draft REMS for long-acting and extended-release opioid drug products. In February 2009, FDA notified the sponsors of long-acting and extended-release opioids that their products would require a REMS to ensure that the benefits of those products continued to outweigh their risks. A Federal Register notice was then issued requesting comments on the components that could potentially be included in a REMS for these products under the authorities granted by the Food and Drug Administration Amendments Act of 2007. The Agency received well over 2,000 submissions to the docket established to receive these comments. In addition, we held a series of stakeholders' meetings in early 2009 to allow for additional comment on the proposal. Over the past year, over 70 FDA employees have been involved in the process of reviewing, summarizing and analyzing the numerous submissions to the docket and the thousands of pages of transcripts from the stakeholders' meetings. After extensive internal discussion, and a two-day retreat that included our Opioid REMS Steering Committee members and the members of the seven Working Groups who reviewed the docket submissions and transcript comments, we have developed the current REMS proposal.

This current REMS proposal has been incorporated into the document entitled, "Proposed Risk Evaluation and Mitigation Strategy (REMS) for Long-Acting and Extended-Release Opioids" that follows this memo and that is intended to serve as a summary for your review prior to the actual advisory committee meeting. This summary document refers to additional documents that we have included in this package and that we hope you will find helpful in preparing for the meeting. The following documents have been included in this package:

1. Introductory Memorandum

2. Proposed Risk Evaluation and Mitigation Strategy (REMS) for Long-Acting and Extended-Release Opioids

3. Appendices
    a. Summary of Comments from the Docket
    b. Working Group Reports
        i. Scope
        ii. Prescriber Education
        iii. Pharmacy Systems
        iv. Access to Opioids
        v. Patient Education
        vi. Pharmacist Education
        vii. Metrics
    c. Summary of Drug Usage Data
    d. Summary of National Survey on Drug Use and Health (NSDUH)
    e. Summary of Drug Abuse Warning Network (DAWN)

The misuse and abuse of the long-acting and extended-release opioid drug products have resulted in a widespread and serious public health crisis of addiction, overdose and death. The FDA can intervene in some aspects of this problem, but thoroughly addressing the problem will require a much broader set of interventions coming from the numerous stakeholders affected by this crisis. It is critical that we find ways to intervene that will limit the increasing problems of addiction, overdose and death associated with the long-acting and extended-release opioids, while maintaining the necessary balance to assure continued access to these important analgesic drug products for people with chronic pain. We are hopeful that the REMS will prove to be a useful tool in this effort, and your discussion and feedback regarding its components will be invaluable to us as we finalize this plan. On behalf of all of the many FDA experts who have worked on this proposed REMS, I would like to thank you in advance for agreeing to participate in what will surely be an extremely important meeting.

June 18, 2010

Proposed Risk Evaluation and Mitigation Strategy (REMS) for Long-Acting and Extended-Release Opioids

FDA has determined that a REMS is necessary to address the serious adverse outcomes of overdose, addiction, and death that result from long-standing problems of inappropriate prescribing, misuse, and abuse of long-acting and extended-release (LA/ER) opioid drug products. FDA is presenting this proposal at the July 22 and 23, 2010, joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee and to the public. The goal is to gather additional feedback and comments on FDA's proposal to require a REMS for this class of long-acting and extended-release opioid drug products. Once we have fully analyzed the advice from the Committees and from public comments, we will issue a REMS request letter to the sponsors that describes the proposed REMS and provides a timetable for the submission of the REMS and its implementation. All sponsors of marketed and new members of the class of LA/ER opioids will be required to implement the REMS, once it is approved.[1]

I. BACKGROUND

Chronic pain constitutes a major public health problem in the United States. It is estimated that 25 to 33% of Americans suffer from chronic, non-cancer pain (e.g., arthritis, low back pain, fibromyalgia).[2] In 1995, the American Pain Society recommended that pain be treated as the fifth vital sign to ensure that it would become common practice for healthcare practitioners to ask about pain when conducting patient evaluations. In 1999, the Joint Commission on the Accreditation of Healthcare Organizations declared pain to be the fifth vital sign.[3] In late 2000, Congress passed into law a provision that declared the 10-year period that began January 1, 2001, as the Decade of Pain Control and Research.[4] During the past decade, the use of opioid analgesic drug products to treat non-cancer, chronic pain has increased exponentially in response to this new paradigm. Over the last 20 years, numerous new formulations of existing opioid drugs have been developed, in part as an effort to address the unmet medical needs of patients living with inadequately treated pain.

A. Long-Acting and Extended-Release Opioids Have Been Linked to a Public Health Crisis of Addiction, Overdose, and Death

During this same time period, however, there has been an increasing problem with the inappropriate prescribing, misuse, and abuse of prescription opioid drug products in the United States that has resulted in a significant public health crisis of addiction, overdose, and death. Many people directly affected by this crisis have been previously healthy and

[1] The affected products include long-acting and extended releases products formulated with the active ingredients fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone.
[2] Nelson, R. Lancet 362(9390); 1129, 2003.
[3] Joint Commission Perspectives, Sept/Oct 1999.
[4] H.R. 3244, Title VI, Sec. 1603

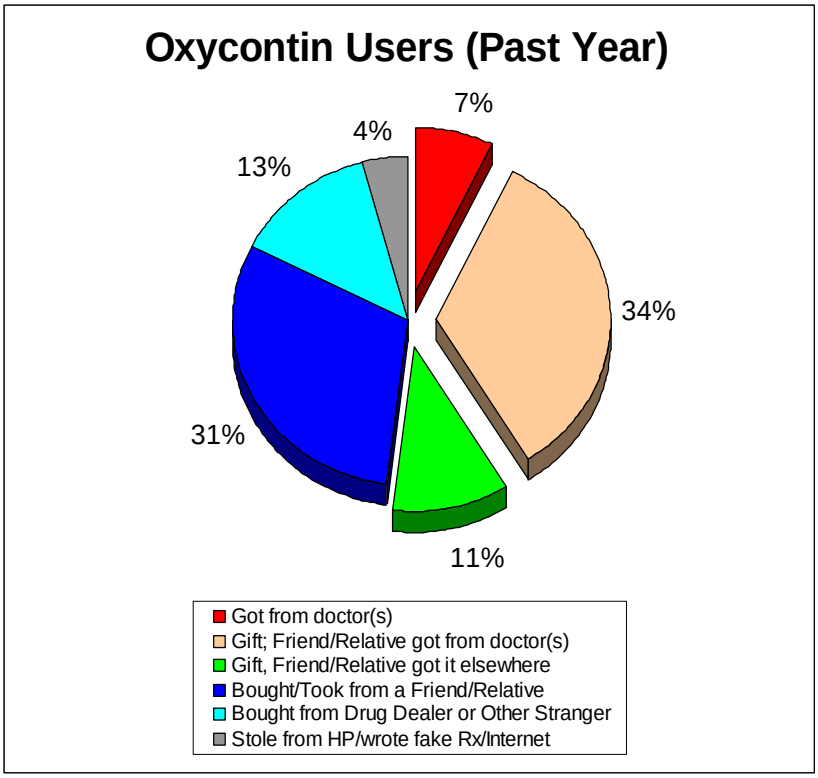
have had no history of substance abuse. Data on unintentional drug poisoning in the United States from the Centers for Disease Control and Prevention have shown that drug overdose death rates in the United States have never been higher and that they have increased approximately five-fold since 1990.[5] This increase in drug overdose death rates is largely due to prescription opioid drug abuse and misuse. For deaths attributed to drugs, the most common drug categories are cocaine, heroin, and opioid prescription drug products.[6] By 2006, data showed that prescription opioids were involved in more overdose deaths than heroin and cocaine combined.[7]

Initial reports of an increasing problem with prescription opioid abuse centered on OxyContin. Following approval in 1995, the annual number of prescriptions dispensed for OxyContin increased more than sevenfold from approximately 821,000 prescriptions in 1997 to approximately 6.2 million prescriptions in 2002, and approximately 85% of the diagnoses associated with the use of OxyContin were for non-cancer pain during that time period.[8, 9]

It is important to ensure that opioids continue to be prescribed for patients for whom the use of an opioid analgesic is appropriate. However, it is also essential to ensure that the long-acting and extended-release opioids are prescribed carefully. A large proportion of the prescription opioid analgesics that are misused and abused are reportedly obtained by friends and relatives from patients with prescriptions. As shown in Figure 1 below, SAMHSA's 2008 National Survey on Drug Use and Health (NSDUH) indicated that just over 40% of the OxyContin used non-medically can be traced to individuals who obtained prescriptions or to family or friends of such individuals.[10] These data suggest that education focused on the physican and the interactions they have with their patients prior to and during the use of these products can have a positive effect to reduce their inappropriate use. The remaining non-medical use of OxyContin was attributed to illegal activities or sources other than a legitimate prescriptions.

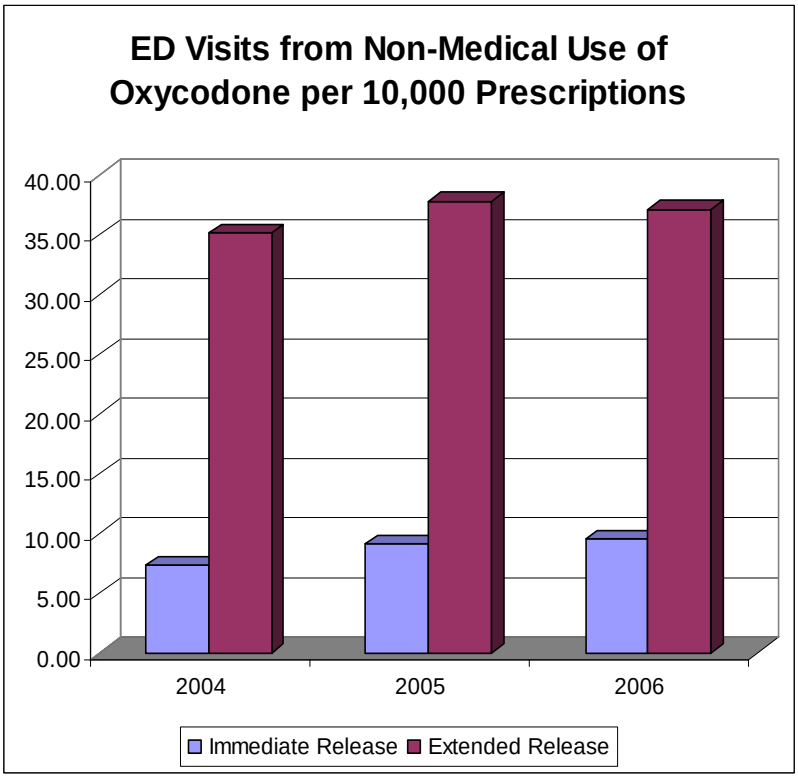
[5] CDC's Issue Brief (3/18/10).
[6] CDC's Issue Brief (3/18/10).
[7] CDC's Issue Brief (3/18/10).
[8] SDI, Vector One®: ®: National, Years 1995 – 2009, Extracted 5/10.
[9] SDI, Physician Drug and Diagnosis Audit, Years 1997 – 2002, Extracted 5/10.
[10] National Survey on Drug Use and Health, 2008, SAMHSA

Figure 1: Sources of OxyContin for recent non-medical use among OxyContin users, NSDUH Survey 2008



Long-acting and extended-release opioid products present unique risks to patients due to their formulations and pharmacokinetic properties. In the case of oxycodone, recent data indicate a greater problem of serious adverse outcomes linked to the misuse of OxyContin — the extended-release form of oxycodone — when compared to immediate-release oxycodone products. An analysis of emergency department (ED) data from the Drug Abuse Warning Network and SDI/VONA (see Figure 2) shows that the rate of ED visits per 10,000 prescriptions was about five times higher for OxyContin compared to oxycodone over a recent three-year period.

Figure 2: Emergency department visits from non-medical use of immediate- and extended-release oxycodone 2004-2006, per 10,000 prescriptions



This higher rate of serious adverse outcomes among long-acting and extended-release opioids results in significant financial costs to society in addition to the costs to individuals and families. About 60% of the hospital costs related to opioid overdoses are paid for with public funds.[11] There were nearly 50,000 ED visits related to opioids in 2006, and more than 10,000 of those visits were by uninsured patients.[12] In 2007, opioid overdoses led to nearly 30,000 hospital visits and the cost of these visits was over $700 million, the majority of which was paid for by Medicare or Medicaid.[13] Additional details about the data that describe the use and misuse of long-acting and extended-release opioids are provided in Attachment 1.

FDA recognizes that a variety of behaviors are likely contributing to the misuse and abuse of long-acting and extended-release opioids. Prescribers may not be prescribing the right doses or quantities to patients; they may not be selecting appropriate patients for these drugs; and they may not be engaging patients in the right counseling, monitoring, and follow-up necessary for these drugs. Once patients receive their medications, they may not be using the drugs appropriately, or they may not be storing and disposing of

[11] AHRQ, Healthcare Utilization Project (HCUP)
[12] AHRQ, Healthcare Utilization Project (HCUP)
[13] AHRQ, Healthcare Utilization Project (HCUP)

them properly to prevent exposure among other household members. Finally, FDA recognizes that diversion and other illegal activities also contribute to opioid misuse and abuse.
FDA can influence some of these behaviors under its authority to require sponsors to implement a REMS, while others may be influenced more directly through actions outside of FDA's regulatory purview.

B. FDA and Others Have Taken Steps To Address the Problem, But Abuse and Misuse Continue to Increase

FDA, drug sponsors, and others have taken a number of steps during the past decade to prevent inappropriate prescribing, misuse, and abuse of the long-acting and extended-release opioid products. These steps have included adding warnings to product labeling, developing risk management plans, creating inter-agency collaborations, and communicating directly with both prescribers and patients. Despite these efforts, unintentional overdose, addiction, and death resulting from these products continue to increase. Summaries of the efforts of other federal agencies to reduce prescription drug abuse are provided in Attachment 2.

C. In 2007, Congress Gave FDA New Authority to Require REMS to Better Manage Drug Safety Problems

Title IX, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85) gave FDA the authority to require a REMS when FDA determines a REMS is necessary to ensure the benefits of a drug outweigh the risks (21 U.S.C. 505-1). For products initially marketed without a REMS, FDA may determine, based on new safety information, that a REMS is necessary to ensure that the benefits of the drug outweigh the risks.

A REMS describes the steps a sponsor of a marketed drug product must take to manage the risks of the product. Because a REMS must be implemented by the sponsor and because FDA does not directly regulate other participants in the healthcare community such as prescribers and pharmacists, a REMS can only include requirements that sponsors can implement.

FDA may require a REMS to include some or all of the following: a Medication Guide, a communication plan, and elements to assure safe use. All REMS must include a timetable for assessment of the REMS.

Under elements to assure safe use, the REMS may require:

- Healthcare practitioners who prescribe the drug to have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug to be specially certified

- The drug to be dispensed only in certain healthcare settings
- The drug to be dispensed to patients with evidence of safe-use conditions
- Each patient to be subject to monitoring
- Patients to be enrolled in a registry

Before requiring a REMS, FDA must consider the following factors:

- The estimated size of the population likely to use the drug
- The seriousness of the disease or condition that is to be treated with the drug
- The expected benefit of the drug with respect to the disease or condition
- The expected or actual duration of treatment with the drug
- The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
- Whether the drug is a new molecular entity

In addition, for REMS with elements to assure safe use, the elements to assure safe use must:

- Be commensurate with the specific serious risk listed in the labeling of the drug
- Not be unduly burdensome on patient access to the drug, considering the risk and in particular, patients with serious or life-threatening diseases or conditions and patients who have difficulty accessing healthcare (such as patients in rural or medically underserved areas)
- To the extent practicable, conform with elements to assure safe use for other drugs with similar serious risks
- Be designed to be compatible with established distribution, procurement, and dispensing systems for drug

D. FDA Has Said It Will Require a REMS for Long-Acting and Extended Release Opioids Using Its New Authority

In February 2009, FDA notified the sponsors of long-acting and extended-release opioids that their products would require a REMS to ensure that the benefits of those products continued to outweigh their risks. Although each individual sponsor will be required to submit a REMS, FDA asked the sponsors to work together to develop a class-wide REMS for the class of long-acting and extended-release opioids.

After notifying industry that it would require a REMS, FDA met with sponsors and other stakeholders over the next several months to collect comments and opinions on how a REMS could be designed to minimize the risks of these drugs while also not overly burdening the healthcare system or reducing legitimate and appropriate access to these medications for patients. This public comment process included a two-day public meeting in May 2009 and a comment period in FDA's public docket.

After these meetings, an FDA Steering Committee created seven working groups, comprising staff from the Center for Drug Evaluation and Research and from the Office

of Special Health Issues to review the data and public comments.[14] The seven working groups were assigned the following topics:

- Scope of the REMS
- Prescriber education
- Pharmacist education
- Patient education
- Pharmacy systems
- Access to pain medications
- Metrics

The working groups gathered additional information from external stakeholders, analyzed the information, and developed recommendations for the design of the REMS. Summaries of the working group efforts are provided in Attachment 3, and a summary of comments to the docket is provided in Attachment 4.

During a two-day retreat in January of 2010, the Steering Committee and the working group members synthesized the data and recommendations of the working groups and developed a proposal for an initial REMS program for all long-acting and extended-release opioids.

II. Proposal

A. FDA is Proposing a REMS Be Developed for the Class of Long-Acting and Extended Release Opioids

After considering the comments to the docket and other information available to it, FDA is proposing that a REMS be developed for the class of long-acting and extended-release opioids. These products present unique risks to patients related to their formulations and their pharmacokinetics, and they have been implicated in a significant and growing problem of serious outcomes for patients and others due to misuse and abuse.

FDA received numerous comments indicating that a REMS limited to only long-acting and extended-release opioids would simply shift prescribing behavior to immediate-release opioid products. These commenters argued that the REMS should be required for immediate-release products as well to avoid this potential problem. Although immediate-release Schedule II[15] opioids also present serious risks to patients when they are not used

[14] In addition, an eighth working group was created to handle external communications about the REMS. That working group was not involved in the review of comments and did not create a report.

[15] Under the Controlled Substances Act, certain drugs are assigned to one of five schedules (Schedule I-V). This placement is based on the substance's medical use, potential for abuse, and safety or dependence liability. Drugs in Schedule I and Schedule II have the highest abuse potential, whereas drugs in Schedule V have the lowest abuse potential. Schedule I substances do not have approved medical use. Drugs in Schedule II, III, IV and V have approved medical use. Each schedule under the Controlled Substances Act includes a set of controls (e.g., limitations on dispensing and prescribing, record-keeping and reporting

properly, broadening the REMS to include all of these agents is difficult to justify based on the difference in magnitude of adverse outcomes associated with the products (as discussed earlier, see Figure 2). In addition, including these products in the REMS would affect an even greater number of patients, creating a much greater burden on the healthcare system. The broader problem of misuse and abuse of all opioid analgesics is more appropriately addressed through other actions with appropriate stakeholders.

B. FDA Is Proposing to Require the Sponsors of Long-Acting and Extended Release Opioids to Develop a REMS

The REMS FDA is proposing would include the following:

Goal

The proposed goal for the REMS would be:

- Reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of long-acting and extended-release opioids while maintaining patient access to these medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

This will be accomplished by educating prescribers in appropriate patient selection, dosing, and patient monitoring and by educating patients in the safe use, storage, and disposal of opioids.

Elements of the Proposed REMS

In addition to the Goals, the REMS would include a Medication Guide, Elements to Assure Safe Use, and a Timetable for Assessment of the REMS.

Medication Guides

The Medication Guides would include "class" language regarding the safe use of all opioid drug products and may also include product specific information.

Elements to Assure Safe Use

The proposed elements to assure safe use include prescriber and patient education.

Prescriber Education

Stakeholder comments and the available data suggest that prescriber and patient education will be the key components of a successful risk management program.

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requirements) that are most restrictive for the Schedule I and II substances and are relatively less restrictive for the Schedule III to V drugs, respectively.

Therefore, FDA is proposing that sponsors be required to develop an educational program that would educate prescribers about appropriate patient selection, dosing, and patient monitoring. Prescribers would also be trained to counsel patients on the safe use, storage, and disposal of opioids.

FDA would encourage sponsors to develop the prescriber training in partnership with an appropriate, independent third party, and FDA would approve the training content. Sponsors would also be encouraged to explore appropriate incentives (e.g., CME credit) to encourage prescribers to undertake the training. Although prescribers would not be required to demonstrate evidence of training to prescribe these products, sponsors would be required to demonstrate that prescribers have been trained and that knowledge of appropriate use has improved via surveys of the prescribing community.

Patient Education

Sponsors would also be required to provide patient education sheets for prescribers to use in their interactions with patients, and sponsors would be required to encourage the prescribers to use these sheets when counseling patients. The content of these patient education sheets would be FDA approved.

FDA considered proposing that the REMS require individual prescribers or patients to enroll in a REMS program and real time verification of prescriber training at the pharmacy level, but decided that the proposed REMS should not include these requirements at this time. FDA heard from commenters that a requirement for individual prescriber registration and real-time verification of training at the pharmacy before filling an opioid prescription could cause some prescribers and pharmacies to "opt out" of the program with potential adverse consequences to access to pain medications. More than 1 million prescribers are registered with the Drug Enforcement Administration to prescribe opioids. Approximately 700,000 of these prescribers prescribe long-acting and extended-release opioids. Approximately 66,000 pharmacies are registered with DEA.[16] In the long term, linking the education to the existing DEA registration system would more efficiently ensure appropriate education of physicians, but would require legislation.

FDA also considered whether the proposed REMS should include enrollment of patients in a registration system. Numerous comments at the public meeting and in the docket stated that a REMS that employs a patient registration system would be overly burdensome and create a stigma for pain patients that could adversely affect patient access to necessary medications. Nearly 4 million patients are prescribed long-acting or extended-release opioids annually,[17] and enrolling this

[16] https://www.deadiversion.usdoj.gov, Population Summary, Registrant Population by Business Activity

[17] SDI, Vector One®: Total Patient Tracker, Year 2008, Extracted 12/09

many patients in a patient registration system would be an enormous undertaking with unpredictable effects on patient access.

For these reasons, FDA is proposing a more limited REMS at this time, but will carefully monitor the effects of the program and may consider further steps if the REMS does not prove effective in curbing serious adverse outcomes resulting from inappropriate prescribing, abuse and misuse.

Timetable for Assessment and Metrics

All REMS are required to contain a timetable for assessment, and for a REMS of this size to address a problem of this complexity, assessing the effectiveness of the program as well as its impact on appropriate access to pain medications is critical. Understanding whether the proposed REMS, once implemented, has been successful in reducing serious adverse outcomes from the misuse and abuse of long-acting and extended-release opioids is important and will determine whether additional efforts or future REMS modifications are necessary. However, measuring the outcomes associated with the proposed REMS will be a challenge.

The recommendations for assessing the proposed REMS include using multiple metrics and data sources that focus on outcomes related to both extended-release products as well as all opioids. The existing databases are insufficient to adequately measure the impact of the REMS, and in addition to working to improve these databases FDA is exploring new data sources and methodologies for making better use of available data. To do this, FDA has initiated collaborations with a number of its Federal partners to develop metrics to monitor changes in prescribing behavior, non-medical use of opioids, and certain adverse outcomes (overdose, addiction, and death). In addition to these FDA initiatives, sponsors will be expected to assess the REMS, and FDA and sponsors will need to coordinate their efforts to provide the most complete evaluation. Sponsors will also be required to provide the support and resources necessary to improve the currently available data sources and to create novel and more efficient and effective metrics for measuring the impact of the REMS on abuse and misuse of opioid analgesics, as well as the impact on patient access to these products.

Table 1: Elements of the Proposed REMS

REMS ELEMENT	CONTENT
Goals	• Reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of long-acting and extended-release opioids while maintaining patient access to these medications. Adverse outcomes of concern include addiction, unintentional overdose, and death. This will be accomplished by educating prescribers in appropriate patient selection, dosing, and patient monitoring and by educating patients in the safe use, storage, and disposal of opioids.
Medication Guides	• Language regarding the safe use of all opioid drug

	products • Product specific information.
Elements to Assure Safe Use	
Prescriber Education	• Information about appropriate patient selection, dosing, and patient monitoring. • Training for patient counseling on the safe use, storage, and disposal of opioids. • Demonstration by sponsor of prescriber training and that knowledge of appropriate use has improved via surveys of the prescribing community. • No formal prescriber enrollment or real time verification of training at pharmacy.
Patient education	• Counseling by physicians based Patient Education Sheets. • No patient registry required.
Timetable for Assessment	• All REMS are required to contain a timetable for assessment. • Assessments to include – the effectiveness of the program in reducing serious adverse outcomes from the misuse and abuse – the impact on appropriate access to pain medications
Metrics	• Metrics will include process measures, measures of patient and prescriber knowledge, certain behaviors (such as nonmedical use of prescription opioids), adverse events (unintentional overdose, , addiction, and deaths related to prescription opioids), and access to care..

C. FDA Will Undertake Other Actions to Address Abuse and Misuse of Opioids in Addition to Requiring a REMS

In addition to requiring sponsors to implement a REMS for the class of long-acting and extended-release opioids, FDA intends to partner with other Federal agencies and appropriate stakeholders in the private sector under the Agency's Safe Use Initiative to implement programs to more broadly address the problem of misuse and abuse of prescription opioids, including appropriate storage and disposal and avoidance of improper sharing for therapeutic use, misuse, or abuse. It is essential to work with Federal and non-Federal partners outside of the REMS to improve the safe storage and disposal of Schedule II opioids as much of the abuse and misuse of these products results from easy access to them in patients' homes. Such partnerships have been encouraged by and are consistent with the President's *2010 National Drug Control Strategy*, a blueprint for reducing illicit drug use and its harmful consequences in America (see http://www.ondcp.gov/publications/policy/ndcs10/ndcs2010.pdf).

As one aspect of the Safe Use Initiative, the use of patient/provider agreements that are signed at the time an opioid is prescribed have been suggested to educate patients about the safe use, storage, and disposal of opioids. These agreements are used by some prescribers to define the responsibilities of the patient regarding use of the opioid

analgesic and the patient's consent to appropriate monitoring of the patients medication use and behavior by the physician. Although FDA is not proposing to require pain treatment agreements or patient/provider agreements under the REMS, as suggested by some of the comments in the docket and at the public meeting, FDA plans to partner with the medical community under the Safe Use Initiative to make existing models for these agreements more broadly available for voluntary use by prescribers.

III. Continued Public Input on the Opioid REMS

FDA welcomes comments from the Advisory Committees and the public on this proposal. FDA will present this proposal at the July 22 and 23, 2010, joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee and looks forward to receiving advice from the Committees, as well as comments from members of the public, on whether these proposed elements of a REMS are appropriate and on appropriate metrics to evaluate the effectiveness of the REMS.

Opioid REMS Comment Overview

June 2010

TABLE OF CONTENTS

EXECUTIVE SUMMARY

In early 2009, FDA sent letters to manufacturers of certain opioid drug products, indicating that these drugs will be required to have a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drugs continue to outweigh the risks. FDA explained that the REMS would include elements to assure safe use to make certain that prescribers, dispensers, and patients are aware of and understand the risks and appropriate use of these products. FDA also stated that, with limited exceptions, the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires generic and innovator products to use a single shared system to implement the elements to assure safe use. The affected opioid drugs include long-acting and extended-release brand name and generic products and are formulated with the active ingredients fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.

FDA held a series of meetings[1] with relevant stakeholders to obtain public input on how best to design a REMS for this class of drugs, and on April 20, 2009, FDA opened a public docket to receive public comments on relevant issues.[2] This document provides an overview of the written comments submitted to the docket as of July 31, 2009,[3] as well as of the comments provided at the May 2009 stakeholder meetings and public meeting.[4] In total, over 2,170 written

[1] May 4 and 5, 2009; May 27 and 28, 2009; December 4, 2009.

[2] The meeting minutes of the May 4 and 5 stakeholder meetings and transcripts of the May 27 and 28 and December 4 meetings are in the docket and on FDA's Web site at http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm.

[3] In its April 20, 2009 notice, FDA requested that comments be submitted to the docket by June 30, 2009. To ensure that all comments submitted in response to this request are covered by this document, it includes comments submitted up to a month after the deadline (i.e., July 31, 2009). As of June 6, 2010, an additional fifty-four comments have been submitted to the docket. FDA has considered these comments, but they are not included in this overview.

[4] Please note that this overview only covers comments submitted regarding the opioid REMS. While the Agency will appropriately consider comments that discussed topics beyond the scope of the REMS (e.g., comments

comments were submitted to the docket within this time period;[5] more than 1,450 pages of transcripts from the May 2009 stakeholder meetings and public meeting also were reviewed. Although every comment has been read and considered, it was impossible to summarize all of them here. Instead, this document categorizes the comments, highlights common themes and areas of disagreement, and provides illustrative examples from diverse stakeholders.[6]

Following this Executive Summary, a more detailed discussion is provided of the comments submitted in the following categories:

- Rationale Behind the REMS
- Scope of the REMS
- Access to Pain Medication
- Prescriber Education and Certification
- Pharmacist Education and Certification
- Patient Education
- Public Education
- Methods to Curb Diversion
- Pharmacy Systems
- REMS Evaluation and Metrics

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regarding products other than opioids, comments regarding the development of REMS generally), those comments are not discussed in this document.

[5] Please note that the total number of submissions to the docket is higher than this number, but in the interest of accuracy, exact duplicates (e.g., the same comment submitted by the same submitter multiple times) have been counted only once. Please also note that this number includes both comments available to the public via regulations.gov and those that are not publicly-available out of concern for the submitter's privacy. Both public and non-public comments are referenced in this document, but in a manner that continues to protect the identity of the submitters of non-public comments.

[6] Please note that the overview is organized into consecutively-numbered paragraphs with each paragraph discussing comments submitted about a particular issue. This document merely summarizes the contents of the comments; FDA cannot vouch for the accuracy of the data and information submitted by the stakeholders.

- A Single System for Generic and Branded Products
- REMS Development and Implementation

One of the most frequently recurring comments from diverse stakeholders emphasized the importance of continuing the dialogue about the opioid class REMS. These stakeholders requested additional opportunities to offer input and assistance in developing and implementing the REMS, noting that stakeholder support will be critical to REMS success.

Many stakeholders expressed concern – and in many cases opposed the REMS – due to its potential effect on legitimate patient access to pain medication and, specifically, its potential to reduce access for vulnerable populations. Comments asserted that the REMS could exacerbate a widespread problem of undertreated pain and described a pain management environment where prescribers are already fearful of prescribing REMS drugs. In addition, comments asserted patients are stigmatized and burdened by restrictions on their medications. These comments highlight the importance of REMS drugs both in enabling chronic pain patients to function and also in relieving severe pain and breathlessness in end-of-life patients. Many comments argued that these legitimate patients should not have to suffer to protect individuals who have chosen to abuse REMS drugs. Furthermore, many comments suggested that if the REMS only applies to long-acting opioids, there will be shifts in prescribing to immediate-release products or other pain relievers even if they are less effective for the patient.[7] Finally, a contingent of comments asserted that there is a lack of reliable data to support a linkage between legitimate prescribing and opioid abuse and misuse, which means that legitimate patients could suffer reduced access

[7] Many comments cited the potential for shifts in prescribing – and abuse – in advocating for expanding the scope of the REMS to include both long-acting and immediate-release opioids. Opponents, however, asserted that such an expansion would exponentially increase the complexity of the REMS.

without a reduction in misuse and abuse. Certain comments also questioned whether FDA is even the appropriate agency to tackle these issues.

Other comments, however, called on FDA to take quick and decisive action to curb growing problems of opioid dependence and addiction and adverse events in patient and non-patient populations. These comments recommended that significant restrictions be immediately imposed on REMS drugs, including limitations on their indications for use, a temporary moratorium on prescribing while the REMS is being developed (with a compassionate use exemption), and a ban on OxyContin, which certain comments suggested is particularly problematic. These comments refuted the arguments that there is a problem of undertreated pain. They asserted that REMS drugs are widely over-prescribed. Furthermore, they asserted that the only advantage of REMS drugs is dosing convenience and that this benefit does not justify their added risks.

Generally, comments suggested that if a REMS is implemented, less restrictive elements should be implemented first to determine if they are effective in mitigating risk while preserving access. To that end, many comments focused on education-based elements. Although some comments suggested that education programs for prescribers and pharmacists are unnecessary, could reduce the number of health care professionals willing to provide pain management, and shift prescribing to non-REMS drugs, other comments highlighted the benefits of such programs and suggested that unintended consequences could be minimized by designing a program that is minimally burdensome, encourages participation, facilitates learning, and focuses on practical application of knowledge. Furthermore, if education is mandated, comments from a wide variety of stakeholders suggested linking REMS certification to Drug Enforcement Administration (DEA) registration to maximize participation, minimize cost, and streamline the prescription

process. Several comments also suggested that FDA communications and/or labeling changes could assist health care professionals in mitigating risk and using REMS drugs more effectively in their practice.

Comments from a wide variety of stakeholders highlighted potential benefits to educating patients and their caregivers regarding safe use, storage, and disposal of opioid medications, in addition to broader education on pain management and the benefits and risks of opioid treatment. In addition to discussing improvements to traditional patient education materials (e.g., Medication Guides), diverse stakeholders expressed support for increasing the use of prescriber-patient agreements (PPAs) – although certain comments expressed concern that PPAs can stigmatize the patient and be inappropriately used by prescribers as a substitute for a meaningful conversation with the patient. In addition to targeting education to the patient population, many comments suggested educating the public – through a variety of media – about how to safely use, store, and dispose of opioid medications and issues related to overdose, abuse, and misuse.

With regard to more restrictive potential elements under the REMS, widespread support did not exist for regulating the distribution of opioid medications – although there were comments supporting other methods of reducing diversion (e.g., take-back or buy-back programs, increasing sanctions for diversion, increasing patient monitoring). Similarly, many comments opposed implementing a patient registry, citing the potential for stigma, privacy concerns, and REMS avoidance. However, there was significant support for expanding and enhancing state prescription drug monitoring programs (PMPs), with comments highlighting the potential benefits of implementing fully the National All-Schedules Prescription Electronic Reporting Act (NASPER).

With regard to designing a system for implementing the REMS, stakeholders offered a wide variety of proposals. Common recommendations were that the system be transparent, real-time, technologically advanced, interoperable with existing pharmacy systems, seamlessly integrated with the current workflow of health care professionals, and proactively designed to address failures and facilitate REMS evaluation. With regard to this final characteristic, comments suggested that the REMS should be evaluated frequently using predetermined metrics and a predetermined definition of "success." In particular, comments highlighted that the REMS metrics and definition of success must consider not only the effectiveness of implemented elements in mitigating risk, but also their unintended consequences (e.g., reduction in legitimate patient access, shifts in prescribing to less desirable pain medications, burdens imposed on the health care system). To help avoid these unintended consequences, comments suggested implementing only proven or pre-tested elements, with many comments recommending a pilot program or phased-in implementation of the REMS. Both with regard to assessing elements pre- and post-implementation, comments noted that new and/or improved data sources could facilitate more rigorous evaluation.

In identifying potential hurdles to effective REMS implementation, comments highlighted that the opioid REMS will be the largest and most complex program of its kind. In particular, with regard to implementing a single system for generic and branded products, comments noted that if the cost of implementing the REMS is too great, it could reduce the incentive to manufacture generics. Furthermore, although comments – particularly from the pharmacy community – suggested that the number of different REMS should be minimized to avoid confusion and reduce the burden on the health care system, not all comments supported a single

classwide opioid REMS. Notably, manufacturers of methadone suggested it should have a separate REMS due to its unique characteristics.

I. INTRODUCTION

In early 2009, FDA sent letters to manufacturers of certain opioid drug products, indicating that these drugs will be required to have a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drugs continue to outweigh the risks. FDA explained that the REMS would include elements to assure safe use to make certain that prescribers, dispensers, and patients are aware of and understand the risks and appropriate use of these products. FDA also stated that, with limited exceptions, the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires generic and innovator products to use a single shared system to implement the elements to assure safe use. The affected opioid drugs include long-acting and extended-release brand name and generic products and are formulated with the active ingredients fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.

To obtain public input on how best to design a REMS for this class of drugs, FDA held a series of meetings with relevant stakeholders (May 4 and 5, 2009; May 27 and 28, 2009; December 4, 2009) and on April 20, 2009, opened a public docket to receive public comments on relevant issues. Meeting minutes of the May 4 and 5 stakeholder meetings and transcripts of the May 27 and 28 and December 4 meetings are in the docket and on FDA's Web site.[8]

[8] *See* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm.

To help facilitate ongoing discussions about the opioid REMS, this document provides an overview of the written comments submitted to the docket as of July 31, 2009,[9] as well as comments provided at the May 2009 stakeholder meetings and public meeting.[10] In total, over 2,170 written comments were submitted to the docket within this time period;[11] more than 1,450 pages of transcripts from the May 2009 stakeholder meetings and public meeting also were reviewed. Although every comment has been read and considered, it was impossible to summarize them all here. Instead, this document categorizes the comments, highlights common themes and areas of disagreement, and provides illustrative examples from diverse stakeholders.[12]

Specifically, this overview discusses comments submitted in the following categories:

- Rationale Behind the REMS
- Scope of the REMS
- Access to Pain Medication

[9] In its April 20, 2009 notice, FDA requested that comments be submitted to the docket by June 30, 2009. To ensure that all comments submitted in response to this request are covered by this document, it includes comments submitted up to a month after the deadline (i.e., July 31, 2009). As of June 6, 2010, an additional fifty-four comments have been submitted to the docket. FDA has considered these comments, but they are not included in this overview.

[10] Please note that this overview only covers comments submitted regarding the opioid REMS. While the Agency will appropriately consider comments that discussed topics beyond the scope of the REMS (e.g., comments regarding products other than opioids, comments regarding the development of REMS generally), those comments are not discussed in this document.

[11] Please note that the total number of submissions to the docket is higher than this number, but in the interest of accuracy, exact duplicates (e.g., the same comment submitted by the same submitter multiple times) have been counted only once. Please also note that this number includes both comments available to the public via regulations.gov and those that are not publicly-available out of concern for the submitter's privacy. Both public and non-public comments are referenced in this document, but in a manner that continues to protect the identity of the submitters of non-public comments.

[12] Please note that the overview is organized into consecutively-numbered paragraphs with each paragraph addressing comments submitted about a particular issue. This document merely summarizes the contents of the comments; FDA cannot vouch for the accuracy of the data and information submitted by the stakeholders.

- Prescriber Education and Certification
- Pharmacist Education and Certification
- Patient Education
- Public Education
- Methods to Curb Diversion
- Pharmacy Systems
- REMS Evaluation and Metrics
- A Single System for Generic and Branded Products
- REMS Development and Implementation

II. RATIONALE BEHIND THE REMS

In its April 20, 2009 notice, FDA discussed the risks associated with REMS drugs and the efforts that have been made to mitigate those risks while maintaining access. The Agency also explained why it was proposing a REMS as an additional measure. In its explanation, the Agency noted that data from the Centers for Disease Control (CDC) and the Substance Abuse and Mental Health Services Administration (SAMHSA) indicate that prescription drug misuse and abuse have increased over the past decade and in particular that much of the misuse has involved extended-release opioid analgesics and methadone. The Agency stated that to address this public health problem, it will require a REMS for certain opioid products.

In response, many comments discussed (A) whether FDA has justified the need for a REMS and (B) whether FDA is acting within its mandate and statutory authority in requiring a REMS.

A. Has FDA Justified the Need For A REMS?

i. FDA Has Justified the Need for a REMS

1. Many comments from diverse stakeholders shared FDA's concern regarding misuse, abuse, overdose, and inappropriate prescribing of REMS drugs. For example: (a) In the words of one comment, "FDA has recognized an urgent need to address the spiraling increase in adverse events caused by the misuse and abuse of prescription opioid analgesics." (b) Multiple comments from individuals highlighted that while REMS drugs can be highly effective analgesics, they also have significant risks and commended FDA in seeking to mitigate them. (c) A pain society stated it was saddened by the increase in opioid-associated deaths in the past decade and suggested that the problem was due to a variety of factors including: (i) increased availability of opioids for therapeutic use leading to increased availability for diversion; (ii) inadequate public understanding of the narrow therapeutic window for prescription opioids, leading to sharing or inadequate securing of these medications; (iii) inappropriate prescription practices (e.g., rapid dose adjustments, inappropriate patient selection); (iv) frequent mixing of other sedatives with opioids; and (v) possible unique mechanisms of chronic opioid action which may make prescribing chronic opioids more difficult (e.g., genotypic or phenotypic differences between mechanisms of tolerance to the analgesic effects of opioids and their respiratory depressant effects). (d) Advocates for opioid drug reform supported FDA's risk mitigation efforts and actually suggested that more stringent restrictions are warranted to ensure the REMS is effective. According to these comments, between 1998 and 2007, the increase in opioid prescribing was nearly forty times that of the country's population, and the rise in opioid abuse/addiction was seven times as great. They asserted that prescription opioids are now

the second most commonly abused drug and the most frequent cause of drug-related death in the country. Furthermore, they stated that the chemical structure of certain long-acting opioid drugs leads to the accompanying risks of addiction, hyperalgesia, overdose toxicity, and death; and the risk of addiction and death accompany the drug even when used as directed. (e) Similarly, a vendor stated that in most instances opioid abuse/misuse can be traced to a prescribed medication and suggested more than forty percent of narcotic analgesics are misused or abused. (f) Moreover, the industry working group noted that despite past efforts (e.g., education programs tailored to specific products), problems with REMS drugs are not decreasing. The industry working group highlighted a growing trend toward the misuse and abuse of prescription opioids leading to death, poisoning, teen suicide, and addiction.

2. Comments received from health care professionals cited the risks associated with REMS drugs. For example: (a) A physician noted that in her experience, she has seen more abuse/misuse than proper use of opioids, particularly during long term treatment. (b) Another prescriber stated that in the past four years, he has had to discharge over three-hundred and fifty patients for abuse, diversion and doctor shopping.

3. Personalizing the devastating effects of the problems discussed above, a number of bereaved families shared their stories. Advocates for opioid drug reform provided pictures of those who had been lost due to overdose, misuse and abuse. Many of these comments expressed anger at industry and the government. For example: (a) A bereaved father became an advocate for opioid drug reform after his eighteen-year-old daughter died after taking an OxyContin pill given to her by a family member. (b) Another bereaved father became an advocate for opioid drug reform when he started a website after his son’s death

and discovered how many other families were experiencing loss due to opioid misuse. (c) A bereaved mother lost her twenty-five year old son to a combination of opioids, which were prescribed to him despite a history of addiction. (d) A bereaved husband lost his wife, a pain patient, to an accidental overdose while taking opioids prescribed to her for back pain. (e) A bereaved mother lost her son to diverted methadone. She also shared stories of other young adults lost to methadone-related deaths.

4. Several of these comments noted that industry was continuing to market opioids for non-severe pain and prescriptions for opioids were increasing.

5. Moreover, these comments noted that to suggest that opioid abuse is strictly an issue of personal responsibility is inappropriate because of individual circumstances. For example, an advocate for opioid drug reform called for compassion and noted that is wrong to have a policy that because someone made a bad decision, they should simply be left to die. Similarly, one of the bereaved mothers mentioned above emphasized that her son did not seek to abuse medication; he was prescribed opioids and became addicted.

ii. There Are Insufficient Data To Justify A REMS At This Time

6. While not necessarily disputing the seriousness of the risks posed by opioids, many comments called upon FDA to better define the rationale for the REMS and to conduct additional research to identify the specific behaviors that the REMS is intended to mitigate. For example: (a) A few comments from health care professional organizations recommended that FDA more specifically define the risks it is seeking to mitigate, noting that it was unclear whether the Agency intends to prevent non-medicinal use of opioids, or address risks associated with legitimate use, or both. Similarly, a comment from a pain organization suggested FDA better define its goals for the REMS and what it will consider

to be a successful program. (b) A manufacturer suggested that FDA needs to more clearly communicate the intended scope and reach of any REMS, acknowledge the limitations of the REMS to reach beyond the patient population, and actively collaborate with other state and federal agencies to identify other root causes for the increase in opioid-related deaths to comprehensively address the issue. This comment noted that it is beyond the reach of industry to address abuse and misuse issues beyond the bounds of the prescriber-pharmacist-patient relationship.

7. Many comments suggested that FDA's rationale was undermined by the lack of reliable data to clearly define the public health problem related to opioid abuse. In particular, many noted that there is little data supporting a connection between opioid drug abuse and those prescribing, dispensing or receiving opioids for legitimate medical use. Many of these comments noted that better research is needed as National Institute on Drug Abuse (NIDA) and SAMHSA surveys have not yet provided a clear determination of the root causes of abuse. These comments suggested that to design an effective REMS, the risks it seeks to mitigate and their effects on the public health must be better understood. For example: (a) A policy group asserted that there is insufficient understanding of the public health issue of opioid abuse/misuse to develop a safe and effective REMS. This comment noted that there is no published evidence of how legitimate prescribing is linked to misuse/abuse. Although the comment acknowledged that there are data suggesting that people misusing opioids often obtain them from a family member or a friend, this comment suggested that the data do not connect that behavior to prescribing. Similarly, this comment noted that it is difficult to connect deaths from opioids to inappropriate prescribing. (b) A comment from academia concurred that data are lacking regarding the public health problem and stated that what

data are available lack specificity (e.g., it is unknown how many people have died from particular products; the data available from the National Center for Health Statistics (NCHS), poison control centers, and SAMSHA are incomplete, not product-specific, and do not indicate the circumstances of ingestion). (c) Similarly, while the industry working group committed to work with FDA to find solutions to the problems of misuse and abuse, it too noted a lack of reliable data. (d) A pain organization suggested that the National Institutes of Health (NIH) should provide more funding to study the relationship between chronic pain and drug addiction to determine the real causes of opioid abuse. (e) A comment from a pain organization – which was endorsed by several other comments – noted that outcome monitoring cannot be established for any REMS if the problem it seeks to mitigate is not well understood. (f) Another comment from academia echoed these sentiments noting that there are insufficient data to either design a REMS or evaluate it. The comment questioned whether FDA could solicit additional funding for research. (g) A comment from a pain organization suggested that FDA should not confuse anecdotal information with accurate statistical data and cautioned the Agency to take extreme care and allot adequate time to conduct the research necessary to formulate an effective REMS.

8. Several comments from health care professionals and their representative organizations underscored the difficulty in linking abuse to prescribing and legitimate patients. For example: (a) A comment from sixteen health care professional organizations stated that among individuals seeking admission to substance abuse treatment programs for issues related to OxyContin, seventy-eight percent of subjects reported that the drug had not been prescribed for them. (b) This sentiment was echoed by a professional nursing organization which noted that patients who receive a legitimate prescription for REMS drugs rarely

abuse them. (c) Similarly, a couple of health care professionals stated that there is no evidence that the REMS will be effective because it appears that abuse and misuse occur outside of the physician-patient relationship. This comment suggested that there needs to be more coordinated research amongst government agencies and academia before a REMS is implemented.

9. Some comments went beyond questioning whether the problem of opioid abuse is sufficiently defined by available data, to questioning whether opioid abuse is truly a significant public health problem. For example: (a) Several pain patients suggested that the problem of opioid abuse has been misrepresented in the media due to the celebrity of some addicts. (b) A health care professional organization questioned whether the public health impact of the abuse of REMS drugs justifies the amount of FDA's attention and resources that the REMS will require. (c) Another comment, while acknowledging the opioid abuse problem, stated it primarily affects particular areas and demographics (e.g., rural areas, undereducated eighteen to fifty-four year-old men). The commenter saw the problem as primarily one of personal responsibility and stated that mandating manufacturers to correct the problem seemed inappropriate. (d) A pain organization suggested that the information cited by FDA to support its assertion that REMS drug abuse and overdose is a problem is not properly put into context. Specifically, this comment asserted that the rate of overdose is relatively low in comparison to the number of prescriptions written for REMS drugs. Furthermore, the comment stated that it had requested information from the Agency regarding overdoses from REMS drugs and did not receive it. The comment concluded that the implementation of the REMS is more based on emotion than fact. However, an

iii. The REMS Will Not Be Effective In Achieving FDA's Goals

10. Not all comments questioning FDA's rationale denied the existence of a public health problem or suggested the problem needs better definition. Instead, several comments questioned FDA's rationale by asserting that the proposed REMS will not be effective in mitigating the risks cited in the rationale.

11. Several comments from a diverse group of stakeholders asserted that the proposed REMS will be ineffective in curbing abuse or diversion. A common theme in these comments is that abusers will abuse and at most all the REMS will do is shift abusers to other drugs, including heroin.[13] For example: (a) A health care professional analogized this situation to prohibition and suggested it had not curbed alcohol abuse, but instead increased criminal behavior. (b) A cancer foundation stated that while enhanced patient and prescriber education is a worthwhile pursuit, such efforts will not stop the intentional misuse of REMS drugs nor drug diversion (i.e., the black market is too lucrative). (c) A health care professional organization expressed serious concerns regarding the REMS' ability to diminish abuse or misuse of opioids. This comment suggested that the potential lack of effectiveness is particularly troublesome in light of the likely reduction in access for legitimate patients. (d) A patient advocacy organization suggested that in the absence of evidence that the REMS will curb diversion of opioids, FDA should abandon the class-wide opioid REMS.

[13] Several comments that suggested the abuse problem cannot be mitigated recommended that the government focus its efforts on improving addiction treatment and its availability. For a discussion of these comments, see Implementation, Section XIII, Subpart C.

12. Another often-cited argument that the REMS will not be effective in mitigating the risks identified by FDA is that it is unnecessary in light of current state and federal regulation, and because the actions that it seeks to mandate are already being performed in health care practice. For example: (a) Several comments highlighted that pain management is already over-regulated at the state and federal level making additional regulation unnecessary. (b) Multiple pain patients stated that the REMS is unnecessary because prescribers are already knowledgeable and monitoring patients, and there are already sufficient regulations to ensure safe legitimate use. (c) Another comment suggested that the REMS will impose an unnecessary burden, noting that health care providers are legally bound by state and federal law to prescribe and monitor controlled substances within their scope of practice.

13. Beyond questioning whether FDA has properly defined the risks associated with REMS or whether the REMS will be effective in mitigating the identified risks, a few comments questioned whether the stated purpose of the REMS was the true rationale and suggested there were other motivations behind the proposed action (e.g., financial motivations of insurance companies or pharmaceutical manufacturers, religious or political agendas). Moreover, several comments suggested that regardless of whether FDA's rationale is defensible, there are actions and priorities that are more worthy of the government's time and resources (e.g., regulation of dietary supplements, increasing sanctions and enforcement for drug activities, improving treatment for addicts).

B. Is FDA Acting Within the Scope of its Mandate and Statutory Authority?

i. FDA's Rationale for the REMS Exceeds its Mandate and/or Statutory Authority

14. Several comments suggested that by addressing abuse and diversion, FDA is exceeding the scope of its authority. A common theme of these comments is that other entities (e.g., the

Drug Enforcement Administration (DEA), state agencies, local law enforcement) are responsible for addressing these issues making FDA's actions inappropriate. For example: (a) A cancer foundation stated that the majority of the problems the REMS is intended to address are within the domain of DEA, not FDA. Specifically, this comment stated that physician behavior and prescribing patterns are not the cause of misuse and abuse of opioids. Instead, the issue is outright theft of narcotics and their diversion after legitimate prescribing. This comment stated that these criminal issues should be addressed by authorities other than FDA. (b) A health care professional organization stated that it is important to distinguish between risks from medical use, which are in FDA's purview and non-medical use (i.e., abuse/diversion) which are vested in other agencies (e.g., DEA, state and local law enforcement.) This comment stated that a REMS could complement the work of other agencies, but FDA should stay focused on safe medical use of drugs. (c) A distributor association noted that such efforts to curb diversion deviate from FDA's usual role. (d) An organization of pain educators suggested that instead of FDA attempting to limit supply, DEA should be willing to enforce the Controlled Substance Act against individuals diverting controlled substances or those who overdose on opioids when they do not have legal authority to consume them. (e) A prescriber suggested that diversion is a criminal issue, not a medical one, and is best left to law enforcement.

15. Several comments questioned whether FDA has the statutory authority to require a REMS at this time. For example: (a) A pain patient stated that FDA does not have nearly enough information at this time to formulate a REMS in accordance with its statutory authority and suggested that action at this time could lead to litigation. (b) A health care professional questioned whether FDA's statutory authority is sufficient to require a REMS for a drug if

the risks it seeks to mitigate do not occur when the drug is used in accordance with product labeling. This comment stated that if FDA is concerned with overdoses from legitimate use of products, than it should focus on improving labeling for the products instead of requiring a REMS. (c) Similarly, another comment questioned whether sufficient effort had been made to use less burdensome methods to mitigate the risks associated with REMS drugs (e.g., through Medication Guides) to justify FDA employing its REMS authority. Moreover, this comment questioned the type of analysis the Agency had performed to justify its use of its statutory authority. (d) A consortium of sixteen health care professional organizations cautioned that FDA should be mindful of FDAAA's requirements that the REMS not be unduly burdensome on patient access and minimize the burden on the health care delivery system. Similarly, a lawyer and a pain patient echoed that FDAAA only permits the implementation of REMS elements that do not unduly burden patient access.

16. The comment from sixteen health care professional organizations also questioned FDA's authority under FDAAA to implement a class-wide REMS. This comment noted that implementing a REMS for a group of drugs is novel. Specifically, this comment noted that if FDA determines "conditions for safe use" for the class of drugs, it might right afoul of statutory requirements mandating individualized findings. A comment from a manufacturer echoed these concerns suggesting that a class-wide REMS may not be feasible since different content would be required for different products. Instead, this comment recommended the implementation of several product REMS that would be interconnected.

ii. FDA Is Acting Within Its Mandate and Authority in Implementing the REMS

17. Contrary to comments suggesting the FDAAA bars FDA action, a health care professional organization stated that FDAAA has put FDA in the unenviable and untenable position of preventing the criminal and medical problems relating to the diversion, abuse, and addiction associated with prescription opioids.

18. With regard to FDA's authority to implement a class-wide REMS, the industry working group disagreed with the health care professional organizations' comment cited above. It asserted that a class-wide REMS is feasible under FDAAA as long as it is carefully designed to address specific risks without placing undue burdens on patients or the health care system. Similarly, a comment from an organization representing liability carriers advocated for a class-based REMS as opposed to individualized REMS and many comments from organizations representing pharmacists and pharmacies stated that individualized programs would unduly burden the health care system.

III. SCOPE OF THE REMS

In its April 20, 2009 notice, FDA described the drugs that will be covered by the proposed REMS as certain brand name and generic opioid drug products that are formulated with the following active ingredients: fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. Moreover, the agency discussed the REMS as covering long-acting and extended-release opioids. Many comments were received from a diverse group of stakeholders offering suggestions regarding this proposed scope for the REMS. Comments regarding scope fell into the following categories: (A) comments suggesting that the scope of the REMS should be expanded to include immediate-release and other opioid products, (B) comments suggesting that

the scope of the REMS is appropriate and should not be expanded, and (C) comments suggesting that methadone have a separate REMS distinct from the class REMS.

A. FDA Should Expand Scope of REMS

i. Scope of the REMS Should Be Expanded to Include Immediate-Release Products

19. Many comments from a diverse group of stakeholders – including a pain organization that submitted a petition with four thousand and seventy-five signatures – stated that if a REMS is implemented (and some expressly opposed implementation of the REMS), the program should include immediate-release opioid medications. Generally, these comments acknowledged that the REMS is already a significant undertaking and expanding the scope would increase its complexity. For example, a municipal agency supported expanding the scope of the REMS even though it acknowledged that the REMS as proposed would already be larger and more complex than past REMS (i.e., multiple drugs, multiple risks that are non-biological, multiple adverse outcomes in both patients and non-patients). Similarly, another comment noted that expanding the scope of the REMS would also increase the number of affected stakeholders (e.g., an expanded REMS would affect dentists). Despite this increase in complexity, the vast majority of comments discussing the scope of the REMS supported an expansion stating that only regulating one subset of opioids will have unintended consequences. Specifically, common themes in these comments were that if immediate-release products are excluded from the REMS: (a) it will cause a shift in prescribing and a shift in abuse/misuse to the less-regulated opioid products, (b) it will further stigmatize REMS drugs while creating a false sense of safety regarding immediate-release products, and (c) it will hamper REMS effectiveness.

20. Comments supporting an expanded scope expressed concern that regulating one portion of the class will simply cause a shift in prescribing. Specifically, these comments suggested that if long-acting opioids are subject to REMS requirements, and immediate-release products are not, prescribers will circumvent the REMS by prescribing immediate release-products, even if long-acting would be more appropriate. For example, comments expressed concern that chronic pain patients will suffer needless breakthrough pain if prescribers favor immediate-release products. Furthermore, dose escalation could occur for these patients due to the "reward" effect of immediate-release formulations. Comments noted that when states have implemented restrictions on one subgroup of opioids, this has consistently led to a "ballooning" of prescribing for the less-stringently-regulated subgroup.[14] On the other hand, an advocate for opioid drug reform, while agreeing that there would be shifts in prescribing, suggested that it might be a positive development because REMS drugs are much more dangerous than immediate-release formulations.

21. Comments also expressed concern that excluding immediate-release products would decrease the REMS effectiveness in mitigating opioid risks – both for risks associated with legitimate prescribing and those associated with abuse and misuse. These comments noted that particularly in light of the similarities between immediate-release products and REMS drugs (e.g., similar active ingredients, pharmacologic class, mechanism of action, tolerance, dependence, and risks associated with abuse, misuse, diversion, respiratory depression and death), it does not make sense to treat immediate-release products differently than REMS drugs. Comments expressed concern that doing so would exacerbate the stigma associated with REMS drugs and inaccurately suggest that immediate-release products are safer than

[14] For a more detailed discussion of behavioral economics, the potential for shifts in prescribing, and specific examples of state regulations that resulted in "ballooning," please see Access to Pain Medication, Section IV, Subpart F (ii).

their REMS counterparts (i.e., providing prescribers and patients with a false sense of security about immediate-release products). Moreover, assuming there is a shift in prescribing to immediate-release products, these comments expressed concern regarding the resulting impact on abuse and diversion. These comments suggested that addicts will seek out immediate-release products if the supply of REMS drugs is reduced and there will likely be a large number of immediate-release pills available for diversion. Comments noted that this is due to the need to prescribe multiple immediate-release pills to control pain over the same time period as a REMS drug. Therefore, comments suggested that by excluding immediate-release products from the REMS, the program's effectiveness in mitigating risks, including abuse and diversion, will be diminished. For example: (a) A health care professional organization stated that while the media focuses on extended-release products, immediate-release products are actually the most abused opioids. (b) A pain organization noted that all opioids are on the same DEA schedule, have the similar pharmacodynamic characteristics, and the same potential for abuse. (c) A lawyer advocated for ultimately expanding the scope of the REMS to include all opioids, noting that immediate-release products are actually the subject of problems before state medical boards and the federal courts more often than their long-acting counterparts.

22. Several comments stated that widening the scope of the REMS would enhance its effectiveness and streamline its implementation. For example: (a) A comment suggested that including all opioids in the REMS would assist in knowledge retention and compliance with REMS requirements, presumably because prescribers would not be confused regarding which drugs were covered by the REMS. (b) A similar comment asserted that if the REMS covered all opioids, its education programs would provide information on both long-acting

and immediate-release opioids and typically, they are both needed to treat patients. (c) Another comment stated that it does not make sense to implement a REMS for long-acting opioids now and then in a few years implement a REMS for immediate-release products. This comment concluded that since the major elements of the programs will be similar (e.g., education, infrastructure, evaluation), it is logical to implement them at the same time. (d) A health care professional organization noted that the inclusion of immediate-release products would also mirror the National All Schedule Prescription Electronic Reporting Act (NASPER) and allow for easier integration of NASPER and the REMS.[15] (e) Finally, a surveillance organization noted that, at minimum, monitoring of immediate-release products is critical to REMS evaluation.

ii. Scope of the REMS Should be Expanded to Include Other Opioid Drug Products

23. In addition to the many comments suggesting immediate-release products should be included in the REMS, there were a few comments recommending that other opioid products be included. For example: (a) An individual stated that buprenorphine is being used off-label by doctors to treat chronic pain and suggested that the Agency consider issues relating its appropriate prescribing as well. (b) Another comment suggested that naloxone be covered by the REMS.[16]

B. REMS' Scope is Appropriate: Immediate-Release Products Should Not Be Included

24. Among comments addressing the scope of the REMS, the majority by a large margin favored including immediate-release products. There was, however, a minority of

[15] For a detailed discussion of NASPER, please see Methods to Curb Diversion, Section IX, Subpart C.
[16] As discussed above, this document is focused on the opioid REMS, Therefore, comments regarding risk mitigation for other controlled substances will be considered, but not discussed here.

comments stating that the scope of the REMS as proposed in FDA's notice was appropriate. For example: (a) A vendor noted that if FDA's goal is to reduce the prescribing of long-acting opioids to opioid naïve patients, than the scope of the proposed REMS is appropriate. While acknowledging the argument that there may be shifts in prescribing if the scope is limited to REMS drugs, this comment highlighted that expanding the scope to include immediate-release products would cause the REMS to cover many more prescriptions and it is already going to be difficult to implement because it will be the largest REMS ever. This vendor noted that including immediate-release products in addition to long-acting opioids would increase the number of REMS-affected prescriptions tenfold each year (i.e., two hundred million prescriptions as compared to twenty to thirty million). (b) Another vendor noted that unlike past REMS, even without expanding its scope, the opioid class REMS will be highly complex – covering seven active ingredients, produced by twenty-five manufacturers, and used for two indications. Moreover, the products have diverse pharmacological properties and formula-specific recommendations. (c) In addition, multiple comments, one from a consortium of sixteen health care professional organizations, and another from a vendor, opposed including immediate-release opioids, at least at this juncture, since the proposed REMS is already a massive undertaking and including immediate-release products would increase it exponentially.

25. In addition to concerns about the complexity of the REMS, other comments refuted the assertion that immediate-release opioids are sufficiently similar to their REMS counterparts to warrant the same level of regulation. For example: (a) An advocate for opioid drug reform commented that long-acting and extended-release opioids are much more widely abused than immediate-release opioids. (b) Similarly, a physician stated that sustained-

release opioids are of a higher potency than conventional opioids, increasing the associated risks of addiction and abuse, and inadvertent overdose.

C. Should the Scope of the Opioid Class REMS Exclude Methadone?

i. Advantages to a Separate Methadone REMS

26. Methadone manufacturers suggested that methadone should not be included in the proposed opioid class REMS. Instead, they proposed a separate methadone REMS. Under their proposal, the methadone REMS would work in conjunction with the class REMS with both REMS having common elements. The manufacturers suggested that a separate methadone REMS would allow its unique characteristics to be addressed (e.g., in educational materials) including: (a) its two indications (i.e., pain and opioid addiction treatment) which require different dosing schedules and different treatment settings; (b) the fact that methadone is not universally considered a first-line pain medication; (c) methadone's unique pharmacological properties (e.g., its highly variable half-life, different pharmacokinetic and pharmacodynamic characteristics); (d) the fact that unlike other REMS drugs, methadone is not formulated as a controlled-release medication; and (e) methadone's unique safety issues (e.g., cardiac arrhythmia complications).

27. Moreover, several other stakeholders agreed that methadone's unique characteristics distinguish it from other REMS drugs. For example: (a) An advocate for opioid drug reform suggested that methadone should be treated separately due to its unique pharmacological profile and the fact it is responsible for a disproportionate amount of harm as compared to the number of prescriptions (e.g., only four percent of opioid prescriptions are for methadone, but forty percent of opioid deaths are methadone-related). (b) A pharmacist stated that while he does not believe other opioids require special skill to

administer, methadone does because of its unique pharmacokinetics. (d) Similarly, a health care professional organization highlighted that a disproportionate number of adverse events are associated with methadone, although it stated that most issues are with non-medical use.

28. On the other hand, not all of the methadone manufacturers' proposals were universally embraced by other stakeholders. For example, methadone manufacturers suggested that opioid treatment centers should be included in the methadone REMS. Specifically, the manufacturers stated that since the intent of the REMS is patient safety, methadone maintenance clinics should be included under the REMS since the risks do not vary based on intended use. An addiction treatment center opposed such an expansion, however, stating that the Agency was correct in excluding methadone from the REMS when it is used for addiction treatment. This comment noted that based on SAMSHA data, methadone maintenance clinics were not implicated in recent methadone deaths.

ii. Implementing a Methadone REMS

29. If FDA concurs with their recommendation for a separate methadone REMS, manufacturers suggested that they would offer a proposal for stakeholder input, which would include (a) prescriber, dispenser, and patient education; (b) a Medication Guide addressing both of the drug's indications and its risks and benefits; (c) an improved monitoring system, which maintains patient privacy, of starting and maintenance dosing in opioid treatment centers and identification of special populations; and (d) a timetable for evaluation. Furthermore, the manufacturers suggested that experience gained from opioid treatment programs could be used to develop the REMS (e.g., enhanced communication, improved labeling and increased prescriber and patient education). Furthermore, the manufacturers stated that the

REMS should follow federal guidelines, including current addiction treatment guidelines, and state regulations (e.g., mechanisms for preventing diversion and appropriate credentialing of health care providers would remain in place). Finally, with regard to manufacturers that produce both methadone and other REMS drugs, they would participate in both the methadone and class-wide REMS.

iii. Using the Methadone REMS as a Pilot Program

30. The manufacturers also suggested that an advantage of a methadone REMS would be its usefulness as a pilot. Specifically, the comment suggested that the methadone REMS could be implemented as the first phase of the class-wide REMS and the experience gained could allow for refinement of elements prior to wide scale implementation. A vendor agreed with this recommendation noting that a methadone pilot would not only permit the testing of REMS elements in a smaller population, it would also engage all of the relevant stakeholders. Moreover, this comment cited numerous reasons to support using methadone for the pilot including that it is one of the most researched of the REMS drugs, there has been a recent increase in methadone deaths, and it is unique in that it has neither been the subject of extensive education nor direct promotion. Therefore, the increase in methadone prescribing must be due to other influences (e.g., insurance rules, professional organizations), which make it a unique opportunity to test REMS elements. For a discussion of other proposed formats for pilots, please see REMS Development and Implementation, Section XIII, Subpart F.

31. With regard to timing, the vendor suggested that certain aspects of a methadone REMS initial phase could be expanded on a rolling basis to eventually address all REMS drugs, including (a) improved Medication Guides, (b) baseline data for other REMS drugs could

be collected during the methadone pilot, and (c) elements could be phased-in to evaluate their impact. This comment suggested it would take seven to twelve months to collect baseline data and implement a methadone pilot, followed by three years of pilot monitoring with annual reports being reviewed and discussed by all stakeholders.

32. Even advocates for a methadone pilot, however, noted its potential drawbacks. Specifically, methadone's distinguishing features including its dual indications, unique dosing schedules and usage settings, highly variable pharmacological properties, and the fact it is not a first-line pain medication would undermine its usefulness as a model. Moreover, a surveillance organization noted that since different formulations of methadone are used for analgesia and management of opioid dependence disorders, evaluation of a pilot may be more difficult. Moreover, if implementing the methadone REMS prior to the class-wide opioid REMS led to shifts in prescribing away from methadone, it could create problems for certain patients who stated that after trying variety of treatments, they discovered methadone worked best for their pain management.

iv. Comments Opposed to a Methadone REMS

33. Not all comments were supportive of creating multiple REMS for opioid products. For example, (a) As discussed in greater detail below, pharmacist and pharmacy organizations opposed increasing the number of REMS, favoring the minimization of requirements and confusion to the extent possible. (b) An organization representing distributors stated that if a separate methadone REMS is implemented, it should work seamlessly with the opioid REMS. This comment highlighted that multiple layers of restrictions and different requirements are unduly burdensome.

34. Beyond concerns for the added burden of multiple REMS, a few comments appeared to believe methadone's risks require more rigorous restrictions than suggested by manufacturers. For example: (a) An advocate for opioid drug reform and family member of a patient who died on methadone recommended more extensive restrictions on methadone prescribing, including that it only be prescribed for pain after other drugs have failed and only then when prescribed with an antidote (e.g., naloxone). (b) Similarly, another bereaved family member and health care professional suggested a methadone REMS should mandate education and certification of all prescribers (e.g., training prescribers that methadone, due to its half-life cannot be prescribed "as needed;" federal guidelines for methadone prescribing), prescriber-patient agreements, a national methadone patient registry, and active evaluation (i.e., cannot rely on voluntary reporting of methadone deaths).

IV. ACCESS TO PAIN MEDICATION

Of all the considerations highlighted by stakeholders regarding REMS implementation, by far the most often discussed was access to REMS drugs. As detailed below, comments varied greatly in their assessment of the current availability of opioid medications, with advocates for opioid drug reform stating that they are over-prescribed and too widely available, leading them to call for a ban on REMS drug prescribing. At the other end of the spectrum, many pain patients discussed their difficulty in obtaining their medications and, rather than supporting additional restrictions, they called on the Agency to reduce the regulation of opioids. Even comments falling into the middle of this spectrum, however, emphasized the importance of preserving access for the general patient population and for particularly vulnerable populations.

A. REMS Drugs Are Over-prescribed and Their Availability Is Leading To Abuse And Misuse

35. Several comments from a variety of stakeholders asserted that REMS drugs are over-prescribed and too widely available. For example: (a) An advocate for opioid drug reform stated that assertions that physicians are afraid to prescribe REMS drugs are misleading, because in reality there is little enforcement except in cases where prescribers have essentially become drug dealers. This comment noted that DEA does not have sufficient resources to prosecute anything but the most egregious cases. In a similar vein, another comment noted that in Florida there are clinics advertising that they sell Xanax and OxyContin and there are no repercussions or enforcement. (b) Several comments disputed the assertion by pain patients and their advocacy organizations that there is a problem with pain being undertreated. One such comment noted that it is unclear who is being counted as a pain patient, and there are no data to support assertions that pain is undertreated. Moreover, an advocate for opioid drug reform noted that the sales of REMS drugs belie the argument that they are difficult for legitimate patients to obtain. (c) Another comment from a chronic pain patient and pain management physician, while asserting that opioid medications are necessary, suggest that the practice of pain management is insufficiently regulated which has led certain doctors to essentially become drug dealers (i.e., "pill mills"). (d) A pain patient who had a negative experience with opioids (e.g., fell asleep while driving while on opioid medications) concurred that they are over-prescribed.

36. Several comments from bereaved friends and family members of individuals lost to opioid inappropriate prescribing, abuse, or misuse; health care professionals who have dealt with addicts in their practices; recovering addicts; and activists shared accounts of how the dangers of REMS drugs have caused loss and grief in their lives, in the lives of their family

or friends, and the lives of their patients or others they have sought to help. In addition, a comment from an advocate for opioid drug reform included a link to a website where thousands of individuals have shared additional stories of addiction and loss due to REMS drugs.

37. Several of these comments suggested that significant action – including banning the prescription of at least certain REMS drugs – is necessary to mitigate the risks they pose. For example, a prescriber noted that a twice-daily eighty milligram prescription of OxyContin is worth eighty-six thousand dollars a year in his region of Appalachia and suggested that the economic incentives are going to make this problem difficult to tackle without significant measures. Another comment called for the removal or limitation of access to opioid medications, citing increasing abuse and noting that they only should be prescribed when absolutely necessary, and then only for the shortest duration possible.

B. Immediate Temporary Moratorium on REMS Drug Prescribing is Necessary

i. Proposed Temporary Moratorium on REMS Drug Prescribing

38. An organization advocating for opioid drug reform suggested that FDA immediately implement a temporary moratorium on the prescribing of REMS drugs, while the Agency develops the REMS. In particular, this comment suggested that prescribers should be barred from prescribing REMS drugs, other than for severe cancer-related pain. Although the restriction would apply to methadone for the treatment of pain, the ban would not affect the use of methadone for addiction treatment or the use of immediate-release opioids.

39. The moratorium would remain in place until discontinued by FDA, in conjunction with an Advisory Committee of stakeholders upon determination that an effective REMS program had been developed. This commenting organization defines an effective REMS as

including: permanent competency requirements for prescribers; meaningful monitoring and enforcement; preventative public education; enhancement of addiction treatment; initiation of research to address deficiencies in knowledge regarding effectiveness and abuse potential for opioids in treating chronic pain, particularly moderate chronic pain; increased regulation of opioid marketing practices; development of secure dispensing practices; and the replacement of current formulations with truly abuse-resistant formulations.

ii. Compassionate Use Exemption Program (CUE)

40. In support of the temporary moratorium, a comment stated that advocates for opioid drug reform are not opposed to conventional opioids or the prescribing of REMS drugs, when truly warranted by thorough patient evaluation. To that end, advocates of the moratorium suggested developing and implementing a Compassionate Use Exemption (CUE) program. The CUE would allow prescribing of certain REMS drugs during the moratorium if defined criteria were met. Specifically, the CUE would permit patients with severe non-cancer-related pain to be treated with long acting opioids – other than OxyContin. Patient selection for the CUE by a physician certified to participate in the program would be based on diagnostic tests and the documented failure of four to six weeks of alternative pain treatment. CUE patients would be permitted to be treated for six to eight weeks with long-acting opioids, with limits on the quantities of drug that could be dispensed during that time. Its proponents suggested that the CUE should be overseen and enforced by FDA, DEA and the Department of Justice.

41. Physicians from the organization proposing the moratorium offered to work with FDA on the CUE's development and implementation.

C. Should Special Restrictions Be Placed on OxyContin?

42. As proposed, the CUE program would specifically exclude OxyContin and comments supporting a temporary moratorium were not the only ones that suggested that OxyContin should be treated differently than other REMS drugs. Several comments suggested OxyContin is over-prescribed and responsible for a disproportionate amount of opioid addiction without accompanying benefits. For example: (a) A detoxification center director stated that ninety-percent of people entering treatment for opioid withdrawal are addicted to OxyContin. (b) A pain patient who became addicted to OxyContin stated that she was lied to about its effects. (c) A bereaved parent of a child who died on OxyContin cited aggressive marketing tactics by its sponsor. (d) Another bereaved parent stated that OxyContin is causing much more pain than it is relieving and highlighted its over-prescription, particularly for non-severe pain. (e) Another comment stated that not everyone who has been harmed by OxyContin are abusers, patients have also been harmed.

43. Common themes of these comments include that OxyContin should be subject to greater regulation due to: (a) aggressive marketing tactics[17], (b) its unique role in addiction and dependence problems, (c) the fact it has no benefits over other opioids other than dosing convenience, (d) when OxyContin is withdrawn, patients actually report lower pain than when taking the medication, and (e) OxyContin is fueling demand for heroin (e.g., patients become addicted to OxyContin and eventually turn to heroin).

44. For these reasons, several comments – including one that cited a "ban OxyContin" website with over six thousand seven hundred supporting signatures – recommended that OxyContin be banned. For example: (a) The comment citing the online "ban OxyContin"

[17] In particular, these comments highlighted that in 2007, executives of OxyContin's sponsor pled guilty to felony misbranding.

petition recommended immediately stopping the prescribing of OxyContin to new patients, but permitting continued use by people who are dependent or addicted before completely ceasing production. The comment also stated that REMOXY should be permitted on the market but it would be reserved for existing OxyContin patients or new patients who fit the criteria for terminal or debilitating pain. (b) A bereaved parent and the founder of a regional organization advocating for opioid drug reform noted that there were ten opioid-related deaths within her organization in less than half a year. She suggested banning OxyContin and replacing it with a tamper-proof formulation. (c) Another parent of a recovering addict also supported a ban on OxyContin stating that it never should have been approved in the United States. This comment stated that tamper-resistant formulations have not come soon enough and the cost of her son's addiction goes beyond her family's costs – it has cost the justice system and society. This comment suggested that pain patients could use immediate release opioids or possibly medical marijuana instead.

D. Comments Opposing the Proposed Ban or Temporary Moratorium on REMS Drug Prescribing

45. Many comments – including hundreds from pain patients – expressly opposed a ban of REMS drugs. As discussed below, thousands of pain patients, friends and family of pain patients, and their health care providers submitted comments, including via petition to a pain organization. The most common themes of these comments were that (a) opioid medications enable pain patients to live, work, and take care of their families or, for end-of-life patients, die in greater comfort, and (b) access to opioid medications should not be denied. Please see Subpart F of this section for a more detailed discussion of comments supporting continued access to REMS drugs.

46. In addition to comments opposing a ban, generally, several comments took issue with specific points of the proposed moratorium. For example: (a) A patient advocacy organization – while acknowledging the carve out from the proposed temporary moratorium for cancer-pain – stated that it is inadequate because even after cancer is managed, pain can continue. Therefore, the line between cancer and non-cancer pain may not be distinct. Similarly, a hospice nurse noted that not all end-of-life patients requiring extended-release opioids were cancer patients. (b) The industry working group stated that there are no regulations for the proposed CUE program and the process for obtaining such an exemption during an investigational new drug (IND) program or clinical trial is lengthy and burdensome. Similarly, a comment from an individual stated that the CUE program is unworkable because it would require innocent patients currently treated with REMS drugs for chronic pain to submit documentation to the government. This comment questioned whether patients denied access to the CUE program would have a legal appeal requiring an attorney. This comment also noted that physicians from the opioid reform organization could not craft an adequate CUE program without knowing the particulars of every patient history and that prescribing should be left between the patient and his or her personal physician. A vendor echoed similar concerns noting that if a CUE program is to be implemented, research would have to be done to overcome challenges (e.g., who would be eligible and the role of the insurance provider in determining eligibility.)

47. Several comments from industry, individuals, patient advocacy organizations, and health care professionals opposed the proposed ban or temporary moratorium stating that with millions of people currently being treated with REMS drugs for chronic pain, a moratorium on any drugs – including OxyContin – will likely shift problems to other drugs, including

immediate-release products and illegal drugs. Moreover, a patient advocacy organization noted that if patients do shift to immediate-release products they will experience pain peaks and valleys. A pharmacist and chronic pain patient who is treated with OxyContin – after trying other treatments – expressed concern that a ban or moratorium will create a black market as addicts seek alternative drugs.

48. A policy group stated that a ban or temporary moratorium would be an unbalanced, and therefore, inappropriate policy. In particular, this comment cited the United Nations Single Convention on Narcotic Drugs of 1961 in support of its assertion that the United States is obligated to ensure that controlled substances, including opioids, are available in adequate amounts for medical and scientific purposes.

49. A hospice professional stated that she disagreed with arbitrarily banning certain concentrations of certain commonly-prescribed opioid medications, as it is contradicts compassionate evidence-based medicine. She stated that this should be an intervention of very last resort.

E. Alternatives for Limiting the Over-Prescription of REMS Drugs Without Implementing A Ban

i. Suggestions for Reducing the Over-prescription of REMS Drugs Short of a Ban

50. Several comments, while agreeing with advocates for opioid drug reform that REMS drugs are over-prescribed, did not necessarily support a ban on prescribing. Instead, they suggested reducing the prescribing of REMS drugs for chronic pain conditions. For example: (a) Multiple health care professionals suggested that long-lasting opioids should no longer be permitted to be used for the treatment of chronic pain noting they are ineffective when used long term and there is a concern for abuse. One of these comments

cited literature suggesting that opioids were not effective in the treatment of chronic pain and noting that there was a high addiction rate. In his personal practice, this physician stated that he has ceased to prescribe opioids for chronic pain because he believes the costs far outweigh the benefits both for the patient and society. Similarly, another health care professional submitted a white paper suggesting that opioids should not be used for the treatment of headache. Specifically, this comment noted that while opioids are initially effective, they actually lengthen the time to headache resolution and can lead to dependence and misuse. (b) Another comment suggested that sustained-release products and methadone should be used principally for chronic cancer pain. This comment would permit prescribing to patients in chronic pain due to other conditions, but only after other treatments have proven ineffective. (c) Another health care professional stated that the most significant risk for dependency, addiction, immunosupression, and illegal trafficking occurs when opioids are used for long-term management of chronic pain when there is a significant lack of pain-generating pathological findings. This comment suggested that opioid prescribing should be curtailed in this situation and guidelines should be established. (d) Similarly, a health care professional also suggested focusing attention on prescribing for chronic pain by exempting patients in acute pain from REMS requirements because they receive the medication for a short period of time.

51. Another comment did not suggest condition-based restrictions on REMS drugs, but rather population-based. Specifically, this comment stated that while REMS drugs should not be banned, they are over-prescribed and they should not be provided to certain high-risk patient populations (e.g., young adults, patients with addiction or criminal history).

52. Multiple comments also suggested creating processes to enable greater scrutiny of REMS drug prescribing. For example: (a) A pharmacist, while opposing the REMS, suggested that if additional regulation is deemed necessary, it would be better to define dosage or usage levels for each drug product whereby prescribing above the defined-level results in the risks of treatment outweighing the benefits. This comment suggested that if a physician wished to prescribe the product above the defined-level, he or she would have to justify it according to guidelines set by a regulatory agency. This comment allowed for exceptions to be made for medical conditions known to require higher doses of pain medication and hospice/palliative care. (b) Another comment stated that the use of opioids for non-terminal disease conditions should cease or be subject to a panel of medical experts for approval, but would allow opioids to be used for short term acute pain for a defined amount of time.

53. Another comment, while not advocating for a ban of currently-available opioid products, recommended a ban on new product approvals. Specifically, this comment expressed concern regarding addiction and dependence in the patient population, and proposed a moratorium on the approval of any new opioid products. In short, this comment stated that the United States pharmaceutical market does not need any new molecular entities to address pain.

54. Other comments suggested that current pain treatment in the United States favors opioid prescribing and the reasons should be examined. For example: (a) A comment from a vendor noted that the United States treats pain differently than the rest of the world and suggested that it might be useful to engage in an international discussion regarding why physicians here prescribe more opioids. (b) Multiple comments noted that the current reimbursement structure for non-pharmacological interventions favors opioids.

ii. Suggestions to Reduce the Over-prescription of OxyContin Short of a Ban

55. Short of banning OxyContin, several comments recommended restrictions to limit its over-prescription and abuse. Similar to comments discussed above, these comments often suggested that the use of OxyContin should be restricted to treating certain conditions. For example: (a) A bereaved parent asserted that OxyContin should be restricted – through labeling – to severe cancer pain. Moreover, this comment stated that family practice physicians, doctors of osteopathy, and nurse practitioners should not be permitted to prescribe OxyContin. (c) Another comment, while supporting a ban on OxyContin, suggested that in the alternative, its indications should be limited. (d) Similarly, a hospice professional noted that problems with OxyContin are not related to end-of-life care but rather when it is prescribed for chronic back pain.

56. Multiple comments suggested other interventions to combat OxyContin abuse and diversion. For example: (a) A pharmacy technician noted several instances of robberies or criminal activity related to OxyContin and suggested that appropriate controls should be instituted at pharmacies. (b) A family practice physician of twenty-nine years stated that overall, he believes OxyContin has resulted in more harm than good. Nevertheless, he opposed a ban and instead advocated for other interventions (e.g., education, monitoring) and stakeholder responsibility.

57. Not everyone agreed with comments recommending stricter regulation or prohibition of OxyContin prescribing. These comments emphasized that OxyContin is uniquely effective for certain patients and conditions and suggested access must be preserved. For example: (a) Multiple pain patients stated that they have tried other pain medications and OxyContin is most effective for their treatment. For example, a pain patient described how she had

received treatment from incompetent pain specialists in the past, and although she was over-medicated, she was still in pain. This patient noted her current pain management physician prescribed OxyContin, and it has made her pain tolerable and enables her to have some quality of life. (b) A pain organization stated that eighty-five hundred deaths due to OxyContin overdose must be compared to the one hundred and fifty million doses of OxyContin prescribed each year. An advocate for opioid drug reform and a bereaved parent took issue with this statement, however, suggesting it is insulting, and the data are misleading.

F. Access to Pain Medication is Already Limited and the REMS Must Preserve Access

58. Many comments received from a diverse group of stakeholders expressly – and in many cases vehemently – opposed the implementation of a REMS.[18] By far, the most common theme of these comments was a concern for access by legitimate patients to pain medication. For example: (a) A physician with eighteen years of experience called the REMS proposal nonsensical and stated he was very concerned that the proposed changes will radically effect the delivery of appropriate care to patients with both acute and chronic pain. (b) A hospice professional in rural Ohio suggested FDA consider alternatives to the REMS before implementing a government program that would reduce access to valuable medications. (c) A health care professional who is also a pain patient expressed serious concerns regarding the REMS, and while acknowledging that certain interventions may be warranted, she stated that a decade of strides in pain management access would be undone by the REMS as described in the notice. (d) A state pain commission expressed serious

[18] In addition, as discussed above, many comments opposed banning REMS drugs. However, it was not always clear from these comments whether they would also oppose less restrictive interventions.

concerns about the REMS. This comment acknowledged the serious crisis that misuse and abuse of opioids represents, but also highlighted the devastation that undertreated pain creates for patients and their families.

59. Exemplifying this concern for access were comments submitted by over twelve hundred pain patients and their friends and family. Similar to the comments mentioned above, these comments almost universally expressed concern regarding continued access for legitimate pain patients to REMS drugs. Comments were received from patients with a wide variety of painful conditions (e.g., cancer, reflex sympathetic dystrophy syndrome (RSD), fibromyalgia, scoliosis, interstitial cystitis, complex regional pain syndrome, lupus, injuries due to accidents, multiple sclerosis, degenerative disc disease, on-the-job injuries, birth defects, war injuries). Many of these patients submitted detailed accounts of their struggle to achieve adequate pain management, and their daily struggle to work and take care of their families. Some patients also appended pictures of themselves to personalize their stories. While it is impossible to fully detail these comments in this document, the overriding message was that their medications enable them to function, stay off disability, take care of their responsibilities (e.g., elderly parents, young children, marital responsibilities), and enjoy some quality of life. They stated that to deny them access would be devastating. In fact, over fifty comments mentioned that pain patients will commit suicide if denied access to their medications. Similarly, a survey of over five hundred RSD sufferers submitted by a patient advocacy organization, suggested that their average pain score is a seven point nine on a scale of ten and fifteen percent have attempted suicide.

60. Moreover, access was not only a concern for pain patients and their loved ones. It was also the most commonly cited concern among a diverse group of other stakeholders including health care professionals and their representative organizations, patient advocacy organizations, and health care facilities. The following common themes emerged throughout these comments.

i. The Problem of Undertreated Pain and Its Effects

61. These comments asserted that there is a pervasive problem of undertreated pain in the United States. For example: (a) A patient advocacy organization noted that sixty-five percent of calls to their toll-free number are from patients in untreated pain. (b) Another patient advocacy organization cited the example of pancreatic cancer – an excruciatingly painful and lethal form of cancer – and noted that the patient's pain is often undertreated. (c) Another pain organization noted that pain is undertreated particularly in vulnerable populations such as the poor and certain minority groups. This organization called upon FDA to acknowledge that chronic pain is one of the most significant pain problems in the country. (d) A pain patient noted that research animals are given pain treatment, but humans' pain is undertreated. (e) Finally, in asserting that the proposed REMS is a "tragic folly," a comment from a pain organization stated that for every one opioid abuser there are five thousand patients in untreated pain and the REMS will exacerbate the problem of undertreated pain. An advocate for opioid drug reform, however, questioned the data presented in this comment.

62. Moreover, these comments highlighted the detrimental effects of undertreated pain. For example: (a) A health care professional organization stated that undertreated pain has serious emotional and economic consequences and is a significant public health problem in

the United States. (b) A health care professional stated that undertreated pain can kill through hypertension and stroke. (c) A pain patient who is also a nurse discussed how inadequate treatment with immediate-release opioids exacerbated her condition. (d) Other comments stated that undertreated pain results in alcoholism, disability, suicide, illegal drug use, and brain atrophy. (e) Exemplifying this concern, a husband commented that his deceased wife's undertreated pain led to alcoholism. And a bereaved mother stated that her son – an RSD sufferer – committed suicide due to undertreated pain.

ii. The Devastation of Pain and the Resulting Need for REMS Drugs

63. Another common theme of these comments was how pain robs patients of quality of life. As mentioned above, many pain patients detailed their struggle to function while enduring pain. They discussed how the simplest task can become unbearable and how pain takes over their life. A recurring comment from pain patients was that FDA should "walk in their shoes" and become more familiar with their struggles (e.g., visit a pain clinic and talk to patients) before considering restricting their medications. For example: (a) A pain patient stated that the proposed REMS is divorced from the realities of pain treatment. (b) Another comment stated that while minor necessary inconveniences must be borne for the greater good, it is not true for pain patients with regard to the REMS because they need their pain treated to maintain their personhood. (c) Finally, in the words of a pain organization, chronic pain patients require REMS drugs to lead a next to normal life.

64. Comments concerned about preserving access to REMS drugs also highlighted the medications' unique benefits. In particular, these comments refuted the assertion that the dosing convenience of REMS drugs does not justify their increased risks and sought to highlight how dosing convenience is a significant advantage to patients. For example: (a)

Pain patients noted that REMS drugs allow for continuous pain control without the peaks and valleys experienced with immediate-release products. (b) In addition, an oncologist noted that the dosing advantages of REMS drugs far outweigh their risks. (c) The advantages of REMS drugs were also touted in comments discussing end-of-life patients. For example, many comments from hospice and palliative care professionals stated that REMS drugs prevent terminal patients from dying in severe pain and breathlessness while their families watch. They also highlighted that REMS drugs enable end-of-life patients to avoid taking ten to twenty pills a day and allow patients and their caregivers adequate time to sleep (e.g., with immediate-release products, they must give/receive medication at night to avoid the patient waking up in pain.)

65. In addition to highlighting the benefits of REMS drugs on their own, comments also emphasized the need to have diverse pain medications available to enable prescribers to tailor treatment to the individual patients. As discussed above, these comments expressed the concern that if opioid medications are restricted or require additional work to prescribe, physicians will shift their patients to other pain treatments, even if less appropriate. As noted in a comment from a scientific organization, behavioral economics suggests that if you raise the cost of one behavior (e.g., imposing requirements on prescribing REMS drugs), you will shift people to the less expensive behavior (e.g., prescribing other treatments). The comment likened the effect to squeezing one side of a balloon causing the other side to swell. For example: (a) An individual who is both a prescriber and a pain patient analogized the REMS requirements to Indiana's implementation of a triplicate prescription for long-acting opioids. According to this comment, the result of the regulation was that providers stopped prescribing the affected drugs. This resulted in

patients taking excessive doses of hydrocodone to control pain and a rise in acetaminophen-related adverse events and deaths. (b) A vendor noted that when pseudoephedrine products were moved behind the counter, drug abuse may have been reduced, but legitimate use of these products was definitely reduced and shifted to less effective products. (c) Multiple comments from health care professional organizations and health care professionals expressed concern that in addition to the potential for shifts in prescribing from long-acting opioids to immediate-release products, the REMS could also encourage prescribers to shift patients to less appropriate non-opioid therapies that could have other deleterious effects (e.g., non-steroidal anti-inflammatory drugs (NSAIDs) are associated with gastrointestinal complications).[19]

66. Comments concerned about the availability of REMS drugs and the potential for shifts in prescribing often suggested that pain treatment should be left within the confines of the prescriber-patient relationship and that the government should have more respect for that relationship. For example: (a) A pain organization stated that the REMS should not interfere with the ability of prescribers and other appropriate health care practitioners to responsibly develop, provide and adjust pain-care management regimens for their patients. (b) A coalition of pain organizations – which was supported by several other comments – noted that opioids are needed as a part of a multi-modality approach to treating pain. (b) A patient advocacy organization stated that prescribers should have a wide variety of opioid analgesics at their disposal to address the individual needs of pain patients. (c) Multiple comments also noted that prescribers are already limited in their treatment options by

[19] On the other hand, an advocate for opioid drug reform disputed that shifting prescribing away from long-acting opioids would have a detrimental effect on pain management. To the contrary, the comment asserted that in combination with other therapies (e.g., counseling, exercise), immediate-release products could adequately address pain.

insurance coverage and asserted that their options should not be further limited. (e) A pain patient noted that patient cases should be addressed individually, not in the aggregate.

67. To exemplify the argument that the availability of a variety of pain treatments is necessary, pain patients discussed their struggle to achieve the best treatment for their condition. For example: (a) A pain patient stated she used to be on immediate-release products, but struggled with pain peaks and valleys. She now is on a patch and the treatment has been more effective. (b) A pain patient who underwent several ineffective treatments before his physician prescribed an effective medication for his condition suggested that the REMS should allow for maximum flexibility in the doctor-patient relationship and allow prescribers to modify treatment based on the patient's particular circumstances. (c) Several pain patients noted that they use a combination of opioid medications to provide continuous pain control (e.g., REMS drugs used in combination with immediate-release products for breakthrough pain). (d) Another pain patient noted she prefers REMS drugs because immediate-release products leave her feeling groggy and she is concerned about overdose. (e) A patient stated opioid medications are crucial to his pain management; he cannot take NSAIDs because he only has one kidney.

68. Several of these comments emphasized that as opposed to restricting pain treatment options, the government should be seeking to expand access, not just to pain medication, but also other pain treatments. For example: (a) A pain patient suggested that a means of reducing opioid prescribing while preserving access is to improve reimbursement for alternative pain therapies. (b) Another comment noted that there needs to be access not just to pain medication, but also other therapies (e.g., cognitive behavioral therapy), which should be the first line of treatment.

iii. Opioids Are Already Extensively Regulated Resulting in Reduced Access and Burdened Stakeholders

69. Another common theme of comments concerned with access was that opioid prescribing is already extensively regulated at the state and federal level leading to reduced access. Specifically, these comments described a pain management community fearful of DEA enforcement and burdened by paperwork and documentation, leading to a dearth of REMS drug prescribers. For example: (a) A primary care and hospice physician stated that the REMS will only compound the problem of inadequate pain control for legitimate patients. He noted that currently many physicians do not use stronger narcotics for fear of litigation, diversion and the necessity of special prescription pads. (b) Many comments stated that physicians are afraid to prescribe due to DEA oversight. (c) In a similar vein, a health care professional who is also a cancer patient stated that the DEA needs to be removed from the practice of medicine or a division must be created at DEA which has a public health mission and focus on patient care. (d) Finally, a bereaved father commented that due to fear of DEA enforcement, prescribers were hesitant to treat his daughter's pain until it was too late.

70. Exemplifying the problem of a limited prescribing pool, several health care professionals described an environment of limited access to pain management. For example: (a) A physician noted that there are already too few providers who manage pain and therefore pain continues to be undertreated. He expressed fear that the REMS will further reduce the number of pain management-providers which will adversely affect patients. (b) A prescriber in a pain management field noted it is already difficult to get primary care providers to handle opioid prescriptions even when patients are on stable doses.

71. These comments also noted that reimbursement and insurance issues limit the pool of available prescribers. For example: (a) A patient advocate noted that malpractice insurance companies are limiting the ability of primary care providers to prescribe opioids, and yet there is insufficient access to pain specialists. (b) A patient advocacy organization noted that many individuals with RSD/CRPS, for example, are uninsured or underinsured and must rely on primary care providers for their analgesic medications. Moreover, this comment noted that many patients live hundreds of miles away from pain specialists.

72. Many pain patients explained how current extensive regulations create hardships on REMS-drug patients and expressed concern that the REMS would exacerbate the problem. Several of these comments stated that FDA should be implementing measures to make it easier for pain patients to get treatment, not harder. Often-cited burdens by pain patients included: (a) the limited number of prescribers, which often results in long trips to receive treatment, (b) limitations on refills leading to patients having to get a new prescription every month, (c) difficulties created by refill restrictions (e.g., cannot get vacation supplies, cannot submit refills by telephone), and (d) the lack of reimbursement for patient monitoring (e.g., toxicology screening). In particular, with regard to the long distances patients must travel every month, several of these comments noted that this particularly difficult considering the population at issue is in significant pain. For example: (a) A pain patient noted that the nearest pain specialist is thirty-miles away and due to prescription limitations, the patient must travel there every month to get a new prescription, and submit to toxicity screens which are not covered by insurance. (b) Another pain patient living in a rural mountainous area drives twenty miles to get medications. (c) Another pain patient noted that a “waiting period” is common before prescribers are willing to prescribe even when the patient is in

extreme pain. (d) Another patient noted since only one doctor in her area prescribes REMS drugs, there is a three hour wait at his office. (e) In the words of one pain patient, when someone is in chronic pain, any additional obstacle becomes a significant burden. Therefore, as opposed to adding requirements, several pain patients requested the elimination of certain requirements (e.g., several asked that refills be permitted) to reduce the cost and burden associated with opioid access.

iv. The REMS Will Exacerbate the Stigma Associated with Opioid Treatment, Leading to Reduced Access

73. Another common theme of comments from stakeholders concerned about access is how extensive regulation of opioid prescribing has led to stigmatization of pain patients and prescribers. These comments expressed concern that the REMS will not only further burden pain patients and the health care community, but also serve to further stigmatize pain management resulting in reduced access to treatment. These comments noted that the stigma is pervasive – leading prescribers to be fearful of writing prescriptions and leading patients to be labeled addicts and criminals. Furthermore, these comments suggested that the stigma not only decreases appropriate access to pain treatment by decreasing the prescribing pool, but also may cause patients to refuse to undergo opioid treatment due to a fear of addiction. For example: (a) A social worker noted that there has been a breakdown in the relationship between the prescriber and patient. Specifically, this comment suggested that there is a stigma that patients are addicts, and the implementation of elements such as registration suggests a methadone-like system which could increase that stigma. (b) Multiple comments noted the negative stigma associated with opioids among prescribers has prevented early and aggressive treatment of pain symptoms. (c) A pain patient stated she is monitored to the point of humiliation by her prescriber. (d) Another pain patient said

she has been labeled a drug seeker. (e) A pain management nurse noted that statistics indicate that fifty percent of chronic pain patients believe that access to treatment has been limited or denied due to stigma and misinformation. (f) Finally, several comments suggest that the stigma associated with opioids is due, at least in part, to a misunderstanding regarding the difference between dependence and addiction. These comments discussed how while a pain patient may be dependent on opioids, that dependence is similar to a diabetic's dependence on insulin. Patients asserted that due to the chemistry of pain and pain treatment, their medications do not provide them with a "high." While they acknowledged that they are dependent on REMS drugs – and expressed concern for withdrawal symptoms if their access is denied – pain patients also stated that it is inappropriate to label them addicts due to their dependence.

74. Multiple comments suggested that FDA's proposal of the REMS is considered acceptable because of the stigma associated with pain management. For example: (a) Multiple comments suggested that FDA would not treat patients with other diseases (e.g., epilepsy, HIV/AIDS, diabetes) the same way as they are treating pain patients. (b) In the words of one patient, the pain community may be made to suffer because they do not have a socially-acceptable illness. (c) Multiple comments also questioned why the government was singling out opioid medications when other substances have caused similar harm (e.g., alcohol has caused addiction, death, criminal behavior, destroyed families).

75. Finally, several comments raised other issues related to stigma in their comments. For example: (a) Several comments suggested that a concern for privacy under the REMS could lead to fewer patients seeking pain treatment. (b) Several comments also noted that the way the media portrays opioid issues has served to increase stigma and reduce access (e.g.,

celebrity addictions lead to suspicion of legitimate patients, inappropriate portrayal of prescription opioid use and abuse on television programs).

v. Legitimate Pain Patients Should Be The Top Priority and They Should Not Suffer Because Of Abusers

76. Many comments – including almost five hundred comments from individual pain patients, family members and friends of pain patients, and health care professionals – emphasized that FDA's top priority should be legitimate pain patients. Moreover, these comments asserted that their access to pain treatment should not suffer because other people have chosen to abuse REMS drugs. For example: (a) A pain patient stated that abusers should not be able to reduce access to medications for legitimate patients. (b) A hospice health care professional stated that the legitimate medical uses of opioid analgesics must be given consideration equal to or greater than the criminal misuse of these medications. (c) A pain organization submitting a petition from four thousand and seventy-five pain patients noted that many of its signatories had expressed anxiety, fear and anger, particularly that those living with pain and their health care providers are being unfairly blamed for the drug abuse and misuse of prescription drugs. (d) An organization of educators noted that the only way for FDA to impact diversion, abuse and misuse is to reduce supply at the expense of patients in significant pain who could clearly benefit from REMS drugs. This comment suggested that such actions will not be effective in mitigating risks, particularly in the non-patient population who is actively choosing to be self-injurious (e.g., abusing opioids). (e) Another comment echoed this sentiment stating that limiting supply will not curb abuse and to actually reduce abuse, it is imperative to address demand.[20] This comment also asserted that restrictions will not stop abusers, but will destroy the lives of pain patients. (f) Several

[20] Advocates for opioid drug reform, however, refuted this assertion stating that there is a strong correlation between opioid supply and abuse.

comments also expressed concern that while the REMS will reduce legitimate access to pain medications, it will not stop opioid abuse. Instead, abusers will shift to heroin.

77. Several comments from individuals with first-hand knowledge of the dangers of abuse and addiction still emphasized that legitimate patients ought to be prioritized. For example: (a) A pain patient who lost her daughter to heroin addiction suggested that legitimate users should not suffer due to abusers. (b) A recovering prescription drug addict advocated for ensuring that legitimate patients have access. (c) A health care professional specializing in addiction treatment stated that preserving legitimate use is more important than curbing diversion. (d) Another comment from academia stated that the number of patients with serious and complex illnesses and disabling chronic pain dramatically outweigh the number of deaths from overdose and substance abuse.

78. Moreover, these comments also emphasized personal responsibility. Specifically, these comments assert that legitimate pain patients are doing the right thing (e.g., adhering to appropriate use and storage procedures) and suggested that they should not be punished to protect those who are engaging in criminal behavior. For example: (a) A prescriber in a pain management field noted that very few legitimate patients abuse opioids. (b) A pain patient noted that she stores her medications in a locked box, signed a PPA and undergoes drug monitoring. (c) Another pain patient noted that she keeps her drugs hidden and tells no one about them and suggests if everyone did the same, there would be no diversion or abuse.

79. Several comments were received regarding veterans and their need for REMS drugs. These comments asserted that those who have served our country should not be denied access to pain relief to protect abusers. For example: (a) A Gulf War veteran commented that the

pain from his injuries and the injuries of his fellow veterans require REMS drugs and they should not be punished because criminals have chosen to abuse them. (b) An eighty-year old veteran who was fifty-eight percent disabled in the Korean conflict and has severe arthritis and disc compression expressed concern that access to the opioid medication he requires to provide him with a reasonable quality of life may be restricted. (c) A wife of a disabled veteran expressed her fear that if he was denied access to his medications, he would suffer withdrawal or commit suicide. (d) Similarly, an individual associated with the Veterans Administration also emphasized the importance of REMS drugs for veterans.

80. As opposed to reducing access, these comments highlighted potential alternatives for decreasing abuse without punishing legitimate patients. For example: (a) Several comments called for increased sanctions and enforcement against health care professionals and individuals engaging in diversion and abuse (e.g., a pain patient suggested that unethical doctors should be jailed or lose their licenses). (b) Another option suggested by a pain organization was that as opposed to adopting measures to limit supply as a means of curbing the abuse problem, FDA should work in collaboration with other federal agencies (e.g., the Department of Education, the National Institutes of Health) to educate the public about drug abuse and getting treatment. This comment also encouraged the agency to actively encourage physicians to treat pain.

vi. Concern for the Logistical and Financial Burdens Imposed by the REMS

81. Another common theme in comments expressing concern about continued access to REMS drugs was the logistical impact of the REMS. For example: (a) A pain organization noted that patients are concerned that they will be confused by the REMS and not understand how to receive their medications. (b) A health care professional organization stated that the

82. Comments also expressed concern about the financial impact of the REMS and its potential to reduce access. For example: (a) Several comments questioned the impact the REMS would have on the availability of generics and the disincentives it could create for the opioid product pipeline. (b) Another comment feared that the REMS could result in the cornering of the market and increased medication costs. (c) A patient expressed concern that insurance companies will use the REMS as an excuse to not reimburse for these medications.

83. Several comments noted that impeding access with a REMS could have financial costs beyond the health care sector. They noted that the cost of pain includes not only the direct costs such as doctor visits, diagnostics, and medications, but also indirect costs such as lost wages and productivity not only of patients, but their families and caregivers. Moreover, patients noted that REMS drugs are often the only reason they are able to continue working and avoid disability or unemployment.

vii. Seeking Balance and Is It Achievable?

84. Comments that expressed concerned for access but were not strongly opposed to the REMS often suggested that the Agency should seek balance its implementation. Specifically, these comments suggested developing a REMS program that will preserve access while mitigating risk. For example, a chronic pain patient acknowledged that it is important to keep opioids out of the hands of criminals, but also emphasized that it is most important to

ensure access for legitimate pain patients. She urged FDA to craft the REMS carefully. She was not the only pain patient willing to accept some additional regulation if it achieved a greater good. Several pain patients expressly stated that as long as REMS drugs were not banned, they could accept a REMS. Similarly, several pain patients acknowledged the risks associated with opioids and the societal problem of abuse, misuse, and inappropriate prescribing. These comments suggested that education, monitoring, patient education, public education, or prescription drug monitoring programs may be reasonable solutions. For example: (a) A patient stated that prescribers lack knowledge regarding diagnosing and treating pain which leads to a fear of prescribing. (b) Another pain patient suggested that the development of nationwide prescribing guidelines and a nationwide prescription monitoring program could be helpful.

85. Other comments, however, suggested "balance" could be difficult to achieve. For example: (a) A pain patient stated that balance is a euphemism because it is already difficult to find physicians willing to prescribe opioid medications or pharmacies willing to dispense. (b) While a pain initiative concurred with the goal of maintaining a balance between preserving access to opioids for legitimate patients and curbing diversion, it stated that the REMS proposed in FDA's April 2009 notice did not achieve that balance and it will have a seriously detrimental effect on patient care. (c) Another comment suggested considering the incentives and disincentives the REMS will create. If it disincentivizes product development, it could limit access. While this comment stated that balancing access while curbing abuse is an attainable goal, it said it will be dependent on having a science foundation that includes rapid, responsive, and informative surveillance.

G. Access Must Be Preserved for Vulnerable Populations

i. Access Must Be Preserved for Patients Who Already Have Limited Health Care Access

86. In considering issues of access, many comments expressed particular concern for vulnerable patient populations (i.e., populations who already have limited access to pain treatment and health care due to unique circumstances), although these comments defined the relevant populations somewhat differently. For example: (a) A comment suggested that the REMS be developed with special consideration for already-underserved populations (e.g., patients with limited health literacy or language barriers, immigrants, patients with a history of addiction or cognitive deficits, and rural residents). This comment expressed concern that the burden of the REMS may be disproportionately felt by those who are least able to cope. (b) The industry working group expressed concern about limiting access for those who are already vulnerable to health care disparities, including the elderly, ethnic minorities, the impoverished, recent immigrants, residents of medically-underserved regions, and non-English speakers or readers. (c) A patient advocacy association noted that their members were fearful that REMS drugs will be limited to specific settings and that those living in rural or urban areas, the elderly, and those with limited mobility will not have the ability to travel to the sites where medications will be available. (d) The medical director for a palliative care program serving vulnerable populations in New York City (e.g., immigrant, indigent, and uninsured) stated it is already difficult to obtain necessary medications and services for her end-of-life patients and expressed concern about additional regulation. (e) A comment from sixteen health care professional organizations suggested decreasing access to Schedule II drug products is likely to have a deleterious impact on the most vulnerable, underserved communities across the country, further stigmatize pain

patients, and increase suffering amongst those with chronic pain, cancer pain or end-of-life patients. To avoid these unintended consequences, this comment recommended that FDA work closely with SAMHSA and DEA to implement positive incentives for physicians who are willing to provide appropriate pain management to patients.

87. Comments from pain patients exemplified the limited access already experienced by certain populations. For example: (a) A pain patient stated that she has experienced a discrepancy in care because of her race and gender. (b) A few patients commented that the poor have a difficult time finding pain management physicians who accept Medicaid insurance. (c) A disabled pain patient suggested that the disabled should be exempt from any REMS requirements due to the obstacles they face.

ii. Access Must Be Preserved for Cancer Patients

88. Several comments expressed particular concern with regard to access to pain medications for cancer patients. For example: (a) A comment from academia noted that doctors are already concerned about writing prescriptions for opioids – particularly in the high doses needed to treat cancer pain – and any additional burden or stigma created by the REMS will have a negative effect on cancer patients. (b) Similarly, a patient advocacy organization echoed these concerns and stated that there are already many barriers to pain treatment for cancer patients – not only a reluctance of doctors to prescribe but also a fear of addiction amongst patients. This comment stated that many of the proposed interventions under the REMS assume diversion originates within the doctor-patient relationship, but that has not been proven. As a result, the interventions may impede access for cancer patients without mitigating risk. (c) A cancer foundation noted that prescribers are already scared to treat pain due to ignorance and government regulation and expressed concern that cancer

patients will suffer if the REMS is implemented, and that their suffering will not be heard by FDA. (d) A cancer patient advocacy organization stated that patients are already wary of asking for pain relief in the final stages of cancer and expressed concern about additional restrictions. (e) A health care professional organization expressed concern for the REMS' potential to: (i) impede appropriate pain management for cancer patients, (ii) impose additional administrative burdens on oncologists who are already struggling to deal with today's challenging regulatory environment, and (iii) stigmatize either the cancer patients who receive these drugs or the oncologists who prescribe them. (f) A patient advocacy organization and a health care professional organization stated that it appears that cancer pain is undertreated citing a patient education project and journal articles, respectively. (g) A social worker noted that the terminal cancer patients she works with are terrified of a painful death and emphasized the importance of maintaining access.

89. Exemplifying the concern with regard to cancer patient access, a pancreatic cancer patient advocacy organization noted that that in its experience, too often cancer patients are dying in extreme pain and suggested that this lack of pain control could be due to a variety of factors including: (a) patients are not aware that options exist that can help them and/or that they are reluctant to discuss the problem with their health care team, (b) patients may be wary of discussing their pain out of fear (e.g., fear that the pain indicates that the disease is progressing), (c) fear of the effect that pain medications could have on their ability to function, and (d) concern for their family's perceptions of how pain medications will affect them. Furthermore, they stated that while they strongly support the goal of curbing misuse, abuse, and diversion of opioid medications, it is essential to move forward with a balanced

approach that first does no harm to patients who legitimately need these medications, such as pancreatic cancer patients.

iii. Pediatric Access Must Be Preserved

90. Several comments – particularly from stakeholders whose focus is pediatric medicine – expressed concern regarding the REMS' effect on children's access to REMS drugs. For example: (a) Multiple health care professional organizations stated that although not labeled for pediatric use, off-label use of REMS drugs is necessary for the treatment of many painful conditions in children including cancer, sickle cell anemia, trauma and surgical recovery, and hemophilia. Moreover, as opposed to conventional opioids alone, long-acting opioids are necessary in many cases (e.g., when a child develops opioid tolerance). (b) A pediatric palliative care physician echoed this concern noting that REMS drugs are a mainstay of his practice. (c) A pediatric hospital agreed stating that opioids are a mainstay of analgesia for patients from vulnerable neonates to children battling terminal illnesses. (d) A patient advocacy organization expressed concern that pediatric sickle cell patients will suffer very poor pain control if denied access to long-acting opioids. This comment also noted that this denial of pain treatment would disproportionately affect minority children. These concerns were echoed by a social worker assisting pediatric sickle cell patients who noted that REMS drugs enable her patients to go to school and to participate in a social and family life. She noted that their physicians are very careful about engaging in monitoring and that they should be trusted with their patients' treatment. She also noted a stigma is already endured by sickle cell patients. (e) A neonatologist and pediatric palliative care physician also highlighted that REMS drugs enable pediatric patients to leave the hospital which benefits the patients, their families and the health care system. (d) A health care

professional organization representing pediatric hematologists and oncologists noted that because their patients often require pain management, and non-narcotic pain medications are often contraindicated due to anti-platelet effects, they are experts in appropriately prescribing REMS drugs for this population. This organization highlighted a particular concern for continued access for children in rural areas.

91. A health care professional organization also noted that there is little evidence regarding whether the "adult concerns" cited as the rationale for the REMS apply broadly to pediatric patients or what the incidence may be of any of the listed problems in children. Although the comment acknowledged that there have been reports of abuse, misuse and overdose in the pediatric population, it stated there are no clear indicators to identify the exact mechanisms that give rise to them or clearly define policy responses. There is also no available evidence to demonstrate that any of the proposed methodologies of the REMS will address the concerns prospectively. On the other hand, a pediatric hospital stated while there is little concern for diversion within the pediatric population itself (with the exception of adolescents), it is possible that their caregivers may be implicated. This comment recommended developing methods to ensure access by pediatric patients, while limiting access to the medications by their caregivers. Another pediatric prescriber echoed this comment emphasizing the importance of maintaining pediatric access while acknowledging a concern for diversion, misuse and abuse risks in the adolescent population and family members of pediatric patients.

92. Multiple comments recommended caution on the part of FDA to ensure that pediatric access to opioid medications remains unimpeded and noted that imposing elements such as drug testing, prescriber-patient agreements, and monitoring programs on children is

completely inappropriate. These comments recommended exempting pediatric patients, their providers and pediatric hospitals from these requirements and one comment recommended exempting these entities from all REMS requirements.

iv. Hospice and Palliative Care Access Must Be Preserved

93. Over five hundred comments – predominantly from hospice and palliative care professionals and including a comment from a coalition of hospice and palliative care entities that was endorsed by many other comments – expressed concern regarding the REMS' impact on their practice. Although many of these comments supported FDA's efforts to curb abuse and misuse of opioids, they urged FDA to ensure such efforts do not negatively impact access for end-of-life patients. In the words of many of these comments, end-of-life patients should be considered first when developing the REMS. Common themes included: (a) REMS drugs are critical to caring for hospice patients (e.g., for shortness of breath which occurs in eighty-five to ninety-five percent of end-of-life patients); (b) in addition to the pain experienced by the patient, witnessing a dying patient in severe pain and breathlessness also takes a significant toll on their family members and caregivers; (c) shifting prescribing to immediate-release products will mean end-of–life patients and their caregivers will be on a twenty-four hour schedule to allow for adequate pain management at night; (d) adding to the already substantial regulation of hospices will lead to a decrease in physicians willing to provide hospice care (e.g., hospices already have extensive policies, processes and documentation addressing the issues raised by the REMS); (e) recent agency actions have already detrimentally impacted hospice patient care (e.g., there have been liquid morphine shortages when liquid formulations are particularly critical for dying patients who have difficulty swallowing); (f) the risk that a patient will

become dependent or addicted to opioids is not relevant to the end-of-life population; and (h) FDA should visit hospices prior to developing the REMS to obtain first-hand knowledge regarding the needs of their patients, the expertise of the health care professionals, and the processes already in place with regard to REMS drugs. Overall, these comments requested that REMS implementation occur with the least disruption to managing pain and breathlessness for end-of-life patients.

94. Several hospice and palliative care professionals stated that they are committed to pain management for end-of-life patients and any regulation or registration of practitioners or patients will be an obstacle to providing appropriate end-of-life care. Exemplifying this concern was a primary care provider in central Missouri with decades of experience in end-of-life care. He stated that he would be concerned to attempt such care without access to REMS drugs, but he also already spends approximately one-third of his time on paperwork. Therefore, he opposed any measures that will increase paperwork and create delays in access for his patients, whom he noted have limited access to pain specialists. Similarly, a hospice nurse noted that requiring additional certification or registration will only deter health care professionals from using REMS drugs which will lead to unmanaged symptoms and inadequate end-of-life care.

95. Several comments expressly requested an exemption from REMS requirements for credentialed hospice and palliative care professionals employed by accredited hospices and hospital-based palliative care programs and their patients. One comment suggested that such an exemption is not without precedent – in Nevada, hospices are exempt from certain state requirements to protect appropriate end-of-life patient care. Common themes in comments recommending an exemption included: (a) Current practice and the Centers for

Medicare and Medicaid Services (CMS) regulations already require many of the same interventions being considered under the REMS. For example, patient and provider education is already occurring in the hospice community with the management of pain and breathlessness and the dangers of diversion being taught in fellowship programs and as part of hospice training. Moreover, CMS' Conditions of Participation already mandate the documentation of patient education on medication risks/benefits and disposal. (b) The risk of addiction or dependence is not relevant to this patient population. (c) Decreasing reimbursement for hospice care has already reduced the number of practitioners willing to provide end-of-life care, and the REMS will further reduce access. (d) Based on the experience of health care professionals, there is very little evidence of abuse with opioids in the hospice and palliative care population. (e) End-of-life patients typically are in hospice care for a short period of time, making delays in care due to the REMS particularly inappropriate. (f) Hospices are already engaging in patient monitoring (e.g., they perform pill counts, inform patients that if diversion issues arise they will work in coordination with law enforcement). Furthermore, these comments stated that other forms of monitoring (e.g., toxicology screening) would be burdensome to end-of-life patients.

96. Multiple comments highlighted issues of particular concern in hospice and palliative care. For example: (a) A hospice professional in a rural area highlighted that currently it is difficult to get necessary opioid medications and the REMS will further frustrate rural hospice access. (b) A hospice nurse stated, in particular, there needs to be access to pain relievers for end-of-life patients at twenty-four hour commercial pharmacies. (c) Another hospice professional noted that hospices have policies and protocols for the storage and

disposal of opioids, as required by CMS, but storage and disposal of unused medications continues to be a major problem.

97. Many of these comments recommended that FDA monitor the effects of the REMS on access by at-risk populations

v. Institutional Access and Access for the Elderly Must Be Preserved

98. Several comments expressed concern for patients being treated in an institutional setting. For example, a health care professional organization recommended exempting medications that are prescribed for patients residing in long-term care facilities, assisted living facilities or hospitals.

99. Another health care professional organization focused solely on hospitals and recommended that they be exempt from the REMS because: (a) implementation could result in delays in care; (b) the REMS is less necessary in the hospital setting because there is an interdisciplinary care model with checks on each of the health care providers. Moreover, patients do not self-administer drugs and there is always a health care professional in the general vicinity of the patient when medications are administered; (c) many hospitals and health-systems have decision support systems in place to prevent inadvertent overdoses of medications; and (d) hospital personnel have extensive experience in prescribing and administering opioid medications. On the other hand, another comment suggested that death due to ventilatory depression was an issue in hospitals and better education is necessary.

100. Several comments focused on preserving access to REMS drugs in long-term care facilities, noting that they are already extensively regulated, long-term care providers are already experienced and knowledgeable regarding opioid medications, and there is already an issue

of limited access in these facilities. Moreover, a comment from a health care professional organization specifically recommended that long-term care facilities be exempt from the REMS for the above reasons and also because of the lack of opioid problems with patients over fifty-five years of age. In addition to this broad request for an exemption, this comment specifically requested an exemption for long-term care facilities from patient registries, prescriber-patient agreements, informed consents, and any regulations mandating the use of tamper-resistant formulations. Particularly with regard to the first three of these elements, this comment noted that long-term care residents require an exemption because they have ceased to be able to actively participate in their own care (e.g., they cannot read for comprehension, understand legal documents, call toll-free numbers to make inquiries) and many do not have legal guardians to assist them.

101. Similarly, a health care professional organization noted that the REMS should be sensitive to the unique process for filling prescriptions in nursing homes and assisted living facilities. This comment used the example of Medication Guides, noting that they are not required in this setting because staff members – as opposed to patients – are administering all medications.

102. Comments also expressed concern for continued access for the elderly beyond those living in assisted living or long-term care facilities. For example: (a) With regard to continuing care retirement communities, a comment recommended flexibility or targeted monitoring to ensure that the REMS does not impede access. (b) Multiple comments from health care professionals expressed concern for the elderly's access to pain medications noting that they may not be able to navigate obstacles created by the REMS. (c) A health care professional organization noted that chronic pain disproportionately affects older adults and

undertreatment is a widespread problem. (d) Finally, multiple comments that expressed particular concern for the REMS' impact on geriatric access cited a statement by the American Geriatrics Society suggesting that opioids may be a better pain treatment for older patients than NSAIDs.

vi. Rural Access Must Be Preserved

103. Several comments from a variety of stakeholders expressed concern that the REMS could have a disparate impact on access for patients and health care professionals in rural areas. For example: (a) A health care professional in rural family practice noted that increasing the burdens and costs of prescribing opioids will lead family practitioners to abandon pain management practice. In turn, patients will have to go to specialists increasing their travel costs. For example, this practitioner noted that she had to cease participation in a current REMS because of the associated burdens and costs. She now has to refer patients to a participating specialist, but it is difficult because there are few participating specialists in the area and it is even more difficult to find one that takes Medicaid. (b) A health care professional who is also a pain patient expressed concern regarding the impact of the REMS because she lives in a rural area. Specifically, she noted if an optional certification program was implemented, it might be difficult to find a "certified" prescriber to provide her with pain management. (c) A health care professional in a small rural community who is also a hospice medical director noted that he prescribes REMS drugs on a daily basis with good results for his patients and urged FDA not to limit access. (d) A hospice professional echoed the concern about access urging FDA to consider the unintended consequences of additional requirements on rural end-of-life patients. (e) A nurse suggested that small town physicians will not become certified which will result in patients

having to use prescribers who are less familiar with their condition (e.g., rely on a hospice medical director who may not have physically assessed the patient). (f) A state pain initiative echoed these concerns, noting that patients in rural areas have inadequate access to pain specialty services and are at high risk of having pain poorly treated or not treated at all. This comment also echoed those from the hospice community discussed above in noting that people with a terminal illness must be protected in considering any REMS and used shortages of high-potency liquid morphine as a negative example of how FDA actions can detrimentally affect care. (g) A state medical board expressed concern that elements including, but not limited to, prescriber certification could reduce access to pain management in their rural state.

104. Exemplifying the concern for rural access, several patients and health care professionals commented on the difficulties endured by pain patients in rural locations. For example: (a) A pain patient who noted she lives in a small community expressed concern that she will lose access to her medications if there is a certification requirement and her hometown pharmacy does not become certified. (b) A rural doctor expressed concern for access and cited that in twenty years, she has had less than five experiences with issues of diversion. [21] (c) A hospice professional in a rural area noted that in the week prior to submitting her comment, there was only one thirty cubic bottle of liquid opioid available in her entire county and she had eighteen patients to treat. (d) A hospice nurse in a semi-rural area of Missouri noted that the most reliable pharmacy in her area is having difficulty securing opioids and hospice workers have to drive to larger communities to obtain necessary medications, which increases the cost of hospice.

[21] On the other hand, comments also suggested that opioid abuse and misuse may also be more prevalent in rural areas.

vii. Veterinary Access Must Be Preserved

105. A comment from a health care professional organization representing veterinarians expressed concern regarding their animal patients having continued access to long-acting opioids post-REMS implementation. This organization noted that opioids labeled for humans are used in animals for sedation and to treat pain (e.g., cancer pain, orthopedic pain). Furthermore, this organization noted that while it is not aware of issues of overdose in veterinary patients, it appreciates the need for all health care professionals to be vigilant with regard to diversion. At minimum, this comment requested that DEA-registered, licensed veterinarians be given the opportunity to participate in the REMS prescriber certification program, if one is implemented, so they can continue to prescribe opioids. Ideally, however, this comment recommended that veterinarians be exempt from REMS requirements and stated that if such an exemption is not feasible, it would like to engage in further discussion with FDA.

V. PRESCRIBER EDUCATION AND CERTIFICATION

In its April 20, 2009 notice, FDA suggested a number of education elements for inclusion in the REMS. Comments from a wide variety of stakeholders supported these efforts, although often for different reasons. For example, many members of the pain community supported education as a means of discussing the benefits of REMS drugs and reducing the stigma associated with legitimate pain management. On the other hand, comments concerned with the over-prescription of REMS drugs emphasized that education should be a means of informing health care professionals and patients about the risks associated with the drugs, the importance of patient assessment and the dangers of inappropriate prescribing. Comments opposing education also had diverse submitters and

reasons for their opposition. For example, many comments from the pain and health care community were concerned about education requirements limiting access to REMS drugs and questioned whether such efforts were necessary. On the other hand, advocates of opioid drug reform asserted that education alone is not enough to address the issues associated with REMS drugs. The comments received regarding REMS education programs are summarized below in the following categories: Prescriber Education and Certification; Pharmacist Education and Certification; Patient Education; and Public Education.

The most voluminous comments received regarding education addressed the education of prescribers. In the April notice, FDA had announced that prescriber education would be an important component of the REMS and requested comment regarding the type of education that should be provided and how the certification process should be administered. In response, comments discussed (A) the benefits of prescriber education, (B) who should develop and oversee prescriber education, (C) what type of prescriber education should be provided, (D) how prescriber education should be delivered, (E) how the certification process should be administered,[22] and (F) concerns regarding prescriber education and certification.

[22] With regard to both prescriber and pharmacist education, different comments had different definitions of the word "certification." For example, certain comments defined certification within the confines of the REMS (i.e., a health care practitioner would fulfill the education requirements under the REMS and become "certified" to prescribe REMS drugs), while other comments appeared to define certification in terms of board certification and treated REMS education separately. For example, one comment from a health care practitioner stated that prescribers should be required to be educated for DEA registration, but opposed "certification." The Agency has sought to fairly represent all comments.

A. Benefits of Prescriber Education and Certification

106. Many comments from a variety of stakeholders supported prescriber education. However, the comments were divided as to whether such education should be mandatory.[23] A recurring theme in comments supporting prescriber education was the lack of knowledge regarding pain management and REMS drugs among prescribers. For example: (a) Several comments highlighted the lack of pain management training in medical school and other professional schools. (b) One comment from an advocate for opioid drug reform stated that clinical research suggests that prescribers are inadequately trained. (c) Several other comments noted a widespread lack of education and support for physicians involved in pain management. (d) Another comment from a continuing education (CE) provider suggested even among prescribers trained in pain management, prescriber education under the REMS may be helpful. In particular, this comment cited a survey of the pain management community indicating that the prescribing environment for opioid products is complex and that even educated and experienced physicians are interested in receiving additional training in pain management and addiction. Therefore, the comment suggested that the REMS education program should not just target general practitioners, but also pain management experts. Similarly, one comment from a pain patient suggested that a physician should not be able to claim to be a pain management expert solely because he/she is DEA-registered, instead he/she should be educated in pain management. (e) Finally, a comment from a vendor recommended that the REMS be education-based, noting that prescriber education could effectively mitigate risk if it is thoughtfully planned and

[23] With regard to prescriber, pharmacist and patient education, comments were not always clear as to whether the submitter supported mandating such education or simply making it available for voluntary participation. Moreover, some comments opposed implementing education programs under the REMS but still offered comments on how such programs should be designed, if implemented. Again, the Agency has sought to fairly represent all comments.

designed to address underlying behaviors. Specifically, this comment mapped the prescribing process to identify possible points of failure (e.g., a patient fails to provide a relevant piece of medical history). The comment then suggested that the REMS specifically target education to aid prescribers in avoiding those failures (e.g., providing prescribers with a list of questions to ask each patient).

107. Even comments supporting prescriber education, however, acknowledged the potential unintended consequences of implementing such a program. Therefore, as described in more detail below, these comments recommended developing a program that facilitates learning and minimizes the burden imposed on prescribers. For example, one comment from a scientist, while acknowledging that prescribers will likely not welcome the additional requirements, suggested an education program would have value if it could be incorporated into the existing practice and education structure.

108. Several comments recommended that FDA gather information prior to implementing the education program. For example: (a) One comment stated that prior to developing the program, the current state of prescriber education should be researched and assessed. (b) Similarly, another comment stated that for education to be effective, FDA must be specific as to what adverse outcomes it is attempting to mitigate. (c) Other comments noted that there are already education programs and state initiatives (e.g., Utah's education efforts) that should be examined. (d) One comment from a health care professional organization stated that it has been educating prescribers regarding opioids and would be willing to evaluate whether the program has been successful in changing prescribing behavior.

109. Several comments emphasized the importance of including all prescribers in any education program. These comments noted that prescribers and health care providers other than

physicians (e.g., nurses, nurse practitioners, physician assistants, certified registered nurse anesthetists) should (i) be considered when developing education and certification programs, (ii) receive CE credit within their respective discipline for the completion of the education program, and (iii) have their representative organizations included in stakeholder discussions. For example: (a) A professional nursing organization stated that nurse practitioners are often integral to pain treatment in underserved areas. (b) Another comment noted that FDA had not specifically mentioned state nursing boards as a stakeholder and asked for state nursing boards to be included in discussions regarding the development of the education program. (c) Additional comments noted that certain states allow health care professionals other than physicians (e.g., pharmacists) to prescribe drugs and the education program would need to include these prescribers. (d) Finally, one comment from a veterinary medical association stated that it hopes DEA-registered licensed veterinarians will continue to be allowed to prescribe opioids without any additional federal or state regulations. However, at minimum, this comment stated that veterinarians should be permitted to participate in the certification procedure, if necessary, in order to continue to prescribe. For a more detailed discussion of veterinary access, please see Access to Pain Medication, Section IV, Subpart G (vii).

110. Finally, several comments suggested that certain prescribers should be exempt from REMS education requirements, if the prescriber has received pain management training in another arena. For example: (a) As discussed in greater detail above,[24] hospice and palliative care professionals requested an exemption from REMS requirements. (b) Another comment recommended exempting board certified experts in pain medicine, palliative medicine and addiction medicine from an additional certification under the REMS. (c) Another comment

[24] *See* Access to Pain Medication, Section IV, G, (iv).

from a health care professional organization stated that prescribers in hospitals should be exempt from REMS certification because they so frequently prescribe opioids. As a result, this comment suggested that they are very knowledgeable about appropriate prescribing and the relevant risks. Therefore, education and certification of these prescribers will not have a significant impact.[25]

B. Who Should Develop and Oversee Prescriber Education?

111. Comments supporting REMS prescriber education generally recommended that the curriculum be developed collaboratively with stakeholders (e.g., pain organizations, prescribers and their representative organizations, patient advocacy organizations) and organizations experienced in education delivery. Comments were divided as to exactly which organizations should be included with most comments recommending one or more of the following: (a) Pain management societies; (b) health care professional societies; (c) accredited continuing medical education (CME) providers; and (d) state health care professional boards. For example, industry specifically recommended the establishment of a stakeholder working group to develop the educational program and also requested input from prescribers regarding the certification process. In a similar vein, a nursing society recommended that an oversight body, including representation by the various stakeholder professional organizations, be created with the approval of FDA and the state health care professional boards. The body would have ongoing responsibility after REMS implementation to ensure that the education program remains up-to-date and provide insights regarding program improvements.

[25] *See* Access to Pain Medication, Section IV, G, (v).

112. Several comments recommended that federal agencies, including but not limited to FDA, be involved in the development and oversight of the education program by suggesting curriculum components, approving the curriculum prior to implementation, delivering elements of the program (e.g., through letters, press releases, other media), and/or monitoring the program once implemented. For example: (a) One comment from a vendor suggested that such federal administration could ensure national uniformity. (b) Several comments recommended that the Department of Health and Human Services (HHS) and FDA, after consulting with stakeholders, approve the basic principles and content areas for the program and then have appropriate medical societies, nursing societies, and state boards develop the program. (c) Another comment from a pain organization suggested a reverse order for the process with pain management clinicians drafting the curriculum for FDA and HHS approval. (d) One comment from a vendor suggested that FDA and industry develop a robust, multipronged communication plan to disseminate educational materials via a trusted third party. (e) Finally, a couple of comments suggested that DEA be involved in developing the REMS curriculum. On the other hand, several comments objected to DEA involvement in education both because (i) FDAAA did not specifically include DEA in its language and (ii) DEA is associated with law enforcement, which has a negative stigma.

113. Not every comment, however, sought the inclusion of all the above-mentioned stakeholders. For example: (a) A vendor opposed professional organization, agency, or health care professional board involvement in the REMS beyond the initial "input" stage. Specifically, the vendor suggested that while these organizations could serve as an effective communication channel with their members, they should not be involved in the development and delivery of the educational components because they are: (i) biased; (ii)

unlikely to use innovative approaches; and (iii) out-of-touch with the realities of medical practice. Instead, the comment stated that the information necessary for education is available in literature and the education program should be implemented by an experienced third party. (b) Another comment also opposed working through pain societies, reasoning that educating their members would be preaching to the choir. (c) Finally, another comment recommended that the program be agreed upon by medical authorities other than pharmaceutical companies or government agencies.

114. Several comments expressed concern with industry developing and overseeing the education and certification requirements due to potential bias. For example: (a) One of these comments from a hospital suggested that FDA, in combination with a taskforce of clinicians, should oversee the program. (b) A couple of vendors suggested that third-party companies were better equipped to develop and implement the program. (b) A comment from a pain society suggested a program developed by industry would be inadequate in mitigating risks because it would not reach a sufficient number of prescribers. (c) Another comment from a consortium of health care professional organizations stated that the REMS proposal comes at a time when physician-industry interactions are subject to rigorous scrutiny and questioned why FDA would vest authority over the appropriate use of opioids with manufacturers. (e) Finally, a comment from an opioid drug reform advocate recommended that the federal government oversee the educational program as opposed to industry.

C. What Type of Prescriber Education Should Be Provided?

i. Considerations When Developing the REMS Curriculum

115. A variety of comments were submitted by stakeholders regarding the contents of prescriber education, with some offering suggestions for particular topics that should be covered and others providing detailed curricula and/or appending examples of education materials. Of these comments, some emphasized a more generalized approach focusing on pain management, controlled substance prescribing, and substance abuse disorders and others focused more specifically on the medications at issue and REMS logistics. Similarly, comments differed regarding the degree to which the program should focus on specific products. One option offered was to provide a standard course for all products with special sections on particular products (e.g., methadone).

116. Despite the variation in emphasis, multiple comments suggested each of the following topics: (a) Principles and importance of pain management (e.g., identifying patients for pain management, non-pharmacological alternatives for treating chronic pain, eradicating stigma and fear of DEA, progression of pain management treatment); (b) principles of addiction (e.g., how to distinguish addiction from dependence, the treatment of addiction, identifying pseudoaddiction); (c) therapeutic overview of the class of drugs and individual drugs, emphasizing both benefits (e.g., extended pain relief) and risks (e.g., misuse, the risk of overdose if certain products are chewed, respiratory depression and the use of ventilator monitoring, dangers of polypharmacy); (d) how to apply the risk/benefit analysis to particular patients; (e) opioid pharmacokinetics and pharmacodynamics; (f) appropriate patient selection (e.g., using available tools to determine if patient is opioid tolerant, has sleep apnea, is at higher risk for addiction, is open to patient education regarding

medications); (g) clinical treatment issues (e.g., best practices regarding safe use, storage, and disposal, appropriate rotation and titration of opioids); (h) appropriate dosing and length of treatment (e.g., appropriate dosing for the specific patient, including appropriate dosing adjustments for patients with concomitant conditions such as asthma); (i) signals suggesting a drug is likely to be misused or diverted; (j) relevant clinical guidelines and policies (e.g., guidelines from pain societies, state medical board policies); (k) legal aspects of pain management (e.g., relevant state and federal regulations, the Controlled Substances Act, informed consent); (l) best practices regarding patient counseling and monitoring (e.g., tools for patient communication, prescriber-patient agreements, drug screening); and (m) information regarding the REMS (e.g., the components of the REMS, the risks it seeks to mitigate, the responsibilities of various parties, REMS logistics in clinical practice).

117. In its comment, industry suggested having two stages of education with the initial curriculum providing a broader knowledge foundation and the renewal curriculum being less burdensome -- focusing on reinforcing information on patient selection, dosing, safe storage and disposal and introducing any newly available information.

118. One comment from a health care professional recommended that facilities should be encouraged to do programs that go beyond diversion education to encompass drug utilization evaluation.

119. In general, comments recommended that all prescribers be educated with a standardized curriculum. However, several comments noted areas that might qualify for special mention or tailoring of the curriculum. (a) Multiple comments suggested that the curriculum could be tailored to different specialties (e.g., pediatrics, hospice, geriatrics). (b) Several comments suggested tailoring the curriculum to include information on different disease

ii. Relying on Existing Programs and Guidelines For Prescriber Education

120. Several comments recommended considering existing guidelines and programs when developing the curriculum for REMS prescriber education. For example, comments recommended drawing on curricula from a variety of programs and board certifications offered by health care professional societies and pain organizations either as models for the REMS program, or actually adopting them as the REMS program. For example, a comment from a consortium of health care professional organizations noted that the American Medical Association (AMA) has developed a twelve-hour Pain Management CME program that is currently available in both online and print versions, with planned improvements in the near future to address concerns regarding REMS drugs and to complement a CME program developed by HHS. The comment noted that the AMA has been collaborating with medical schools to develop similar education programs for medical students and residents.

121. Beyond professional society certifications and programs, several vendors stated that they had existing programs that could be tailored to satisfy the needs of the REMS prescriber education program. In addition, a couple of comments from a health care professional and liability carriers advisory committee recommended coordinating the REMS with insurance companies' existing risk management programs and promoting participation in risk

management. Similarly, a lawyer noted that the Texas worker's compensation program has made efforts to curb the inappropriate prescribing of opioids to injured workers and suggested that those efforts should be expanded.

122. Similarly, as noted above, several comments suggested employing and/or developing clinical guidelines as part of the prescriber education program. These comments either attached guidelines with their submissions or suggested resources (e.g., the Federation of State Medical Board Model Policy, the American Academy of Pain Medicine / The American Academy of Pain Management / American Pain Society Guideline for Chronic Opioid Therapy). One comment noted that REMS drugs are often prescribed outside of evidence-based guidelines and recommended that prescribers need to be more aware about the evidenced-based role of narcotic analgesics in treating pain. In addition, several comments recommended that the treatment of children be addressed in any guidelines incorporated into the REMS, although most products are not labeled for such use.

123. Not all comments, however, supported strict adherence to guidelines. For example: (a) One comment from a pain institute urged cautioned in adopting some guidelines developed by certain pain organizations. This comment expressed concern that the guidelines were indirectly financed by industry and, as a result, may be biased. Instead, this comment suggested that prescribers should be pre-qualified to engage in chronic pain management – which does not have the urgency of acute pain management – to ensure that they properly determine the appropriate treatment; monitor the patient appropriately; and are willing to discontinue opioid therapy, if necessary. (b) One comment stated that the curriculum should acknowledge that while guidelines and standards are useful, some patients with extraordinary conditions may require treatment exceeding usual and customary practices.

D. How Should Prescriber Education Be Delivered?

i. Designing a Prescriber Education Program

124. Comments supporting REMS prescriber education almost universally recommended designing a program that will minimize the burden on prescribers, encourage participation, facilitate learning, present objective information, demonstrate competency, utilize proven methods, and focus on implementing the education in practice.

125. To that end, the vast majority of these comments supported a program that is (a) easily accessible to prescribers located all across the country and in a variety of practice settings, (b) succinct, (c) eligible for CE and maintenance of certification (MOC) credit, (d) presented in a variety of media formats to suit provider preferences and various learning styles, (e) concluded with a test of competency; and (f) based on methods that have been successful in changing prescribing behavior in the past.

126. Several comments recommended offering the program in a variety of formats to ensure accessibility and increase participation. Suggested modalities included: live sessions, journal clubs, websites (both pre-existing and REMS-specific), written materials, clinical case studies, "ask the experts" sessions, podcasts, CD ROMs, and a hotline. In support, one comment stated that multi-media education will more likely lead to behavior change than reviewing a slide show or article. Another comment offered survey data to support the importance of using multiple modalities.

127. Another comment from a vendor recommended that participants in the education program be: (a) actively involved in the program; (b) responsible for their own learning; (c) stimulated in a variety of ways; (d) comfortable in their learning environment; and (e)

required to show that they can apply their knowledge to clinical situations to demonstrate that education has led to behavioral change.

128. Several comments offered specific ideas as to how a web-based program could be designed. For example: (a) A couple of comments from health care professional organizations – including one from a consortium of sixteen such organizations – recommended a well-designed web-based CME course. (b) Multiple comments suggested prescribers be required to complete a short test to demonstrate competency. If unable to complete the test successfully, they would be offered a brief online training (no more than two hours) and permitted to retake the test, the passage of which would be a prerequisite to certification. (c) A comment from a vendor offered to develop an online certification program where participants would complete tests after reviewing education modules, receive a document of completion, and after completing all modules, would be listed on a website as certified. (d) Another comment recommended that the educational program be delivered through a computer interface and require no more than one hour of the prescriber's time. (e) A health care professional organization recommended that all required forms and documents for the REMS be placed in electronic modules in one database with one website interface and an all-inclusive verification form to streamline and minimize regulatory requirements. (f) Another health care professional organization suggested that prescriber and patient education modules be centralized, and used its own website as an example. (g) A vendor stated that they could develop a website for the REMS which would: (i) include all Medication Guides, and (ii) host training and generate a report to the manufacturer when certification was complete. This comment stated that marketing of the website could be

done via e-mail blasts to health care professionals, and advertisements in professional journals and websites.

129. A couple of comments from vendors suggested using their technology. For example: (a) One vendor suggested using its web-based system that tracks the participants understanding and completion of the material. (b) Another vendor suggested that its website, offering a bi-directional channel of communication with prescribers, could be used in the REMS educational program.

130. Other comments offered alternative delivery and testing methods. (a) A comment from a prescriber recommended a yearly CME course and a standardized national board examination for physicians to become certified in pain management. (b) A comment from a CME provider recommended a one-day live course followed by a comprehensive examination. The program would be offered approximately once every couple of months in different areas of the country. (c) A comment from an opioid drug reform advocate recommended that prescribers be certified after a background check and the completion of a course and written exam. (d) Another comment recommended that there be an initial education program and then renewal programs, lasting no more than one hour. (e) A comment from a hospice provider recommended that certification involve the completion of an approved course, self-study, or conference and successful completion of an examination. (f) A comment from a health care professional organization suggested using provider notification networks to educate providers (e.g., provide informational letters, medication guides, package inserts, knowledge assessments and CME applications) noting that it will reduce administrative burdens and confusion since many professional organizations are already employing such networks. This comment was echoed by the liability carriers

131. Other comments, however, suggested that some of the elements of the above proposals may not be practical. For example: (a) One comment stated that one day (eight hours) would be insufficient to cover all opioids. This comment noted that buprenorphine training is eight hours long and covers only a single drug. (b) One comment questioned the feasibility of enforcing a national certification examination considering the number of affected prescribers and suggested that at the most FDA will likely only be able to require that prescribers have a certain number of hours of training. Furthermore, this comment suggested that the latter option is preferable. (c) One comment recommended that the educational program be mindful of accessibility for prescribers in rural practices who may find it difficult to attend a live seminar.

132. Several comments recommended that education be repeated or reinforced at set intervals. Comments presented a range of options with regard to how often education should be required. For example: (a) A comment recommended every six months; (b) another comment recommended every year; (c) a couple of comments recommended every other year; (d) another comment recommended every three years; and (e) another comment simply suggested that renewal be within a "reasonable" time. Similarly, a comment from a prescriber discussed how his state, California, has mandatory education in pain control but noted that the program is only every few years, which has undermined its effectiveness.

133. Several comments recommended that the educational components of the REMS include redundancy in messaging for maximum effectiveness. For example, a couple of comments

highlighted that pharmaceutical marketing tactics are very successful in changing prescribing behavior and that similar strategies should be employed under the REMS. One of these comments noted that a key element of drug marketing is redundancy with constant repetition and reminders.

134. One comment from a lawyer recommended considering the qualifications of instructors and employing a multidisciplinary approach. In particular, this comment noted that teachers in the REMS education program should be experts in their particular topics (e.g., physicians should not be teaching other physicians about the law).

ii. Extending Education Into Practice

135. Several comments suggested that beyond a course or examination, the REMS prescriber education program should include a practical component either within the confines of the course or by extending the program into the prescriber's practice. For example, one pain patient recommended that a portion of the education program be "hands on." Another comment suggested reinforcing education in the prescriber's practice (e.g., sending e-mails and newsletters to prescribers with consistent messaging). Finally, another comment discussed providing CME credit not only for attending the course but also additional CME credit for actually implementing practice changes in response to the training.

136. Multiple comments suggested education should be ongoing with the implementation of a physician mentor program or hotline for prescribers to call or e-mail with questions regarding pain control, substance abuse, and addiction. For example: (a) One comment suggested creating national support groups to assist primary care providers by telephone. This prescriber noted he was involved in a pilot of local program of this type which was highly successful. (b) A few comments from a health care professional organization and a

consortium of such organizations recommended that physician mentoring programs be fully funded and more widely implemented. This comment suggested that physician behaviors are most likely to change when assisted by other physicians and cited positive experiences with other mentorship programs. (c) One comment suggested that a mentor program could be potentially most beneficial to rural prescribers.

137. Multiple comments recommended that prescribers be provided with tools or tool kits to incorporate into their practices. For example: (a) One comment suggested offering prescribers guidance on how to question patients to obtain the information necessary for appropriate patient selection and treatment (e.g., do not just ask if the patient is taking his/her medication as prescribed, but rather how many pills he/she is consuming a day). (b) Another comment from a vendor mentioned a tool that it had developed for patient assessment and selection, but noted that for it to be effective, prescribers had to be educated in pain management. Other comments included tool kits in their submissions. For example, one comment from a vendor attached its tool kit including a multimedia collection of resources focusing on patient assessment and monitoring and provided survey data regarding its current use. Another comment from a lawyer suggested that prescribers should receive informed consent and treatment agreement kits to assist them in their practice (e.g., a CD Rom for the prescriber, a list of resources for further study).

138. One example of a multiple-modality education program that provided prescribers with practical tools was described in a comment from a coalition of health care entities working to address opioid issues in Washington State. Based on their experience, they recommended a multipronged approach including (a) empowering physicians with tools for education, (b) patient screening, (c) feedback and monitoring, (d) an outcomes registry, (e)

working with law enforcement and drug courts, and (f) a hotline like "1-800-pain-doc" for real-time guidance.

iii. FDA's Role in Educating Prescribers

139. Several comments stated that FDA should educate prescribers, either exclusively or in addition to other educational components. For example, a comment suggested FDA issue press releases regarding opioid prescribing.

140. Multiple comments recommended that FDA revise the labeling of REMS drugs to better inform prescribers as to their appropriate use. (a) As discussed above, multiple comments recommended that FDA limit the indications for certain REMS drugs (e.g., restricting the use of extended-release products to severe pain).[26] (b) Another comment recommended providing a safe conversion factor in each product's labeling to assist prescribers when patients are moved from one opioid product to another. (c) Another comment suggested adding a black box warning focusing providers on the ethical considerations in prescribing extended-release opioids. (d) Another comment recommended a heightened warning regarding the risk of respiratory depression and methods to reduce the risk through ventilator monitoring. (e) Another comment recommended placing dosing limits on REMS drugs when used to treat non-cancer pain. The prescriber submitting this comment noted that he has never had a patient respond positively to extended release oxycodone when dosed above ninety to one hundred milligrams a day and it can cause hyperalgesia. (f) One comment recommended: (i) improving the consistency in labeling, including between generics and innovators; and (ii) providing more appropriate dosing and prescribing information (e.g., immediately clarify appropriate starting doses in opioid naïve patients). This comment noted that the labeling changes should precede any other education

[26] *See* Access to Pain Medication, Section IV, Subpart E.

requirements so prescribers receive accurate information. (f) Finally, a comment from a consortium of health care professional organizations strongly urged FDA to consider comments regarding improving the labeling of REMS drugs and, in particular, address appropriate therapeutic ranges for methadone.

141. A couple of comments from a manufacturer and a lawyer recommended that FDA mandate that "safe use" recommendations be included in REMS drugs labeling, including direct references to the prescriber's responsibility to engage in risk assessment and patient monitoring (e.g., periodic urinalysis, prescription drug monitoring database queries). One of these comments provided particular language for inclusion in the labeling.

142. Another comment requested that FDA immediately issue a "Dear Colleague" letter to every doctor authorized to prescribe methadone stating that in the absence of proven tolerance, dosages above thirty milligrams per day can be fatal.[27] The comment noted that this measure could be undertaken at essentially no cost.

143. As discussed in greater detail below, several comments suggested that FDA improve Medication Guides (Med Guides) and package inserts to better inform practitioners and patients. *See* Patient Education, Section VII, Subpart D (ii).

144. Multiple comments recommended that FDA more stringently oversee the promotion of REMS drugs to ensure that physicians receive accurate information regarding appropriate prescribing and use. For example: (a) A comment stated that industry is misinforming prescribers and medical schools. (b) Another comment from a health care professional stated that industry controls the studies performed, so prescribers receive inaccurate information. (c) Similarly, another prescriber requested unbiased information to counter the marketing materials he receives. In particular, this prescriber requested information

[27] This comment noted that this guideline is still four times higher than recommended by pain organizations.

which solely focuses on good patient care. (d) An advocate for opioid drug reform stated that the communications from opioid manufacturers on the Internet and targeting pain societies should be monitored to ensure accuracy. (e) Finally, another comment suggested that all marketing incentives to prescribe REMS drugs should be eliminated.

145. One comment requested that FDA set a "standard of care" for prescribers treating patients which would trigger legal rights for the patient to sue if a prescriber violated the standard. The comment noted that often there are not sufficient resources to support prosecution of prescribers. A liability insurance carrier noted that having a standard of care would allow prescribers to demonstrate that they have met the standard, which would minimize their liability.

E. How Should The Certification Process Be Administered?

i. Linking REMS Certification To DEA Registration

146. Numerous comments from a wide variety of stakeholders – including one from a pain organization attaching a supporting petition with four thousand and seventy-five signatures – recommended certifying prescribers by making the successful completion of the REMS education program a prerequisite to DEA registration, both at the time of initial registration and renewal. In support, these comments noted that linking REMS certification to DEA registration would: (a) maximize prescriber participation; (b) minimize cost; and (c) allow pharmacists to confirm a prescriber's certification through existing systems (i.e., a pharmacist already verifies that a prescriber is DEA-registered prior to filling an opioid prescription, so there would not be an additional step). For additional comments regarding education verification through existing pharmacy systems, see Pharmacy Systems, Section X.

147. In its comment, industry expressed interest in exploring whether REMS education could be linked to DEA registration. In particular, it stated that DEA linkage could be beneficial not only for the reasons cited in the above paragraph but also because it would: (a) reduce the appearance of bias because a government agency would certify prescribers as opposed to manufacturers, (b) provide industry with a method of ensuring that non-physician prescribers are included, as all prescribers must register with DEA, and (c) have the potential to be expanded, if necessary, to include additional controlled substances.

148. Several comments, however, questioned the feasibility of linking REMS certification to DEA registration. For example: (a) Multiple comments noted logistical concerns. For example, prescribers in certain institutional or hospital settings are not required to have an individual DEA number. Therefore, linking certification to DEA registration could effectively bar these practitioners from prescribing REMS drugs. Another issue raised was that there is not currently a real-time electronic database for verifying DEA registration. (b) A comment questioned how a prescriber's knowledge could be certified by DEA other than DEA asking questions in its application regarding the prescriber's educational background and stated that DEA should not be responsible for educating prescribers or enforcing education requirements. On the other hand, another comment suggested the solution of having a separate DEA registration category for providers who complete REMS training, similar to the process for certifying buprenorphine prescribers.

149. Multiple comments questioned whether the statutory authority exists to link REMS certification to DEA registration. Similarly, a society of pain educators stated that while FDA lacks the authority to compel DEA or any other federal or state authorities to administer certification, FDA also lacks the authority to regulate health care practice.

Therefore, this comment concluded that certification must be recognized by an entity other than FDA (e.g., DEA, professional liability insurers).

150. Finally, multiple comments opposed linking certification to the DEA because of its association with law enforcement. As discussed below, a couple of these comments recommended certification be administered by state licensing boards. Additionally, one of these comments questioned why DEA would be involved in education since FDAAA did not provide for DEA involvement.

ii. Alternatives to Linking Certification to DEA Registration

151. Several comments suggested that state government agencies could also be involved in REMS certification including: (1) State medical boards, by making certification a prerequisite for licensure; (2) state departments of health; and (3) state drug enforcement agencies. For example, one comment recommended linking certification to state licensure because it would prevent prescribers from simply not registering with DEA to avoid the requirements; all prescribers must retain state licensure. Another comment suggested that REMS education could be a prerequisite to Controlled Dangerous Substance (CDS) registration.

152. A few comments suggested that FDA could send reminder notices to prescribers in advance of DEA registration or state licensure.

153. Multiple comments supported the development of a REMS database/website listing all certified prescribers. One comment suggested that in the database, the certification could be recorded along with the prescriber's DEA number and National Provider Identifier (NPI). Another comment emphasized that the certification information provided in the database would need to be real-time.

154. Finally, as noted above, the petition submitted by the pain organization supported linking prescriber education to DEA registration. However, in the event DEA-linkage is not possible, the respondents supported the alternative of incorporating incentives into REMS education to maximize participation. For a more detailed discussion of possible incentives, see Subpart F (ii) of this section.

iii. Timeline for Certification

155. With regard to when certification requirements should take effect, one comment stated that FDA should specify a deadline. The comment recommended allowing prescribers two to four years to become certified.

156. A couple of comments suggested prescriber education and certification should be implemented in phases. Specifically, one pharmacy recommended that the education requirements be phased-in to prevent prescriptions from being rejected by pharmacists while prescribers are in the certification process. Similarly, industry suggested a phased-in approach to the educational components with actions being broken into three phases. For a more detailed discussion regarding the timing of REMS implementation, see Implementation, Section XIII, E.

iv. Financial Considerations Regarding Prescriber Education and Certification

157. Numerous comments expressed concern regarding the financial cost of education and certification requirements. One pharmacy was concerned about the cost of maintaining a REMS database of certified prescribers and suggested the cost should be borne by the manufacturers and FDA. Another comment from the state medical boards' representative organization stated that the REMS educational component needs to be adequately funded so it does not become an unfunded mandate on the states.

158. Several comments suggested that to maximize participation, the cost of education should not be borne by the prescriber. Many of these comments suggested that all aspects of REMS certification should be provided free to prescribers. Another comment suggested that industry should share the cost of training with the prescriber.

159. A comment suggested that while prescriber education will be costly, in the end the benefits (e.g., continuity of care, less money spent on enforcement activities related to diversion) will save money.

160. In conjunction with education, a couple of comments stated that there should be reimbursement codes (e.g., International Classification of Diseases codes) for patient assessment and monitoring to encourage behavior change once prescribers are educated.

161. Multiple comments from pain patients, in opposing certification of prescribers, cited the concern that such a requirement would drive up medication costs.

F. Concerns Regarding Prescriber Education and Certification

i. Concern For Access to Medication[28]

162. Many comments from a diverse group of stakeholders strongly opposed, opposed or expressed serious reservations about mandating education to prescribe REMS drugs. Specifically, these comments cited the following reasons for their concerns: (a) The majority of prescriptions for opioid products are written by generalists who likely would not take the time to become certified, which in turn would reduce the number of prescribers of these medications and limit patient access, particularly in already underserved areas (e.g., one comment analogized REMS educational requirements to buprenorphine training and noted that few prescribers have taken the training which has resulted in limited patient

[28] *See also* Access to Pain Medication, Section IV, F.

access). (b) If generalists fail to become certified, pain clinics could become inundated causing delays in patient care. (c) As a related concern, the education program would be a significant financial and time burden both for individual prescribers and in the aggregate (e.g., all REMS drugs prescribers). (d) Requiring certification to prescribe REMS drugs could shift prescribing to other pain medications, even if less appropriate for the patient. (e) It is possible that being designated a "certified" prescriber could lead to overconfidence and, as a result, prescribers who complete REMS education could over-prescribe opioids (e.g., one comment stated that the message in certifying prescribers could be that opioids are the primary tool in pain management). (f) It is already difficult for patients to obtain REMS drugs and burdening access more will undermine appropriate treatment. (g) Singling these drugs out for an education program could increase their stigma (e.g., a comment compared the education program to the system currently in place for prescribing methadone for the treatment of addiction where only enrolled prescribers, dispensers, and patients may participate). This concern for access led several patients and other concerned individuals to expressly support education, but not necessarily certification, of prescribers. (h) While education is important, it is a function of the states, not federal government.

163. As an example, one comment from a prescriber currently engaged in palliative care practice stated he would, in his current field, undertake certification. However, this prescriber had previously been a primary care provider and stated that as a generalist, he never would have gone through certification. Therefore, he opposed prescriber certification because in addition to reducing access, he believes it would have limited value. In his opinion, chronic pain specialists are more likely to over-prescribe than primary care providers.

164. Multiple comments from pain patients noted that if prescribers fail to become certified, patients will have to seek out other physicians which will damage patient care. Specifically, a couple of these comments noted that the new physician will not know the patient and their background which will inhibit appropriate treatment. Another comment expressed concern that the pool of certified prescribers will be limited and, as a result, powerful, since patients will have few alternatives.

165. Multiple comments expressing concern regarding the education program's impact on access suggested that voluntary education efforts be tried first. For example: (a) A consortium of health care professional organizations opposed mandatory education and certification stating it should only be used as a last resort to keep high-risk products with unique and important benefits on the market. Their opposition was based on concerns for physicians opting-out of certification and damaging access, particularly for patients in underserved areas, and possible shifts in prescribing. This comment cited several state initiatives that resulted in reduced access. Furthermore, it stated that FDA should evaluate alternative strategies to industry-based activities and promote voluntary provider education. (b) Similarly, another comment suggested that to ensure prescriber education does not impinge on patient access to medications, mandatory education should only be considered after determining whether a voluntary education program could be effective in mitigating risks. (c) Finally, another comment stated that prescriber education should be encouraged, but not mandated.

166. Several comments expressed particular concern for burdening prescribers in rural areas and noted the importance of ensuring that the requirements do not shrink the prescriber pool to the point of creating geographical gaps in care where patients in extreme pain have to travel

long distances to get relief. For a more detailed discussion of comments discussing rural access, please see Access to Pain Medication, Section IV, G (vi).

ii. Possible Solutions to the Concern for Access

167. With regard to the question of whether generalists would avoid certification, and thereby reduce access to REMS drugs, one comment recommended conducting a survey prior to REMS implementation to determine whether this is a genuine concern.

168. Several comments stated that sufficient access to REMS drugs could be preserved even with a mandatory education program if prescribers were not permitted to opt-out of certification. For example, one comment from a health care professional noted that in state of Tennessee, the licensing authority made an across-the-board requirement for licensure renewal that all physicians take a two-hour, online CME course on Schedule II and long-acting narcotics. This comment noted that by not allowing an "opt-out" there was no loss of prescribers. One comment from a health care professional also noted that not allowing prescribers to opt-out will ensure that they are all adhering to best practices.

169. As another possible solution, several comments recommended providing incentives to prescribers to maximize participation and, therefore, preserve access to pain medications. In particular, a couple of comments suggested waiving the prescriber's DEA registration fee in exchange for participation. Another comment recommended that participation in REMS education should provide some liability protection for prescribers.

170. One comment stated that as opposed to mandating certification under the REMS, FDA should support the efforts of professional societies to educate and certify members (e.g., the American Osteopathic Association). Similarly, another comment stated that national societies offer great educational opportunities and FDA should not duplicate these

resources. However, this comment suggested the agency might want to establish some minimum standards.

171. As noted above, of particular concern is the impact of prescriber certification on generalists or primary care providers (PCPs) and the resulting potential decrease in access. To that end, comments offered a wide array of solutions: (a) One comment stated that REMS certification would drive PCPs out of pain management, and suggested that apprenticeships for PCPs be developed. (b) One comment suggested that board certified prescribers in any pain specialty (e.g., pain management, anesthesiology, physiatry, neurology, rheumatology) should be permitted to continue to prescribe REMS drugs without additional certifications. Moreover, PCPs who are experienced in pain management and active in the pain management community should also be permitted to prescribe – without certification – if three board certified pain specialists endorse them. (c) Another comment suggested that pain specialists be required to complete REMS certification. Those prescribers would then be responsible for the initial treatment of all patients, and for providing a letter to the patient's PCP. Then, as long as the PCP maintained the letter in his/her files, he/she would be permitted to continue the patient's treatment. (d) One comment stated that while a patient is on a stable dose of REMS drugs, a PCP could provide treatment, but to change the prescription, the patient would have to see a pain specialist. (e) Similarly, another comment recommended that a treatment parameter or threshold be set, which would trigger a requirement that a PCP consult with a pain specialist, either in person or by teleconference. (e) Finally, one comment suggested that in non-emergency situations, all patients would be required to see a pain specialist, but for a short time or in emergency situations, PCPs would be eligible to prescribe. This comment noted, however, that the

trigger for referring the patient to a specialist would have to be expressly defined. (f) Another comment stated that pain management practice should be limited to those prescribers who had pain management training in medical school (e.g., pain fellows) and the prescribing of REMS drugs by PCPs should cease.

xii. Concern for Whether REMS Prescriber Education is Necessary[29]

172. Several comments questioned the need for a REMS education program, stating that medical school is the appropriate venue for pain management education and that the expectation should be that every physician is adequately trained in pain management, as opposed to only those "certified." Furthermore, one comment stated that instead of a REMS education program, the government should encourage medical schools to enhance their pain management education with the threat of withholding federal funding if they fail to do so. This comment stated that this is a more proactive approach than trying to educate prescribers already in practice.

173. Similarly, numerous comments stated that state licensing boards are already responsible for ensuring that every prescriber is sufficiently knowledgeable to safely prescribe opioids, without there being a separate REMS certification procedure. Even among comments supporting additional education for prescribers, many of them noted that the education of health care professionals is the purview of the states as opposed to the federal government. For example: (a) One comment from a health care professional suggested that states should require CME in pain management as has been proposed in Michigan. (b) Another comment suggested that there should be a National Best Practice developed, but its enforcement

[29] Numerous comments from the hospice and palliative care community opposed prescriber education requirements. In addition to concerns for diminished access, these comments also stated that prescriber education was unnecessary in their community because they are already highly trained in the use of opioids. For a discussion of their concerns and request for an exemption from REMS requirements, please see Access to Pain Medication, Section IV, G, (iv).

should be through the state professional boards. (c) A state medical board questioned whether FDA had considered putting REMS resources into state programs, since issues with REMS drugs vary by state. (d) Finally, the state medical boards' representative organization confirmed that the boards are already actively educating physicians regarding appropriate prescribing of controlled substances and questioned the need for a REMS prescriber education program. On the other hand, another comment criticized certain state education programs, singling out Oregon's program in particular.

174. One comment from a pain patient questioned why it would be necessary for prescribers of REMS drugs to become certified when they are not required to be certified to prescribe other drugs that have been misused or over-prescribed, for example, Ritalin.

175. One comment from a health care professional organization stated that a separate REMS certification procedure is unnecessary and instead suggested that education should be through board recertification for each medical specialty for all disciplines that intersect with that specialty. This comment acknowledged that this method would not capture every prescriber, but suggested it was preferable to a REMS education program.

176. Finally, several comments from health care professionals and patients stated that additional prescriber education is unnecessary because prescribers are already very knowledgeable and engaged in responsible prescribing. In addition, many patients, while not specifically relating their comments to the proposed prescriber education requirements, discussed how their prescriber already ensures appropriate use of opioids (e.g., through patient monitoring, prescriber-patient agreements). In a similar vein, a pain patient stated that if a prescriber needs additional information, they will seek it out. On the other hand, several other pain patients and health care professionals had interactions with undereducated prescribers. For

example: (a) One comment stated that health care providers receive inadequate training in pain management in school which, in fact, reinforces bias, stigma, and misinformation. (b) Another comment from a member of a state complaint review board noted that the primary origin of complaints with regard to opioid prescribing is a lack of knowledge even when the prescriber is board certified. (c) Finally, several comments from pain patients, including a couple who struggled with addiction, stated that they had been treated by doctors lacking knowledge regarding pain management. One noted that sometimes prescribers are less knowledgeable than their patients.

xiii. Concern for the Effectiveness of Prescriber Education and Possible Solutions

177. Several comments stated that education and/or testing alone will be insufficient to mitigate risks, although these comments cited different reasons for their concern. (a) One contingent of comments stated that there is a lack of data to suggest that prescriber education will be effective particularly since many of the risks to be mitigated are not inherent in the product, but rather the result of abuse or misuse. (b) Another contingent suggested that prescriber education will be ineffective because the only prescribers who will become certified are the "pill mill" doctors who are responsible for the problems with REMS drugs. These comments asserted that educating prescribers will not result in a change in behavior. They asserted that these prescribers are already aware – but indifferent – to the dangers posed to their patients. These comment expressed concern that other doctors who are responsible, but overworked may not become certified due to the burden. Generally, these comments supported efforts targeted at diversion. For a more detailed discussion of recommendations for reducing diversion, see Methods to Curb Diversion, Section IX. (c) Other comments, however, did not question the correlation between physician behavior and risk mitigation,

but instead suggested that education alone would be insufficient to change prescribing behavior. In particular, multiple comments stated that even when followed by examinations, traditional education rarely influences prescribing practices. In a similar vein, one comment noted that it may take years before publications even in prestigious medical journals have any impact on clinical practice.

178. As a possible solution to enhance the effectiveness of prescriber education, one comment from a vendor suggested using an audit and feedback system where prescribers would submit prescriptions for analysis. Using clinical algorithms, prescriptions that deviated from evidence-based practice or raised concerns about abuse or misuse would be identified. Then, education would be targeted to the specific prescriber at issue. In particular, the prescriber would be notified, the problem explained (e.g., inappropriate patient selection, patients receiving opioids from multiple sources, frequent dose increases), and alternative strategies suggested with references to medical literature. The prescriber would be permitted to provide feedback in instances where he/she believed the prescription was justified. This comment cited positive experiences with audit and feedback systems and noted that such a system (a) would not require a prescriber to remember CME and apply the lessons at a later date, (b) could be implemented quickly, (c) could be tailored to suit the needs of payors, and (d) could be enhanced to include a patient monitoring component.

179. Several comments suggested that without proof of effectiveness, the risk of limiting patient access to medications is not worth any potential benefits of mandating education. On the other hand, one of these comments noted that education has been effective in lowering the over-prescription of antibiotics. This example suggests that education could be effective with regard to opioid prescribing as well. Similarly, a couple of comments cited

buprenorphine training as a successful example of an education program and recommended that the REMS education program be informed by that experience.

180. To resolve the issue of whether education would be effective and at what cost, several comments recommended that the elements of the REMS be pre-tested prior to implementation. In particular, one comment suggested that the program be pre-tested to ensure it meets desired outcomes not just in knowledge acquisition but also with regard to knowledge application in the clinical setting. Another comment suggested pre-testing to ensure the educational components are not overly burdensome. For more information regarding the pre-testing of REMS elements, see REMS Evaluation and Metrics, Section XI, B.

VI. PHARMACIST EDUCATION AND CERTIFICATION

In its April 20, 2009 notice, FDA suggested education of pharmacists could be an important component of the REMS. Significantly fewer comments were received regarding pharmacist education than prescriber education. However, many of the themes presented in the comments were similar. In particular, FDA had requested comment on the type of education that should be provided and how the certification process should be administered. In response, comments discussed (A) the benefits of pharmacist education (B) who should develop and oversee pharmacist education, (C) what type of pharmacist education should be provided, (D) how pharmacist education should be delivered, (E) how the certification process should be administered, and (F) concerns regarding pharmacist education and certification.

A. Benefits of Pharmacist Education

181. Comments from a variety of stakeholders supported pharmacist education under the REMS. In addition, several comments opposing pharmacist education still offered suggestions for implementation in the event this element is incorporated into the REMS. Similar to prescriber education, comments widely recommended developing the program with extensive stakeholder and expert input (e.g., practitioners and their representative professional organizations).

B. Who Should Develop and Oversee Pharmacist Education?

182. Several comments recommended the creation of an expert panel to develop and/or oversee the pharmacist education program. For example: (a) One comment from a health care professional organization recommended that pharmacist education be overseen by a panel of government and non-government experts – with state pharmacy boards being involved as appropriate – to ensure the program is up-to-date and its goals are being met. (b) Similarly, a comment from a pain organization recommended the development of an oversight body with representation from various stakeholder professional organizations. It recommended that the panel be approved by HHS, as well as the state professional boards as appropriate. (c) Another comment recommended the development of a multidisciplinary advisory body and noted that any program that leaves education to industry alone will be inadequate and fail to reach the broadest base of participants.

183. Several comments recommended that federal agencies be involved in the development and/or delivery of the program. For example: (a) Comments suggested that HHS and FDA, after consulting with stakeholders, approve the basic principles and content areas for the program and then have appropriate pharmacist professional organizations and state boards

develop the program. (b) Similarly, another comment recommended a reverse process with a panel of current practitioners drafting the curriculum for FDA and HHS approval. However, not every comment welcomed government involvement in the development of the program. One comment from a pain organization specifically stated that government agencies should not develop competency requirements and instead recommended that they be developed with the expert input of specialty pain organizations.

184. Several comments recommended that education be delivered through the state boards of pharmacy. For example: (a) One comment from a health care system supported an education program for all pharmacists that was developed by pain and palliative care experts and promulgated through the state boards of pharmacy. (b) Similarly, one comment suggested that there should be a National Best Practice developed, but that its enforcement should be through the state professional boards. (c) Finally, one comment stated that pharmacist education should primarily be the responsibility of the state pharmacy boards, working in conjunction with the state medical boards.

185. One comment suggested that pharmacy schools should expand their pain management offerings to include the full spectrum of pain management strategies and the appropriate role of medications.

C. What Type of Pharmacist Education Should Be Provided?

186. Many of the same topics that were recommended for the prescriber education program were also included in pharmacist education comments. However, several comments highlighted that certain pharmacist-specific issues would need to receive particular attention. For example, one comment highlighted the need to educate pharmacists on identifying fraudulent prescriptions. Other recommended topics for the pharmacist curriculum

included: (a) class and product-specific benefits and risks (e.g., dangers of dissolving or crushing extended-release formulations, assessing benefits and risks with regard to a particular patient, risk of respiratory depression); (b) information on the structure and implementation of the REMS itself; (c) practice guidelines; (d) dosing and administration information (e.g., dosing based on opioid tolerance), (e) identifying non-legitimate patients, (f) information on safe storage and disposal, (g) the importance of patient education, (h) distinguishing between tolerance and addiction and the treatment of the latter, (i) the pharmacology of REMS drugs (e.g., possible drug-drug interactions), (j) general principles of pain management (e.g., pain assessment, non-pharmacological alternatives), (k) clinical opioid management issues (e.g., the titration of opioids); and (l) the legal aspects of controlled substance prescribing (e.g., state and federal regulation).

187. With regard to whether the curriculum should be standardized or tailored to different participants, one comment from a vendor emphasized the need to focus on practice-specific challenges. Another comment recommended having a standardized curriculum with special sections for particular products.

188. One comment from a pain organization suggested that the curriculum include core principles of prescribing and practice such as those proposed by the Federation of State Medical Board Model Policy, the American Academy of Pain Medicine / The American Academy of Pain Management / American Pain Society Guideline for Chronic Opioid Therapy and other authoritative sources.

189. As discussed above,[30] several comments recommended that FDA change the labeling of REMS drugs and suggested that until those changes are made, education will be ineffective.

[30] *See* Prescriber Education and Certification, Section V, D (iii).

In addition, one comment recommended that FDA issue press releases to educate health care practitioners regarding REMS drugs.

190. Multiple comments discussed the current availability of pharmacist education. One comment distinguished the availability of pain management training for pharmacists as compared to prescribers noting that pharmacists cannot become board certified in pain management. However, this comment noted that they can receive education and credentialing in pain management through the American Academy of Pain Management. Another comment mentioned that Utah had included pharmacists in a program where opioid education pamphlets were distributed to health care professionals.

D. How Should Pharmacist Education Be Delivered?

191. Similar to prescriber education, pharmacist education comments emphasized the importance of ensuring accessibility and minimizing the burden on participants to encourage participation and facilitate learning. To that end, comments supported a program that is (a) easily accessible (e.g., offered by more than one provider; easily incorporated into existing schedules and programs), (b) eligible for CE credit towards licensure renewal, (c) presented in a variety of media formats and through a variety of channels to suit participant preferences and learning styles, and (d) based on proven approaches. For example: (i) One comment, while acknowledging that pharmacists would likely not welcome the additional requirements, suggested an education program would have value if it could be incorporated into the existing practice and education structure. Similarly, a pharmacy noted that state boards currently require CE, approved by the American Council on Pharmaceutical Education, for license renewal. This comment strongly recommended that any required pharmacist education be managed within the existing pharmacist

continuing education system. (ii) Similarly, multiple comments recommended that the education and certification process be accessible through several accredited CE providers to reach the widest number of participants. One comment suggested that pharmacies should then be able to choose which accredited program pharmacists complete. Another comment noted that offering the program through multiple providers will ensure maximum compatibility with company communication systems.

192. Several comments recommended a flexibly scheduled, interactive, and accessible program employing a variety of media. For example, comments suggested the program be available through electronic, print, telephone and live sessions. Comments also recommended that the educational materials be available in a wide variety of formats including: web-based activities, didactic presentations, podcasts, case based presentations, journal clubs, websites, keyword activities, clinical case studies, "ask the experts" sessions, podcasts, CD ROMs, and a hotline. As corollaries to these recommendations, comments also emphasized the need for redundancy in messaging and objectivity in the information provided.

193. Several comments highlighted the need for a demonstration of competence at the conclusion of the program. For example: (a) One comment stated that certification should involve participation in an approved course, self-study, or conference and successful completion of an examination. (b) Another comment from a vendor offered to develop and manage an online certification program with comprehension testing after each module. (c) Another comment from a pain organization recommended that pharmacists be required to complete a brief online examination. If unable to complete the test successfully, they would be offered educational options for enhancing their knowledge prior to a retest. (d) Finally, another comment recommended that participants in the education program be: (i)

Actively involved in the program; (ii) responsible for their own learning; (iii) stimulated in a variety of ways; (iv) comfortable in their learning environment; and (v) required to show that they can apply their knowledge to clinical situations to demonstrate that education has led to behavioral change.

194. Several comments offered suggestions regarding the timing and scheduling of the pharmacist education program. With regard to the length of the program, multiple comments from a vendor, health care professional organization, and pain organization recommended that the course be an hour in length. Comments also addressed how often the program should be reinforced. One comment suggested that after the initial encounter, there should be sessions every six months while another comment recommended annual renewals. On the other hand, multiple comments suggested that if required, REMS pharmacist education should only have to be completed once. A couple of these comments, from pharmacies, did suggest that reinforcement may be appropriate if there is evidence of inappropriate dispensing.

195. One comment from a lawyer suggested that FDA may consider creating tools for pharmacists to use in practice similar to the informed consent and prescriber-patient agreement kits she provides to prescribers.

E. How Should the Certification Process Be Administered?

196. Several comments, including one from a pain organization attaching a petition with four thousand and seventy-five signatures, recommended that pharmacist education be a prerequisite to DEA registration as a means of maximizing participation and minimizing the cost and burden on pharmacists. On the other hand, comments from industry and health

care professional organizations noted that DEA linkage would be difficult since only pharmacies have to register with DEA, not individual pharmacists.

197. Several comments offered alternatives to linking pharmacist certification to DEA registration. For example: (a) Industry suggested that if certification is implemented, an accredited CE provider should develop the program and administer the certifications with CE credits being provided towards license renewal. A pharmacist association, while opposed to certification, seconded this approach if certification is implemented. (b) A vendor recommended linking pharmacist certification to Controlled Dangerous Substance (CDS) registration. (c) Another comment suggested that if FDA requires pharmacist or pharmacy certification, the national boards of pharmacy accreditation program should provide the means to establish and monitor such certifications. (d) A couple of comments recommended that certification be performed through the state board of pharmacy. (e) A comment from a pharmacy association, while opposed to pharmacist education, stated that if such an element is adopted, the certification could be developed through national, state, and local pharmacist associations. (f) The comment attaching the petition referenced above stated that in the event linkage with DEA registration is not possible, an alternative would be to provide incentives to pharmacists to maximize participation

198. In the event that pharmacist certification is implemented, one comment from a health care professional organization recommended that FDA send reminder notices to pharmacists in advance of licensure or DEA registration deadlines.

199. Another option presented by multiple comments was to link pharmacist certification to the DEA registration of the relevant pharmacy – as opposed to the individual pharmacist. Specifically, the pharmacy would attest at the time of DEA registration that its staff is in

compliance with REMS certification requirements. These comments noted that such a procedure could be modeled after the Center for Medicare and Medicaid Services' (CMS) procedure for verifying pharmacist training on waste and abuse and also mimic DEA's verification of pseudoephedrine training. On the other hand, a couple of comments from pharmacies recommended that the completion of education should be the responsibility of the individual pharmacist.

200. One comment from a vendor supported the certification of pharmacies stating that REMS drugs should only be shipped to certified pharmacies registered with the REMS, but added that it should not be limited to specialty pharmacies (i.e., the drugs should be available through retail and hospital pharmacies). On the other hand, one pharmacy objected to a pharmacy registry noting it would limit access without any benefit to patients.

F. Concerns Regarding Pharmacist Education and Certification

201. Several comments from pain patients, pharmacists, pharmacies, and their representative organizations objected to pharmacist education under the REMS. Recurring themes in these comments included: (a) Education is unnecessary because pharmacists are already appropriately trained through pharmacy school and the board licensure process. As a result, they are already aware of the risks associated with these products. One comment, for example, noted that pharmacists have far more pharmacology and pharmacotherapeutic training than any other health care professional. On the other hand, one comment from a distributor, while stating pharmacy certification may not be necessary, suggested that, at minimum, there should still be education about the REMS and the roles and responsibilities of different participants. (b) Another comment stated that the practice of pharmacy is already highly regulated and it is impossible to "regulate" the problems out of the system.

For example, one comment from a pharmacist highlighted the multiple layers of regulation already imposed on pharmacies while stating that any DEA-registered and state-licensed pharmacy should be able to dispense REMS drugs. (c) Certification requirements could lead to pharmacies to simply not stock REMS drugs (e.g., one pain patient stated that pharmacies are already reluctant to stock these medications because of security issues and additional requirements may lead them not to dispense). Although another comment from a pain patient suggested to preserve access, pharmacists could be barred from opting-out of certification. (d) There is no evidence that pharmacist education would reduce abuse/misuse of REMS drugs.

202. In addition, one comment opposed certification of dispensers stating that it creates a stigma (e.g., likens it to methadone for the treatment of addiction where only enrolled prescribers, dispensers, and patients can participate).

203. Another comment from a concerned individual stated that a pharmacist should be able to fill any valid prescription and the burden of ensuring appropriate patient selection, monitoring and patient education should be the prescriber's responsibility.

204. Another comment from a health care professional organization stated that if a dispenser certification requirement is implemented, dispensers in hospitals should be exempt from REMS certification because they are already knowledgeable regarding appropriate use and risks of REMS drugs and, therefore, a certification program will not have a significant impact on this subset of health care professionals. [31]

205. Finally, several comments highlighted the financial burden associated with pharmacist education. One comment questioned who would pay for pharmacist training. Another comment noted that usually CE courses are offered at various price points to enable all

[31] *See also* Access to Pain Medication, Subpart G (v).

pharmacists to participate. Another comment agreed that health care providers need appropriate training in the prescription of REMS drugs and identifying potential problems, but included the caveat that the cost must be considered.

VII. PATIENT EDUCATION

In the April 20, 2009 notice, FDA suggested that patient education could be a critical component of the REMS, and in particular suggested that education be provided in conjunction with a prescriber-patient agreement (PPA). Similar to prescriber education, FDA received voluminous comments on patient education. Generally, stakeholders agreed that patient education is vital to the safe use of REMS drugs. However, not all stakeholders agreed that education should be in conjunction with a PPA and some expressed concern regarding the burden association with patient education. Overall, the comments discussed: (A) what type of patient education should be provided, (B) who should provide patient education, (C) what topics should be covered by patient education, (D) how patient education should be provided, and (E) concerns regarding patient education.

A. What Type of Patient Education Should Be Provided?

206. Many comments from a variety of stakeholders supported the development and implementation of a REMS patient education program. Recurring themes in these comments included the following: (a) Comments emphasized the importance in finding a balance between access and patient safety. Particularly within the pain management community, comments often highlighted that education should not only focus on risk mitigation issues related to abuse/misuse but also the benefits of the prescribed drug. In particular, comments cautioned that patient education should not scare patients from necessary treatment, nor be so burdensome on prescribers as to create shifts in prescribing

practices. On the other hand, comments from advocates for opioid drug reform and family members of individuals who had been harmed by opioid use stressed the importance of warning patients of the potential dangers of these medications. (b) Comments highlighted the importance of educating family members and caregivers, in addition to patients. In particular, they suggested that since the patients at issue are in pain, their ability to focus on information may be impeded, making the education of their family and caregivers critical. (c) As discussed in greater detail below,[32] comments recommended pre-testing patient materials for understandability and effectiveness (e.g., retention of information) and ongoing evaluation of the patient education program. (d) Comments were divided as to whether to education materials should primarily be product-specific or cover the class of drugs, but highlighted that there is a need to educate about both product-specific risks (e.g., risks pertaining to active ingredient, delivery method) and class risks. (e) Comments noted the importance of redundancy and consistency in messaging to achieve understanding. For example, one comment from a hospice nurse emphasized the need to educate patients at every visit, not just at the start or end of a prescription. In addition, when educating her patients, she has found asking them to repeat the information back to her to be effective. This comment also suggested that practitioners need to speak so the patient can understand the information. (f) Comments highlighted the importance of conversation over documentation. In particular, they suggested that a meaningful conversation between the prescriber and patient is critical to effective patient education as opposed to simply having the patient review and sign a document. (g) Comments suggested FDA rely on existing expertise and input from stakeholders in developing a patient education program. (h) While

[32] *See* REMS Evaluation and Metrics, Section XI, B.

supporting patient education, comments noted that the time required to adequately educate a patient is significant and noted that in a busy prescriber setting, time equates to financial burden.

207. Several comments from pain patients related experiences that supported the implementation of a formal patient education program. For example: (a) A pain patient who became addicted to an opioid she received stated that better patient education with regard to dosing could have prevented the problems that she experienced. (b) Another patient noted that during the entire course of her treatment, not one doctor or nurse has ever educated her about opioids. (c) Another patient discussed having to do research on his own to educate himself about his treatment. (d) Finally, a petition submitted by a pain organization with four thousand and seventy-five signatures noted that patient education materials can be developed to assist prescribers and dispensers in providing patients with appropriate use, storage and disposal information, and any specific precautions relating to particular products.

B. Who Should Provide Patient Education?

208. Several comments discussed the issue of who in the health care system should be responsible for patient education. While comments from diverse stakeholders sought to clearly define roles and responsibilities for education delivery, comments generally supported providing patient education, at minimum, at the point of prescribing. For example, several comments discussed the importance of engendering communication and trust in the prescriber-patient relationship to ensure patients are open to education. Similarly, one comment from a pharmacy stated that prior to leaving a prescriber's office, a patient should be sufficiently educated to feel confident that they have a legitimate

prescription. On the other hand, a vendor noted that part of the lack of current patient education is related to the brevity of the physician-patient encounter. To that end, several other comments noted that non-physician staff at the point of prescribing (e.g., physician assistants, nurses) can be integral to patient education and reduce the burden on the physician. Furthermore, one comment from a health care professional organization cited studies suggesting that nurse-provided education has been effective with patients. Similarly, the liability carriers advisory committee recommended creating elements that largely can be handled by office staff.

209. Although comments supported patient education at the point of prescribing, several comments asserted that it should not end there. Instead, these comments supported education both at the point of prescribing and dispensing. (a) A health care professional organization suggested that patient education should occur at several points from initial education with the prescriber to the dispenser. (b) Similarly, multiple comments recommended that patient education begin with the prescriber and be reinforced at the point of dispensing. For example, a patient communication company stated that the messages provided by the prescriber and the dispenser need to be coordinated with the prescriber providing the message at the point of prescribing and the dispenser providing a clear, concise document reinforcing the message at the point of dispensing. (c) Another comment from a pain organization that was supported by a petition with four thousand and seventy-five signatures also suggested that dispensers be involved in patient education by recommending that patient education materials be developed for individual products to assist both prescribers and dispensers in their practice. (d) A manufacturer stated that there needs to be consistent and repetitive messaging to patients so if one health care professional

fails to educate, there will be fail-safe. (e) Furthermore, a couple of comments from pain patients described positive experiences with pharmacist-provided education, with one noting that receiving education from both prescriber and pharmacist led him to keep his medications locked and not tell anyone about them. (g) Finally, multiple vendors agreed that there needs to be patient interventions after the point of prescribing. One noted that multiple exposures to messages can drive behavior change with continued – albeit less frequent – messaging needed to maintain changes. Another vendor stated that pharmacists are actually better able to provide education because (i) it is one of their primary functions, (ii) they are extensively trained in the clinical aspects of drugs and drug use, and (iii) pharmacists can reinforce any education that a busy prescriber may have provided. This vendor suggested that its training system could assist pharmacists in educating patients and providing follow-up after dispensing.

210. Moreover, it would appear both prescribers and dispensers are already involved in patient education. One comment submitted a survey of one hundred opioid patients and a large majority of the respondents indicated their prescriber had at least mentioned the risks of their medication. While the percentage of respondents indicating that their pharmacist had mentioned the risks was lower, it was still a majority.

211. On the other hand, several comments from pharmacies, pharmacy chains, pharmacists and pharmacy representative organizations asserted that patient education should primarily be the responsibility of the prescriber with pharmacy counseling being secondary. While many of these comments stated that pharmacists could provide a patient education document (e.g., a Med Guide or one document solution), and one suggested that pharmacists could be available to answer questions, they also asserted that: (a) pharmacists are not in the position

to ensure that the right product was prescribed for the patient under the right conditions (i.e., unlike the prescriber); (b) a patient should not have to wait until reaching the pharmacy to learn about the benefits and risks of the prescribed medication; and (c) it is ineffective for a pharmacist to warn patients about risks (e.g., possible interactions) and label the prescription bottle if the prescriber did not educate the patient. Similarly, one comment from a vendor agreed that prescribers are best positioned and equipped to discuss a medication's benefits and risks.

212. One comment from a pharmacist professional association recommended that FDA examine how an expanded role of pharmacists could be used in the REMS to provide patient education such as medication therapy management services, but cautioned that such services would require an appropriate compensation model. Similarly, one comment from a pharmacy representative organization noted that if a pharmacist is available to answer questions at the point of dispensing, that time should be eligible for reimbursement.

213. Beyond the prescription process, one comment suggested patient education could be provided through health departments.

C. What Topics Should Be Covered By REMS Patient Education?

214. Several comments suggested that the REMS patient education program should draw on existing expertise (e.g., state programs, patient and professional organizations). For example, a comment from a health care professional organization noted that it has already developed a patient curriculum in association with academic and government organizations. Similarly, a patient advocacy organization stated that it produces materials for patients to assist them in working with their prescribers and suggested that FDA work with organizations such as their own to develop effective patient education tools.

215. Similar to the comments received regarding prescriber and pharmacist education, comments offered diverse suggestions for topics that should be covered during patient education. The most frequently cited topic was the safe use, storage and disposal of the medications. For example, a submitted survey of one hundred opioid patients indicated that currently patients are less likely to be educated about the storage of their medications than about the risks associated with them. In addition to safe use, storage and disposal, other recurring suggestions for the topics to be covered by patient and caregiver education included: (a) benefits of treatment with opioids and a patient treatment plan; (b) product and class risks (e.g., the risk of respiratory depression); (c) safe use (including dosing and administration); (d) important warnings (e.g., risk of overdose, dangers of chewing extended-release formulations, importance of keeping medications away from children); (g) concerns for diversion (e.g., "these medication must never be shared with anyone"); (h) interaction issues (e.g., alcohol, sedatives); (i) tolerance, dependence, and addiction and how to recognize them; (j) REMS rationale and logistics including roles and responsibilities of all the stakeholders (e.g., prescriber, patient and pharmacist) and the risks being mitigated by REMS requirements (e.g., patient monitoring, prescriber-patient agreements); (k) general principles of pain management (e.g., alternative and complementary therapies); and (l) how to self-identify issues that the patient should discuss with his/her prescriber.

216. A couple of comments from advocates for opioid drug reform and bereaved parents asserted that education must be intense regarding the dangers of dependence and addiction to minimize drug demand. One of these comments noted that there also needs to be an expansion of addiction treatment. The other comment highlighted that these warnings are particularly important where there is a family history of addiction.

217. With regard to education regarding diversion, pain patients suggested not only discussing the risk of diversion, but also explaining how that risk relates to patient monitoring and behavior. For example: (a) A pain patient noted it helped clarify the purpose of urine screens and decrease the associated stigma when her prescriber explained that the tests were not intended to find other drugs in her system but rather confirm her prescribed drugs were being taken, and therefore not diverted. (b) Similarly, a pain patient stated that she has had offers to buy her medication and has had her medication stolen. As a result, she no longer tells anyone she takes pain medications and suggests that all pain patients be told to keep their medication information private.

218. With regard to standardization, one comment from a health care professional organization recommended that patient education be the same for both cancer and non-cancer patients.

D. How Should Patient Education Be Provided?

i. Prescriber-Patient Agreements

219. In the April notice, FDA suggested that prescriber-patient agreements (PPAs) could be an important complement to patient education. Numerous comments agreed – with some offering support for the development and use of a standardized PPA and others offering advice based on their personal experiences as patients and prescribers who had executed PPAs. As discussed in greater detail below, however, support for mandating PPAs was not universal. In particular, some comments expressed concern regarding the effectiveness of the PPA as an educational tool.

220. With regard to actual experiences with PPAs, several comments were received from pain patients (or their friends and family) stating that they live by the requirements of their agreement (e.g., agreeing to toxicity screens, a refill schedule, use of a single pharmacy, use

of a lockbox). Some of these comments suggested, however, that the fact that doctors are already employing PPAs voluntarily means that requiring them is unnecessary. One comment submitted data that supported the assertion that PPAs are gaining popularity. Specifically, in a survey of one hundred opioid patients, approximately fifty percent of the respondents had signed a PPA. Approximately forty-three percent of those signing one found it very valuable and thirty percent found it marginally helpful or not helpful.

221. Support for a standardized PPA came from a variety of stakeholders, and the reasons for their support also varied. For example: (a) Industry supported the development of a standardized PPA (i) noting it would provide consistent information to all patients at the point of prescribing and (ii) highlighting that use of such an agreement was supported by state medical boards and a national pain organization. (b) A lawyer noted that state requirements/recommendations regarding PPAs currently vary and advocated for federal uniformity. Similarly, while expressing concern regarding the REMS, a prescriber who already uses PPAs suggested that if there must be additional regulation, PPAs with national uniform standards could be an effective measure. (c) A liability insurance company stated that any materials that standardize the communication between health care professionals and patients reduce risk and liability. Similarly, a liability carrier advisory committee suggested that FDA provide a draft of the standardized PPA to liability carriers for review and comment prior to final adoption under the REMS. (d) Another comment stated that when knowledgeable providers prescribe REMS drugs, the risk of addiction is low if there is a PPA in effect. (e) Multiple comments stated that having a legal document attesting that the patient is aware that REMS drugs are dangerous and acknowledging responsibility for them could help emphasize the seriousness of safeguarding the drugs.

222. While in some cases comments were unclear as to whether they supported mandatory PPAs versus simply offering a standardized PPA to prescribers to voluntarily implement, in other cases, strong opinions were expressed regarding whether PPAs should be required. For example, a prescriber recommended that PPAs should be mandated for every patient in every practice. Similarly, a patient communication company expressed its strong support for mandatory PPAs prior to dispensing. On the other hand: (a) A couple of comments noted that FDA did not have authority to regulate medical practice and therefore questioned its ability to require PPAs. (b) A health care professional organization, while supporting appropriate patient counseling and monitoring, opposed mandatory PPAs or toxicology screening schedules. Similarly, a consortium of health care professional organizations opposed mandating PPAs, instead recommending that they be discussed as part of prescriber education, but not required. (c) A couple of health care professionals noted that while PPAs are appropriate in certain instances, they should not be universally mandated as it reduces the autonomy of the patient and prescriber. (d) Several comments stated that the impact of mandatory PPAs on populations that do not have the capacity to legally contract (e.g., pediatric patients, Alzheimers patients) must be considered. Similarly, one comment from an organization representing consulting pharmacists stated that patient registries, PPAs and informed consents are not viable for long-term care residents because they often cannot participate in their own care (e.g., cannot comprehend these documents or call hotlines for more information) and often do not have legal guardians to act on their behalf. This comment recommended exempting these patients from any such requirements. For a more detailed discussion of comments regarding pediatric and geriatric access, see Access to Pain Medication, Section IV, G.

a. Recommendations for the Content and Format of PPAs

223. Comments suggested a wide variety of provisions for incorporation into a standardized PPA. For example: (a) A pain patient recommended having a stipulation informing the patient that he/she can have his/her pills counted at any time during the duration of the prescription and if the pill count does not match the dosing schedule, the patient will be terminated from opioid treatment. Similarly, another pain patient recommended that patients be given guidelines and if they fail to comply, treatment ceases. (b) A health care practitioner recommended that the PPA stipulate that the prescriber can speak freely with other health care providers and family members of the patient to determine if treatment should continue. (c) A vendor and a health care technology company recommended that the PPA be an acknowledgement that the prescriber has discussed the drug's Medication Guide with the patient. (d) A pain organization stated that the agreement should be clear, understandable and brief, and should include language such as "sharing of medications is an illegal activity." (e) Industry recommended that the PPA: (i) provide standardized benefit and risk information, (ii) reinforce the seriousness with which REMS drugs should be used and handled, and (iii) clearly define the prescriber/patient relationship, including their respective responsibilities and boundaries (e.g., patient must use a single pharmacy, submit to monitoring.) One the other hand, another comment from a health care system recommended PPAs as an alternative to patient monitoring. For a more detailed discussion of patient monitoring, see Methods to Curb Diversion, Section IX, B (i).

224. A comment from an organization of health care educators questioned whether FDA has the authority to require PPAs and suggested as an alternative that patients attest that (a) they have been educated regarding the risks and benefits of their treatment, (b) received

appropriate education materials (e.g., a Med Guide), and (c) will take necessary measures to safeguard their medication. The comment noted that such a document could provide DEA with basis for legal action if the patient subsequently diverts their medication.

b. Recommendations for the PPA Process

225. Beyond the content and format of PPAs, comments also offered recommendations for the agreement process (e.g., presenting, explaining, and signing the agreement). For example: (a) Industry supported a process that includes checking for comprehension at the time the agreement is signed and including the agreement in the health record to document education. (b) A pain patient suggested that patients be required to attend an expert-led course followed by the signing of a PPA with a "refresher" course mandated annually. This patient noted that his own education regarding his treatment was self-directed and he believes a course would have been preferable. (c) A pharmacy representative organization, while not advocating for mandatory PPAs, stated that if mandated, they should be required at the initial prescription and renewed every year thereafter. Moreover, the implementation of PPAs should ensure (i) immediate access for patients after signing the PPA; (ii) seamlessness integration with existing pharmacy systems and e-prescribing; and (iii) modifications based on outcomes.

226. Several comments stated that the REMS should emphasize that it is the discussion surrounding the PPA, not the agreement itself that is critical to patient education. For example: (a) A prescriber stated that executing a PPA is insufficient and that is the conversation surrounding the execution of the agreement that matters. (b) This assertion was echoed by a lawyer who also emphasized the need for a dialogue between prescriber and patient, not just a document. In a similar vein, a prescriber stated that beyond

mandating contracts in his practice, he engages in a discussion not only of self-reported pain scores, but also of how treatment is affecting relationships, work, and quality of mood and sleep.

227. A couple of comments discussed PPAs in the context of informed consent. One comment from a liability carrier advisory committee recommended that a PPA take the form of an "informed consent" for patients to read and sign. Another comment from a lawyer clarified, however, that a PPA is not the same as informed consent. This comment stated that informed consent is a process that should be documented and a PPA is only a component of that process. Instead of focusing on PPAs, this comment suggested employing treatment agreement kits, informed consent kits and dialogue sheets to encourage prescribers to educate the patient instead of just having the patient sign a document. The laywer's kits include not only materials for the prescriber and prescriber's staff, but also for the patient including CD-ROMs of informed consent information and educational materials, along with the treatment agreement and an explanation of same.

228. A pharmacist professional association noted that if PPAs discuss pharmacy issues (e.g., the refill process and timing, using a single pharmacy), the pharmacist should be informed of the relevant elements.

229. A couple of comments questioned if PPAs are required under the REMS who would be responsible for verifying compliance. One comment from a health care professional organization recommended that if PPAs are required, FDA specify who is responsible for verifying its successful completion. Similarly, one comment from another health care professional organization stated that pharmacists should not be responsible for policing compliance.

230. A couple of comments from a pain organization and health care professional organization recommended that the standardized PPA be endorsed by professional organizations and in a format that can be tailored to individual practices as needed in order to maintain compliance. These comments suggested that there be a version of the PPA available in clinician offices, on the pharmacy instruction sheets (electronic information and order fulfillment) and wherever patient encounters take place. Similarly, a health care professional organization recommended that the standardized PPA be available on the Internet and be adaptable to different state regulations and recommendations. The comment from the pain organization also noted that PPA-type materials may not be appropriate for dispensers, so it may be necessary to look at other options, as this may interfere with work flow and counseling of patients.

231. Although in a similar vein to a PPA, one comment offered a different take on documenting patient education. Specifically, it recommended that all prescribers certify to providing patient education when renewing their license or DEA registration and also mandate that patients sign an acknowledgement of education which must be presented with the prescription at the point of dispensing.

c. Opposition to the Implementation of PPAs

232. Support for implementing a standardized PPA was not universal, although the reasons for opposing their implementation varied. For example: (a) A patient advocate expressed concern that PPAs stigmatize the patient. Similarly, a pain patient stated that PPAs are not being used to educate, but rather in the current environment of fear and regulation, physicians are using them to scare patients. (b) Another pain patient questioned the effectiveness of PPAs as an educational tool and noted that a failure to comply does not

necessarily mean the patient was not adequately educated. Furthermore, industry acknowledged the concern that a signed PPA does not guarantee meaningful education. However, it reasoned that all that can be done is (i) provide a document that is understandable, clear and conveys the risks contemplated by the REMS, (ii) test the agreement for comprehension and literacy level, (iii) assess through a survey the knowledge and retention of patients and (iv) if necessary, identify points for re-education through multiple delivery methods.

ii. Med Guides, Patient Package Inserts, and Other Alternatives

233. Comments from a variety of stakeholders recommended that printed materials be developed for the REMS to assist prescribers and dispensers in educating patients. The comments were divided, however, as to whether to continue using standard documents (e.g., Medication Guides and patient package inserts) or develop new materials. Recurring themes regarding the development of printed materials were that they (a) be standardized, concise, understandable (to an the consumer, not the medical community), and sensitive to language, cultural, and literacy differences, and (b) provide directions to additional resources for patients desiring more detailed information. For example, a pain patient recommended that the prescriber provide the patient with a pamphlet – but emphasized that current patient information is too lengthy and confusing. This comment advocated for a one page document with information and warnings. Similarly, a pharmacist stated that it is easy to overload patients with too much information and advocated for making the information simple, easy to read and to the point.

234. Numerous comments from a variety of stakeholders supported patient education through Medication Guides (Med Guides) and/or patient package inserts (PPIs). For example: (a) A

patient communication company supported the use of Med Guides, as long as they were comprehensible. (b) Industry supported the production of a Med Guide to deliver product-specific risk information to patients. Although it acknowledged that the effectiveness of Med Guides has been questioned at Advisory Committee meetings (and as noted below, these concerns were echoed in comments from pharmacy organizations), industry stated that it can work with FDA to standardized Med Guides for REMS drugs and make them more clear and concise. On the other hand, a couple of comments suggested if the REMS includes a Med Guide that it be a class-wide Med Guide.

235. As noted above, several comments from a variety of stakeholders questioned the effectiveness of current Med Guides and PPIs. In general, these comments recommended moving to the single-document solution that was discussed at a recent Advisory Committee meeting. Finally, a couple of comments suggested providing a Patient Education Guide as an alternative to a PPI, perhaps with a PPI available to patients desiring more information.

236. Beyond Med Guides and PPIs, comments offered additional suggestions for the printed patient materials distributed under the REMS. For example: (a) A state-based consortium of pain and health care professional organizations stated that the REMS should establish standardized, generic patient education materials in multiple languages to enable prescribers and dispensers to educate patients in culturally appropriate ways. (b) A hospice and palliative care professional stated that patient education must be kept simple and practical, such as a brief, downloadable handout at the pharmacy. (c) A patient communication company stated that there are too many different types of documents provided to patients and recommended that a REMS education document be written in plain, simple language. (d) A hospice provider stated that since a large portion of the

population is not able to read for comprehension even at a fifth-grade level, there should be multiple versions of patient education materials (including pictures for non-literate patients and translations for non-English speaking patients). Similarly, a health care professional organization and prescriber recommended that patient education materials be available in a variety of formats and be sensitive to language and cultural differences. (e) One comment from a prescriber who believes that patient education materials should be balanced attached a "pain primer" he uses in his own practice. (f) Another comment recommended relying, in part, on established patient education resources including brochures and materials from pain organizations, government agencies, and professional medical associations (e.g., tear-off pads). (g) Finally, industry supported the creation of a two-sided one page Patient Medication Information Sheet with a tear-away wallet card for patients which would discuss class-wide risks (i.e., as opposed to product-specific Med Guides). This document would be distributed at the point of prescribing (either by the prescriber or staff) and would be written for consumer comprehension and available in multiple languages.

237. Beyond the type of materials that should be distributed, comments also offered recommendations regarding the delivery process for printed materials. For example: (a) A distributor association recommended that patients only receive one document and that if it is not physically attached to the drug, that the REMS specify how brochures, guides, contracts, and other materials will be provided to patients and/or health care professionals. This comment also highlighted the importance of considering how these materials will be stored, ordered, reordered, and delivered and how the costs should be allocated. (b) Several comments recommended that pharmacist-provided education materials be sufficiently flexible to permit printing on the different existing pharmacy dispensing systems with

reimbursement for printing and distribution of materials. Similarly, another comment from a patient communication company recommended that the REMS education document be available in electronic format for easy distribution at the point of dispensing. (c) One comment from a pharmacy suggested that the REMS education document be available at prescription pick-up or, if the patient chooses, via e-mail. This comment recommended that the Agency take all steps to implement an electronic and sustainable program and avoid additional costs of printing and distributing Med Guides. (d) One comment from a pain patient recommended updating package inserts and making them available on FDA's website. (e) One comment from a pain organization suggested that patient education brochures be available from professional societies.

238. Similar to comments received regarding PPAs, comments also emphasized that printed materials should not be a substitute for a discussion between the health care provider and patient. For example, a pharmacist professional association noted that past REMS have been effective in highlighting particular risks to patients, but that the patient education program should be in addition to, as opposed to replacing, a prescriber/patient conversation. Similarly, a couple of comments noted that Med Guides are an important tool in helping to avoid improper use of REMS drugs, but only if prescribers are aware of Med Guides and review the information contained therein with the patient.

239. With regard to how often patients should receive printed materials, a survey of one hundred opioid patients suggested that if Med Guides are distributed, they should be distributed only with new prescriptions or when information changes.

iii. Multiple Modality Options

240. Beyond printed materials, numerous comments recommended that the REMS patient education program incorporate multiple modalities of communication. For example, several comments recommended that education be offered through print, Internet, mass media and live counseling. The advantages cited in favor of multiple-modalities included the ability to reach patients with different learning styles and to reinforce key messages. For example: (a) A pain organization recommended employing (i) print (e.g., brochures distributed to patients by prescribers and pharmacies, posters, a safe storage and disposal checklist), (ii) video (e.g., a CD to be shown to patients at the point of prescribing that is interactive with questions to be answered by the patient allowing staff to assess their level of understanding), and (iii) web-based media (e.g., making the materials available on government and other relevant websites). This comment recommended educating patients using graphics and strategies targeted to multiple learning styles and reading levels. (b) A patient communication company and pain educator suggested that patients should receive redundant, consistent information from their prescriber throughout the treatment process. In addition, the information could be reinforced with a Med Guide, information on a REMS website and a call center for questions. (c) Similarly, a health care professional organization stated that there should be easily accessible toll-free numbers and Internet-based support for both patients and health care professionals providing patient education.

241. Several comments offered suggestions as to how the Internet could be incorporated into the patient education program. For example: (a) A pain patient suggested that patient package inserts can have links to the FDA website with an online tutor about safe use, disposal, and storage of medications. (b) A couple of comments from health care professional

organizations suggested that all REMS education materials, including those for health care professionals and patients (e.g., prescriber-patient agreements) should be centralized on one website. One of these comments used its website as an example. (c) A couple of pain patients recommended that patients be encouraged or required to take an online course. One specifically recommended a course provided by the Arthritis Foundation. (d) A vendor noted that its patient-oriented website already offers pain medication safety lessons and competency tests and interacts with another website intended for health care professionals, permitting all stakeholders to receive a common educational message. The vendor suggested its websites could be a turn-key education solution.

242. Several comments recommended that patients take home educational DVDs, both so they can reinforce their own education and educate their friends and family members. For example: (a) A pain patient suggested that the patient education program should include a take-home DVD which could be shared with family members. Similarly, a patient communication company and health care educator professional association stated that patient education should go home with the patient. (b) A member of a regional substance abuse task force described a pilot project in North Carolina where patients were given a kit with a DVD to review and share with their family members along with intranasal naloxone to administer if signs of an opioid overdose were observed. This pilot was conducted in conjunction with a patient, prescriber, and community education program.

243. A couple of comments also recommended requiring patients to complete a live course. For example: (a) A health care practitioner recommended mandating a safety class for patients with the theme “use only as directed” and emphasizing safe use, storage and disposal. (b) A pain patient recommended requiring patient education via a live course, noting that she had

attended a course three to four days a week for twelve to sixteen weeks at the Medical University of South Carolina and found it incredibly beneficial.

244. Multiple comments discussed whether patients should complete a competency test, and if so, how such test should be administered. For example: (a) As noted above, a pain organization suggested that the patient education program include a segment where patients answer questions so prescribing staff can assess their level of competency. (b) In a survey of one hundred opioid patients, the respondents indicated that while skeptical of its usefulness, if patient competency testing is required, they would prefer for the test to be offered in multiple modalities. (b) A vendor recommended that participants in the education program be: (i) actively involved in the program; (ii) responsible for their own learning; (iii) stimulated in a variety of ways; (iv) comfortable in their learning environment; and (v) required to show that they can apply their knowledge to demonstrate that education has led to behavioral change. They also provided an example of patient education developed with their methodology.

E. Concerns Regarding Patient Education

i. Concerns for the Effectiveness of Patient Education

245. While comments were generally supportive of patient education, there were exceptions. Several comments questioned whether education will be effective in mitigating risks associated with REMS drugs. For example: (a) Comments from both a pharmaceutical security organization and an advocate for opioid drug reform supported patient education but stated that education alone is inadequate to curb problems with opioids. (b) While acknowledging that some overdoses could be prevented, another comment stated that ultimately abuse and the lucrative black market will not be cured by education. On the

other hand, a member of a substance abuse task force in North Carolina noted that the majority of opioid-related decedents in his county had a physician visit within two weeks of their death, suggesting that there was an opportunity where education could have intervened.

246. Another contingent of comments also expressed concern regarding the effectiveness of patient education, but not with regard to mitigating risk, but rather with regard to ensuring competency. For example, one comment from a vendor stated that education efforts in past REMS have not assured competency. Similarly, one comment which presented the results of a survey of one hundred opioid patients suggested that they were skeptical of whether competency testing would be helpful in ensuring the safe use of opioids.

ii. Concerns for the Burden Imposed by Patient Education[33]

247. In addition to expressing concern for the effectiveness of patient education, another contingent of comments expressed concern regarding the burden of patient education and the unintended consequences of shifting prescribing to other less-appropriate medications. Several comments expressed concerns about government burdening the prescriber-patient relationship. For example, one patient, while acknowledging the importance of patient education, asserted that it should be doctor, not government, driven. Similarly, a consortium of health care professional organizations opposed substantially expanding patient counseling or record keeping requirements citing the burden on prescribers.

248. As noted above, comments also expressed concern for the financial burden inherent with patient education, both for the practitioner and the patient. For example: (a) A health care professional expressed concern that burdensome requirements for patient education will

[33] Numerous comments from the hospice community suggested that REMS patient education would be duplicative of CMS patient education requirements. For a discussion of their concerns and request for an exemption from REMS requirements, please see Access to Pain Medication, Section IV, G (iv).

discourage prescribing, particularly with the reimbursement climate in primary care. (b) Multiple comments asserted that patient education is important, but time-intensive, and health care providers should be reimbursed for this activity. One comment from a state pain initiative also suggested that there should be reimbursement for follow-up home visits. As a possible solution to the financial burden on prescribers, multiple comments recommended using nurses, physician assistants, and/or pharmacists to educate patients. One of these comments acknowledged that even this approach would result in an additional economic burden, but it noted that another potential benefit would be that nurse educators could effectively collect patient outcome data.

249. Similarly, comments expressed concern that the financial cost of patient education would also adversely affect the patient. For example, one comment stated that if patients are encouraged or required to take a course such a program should be offered at minimal cost. In addition, pain patients expressed concern that education would increase the cost of REMS drugs. On the other hand, another pain patient suggested that while education will be burdensome, the cost will be offset by future savings (e.g., due to continuity of care, less money spent on enforcement activities related to diversion).

VIII. PUBLIC EDUCATION

Unlike prescriber, pharmacist, and patient education, FDA did not specifically request comment regarding public education in its April 20, 2009 notice. However, a diverse group of stakeholders recommended including a public education campaign as a component of the REMS. In particular, the Agency received comments discussing (A) what type of public education should be provided; and (B) how public education should be provided.

A. What Type of Public Education Should Be Provided?

250. Many comments from a diverse group of stakeholders supported implementing a public education campaign. Recurring suggested topics to be covered by the campaign included: (a) safe use, storage and disposal of REMS drugs (both at home and while traveling) to prevent diversion; (b) the need for immediate treatment of opioid-induced sedation; (c) the dangers of diversion and sharing medications with friends and family; and (d) how to identify if a friend or family member has an opioid-abuse problem.

251. Beyond educating the public about the risks associated with REMS drugs, several comments also suggested that public education could highlight the benefits of REMS drugs. For example, a pain patient highlighted that the public needs to be made aware of the benefits of REMS drugs and how they have improved the lives of so many legitimate pain patients instead of only hearing stories of abuse. Similarly, a health care professional suggested beyond educating the public about the dangers of abuse and misuse, the campaign should also emphasize the benefits of the medications to avoid stigmatizing their legitimate use. One comment noted that the campaign should not be used to promote opioid use, however, but rather opioid safe use.

252. Moreover, a couple of comments suggested that the public education campaign go beyond the scope of REMS drugs. Specifically, a health care professional recommended a public campaign regarding the safe use of all medications, not just opioids. Similarly, a pain patient recommended a campaign about the proper use of narcotics, and the difference between addiction and dependence.

253. Comments supporting public education offered a variety of reasons, including: (a) public education would also serve as patient and caregiver education (e.g., one comment noted that

public service announcements could be more effective than printed patient materials particularly for people with low literacy or language barriers); (b) the media has highlighted the struggles of celebrities and television characters with opioid addiction and providing education through the same avenue would prevent misinformation; (c) the risks associated with opioids extend beyond patients and the solution should as well; and (d) if the public was better educated regarding REMS drugs, there may be a reduced need for regulations.

254. A couple of comments suggested modeling the public education campaign after past campaigns that have effectively changed health behaviors. For example: (a) One comment from a pain organization stated that opioid public education should mirror the anti-smoking campaign. (b) Moreover, a health care practitioner noted that public education has been effective in lowering the over-prescription of antibiotics.

255. One comment from a pain organization noted the cost of such a campaign and highlighted that more money is needed to educate the public.

B. How Should Public Education Be Provided?

256. Several comments supported education through news and television outlets. For example: (a) Several comments recommending using the news media and public service announcements (PSAs). (b) Another comment noted that Utah used television commercials to highlight the risk of overdose by legitimate patients with successful results. (c) A health care professional suggested working with the entertainment industry to highlight the dangers of abuse/misuse. Similarly, a pain patient recommended television ads about the dangers of recreational use. (d) Finally, a pain patient expressed concern about how a popular television show portrays chronic pain and addiction and suggested that PSAs should be required to correct misinformation.

257. Several comments recommended a multi-pronged public education campaign. For example: (a) An advocate for opioid drug reform recommended public education as a preventative measure, delivered through a variety of media and targeting critical age, geographic, and population groups. (b) A couple of comments supported a broad public education campaign employing print (e.g., brochures for patients, posters, press releases and fact sheets for media), video (e.g., a CD to be shown to patients but also appropriate to be distributed over the Internet, in libraries and through the television news); and web-based media (e.g., access to the education materials on government websites and other relevant sites and a "Test Your Knowledge" quiz) to address unintentional misuse of opioids. These comments also suggested that the program explain the REMS and help consumers understand it using graphics, appropriate reading levels, and strategies targeted to multiple learning styles. (b) A pain organization stated that it is important to involve journalists and popular television shows to educate about opioids, in addition to PSAs. (c) Similarly, a couple of comments suggested that a public awareness campaign needs to go beyond PSAs and use an entertainment-based approach (i.e., "the Oprah effect"). One such comment from a pain organization recommended using the Ad Council to produce a public relations campaign (e.g., billboards, PSAs, journal advertisements) and also to develop a campaign employing interested celebrities (e.g., Dr. Oz, Dr. Phil, Oprah, Ellen DeGeneres, Mrs. Obama, Mrs. Biden). Another suggested partnering with parent associations at school and educating students through the public school system in addition to entertainment venues. (d) Finally, a pain organization also suggested that the education campaign target youth and recommended that it be implemented in conjunction with a buy-back or give-back program to enable the collection of unused REMS drugs and their appropriate

disposal. For a more detailed discussion of buy-back programs, please see Methods to Curb Diversion, Section IX, Subpart E (i).

IX. METHODS TO CURB DIVERSION

In its April 20, 2009 notice, FDA highlighted the issue of opioid abuse as one of the risks of REMS drugs that prescribers, dispensers and patients must be aware of in order to ensure safe use. The Agency also requested comment on whether distribution controls should be included as part of the REMS. As discussed in greater detail above,[34] comments received in response to the notice were divided as to the appropriateness and practicality of using the REMS to target abuse and diversion. In general, comments did not deny the existence of abuse and diversion issues with opioids. For example, a prescriber noted that in the past four years, he has had to discharge over three hundred and fifty patients for abuse, diversion and doctor shopping. However, many comments from a variety of stakeholders objected to focusing efforts on reducing abuse at the expense of legitimate pain patients. For example, a health care professional specializing in addiction treatment stated that preserving legitimate use is more important than curbing diversion. Moreover, comments questioned whether a REMS is an appropriate vehicle for targeting diversion. For example, a distributor association noted that efforts to curb diversion deviate from FDA's usual role. Furthermore, a prescriber stated that diversion is a criminal issue, not a medical one, and is best left to law enforcement. Another comment suggested that for efforts to be successful, diversion should be targeted at the community level. Moreover, several comments questioned whether the REMS could effectively curb diversion since the interventions would all target supply, and not demand. An advocate for opioid drug reform disagreed – suggesting that there is a strong correlation between supply and abuse – but several

[34] *See* Rationale Behind the REMS, Section II, Subpart B.

comments concluded that efforts to target diversion would be futile as abusers will find a way to obtain opioids.

Despite these concerns, comments offered suggestions on how to design REMS that would reduce the incidence of diversion and abuse. In particular, comments discussed the advantages and disadvantages of implementing (A) distribution controls, (B) patient-focused methods of reducing diversion, (C) enhanced prescription drug monitoring programs (PMPs), (D) improved drug formulations, (E) limitations on REMS-drug availability for diversion, (F) technology-based solutions targeting diversion and abuse, (G) increased enforcement and sanctions on abusers and unethical health care professionals, and (H) other methods for curbing abuse and diversion.

A. Distribution Controls

i. Regulation of Distributors

258. In its notice, FDA specifically requested comment on whether distributors should be regulated under the REMS. In response, several comments voiced opposition to additional regulation of distribution. For example: A representative organization for distributors stated that: (a) distribution is already a tightly regulated industry at the state and federal level, (b) distributors already self-impose additional controls beyond regulatory requirements, (c) overall, distributors are already ensuring the safe handling and delivery of medications, and (d) distributors cannot influence diversion to a significant degree as (i) wholesale distribution is a minor source of diversion and (ii) distributors cannot influence nor report the actions of patients or prescribers once drugs are legitimately distributed (e.g., the IT ability to link distribution data to prescriptions or prescribing practices does not exist – and would raise privacy issues regardless). Furthermore, this organization specifically opposed requiring distributors to (a) verify that customers are in compliance with the

REMS prior to distributing products to them or (b) report on distribution transactions involving REMS drugs. This comment noted that: (i) neither of these controls will provide direct information about the patients receiving the drugs and their use, and (ii) distributors already have to make multiple types of reports to DEA including reports of suspicious shipments and thefts. Moreover, since distributors handle many drugs, not just opioids, burdening them further could impact the timely distribution of all drugs. This would be true particularly for smaller distributors, resulting in a disparate impact on rural drug distribution. The organization requested that if any requirements are imposed on distributors under the REMS that those requirements be integrated into existing DEA systems. Finally, it also requested that it be provided an opportunity to comment on any REMS requirements prior to implementation.

259. In a similar vein, several comments opposed any added regulation of distributors, including implementing a pharmacy registry that a distributor would have to verify. For example: (a) A couple of comments noted that distributors should not be put in the position of having to police pharmacies. (b) A couple of comments from a pharmacy chain and pharmacy association noted that pharmaceutical distribution is already highly regulated. (c) A pharmacy chain stated that the current system of pre-distribution verification from manufacturer to primary wholesaler to intra-company pharmacy distribution network is a sufficient system that does not require further restrictions. Furthermore, a couple of pharmacy chains recommended that if REMS requirements are imposed on distribution, any movement of drugs from a distribution center owned and operated by a company directly to pharmacies under common ownership should be exempted and classified as an intra-company transfer of product, thereby not requiring verification with each shipment. (d) A

health care professional organization stated that verification of REMS compliance should not be a prerequisite to product shipment, but suggested there should be a standardized mechanism in place to easily reconcile dispensing records with shipping records for the purposes of surveillance.

260. Other comments cited concerns about delays and errors in opposing regulation of distribution. For example: (a) A society of educators opposed distribution controls because of their potential to cause shortages. (b) Another comment stated that a current REMS database has created problems for distribution because it is not real-time and contains errors which delays shipment of product.

261. A couple of comments suggested that distribution restrictions exceed FDA's authority or usual mandate.

262. Not all comments, however, were opposed to increased regulation of distribution. For example: (a) A vendor supported having distributors verify that a pharmacy is certified to dispense REMS drugs. This vendor suggested its proposed system would provide distributors with an existing, automated method for ensuring validation prior to shipment. (b) A vendor suggested that shipments to pharmacies that are not registered with the REMS should be blocked, although this comment agreed that the distributors themselves should not have to register. (c) Finally, a pharmacist suggested that distributors should have to register shipments of REMS drugs.

263. If requirements are imposed on distributors, their representative organization stated that the REMS should not restrict any resulting commercial relationships and distributors should be allowed to set market prices for the services they provide.

ii. Restricted Distribution to Certain Settings

264. Among comments discussing restricting distribution of REMS drugs to certain settings, many were opposed to such restrictions. For example: (a) Multiple comments opposed restricted distribution to certain settings because it will compromise access. (b) A couple of comments expressed particular concern for patients who already have limited access (e.g., those living in rural or poor urban areas, patients with limited mobility, the elderly). For example, one comment from a pain patient noted that limiting distribution to pain clinics would be burdensome when the nearest one is a long distance away, as is the case for the commenter. Several pain patients noted that daily activities such as travel can be excruciating. (c) Similarly, a family member of a pain patient noted that restricted distribution would be too burdensome on patients. (d) A health care professional organization expressed concern that restricted distribution would cause delays in treatment. (e) A pharmacy chain suggested that limiting distribution to doctor's offices or hospitals, for example, could limit a patient's access to pharmacist counseling. (f) A health care professional suggested that distribution restrictions would mimic a methadone treatment program and increase the stigma associated with REMS drug use. (g) A pharmacy association opposed restricted distribution because it is not in the best interests of patients to restrict community pharmacies from dispensing. Instead, this comment stated that as long as a community pharmacy can meet the criteria of the REMS, it should be able to stock and dispense REMS drugs. (h) A pharmacist focused on pain management opposed restricting distribution to certain settings due to its negative impact on access, noting that it is not the building that a health care professional works in, but rather their training that is important.

265. On the other hand, a contingent of comments supported restricting distribution to certain settings. For example: (a) A pain patient recommended restricting distribution of REMS drugs to pain specialists to curb abuse. (b) Similarly, another pain patient recommended restricting the distribution of REMS drugs to certified pain management health care professionals in special Pain Management Centers, which would be centrally located across the country. The centers would include practitioners from numerous specialties (e.g., neurologists, rheumatologists, psychiatrists, pharmacists). Patient records would be available to all staff preventing duplication of prescriptions and other opportunities for diversion. This comment noted that since similar centers have existed in the past, it would not be very expensive to implement. (c) Finally, another comment supported restricted distribution to curb theft.

B. Patient-Focused Methods to Curb Diversion

i. Patient Monitoring

266. As noted above,[35] comments were supportive of educating prescribers regarding monitoring of patients on chronic opioid therapy to curb diversion (e.g., pill counts, toxicity screens to ensure medications are being consumed by the patient, restricting patients to a single pharmacy). However, comments were more divided with regard to mandating monitoring under the REMS.

267. Several comments supported patient monitoring but did not expressly state whether such monitoring should be mandated. For example: (a) A prescriber stated that risks from REMS drugs can be minimized with proper monitoring in combination with appropriate rotation, education and patient selection. (b) Another comment noted that patient

[35] *See* Prescriber Education and Certification, Section V, Subpart C.

monitoring can be useful not only in spotting diversion, but also addictive behavior. (c) Another comment supported restricting dispensing to patients based on evidence of safe use conditions such as laboratory test results, but stated that hospice patients should be exempt.

268. Comments from pain patients and health care professionals suggested that some prescribers are already engaging in patient monitoring. For example: (a) Several pain patients noted that they are currently subject to monitoring. Moreover, approximately half of them expressly stated that they were comfortable with their current monitoring and some would even submit to increased monitoring. (b) Moreover, one pain patient expressly stated that all prescribers should engage in monitoring. On the other hand, another pain patient stated that the fact prescribers are already monitoring suggests there is no need for additional regulation. Overall, however, it was unclear from most comments whether patients believed that monitoring should be mandatory.

269. Several comments expressly opposed mandating patient monitoring or expressed serious concerns with monitoring. For example: (a) A pain organization advocated for leaving patient monitoring within the confines of the prescriber/patient relationship. (b) Similarly, a couple of comments from health care professional organizations – including one from sixteen health care professional organizations – acknowledged the benefits of patient monitoring and supported including information regarding monitoring in the education process. However, these comments opposed mandating monitoring schedules or urine tests. (c) Multiple patients suggested that monitoring is humiliating and increases the stigma associated with opioid use (e.g., makes the patient feel like an addict or criminal). In addition, one patient stated that monitoring is discriminatory. (d) A health care professional

organization stated that if toxicology screening is implemented as an element, there should be an exemption for pediatric patients.[36]

270. Several comments noted that patient monitoring (e.g., toxicity screens) is not currently covered by insurance and must be paid by the patient out-of-pocket. A couple of these comments suggested that patient monitoring should be reimbursed. For example: (a) A lawyer highlighted the benefits of following clinical guidelines in monitoring patients on chronic opioid therapy and recommended that FDA support providers in seeking insurance coverage for these activities. (b) A state pain organization supported International Classification of Diseases-9 (ICD-9) and Current Procedural Terminology (CPT) codes for patient monitoring and reimbursement for urinalysis. (c) Similarly, another comment suggested that urine tests should have a CPT code, like venipuncture.

271. A prescriber noted that random testing for drug presence can pose logistical problems for working patients when lab hours do not accommodate after-work testing.

ii. Patient Registry

272. Many comments from a wide variety of stakeholders strongly opposed implementing a patient registry. In addition, a pain organization submitted a petition with four thousand and seventy-five signatures opposing a patient registry. Recurring themes of these comments included:

- Concerns that a registry would create or magnify the stigma associated with REMS drugs. For example: (a) Several pain patients analogized a REMS patient registry to sex offender registries or noted that a registry would suggest a criminality to the use of REMS drugs. (b) Multiple comments also

[36] For a more detailed discussion of the proposed pediatric exemption, please see Access to Medication, Section IV, Subpart G (iii).

suggested that a registry would unfairly label patients as drug addicts and noted that registries are associated with methadone maintenance programs. (c) Finally, a comment expressed concern that the stigma and burden of a registry would cause patients to not fill prescriptions, and instead live with pain.

- Concerns about privacy associated with a patient registry. (a) A couple of comments from a pain organizations expressed concern that participation in such a registry could damage a patient's personal and professional opportunities (e.g., employment, obtaining insurance coverage). (b) A pain patient suggested that having such a database could, if hacked into, inform criminals where to steal REMS drugs. (c) Another comment from a pain organization suggested that a registry would conflict with the Health Insurance Portability and Accountability Act (HIPAA). (c) Finally, a survey of patients suggested they have strong concerns about the privacy of their health information and thus prefer a de-identified approach to stored information in the REMS program.
- Concerns that a registry would cause a shift in prescribing (i.e., concerns that to avoid the registry, prescribers and/or patients would select less appropriate treatments). For example: (a) A comment noted that a current registry has caused shifts in prescribing. (b) The petition submitted by the pain organization noted that a registry would be an unnecessary barrier to pain care and additional burden on providers.
- Concerns that a registry would create delays in treatment and dispensing. These concerns were often based on experience with current REMS.

Moreover, comments noted that in the case of pain relieving medications, delays are untenable. For example, a pharmacy association stated that if the goal is to have a transparent real-time system where patient access is not inhibited or delayed, a patient registry should not be implemented because it would be a huge barrier to real-time access.

- Concerns regarding the ability of certain patient populations to consent to participation in a registry (e.g., Alzheimers patients, pediatric patients).
- Concerns regarding the burden and financial expense of a registry particularly in light of evidence that other smaller registries have proven burdensome and the size of this REMS would be several times larger.
- The availability of more desirable alternatives. For example: (a) Many comments supported enhancing and expanding existing prescription monitoring programs (PMPs).[37] (b) A health care professional recommended that instead of a registry, implement a system where a prescriber "activates" a prescription prior to the medication being dispensed.
- Concerns regarding the lack of evidence that a patient registry would reduce abuse or misuse.

273. Several comments discussed the legalities of implementing a patient registry. For example: (a) Multiple comments noted that FDAAA does not require a registry, just offers it as an option. (b) A pain patient suggested that implementation of a patient registry would exceed FDA's authority. (c) Another pain patient questioned whether such a registry would be

[37] For a more detailed discussion of PMPs, see Subpart C of this section.

lawful under the Americans with Disabilities Act and stated that the government would not consider registering patients with other diseases, such as HIV/AIDS.

274. Multiple comments, while not supporting a registry, offered recommendations in the event one is implemented. For example: (a) A health care professional organization stated that if a registry is developed, it should be carefully designed (e.g., to ensure privacy, to not be duplicative). (b) A pharmacy organization stated that if a registry is implemented, it should be designed to ensure (i) immediate access by legitimate patients while denying access to others; (ii) interoperability with existing pharmacy systems and e-prescribing; and (iii) it could be modified as necessary. (c) Another comment from a health care professional organization stated that if a registry is implemented, it should be (i) interoperable with existing systems and (ii) online, not telephone-based. (d) A pharmacy transaction processing network stated its system could support a registry, if implemented. (e) A scientist, while not necessarily favoring a registry, stated that some tool must be implemented to prevent doctor shopping and other abuses. (f) A pediatric hospital acknowledged that maintenance of a database could be beneficial, but emphasized if one is implemented, the privacy of the information contained in it must be guaranteed and children should not bear a stigma for life labeled as potential abusers of REMS drugs.

275. On the other hand, not all comments opposed a registry. Several comments were open to the development of a registry, but for different reasons. For example: (a) Multiple comments supported a registry to track patients. (b) An advocate for opioid drug reform stated that a registry is necessary to ensure every patient is aware of the risks and appropriate uses of the medications. (b) A vendor suggested a system in which after the prescriber had educated the patient, he or she would enroll the patient in the REMS

program which would permit the pharmacist to dispense the medication. The vendor noted that the enrollment process would be transparent to the patient, so no stigma would attach. (d) A vendor noted that there is a disadvantage to relying on PMPs in lieu of a patient registry. Specifically, this comment noted that unlike a registry, there is no patient consent to participate in a PMP and one such program had a security breach. This vendor asserted that a voluntary registration with the patient's consent is preferable. (e) A comment from academia noted that both a patient registry and enhanced PMPs – either federally funded or funded by industry – could be useful data driven tools. (f) A vendor stated that concerns regarding a registry – including privacy concerns – could be mitigated and possibly outweighed by the potential benefits, including the data collection potential for evaluation.

276. Similarly, although many pain patients and health care professionals objected to a patient registry, there were a few exceptions. For example: (a) Multiple comments stated that legitimate patients should not object to providing their identification and other information to receive their medication. (b) A pain patient noted that a registry would be burdensome but supported its implementation stating that it is important to keep tabs on people receiving REMS drugs. (c) Another pain patient acknowledged the problem of abuse and stated that a registry would be acceptable. (d) Another patient questioned why not implement a registry since patients already have to provide identification to obtain their medication. (e) Another patient stated that if it was a choice between being in a registry and having his drugs banned, he would be willing to be in a registry. (f) Another pain patient -- in addition to a prescriber, and a comment from academia -- stated that the government should develop a database to prevent doctor shopping. One of these comments recommended that patients

be tracked through the database with the pharmacist checking it for drug-seeking behavior. If evidence of such behavior exists, the pharmacist would not dispense.

277. Finally, a couple of comments highlighted the use of registries for data collection and research. For example: (a) An organization submitted a comment promoting its registry of chronic pain patients intended to collect and document different treatment options used in the management of chronic pain. One of the topics to be studied will be opioid abuse. (b) Another comment opposed a registry intended to curb diversion by tracking patients, but supported registries such as the national cancer registry, which collect data and research to inform best practices.

C. Prescription Drug Monitoring Programs (PMPs)

278. As mentioned above, many comments – including one from sixteen health care professional organizations and another that received the endorsement of several other comments – supported the use of PMPs as a means of monitoring prescribing and curbing diversion. Recurring themes in these comments included: (a) PMPs could accomplish the same goals as a registry without (i) the need for an entirely new system or (ii) raising serious concerns about stigmatizing patients. A health care professional organization noted that since many PMPs are already in existence, it would be a faster and more cost-efficient approach as opposed to a new national registry. (b) PMPs would allow prescribers to investigate patients prior to prescribing and reduce adverse events due to doctor shopping or patients using multiple pharmacies.

279. Generally, however, comments did not believe that current PMPs were sufficient. Instead, the following enhancements and improvements were proposed:

- Expand PMPs to include all fifty states. For example: (a) A health care professional suggested that as opposed to creating a REMS registry, FDA should instead build on PMPs, now functioning in thirty-eight states. (b) Another comment noted that while Kentucky's PMP has been effective in curbing abuse within its state lines, abusers and traffickers have simply moved to other states. (c) Finally, industry suggested that a possible intermediate action in their proposed phased-in implementation of the REMS would be to consider the possibility of expanding PMPs.
- Ensure interoperability between state programs. For example: (a) A pharmacist noted that currently, if located near a state line, it is necessary to check the databases of both states. This comment suggested that ideally there would be a central database where it would be easy to verify the patient's social security number, driver's license, insurance coverage and controlled substance purchases. (b) Similarly, a pain organization stated that the PMPs need to be made real-time and link different states, so a patient cannot travel from Virginia to Maryland to doctor shop.
- Make PMPs real-time accessible to prescribers and dispensers to allow them to be proactive in engaging in appropriate prescribing and dispensing practices. For example: (a) A health care professional in rural practice noted that her state's program would be more useful with immediately-available and up-to-date data (i.e., currently there can be a four to six week delay). (b) Another comment supported real-time monitoring of all controlled substances – not just opioids – but highlighted the importance of maintaining privacy.

- Complement the enhancements to PMPs with improved training. For example, multiple comments, including one from sixteen health care professional organizations, suggested educating prescribers, law enforcement, and other PMP users about the purpose and use of PMPs.
- Increase federal funding to pay for improvements. For example: (a) A pain organization stated that Congressional funding should be used to expand PMPs. (b) As discussed below, several comments supported the implementation of the National All Schedules Prescription Electronic Reporting Act (NASPER).
- Ensure the privacy and security of patient data. For example: (a) A social worker commented that patient privacy rights must be included in conversations involving PMPs. (b) Similarly, a health care professional organization suggested that privacy concerns associated with PMPs must be considered – especially with regard to pediatric patients (e.g., labeling a child an opioid user or abuser could have detrimental consequences). For more detailed discussion regarding pediatric patients and the REMS, please see Access to Pain Medication, Section IV, Subpart G (iii).

280. Several comments noted that NASPER was intended to implement the necessary PMP enhancements, but the program has suffered due to limited funding.[38] For example: (a) A couple of comments from health care professional organizations – including one from sixteen health care professional organizations – strongly supported that the development of real-time, state based, interoperable PMPs through fully funding and implementing

[38] Although a couple of comments noted that some NASPER funding was recently made available, most comments supporting the implementation of NASPER noted that additional funding is needed.

NASPER. These comments noted that this solution would be the most effective approach to reducing diversion by addressing both patient and prescriber-based inappropriate behavior. (b) Another health care professional organization stated that if a nationwide prescription monitoring system is implemented it should not duplicate NASPER to reduce the burden on prescribers.

281. In addition to the above widely-recurring suggestions, comments offered other suggestions for the implementation of a nationwide PMP. For example: (a) A state pain initiative recommended that the enhanced PMPs be overseen by the state Departments of Health and Mental Hygiene to maintain a balanced approach and minimize use without cause. (b) A health care professional noted that mail order pharmacies need to be included in an enhanced PMP and it needs to be governed by HIPAA. (c) A pain foundation suggested working with Congress and possibly DEA to improve PMPs. (d) A prescriber suggested that a monitoring system should be developed with experts, not exclusively with manufacturers. (e) A prescriber suggested that manufacturers should financially support PMP enhancements.

282. Several comments suggested that FDA consider effective state programs in developing a nationwide PMP system. For example: (a) A state health care professional organization noted that Michigan's system provides real-time controlled substance prescription data to prescribers and pharmacists and recommended that prescribers be able to access data from a confidential site so the information may be used proactively. (b) An advocate for opioid drug reform recommended the nationwide implementation of a program similar to California's Controlled Substance Utilization Review and Evaluation System (CURES) that would be administered by the Department of Justice (DOJ) and DEA with meaningful

283. In a similar vein to expanding PMPs, multiple comments, although not referencing existing programs by name, suggested that there is a need for a national system to monitor prescribers and patients. For example: (a) An advocate for opioid drug reform recommended more careful monitoring of prescribers, patients and pharmacies through a nationwide multi-agency database. (b) A prescriber recommended more careful monitoring of prescribers. (c) Another comment suggested that instead of imposing additional obligations on prescribers, all pharmacies should be connected and share a forum or list of prescriptions to prevent an individual from receiving opioids from multiple sources. (d) Multiple pain patients, health care professionals, and concerned individuals recommended linking pharmacies so if an individual is doctor shopping and/or receiving large quantities of REMS drugs, a red flag would be raised. One of these patients, in particular, noted that electronic prescribing should assist in electronically linking them. (e) Another pain patient recommended implementing a program similar to the one enacted for pseudoephedrine in order to monitor prescriptions and the patients receiving REMS drugs. (f) A health care

professional recommended having a controlled substance profile for each patient to inform prescribers of the drugs they are receiving.

284. On the other hand, not all comments were supportive of expanding PMPs. For example: (a) A couple of comments suggested that the existence of current PMPs means additional regulation is not warranted, at least in states with real-time programs (e.g., California). (b) In addition, a comment suggested that current PMPs have stigmatized patients and led to reduced legitimate prescribing. (c) Another comment from a health care professional suggested that there are privacy and HIPAA issues with PMPs and suggested FDA weigh those concerns in assessing outcomes. (d) Another comment from two health care professionals noted that not even PMPs can help identify the source of a diverted drug if a prescription was legitimate.

285. Moreover, multiple comments highlighted the importance of evaluating the impact of PMPs on abuse, misuse and diversion as well as prescribing practices. For example: (a) A comment from two health care professionals noted that there has been very little research on the impact of PMPs and what little research has been conducted has focused on paper-based PMPs. Therefore, this comment concluded that there is a need for well-designed studies on the impact of electronic PMPs and the development of validated, reproducible, and usable metrics. (b) On the other hand, while concurring that there has been little evaluation of electronic PMPs and acknowledging that they are not a panacea for diversion issues, a policy group suggested that nascent empirical research is beginning to document the value of electronic PMPs for identifying and addressing abuse and diversion activities. To build on this research, this comment recommended pilot studies to determine how best to enhance existing PMPs' efficiencies and capacities.

D. Improved Formulations

286. Several comments suggested that tamper-resistant formulations could help stem diversion, abuse and REMS drug-related adverse events. For example: (a) A health care professional recommended approving a formulation that would destroy itself in the event of tampering. (b) A health care professional organization recommended fast-tracking review and approval of abuse-resistant formulations. (c) A scientist with experience in the pharmaceutical industry stated that OxyContin should be immediately replaced with a formulation with a much lower abuse potential. This comment noted that the data presented at the advisory meetings showed that newer products release less drug when misused (e.g., when product is chewed or taken with alcohol) than OxyContin. This comment stated that these products provide a substantial increase in the margin of safety over OxyContin and their approval should not be held up during REMS development. (d) Noting that the appeal of a prescription drug for abuse is largely dependent upon the strength and immediacy of the high it creates, a couple of comments suggested that manufacturers should be required to certify that a drug has been formulated to minimize potential for abuse, both intentional and unintentional, to the extent possible without compromising therapeutic effectiveness. Moreover, one of these comments stated that there are examples in literature of *in vitro* tests that would be useful in establishing specific criteria. In particular, this comment suggested that alcohol dose-dumping and physical tampering should be addressed by the certification. The other comment acknowledged that an antagonist sometimes makes a drug unusable for certain patients but suggested that FDA should continue to consider these issues when approving drugs. On the other hand, an advocate for opioid drug reform expressed concern that individuals may believe tamper-resistant formulations are safer than they really are.

One comment questioned whether as tamper-resistant formulations are made available, would REMS elements be evaluated and removed as necessary.

287. In addition to tamper-resistant formulations, comments also addressed other improvements that could be made to REMS drugs. For example: (a) A prescriber advocated for the development of opioid products which have a reduced incidence of respiratory depression. (b) A sickle cell organization suggested that more research is needed to develop more effective, less toxic analgesics. (c) A physician suggested expediting approval of naloxone drug products to reverse opioid overdose.

288. Similarly, multiple comments discussed using pre-market testing to optimize formulations. For example: (a) A clinical research organization recommended engaging in pre-market testing to compare similar products and technologies. (b) Another comment suggested that pre-clinical human abuse liability testing could be effective in predicting the likelihood of real-world abuse of central nervous system medications. (c) Finally, one comment noted that longer-term studies for opioid products are necessary to identify addiction issues.

E. Limiting REMS-drug Availability for Diversion

i. Buy-Back/Take-Back/Disposal Programs

289. Several comments recommended initiating buy-back, take-back or disposal programs to decrease the availability of REMS drugs for diversion or abuse. For example: (a) Several health care professionals noted that allowing pharmacies to take back medications would ensure that they are disposed of properly (e.g., incinerated). One of these comments suggested that such a program would decrease the likelihood of medications entering the water supply. Moreover, most of these comments noted that such a program would allow tamper-proof bingo cards or blister packs to be re-dispensed. On the other hand, while

another health care professional agreed that pharmacies should take back and incinerate unused medications and keep a tally of the quantity incinerated, this comment disagreed with the others regarding allowing drugs to be re-dispensed. This comment stated that even bubble packs should not be re-dispensed due to a concern for product tampering. (b) A health care professional organization recommended implementing a REMS medication-return program and educating stakeholders about it. (c) In addition, several health care professionals stated that a take-back program should be combined with e-prescribing to reduce diversion.[39] (d) One comment from a health care professional and cancer patient suggested that DEA regulations should address patients returning unused controlled substances to the pharmacy.

290. Several comments addressed the issue of REMS drug disposal upon patient death or prescription discontinuation. For example: (a) An advocate for opioid drug reform recommended that when a patient dies, any unused drug be disposed of properly because of the strong monetary incentive to sell it to non-patients. (b) In a similar vein, a hospice nurse noted that in her program every pill is counted when a patient dies and the unused medication is properly disposed of by melting. Another hospice nurse noted that the issue of unused medication and disposal is not just a concern at a patient's death, but also whenever a prescription is changed.

291. On the other hand, multiple comments expressed concerns regarding the implementation of a take-back/buy-back or disposal program. For example: (a) An organization representing distributors stated that any REMS elements involving the disposal of excess drugs by patients needs to be carefully considered in light of multiple legal, regulatory and policy issues (e.g., the Environmental Protection Agency, DEA, law enforcement). (b) A

[39] For a more detailed discussion of e-prescribing and other paperless initiatives, see Subpart F (ii) of this Section.

pharmacy association stated it would not support a mandatory take-back program under the REMS because of cost and logistical challenges. However, it does support community-based take-back initiatives. (c) Similarly, a pharmacist commented that a take-back program could be overwhelming depending on the population served.

ii. Lockboxes and Dispensing Mechanisms

292. Several comments suggested that use of secure storage and dispensing systems could curb diversion. For example: (a) A hospice nurse noted when patients were found to have diverted medication, their medication was put into a lockbox which only dispenses enough medication for each day. (b) A vendor suggested that a lockable prescription bottle top is available at low cost to prevent unauthorized access to medications by family members. (c) A pain organization stated that packaging should be developed to only allow the person for whom the medication is prescribed to open the bottle. (d) Similarly, a health care professional organization recommended considering engineered solutions like dispensing mechanisms, and safe storage systems. Once again, not all comments expressly stated whether they supported mandating use of such dispensing mechanisms. However, one comment from an advocate for opioid drug reform did expressly support the development and mandated use of secure methods to dispense products.

293. Other comments offered alternatives to lockboxes and dispensing mechanisms. For example: (a) A comment from a health care professional and cancer patient stated that patients should have to sign an acknowledgement that they are receiving a dangerous drug and that it should be stored in a locked cabinet or container. (b) Another comment suggested an alternative to lockboxes could be daily delivery of medications or patient monitoring.

iii. Limiting the Quantity of REMS Drugs Per Prescription

294. Another alternative for limiting the supply of REMS drugs available for diversion discussed by multiple comments was reducing the number of pills dispensed to pain patients at any one time. For example: (a) A health care professional recommended decreasing the size of initial prescriptions for chronic pain patients to, for example, three days to determine if the treatment is effective before dispensing a larger prescription. (b) Another health care professional suggested that prescriptions should not be for longer than thirty days and they should be dispensed in seven day cycles. In particular, this comment stated that patients taking opioids have impaired decision-making skills and they should not have more than a seven day supply. (c) Similarly, a health care professional organization recommended changing payor policies with regard to prescriptions. In particular, this comment noted that currently pharmacies may only receive one dispensing fee per month for opioids, leading to monthly prescriptions, even when a smaller prescription would suffice. This comment noted that this practice leads to more REMS drugs being available in the population.

295. On the other hand, several comments from pain patients, as opposed to favoring more restrictions on prescriptions, complained about existing prescription limits. For example: (a) A couple of pain patients advocated for increasing the size of prescriptions noting the burden of a thirty-day limit – particularly when traveling or when their prescriber is a long-distance away – and the inability to take advantage of mail-order services to decrease medication cost. (b) In a similar vein, a prescriber suggested that pharmacies should be permitted to stock small additional supplies to ensure patients do not enter withdrawal while waiting for their prescription to be filled.

F. Technology-based Solutions Targeting Diversion and Abuse

i. Track and Trace and Barcoding Technology Solutions

296. In multiple comments, a couple of vendors suggested that on-dose tracking technologies could assist law enforcement in curbing diversion because diverted drugs – even if repackaged – could be traced to the source. These comments noted the lack of information that currently can be gleaned from seized drugs that are not in the original packaging and suggested that on-dose tracking could provide additional data for defining the diversion problem (e.g., does it originate within the United States or outside, are patients diverting drugs). Furthermore, one of these comments noted the following advantages of employing this technology: (a) it is seamless with current distribution, (b) the information provided is virtually limitless, and (c) it could be implemented at a low unit cost (e.g., under one cent). On the other hand, a distributor association noted that the infrastructure for implementing on-dose tracking is not yet available.

297. A couple of comments from vendors suggested using barcoding technology – in different ways – to curb diversion. For example: (a) A vendor suggested using barcodes on packaging to link a product to the prescriber, dispenser and patient. This comment suggested that barcodes could be used to ensure compliance with the REMS prior to dispensing. (b) Another comment from a vendor suggested adopting a special prescription for REMS drugs which would only be available to certified prescribers and incorporate a barcode at the bottom to facilitate their use in current workflow. The vendor noted that a similar program in New York successfully reduced counterfeit prescriptions for Class II drugs. On the other hand, other comments criticized New York's special prescriptions suggesting the initiative had led to shifts in prescribing. Similarly, a prescriber suggested

that Texas' special prescription for opioids had decreased prescribing with limited, if any, benefits. Another prescriber echoed this comment noting that special prescription pads have not been effective in California.

298. One vendor stated that FDA should incorporate opioid products in its track and trace initiatives. On the other hand, a distributor association, while supportive of track and trace initiatives for all prescription drugs, opposed coordinating them with the REMS because it could delay the progress of those initiatives or REMS development.

ii. Paperless Initiatives

299. Several comments recommended focusing on paperless initiatives – specifically electronic medical records and e-prescribing of REMS drugs. For example: (a) A comment recommended a universal electronic medical record to identify doctor shopping. (b) Several health care professionals suggested e-prescribing of REMS drugs could eliminate forgery and duplication of prescriptions. (b) Another comment suggested e-prescribing could help with tracking prescribers and patients. (c) Another comment suggested e-prescribing helps facilitate communication between providers and pharmacists. (d) A regional pain organization stated that in conjunction with implementing NASPER, electronic medical records and e-prescribing should be adopted. (e) Another comment from a prescriber stated she uses an electronic prescribing system which notifies her if a patient has narcotic prescriptions from another prescriber or different pharmacy – a violation of their PPA. However, this comment noted that she cannot use the system to electronically transmit narcotic prescriptions. Similarly, another comment explained that DEA regulations currently forbid e-prescribing of controlled substances.

300. As noted above, several comments recommended combining paperless initiatives with other efforts to curb diversion.

G. Increasing Enforcement and Sanctions on Abusers and Unethical Health Care Professionals

301. Several comments from prescribers and pain patients stated that there should be stronger enforcement and/or sanctions for health care providers and individuals engaging in abuse and/or diversion. For example: (a) A prescriber supporting stronger sanctions noted a patient of his had been prosecuted for forging fifteen prescriptions. However, the patient was given a light sentence and went on to repeat the same offense with another prescriber. (b) Another comment suggested that instead of implementing the REMS, resources should be put into law enforcement. (c) A pain patient stated that she personally knew of instances where patients diverted and/or misused medications and recommended initiating an anonymous tip hotline to report incidents of diversion/abuse. Moreover, this comment suggested that pharmacists should be encouraged to use the hotline. Finally, this comment recommended that diversion laws be enforced by specially-trained police and aggressively prosecuted. (d) A health care professional stated that the State Boards of Medicine, Pharmacy and Nursing should take immediate and permanent disciplinary action, including censure, against individuals who engage in unscrupulous professional behaviors.
302. In a similar vein, advocates for opioid drug reform suggested that there should be increased enforcement regarding marketing tactics. For example, a comment stated that there should be severe consequences for manufacturers who receive a warning letter.
303. Several comments highlighted that increasing sanctions helps curb abuse without burdening legitimate pain patients.

H. Other Recommendations for Curbing Abuse and Diversion

304. A couple of comments from a vendor suggested that an audit and feedback system could easily identify issues of doctor-shopping, pharmacy shopping, and dose escalation.

305. One comment suggested that there needs to be better data analysis of diversion that occurs before opioids are distributed to patients (e.g., miscounting errors by pharmacists, stolen inventory at pharmacies and warehouses).

306. A pain patient suggested implementing closer monitoring of pharmacists and other members of the distribution chain noting rumors of being able to purchase narcotics from "closing" employees at certain pharmacies. Similarly, a health care professional suggested DEA should receive more funding to audit pharmacies.

307. A pain patient who is also a prescriber recommended (a) forbidding prescribers to publicly advertise any medical services that involve the use of opioids, (b) prohibiting prescribers from treating non-resident patients when there is a demonstrated out-of-state abuse problem, and (c) limiting the number of pain patients any single prescriber can treat long-term with opioids (with certain exceptions).

308. A couple of comments recommended that industry take more extensive measures to combat diversion. For example, a prescriber suggested that industry incentivize its sales force by providing bonuses when there is a reduction in abuse, addiction and death in their territories. Another prescriber suggested requiring pharmaceutical companies to track and report unusual prescribing practices, being sensitive to differences between pill mills and a well-meaning doctor who is over- prescribing.

X. PHARMACY SYSTEMS

In its April 20, 2009 notice, FDA requested input regarding whether there are existing pharmacy systems that could be used to implement the REMS. Comments received in response to this request emphasized the importance of designing REMS systems and processes that are transparent, avoid duplication, and integrate seamlessly with the current workflow of health care professionals. [40] In particular, comments provided both (A) general guidance and (B) specific proposals for integrating the REMS elements into pharmacy workflow.

A. General Guidance for Integrating the REMS Elements into Pharmacy Workflow

309. A recurring theme in comments – particularly from pharmacy associations and pharmacies – was the importance of REMS elements seamlessly and transparently integrating with the workflow of prescribers and pharmacists. For example: (a) Multiple comments suggested that REMS elements be integrated with all medical records and pharmacy management systems. (b) A vendor emphasized that the technology systems used in the REMS need to be interoperable with each other and existing systems and transparent so as not to negatively impact workflow. (c) A pharmacy standard organization noted that the REMS will need real-time processing and transparency both for verification and evaluation and highlighted that approximately ninety percent of dispensed prescriptions are processed as a real-time claim via its telecommunication standard. (d) Finally, a pharmacy chain stated that the program should be fully integrated to avoid having to access multiple databases or manual systems before filling opioid prescriptions.

[40] Several comments discussing pharmacy systems emphasized the need for a common system/process/platform for all REMS and offered comments regarding REMS development generally. These comments are being considered by the Agency, but this document will focus strictly on comments addressing the opioid REMS.

310. Several comments cited experience with current REMS as the basis for their recommendations. For example: (a) In a survey of two-hundred and seventy five pharmacists submitted by a health care professional organization, one-third of respondents cited various verification and registration procedures in current REMS as one of their top challenges. Moreover, one-third also stated that resolving REMS issues has negatively affected their practice and a majority noted that REMS issues have occasionally resulted in dispensing delays. This comment suggested that seamless integration is particularly important for the opioid REMS due to the large number of prescriptions that will be affected. (b) Similarly, several comments supported the use of electronic technology as opposed to paper or telephonic systems, which have been used with other REMS. For example, a pharmacy chain noted that pharmacies use highly-automated and electronic dispensing processes. Specifically, patient records, billing and pricing information, drug interactions, and patient education information are all available via electronic systems. This comment recommended that all required record-keeping, verifications, and reporting requirements under the REMS be executed through an electronic process.

311. The necessary functionalities of a REMS system will depend in large part on what elements are implemented and on what REMS compliance responsibilities are imposed at the point of dispensing. Pharmacists and their representative organizations expressed concern regarding requirements that they police REMS compliance. For example: (a) A pharmacy association emphasized that pharmacy staff should not be required to police compliance nor should patients be denied medications at their community pharmacy. (b) A pharmacy chain supported having pharmacists verify prescriber education by having information available

to pharmacies in a real-time online database, but opposed requiring that pharmacists verify patient education.

312. Several comments recommended employing existing transaction processing networks or claims adjudication systems to implement the REMS to avoid adding additional steps to the pharmacist's workflow. For example: (a) If prescriber verification is required prior to prescription processing, a pharmacy chain recommended using the same switch vendors that verify insurance information to verify that the prescriber's National Provider Identifier (NPI) or DEA number is in a REMS database. The prescription would then be rejected if prescriber compliance with the REMS could not be verified. (b) In a similar vein, a health care professional organization recommended that any requirements for verification be done through a standardized, real-time, system-based approach that is uniform for all REMS and that automatically electronically checks for compliance against a REMS centralized database – triggered by a medication's National Drug Code (NDC) through the pharmacy claims processing procedure. This comment suggested that if compliance could not be verified, an electronic smart message would be sent back to the pharmacy describing the failure and steps to address the issue. This comment noted, however, that if a hard stop is placed on the adjudication process for the failure to comply and the pharmacist must contact the prescriber to resolve the issue, there will be a delay in dispensing the medication to the patient. (c) A health care professional organization suggested that FDA work with pharmacy transaction switches or electronic prescribing intermediaries to design education verification functionalities. This comment suggested that manufacturers are in the best position to fund the implementation, administration, and maintenance of the system. Furthermore, it stated that pharmacies should not have to pay transaction fees if they are

required to access such a system to verify certifications as this would be tantamount to charging pharmacies to enforce the REMS. (d) Another advantage to using an existing transaction network, cited by the parent company of such a network, is that the system would be sufficiently flexible to adapt to changes warranted by evaluation.

313. A couple of comments noted other existing systems that could be useful in REMS implementation. For example: (a) A pharmacy chain suggested that the distribution of Medication Guides should be through current systems that provide electronic data to pharmacies.[41] (b) A hospital pharmacist recommended using the current Medicare and Medicaid systems to the extent possible.

314. One consideration noted by multiple comments for all technology-based solutions implemented under the REMS is the fact that not every pharmacy in the United States has the same technological capabilities. One comment estimated that approximately two hundred pharmacies are not currently engaging in electronic transactions. Another comment targeted the number at one hundred and fifty. Overall, a health care professional organization noted that it is unlikely that a "one size-fits-all" approach to the development, validation and administration of certification systems will work for all providers engaged in pain management.

B. Specific Proposals for Integrating REMS Elements into Pharmacy Workflow

315. A transaction processing network offered to assist with REMS implementation noting that the estimated twenty million prescriptions that would be affected by REMS requirements annually is small in comparison with the total number of prescriptions that they handle each year. In particular, it noted that its system is: (i) scalable, (ii) already part of the pharmacy

[41] For a more detailed discussion comments regarding Medication Guide delivery, see Patient Education, Section VII, Subpart D (ii).

workflow, (iii) interoperable with two state prescription monitoring programs and several controlled substance reporting services, and (iv) already handling a program similar to a registry for the Centers for Medicare and Medicaid Services (CMS). In particular, this company stated its system could support the following elements, if incorporated into the REMS: (a) education verification; (b) patient, pharmacy, and prescriber registration, (c) survey dissemination; and (d) reimbursement for pharmacies. This comment noted that with regard to pharmacist verification of prescriber education, a large majority of their customers supported using its recommended solution. Finally, this comment suggested its network could accomplish the REMS goals without impeding patient access.

316. Although acknowledging that there is not one closed existing system to serve as the REMS platform, another vendor also recommended using existing electronic health care and pharmacy reimbursement systems to support the education and communication components, data capture, and effectiveness measurements of the opioid REMS. This comment rejected web-portal technology noting its preferred system would: (a) cover all products at the manufacturer and form/strength (NDC) level, (b) reduce workflow disruption while allowing for real-time verification of patient, prescriber, and pharmacy compliance, and (c) provide access to de-identified longitudinal patient data that will allow for ongoing analysis of program efficacy while protecting patient privacy. Other benefits of the system cited by the vendor included that it would: (a) capture prescriber and pharmacist certifications from multiple education vendors, (b) prevent dispensing of a prescription if there is a compliance failure in patient education or pharmacist/prescriber certification, (c) collect data to be used in evaluation of appropriate prescribing and patient use, and REMS compliance, (d) provide for communications and/or interventions with the prescriber or

pharmacy when there is evidence of inappropriate prescribing or patient use, (e) adhere to the data privacy provisions of the Health Insurance Portability and Accountability Act (HIPAA) and the American Recovery and Reinvestment Act (ARRA), (f) link to other de-identified longitudinal data including other prescription activity and medical diagnosis information allowing for advanced cohort-based longitudinal studies. On the other hand, possible disadvantages of the system cited by the vendor included: (a) Department of Defense, Department of Veterans Affairs, and in-patient data would not be captured by the system (although the vendor offered possible solutions), and (b) information regarding non-medical use that occurs once a patient receives an opioid prescription could not be captured.

317. Another comment from a vendor, which was supported by a pharmacy association, recommended an e-prescribing approach where only certified prescribers would be able to e-prescribe a REMS drug. In addition, should patient education and certification be required, this system could also handle these components electronically. The proposed process would provide an automated pre-prescribing hard stop should a prescriber, pharmacy or patient not be REMS-compliant. The vendor suggested that the significant advantage of this process is that it checks for compliance at the point of prescribing as opposed to during the dispensing process. The vendor noted that when a prescription is filled, this process could also include (a) a reminder to the pharmacist to deliver patient education and (b) a follow-up contact with the patient several days after dispensing. This comment acknowledged that DEA currently does not permit e-prescribing of controlled substances. Therefore, it also proposed a solution under the current paper prescription system. Specifically, it proposed that the pharmacy management system would – after receiving prescriber and patient information – seek to validate certification and, in the event

of a compliance failure, trigger a hard stop. On the other hand, if all parties were in compliance, the system would issue a proceed order and trigger a pharmacist-provided patient education session with the option to have a follow-up after dispensing.

318. Another vendor offered its own proposal leveraging existing systems. The vendor stated its system (a) would be easy to use, (b) could handle millions of transactions a day, and (c) already has established access in ninety-nine percent of pharmacies. Specifically, it stated that its system could (a) deliver the requisite education and messaging to professional and patient stakeholders, (b) verify stakeholder compliance, (c) link stakeholders easily through existing practice systems, and (d) verify at the pharmacy level REMS compliance prior to a prescription being filled. The system would leverage existing claims adjudication systems and use a prescription card provided by the prescriber to the patient to "attest" that the patient had been educated prior to the first prescription. The card would also have to be "activated" by the patient or caregiver prior to receiving all prescriptions (i.e., a process that would include confirming safety information). At the pharmacy, the card would serve to verify prescriber and patient REMS compliance. Attributes of the system cited by the vendor included that it: (a) is scalable, expandable, and adaptable to changing needs and/or regulatory environments, (b) is not dependent on insurance coverage for verification of REMS compliance, (c) has demonstrated efficiency and effectiveness in stopping behaviors that lead to diversion, (d) serves a role similar to a nationwide PMP in collecting real-time de-identified information regarding stakeholders without having to fund the National All Schedules Prescription Electronic Reporting Act (NASPER). For a more detailed discussion of comments regarding NASPER, see Methods to Curb Diversion, Section IX, C.

319. Another vendor also suggested a card-based system. Specifically, this vendor suggested that education verification could be achieved with its "co-pay reduction" cards, which are already interoperable with existing pharmacy systems. This vendor stated when a prescriber completed the requisite education, he/she would receive cards to provide to patients at the time of prescription. The patient would then provide the card to the dispenser who would be able to electronically verify REMS compliance through a transaction processing network. This comment also noted that their technology could be a conduit for some patient education.

320. Similarly, a comment from a society of pain educators supported the use of co-pay reduction cards to verify that patients, prescribers and dispensers have received the requisite information. This comment noted that new systems are not necessary and the adaptation of existing systems would be preferable and comply with FDAAA.

321. A pharmacy chain suggested that a centralized REMS database be created to ensure compliance of all participants noting that such a system would ensure: (a) pharmacists do not become the gatekeepers of the program, and (b) efficiency by having a central location for REMS training, registration and communication. This comment noted that the cost to create and maintain the REMS database should be borne by pharmaceutical manufacturers and FDA, not pharmacy providers.

XI. REMS EVALUATION AND METRICS

Under its evaluation provisions, FDAAA requires that all REMS include a timetable for the submission of assessments. Furthermore, the statute requires that the timetable, at a minimum, include assessments by eighteen months, three years, and in the seventh year after the REMS is

approved.[42] In its April 20, 2009 notice, FDA specifically requested comment regarding the metrics that should be used to evaluate the success of the opioid REMS. In response, comments from a variety of stakeholders were submitted regarding (A) the appropriate scope and process for evaluation in general, (B) the assessment of elements prior to implementation, (C) the post-implementation evaluation timeline, (D) the appropriate evaluation metrics, (E) the relevant data sources for REMS evaluation, and (F) the interpretation of REMS results.

A. Scope and Process for REMS Evaluation

322. Several comments from a variety of stakeholders recommended developing a comprehensive evaluation plan prior to REMS implementation and choosing elements for the REMS based on their ability to produce measurable effects. For example: (a) A health care professional organization recommended adopting a thoughtful, comprehensive, and rigorous evaluation plan for all elements of the REMS as they are developed; not only to ensure that the system will work well, but also to identify and overcome any harmful unintended consequences. (b) Another health care professional organization stated that there needs to be a comprehensive monitoring system and a plan for evaluation in place prior to REMS implementation. (c) A pain organization submitted a petition with four thousand and seventy-five signatures supporting REMS elements that are designed so they can be measured to determine their effectiveness in reducing the risks of abuse, misuse and overdose.

323. A surveillance organization offered nine guiding principles for evaluation of the REMS. (a) Evaluation should include the effects of opioid REMS on misuse, abuse, addiction, diversion and overdose. (b) All types of opioid products must be included: branded and

[42] Please note that while FDAAA requires evaluation at eighteen months, three years, and seven years, FDA may require more frequent assessments.

generic as well as extended-release and immediate-release. Furthermore, illicitly manufactured opioids (e.g., heroin) should be included. (c) The risks unique to specific formulations of prescription opioids must be measured separately (e.g., patch, tamper resistant). (d) Evaluation should be comprehensive, including not only the risks but also the benefits (e.g., impact on access to medications, shifts in prescribing, impact on quality of life). (e) Multiple perspectives on the natural history of substance use disorders are needed to assess the proposed opioid REMS, measured separately but in parallel. (f) The impact of the opioid REMS on opioid treatment programs must be evaluated. (g) Assessments of opioid REMS must be conducted on pre-scheduled basis. (h) Outcomes in specific populations must be monitored (e.g., young children, adolescents). The effects of the opioid REMS on patients and non-patients (e.g., abusers) must be included. (i) Evaluation must assess whether existing disparities in access to opioid pain medications by vulnerable minorities have been exacerbated.

324. Many comments from health care professionals echoed this final evaluation principle, stating that FDA should develop mechanisms to monitor the effect of the REMs on (i) opioid access for at-risk populations (e.g., nursing home residents, children) and (ii) opioid shortages, particularly in inner cities and rural areas.

325. Several comments highlighted the need for an iterative evaluation process with modifications made based on evaluation results. For example: (a) A pain organization stated that all elements of the REMS must be measurable, accountable, and – if necessary – easily reversible. (b) A health care professional organization stated that there must be a feedback loop to: (i) allow for continuous improvement and (ii) examine the reasons behind patient failures, as opposed to simply documenting them. Specifically, this comment

326. Several comments highlighted that evaluation of the opioid REMS will be complicated by its breadth and scope. For example: (a) In its comment, industry noted that unlike current REMS which are intended to mitigate a single risk from a single active ingredient in patients prescribed the medication, the opioid REMs will be much more complex. The evaluation must include assessment of unintended consequences as well as effectiveness. (b) A prescription drug abuse surveillance organization stated that an evaluation plan should be developed prior to REMS implementation and the plan must be sensitive to the unique characteristics of the REMS including the fact: (i) it includes diverse and numerous products, formulations, and manufacturers, (ii) it seeks to mitigate a number of risks and some of those risks are not strictly biological in mechanism, (iii) adverse outcomes from REMS drugs occur in both patients and non-patients, (iv) actions regarding REMS drugs are occurring at the federal, state, and local level. Therefore, this comment concluded that

the evaluation plan has to: (i) be drug-specific, (ii) acknowledge and monitor the social context influencing substance abuse, (iii) be outcome-specific, (iv) include both patients and non-patients, and (v) be sensitive to changes at all levels. (c) Similarly, a scientific organization noted that multi-factorial, multi-level surveillance is necessary.

327. A couple of comments noted the need to inform stakeholders of how to report REMS failures. For example: (a) A comment suggested (i) implementing a key informant system so that problems with the REMS can be tracked and (ii) establishing a clearinghouse for patient complaints so that if patients are unable to access their medications and/or they are in unrelenting pain, their concerns will be heard. (b) Similarly, a health care professional organization stated that the REMS should be clear as to where and how to report failures in the system (e.g., problems with the REMS, adverse events).

328. Several comments proposed methods for ensuring the integrity of the evaluation process. For example: (a) A research institute recommended that evaluation of REMS effectiveness be objective by: (i) making the data public as opposed to proprietary, (ii) having REMS methodologies be "peer reviewed," and (iii) ensuring that the advisory panels reviewing REMS effectiveness are not biased in favor of industry. (b) Similarly, a pain organization stated that evaluation should be transparent, with published data. (c) A health care professional suggested that data from the REMS evaluation should be accessible by prescribers. (d) A manufacturer of non-opioid products recommended the development of databases that could be accessed by the public to study the impact of the REMS. While this comment acknowledged the complexity of such an approach, it suggested it was important to build public support for REMS and assess their public health impact. (e) Finally, many comments recommended that FDA form a monitoring board to review

collected data on intended and unintended outcomes. Similarly, a health care professional stated that an advisory board of palliative and hospice, oncology, and pain management professionals could (i) design alternative approaches to concerns about safety, (ii) devise effective approaches to collecting data on outcomes, and (iii) predict efficacy of restrictive measures.

329. A scientific organization noted that there is a foundation for beginning the process of REMS development, with strong science in some areas (e.g., assessing abuse liability and determinants of abuse risk) and emerging science in other areas (e.g., identifying which potential risk mitigation strategies actually reduce abuse and diversion, evaluating the likely impact of drug dosage form on real world abuse risk). This comment recommended developing better data to assist in planning and evaluating the REMS (e.g., more National Institutes of Health research).

330. A comment from a pharmacy chain recommended an open discussion of the effectiveness of current REMS to plan for the opioid REMS.

B. Assessment of Elements Prior to Implementation

331. Several comments from diverse stakeholders suggested that elements should be proven effective prior to implementation. While some comments suggested examining state initiatives and historic effectiveness, several comments from a variety of stakeholders also recommended pre-testing elements prior to implementation.[43] For example: (a) A distributor association suggested that pre-testing of prior REMS programs could have avoided some of the difficulties that occurred upon implementation. (b) A health care professional organization recommended ensuring that the components of the REMS are

[43] In a similar vein, many comments recommended piloting the entire REMS prior to full-scale implementation. For a more detailed discussion of comments related to piloting the REMS, see Implementation, Section XIII, Subpart F.

proven to be effective in mitigating specific defined risks and are workable for patients, pharmacists, manufacturers, wholesalers, and system vendors. (c) A comment from academia stated that any interventions should be proven effective in curbing abuse prior to implementation because they will undoubtedly decrease legitimate prescribing. Similarly, a health care professional organization stated that any element implemented should be demonstrated to be effective when balanced with the issue of restricting access. (d) Finally, a health care professional organization stated that prior to implementation, FDA should perform research and gather data to determine which REMS elements will effectively mitigate risk with minimal impact on patient access and care, and minimal burden on hospitals and health systems.

332. While several comments preferred that elements be proven to be effective prior to implementation, they emphasized that in the absence of such proof, rigorous post-implementation assessment would be necessary. For example: (a) A pain organization and pharmacy chain stated that the REMS should only employ proven elements, and if insufficient proof exists, than the element should be subject to rigorous evaluation at predetermined intervals. (e) A comment from a multidisciplinary subgroup of a REMS task force that was endorsed by several other comments recommended that all REMS tools be piloted or at least regularly assessed. (g) A state pain initiative recommended that elements should only be implemented on the basis of proven effectiveness in reducing the risk of abuse, misuse, and diversion and promoting responsible prescribing. If no sufficient evidence exists, the element should be verified or at least reevaluated transparently with published results according to a predetermined timeline.

333. Several comments recommended evaluating education components prior to implementation. For example: (a) A variety of stakeholders recommended pre-testing of education materials for comprehension, reading-level appropriateness, retention, and knowledge application in the clinical setting. (b) A pain organization recommended evaluating several existing, smaller-scale programs for possible use as models for REMS education (e.g., Utah's "Use Only As Directed" program, the National Pain Foundation's PainSafe program).. (c) A vendor stated that educational materials should be evaluated both pre- and post-implementation with sponsors documenting adherence to the standards of behavioral research through protocols, interview guides, data analysis plans and study reports. This vendor emphasized the need for qualitative pre-implementation research within target populations. Based on these assessments, improvements could be made prior to enacting the education programs. This comment suggested that post-implementation, quantitative research and surveys could then be conducted to ensure that patients are receiving, understanding and complying with educational materials.

334. A surveillance organization noted that the post-market setting offers the opportunity to conduct small randomized trials to test and modify different components of the REMS before they are implemented and noted that this would be especially important if methadone is to be the pilot drug. For a more detailed discussion of the proposed Methadone pilot, see Scope of the REMS, Section III, Subpart C (iii) and Implementation, Section XIII, Subpart F.

335. A health care professional organization expressed concern that REMS are unproven and may not solve the problem of opioid abuse while burdening legitimate users. This

comment further expressed concern that FDA had not indicated that it planned to conduct further study prior to REMS implementation.

336. On the other hand, not all comments sought proof of effectiveness prior to the implementation of elements. A comment from a lawyer indicated that even if there is not specific data to show the benefits of proactive risk assessment and monitoring, logic suggests these actions would reap rewards.

C. Post-Implementation Evaluation Timeline

337. Industry recommended a phased-in approach to evaluation with (a) the initial phase including the creation of a stakeholder working group to develop metrics, (b) the intermediate phase including continuous monitoring to refine the metrics and evaluation of the initial phase's elements and (c) the long term phase including evaluation of the prior phases' impact. For a more detailed discussion of industry's proposed phased-in implementation, see Implementation, Section XIII, Subpart E.

338. As discussed above, FDAAA requires evaluation, minimally, at eighteen months, three years and seven years. Generally, however, comments discussing the timing of evaluation recommended more frequent assessments. For example: (a) Several comments recommended "frequent" evaluation of the REMS. A patient advocacy organization stated that frequent and meaningful evaluation of REMS elements is essential to ensure the balance between risk reduction and access to opioids. A state pain initiative recommended regular and frequent evaluation of the education program to determine if it is meeting its goals and whether it requires updates or enhancements. (b) A health care professional organization recommended "periodic" evaluation of metrics and measures. (c) A pharmacy organization suggested that there should be evaluation based on pre-determined

outcomes for success in one to three years and modifications should be made accordingly. (d) A vendor stated that the timeline in FDAAA was not sufficient and recommended more frequent data collection (i.e., every six months) because of potential serious unintended consequences that would warrant immediate mitigation. (e) Similarly, a comment from a manufacturer stated that evaluation of education retention must occur within months – much sooner than required by FDAAA.

339. On the other hand, a comment from a vendor noted that while FDAAA requires evaluation at twelve and eighteen months a REMS that seeks to register, educate and certify all prescribers would likely only be able to document process success at those times. This comment asserted that it is unlikely that an impact on prescribing practice would be measurable at twelve months. However, this comment noted that if an Audit and Feedback system is implemented, it could demonstrate prescribing changes as early as six months and could produce measurable effects on the utilization of emergency rooms and hospital admissions by the twelve and eighteen month marks.

340. A couple of comments recommended that the REMS timeline include "sunset" points for elements that have not proven effective. For example: (a) A pain organization suggested that to avoid layering ineffective elements on top of each other, elements under the REMS should have sunset provisions in the event they cannot prove effectiveness. (b) Similarly, a state pain initiative recommended including sunset provisions so ineffective REMS elements can be eliminated.

D. Evaluation Metrics

i. Developing Metrics

341. Several comments discussed the process for developing evaluation metrics. A recurring theme was the need for stakeholder involvement in determining metrics prior to REMS implementation. For example: (a) Industry recommended creating a stakeholder working group to develop evaluation metrics using transparent methodologies. (b) A vendor agreed that stakeholder involvement is critical and suggested that there needs to be a predetermined series of core metrics. (b) A pain organization submitted a petition with four thousand and seventy-five signatures stating that appropriate metrics are necessary to determine successful outcomes for patient care as well as abuse, misuse and diversion and stated that success thresholds should be predefined, reasonable and achievable. (c) A health care professional organization recommended defining metrics prior to implementation and matching them to an evaluation method, and then pilot testing for effectiveness. (d) A pain organization suggested that FDA develop working groups to discuss metrics, noting that more dialogue is needed.

342. Several comments suggested that additional data would inform REMS evaluation and the development of metrics. For example: (a) A pharmacy stated that more information on current REMS effectiveness would inform what metrics are appropriate for the opioid REMS. (b) A state pain initiative stated that appropriate metrics must be developed to determine REMS success with regard to patient outcomes and the reduction of abuse, misuse and diversion. This comment also noted that the relationship between legitimate prescribing and abuse is unclear, and mitigation strategies have focused on end-users without considering the role of the pharmaceutical industry and those who divert prescribed

medications. This comment noted that this additional information is necessary for evaluation.

343. A recurring theme in comments regarding the development of metrics is that rigorous evaluation of the REMS must include both positive and negative effects of elements. For example: (a) A health care professional organization stated that evaluation should not rely on prescription numbers alone because a reduction in prescriptions could simply mean fewer legitimate patients are getting pain treatment. Instead, this comment stated that metrics must be complex because there are concurrent problems of under-treatment of pain (e.g., cancer pain) and abuse/misuse. (b) Another health care professional organization stated that the unintended consequences of REMS fatigue and shifts in prescribing must be examined. (c) A comment from sixteen health care professional organizations emphasized that negative consequences could result both in patients treated with REMS drugs and in individuals denied adequate pain management due to (i) a lack of certified prescribers, (ii) shifts in prescribing patterns, (iii) resurrection of widespread opioid phobia or (iv) a clinical practice environment that emphasizes preventing misuse and abuse of pain medications at the expense of providing adequate pain relief. (d) A comment submitted by a pain organization – that was endorsed by several other comments – stated that the assessment of each element should include data for its positive and negative aspects (e.g., the element reduced inappropriate prescribing by X% in a predetermined time but there was a Y% reduction in appropriate prescribing, or the number of prescribers authorized to prescribe these medicines under the REMS decreased by Z %). Furthermore, this comment recommended that FDA designate a third party, such as The College on Problems of Drug Dependence to evaluate the intended and unintended effects on abuse and patient care. (e)

Another comment highlighted the need for a multifactor evaluation with the example of buprenorphine. While buprenorphine deaths increased with its introduction to the marketplace, heroin deaths decreased significantly more than that increase. However, both trends needed to be assessed to properly interpret them. (f) Similarly, a comment from a hospice provider stated that while the REMS should result in a decrease in the number of people presenting to addiction treatment centers and a decrease in opioid-related deaths, those metrics would only equal success if there was no decrease in prescribing of REMS drugs to pain patients nearing the end-of-life. (g) Finally, a health care professional organization stated that both patients and non-patients must be assessed to determine the REMS' impact on access as well as curbing abuse.

ii. Potential Metrics

344. Comments varied in how they presented potential metrics. Some comments focused on single metrics or big-picture metrics. For example, a comment from academia identified the overriding metric as the number of adverse events and deaths involving the use of an opioid product and the interventions that the manufacturers use to stop the oversupply and diversion of REMS drugs. On the other hand, several comments provided extensive lists of detailed metrics encompassing all stakeholders. Based on the comments received, the following list summarizes the data proposed to be collected for REMS assessment:

- Data regarding prescribers certified under the REMS[44] and their prescribing practices. For example: (a) the quantity of certified prescribers, (b) specialty, (c) type of practice, (d) geographic location, (e) knowledge regarding appropriate and inappropriate prescribing and application of that knowledge in

[44] To avoid repetition, this list will not add the caveat "if required" to each possible REMS element. However, the relevance of certain metrics will obviously be dependent on which elements (e.g., certification, education) are ultimately required under the REMS.

practice (e.g., are all patients receiving REMS drugs opioid-tolerant), (f) utilization of available tools (e.g., prescription drug monitoring programs), (g) participation in CME pain management courses and mentoring programs, (h) level of REMS compliance prior to writing prescriptions (e.g., are only certified prescribers writing prescriptions), (i) data regarding the comfort level of prescribers post-REMS implementation

- Data regarding prescriptions written/dispensed. For example: (a) the quantity of prescriptions, (b) the demographics of patients receiving prescriptions, (c) the diagnosis of patients receiving REMS drugs (e.g., cancer versus non-cancer pain, fibromyalgia versus back pain).
- Data regarding shifts in prescribing. For example: (a) data regarding the prescribing of pain relief alternatives (e.g., immediate-release products and non-steroidal anti-inflammatory drugs (NSAIDs)) as compared to REMS drugs, (b) data regarding adverse events emanating from shifts in prescribing (e.g., NSAID and acetaminophen toxicity, mortality and morbidity associated with NSAIDs).
- Data regarding the logistics of the REMS. For example: (a) the number of incomplete registrations by stakeholders, (b) data regarding REMS effectiveness on voluntary participants versus mandatory participants, (c) data regarding delays in dispensing due to REMS failures.
- Data regarding pharmacists or pharmacies registered under the REMS and their dispensing practices. For example: (a) the quantity registered, (b) their level of knowledge, (c) changes in patient counseling, (d) changes in

willingness to stock REMS drugs due to REMS requirements, (e) data regarding whether pharmacies are only dispensing to registered patients.

- Data regarding the number and type of adverse events. For example: (a) the number of deaths in non-tolerant patients, (b) the number of accidental drug poisonings, (c) the number of poisonings in young children as compared to other products, (d) data regarding overdoses, including intentional overdoses.
- Data regarding patient education logistics. For example: (a) are patients receiving the various education materials, (b) if so, who is providing the materials, (c) did anyone review the materials with the patient, (d) are pharmacists engaging in counseling.
- Data regarding comprehension of patient education materials and whether such education resulted in behavior change. For example: (a) are patients engaging in safe use, storage and disposal, (b) are patient adhering to PPA requirements.
- Data regarding medications errors. For example: (a) trends in medication errors and (b) trends in medication error reporting.
- Data regarding abuse and misuse in both patients and non-patients. For example: (a) rates of non-medical use of REMS drugs in patients and non-patients, (b) rates of non-medical use of REMS drugs in specific populations (e.g., school-age children), (b) data regarding shifts in abuse (e.g., shifts to immediate-release opioids, shifts to heroin), (c) shifts in abuse practices (e.g., injection practices), (d) data regarding patients admitted to opioid treatment programs (e.g., quantity) and their motivation (e.g., are they actually there to

obtain pain treatment), (e) data regarding geographic shifts in the abuse problem.

- Data regarding diversion and drug availability. For example: (a) data regarding patients receiving opioids from more than one prescriber, receiving large amounts of opioids, or receiving opioids earlier than appropriate, (b) data regarding prescription-drug-related crimes, (c) data regarding counterfeit product availability, and (d) street access to drugs.
- Data regarding access. For example: (a) data regarding the availability of REMS drugs for legitimate patients, (b) data regarding the availability of REMs drugs for specific populations (e.g., rural, urban, elderly, long-term care residents, cancer patients, hospice, minority populations, children and other specific – and potentially vulnerable – populations), (c) data regarding other potential disparities in access, (d) data regarding patients obtaining REMS drugs from foreign countries.
- Data regarding the financial impact of the REMS. For example: (a) changes in coverage for REMS drugs, (b) changes in the inclusion of REMS drugs on insurance formularies, (c) changes in the number and attributes of purchasing pools, (d) changes in drug prices and the government regulation thereof, (e) data regarding patient difficulties in paying for prescriptions, (f) changes in reimbursement for education, (g) the administrative costs and burdens of the REMS program, (h) the REMS' impact on industry's product pipeline.
- Data regarding public awareness and attitudes regarding REMS drugs and pain management.

- Data regarding patient quality of life overall and in specific patient populations. For example: (a) data regarding stigma, (b) prescriber suspicion of patients, (c) difficulties in obtaining REMS drugs at pharmacies, (d) health outcomes, (e) withdrawal from discontinued medication, (f) emergency room visits due to pain-related problems.
- Data regarding the quality of life in patients denied access to REMS drugs due to REMS requirements. For example: (a) suicide rates of pain patients unable to access REMS drugs, (b) rates of disability claims of pain patients, (c) data regarding whether patients are receiving adequate pain relief.

E. Data Sources

i. Recommended Data Sources

345. For the following categories of data, industry recommended the following sources: (a) Data regarding patient education: patient surveys and the National Health and Nutrition Examination Survey (NHANES). (b) Data regarding prescribers and prescribing practices: prescriber surveys and the American Hospital Association and other industry organizations. (c) Data regarding dispensers and dispensing practices: dispenser surveys. (d) Adverse event data: Drug Abuse Warning Network – Emergency Department (DAWN-ED), the National Survey on Drug Use and Health (NSDUH), the Medical Expenditure Panel Survey (MEPS), the National Hospital Discharge Survey (NHDS), the National Poison Data System (NPDS), the National Vital Statistics Report (specifically the National Death Index), Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS), National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO), pharmaceutical proprietary data, and SDI Vector One National Audit (VONA); (e) Data

regarding access: patient surveys, the Community Tracking Study (CTS), MEPS, National Ambulatory Medical Care Survey (NAMCS), National Healthcare Disparities Report, claims data, insurance billing data, prescription drug market share, and the RADARS Opioid Treatment Programs (OTP) survey. (f) Data regarding the impact of the REMS: IMS, McKesson, VONA, MEPS, legislative resources, NAMCS, and DEA registration statistics. (g) Data regarding quality of life: patient, prescriber and dispenser surveys. (h) Data regarding the cost of the REMS: analyses by health economists.

346. A vendor agreed with industry regarding the appropriate data sources for patient education and the cost of the REMS, but suggested some different data sources for other categories. The following are its recommendations: (a) Data regarding prescribers and prescribing practices: prescriber surveys, third-party claims databases, and professional societies. (b) Adverse event data: DAWN, MedWatch, NSDUH, MEPS, NHDS, NPDS, the National Vital Statistics Report, RADARS, NAVIPPRO, pharmaceutical proprietary data, federally sponsored studies, and third-party claims databases. (d) Data regarding access: patient surveys, MEPS, NAMCS, IMS, the RADARS OTP survey, federally sponsored studies, third-party claims databases, and focused studies in specific areas. (e) Data regarding the impact of the REMS: IMS, MEPS, legislative resources, NAMCS, and third-party claims databases. (f) Data regarding quality of life: patient and prescriber surveys using standardized scales for quality of life and in-depth qualitative patient interviews. This comment highlighted the importance of qualitative in addition to quantitative analysis, including formal qualitative studies and evaluation of spontaneous comments generated on the Internet and news media.

347. A surveillance organization split its categories into intended and unintended outcomes and recommended the following data sources: (a) For prescriber training and registration intended outcomes: prescriber surveys, patient research, electronic medical record/administrative medical care data, prescription drug monitoring system (PMP) utilization data, data from multiple RADARS sources and surveys, law enforcement reports, data from multiple DAWN sources, NPDS, vital statistics, claims data and NAVIPRRO. (b) For prescriber training and registration unintended consequences: RADARS poison control data, emergency department data, mortality data, commercial sales data, prescriber and pharmacist attitude surveys, and patient research. (c) For patient registration and prescriber-patient agreement (PPA) intended outcomes: PMP data, claims data, and patient surveys and research. (d) For patient registration and PPA unintended consequences: a database of relevant state and regional policy initiatives, patient surveys, data from multiple RADARS sources and surveys, Monitoring The Future (MTF), NSDUH, qualitative studies, Treatment Episode Data Set (TEDS), NAVIPRRO, and telephone-based polling of the public. (e) For expanded and/or redeveloped Medication Guide intended outcomes: patient surveys and research, MedWatch/Adverse Event Reporting System (AERS), emergency department claims data, and RADARS poison control data. (f) For pharmacist registration intended and unintended outcomes: pre- and post-implementation surveys.

348. Similarly, a pain organization highlighted the following as possible data sources: TEDS, AERS, the American Association for Poison Control Centers' New Core system database, RADARS and NAVIPPRO. This comment suggested that the last two of these resources are the strongest, highlighting that the former was developed explicitly for the purpose of

post-market surveillance and uses both Poison Control Center data and key informant data and the latter has the following benefits: (a) it is not reliant on voluntary reports from the field; (b) it is easily administered; (c) data can be collected automatically; (d) data are transmitted to a central database; (e) it has capacity for real-time reporting; and (f) it has good geographic and demographic distribution. Furthermore, this comment suggested examining data from IMS, the census, GEO mapping, and the Automation of Reports and Consolidated Orders System (ARCOS) to evaluate the REMS' impact on access. Finally, this comment recommended considering the ratio of certified prescribers to the total number of DEA registered prescribers to determine if there is REMS avoidance.

349. In addition to the above comments, which recommended multiple data sources, a number of comments focused on a single data source. For example: (a) A pain organization suggested using data from health care technology companies (e.g., Verispan, IMS) to assess prescribing – considering not only positive but also negative unintended consequences. (b) A hospital pharmacist agreed with the vendor comments discussed above in advocating using MedWatch reports for opioid-related adverse events and death rates related to prescribed opioids. (c) Another comment recommended using a data collection form at each opioid-related death to get more information about the problem. (d) As described in greater detail above,[45] a vendor recommended using its audit and feedback system to implement the REMS and highlighted its usefulness as a data source. This comment suggested that the system could easily determine REMS effectiveness (e.g., by querying whether prescription practices have changed over time both of individual prescribers and in the aggregate, considering outcome data to determine if the REMS is positively affecting emergency room visits and hospitalizations) and assess the unintended consequences of the REMS (e.g., if

[45] *See* Prescriber Education and Certification, Section V, Subpart F (iv).

the REMS reduces access, the problem can be easily identified and remedied). (e) Another comment from a vendor suggested that among other data sources, its system would employ claims data related to overdose and addiction as well as cohort-based data analysis related to the use of opioids. This comment noted that all analyses could be fully conducted on de-identified longitudinal patient data. (f) Another vendor suggested capturing data from addiction treatment centers and, in particular, suggested using its system. (g) A hospice provider stated that REMS success should be measured by the statistics of people presenting to addiction treatment centers and emergency departments for drug misuse and abuse problems. (h) A pain organization suggested auditing PMP data and the education program for evaluation. Similarly, a pharmacist association suggested using state PMPs in the evaluation plan.

350. Similar to the comments described above, several comments recommended using stakeholder surveys as data sources, either independently or in conjunction with other resources. For example: (a) A couple of comments from a health care system and a prescriber recommended conducting web-based surveys of prescribers both to collect data and receive feedback on the REMS. (b) A state pain initiative recommended conducting surveys of both prescribers and patients. (c) A distributor recommended conducting Knowledge, Attitude and Behavior Surveys to assess (i) the influence of the program's educational materials on prescribers' and patients' knowledge, and (ii) the extent to which the materials were effective in influencing behavior. This comment noted that modifications could be made based on survey results. (d) Many health care professionals suggested using web-based surveys of prescribers (e.g., hospice physicians, oncologists) so problems can be tracked and analyzed. On the other hand, a manufacturer of non-opioid

products, while recommending the use of stakeholder surveys, suggested that FDA take action to reduce unnecessary reporting of common adverse events.

351. A vendor suggested working in partnership with payors – both government and private – to implement the REMS noting that they are a rich source of data and that they have a vested interest in ensuring that they are only reimbursing for appropriately-prescribed medications.

ii. Concerns Regarding Current Data Sources and Proposed Solutions

352. Several comments noted challenges with current data sources and with current surveillance systems, in particular. For example: (a) A manufacturer noted that a challenge to REMS evaluation is that most monitoring systems are not sophisticated enough to distinguish between dosage form, strength or manufacturer. (b) A scientific organization suggested that there is a need to develop better data sources and noted in particular that drug use and abuse surveillance needs to be sufficiently sensitive, selective, and broad to detect both intended and unintended trends. (c) A clinical research organization highlighted that typical post-market surveillance systems have several limitations including representativeness, timeliness, sampling bias, and selectivity. This comment instead recommended using traditional cohort or case control epidemiologic designs to detect abuse outcomes. In particular, it suggested that large, publicly funded epidemiologic studies may be appropriate. (d) Another comment stated that traditional surveillance surveys do not provide sufficiently timely, accurate, and sensitive data and suggested that a rapid and informative iterative process will be required. (e) Finally, a surveillance organization suggested the following attributes are necessary for effective surveillance: (i) geographic specificity; (ii) product and formulation specificity (e.g., immediate- vs. extended-release, tamper deterrence.); (iii) timely reporting of data to allow improvement of REMS as early

as possible in the process; (iv) multiple perspectives from different points over the course of the natural history of drug use/dependence; (v) a measure of drug availability in the community; (vi) quality control to assure that data are collected and managed appropriately without sacrificing time; and (vi) representative national coverage.

353. Offering another perspective on surveillance, an advocate for opioid drug reform recommended implementing a mandatory adverse event reporting system with significant disciplinary measures for failures to report.

354. A comment from a surveillance organization noted that both post-market surveillance data and data from existing and novel federally-sponsored post-market studies are needed for REMS evaluation to compensate for the limitations inherent in both data sources because: (i) surveillance will capture information from individuals who will not participate in studies; (ii) surveillance is not limited as prospective studies are (e.g., surveillance is more likely to identify rare events because of its larger scope); and (iii) randomized studies, unlike surveillance, allow for the pre-testing of elements

355. A pain organization noted that while NSDUH, MTF, and DAWN could provide indications of changes in the occurrence of prescription opioid abuse, the reasons for such changes will be largely uninterpretable. Therefore, this comment concluded that these surveys will be of limited utility.

356. A comment from academia stated that the issues related to REMS drugs need to be tracked similar to other health epidemics which will require improved data sources. For example, this comment noted that while there are data regarding the number of deaths attributable to swine flu and where the deaths occurred, there are not accurate data regarding how many deaths are attributable to buprenorphine. In particular, this comment noted the following

challenges with current data sources: (a) National Center for Health Statistics (NCHS) data regarding deaths need to be product specific (e.g., attribute deaths to a specific drug as opposed to "other synthetic narcotic") and available more quickly. (b) There needs to be uniformity in medical examiner reports. (c) Poison control data, while more specific than other data sources (e.g., formulations, reason for use), are not comprehensive; they only represent a small number of opioid-related incidents. (d) The DAWN-ED system is excellent, but underfunded. While it has real-time online capabilities, it has lost coverage of several metro areas. This comment recommended re-establishing coverage in the lost areas, expanding the national sample, and shortening the turn-around time for national estimates. (e) Treatment data could be informative, but there is a significant lag between first use of an opioid and entrance to treatment. In addition, while proprietary systems can identify specific brands or formulations used, TEDS does not employ a lexicon that would identify all the different drugs of interest. (f) With regard to diversion, this comment noted that DEA's ARCOS and the National Forensic Laboratory Information System (NFLIS) could be valuable for monitoring the supply of drugs as well as the demand for them. To this end, the comment suggested that these programs need to be adequately supported so data are real-time and available online to researchers and industry. (g) A number of datasets that could be valuable are proprietary and can only be accessed at a substantial cost. This comment suggested that industry should make basic data available to the public for free as opposed to being reported to the government in documents that are not publicly available. (h) Finally, this comment stated that the REMS should be transparent with all data available to researchers who can monitor supply and demand. Researchers, local public health officials, and law enforcement need to be able to access sufficient data to

determine particular areas of concern with regard to REMS drugs. Moreover, data regarding manufacturers' efforts to mitigate adverse events should be available to the public.

357. A vendor noted similar limitations with certain data sources, for example: (a) NPDS is (i) based on self-reporting, (ii) only provides data after one year, (iii) has discrepancies regarding drug coding, and (iv) does not contain call notes to provide context to the data. (b) DAWN- ED and DAWN-ME monitor drug-related visits to emergency rooms and drug-related deaths investigated by coroners and medical examiners, respectively. However, the DAWN datasets are limited because (i) DAWN-ED monitors episodes, not individuals, so it cannot provide a measure of prevalence, (ii) as noted in the comment above, DAWN has lost some coverage areas, (iii) it does not distinguish between drugs consumed in accordance with a prescription and abuse, and (iv) it is not real-time (e.g., DAWN-ME data is not available for four years). (c) NAMCS, conducted by CDC, obtains information from physicians on the provision and use of ambulatory care services. However, the dataset is limited because (i) providers can list up to eight drugs on the survey, (ii) the survey is limited to information in the medical record, (iii) incidence, prevalence, and state-level estimates cannot be determined, (iv) recently, there has been a decrease in participation, and (v) data are not released for four years. (d) NDTI, a commercial product offered by IMS, monitors thirty-five thousand private practice physicians. On a quarterly basis, the physicians report all patient contacts during a two-day period which could provide data regarding the patient populations receiving REMS drugs and prescribing trends. However, linking diagnoses for chronic conditions to medications may be inhibited by the time-limited sampling. (e) CDC's NHANES assesses health and nutritional status of children and adults in the United States. The survey asks limited questions regarding pain and

medications, and can also provide information regarding behavioral changes in the long term. (f) NAMCS collects data annually from non-institutional general and short-stay hospital outpatient and emergency departments during a four-week period. The data collected includes information regarding the provider, patient demographics, visit characteristics, medication information, and data regarding the opioids prescribed by pain severity. Although the data collected are informative regarding prescribing practices, certain entities are excluded (e.g., Department of Veterans Affairs (VA) hospitals) and incomplete responses and biases due to non-response may affect results. (g) CDC's NHDS is an annual chart abstraction of inpatient discharge records from a national sample of five hundred non-federal, non-institutional, short-stay hospitals. Limitations include (i) its use of International Classification of Disease-9- Clinical Modification (ICD-9-CM) codes, and (ii) the five year delay in data. (h) SAMSHA's NSDUH is a household-based survey on illicit drug use and the non-medical use of prescription drugs. The national- and state-level data on the prevalence, patterns, and consequences of prescription drug use would provide information regarding changes in the non-medical use of prescription pain relievers after the REMS is implemented. However, NSDUH is limited because it (i) only obtains information on the "lifetime" non-medical use of specific prescription brands, and (ii) the survey does not differentiate between abuse by a person for whom the medication was prescribed and abuse by a person for whom the medication was not prescribed. (i) CDC's National Vital Statistics Data can be used to identify the number of overdose deaths in the United States due to prescription opioids. However, (i) there is a four-year delay in data, (ii) the data uses ICD-10 codes which are limited in specificity (however, methadone and heroin do have their own codes), (iii) there is a lack of uniformity in mortality data. (j)

Inflexxion, Inc.'s NAVIPPRO surveillance system collects data from enrollees in substance abuse treatment facilities located in a number of states. The real-time data collected could supplement other sources regarding changes in drug preferences and routes of administration – particularly in the non-patient population. However, the data may be difficult to interpret. (k) The Agency for Healthcare Research and Quality MEPS-HC could be used to determine trends in the use of REMS drugs, the number of prescriptions purchased, and total financial costs as well as trends in disparities in access. However, the data will only reflect the outpatient population and are delayed one year. (l) RADARS collects brand- and geographic-specific data on misuse, abuse, and diversion using six signal detection systems. Historical data go back to 2002, providing baseline information for assessment. Data are reported quarterly, with a one quarter reporting time lag, and are product specific. However, most of the systems rely on self-reporting, a handful of poison control centers do not participate, and there is limited use of standardized scales for assessing drug abuse and dependence. (m) Data from commercial vendors which are product-specific and have a lag time of only a few months can be used to identify prescribing patterns and shifts. However, the data are limited because the number of prescriptions is based on a probability sample giving rise to less precise estimates in rural areas. (n) Third-party payor databases collect prescription information, insurance billing data, and information regarding purchasing pools. However, they vary considerably on their data quality.

358. With regard to how to mitigate the delays in data, a vendor suggested that FDA work with the agencies overseeing federal data sources to see if data could be made available more

quickly for REMS evaluation. This comment also noted that increased staff would likely be necessary if these data sources are to be used for ongoing REMS evaluation.

359. A health care professional organization noted that current data sources make it easier to track opioid-related deaths than NSAID-related deaths. In light of the need to examine not only use and adverse events associated with REMS drugs, but also other pain relievers to assess shifts in prescribing and the resulting adverse events (e.g., kidney damage in NSAID patients, particularly in the elderly population), this comment recommended developing a better method of tracking morbidity and mortality associated with NSAID use prior to REMS implementation.

360. A couple of comments from a surveillance organization and a vendor suggested creating a new policy databank of all actions at the federal, state, and local level that could influence REMS stakeholders to assist in identifying confounders (e.g., is a decrease in prescribing in a particular state due to the REMS or a new prescription policy in that state).

361. Multiple comments emphasized the importance of standardizing how opioid deaths are reported and tracked. For example: (a) One comment suggested that federal funding and coordination is needed to standardize how opioid deaths are tracked nationwide. (b) Similarly, multiple comments noted the importance of training medical examiners and standardizing their reporting. (c) Another comment agreed with this concern noting that currently the number of opioid-related deaths is unknown because medical examiners and state health departments are fractured. (d) In a similar vein, a pharmacist noted that to ensure data integrity there needs to be education of coroners to more carefully establish the cause of death in REMS drug-related cases. This comment noted that many cases of early

362. With regard to using post-market studies as a data source, a prescriber stated that such studies are unnecessary if the drug has been approved for a long time.

363. One comment from a scientific organization stated that data on drug abuse and diversion are not reliable.

F. Interpretation of Evaluation Results

i. Linking Data to REMS Elements and Success

364. Once metrics are defined and data are collected, the next step in evaluation will be interpreting the results. Comments differed about how readily data trends could be attributed to the REMS elements. For example: A pharmacy standards organization noted that the following data and elements could be linked: (a) lower rates of addiction and abuse in patients could be linked to training prescribers on better patient selection and ongoing risk assessment, (ii) lower rates of adverse events due to patient misuse (e.g., overdose) could be linked to key safety messages being conveyed to patients, (iii) lower rates of accidental pediatric ingestion and medicine cabinet theft could be linked to educating patients on secure storage and proper disposal of their medications, and (iv) lower rates of doctor shopping and insurance fraud could be linked to a reduction in abusers being able to obtain opioids via prescription and then sell them on the street.

365. Similarly, multiple comments provided extensive charts linking data to corresponding REMS elements. For example: (a) A surveillance organization appended a chart delineating evaluation strategies for intended and unintended outcomes of various proposed REMS elements, including linking the outcomes to the affected populations of interest,

relevant data sources, and examples of measurements. For example, this comment noted that a potential unintended consequence of patient registration or PPAs could be the denial of REMS drugs to appropriate patients. This comment noted that this outcome could be particularly of issue in minority (e.g., racial, insurance status) populations, rural versus urban populations, and cancer versus non-cancer populations. This comment proposed evaluation through patient research – in particular, a prospective cohort of pain patients – examining the medications received. (b) Similarly, industry and a vendor attached a chart linking metrics with data sources. For example, to evaluate metrics associated with patients' quality of life – including potential stigma, suspicion on the part of the prescriber, difficulties in obtaining their prescription at the pharmacy and their health outcomes – both of these comments recommended using patient, prescriber and dispenser survey data.

ii. Challenges to Evaluation

366. On the other hand, several comments noted the difficulties faced in interpreting results and linking results to REMS elements due to confounders. For example: (a) A vendor noted that the number of deaths in non-tolerant patients is already relatively small and it is possible that heightened ascertainment could inaccurately make it appear that such deaths have increased post-implementation of the REMS. (b) A pain patient noted that interpreting changes in the number of prescriptions is complicated because it could be influenced by factors other than the REMS (e.g., such as an increase in pain patients as baby boomers age). (c) Similarly, a health care professional organization stated that it might be difficult to link specific educational tools to specific outcomes. (d) A surveillance organization stated that the REMS must be cautious in making causal inferences because there are so many factors involved. (e) As a means of possibly reducing confounders, industry

recommended phasing-in elements to allow for greater understanding of their individual impact on the metrics.

367. Additionally, comments noted that determining the success of REMS elements will be complicated by the need to weigh multiple trends in data and data from multiple sources. For example: (a) An advocate for opioid drug reform noted that Utah considered its initiatives a success because of a decrease in the unintentional death rate, but it did not consider heroin deaths (e.g., deaths of abusers who shifted from prescription drugs to heroin). (b) A health care professional organization noted that decreased prescribing does not mean improved prescribing if patients with intractable pain are going untreated due to the burdens imposed by the REMS. To that end, this comment suggested evaluation of the prescribing habits of medical specialty subgroups might yield more valuable information. For example, this comment suggested that if prescribing of REMS drugs by oncologists remains steady or increases after the REMS is implemented, while prescribing by physicians in specialties that do not involve significant pain decreases, that could be more valuable information than general prescribing trends. (c) Another comment noted that determining that lower rates of abuse and misuse of REMS drugs is due to education and not reduced access will prove challenging. (d) A couple of comments noted that a reduction in prescribing does not necessarily equate with REMS success in decreasing abuse or misuse. (e) A pharmacy association suggested that the best metric may be statistics of drug abuse in the general population, however this comment acknowledged that there could be other factors affecting those statistics and they would not help gauge whether pain management is being adversely impacted. (f) A vendor noted since the evaluation of the opioid REMS will require simultaneous input from multiple data sources and population-

and clinic-based studies, reconciling findings across studies will pose a distinct challenge and will require due consideration of methodologies and the potential biases of researchers.

368. Moreover, another challenge to data interpretation cited by several comments is the need for baseline data. For example: (a) A pain organization stated that to properly assess whether the REMS had decreased access to opioids, there needs to be a baseline data for current access and suggested that such data may come from DEA licensure. (b) A health care professional organization recommended establishing six months of baseline data both prior to and after implementation of the REMS. (c) A vendor suggested that data from the first year of REMS implementation could serve as the "baseline" for future years. (d) A pain patient noted that outcome monitoring cannot be established for the REMS if there is no baseline. (e) A health care professional organization noted that there is a need for baseline data from surveys about the number of legitimate patients who are giving drugs to friends or family and recommended conducting follow-up surveys to determine if numbers change.

369. Finally, comments suggested that defining overall REMS success may prove challenging. For example: (a) A vendor stated that the most important and obvious success indicator is a demonstrable reduction in adverse events associated with improper dosing, misuse, and abuse of opioid drugs. (b) On the other hand, other comments focused on maintenance of access as the most important success indicator. A hospice, for example, noted that for the REMS to be successful, there cannot be a decrease in the number of prescriptions for sustained-release opioids written for terminally ill patients. (b) A surveillance organization recommended assessing both positive and negative outcomes from the REMS and considering its overall societal risk-benefit. (c) Finally, industry acknowledged all of the

viewpoints noting that it is currently unclear what will be considered success by all stakeholders. For example, it noted that if there is a reduction in one metric but a rise in another, will that be considered success? This comment recommended defining overall success prior to REMS implementation.

XII. A SINGLE SYSTEM FOR GENERIC AND BRANDED PRODUCTS

In its April 20, 2009 notice, FDA noted that FDAAA requires, with limited exceptions, that innovator and generic application holders use a single shared system to provide a REMS with elements to assure safe use. The Agency requested comment regarding any obstacles that will need to be addressed before such a system is developed. As compared to other topics discussed in the notice, relatively few comments were submitted in response to this request. Those that were submitted, however, fell into two categories: (A) recommendations for implementing a successful single system and (B) obstacles and issues for clarification regarding a single system.

A. Recommendations for Implementing a Successful Single System

370. Several comments supported a single system for brand and generic opioid products and offered recommendations or considerations for the implementation of such a system. For example: (a) A health care professional organization, in expressing strong support for a single system, stated that as the process evolves, FDA should ensure that any REMS program includes specific and accurate information on the equivalency of brand and generic products and whether there are any restrictions on substituting one product for the other (e.g., it is appropriate to switch products after a patient has started the brand or generic version of the medication). (b) A pharmaceutical manufacturer of non-opioid products stated that while a single system may not be appropriate in all circumstances, a single

system has merit for an opioid REMS. However, for it to be successful, this comment stated the system will require the unfettered and consistent resource support of all concerned parties.

371. The pharmaceutical manufacturer of non-opioid products also stated that whether there is a single, shared system or separate systems for innovators and generics, FDA should ensure that such systems are consistent with upholding various exclusivity and patent protections. This comment noted it holds patents directed to the REMS programs covering its drugs and has licensed those patents to other companies.

372. A vendor suggested that a concern of generic manufacturers is having the capability to identify the specific product dispensed to a patient. This comment highlighted that its system can identify the specific product and manufacturer.

373. A pharmacy organization suggested that the development and implementation of a single shared system should include the input of pharmacies and prescribers.

B. Obstacles and Issues for Clarification Regarding a Single System

374. Multiple comments noted that the most significant obstacle to a single shared system will be costs and how they will be borne by generic and innovator manufacturers. For example: (a) A pharmacist focused on pain management noted that the greatest hurdle to a shared system will be the costs. This comment noted that branded product manufacturers should not be saddled with all the costs and generic manufacturers should not have to duplicate existing documents. (b) An organization of educators expressed concern that since generics have more limited resources as compared to innovators, using a single, shared system could drive up drug costs.

375. Similarly, several comments expressed concern that if the cost of the REMS is too great it will disincentivize generic drug manufacturing leading to decreased access. For example: (a) A health care professional organization expressed concern for the decreased incentive to manufacture generic opioids if the cost of developing REMS programs is too great. This comment stated that if the revenue yield from generic opioids is too low, it will eliminate patient access to lower cost alternatives, leaving only costly proprietary medications. (b) Methadone manufacturers echoed this concern noting that generics generate far less revenue per pill than branded products. Therefore, it is possible that if the REMS elements are too expensive to implement, it may reduce the incentive to develop generic versions of REMS drugs and decrease patient access to affordable medications. (c) Similarly, a few comments questioned whether branded pharmaceutical manufacturers actually were seeking increased regulation of opioids to shift patients to non-generic pain relievers. On the other hand, a distributor refuted the notion that generics will be placed at a disadvantage in a single system noting that a shared system for generics and branded products is already in place and by allocating costs on a per transaction basis, any disadvantages to lost-cost generic products are eliminated.

376. In addition to the revenue differences discussed above, methadone manufacturers noted other differences between generic and branded manufacturers. Specifically, this comment emphasized that while both types of manufacturers are similarly committed to the development of an optimal REMS, to use a single shared system the following differences will have to be addressed: (a) Generics are able to offer lower-cost alternatives to branded drugs by limiting their promotional activities (e.g., sales force, free drug samples, CME). However, promotional activities are also product-specific educational activities, so these

activities will need to be considered within the context of a REMS for a broad group of drugs. (b) Generic manufacturers generally have less interaction with FDA with regard to labeling changes (e.g., package inserts, Medication Guides). This comment noted that FDA will need to communicate with both the generic manufacturers and branded manufacturers simultaneously to ensure appropriate communication of safety messages. Another manufacturer also echoed the concern regarding the differences in promotional activities between generics and branded manufacturers. This comment noted that it has created a disparity in the implementation of past REMS and asked FDA to consider and comment on the issue.

377. Multiple comments raised issues for clarification related to a single, shared system. For example: (a) A pharmaceutical manufacturer of non-opioid products noted that for a single, shared system to apply to different products with different indications and pharmacologies, but similar risks, clarification of the purpose for the restrictions, and what flexibility of controls and outcomes are permissible, is necessary. The comment noted that this is especially true where benefits and risks are experienced differently, depending on disease severity, patient perception, and individual response to drugs. (b) This comment also requested clarification regarding the definition of a "single system." Specifically, this comment asked whether a single, shared system meant all elements must be identical. In the alternative, this comment suggested a single system may only necessitate a single user interface for patients, health care providers, and pharmacists, with each manufacturer or its contractor safely and effectively implementing its own program with adequate resources, quality assurance, and operative capacity behind the interface. (c) Finally, a manufacturer

requested more guidance from FDA regarding how generics and branded product manufacturers should work together.

XIII. REMS DEVELOPMENT AND IMPLEMENTATION

FDA did not expressly request comment on REMS development and implementation in its April 20, 2009 notice. However, a number of comments were received from diverse stakeholders regarding the following topics: (A) the REMS development process, (B) how quickly FDA should initiate the REMS, (C) considerations for REMS implementation, (D) how long it will take to roll out the REMS, (E) suggestions for phased-in implementation, and (F) suggestions for pilot programs.

A. REMS Development Process

378. Several comments had suggestions for the REMS development process going forward. A recurring theme of these comments was the importance of continued stakeholder involvement. Generally, comments were pleased with FDA's involvement of stakeholders thus far, and they emphasized that the collaboration needs to continue. To that end, a wide variety of stakeholders offered their assistance in developing a REMS and some comments also suggested additional stakeholders that should be included in the process (e.g., representatives of insurance companies). For example: (a) A health care professional organization recommended having meetings including stakeholders, other government agencies, professional societies, and third-party payors to determine the viability of REMS elements. (b) Another health care professional organization stated that while FDA only regulates manufacturers, stakeholders who actually have to implement the REMS in their workflow need participate in the conversations about REMS development. (c) A health care professional organization stated that FDA is neither equipped to deal with all of the

issues related to REMS drugs, nor should it begin to deal with them without the full collaboration of DEA, professional medical societies, agencies involved in the education of the public, and state health care professional boards. (d) A vendor commended FDA's engagement of stakeholders so far in the process and suggested that it should continue to ensure that stakeholders including industry, health care professional organizations, insurance providers, patients and caregivers, researchers, government agencies, and data sources continue to act in concert. (e) A liability carriers advisory committee stated that they want to expand the dialogue between liability carriers and FDA because they both want to decrease prescriber risks from opioids. Moreover, this comment suggested a poorly designed REMS could actually increase prescriber risk. (f) One comment that was not pleased with FDA's involvement of stakeholders thus far was submitted by a pain patient advocacy organization. This organization expressed strong opposition to the REMS and differentiated its viewpoints from those of other pain patient advocacy groups that had spoken at the public meeting (e.g., this organization stated that there is no evidence that an epidemic of prescription drug abuse exists and stated that pain organizations that are willing to cooperate in addressing it are "legitimizing [a] mammoth deception"). Noting that they had not been asked to speak at the public meeting, this organization requested an opportunity to be heard.

379. Several entities also requested the opportunity to review and comment on the proposed REMS once it is developed. For example: (a) A health care professional encouraged FDA to allow physicians to review any REMS proposal to avoid unintended consequences. (b) Similarly, a comment from sixteen health care professional organizations recommended that once a proposed REMS has been developed, FDA should solicit public comment on the

380. As touched on in a number of sections of this document, multiple comments recommended that FDA examine state initiatives as part of the REMS development process to determine how much additional regulation is needed and assess which interventions have been most successful. For example: (a) A couple of comments recommended examining states with pain commissions comprised of stakeholders as a model for federal implementation. (b) A pain patient suggested FDA examine state systems and select the best elements for nationwide implementation.

381. Several comments from a variety of stakeholders suggested FDA gather additional information before finalizing a REMS plan. For example: (a) As discussed above, several pain patients suggested FDA needs to visit pain clinics and speak to pain patients before implementing a REMS. (b) A hospice professional suggested FDA survey members of the American Society of Clinical Oncology and hospice and palliative care professionals prior to implementing a REMS. Similarly, a hospice and palliative care health professional stated that FDA should be interviewing physicians to understand why access to these medications is important.

382. As discussed above,[46] several comments suggested that more research is necessary prior to REMS implementation. For example, a health care professional organization stated that FDA should study opioid abuse/misuse further prior to launching a REMS nationwide.

[46] *See* Rationale Behind the REMS, Section II, Subpart A (ii).

This comment expressed concern that at the public meeting, FDA did not indicate it was going to conduct further study as to the sources of opioid diversion. This comment stated that this type of research is necessary prior to REMS implementation to determine which interventions will be most effective.

383. When a REMS plan is developed, a vendor recommended that a standard request for proposal (RFP) or request for quotation (RFQ) process be used to solicit education programs.

B. How Quickly Should FDA Initiate the REMS?

384. Comments were divided with regard to how quickly action should be taken on the REMS. Some comments urged FDA to take swift action. For example: (a) A health care professional noted that in her twenty-year career, she has seen deaths and family destruction due to prescription drug abuse and said that the REMS cannot be implemented soon enough. (b) Similarly, advocates for opioid drug reform emphasized the seriousness of the public health problem regarding REMS drugs and urged FDA to act quickly by issuing a temporary moratorium on REMS drug prescribing to allow for development of a complete REMS. For a more detailed discussion of this proposal, please see Access to Pain Medication, Section IV, Subpart B.

385. Other comments, while not supporting a ban, offered other immediate actions that could be taken to quickly mitigate risks from REMS drugs. For example: (a) Several comments recommended labeling changes and government communications that could be initiated quickly.[47] (b) A lawyer suggested that the development and use of a more standardized

[47] *See* Prescriber Education and Certification, Section V, Subpart D (iii).

process for informed consent and treatment agreements could be undertaken quickly. The comment termed this action an "informed consent blitz."

386. Generally, however, comments discussing how quickly a REMS should be implemented emphasized caution and deliberation over speed. In particular, these comments noted that taking time to develop the REMS will allow for stakeholder input and prevent negative consequences. For example: (a) A pain organization's comment – which was endorsed by several other comments – expressed their concern for unintended negative consequences from the REMS and cautioned FDA to go slowly and be thoughtful**.** (b) A health care professional organization stated while it recognizes FDA is under pressure to move quickly to curb abuse, it recommends deliberation to ensure legitimate patients maintain access. (c) A health care professional advised caution in implementing the REMS stating that the benefits are unclear and there will be significant costs. (d) A health care professional organization cautioned the Agency to take time with REMS development because it does not make sense to implement a program that does not achieve its desired outcomes and the REMS elements that have been tried and proven in the past were not geared toward misuse/abuse. (e) A hospice nurse urged FDA to slow down because prior agency actions have decreased medication access for hospices. (f) A pain organization cautioned that time should be taken in implementing the REMS and that it should be based on data, not anecdotal evidence with a concern for unintended consequences. (g) A pharmacy, while acknowledging the pressure on FDA to act, recommended that it take time to develop a system.

387. Other comments, while also advocating for a slower REMS development process, cited different reasoning for taking additional time. For example: (a) A couple of comments

recommended that FDA possibly wait to implement the REMS until better metrics for determining success are developed.[48] (b) A pain patient suggested FDA wait to implement a REMS until action is taken on the National Pain Policy Act of 2009. This comment interpreted the bill as encouraging fewer restrictions on opioids, not more.

C. Considerations for REMS Implementation

388. Several comments highlighted that implementation of the REMS must be sensitive to unique situations and circumstances to prevent unintended consequences. For example: (a) A pharmacist focused on pain management noted that in implementing a REMS, FDA must consider that literature supports off-label use of certain REMS drugs. For example, this comment noted that many opioids only have an approved indication for cancer pain, but they work just as well for chronic non-cancer pain. Without such a focus on off-label uses, this comment expressed concern that there will be persecution of practitioners and failure of third-party payors to reimburse for treatment, at the expense of the patients. (b) A vendor stated that REMS implementation must be particularly sensitive to the impact on smaller pharmacies, smaller sponsors, and smaller organizations. (c) Several comments emphasized the need for the REMS to be inclusive of all relevant stakeholders. To that end, a health care professional organization stated that the REMS needs to include all prescribers and dispensers (e.g., dentists, podiatrists, physicians, pharmacists, physician assistants, nurse practitioners, advanced nurse practitioners), and another health care professional organization stated that any willing pharmacist, physician or other prescriber should have the opportunity to participate in the REMS. (d) A regional pain advocacy organization suggested that the REMS must be flexible with regard to state-by-state differences and

[48] *See* REMS Evaluation and Metrics, Section XI, Subpart D (i).

cultural diversity while still promoting standardized national policy and consistent standards and guidelines.

389. Several comments emphasized the importance of communication in the REMS implementation. For example: (a) A comment from a pain organization that received support from several other comments highlighted the importance of a communication plan from the party responsible for the REMS to end-users regarding the program, its purpose, and its requirements. This comment noted that the communication plan could be standardized across all manufacturers. (b) A health care professional organization, in multiple comments, recommended that the REMS explicitly detail its processes and the roles and responsibilities of each stakeholder. Specifically, the organization stated that manufacturers should provide information on REMS logistics prior to implementation so that practitioners are aware of all REMS requirements prior to writing or dispensing a medication as part of the REMS program. Furthermore, this organization stated that the roles of each stakeholder should be clearly defined for accountability.

390. Many comments – from stakeholders supporting a ban of certain REMS drugs to those opposing any additional regulations – suggested that improving addiction treatment and widening its availability would complement the REMS. For example: (a) An advocate for opioid drug reform stated that there should be an expansion and improvement in opioid drug abuse and addiction treatment capabilities and suggested that the improvements should be a joint effort of private and government health insurers, philanthropic and community groups, and industry. (b) Several comments from a variety of stakeholders suggested that since the risk of addiction cannot be eliminated, efforts and resources should focus on treatment. (c) Similarly, several comments noted that in addition to preserving access to

pain medications, there is also a need for enhanced access to addiction treatment. (d) A comment from academia noted that if the REMS is successful in shutting off the supply of diverted drugs, addicts will still exist. This comment questioned whether there will be adequate addiction treatment available and suggested that there may be a responsibility for the REMS to provide such treatment. (e) A comment from a prescriber noted that not only should patients have increased access to addiction treatment, but also to mental health professionals. In particular, this comment suggested that pain patients with mental health conditions (e.g., bipolar disorder, depression) should be co-treated by mental health professionals to monitor for red flags that could lead to inappropriate use of opioids.

391. In its comment, the industry working group noted that it is unable to do certain things including (a) act as an enforcement arm of the government, (b) mandate education for all health care professionals or patients, or (c) control people outside of the physician/patient relationship. Moreover, industry stated that it will need to work with FDA and other stakeholders to implement an effective REMS. Stakeholders agreed and suggested that industry cannot and should not implement the REMS on its own. To that end, many stakeholders offered their own expertise and/or offered suggestions as to who should be involved in REMS implementation. For example: (a) Several vendors noted their qualifications to implement the REMS citing their experience and impartiality. (b) A scientific organization recommended harmonizing drug scheduling efforts under the Controlled Substances Act and REMS efforts under FDAAA and offered its assistance and expertise in this regard. (c) A representative organization of state medical boards stated that implementation of the REMS should be collaborative and FDA should initiate an advisory group, including other representatives of the Executive Branch and federal agencies, and

state health care professional boards as well as other stakeholders, to ensure that the work on opioid issues is collaborative. (d) A comment from academia recommended that REMS methodologies and protocols proposed by the manufacturers should be reviewed by expert panels, similar to the peer review process for journal articles. Moreover, this comment recommended that in addition to oversight by FDA, REMS oversight should also include researchers and advisory panels who have no financial ties to manufacturers. (e) A pharmacy organization stated that pharmacies should be included in REMS planning and when implemented, sufficient time should be allowed to permit the development of corporate policies and training of pharmacy staff. (f) An advocate for opioid drug reform stated that industry cannot self-design, self-regulate or oversee the REMS. Instead this comment recommended using an impartial third-party such as FDA or DEA. This comment suggested that monitoring and oversight should be through multi-agency databases.

392. As discussed throughout this document, concerns for the financial burden imposed by REMS implementation was a common comment from a variety of stakeholders. For example: (a) A health care professional organization questioned who would pay for all the time the REMS would require of health care professionals. (b) An advocate of opioid drug reform stated that opioid manufacturers should financially support any education, monitoring, and regulatory programs that FDA deems necessary. Similarly, a vendor stated that funding for education should be through government grants or grants from pharmaceutical organizations. (c) A state medical board and a federation representing state medical boards expressed concern as to whether there will be sufficient funding for all REMS iniatives, noting that a lack of resources could put an unfunded mandate onto the

D. Timing of REMS Rollout

393. A distributor association recommended that the implementation of the REMS be informed by past experience with REMS rollouts.

394. There was significant variation in the estimates for the time it would take to rollout the REMS. For example: (a) A vendor suggested its program could be implemented on a limited scale within sixteen to twenty weeks. (b) Another vendor, however, stated that a longer program development period would be needed because of unprecedented multi-sponsor involvement. This vendor estimated that it would take a year to develop and implement the REMS. Within the year, this vendor stated that a pilot could be initiated but noted that a longer development time would be necessary for full implementation due to legal and privacy issues and the need for each sponsor to have a multi-disciplinary team including a drug safety program, a regulatory program, a data management program and a customer interaction program. This comment noted that systems within companies could

be helpful in REMS implementation. (c) Another vendor concurred with this projection – stating that the year estimate was accurate.

E. Phased-In Implementation

395. Many comments recommended that the REMS be rolled out in stages. For example, a health care professional organization stated that since the REMS is a huge undertaking, there should be a pilot or the elements should be phased-in. However, comments offered a wide variety of proposals with several comments recommending a phased-in approach to implementation and many others suggesting a pilot program. However, even those recommending a pilot did not agree on the details.

396. Several comments recommended a phased-in approach to the REMS rollout with elements being introduced in stages to permit evaluation of their effectiveness. For example: (a) A comment supported by sixteen health care professional organizations noted that less intrusive elements as specified in FDAAA should be tried prior to more intrusive interventions. (b) A health care professional organization recommended implementing the REMS in a stepwise fashion with elements most likely to curb abuse and diversion implemented first. If the element is not found to be effective, the comment stated it should be discontinued.

397. The industry working group also favored a phased-in implementation noting that time must be taken up-front because it would be inappropriate to implement unproven elements. Industry proposed a three phase approach that would culminate with a vendor-implemented REMS. (a) Immediate Actions: This phase would include (i) developing or improving patient education materials, (ii) creating stakeholder working groups, (iii) exploring credentialing DEA registration, and (iv) developing educational tools for prescribers,

dispensers and patients. (b) Intermediate Actions: This phase would include (i) continuous monitoring to refine metrics and the action plan, (ii) investigating processes for certifying prescribers and dispensers, (iii) considering the expansion of PMPs, (iv) evaluating the impact of the prior-phase's actions on risks, and (v) evaluating vendors for implementation of the REMS. (c) Long-Term Plan: This phase would include (i) implementing the REMS for extended-release opioids and methadone, and (ii) evaluating the effects of the two prior phases' actions on risks. Industry highlighted that the goal would be to assess and, if possible, use systems and elements that are already in existence to maximize effectiveness, flexibility and efficiency.

F. Recommendations for a Pilot Program

398. Many comments from a variety of stakeholders – including a petition submitted by a pain organization with four thousand and seventy-five signatures – recommended piloting the REMS prior to full-scale implementation. In support, these comments noted that difficulties with past REMS rollouts could have been avoided if they had been piloted and suggested a pilot would enable the effectiveness of elements to be determined prior to their full-scale implementation, which would minimize the impact on access. For example: (a) An organization representing state medical boards strongly recommended a pilot to test effectiveness of proposed elements both on curbing abuse and maintaining access. (b) A health care professional organization noted that in a survey of two-hundred and seventy-five pharmacists, nearly all respondents supported a pilot. (e) Another health care professional organization stated that a pilot is necessary to gather prospective data on strategies that best mitigate risk with the most minimal impact on access. (f) A regional pain advocacy organization stated that the REMS should be piloted with predefined metrics

adequate to determine their effectiveness. This comment suggested that after evaluating pilot outcomes and considering stakeholder observations, appropriate adjustments could be implemented and the REMS program could be expanded to the nation. (g) A health care professional organization noted that in addition to a pilot, there needs to be a contingency plan if system failures create a problem with legitimate access to medications.

399. Despite agreement about the desirability of a pilot, comments varied in the type of pilot they envisioned. The majority of comments received on this topic recommended a geographic pilot. For example: (a) A pain organization suggested that due to the unprecedented scale of the opioid REMS, initial interventions should be limited to select geographic locations (e.g., regions of the country identified at higher risk for opioid abuse, misuse, and overdose). Then, interventions found to yield positive results could be selected for more widespread implementation, unless there was evidence of unintended consequences (e.g., practitioners opting-out of the program, exacerbation of health care disparities). (b) A vendor also envisioned a geographic pilot and noted that it had identified a state that would serve as a good location due to a higher than average level of challenges (e.g., above average issues with misuse and abuse of opioids, lower than average health literacy, and a lack of common technologies statewide). (c) A patient advocate suggested "beta" testing the REMS in certain geographic areas prior to a nationwide rollout. (d) Another vendor suggested doing more than one pilot prior to nationwide implementation. This comment recommended using different methods in different parts of the country and then evaluating them for effectiveness. (e) A pharmaceutical manufacturer of non-opioid products suggested a pilot that: (i) uses claims databases to capture information on opioid adverse events, hospitalization and death; (ii) surveys pain patients regarding perceptions of

pain control and their treatment; and (iii) surveys health care professionals regarding the REMS implementation. This comment noted that patients could serve as their own control pre-and post-implementation, although it acknowledged that the method could be subject to some confounding. (f) A pain organization suggested that education programs be piloted in a given geographic area or for a specific patient subtype or defined criteria point. (g) A health care professional organization recommended piloting the REMS possibly in a specific geographic location or patient cohort to determine points of diversion and the REMS' effectiveness in mitigating risk before national implementation.

400. Not all comments supporting a pilot, however, recommended a geographic-based design. For example, as discussed in greater detail above[49] methadone manufacturers recommended an active-ingredient-based pilot. Specifically, they recommended using a methadone REMS as the initial phase of implementation to evaluate the program prior to wide scale implementation of an opioid class REMS. A vendor echoed the recommendation for using methadone as a pilot. This comment noted that a geographic pilot would only (a) shift problems to neighboring regions, (b) create confusion in the medical system, and (c) confound pilot results rendering them unhelpful due to regional differences in prescribing, clinical practice, insurance coverage and access disparities.

401. A few comments recommended a study-based design for the pilot program. For example: (a) A vendor suggested conducting pilot studies and analyzing outcomes prior to full-scale implementation. (b) Another comment advocated for piloting the REMS in a double-blind controlled trial in a limited population with the results being peer reviewed, not only for effectiveness in curbing drug abuse but also for impact on legitimate access. (c) A policy

[49] *See* Scope of the REMS, Section III, Subpart C (iii).

group recommended pilot studies to determine how best to enhance existing prescription drug monitoring systems (PMPs) efficiencies and capacities.

402. A few comments highlighted that a pilot would not need to be large to be valuable. For example: (a) A vendor suggested that a small pilot should be used to identify possible issues, but that it does not need to include hundreds of patients. (b) This comment was echoed by a health care professional who recommended piloting the REMS in a small subset of patients to determine its value. (c) A hospice provider suggested that once the certification process for prescribers and dispensers is selected, there should be implementation within a small number of providers and sites to "test drive" the proposal.

403. With regard to evaluating the pilot, a pain organization recommended that there be one system for the collection of data (e.g., SAMSHA, DAWN, RADARS). This comment also suggested including the state Attorneys General to provide oversight of data collection and programming efforts.

404. One comment, however, questioned whether FDA had the statutory authority to implement a pilot program.

Risk Evaluation and Mitigation Strategy for Opioid Analgesics
Final Report of the Scope Working Group

June 2010[1]

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BACKGROUND

In early 2009, FDA sent letters to manufacturers of certain opioid drug products, indicating that these drugs will be required to have a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drugs continue to outweigh the risks. FDA explained that the REMS would include elements to assure safe use to make certain that prescribers, dispensers, and patients are aware of and understand the risks and appropriate use of these products. FDA also stated that, with limited exceptions, the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires generic and innovator products to use a single shared system to implement the elements to assure safe use. The affected opioid drugs include long-acting and extended-release brand name and generic products and are formulated with the active ingredients fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.

FDA is mindful of provisions in FDAAA that require elements to assure safe use to be, among other things, commensurate with the specific serious risk listed in the labeling of the drug, not unduly burdensome on patient access to the drug, and designed to be compatible with established distribution, procurement, and dispensing systems.

To obtain public input on how best to design a REMS for this class of drugs, FDA held a series of meetings with relevant stakeholders (May 4 and 5, 2009; May 27 and 28, 2009; December 4, 2009) and opened a public docket to receive public comments on relevant issues. Meeting minutes of the May 4 and 5 stakeholder meetings, and transcripts of the May 27 and 28, and December 4 meetings are in the docket and on FDA's Web site.[2] FDA plans to provide an additional opportunity for public input before finalizing the elements of the REMS.

[1] The WG formulated its recommendations in January 2010; this report has been finalized in preparation for the July 2010 Advisory Committee meeting.
[2] See http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm.

Following the meetings, FDA formed an Opioid REMS Steering Committee, a multidisciplinary team from throughout the Center for Drug Evaluation and Research. To thoroughly analyze the substantial public and stakeholder input received on the development of the REMS and to conduct additional research, the Steering Committee formed seven[3] work groups to focus on the various aspects of an opioid REMS and the effects of possible components of the REMS on use.

Following their analysis, the work groups were asked to provide recommendations to the Steering Committee for consideration as it develops options for what should be included in the REMS. The seven work groups addressed the following areas:

- Scope of an opioid REMS
- Prescriber education
- Pharmacist education
- Patient education
- Pharmacy systems
- Effect of possible restrictions on patient access to pain medication
- Metrics

This is the report and recommendations from the Scope Working Group (WG).

GOAL OF THE SCOPE WORKING GROUP

We were charged with exploring the potential scope of an opioids REMS. The public comments provided the impetus for the formation of the WG. From August 2009 to January 2010, we reviewed the docket and transcripts, generated hypotheses, evaluated and analyzed data, reviewed published literature, shared information within CDER, and talked to external experts. We considered a series of options while exploring the potential scope of the REMS, including limiting the REMS to the drugs specified in the March 3, 2009, meeting with industry (all oral long-acting (LA) formulations of morphine, oxycodone, hydromorphone, and oxymorphone, all formulations of methadone (when prescribed for pain), and all formulations of transdermal fentanyl); limiting the REMS to methadone (for pain) only; and expanding the REMS to all opioids.

SUMMARY OF RECOMMENDATIONS

We ***recommend*** that the opioid REMS cover all opioid drugs, but be limited to requiring only prescriber education. We acknowledge that this recommendation goes beyond the narrow question of which drugs should be included in the REMS. In researching this issue, it became obvious that a thoughtful assessment of scope would require us to think beyond that narrow question. Specifically, what was proposed to Industry by FDA at the March 3, 2009, meeting was narrow in scope (relatively few drugs), but relatively deep (multiple components). The available data strongly suggest to us that a narrow REMS would be easily circumvented with potentially substantive consequences (under- and non-

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[3] In addition, an eighth working group was created to handle external communications about the REMS. That working group was not involved in the review of comments and did not create a report.

treatment, use of inappropriate substitutes posing safety problems). Thus, in proposing to broaden the scope of the REMS, we attempted to balance that with fewer requirements.

SUMMARY OF ISSUES / CONCERNS

As we considered the various options and related issues, we identified a number of concerns. They are summarized here.

The data to support decision making are not strong

In making our recommendation, and consistent with the science-based nature of FDA's policies, we took seriously the charge of the Small Steering Committee to make our recommendations as "data-driven" as possible. Our recommendation represents our best interpretation of available data. However, as noted throughout this memo, the data to inform our recommendation are not particularly strong.

The data do not support that the ER/LA opioids pose the highest risk

The data in the metric systems FDA usually uses for assessing the relative risk of opioids [Drug Abuse Warning Network (DAWN), Emergency Department (ED) visits for Non-Medical Use of Prescription (NMUP), normalized for drug use] do not necessarily support the conclusion that the long-acting and extended-release (ER) (LA/ER) opioids proposed at the March 3, 2009, meeting with industry pose the highest risk.

Substitutes for the LA/ER opioids are medically suboptimal

We assessed how the drug products that were proposed at the March 3 meeting with industry for inclusion in the REMS are currently used, and our analysis indicates that few of the potential substitutes (e.g., hydrocodone/acetaminophen or meperidine) would be medically acceptable. We expect that the best substitutes would require the patient to have to wake up at least once per night to redose, resulting in a reduction in quality of life. Additionally, potential substitutes for the long-acting and sustained-release opioids all pose issues of safety (dose-limiting toxicities of the opioid or second active ingredient) or have dose ceilings, making them unsuitable for the average patient who is currently using the products proposed for inclusion in the REMS.

The "Balloon Effect"

We were concerned that, if the REMS includes potentially effective elements and targets a subset of opioids, prescribers may change their prescribing behavior. The changes in prescriber behavior have been called the "balloon effect," which means decreasing the magnitude of a part of a problem while other parts of the problem enlarge, as a balloon does when squeezed. In this document, we have chosen to be more accurate and use the term "changes in prescribing behavior." Although positive changes in prescribing behavior would be a desirable outcome of the REMS, negative changes, such as those based on convenience to the prescriber, are also likely. Changes in prescribing behavior could result in prescribing potentially less appropriate drugs not covered under the REMS and in the undertreatment and nontreatment of patients with pain who are candidates for the drugs included under the REMS. It was particularly concerning that undertreatment and nontreatment of pain would be a setback following a decade of progress in the medical practice of pain management.

During our analysis, we assumed that the REMS would include Elements to Assure Safe Use (ETASU) which would make the task of prescribing the drugs included in the REMS more burdensome for prescribers, would result in burdens to pharmacists and patients, and would impose substantial costs to the healthcare system. We assumed that the rationale for proposing multiple ETASU was that a more restrictive REMS was thought to have a greater chance of being effective. However, data to support or refute this notion were not available.

There are restrictive REMS elements that we think have the potential to be effective (e.g., restricted distribution). However, given the scale of the opioid REMS recommended by the Scope WG (inclusion of all opioids), these are not likely to be feasible or cost-effective. There was, however, consensus that prescriber education would add intrinsic value, and when effectively executed, would be a critical tool for ensuring that patients receive care that is safe and effective. Therefore, in our final recommendation, we have specified that the REMs should include prescriber education.

DETAILED DISCUSSION OF SPECIFIC ISSUES

Framework for the Discussion

A recurrent message from the public during the stakeholder and public meetings and in the comments to the docket was that the scope of the proposed REMS (LA opioids and methadone) was insufficient. Many of the commenters opined that the REMS would have the effect of shifting use away from long-acting opioids toward short-acting opioids because, under the proposal, the short-acting drugs would not be subject to the restrictions. They also commented that singling out long-acting opioids would only further stigmatize patients using these medications for chronic pain. It should be noted that these comments were provided at a time when the public and stakeholders were unaware of what ETASU would ultimately be required in the REMS or how restrictive an overall program may ultimately be.

During our deliberations, we carefully considered three key options for the scope of an opioid REMS:

- Should it include only the drugs specified in the March 3, 2009, meeting with industry?
- Should it include only methodone (for pain)?
- Should it cover all opioids?

Given our decision that the scope should be expanded to cover all opioids, we considered what other issues should be considered as the REMS is developed. What structure should the REMS take and what else should be included? Should a tiered program be used, with all opioids covered in Tier 1 (a less restrictive program) and the long-acting opioids and methadone being subject to additional REMS elements (Tier 2)? Should such a comprehensive opioids REMS be undertaken at this time?

The following sections lay out the various options we explored and discuss in detail relevant considerations, available data, and our conclusions.

OPTION: The REMS should include only the drugs specified in the March 3, 2009, meeting with industry (all oral long-acting formulations of morphine, oxycodone, hydromorphone, and oxymorphone, all formulations of methadone (when prescribed for pain), and all formulations of transdermal fentanyl).

We did not support this option for a number of reasons, including prescribers "prescribing around" the LA/ER opioids and prescribing substitutes that might not be in the best interest of the patient; decreased access to the specified opioids, and lack of data to support the determination that the LA/ER opioids are the most problematic. Our concerns are discussed in greater detail in other sections of this report.

OPTION: The REMS should include methadone (for pain) only.

We also considered this as a possible option because several sources indicate that methadone has the highest death rate of the opioids. Furthermore, a "methadone-only" REMS could serve to pilot a REMS for the larger group of opioids. Use of a pilot program to optimize logistics and identify unintended consequences was recommended in the docket. The rationale for targeting methadone relates to methadone's perceived risk. Hall et al. studied unintentional deaths due to prescription drugs in West Virginia in the year 2006. They reported that methadone contributed to the largest number (112) and proportion (40%) of deaths.[4]

From a pharmacological perspective, methadone also has higher risk compared to other opioids. FDA's Website notes the following[5]:

> FDA has reviewed reports of death and life-threatening side effects such as slowed or stopped breathing, and dangerous changes in heart beat in patients receiving methadone. These serious side effects may occur because methadone may build up in the body to a toxic level if it is taken too often, if the amount taken is too high, or if it is taken with certain other medicines or supplements. Methadone has specific toxic effects on the heart (QT prolongation and Torsades de Pointes). Physicians prescribing methadone should be familiar with methadone's toxicities and unique pharmacologic properties. Methadone's elimination half-life (8-59 hours) is longer than its duration of analgesic action (4-8 hours). Methadone doses for pain should be carefully selected and slowly titrated to analgesic effect even in patients who are opioid-tolerant. Physicians should closely monitor patients when converting them from other opioids and changing the methadone dose, and thoroughly instruct patients how to take methadone. Healthcare professionals should tell patients to take no more methadone than has been prescribed without first talking to their physician.

Given these statistics, we considered whether a methadone-only REMS would be useful. Because methadone is not heavily used, the economic and personal burdens would be less. Furthermore, a methadone REMS could serve to pilot a future, more inclusive REMS by helping us to understand the impacts on access and allowing us to work out the technical glitches without affecting too many patients. However, assessments would be confounded by the fact that a large number of methadone patients are being treated for addiction rather than pain, which may bias the outcomes. In addition, a

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[4] Hall AJ, Logan JE, Toblin RL, et al. Patterns of Abuse Among Unintentional Pharmaceutical Overdose Fatalities. *JAMA* 2008;300(22)2613-20.

[5] See http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142827.htm.

methadone REMS could also result in prescribers substituting another drug, which may not be the best choice for the patient. There would be little effect in reducing bad outcomes resulting from use of other opioids. Last, a methadone-only REMS would delay the implementation of a more comprehensive REMS that has greater potential to affect public health.

OPTION: The REMS should cover all opioids.

The key question we were asked to research was which opioids should be included in the REMS. To address this question, we explored the following issues, which are discussed in detail later in this document:

1. The data that support the notion that the extended-release and long-acting opioids pose the highest risk. The Drug Abuse Warning Network data, normalized for drug use, are the data that have been most widely used by FDA to assess risk in this context.
2. How prescribers change their behavior when programs that have the effect of increasing prescriber burden are initiated, we conducted a literature search assessing the following:
    a. The New York State Triplicate Program for benzodiazepines
    b. Prescription Monitoring Programs
    c. The effects of the implementation of Risk Management Programs
3. Assessment of what the putative effects would be of "turning back the clock" to circa 1999, when two conditions existed:
    a. The use of ER and LA opioids was less prevalent
    b. Prescription opioid abuse was not a significant public health issue
4. Alternatives available and how they might be used if the scope of the REMS is limited to the extended-release and long-action opioids identified at the March 3, 2009, meeting and prescribers "prescribe around" those drugs.
5. Possible REMS elements, how burdensome they would be, and what evidence there is to support their use.

Theoretically, the LA/ER opioids specified at the March 3, 2009, meeting with industry should pose the highest risk. These drugs are all high-potency opioids. Furthermore, since many of these products are designed to deliver 12 to 72 hours of drug in a single dosage form, they contain substantial amounts of opioid. Last, the drug products specified at the March meeting are all single-ingredient products, which do not have dose-limiting active ingredients such as acetaminophen.

Both IR and ER Opioids Are Widely Abused and Misused

The available data do not necessarily support the conclusion that the LA/ER opioids pose the highest risk when used inappropriately. The Agency has been using the DAWN NMUP (Non-Medical Use of Prescription) emergency department (ED) mentions normalized by drug use as a measure of the relative risk of different opioid products. Table 1 shows the rates of DAWN NMUP mentions, normalized for use.

Table 1: DAWN NMUP normalized for drug use (2004-7)

	2004	**2005**	**2006**	**2007**
Oxycodone ER	42.4	50.3	56.9	61.6
Hydromorphone IR	34.6	39.7	48.8	58.7
Fentanyl transdermal	23.5	25.8	33.1	30.4
Morphine ER	17.0	6.9	12.5	13.9
Oxycodone IR (includes combination drugs)	7.2	6.9	9.2	9.5
Hydrocodone IR (HC/APAP)	4.1	4.5	5.1	5.5

The LA/ER opioids were originally identified because it was believed that they pose the highest risk to patients and that they make up a relatively small subset of all opioids (~9% of all opioid prescriptions), which strikes a balance between the potential benefit and the anticipated burden. However, as shown in Table 1, hydromorphone, which is available only as an immediate-release (IR) formulation, appears to pose a risk similar to ER oxycodone, which has the highest risk as estimated by DAWN NMUP, normalized for use. The normalized data also show that ER morphine poses a risk not dissimilar to immediate-release (IR) oxycodone, which is not one of the LA/ER drugs.

We note that the normalized DAWN NMUP ED ratio may not be an ideal metric from which to stratify these drugs for risk, particularly with regard to assessing deaths. However, as of January 2010, it is felt to be the best metric available. In addition, this metric has been used to stratify drugs for risk at every recent FDA Advisory Committee meeting, and this metric has been vetted by relevant Agency groups. At the time we finalized the draft of this report, the Metrics Working Group was continuing to research potentially more useful metrics, and we are hopeful that a metric can be identified or developed that could distinguish bad outcomes in patients versus abusers, and that better reflects the goals of the Opioid REMS. We also note that hydromorphone has been shown to be one of the higher risk drugs (when events are normalized for use) in several Researched Abuse, Diversion and Addiction-Related Surveillance System (RADARS) databases. In conjunction with a December 17, 2009, teleconference with this working group and the Metrics Working Group, RADARS has shared certain data regarding hydromorphone with FDA. Table 2 shows summary data from some RADARS databases.

Table 2: Summarized RADARS data, normalized for Unique Recipient of Dispensed Drug[6]

Rates per 1,000 URDD, All Sites
2nd quarter 2009

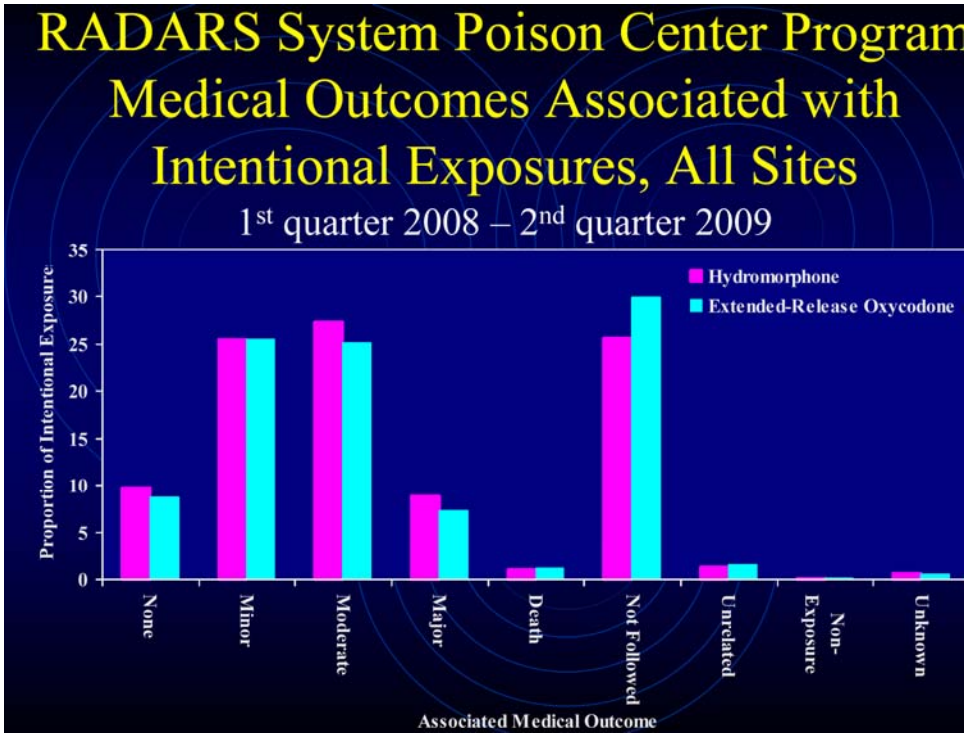
Rank	Poison Center	Opioid Treatment	SKIP	Drug Diversion	College Survey*
1	Methadone (1.45)	**Hydromorphone (5.11)**	Methadone (2.44)	Methadone (0.86)	Methadone (0.14)
2	Buprenorphine (0.98)	Morphine (3.76)	**Hydromorphone (2.15)**	**Hydromorphone (0.76)**	Fentanyl (0.13)
3	Morphine (0.56)	Methadone (3.35)	Morphine (0.93)	Buprenorphine (0.73)	Buprenorphine (0.09)
4	**Hydromorphone (0.52)**	Fentanyl (1.47)	Fentanyl (0.80)	Morphine (0.49)	Morphine (0.08)
5	Fentanyl (0.37)	Buprenorphine (0.62)	Buprenorphine (0.32)	Oxycodone (0.38)	**Hydromorphone (0.07)**
6	Oxycodone (0.31)	Oxycodone (0.56)	Oxycodone (0.32)	Fentanyl (0.35)	Oxycodone (0.02)
7	Hydrocodone (0.24)	Hydrocodone (0.27)	Hydrocodone (0.14)	Hydrocodone (0.17)	Hydrocodone (0.02)

These data are derived from five of the six RADARS databases[7] and include Poison Center (audited and cleaned poison control center data), Opioid Treatment Program (predominantly methadone clinics), Survey of Key Informant's Patients (predominantly buprenorphine treatment centers), Drug Diversion (specially trained law-enforcement officers who report on actions related to prescription drugs), and College Survey (surveys of college students) occurrences, normalized for the number of patients dispensed drug. The data show that hydromorphone, which is only available in an immediate-release oral formulation, appears near or at the top of most of these databases.

RADARS provided information regarding outcomes for the Poison Center Program data for extended-release oxycodone and hydromorphone, shown in Figure 1.

[6] Provided and described by Nabarun Dasgupta, MPH (University of North Carolina and RADARS).
[7] Provided and described by Nabarun Dasgupta, MPH (University of North Carolina and RADARS).

Figure 1: Medical outcomes from Poison Center Data



The figure shows that hydromorphone closely approximated ER oxycodone for all outcomes, including death. Furthermore, RADARS data show that a substantial proportion of the bad outcomes (DAWN ED mentions) appear to have occurred in patients, the target population of the REMS.

Table 3 shows the DAWN ED data for hydromorphone broken down by type.[8]

Table 3: DAWN ED data, hydromorphone, 2004-6

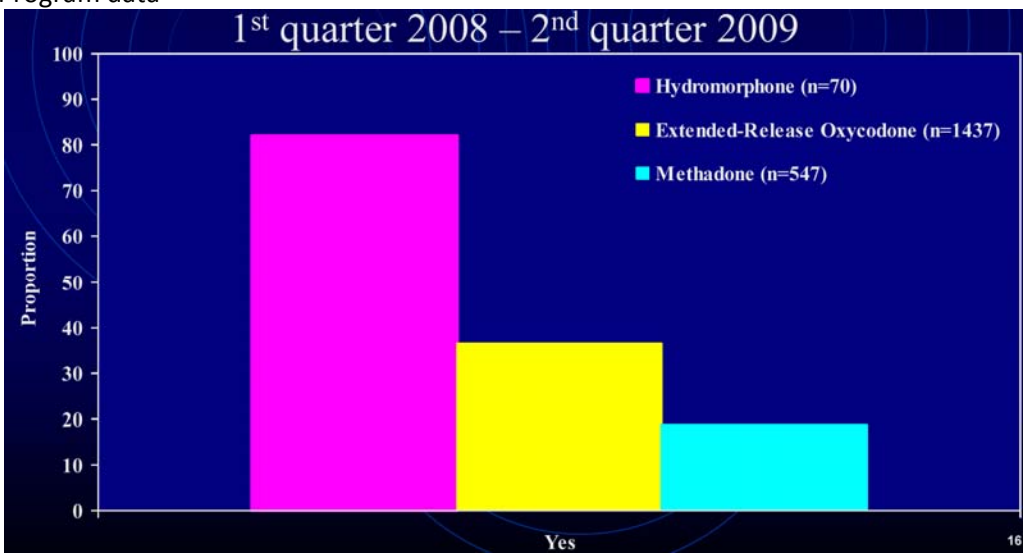
	2004 National Estimate (95% Confidence Interval)	2005 National Estimate (95% Confidence Interval)	2006 National Estimate (95% Confidence Interval)
All misuse and abuse	3992 (1969, 6014)	4967 (2839, 7094)	7429 (4186, 10961)
Adverse reaction	1299 (527, 2072)	4252 (1356, 7147)	4109 (1078, 6141)
Seeking detox	962 (125, 1799)	617 (15, 1219)	…
Suicide	…	…	262 (8, 516)

[8] Ibid.

These data show that a substantial proportion (36% in 2006) of these bad outcomes appear to be occurring in patients (because they are coded as "adverse reaction").

Figure 2 shows the proportion of patients who reported drug injection (generally considered more advanced drug use).

Figure 2: Proportion of patients who reported injecting drug from Opioid Treatment Program data[9]



These data show that hydromorphone was reported to have been injected by patients under treatment for addiction at a higher rate compared to ER oxycodone or methadone. Since these data are limited to patients being treated for addiction, they do not help us distinguish whether bad outcomes are occurring in patients or addicts, one of the goals of the REMS.

The absolute numbers of patients being harmed by IR opioids is substantially higher than those being harmed by ER opioids. The 2007 DAWN NMUP ED data show that ~286K visits were related to the ingestion of IR opioids compared to ~148K for ER opioids.

Restrictions on the Use of ER Opioids Will Affect IR Opioid Prescription and Use

If the REMS does not cover all opioids, one can predict changes in prescriber behavior that may involve switching from one drug to another (generically known as "balloon effect"), undertreatment of patients or non-treatment of patients. We base this conclusion on past experience with programs such as the Triplicate program applied to benzodiazepines in New York; Prescription monitoring programs, and Risk Management Programs.

Analyses of prescription patterns before and following the implementation of such programs have shown that prescribers change their prescribing behavior. The preponderance of these data show that the shift away from the affected drug(s), as reflected by the decrease in drug use, is in the range of 50%.

[9] Provided and described by Nabarun Dasgupta, MPH (University of North Carolina and RADARS).

The New York State Triplicate Program for Benzodiazepines

In 1989, for the purpose of reducing diversion and inappropriate prescribing of benzodiazepines (BDZ), BDZ were added to the triplicate program in New York State. Triplicate prescription programs require that applicable prescriptions be written on special prescription forms. These prescription pads are printed by the State and sold to registered practitioners after the prescriber applies to the program. After a triplicate prescription is written, the prescriber keeps one copy and gives two copies to the patient. When the prescription is filled, the pharmacist keeps one copy and forwards the third copy to the Department of Health.

A large number of journal articles were published subsequent to this change, analyzing the results of the program. Key findings are summarized here.

- Use of alternatives and nontreatment

  Weintraub et al.,[10] published a study reporting the use of BDZs and other psychoactive drugs (antidepressants, antipsychotics, anxiolytics, sedatives, hypnotics) in New York around the time the triplicate regulation went into effect. California (demographically similar), North Carolina, and New Jersey (neighboring state) were used as comparators. This group used data from Medicaid, Blue Cross/Blue Shield, and IMS to estimate drug use. Briefly, Weintraub et al., found a marked decrease in BDZ prescriptions in New York following implementation of the triplicate program that was not observed in the comparator states. This group found a large increase in the prescribing of alternatives such as meprobamate, ethchlorvynol, methprylon, chloral hydrate, and butabarbital in New York. Weintraub et al. assert that the use of alternatives did not completely replace the decrease in BDZ prescribing, implying that some patients were not being treated.

- Use of alternatives and alcohol

  Reidenberg[11] published a retrospective study examining the use of BDZ prescriptions in New York and Pennsylvania around the time of implementation of the regulation. He also examined alcohol use, inferred from data from the New York State Department of Taxation and Finance and the Pennsylvania Liquor Control Board. Similar to Weintraub et al., Reidenberg found a precipitous drop in BDZ prescriptions (1,439,000 to 625,000). In Pennsylvania, the number of BDZ prescriptions dropped slightly from 1,216,000 to 1,084,000 over the same period. Reidenberg also found an increase in prescriptions for meprobamate, buspirone, chloral hydrate, and hydroxyzine. In Pennsylvania, prescriptions for those alternative drugs decreased or were unchanged over the study period. The consumption of wine and spirits increased in New York (5.6% and 3.6%, respectively) compared to a decrease of 2.6% and 2.7% in Pennsylvania, potentially consistent with self medication with an anxiolytic/sedative.

- Clinically vulnerable populations

[10] Weintraub M, Singh S, Byrne L, Maharaj K, Guttmacher L. Consequences of the 1989 New York State Triplicate Benzodiazepine Prescription Regulations. *NIDA Res Monogr* 1993;131:279-93.
[11] Reidenberg MM. Effect of the requirement for triplicate prescriptions for benzodiazepines in New York State. *Clin Pharmacol Ther* 1991;50(2):129-31.

Simoni-Wastila et al.,[12] published a retrospective analysis of the impact of the triplicate program on clinically vulnerable Medicaid populations. This group examined psychoactive medication use in patients with diagnoses of schizophrenia, schizophreniform disorder, schizoaffective disorder, schizoid personality disorder, or schizotypal personality disorder, bipolar disorder, epilepsy, and/or panic disorder, agoraphobia with or without panic disorder, social phobia, or specific phobia. These authors analyzed data from New York and New Jersey, both before and for 6 months after implementation of the triplicate program. Simoni-Wastila et al., found that the use of BDZ dropped by ~48% in the patients in New York and that there was no decline in use in patients in New Jersey. According to these authors, the use of substitute drugs increased slightly in New York but not sufficiently to offset the decrease in BDZ use. The authors concluded that the data suggest that many patients previously receiving BDZ therapy did not receive any pharmacologic intervention.

The data from the New York State Benzodiazepine Triplicate Program are clear. When confronted with more controls on prescribing, prescribers will "prescribe around" the pertinent drug or drug group. It is concerning that the data from New York suggest that some patients will go untreated. However, it is possible that some patients were previously inappropriately being prescribed BDZ and that the program caused prescribers to reassess the most appropriate therapy of these patients. We found no studies that evaluated this explanation.

Prescription Monitoring Programs

In the report titled, *An Evaluation of Prescription Drug Monitoring Programs*,[13] sponsored by the United States Department of Justice, Office of Justice Programs, and Bureau of Justice Assistance, research examines the effects of prescription monitoring programs (PMPs) on the supply and abuse of prescription drugs. Information from the Automation of Reports and Consolidated Orders System (ARCOS) is used to develop measures of supply, and information from the Treatment Episode Data Set (TEDS) maintained by SAMHSA is used to develop measures of abuse. The focus was on Schedule II pain relievers and stimulants.

The authors distinguish between states that do not have a PMP program ("non-PMP") and states that have a PMP. Use rates (as derived from ARCOS) for pain relievers are higher in non-PMP states than in PMP states for all pain relievers with the exception of hydromorphone. This is what we would expect if the PMP programs reduce use. The authors define a composite per capita measure for pain relievers to account for the various drugs reported. With this composite measure, they show use is higher per capita in non-PMP states than in PMP states. From 1997 to 2003, using their composite measure, use in non-PMP states increased 47% but use in PMP states increased 41%. It should be noted that abuse rates between PMP and non-PMP states, which the authors define based upon treatment admissions in the TEDS database, contradict the notion that less prescribing would lead to less abuse. These data indicate that the rate of pain reliever admissions to state-licensed drug treatment programs in the U.S is lower in non-PMP states than in PMP states.

[12] Simoni-Wastila L, Ross-Degnan, D, Mah C, Gao X, Brown J, Cosler LE, Fanning T, Gallagher P, Salzman C, Soumerai SB. A Retrospective Data Analysis of the Impact of the New York Triplicate Prescription Program on Benzodiazepine use in Medicaid Patients with Chronic Psychiatric and Neurologic Disorders. *Clinical Therapeutics* 2004;26(2):322-36.

[13] Simeone R and Holland L. "An Evaluation of Prescription Drug Monitoring Programs."

The report, *Impact Evaluation of Maine's Prescription Drug Monitoring Program,* [14] is an evaluation of the early implementation of Maine's Electronic Prescription Monitoring Program. The Maine PMP started in July of 2004 and had 50 prescribers and 66 dispensers registering for the program by summer 2005.

Under the program, all transactions from pharmacies dispensing prescriptions of Schedules II, III, and IV drugs are submitted electronically to a database. This database is used to issue threshold reports to clinicians indicating a potential "red flag" on individuals who may be receiving dangerous levels of prescription drugs. Clinicians may also query the database to request a patient history report.

Forty-one percent (41%) of the prescribers surveyed reported that the availability of the PMP changed the way or the amount of controlled substances they prescribed. Twenty-one percent (21%) reported that they prescribed about the same; eight percent (8%) reported that they prescribed more, and sixty-five percent (65%) reported that they prescribed fewer controlled substances than two years ago.

It is unclear from these data whether changes in prescribing behavior are positive (physicians more informed about patient history and thus prescribing more appropriately) or negative (physicians avoiding opioid prescriptions in patients who need them).

Risk Management Assessment Plans (RiskMAP)

The more direct body of evidence indicating that imposition of a REMS is likely to decrease prescribing of the affected drug consists of data that have been collected following the imposition of a Risk Management Program (RMP) or Risk Minimization Action Plan (RiskMAP), which are plans implemented by sponsors of FDA-approved applications before FDAAA to manage the risks of certain drugs. There are several drugs that have restrictive RiskMAPs/RMPs that were implemented before FDAAA including Lotronex (alosetron), Tracleer (bosentan), Letairis (ambrisentan), Thalomid (thalidomide), and Accutane (isotretinoin). None of these programs is directly analogous to the current situation. For example, bosentan and thalidomide were never marketed without a RiskMAP. Thus, it is not possible to understand the before and after effects of the RiskMAP on prescribing habits for those products.

The product that is most representative of the current situation can be debated. However, Lotronex has certain features in common with the LA/ER opioids. Lotronex was approved in February 2000 for diarrhea-predominant irritable bowel syndrome. Nine months later (after 8 months of marketing) it was withdrawn from the market because it was associated with serious gastrointestinal adverse events, most notably ischemic colitis.

In October 2002, pursuant to the recommendations from an Advisory Committee, Lotronex was reintroduced to the market under a restrictive RiskMAP. The use of Lotronex was reported by Traynor who wrote, "Collectively, the 10,000 patients who used alosetron in the 14 months since the product's reintroduction obtained about 30,000 prescriptions for Lotronex, generating sales of about $5.9 million at today's Red Book price. In contrast, GSK reported $54 million in sales from Lotronex during the eight months that the product was marketed in 2002."[15] The Lotronex scenario is substantially different from

[14] Lambert, D. (2007, March). Impact evaluation of Maine's Prescription Drug Monitoring Program. University of Southern Maine, Muskie School of Public Service, Institute for Health Policy.

[15] Traynor K. Alosetron use drops dramatically with risk management. *Am J Health-Syst Pharm* 2004;61:1210-2.

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the one we face today since Lotronex was withdrawn from the market for a potentially lethal adverse event in relatively healthy patients. Hence, it is reasonable to expect that the change in prescribing habits observed is an overestimate of what we would expect to see when the Opioid REMS is implemented. Nonetheless, what happened with Lotronex supports the notion that imposition of a RiskMAP/RMP/REMS is likely to decrease prescribing of the affected drug.

Of concern is that many of the substitutes for the LA/ER opioids are not suitable for the patients currently taking these drugs. In addition, as reflected in the approved labeling for the relevant products, it is well established that the duration of action and dosing interval for the LA/ER opioids is 8-72 hours and most non-long-acting opioids have durations of actions in the range of 3-6 hours. Thus, substituting short-acting opioids for long-acting opioids would be expected to decrease patients' quality of life.

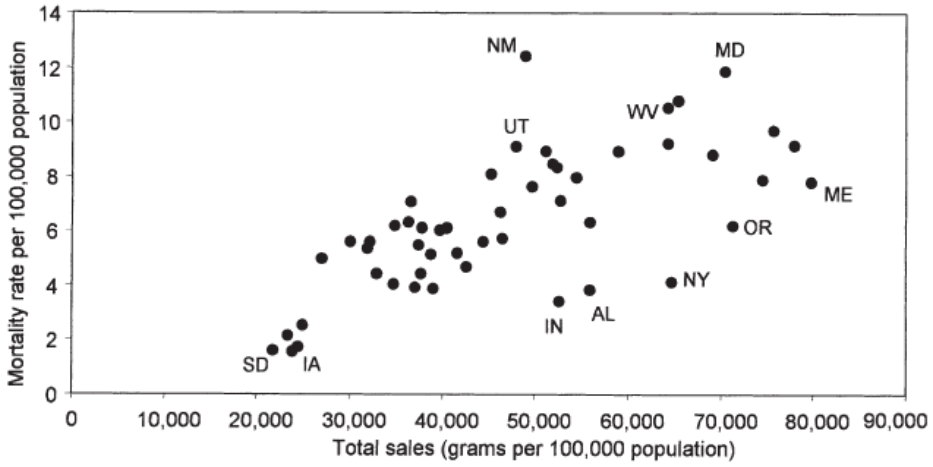
Encouraging the Use of IR Opioids Can Have Unintended Negative consequences

It can be argued that, if the result of the REMS proposed on March 3 returns prescribing practices to those circa 1999, that shift could represent a benefit to the public health because prescription opioids were not considered to be a public health issue at that time. However, a return to prescribing practices to those circa 1999 may also indicate a reversal of the progress in pain management made in years since.

Would Turning Back the Clock Bring Any Benefits?

Dr. Leonard Paulozzi, at the CDC, published two papers[16,17] that explored the relationship between unintentional drug poisoning deaths and opioid use. He used data from the CDC (National Center for Health Statistics) to estimate unintentional deaths and data from the DEA (Automated Reports and Consolidated Orders System) to estimate drug sales. In one paper, he correlated these variables by state; in the other, he used aggregate US data and studied the effects over time. Figure 3 and Table 4 are reproduced from the papers.

Figure 3: Total opioid analgesic sales versus unintentional and undetermined drug poisoning mortality rates by state, 2002 (reference 14)



[16] Paulozzi LJ, Ryan GW. Opioid Analgesics and Rates of Fatal Drug Poisoning in the United States. *Am J Prev Med* 2006;31(6):506-11..;

[17] Paulozzi LJ, Budnitz DS, Xi Y. Increasing deaths from opioid analgesics in the United States. *Pharmacoepi Drug Safety* 2006;15:618-27.

Table 4: Death certificate poisoning occurrences and sales of opioids, 1999 and 2002[18]

Type of opioid analgesic	1999	2002
'Other opioid' type		
Number of occurrences	2520	3967
Sales		
Codeine	23 917.1	22 633.7
Oxycodone	9 717.6	22 376.9
Hydrocodone	12 101.6	18 822.6
Morphine	6 804.9	10 264.3
Hydromorphone	292.5	473.4
Total in morphine equivalents†	33 381.7	56 752.3
Occurrences/total sales	0.08	0.07
Methadone		
Number of occurrences	754	2361
Sales		
Through narcotics treatment programs	3671.8	5263.4
Through other outlets	965.0	2649.6
Total in morphine equivalents†	34 775.7	59 347.2
Occurrences/Total Sales	0.02	0.04
'Other synthetic narcotic' type		
Number of occurrences	481	982
Sales		
Fentanyl	107.1	242.0
Meperidine	5539.6	5412.4
Total in morphine equivalents†	8589.5	18 693.3
Occurrences/Total Sales	0.06	0.05
Total		
Number of occurrences	3755	7310
Sales in morphine equivalents†	76 747.0	134 792.7
Occurrences/total sales	0.05	0.05

Figure 3 shows a roughly linear relationship between deaths and sales; the more opioid sold in a state, the more deaths occurred in that state.

The interesting row in Table 4 is the last one. When the ratio of the occurrences (deaths) divided by sales is compared between 1999 and 2002, the ratios are identical. The "by-year" data are consistent with the "by-state" data; the more drug sold, the more deaths occurred. It is unfortunate that the years compared were 1999 and 2002, which only covers a span of three years. However, our search of the literature failed to identify other studies that informed this issue.

It is difficult to ascertain whether a return to conditions 10+ years ago would be beneficial, neutral, or harmful. We have drug use data for all ER and IR opioids for the period 1991 to 2008, shown in Figures 4 and 5.

[18] Ibid.

Figure 4: Total outpatient prescription data, all ER opioids, by specialty (SDI, Vector One®: National. Year 2008, Extracted 12/09)

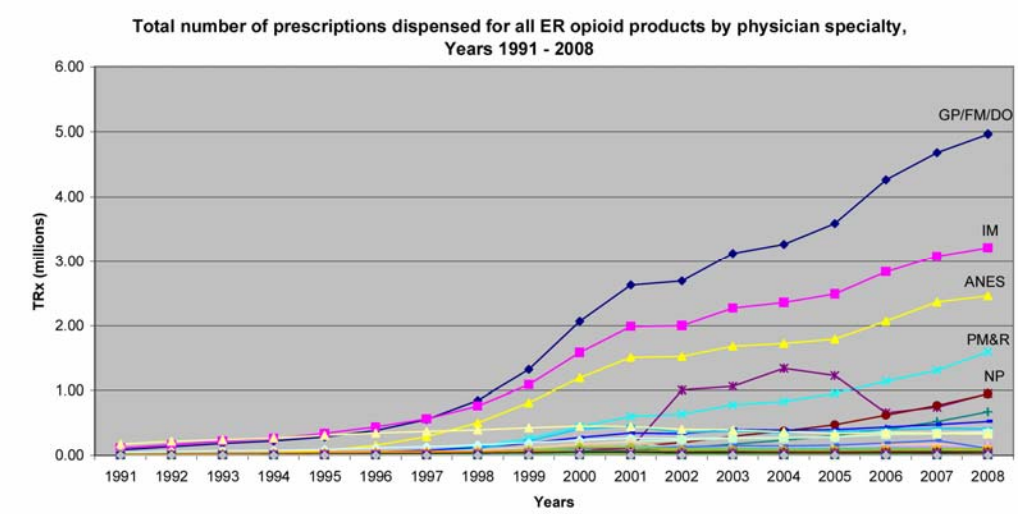
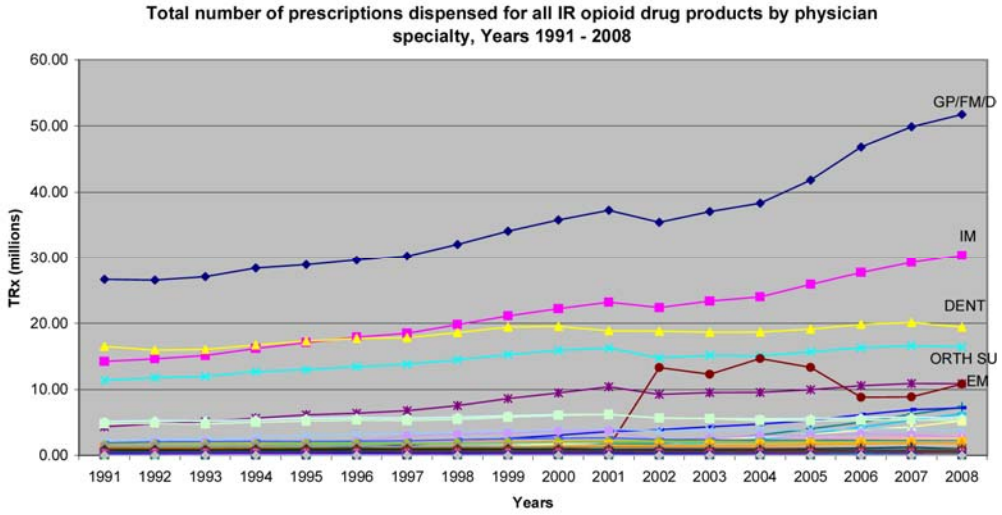


Figure 5: Total outpatient prescription data, all IR opioids, by specialty (SDI, Vector One®: National. Year 2008, Extracted 12/09)



Briefly, these data show that the overall use of opioids has been sharply increasing over the past decade. The rate of increase over the past year for ER opioids has been greater than for IR opioids. However, the use of IR opioids is approximately one order of magnitude greater than for ER opioids. The problem in trying to assess conditions in 1999 is that the standard metric by which FDA has assessed the risk of opioids (DAWN NMUP ED visits) is not comparable between 1999 and 2008 because the DAWN system changed substantially in 2003 ("new" versus "old" DAWN). Thus, we cannot directly track and compare trends during the entire 10 year period.

<u>What Substitutes Might Prescribers Turn to?</u>

To better understand which drugs prescribers might turn to as they prescribe around the drugs included in the REMS, the WG conducted a literature search to understand the use of the LA/ER opioids. Two

articles contained relevant information.[19,20] These investigators studied patients with chronic pain not due to malignancy, and they recorded opioid analgesic requirements. The data were fairly consistent and showed that, on average, these patients required ~300 mg morphine equivalent/day, plus additional opioid for rescue.

In that context, we assessed what alternatives are available to prescribers to substitute for the LA/ER opioids. The substitutes could be placed into the following six groups:

- Single-ingredient, potent (oxycodone, morphine, hydromorphone, oxymorphone)
- Single-ingredient, weak (tramadol, codeine)
- Combination, potent (oxycodone/acetaminophen (APAP))
- Combination, weak (codeine/APAP, propoxyphene APAP)
- Hydrocodone/APAP
- Mixed agonist/antagonist (pentazocine, butorphanol, buprenorphine)

Based on year 2008 outpatient dispensed prescription data, the following proportions of use were estimated for the opioid market (Table 5).

Table 5: Outpatient dispensed prescription data, immediate-release, by group, year 2008

Single-ingredient, potent (oxycodone, morphine, hydromorphone, oxymorphone, tapentadol)	14%
Single-ingredient, weak (codeine, tramadol, meperidine)	9%
Combination drug, potent (oxycodone/APAP)	12%
Combination drug, weak (codeine/APAP, tramadol/APAP)	16%
Mixed agonist-antagonist (buprenorphine, butorphanol)	1%
Hydrocodone/APAP (combination drug, moderate potency, very high drug utilization)	48%

Source: SDI, Vector One®: National. Year 2008, Extracted 8/09

Of these six groups, realistically, only the single ingredient/potent opioids would suffice to treat an average patient using ER oxycodone or transdermal fentanyl. The other groups either pose safety concerns due to the other active ingredient (usually APAP), are believed to have a ceiling effect (mixed agonist/antagonist) or would be expected to have intrinsic dose-limiting side effects (constipation for single-ingredient codeine or seizures for meperidine).

Because of the safety or efficacy issues related to many of the alternatives, prescriber education would be useful to remind prescribers of what drugs are available and what the limitations of the substitutes are. If prescribers decide to "opt out" of prescribing the drugs specified for REMS, it is also important

[19] Milligan K, Lanteri-Minet M, Borchert K, Helmers H, Donald R, Kress HG, Andriasensen H, Mouline D, Jarvimaki V, Haazen L. Evaluation of long-term efficacy and safety of transdermal fentanyl in the treatment of chronic noncancer pain. *J Pain* 2001;2(4);197-204.

[20] Ackerman SJ, Mordin M, Reblando J, et al.,. Patient-Reported Utilization Patterns of Fentanyl Transdermal System and Oxycodone Hydrochloride Controlled-Release Among Patients with Chronic Nonmalignant Pain. *J Man Care Pharm* 2003;9(3):223-231;

that they understand the hazards of the drugs they will be prescribing. As discussed at the June 29-30, 2009, Advisory Committee meeting, acetaminophen toxicity is a substantial public health problem and acetaminophen overdose is the most common cause for acute liver failure in the United States. Since many of the alternatives are combination drugs that include acetaminophen, it is imperative that prescribers understand this.

The alternatives to the LA/ER opioids are shown in Table 6, following.

Table 6: Characteristics of potential substitutes for LA/ER opioids (highest opioid/other analgesic ratio selected for combinations)

Established name	Formulation	C	High Strength (ME)	Relative potency (mg oral morphine)	Dosing Interval	Comments
Buprenorphine	IR tablet	III	16 mg		Q6h for pain	Partial agonist, Purported ceiling effect at 16 mg
Buprenorphine	IR w/ naloxone	III	16 mg			
Butorphanol	Nasal spray	IV	1 mg/spray		Q3-4h	Mixed agonist/antagonist
Codeine	IR tablet	II	60 mg (20 mg)	0.33	Q4h	
Codeine	IR w/ APAP	III	60/300 (20 mg)	0.33	Q4h	Max daily dose of codeine = 780 mg
Dihydrocodeine	IR w/ caffeine & APAP	III	32/713 (APAP) (11 mg)	0.33		
Hydrocodone	IR w/ APAP	III	10/325 (18 mg)	1.8	Q4-6h	Max daily dose of hydrocodone = 120 mg
Hydrocodone	w/ ibuprofen	III	10/200 (18 mg)	1.8	Q4-6h	Max daily dose of hydrocodone = 120 mg
Hydromorphone	IR tablets	II	8 mg (64 mg)	8	Q4-6h	
Hydromorphone	Oral solution	II	5 mg/5mL (40 mg)	8	Q4-6h	
Levorphanol	Tablets	II	2 mg (30 mg)	15	Q6-8h	
Meperidine	Tablets	II	150 mg (30 mg)	0.2	Q3-4h	Risk of seizure due to metabolite
Meperidine	Oral solution	II	50 mg/5 mL (10 mg)	0.2	Q3-4h	
Morphine	IR tablets	II	30 mg	3	Q3-4h	
Morphine	Oral solution	II	20 mg/mL	1	Q3-4h	
Oxycodone	Single-agent IR	II	30 mg (60 mg)	2	Q3-4h	
Oxycodone	Combo IR	II	10 mg [+325 mg APAP) (20 mg) 5 mg + 400 mg ibuprofen (10 mg)]	2	Q6h	Max daily dose = 120 mg oxycodone
Oxymorphone	IR tablet	II	10 mg (40 mg)	4		
Pentazocine	Combo w/ APAP or naloxone	IV	50 (w/ naloxone)		Q3-4h	Mixed agonist/antagonist
Propoxyphene	Single-agent	IV	100 mg		Q4h	Purported to have cardiotoxic metabolite.
Propoxyphene	w/ APAP	IV	100/325		Q4-6h	Max daily dose = 120 mg PPX
Tramadol	ER	N/A	300 mg		BID to QD	
Tramadol	IR	N/A	50		Q4-6h	
Tramadol	w/ APAP	N/A	37.5/325		Q4-6h	Max daily dose due to APAP
Tapentadol	IR tablet	II	100 mg (33 mg)	0.33	Q4-6h	SNRI activity

Because, on average, a chronic pain patient using ER oxycodone or transdermal fentanyl will require approximately 300 mg morphine equivalents/day, the only group of products that can safely deliver that much opioid are the potent, single-ingredient opioids. The other products are dose-limited in some way.

It is also important to note that prescribers may undertreat pain if they understand the dose limits, but the patient's pain requires higher doses of opioid. Last, patients may overdose on APAP by doctor shopping and obtaining multiple prescriptions for an opioid/APAP combination.

In docket entries and statements made at stakeholder and public meetings, members of the public expressed a strong preference to expand the scope of the REMS. We reviewed relevant docket entries and statements made during the meetings. Of 34 such statements, 25 recommended expanding the scope in some form [either to all opioids (15) or to include the short-acting opioids (10)]. In the context of the LA/ER opioids, it is unclear what the difference is between adding all and short-acting opioids. We note that not all of the comments regarding scope recommended expanding the scope; three persons recommended limiting the REMS to methadone-only.

We recognized that there are some disadvantages to expanding the scope of the REMS. Expanding the scope as described would increase the costs of the REMS and increase the number of drug manufacturers involved. However, the costs of the program are dependent on the elements proposed.

We discussed the concern that there may be little justification, legal or otherwise, for including more benign drugs (e.g., codeine/APAP) in the REMS. However, the requirement in the Food and Drug Administration Amendments Act of 2007 is "new safety information…about…a serious risk or an unexpected serious risk associated with the use of the drug…" Therefore, although we did not conduct a search of the Adverse Event Reporting System, it seems likely that some kind of new safety information exists for all opioids. However, it is unknown whether such information would exceed the threshold to be considered "serious" or "unexpected."

Finding dramatic new adverse event reports attributable to a drug like codeine/APAP seems unlikely. However, given that changes in prescriber behavior are entirely predictable, it seems reasonable to attempt to predict the outcome of the overuse of some products that currently appear low risk.

With regard to codeine/APAP, due to the low potency of codeine and its combination with APAP, a hepatotoxin, significant overdose with codeine/APAP is not inconceivable, especially if a patient is self-medicating due to inadequately treated pain. Patients may elect to use an over-the-counter analgesic such as APAP itself in an attempt to achieve adequate pain relief. Patients would be particularly susceptible to APAP toxicity if there is concomitant use/abuse of alcohol. There is evidence[21] to support the notion that the rate of alcohol use and abuse is high (31-46%) in patients with chronic non-cancer pain.

Although it is possible that FDA may find new safety data to support inclusion of all opioids under the proposed REMS, it is important to note that the Agency has historically taken a stepwise approach toward drug safety, generally starting with labeling changes and public health advisories before taking

[21] Reid MC, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, O'Connor PG. Use of Opioid Medications for Chronic Noncancer Pain Syndromes in Primary Care. *J Gen Intern Med* 2002;17(3):173-9.

more stringent steps, should they ultimately be deemed necessary. Excluding opioids that are perceived to be relatively benign from a comprehensive REMS is consistent with this approach.

Usefulness of Prescriber Education

We acknowledge that some avenues that we explored are not strictly related to scope, which was narrowly defined as what drugs should be included in the REMS. However, we believe the question of scope cannot be adequately addressed in a vacuum; there is an interdependence of scope with other aspects of the REMS. Thus, we have given thought to topics outside the narrowly proscribed assignment.

Given the recommendation that the REMS be expanded to all opioid products, we concluded that prescriber education would be useful. Because prescribers are privy to the most personal information about patients, they can use this information to risk-stratify and ultimately make a decision about whether opioid therapy is appropriate for a patient. Prescribers also decide which opioid product to use. The prescriber's mandatory face-to-face contact and communication with the patient allow him/her to effectively counsel patients and warn them of the risks associated with opioid therapy. Prescribers also examine patients and conduct laboratory tests such as urine drug screens to monitor for problems arising from the use of prescribed opioids. Prescribers can decide to discontinue opioid therapy or refer patients for treatment if addiction develops. Last, prescribers have control over the quantity of drug dispensed, which could impact the problem of prescription opioid abuse related to too much drug being available in the community.

There is some evidence in the literature[22] that prescriber education is effective, and prescribers who attempt to prescribe around the drugs included the REMS may be in the greatest need of additional information.

To help estimate the impact of a prescriber education program, we attempted to assess how many more prescribers would have to be educated if universal prescriber education were to be implemented.

The DEA provided the following information.[23]

- There are 998,083 practitioners with a degree of MD, DO, DPM, DMD, or DDS.
- Of that number, 1.07% (10,690) do not have Schedule 2 on their registration.

So, hypothetically, the number of prescribers to be educated is large, approximately one million people. DEA was not able to help distinguish the numbers of prescribers certified to prescribe Schedule 2 drugs who choose not to prescribe the LA/ER opioids. To further assess this, an analysis was conducted by SDI Health, a healthcare analytics organization that services the pharmaceutical industry, the federal government and other top healthcare organizations. In the unprojected sample of prescribers in the Vector One: National database, SDI assessed the numbers of unique prescribers prescribing oxycodone, morphine, oxymorphone, and hydromorphone by release characteristics in year 2008. In their analysis, SDI found the following (Table 7).

[22] Marinopoulos SS, Dorman T, Ratanawongsa N, Wilson LM, Ashar BH, Magaziner JL, Miller RG, Thomas PA, Prokopowicz GP, Qayyum R, Bass EB. Effectiveness of Continuing Medical Education. Evidence Report/Technology Assessment No. 149 (Prepared by the Johns Hopkins Evidence-based Practice Center, under Contract No. 290-02-0018.) AHRQ Publication No. 07-E006. Rockville, MD: Agency for Healthcare Research and Quality. January 2007.
[23] Email from Johanna Clifford, M.SC, RN, BSN.

Table 7: Physicians who prescribed oxycodone, morphine, oxymorphone, and hydromorphone, year 2008

Number of Unique Prescribers	N
Physicians who prescribed both IR and ER	174,167
Physicians who prescribed only ER	53,688
Physicians who prescribed only IR	102,169

SDI, Vector One®: National. Prescriber Counts for Opioid Market by Form, Product and Specialty Group Custom Analysis. Year 2008. Extracted 1/10.

SDI found that approximately 227,000 prescribers (174K + 53K) prescribe ER formulations of oxycodone, morphine, and oxymorphone (hydromorphone is not approved as an ER formulation). Thus, given that there are ~1,000,000 prescribers who could prescribe any opioid, the universal prescriber education recommended by this working group would increase the numbers of prescribers requiring prescriber education by a factor of four. On its face, that appears to be a substantial number of additional people to educate and those costs could be high. However, economies of scale would be expected to apply so the costs would not necessarily be four times as high.

Given that this working group is not recommending other measures such as patient education or pharmacy certification, it is unclear whether economic costs would be higher under the REMS proposed on March 3 or if a prescriber-education-only REMS were implemented. A formal cost–benefit analysis is outside the scope of this working group's expertise.

Some comments to the docket suggested that prescriber education would not be enough. However, we believe that the only element of REMS that was proposed on March 3 that had some evidence of effectiveness was prescriber education. Although frequent assessments and continued study of the effectiveness of other REMS elements is critical, prescriber education seems to be a reasonable place to start.

Should a Comprehensive REMS (i.e., all opioids) Take a Tiered Implementation Approach?

We considered that, if all opioids are included, a tiered approach to implementation should be considered. For example, all opioids could be covered in Tier 1 of the REMS, and Tier 1 would include prescriber education. The drugs specified on March 3, 2009, could be subject to additional REMS elements, which might include patient-provider agreements, pharmacy certification, and other elements.

Because a balloon effect is likely, resulting in substitution, undertreatment, and nontreatment, if prescribers are not better educated, the practice of prescribing around the LA/ER opioids is likely to result in higher morbidity and mortality due to inappropriate use of substitutes. We believe that the prescriber is the best single point of control and that modifying prescriber behavior will have the greatest effect on this problem. Thus, universal prescriber education is necessary, regardless of which opioids a prescriber prescribes. Although prescriber education appears to have the most promise to positively affect outcomes, other elements could be added and studied, but only on a subset of opioids. The extra measures should be limited to the drugs specified in the March 3 industry meeting for the following reasons:

- If applied to all opioids, the additional elements would result in substantial additional costs and burdens to physicians and patients. For example, if a prescriber-patient agreement is imposed, that would seem unduly burdensome for a patient who requires a 7-day supply of hydrocodone/APAP following moderate trauma or surgery.
- Similarly, many of the products that are not LA/ER opioids are used short-term and, therefore, the burdens of additional ETASU are not warranted.

Although such a program would most likely result in greater economic costs and burdens to the healthcare system, as well as issues related to access, we believe that prescriber education alone may not be sufficient.

Should a Comprehensive REMS Be Undertaken at this Time?

We considered whether a comprehensive REMS should be postponed, pending further study. The REMS proposed at the March 3, 2009, industry meeting is a program of unprecedented size. Despite our best efforts to mitigate problems and anticipate unintended consequences prior to launch, the economic costs, burdens to the healthcare system, and barriers to access for patients would be expected to be considerable. Furthermore, at this time, the metrics to assess the effectiveness of this program do not appear adequate. On the other hand, the detriment to the public health due to prescription opioid abuse and overdose is also considerable. If we are to assume that the REMS will have some level of effectiveness, postponing activities to mitigate the public health problem of prescription opioid abuse is not a viable option.

CONCLUSION

Assuming that the Opioid REMS includes sufficient elements to have a reasonable chance to mitigate, to at least some extent, prescription opioid overdose, abuse, misuse, and addiction, the scope of the REMS should be expanded to all opioids. The primary rationale for our proposal is that imposition of the REMS on a subset of opioids can be predicted to result in a shift in prescribing to other drugs that may not be appropriate for patients.

Risk Evaluation and Mitigation Strategy for Opioid Analgesics
Final Report of the Prescriber Education Working Group

June 2010[1]

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BACKGROUND

In early 2009, FDA sent letters to manufacturers of certain opioid drug products, indicating that these drugs will be required to have a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drugs continue to outweigh the risks. FDA explained that the REMS would include elements to assure safe use to make certain that prescribers, dispensers, and patients are aware of and understand the risks and appropriate use of these products. FDA also stated that, with limited exceptions, the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires generic and innovator products to use a single shared system to implement the elements to assure safe use. The affected opioid drugs include long-acting and extended-release brand name and generic products and are formulated with the active ingredients fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.

FDA is mindful of provisions in FDAAA that require elements to assure safe use to be, among other things, commensurate with the specific serious risk listed in the labeling of the drug, not unduly burdensome on patient access to the drug, and designed to be compatible with established distribution, procurement, and dispensing systems.

To obtain public input on how best to design a REMS for this class of drugs, FDA held a series of meetings with relevant stakeholders (May 4 and 5, 2009; May 27 and 28, 2009; December 4, 2009) and opened a public docket to receive public comments on relevant issues. Meeting minutes of the May 4 and 5 stakeholder meetings, and transcripts of the May 27 and 28, and

[1] The WG formulated its recommendations in January 2010; this report has been finalized in preparation for the July 2010 Advisory Committee meeting.

December 4 meetings are in the docket and on FDA's Web site.[2] FDA plans to provide an additional opportunity for public input before finalizing the elements of the REMS.

Following the meetings, FDA formed an Opioid REMS Steering Committee, a multidisciplinary team from throughout the Center for Drug Evaluation and Research. To thoroughly analyze the substantial public and stakeholder input received on the development of the REMS and to conduct additional research, the Steering Committee formed seven[3] work groups to focus on the various aspects of an opioid REMS and the effects of possible components of the REMS on use.

Following their analysis, the work groups were asked to provide recommendations to the Steering Committee for consideration as it develops options for what should be included in the REMS. The seven work groups addressed the following areas:

- Scope of an opioid REMS
- Prescriber education
- Pharmacist education
- Patient education
- Pharmacy systems
- Effect of possible restrictions on patient access to pain medication
- Metrics

This is the report and recommendations from the Prescriber Education Working Group .

GOAL OF THE PRESCRIBER EDUCATION WORKING GROUP

The Prescriber Education Working Group (WG) was charged with evaluating issues related to requiring prescriber education as part of a REMS for long-acting (LA) and extended-release (ER) opioid brand name and generic products. The WG reviewed published literature, the content of continuing medical education (CME) programs, and comments submitted to the docket following FDA public meetings on opioid drugs.

The recognition that prescribers should be better educated in this area was a common theme in the comments submitted to FDA's public docket on the opioid REMS. Along with recommending that prescriber education be included in the opioid REMS, some stakeholders made recommendations about the content of prescriber education, who should conduct the educational program, and who should design the program. The Prescriber Education WG used this information along with the available research literature and teleconferences with relevant stakeholders, to develop its recommendations regarding inclusion of a prescriber education component of the proposed risk evaluation and mitigation strategy (REMS) for opioid products.

The discussion that follows focuses on the following questions:

- Is prescriber education needed to help ensure safe use?
- Should prescriber education be mandatory or voluntary?

[2] See http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm.
[3] In addition, an eighth working group was created to handle external communications about the REMS. That working group was not involved in the review of comments and did not create a report.

- What are the burdens to the healthcare system, and how can they be offset?
- What is needed to implement a prescriber education program (program operations)?
- What should the program look like (program characteristics)?

SUMMARY OF RECOMMENDATIONS

The WG makes the following recommendations:

- The proposed opioid REMS should include mandatory, FDA-endorsed training for prescribers of outpatient opioids, with potential exemptions of certain prescribers. Mandatory education would require that healthcare professionals who want to prescribe opioids (and who have fulfilled all federal and any state requirements) obtain specific training before being able to prescribe opioids. Other options, such as providing training incentives, should be considered.
- Resources should be focused on prescribers who have not had adequate training in chronic pain management and use of opioids and prescribers with certain qualifications, such as board-certification in sub-specialties like analgesia, hospice and palliative care, and pain management, should be exempt from training.
- Prescribers should be exempted who exclusively prescribe to inpatients, so that risk management activities can be focused on outpatient settings, where there is less oversight to ensure patient safety.
- FDA should develop high-level learning objectives and provide final approval of the educational content and training platform; the details of the educational content and the training platform should be developed by experts outside of the pharmaceutical industry.
- The goal of the educational program should be to not only ensure that prescribers are educated about the safe use of opioids, but also to ensure that this education leads to improved patient outcomes and population health.

SUMMARY OF ISSUES / CONCERNS

The WG believes that mandatory prescriber education is an essential part of a comprehensive, multifaceted approach for preventing adverse outcomes resulting from inappropriate prescribing and misuse and abuse of pain medications while potentially improving patient access to quality pain care. Requiring prescriber education, however, despite its obvious benefits, raises a myriad of issues that need to be considered, including determining what prescribers need to be taught, and how to effectively teach it. There is limited evidence to associate specific prescriber behaviors with reduced abuse and misuse among their patients being treated with opioids. Additionally, evidence for the effectiveness of continuing medical education in changing prescriber behaviors is limited. Questions also arise about who would develop the training.

The WG considered issues related to the additional burdens on the healthcare system that would be created by mandatory training. For example, the WG considered the burdens related to the time and effort it would take to implement a mandatory education program, especially if

verification of training is required, as well as burdens on prescribers to meet the requirements of mandatory training. Of special concern to the WG is the possibility that mandating prescriber education could result in patients experiencing difficulties obtaining their pain medications.

DETAILED DISCUSSION OF SPECIFIC ISSUES

The opioid REMS provides an opportunity to address two important public health needs: improved access to quality care for chronic pain patients and reduced prescription opioid morbidity and mortality. Chronic pain is a complex and widespread medical condition, requiring significant resources and clinical skills to manage effectively. Opioid analgesics are an essential tool in managing chronic pain, but they are also associated with serious adverse outcomes including abuse, addiction, and fatal overdose. Prescribers have a critical role to play in preventing these serious adverse outcomes, yet they often lack the specialized training needed to ensure safe use of these products.

The need for prescriber training was a common theme in comments submitted to the docket, and has also been described in the literature. For example, a recently published study collected information from drug abusers, drug dealers, and law enforcement officials to identify the primary sources for prescription drugs. Investigators found that physicians are often inadvertently serving as a source for abused prescription opioids.[4] Based on these findings, the investigators concluded there is a need to educate prescribers about substance abuse, including how to recognize a patient that is misusing their prescribed medication, how to assess a patient's risk for opioid misuse before starting therapy, and understanding the variation in the abuse potential of different opioid drugs. Incorporating a prescriber education program into the opioid REMS has the potential to close these knowledge gaps.

Although, special attention needs to be given to ensuring that the program is not so burdensome that prescribers opt-out thereby reducing patient access to opioid therapy. Exempting certain prescribers will help reduce the burden on the healthcare system by minimizing training redundancy for those who are adequately trained. Additionally, limiting the training requirement to the outpatient setting should focus the risk management activities to settings where there is less oversight to ensure patient safety.

Developing an effective opioid training program requires a sound understanding of the problem at the system, practice, practitioner, and patient levels, as well as a toolbox of evidence-based interventions. As described previously, we have some insight into existing gaps in prescriber knowledge, but there is a lack of consensus about how to safely prescribe opioids. This is exemplified by variations in patterns of opioid analgesic use and pain treatment, including regional differences and potential ethnic disparities.[5] Although clinical practice guidelines

[4] Inciardi JA, Surratt HL, Cicero TJ, Beard RA. Prescription opioid abuse and diversion in an urban community: the results of an *ultra*-rapid assessment. *Pain Med*; 2009: 10: 537-548.
[5] Olsen Y, Daumit GL, Ford DE. Opioid Prescriptions by U.S. Primary Care Physicians From 1992 to 2001. *The Journal of Pain;* 2006:7:4: 225-235.

related to the safe use of opioids have been developed, there is little evidence to suggest the existing guidelines contribute to greater patient safety and/or a reduction in harm.[6]

Even if we knew exactly what to teach prescribers to improve health outcomes, the WG considered concerns about the current CME/CE system's ability to effectively teach it. CME/CE activities are essential tools for healthcare practitioners to fulfill their commitment to lifelong learning and professional competence. However, recent evaluations of CME's effectiveness in changing behavior and improving health outcomes were often equivocal.[7, 8] Additionally, a December 2009 report from the Institute of Medicine states that, "There are major flaws in the way CE is conducted, financed, regulated, and evaluated." These rigorous evaluations, however, have also included recommendations and a proposed framework for improving the effectiveness of CME/CE, both at the macro- and micro-level.

Despite these issues, opioid-related adverse events remain a major public health concern that requires action. The science must continue to be strengthened, and new strategies for safe and effective care must be developed. A short-term strategy for prescriber education must be identified as well as a research agenda for the continual improvement in the curriculum and educational platform. A baseline should be created from which to begin understanding how different care models and training interventions affect patient outcomes and provide a foundation for the development of best practices related to improved patient outcomes. Additionally, an initiative to incorporate these strategies into postgraduate medical and residency training should be part of the long-term strategy.

Finally, the importance of a collaborative response to this issue was noted in many of the comments submitted to the opioid REMS docket. A collaborative response will help reduce redundant educational activities and requirements by aligning objectives with specialty boards, professional societies, and other organizations that require similar training in safe opioid prescribing. Collaboration will also help leverage the multiple perspectives and breadth of expertise of the varied stakeholders.

Should Training Be Mandatory or Voluntary?

The WG discussed the implications of mandatory versus voluntary training. In the short term, voluntary training offers some benefits. It would be less burdensome for healthcare practitioners and the healthcare system as a whole. There would be no need to verify that training had occurred, so a tracking system would not be required. Voluntary training could help ensure that prescribers who want training can get it while allowing prescribers with prior training to opt out of this additional training with no impact to their ability to prescribe. Since

[6] Chou R, Ballantyne JC, Fanciullo GJ, Fine PG, Miakowski C. Research Gaps on Use of Opioids for Chronic Noncancer Pain: Findings From a Review of the Evidence for an American Pain Society and American Academy of Pain Medicine Clinical Practice Guideline. *The Journal of Pain*; 2009:10:2:147-159.
[7] Moores LK, Dellert E, Baumann MH, Rosen MJ. Executive summary: effectiveness of continuing medical education: American College of Chest Physicians evidence-based educational guidelines. *Chest*; 2009: 135: 1S-4S.
[8] Institute of Medicine. (December 2009) *Report brief: redesigning continuing education in the health professions.* http://www.iom.edu/~/media/Files/Report%20Files/2009/Redesigning-Continuing-Education-in-the-Health-Professions/RedesigningCEreportbrief.ashx.

training would not be a barrier to prescribing, it would not adversely affect patients' access to medication.

However, implementing a voluntary training program would essentially be preserving the current system, a system that has not been effective. An opioid REMS without a mandatory education component would make it possible for untrained or inadequately trained prescribers to continue to prescribe opioids. Many practitioners never receive appropriate training in prescribing these products. Other practitioners received training so long ago (e.g., during medical school) that the training may no longer be relevant, especially for prescribing extended-release formulations. Unless another method for ensuring proper prescribing and effective patient monitoring (e.g., decision support or performance-feedback systems, clinic information order sets, disease management programs) is included in the opioid REMS, it is hard to see how a REMS with only a voluntary training would provide any value beyond the status quo.

Universal prescriber education would help address the increased demand for effective chronic pain management and increase the number of physicians with the training necessary for the safe and effective prescribing of opioid analgesics. We recommend a standardized curriculum to ensure that all prescribers have a minimum level of training. Additionally, a standardized curriculum might help reduce variability in opioid prescribing practices and training across medical specialties.

Will Mandatory Training Be Too Burdensome?

The WG discussed the potential burdens a mandatory prescriber education program would impose on our healthcare system, and discussed options for minimizing those burdens. Specific issues and concerns are discussed in the following paragraphs.

- Mandatory training could be too burdensome for prescribers to complete.

If prescribers perceive the training as too burdensome, they may opt out of prescribing the opioids that are included in the REMS, a decision that could negatively affect patient access to these medications. One approach to minimizing the burden could be to provide on-line, self-paced training. This would facilitate access for prescribers (particularly those in isolated areas of the country) and help prescribers fit training into their busy, often unpredictable, schedules.

Providing incentives, such as malpractice insurance credits or continuing medical education (CME)/continuing education (CE) credits may be another way to mitigate the perceived burden of a training requirement (see *Incentives*). Many of the prescribers who have assumed the responsibility for addressing the unmet need for pain treatment (such as primary care and family physicians) are already reported to be facing significant challenges in managing these time intensive chronic pain cases, often with little financial or intrinsic reward. The training itself may be an incentive if it provided strategies for prescribers to efficiently and effectively manage these very complex patients.

- Mandatory training could be too burdensome to implement.

If mandatory training is a requirement to prescribe opioid analgesics, a system would need to be developed to capture prescribers' training status. Additionally, pharmacists would need to be

trained on how to access this system and would need to verify that a prescriber has been trained prior to dispensing. Such a system would require significant resources up front to implement; however, long-term benefits may be realized by leveraging this system for use with other opioid and non-opioid REMS programs.

An option for reducing the implementation burden would be through the use and possible enhancement of existing prescribing-related systems (see *Implementation of a Training Verification System*). For example, training could be tied to and verified through DEA registration or through the American Board of Medical Specialties database. If pharmacies were required to verify training before dispensing, the verification step could be incorporated into the pharmacy workflow. For example, in most cases, billing transactions are automatically routed through switch companies, which then route the transaction to the appropriate payer. These existing data channels could be used to access and verify prescriber training data, thereby minimizing the burden to the pharmacist. Finally, at the time the WG convened, electronic prescriptions for Schedule II opioids were not an option for prescribers. However, with the implementation of Drug Enforcement Administration's (DEA) final rule on "Electronic Prescriptions for Controlled Substances," it has since become an option. Enabling prescribers to submit prescriptions electronically has the potential of reducing the implementation burden, as improper opioid prescribing could be stopped at point of care.

Program Operations and Implementation

- Who Should Develop the Content?

The WG discussed who should develop the content of the prescriber opioid training. An industry working group, or other multi-sponsor collaboration, could develop the content since they have the resources and a vested interest in the subject. However, multiple stakeholders who submitted comments to the opioid REMS docket expressed concerns about industry funding and/or developing educational programs because of potential conflicts of interest. Another option is for FDA to develop the content. This approach would give FDA primary control over the information. However, FDA currently does not have the necessary resources. Finally, an expert panel, including representatives from specialty boards, medical societies, academia, FDA, and other relevant government agencies could collaborate to develop an educational program. This scenario would provide the broadest perspective and assembly of expertise and would be acceptable to the majority of stakeholders. However, it is not clear who would pay for the panel's time and expertise.

- Implementation of a Training Verification System

To verify that a prescriber has been adequately trained on the safe use of opioids, documentation of this training must be captured. It is not clear how this information will be stored and accessed, or who will have access to it. However, it is clear that to minimize the burden on the healthcare system, all products in the REMS should be captured in a single system. Several options were discussed.

  - DEA Registration System

The current DEA registration process could be changed to make education on the safe use of opioids a requirement for obtaining (or maintaining) a DEA number for prescribing Schedule

II products. This approach has several efficiencies, including leveraging an existing data capture system, leveraging an existing registration requirement for prescribers, and leveraging a standard process in the pharmacy workflow (verifying DEA registration). However, implementation of this approach may not be feasible in the short term, as additional legislation may be required.

- Federation of State Medical Boards (FSMB)

According to their Website, FSMB represents the 70 medical boards in the United States and its territories. This existing network and infrastructure could provide a foundation for the support, delivery, and documentation of prescriber training.

- Centralized Accredited CME/CE Provider

There are multiple accredited CME providers who sponsor online training (e.g., MedScape CME, medical specialty societies, and academic institutions). Many of these organizations also provide customers with centralized, web-based tracking of completed CME/CE activities. FDA could work with one or more of these continuing education organizations to adopt and/or help develop a REMS prescriber education program and to enable electronic access to information in their tracking databases for training verification (possibly through existing data channels in the standard pharmacy workflow).

- Sponsor-Developed Centralized Database

An alternative to using a pre-existing, centralized database (as described above) would be to require sponsors to work together to develop a centralized database to document prescriber training. This database could be accessed directly or through existing data channels in the pharmacy workflow (i.e., claims processing and the use of switch companies).

- Incentives

As discussed previously, use of an incentive or combination of incentives would be important to offset the perceived burden of mandatory training and to help encourage prescribers to participate in the REMS. The WG considered a number of options to encourage prescriber participation. The following incentives were discussed:

- Discounts on DEA Registrations and Registration Renewals

Prescribers are required to register with the Drug Enforcement Agency (DEA) to prescribe opioids and other schedule II medications. Registration costs more than $500, and must be renewed every three years. This fee is often paid by the prescriber. To encourage practitioners to participate in the REMS, the DEA might consider providing a discount on registrations/renewals to prescribers who have completed the REMS required training (this recommendation was proposed by several stakeholders). Linking training to DEA registration could also facilitate implementation of a mandatory training program, as training could be documented and validated through the DEA registration system (see *Implementation of a Training Verification System*).

- CME/CE Credits

CME and CE credits are currently required to maintain medical licensure. Sixty-two state boards require CME for license re-registration.[9] Among these state boards, five require (CA, MI, OR, RI, WV) and four encourage (FL, NM, OH, TX) prescribers to obtain CME credits in areas such as pain management, treatment of terminally ill patients, and end-of-life care.[10] A number of organizations, including the Federation of State Medical Boards (FSMB), offer CME accredited training in these areas. However, if a preexisting, accredited program were used, as suggested in several submissions to the docket, it is unclear if FDA could have influence over the content.

The WG reviewed multiple training programs, from a variety of public and private sources, and found that many contained information that was not evidence-based or supported by product labeling. Therefore, the WG concluded that it would be important for FDA to have some control over training content. It may, however, be possible to seek CME accreditation for a program that is developed to FDA specifications.

- Performance-Based Incentives

Healthcare practitioners are already challenged to find enough time to spend with their individual patients, so it is not hard to imagine the challenges they face finding time to invest in CME. Current CME, with all of its deficiencies, provides few incentives for practitioners to invest their time or money, other than to fulfill state licensure requirements. If, as Campbell and Rosenthal[11] point out in a recent commentary, practitioners faced meaningful economic incentives for practicing high-quality, efficient medicine, they may be encouraged to participate in educational activities and make practice improvements that support these objectives. In the case of opioid prescribing, practitioners who invest in training or reorganize their practices to ensure adequate patient counseling and effective patient management could be eligible for financial rewards. Incentives linked to optimized-performance and improved patient outcomes could be reinforced through payment systems at the institutional level (e.g., hospital) or through liability insurers that offer performance-linked reductions in premiums or premium credits to physicians who demonstrate an investment in improving patient outcomes. This may also "put new demands" on the quality of CME offerings.

Discussion of Program Details

- Scope of Training Content/Learning Objectives

The WG discussed the scope of the content of the prescriber training materials. The challenges of developing a training intervention in an area where the causes of the problem are not fully understood and the evidence-base for effectively dealing with the problem is limited have already been discussed. Additionally, it will depend on what the goals of the REMS are and how they are interpreted; an educational intervention designed to ensure safe prescribing of opioids

[9] *State Medical Licensure Requirements and Statistics 2010*. American Medical Association Press (November 2009).

[10] Pain and Policy Study Group. *State continuing education policies for pain and palliative care*. http://www.painpolicy.wisc.edu/domestic/cme.htm.

[11] Campbell EG, Rosenthal M. Reform of continuing medical education. Investments in human capital. *JAMA.* 2009; 302 (16): 1807-1808.

would have much different requirements than an intervention that was expected to improve the ongoing management of patients using opioids. If the products that are ultimately included in the REMS are limited to the originally proposed, extended release formulations, training content could be limited to these products. This would keep the training more focused and potentially shorter. Basic information is available about opioids and about the management of patients taking opioids which would be important for prescribing any opioid, including short-acting, long-acting, and extended release formulations. Therefore, a general overview of opioid prescribing with a special section on LA opioids may be more appropriate. This could, however, unnecessarily lengthen the training and dilute the messages (see *Training Length*).

- Training Characteristics

Although there is variability in terminology across studies, discussions of training characteristics or *instructional design* typically involve discussions of the instructional media (e.g., live, online), instructional technique (e.g., interactive, didactic), and frequency of exposure. Past studies have found that traditional CME, delivered through lectures and printed materials, has little to no effect on physician behavior or the health outcomes of their patients.[12,13,14,15,16] Therefore, the stakeholders and the WG recommend that the REMS prescriber training be designed to exceed the goal of traditional CME methods (knowledge acquisition) and instead aim to demonstrate optimized practitioner performance and improved patient outcomes. Although it is clear that much remains to be learned about effective CME, an important foundation has been laid, and the field is rapidly changing. FDA can leverage what has been learned to date and continue to incorporate the best evidence as it becomes available. Recent reviews of CME's effectiveness have shown that some methods appear to be more effective than others.[17] The following are examples of training techniques and delivery methods that have shown evidence of effectiveness:

- Interactive Teaching Methods

Interactive Teaching Methods include group case discussions, role-playing, simulations, and hands-on practice sessions. Interactive methods have been shown to be more successful than traditional methods, and are among the most effective ways to improve physician

[12] Marinopoulos SS, Dorman T, Ratanawongsa N, Wilson LM, Ashar BH, Magaziner JL, Miller RG, Thomas PA, Prokopowicz GP, Qayyum R, Bass EB**.** Effectiveness of Continuing Medical Education. Evidence Report/Technology Assessment No. 149 (Prepared by the Johns Hopkins Evidence-based Practice Center, under Contract No. 290-02-0018.) AHRQ Publication No. 07-E006. Rockville, MD: Agency for Healthcare Research and Quality. January 2007**.**

[13] Bloom BS. Effects of continuing medical education on improving physician clinical care and patient health: a review of systematic reviews. *Int J Technol Assess Health Care*. 2005;21(3):380-5.

[14] Smith WR. Evidence for the effectiveness of techniques to change physician behavior. *Chest*. 2000;118(2 Suppl):8S-17S.

[15] Davis D, O'Brien MA, Freemantle N, et al. Impact of formal continuing medical education: do conferences, workshops, rounds, and other traditional continuing education activities change physician behavior or health care outcomes? *JAMA*. 1999;282(9):867-74.

[16] Browner WS, Baron RB, Solkowitz S, Adler LJ, Gullion DS. Physician management of hypercholesterolemia. A randomized trial of continuing medical education. *West J Med.* 1994;161(6):572–578.

behavior and patient outcomes.[10,12] Unfortunately, many of the methods used in interactive education are resource-intensive and can be difficult to reproduce on a large scale.

- Audit and Feedback

Audit and feedback is a method that evaluates a healthcare practitioner's performance against an established standard and reports the results of the evaluation to the practitioner. This method can be used both to reinforce lessons learned and enhance their application in clinical practice. Evidence is mixed with regard to *audit and feedback's* effectiveness, some finding it to have a small to moderate impact,[18] and others finding it to be one of the most effective forms of education.[19] More intensive applications of audit and feedback tend to be more effective, particularly when physician compliance with a recommended practice is already low, but more research is still needed to determine which forms of this method work best, and in which situations.

- Multiple sessions and multiple exposures to the material

Recent reviews of CME studies recommend more than one exposure to a topic for the most effective educational outcome.[20,21,22] Educational programs that involve multiple sessions, over a period of time are more effective than single-session programs, possibly because they allow reinforcement of the training, offer physicians the opportunity to practice what they have learned, and bring relevant experience into the next learning session.[23] Another option for reinforcing the training is through study groups, list-serves, and teleconferences.

- Online Education

Online CME has the potential to provide healthcare practitioners with increasingly interactive and clinically relevant training experiences. Online educational activities are self-directed and can be tailored to a practitioner's demanding schedule and individual learning needs. A number of recent studies have found that online CME programs can yield increases in physician knowledge comparable to those found in similar face-to-face

[18] Smith WR. Evidence for the effectiveness of techniques to change physician behavior. *Chest*. 2000;118(2 Suppl):8S-17S.

[19] Bloom BS. Effects of continuing medical education on improving physician clinical care and patient health: a review of systematic reviews. *Int J Technol Assess Health Care*. 2005;21(3):380-5.

[20] Davis DA, Thomson MA, Oxman AD, Haynes RB. Changing physician performance. A systematic review of the effect of continuing medical education strategies. *JAMA*. 1995;274(9):700-5.

[21] Marinopoulos SS, Dorman T, and Ratanawongsa N, et al. Effectiveness of Continuing Medical Education. Evidence Report/Technology Assessment No. 149 (Prepared by the Johns Hopkins Evidence-based Practice Center, under Contract No. 290-02-0018.) AHRQ Publication No. 07-E006. Rockville, MD: Agency for Healthcare Research and Quality. January 2007; see also Moores LK, Dellert E, Baumann MH, Rosen MJ. Executive summary: effectiveness of continuing medical education: American College of Chest Physicians evidence-based educational guidelines. Chest; 2009: 135: 1S-4S.

[22] Moores LK, Dellert E, Baumann MH, Rosen MJ. Executive summary: effectiveness of continuing medical education: American College of Chest Physicians evidence-based educational guidelines. *Chest*; 2009: 135: 1S-4S.

[23] Davis D, O'Brien MA, Freemantle N, et al. Impact of formal continuing medical education: do conferences, workshops, rounds, and other traditional continuing education activities change physician behavior or health care outcomes? *JAMA*. 1999;282(9):867-74.

programs .[24,25,26] Unfortunately, there remain few high-quality evaluations of its effectiveness in affecting outcomes. More research is needed to determine how online education affects practitioner behavior and patient outcomes, and which forms of online education are most effective. Additionally, prescribers based in rural communities may lack sufficient electronic resources.

- Outreach and Academic Detailing

Academic *detailing* involves one-on-one educational outreach visits to prescribers, usually by other physicians or pharmacists. It is similar to a technique that many pharmaceutical companies use to promote their products, and has proven to be an effective educational technique in many controlled trials.[27,28,29]

- Combining Multiple Education Methods

Combinations of multiple educational delivery methods (such as a lecture with small-group sessions) are more likely to positively affect physician behavior and patient outcomes. Not surprisingly, combinations of the most effective educational delivery methods will have the greatest impact, but even delivery methods that are ordinarily ineffective may have an impact when combined with more effective methods.[30,31] For example, many programs will use interactive components to reinforce lessons learned in lectures.

- Pre- and Post-testing

Inclusion of a pre- test can help determine practitioner baseline understanding of the concepts to be presented. Inclusion of a post-test has intrinsic value as an incentive to pay attention. Comparison of pre- and post-test scores provides an assessment of the most basic measure of training effectiveness, knowledge acquisition. Although inclusion of a pre- and/or post-test potentially adds more time to the training activity, pre-testing facilitates needs-based customization of the training. If the training activity were customized to individual prescribers' learning needs, the overall training time could potentially be reduced, making it worth the extra time investment up front.

- Other Enabling Elements

Educational programs are more effective when they include *enabling elements*, or tools that reinforce the learning objectives and enable physicians to incorporate what they have

[24] Ryan G, Lyon P, Kumar K, et al. Online CME: an effective alternative to face-to-face delivery. *Med Teach*. 2007;29(8):e251-7.
[25] Fordis M, King JE, Ballantyne CM, et al. Comparison of the Instructional Efficacy of Internet-Based CME With Live Interactive CME Workshops: A Randomized Controlled Trial. *JAMA*. 2005;294(9):1043-1051.
[26] Jr JMH, Elliott TE, Davis BE, et al. Educating Generalist Physicians about Chronic Pain: Live Experts and Online Education Can Provide Durable Benefits. *Pain Medicine*. 2008;9(5):555-563.
[27] Bloom BS. Effects of continuing medical education on improving physician clinical care and patient health: a review of systematic reviews. *Int J Technol Assess Health Care*. 2005;21(3):380-5.
[28] Smith WR. Evidence for the effectiveness of techniques to change physician behavior. *Chest*. 2000;118(2 Suppl):8S-17S.
[29] Avorn J, Soumerai S. Improving drug-therapy decisions through educational outreach. A randomized controlled trial of academically based "detailing." *N Engl J Med*. 1983;308(24):1457-1463.
[30] Davis DA, Thomson MA, Oxman AD, Haynes RB. Changing physician performance. A systematic review of the effect of continuing medical education strategies. *JAMA*. 1995;274(9):700-5.
[31] Bloom BS. Effects of continuing medical education on improving physician clinical care and patient health: a review of systematic reviews. *Int J Technol Assess Health Care*. 2005;21(3):380-5.

learned into their practice. Examples of tools include checklists, patient counseling and education materials, automated reminder systems, and decision-support systems.[32]

In general, the most effective CME programs incorporate a diversified approach to education, using a combination of multimedia (e.g., video, print); multiple, preferably interactive, instructional techniques (e.g. simulations, case-based learning, audit/feedback); and multiple exposures to the topic areas (e.g., metered re-training, practice study groups, list-serves, teleconferences).

- Training Length

The length of the training would be driven in large part by the learning objectives and associated content. The main concern is that the longer the program, the more likely that it will be seen as a burden, which increases the risk of prescribers opting out of prescribing opioid products that are included in the REMS. The length of existing pain management/opioid prescribing programs varies considerably; those reviewed by the WG ranged in length from a one-hour, online training program to a two-day training program provided at a professional conference. Unfortunately, there are no data to determine the optimal balance between content and length. Some experts and stakeholders say that training should not be more than an hour, as most people can only focus their attention for that length time. This would help ensure that the focus of the program is concentrated on the most important information. MedScape, a commercial CME provider, informed us that they are aiming to keep their courses to between 30-60 minutes. However, the WG believes that concerns about length should not override decisions about content; a well-designed program can be effective, regardless of its length.

One option considered was developing a training course that is broken into multiple 30- to 60-minute modules. Such an approach would allow for more information to be covered, break the training into smaller blocks of time, and provide flexibility for prescribers to fit training into busy clinical schedules. Additionally, the modular approach would make a flexible design possible, so that some modules could be mandatory and others voluntary. For example, a considerable amount of information important for the safe use of opioids is considered part of the practice of medicine, an area FDA does not regulate. This type of content could be made voluntary, but still easily accessible. Such flexibility could also facilitate creation of a tiered REMS, with training stratified by the type of opioid being prescribed (e.g., immediate release vs. extended release) and facilitate exemption of certain prescribers/healthcare settings from certain modules. As discussed previously, the use of modules could facilitate a performance-linked training system, where the content/modules that are presented are linked to a prescriber's performance on a pre-test.

- Who Would Deliver the Training?

The question of who would deliver the training has not been discussed in depth by the WG, except to say that it should not be delivered by sales representatives or any other industry

[32] Davis D, O'Brien MA, Freemantle N, et al. Impact of formal continuing medical education: do conferences, workshops, rounds, and other traditional continuing education activities change physician behavior or health care outcomes? *JAMA*. 1999;282(9):867-74.

representative. The identification and use of key opinion leaders may improve acceptance and subsequent implementation of the concepts presented.

CONCLUSIONS

The opioid REMS provides an opportunity to address two important public health needs — improved access to quality care for chronic pain patients, and reduced prescription opioid morbidity and mortality. Through the inclusion of a mandatory education program in the opioid REMS, prescribers can be trained on the safe use of opioids in the management of chronic pain and informed about how to manage patients with potential abuse problems, thereby minimizing the risk of serious adverse events.

A mandatory prescriber education program, if effectively designed and implemented, has the potential to improve prescribers' knowledge, change prescriber behavior, and reduce adverse patient outcomes. Prescriber education is an essential part of a comprehensive, multifaceted approach to helping improve chronic pain management while preventing the abuse and misuse of pain medications.

Risk Evaluation and Mitigation Strategy for Opioid Analgesics
Final Report of the Pharmacy Systems Working Group

June 2010[1]

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BACKGROUND

In early 2009, FDA sent letters to manufacturers of certain opioid drug products, indicating that these drugs will be required to have a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drugs continue to outweigh the risks. FDA explained that the REMS would include elements to assure safe use to make certain that prescribers, dispensers, and patients are aware of and understand the risks and appropriate use of these products. FDA also stated that, with limited exceptions, the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires generic and innovator products to use a single shared system to implement the elements to assure safe use. The affected opioid drugs include long-acting and extended-release brand name and generic products and are formulated with the active ingredients fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.

FDA is mindful of provisions in FDAAA that require elements to assure safe use to be, among other things, commensurate with the specific serious risk listed in the labeling of the drug, not unduly burdensome on patient access to the drug, and designed to be compatible with established distribution, procurement, and dispensing systems.

To obtain public input on how best to design a REMS for this class of drugs, FDA held a series of meetings with relevant stakeholders (May 4 and 5, 2009; May 27 and 28, 2009; December 4, 2009) and opened a public docket to receive public comments on relevant issues. Meeting minutes of the May 4 and 5 stakeholder meetings, and transcripts of the May 27 and 28, and December 4 meetings are in the docket and on FDA's Web site.[2] FDA plans to provide an additional opportunity for public input before finalizing the elements of the REMS.

Following the meetings, FDA formed an Opioid REMS Steering Committee, a multidisciplinary team from throughout the Center for Drug Evaluation and Research. To thoroughly analyze the substantial public and stakeholder input received on the development of the REMS and to conduct additional research,

[1] The WG formulated its recommendations in January 2010; this report has been finalized in preparation for the July 2010 Advisory Committee meeting.
[2] See http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm.

the Steering Committee formed seven[3] work groups to focus on the various aspects of an opioid REMS and the effects of possible components of the REMS on use.

Following their analysis, the work groups were asked to provide recommendations to the Steering Committee for consideration as it develops options for what should be included in the REMS. The seven work groups addressed the following areas:

- Scope of an opioid REMS
- Prescriber education
- Pharmacist education
- Patient education
- Pharmacy systems
- Effect of possible restrictions on patient access to pain medication
- Metrics

This is the report and recommendations from the Pharmacy Systems Working Group.

GOAL OF THE WORKING GROUP

The Pharmacy Systems Working group (WG) was charged with evaluating how best to verify and track possible elements of an opioid REMS. The WG looked primarily at verification of prescriber education/certification. The WG considered a number of options, including a system similar to those being used to support existing REMS, adapting the Drug Enforcement Administration's (DEA's) system, and adapting existing retail pharmacy systems.

SUMMARY OF RECOMMENDATIONS

The WG recommends that FDA ask relevant sponsors to develop a system that works within the existing retail pharmacy system to verify prescriber education/certification prior to dispensing of drugs. The system should:

- Be compatible with existing pharmacy practice management systems used to facilitate and coordinate the routine activities of the pharmacist
- Contain "hard stops" to ensure that patients cannot inadvertently be dispensed drugs that are prescribed by non-certified prescribers; and
- Incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate

SUMMARY OF ISSUES / CONCERNS

After considering a number of issues, the WG recommends a sponsor-developed system that would be compatible with our current regulatory authority; could be easily adapted to meet FDA needs; would be supported by many stakeholders in the pharmacy setting, including APhA and NACDS; and could incorporate the use of hard stops. However, the WG recognizes such a system could be costly for sponsors to implement and would cover only the drugs made by relevant sponsors.

[3] In addition, an eighth working group was created to handle external communications about the REMS. That working group was not involved in the review of comments and did not create a report.

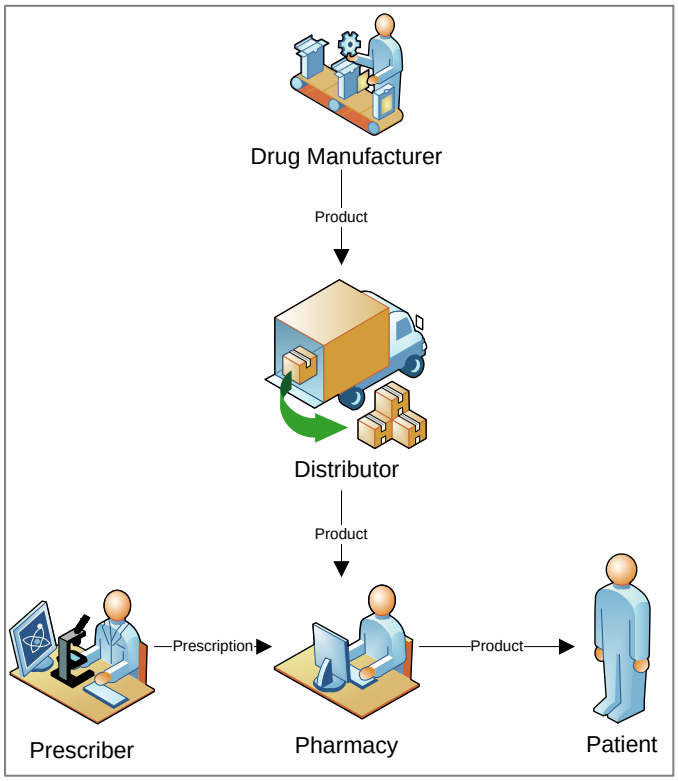
The WG recommends against the proposal that the existing DEA prescriber and pharmacy registration system for prescribers that prescribe and pharmacies that dispense controlled substances be adapted and used to verify prescriber education/certification. Changes to the DEA system, if needed, would be time-consuming and difficult to implement because legislation and regulations would be necessary, and the existing system has limitations such as no real-time verification of valid registration. In addition, the DEA system is limited to controlled substances and could not be adapted for use with non-controlled substances that might need REMS, and it is viewed as a law enforcement system, not a public health system because it is implemented by the DEA. Finally, using the DEA system would limit FDA's flexibility to make changes to the REMS should they prove necessary.

A well-designed sponsor-developed system would be effective in minimizing the burden on the healthcare system, could be implemented in a shorter timeframe, and would require no additional legislation.

DETAILED DISCUSSION OF THE SPECIFIC ISSUES

The Retail Pharmacy System

The diagram to the right illustrates the conventional retail pharmacy system that is currently used in the distribution, procurement, and dispensing of most long-acting and sustained-release opioids.



Manufacturers and Distributors

Drug manufacturers rarely ship their drugs directly to pharmacies, prescribers, or patients. Instead, they ship the products to wholesale distributors, who then resell the drugs to third parties, including pharmacies, chain drug store distribution centers, and secondary wholesalers.

Because opioids are controlled substances, distributors are required to report their purchases and sales of these drugs to the DEA on a quarterly basis, and may only distribute the drugs to DEA-registered pharmacies.

The majority of distributors and manufacturers exchange purchase and sales information in a standard format, known as Electronic Data Interchange (EDI).[4] By using the EDI data standard for transactions, distributors and manufacturers can easily share sales information. In addition, several third-party vendors purchase this drug sales data from distributors. Since the drug sales data are exchanged in a

[4] Center for Healthcare Supply Chain Research. *2009-2010 HDMA Factbook*. 2009.

standardized format, vendors are able to aggregate the data and resell it to those who wish to use it for marketing or research purposes. In the past, manufacturers who must implement REMS have been able to use this information to assist in REMS enforcement.

Prescribers and Pharmacies

In most cases, retail pharmacies obtain their ER/LA opioids from distributors: either healthcare wholesalers or chain drug distribution centers.

In their day-to-day practice, retail pharmacists rely heavily on their pharmacy practice management systems. These are the computer systems that pharmacists use to enter patient and prescription data, file claims with insurers, identify potential drug-drug interactions in their patients, and receive e-prescriptions. Pharmacy management systems communicate with insurers, prescribers, and each other using well-defined telecommunications standards established by standards-setting organizations such as the National Council for Prescription Drug Programs (NCPDP) and the American Society for Automation in Pharmacy (ASAP).

Pharmacy practice management systems are particularly important in electronic prescription drug claims adjudication. Once a pharmacy receives a patient's prescription and information system, the information is sent to a pharmacy "switch." The switch acts as a virtual "post-office" for claims data, routing the claim to the appropriate insurer. The insurer then can inspect the claim and send claim payment data back to the pharmacist. This transaction takes only seconds, allowing pharmacies and patients to know whether or not their insurer will pay for a claim as soon as the patient arrives to pick up his or her prescription.

Another key role of the pharmacy practice management system is verifying the validity of a prescriber's DEA number. Since opioids are controlled substances, pharmacists may only fill prescriptions written by prescribers with valid DEA numbers. Pharmacists usually check the validity of the DEA number through a simple mathematical algorithm: First they add the 1st, 3rd, and 5th digit of the DEA number. Then they add the 2nd, 4th, and 6th digits of the number and multiply it by two. Finally, they add these two sums together. If the DEA number is valid, the rightmost digit of this sum will equal the 7th digit of the prescriber's DEA number. While this calculation is somewhat difficult to perform by hand, pharmacy practice management computer systems are easily capable of performing these calculations automatically.

Options Considered by the WG

The system used to verify prescriber education/certification would play a crucial role in the success of the opioid REMS. Given the unprecedented size of the REMS, a system that disrupts the workflow of the prescriber and pharmacist could impose huge costs on the healthcare system and impede access to medications for millions of patients. If the number of REMS requiring verification systems continues to grow, these costs may continue to grow as well unless REMS systems are implemented carefully.

Pharmacy systems can play a key role in ensuring the REMS meets the requirements set out in FDAAA: the REMS is commensurate with the risk it is designed to mitigate, is not unduly burdensome on patient access to the drug, and to the extent practicable to minimize the burden that the REMS places on the healthcare delivery system, is compatible with existing systems for the procurement, distribution, and dispensing of drugs.

With these considerations in mind, the WG explored several systems that the sponsor might use to verify that prescriber education is in place. The following is a brief discussion of existing systems used to verify elements to assure safe use. Similar systems could be used to implement the opioid REMS.

Centralized Pharmacy

Some existing REMS use one or more centralized specialty pharmacies to distribute and dispense REMS drugs. In these REMS, the manufacturer contracts with one or more centralized pharmacies, shipping their drug directly to that specialty pharmacy. The pharmacy then agrees to ship the drug directly to patients only after the requirements of the REMS are met.

Centralized pharmacies have been used in past REMS because they are easier to manage; the centralized pharmacies work closely with the manufacturers to ensure that the REMS is being carried out correctly. In addition, if the REMS requires pharmacy registration and pharmacist training, using a small number of centralized pharmacies reduces the amount of registration and training required.

Despite these benefits, the WG recommends against this approach because it would entail significant changes in the distribution, procurement, and dispensing of REMS drugs. In addition, the direct shipment of certain opioids to patients may be costly and may result in unnecessary delays in treatment.

Manual Verifications in the Retail Pharmacy

Other REMS with elements to assure safe use do use the retail pharmacy system to distribute drugs. In these REMS, retail pharmacists are asked to manually verify that elements to assure safe use are in place. For example, prior to dispensing isotretinoin, pharmacists are asked to visit a Website to verify that the patient is authorized to receive the drug.

FDA has received numerous comments in the docket stating that such an approach would be inappropriate in the opioid REMS.[5] According to these docket respondents, performing manual verifications such as those needed for isotretinoin would be extremely burdensome to pharmacists, particularly given the large quantities of extended-release and long-acting opioids currently dispensed in retail pharmacies. The WG also notes that these systems fail to provide a "hard stop," should the safe use requirements not be met. For example, if a pharmacist fails to check the Website prior to dispensing isotretinoin, pharmacies may lack a mechanism to prevent the pharmacist from dispensing that drug. As a result, FDA regularly receives reports of unauthorized dispensing of isotretinoin.

For these two reasons, the WG recommends against use of manual pharmacist verification systems in the opioid REMS.

Systems Proposed in the Docket

Docket respondents generally agreed that the systems used to verify elements to assure safe use in previous REMS would not be suitable for the opioid REMS. As a result, the WG focused primarily on the benefits and drawbacks of two alternative systems:

- IWG's proposed system to use the DEA registration system to verify prescriber training

[5] Groups that opposed existing manual REMS systems included Walgreen Co., NACDS, and CVS Caremark.

- Proposals to automate verification using existing retail pharmacy systems

One key difference between these two systems is that the first would be accomplished through legislation while the second would be developed and implemented by relevant drug manufacturers.

IWG's Proposed System

IWG has proposed that prescriber verification take place through a modification of the existing DEA registration system. IWG would like the program to function like the system established for the drug buprenorphine used for the treatment of opioid dependence under the Drug Abuse Treatment Act of 2000 (DATA 2000). That Act requires prescribers of buprenorphine to be specially trained or certified and obtain a unique DEA number before they can prescribe buprenorphine.

Under IWG's proposal, a checkbox would be added to the DEA prescriber registration form in which prescribers indicate that they are qualified through training or previous certification in the safe use of opioids. Prescribers who wish to obtain a license to prescribe Schedule II narcotics would need to check off the box, and in doing so attest that they have taken the necessary training. According to IWG, FDA would have authority over the content and format of training to be offered to prescribers, and DEA would implement and enforce the requirement and sanction prescribers who check the box without having taken the necessary training.

There are several benefits to this proposal:

- It builds on a system that is already in use in pharmacies, the system used to ensure that prescribers have valid DEA numbers before they are permitted to prescribe certain controlled substances. The system would create little additional burden on prescribers, pharmacists, or other stakeholders.
- The system would impose educational requirements on prescribers of both short-acting and long-acting opioids. In the December 14 public meeting with FDA, the IWG expressed the belief that this will reduce the number of prescribers who opt out of the training and "prescribe around" the long acting opioids.
- The system would reduce the burden on the sponsor. The sponsor will not be responsible for creating and maintaining a DEA-based prescriber verification system.
- Many stakeholders, including IWG, favor this approach, and have expressed their preference in their submissions to the docket.[6]

Although the benefits of using the DEA system for verification are multiple, there are several drawbacks that merit consideration:

- The DEA system would not require validation before dispensing. In other REMS with prescriber certification, pharmacies are required to determine whether a prescriber is certified prior to dispensing the prescription. To assist in this, FDA has asked sponsors to maintain databases of eligible prescribers. Under the current DEA system, as well as under DATA 2000, pharmacists are not required to check the validity of a prescriber's DEA number against a real time database of certified prescribers. The pharmacist would use a simple mathematical formula to ensure

[6] Groups that favor this option include the American Society of Consultant Pharmacists, the American Society of Addiction Medicine, the American Academy of Physician Assistants, and the American Academy of Pain Management.

that the DEA number is formatted properly, and therefore likely to be assigned to a registered prescriber, although the prescriber may not, in fact, have a valid registration. Such a system would make it difficult for FDA or the sponsor to audit the program and determine how often patients are receiving opioids from non-certified prescribers.

- The DEA verification system would create an additional REMS system. Prescribers already have to contend with several other existing REMS systems, and each system imposes different requirements on prescribers, pharmacies, patients, and other stakeholders. To minimize the burden on the healthcare system, it would be preferable to limit the number of REMS systems, and ensure that the REMS systems that do exist are compatible with a variety of different REMS. A DEA system could not easily be adapted to include other REMS drugs that are not controlled substances. It is also difficult to see how the DEA system could be adapted to include elements to assure safe use other than prescriber certification. This could also prove problematic if FDA later decides that additional elements to assure safe use are necessary for long-acting or extended-release opioids.

- The system would require new legislation. Legislation cannot be guaranteed and may not be enacted for some time, if ever. After enactment, necessary changes in the program could be difficult to make if additional legislation is required.

- Verification of training requires investigation by law enforcement officers. Under IWG's proposal, the prescriber would attest that he or she has received the necessary education by simply checking the appropriate box on their DEA registration form. The DEA system would provide no means other than an investigation by law enforcement officers to verify that a prescriber had been educated. Potential legislation authorizing DEA to perform these enforcement activities should include additional means to verify that a prescriber has been educated.

- The system could be costly for FDA and DEA to implement. Developing the legislation, making the necessary changes to the DEA registration system, and implementing the new requirements could be costly for FDA and DEA.

- Implementation could take up to three years. DEA registration is required of physicians only once every three years, so the REMS would need to be in place for 3 years before all prescribers meet the training requirement, unless prescribers were required to reregister early. The same limitation would apply to any modification of the program.

- The system could cause some prescribers to opt out of prescribing Schedule II narcotics entirely. Although the proposed system may reduce the number of prescribers who "prescribe around" long-acting opioids in favor of short acting opioids, under the proposed system prescribers may prescribe around *all* Schedule II opioids, limiting patient access to these medicines.

Sponsor-Developed Automated Verification System

Modern pharmacists rely heavily on their "pharmacy practice management systems", the computer software that facilitates the dispensing of drugs and the transmission of safety information, prescription data, and insurance claims. Several docket respondents have proposed REMS systems that use these

pharmacy practice management systems, minimizing the additional burden placed on pharmacists.[7] Although the system would still require the active participation of the pharmacist, many of the tasks that pharmacists currently perform manually would be automated. In addition, since these proposed systems would be incorporated into the computer systems used to assist in the dispensing of drugs, they would be able to automatically provide a "hard stop," preventing the dispensing of drugs should the REMS requirements not be met.

Although such systems have never been used to support a REMS, they have been used to support programs far larger in scope, such as Medication Therapy Management reimbursements and the processing of insurance claims for Medicare Part D. To implement Medicare Part D, CMS asked pharmacies to install a special "patch" in their pharmacy management system that modified the software responsible for submitting claims. This patch allowed pharmacies to automatically send and receive Medicare eligibility information, which is routed through the pharmacy switch to a computer system known as a "TrOOP Facilitator," which coordinates benefits across various Medicare Part D plans. Thanks to the patch, the majority of Medicare-related claims adjudication now takes place "behind the scenes" and places no additional burden upon the pharmacist, while covering tens of millions of patients. Some vendors have suggested that a similar patch system be used to implement an opioid REMS.

Although the systems proposed in the docket vary in the specifics of their implementation, all offer the following benefits:

- A sponsor-developed system would be compatible with our current regulatory authority. Under FDAAA, if FDA determines that elements to assure safe use are necessary, the manufacturer must develop the systems necessary to track and verify that these elements are in place. Unlike the DEA system, no additional legislation would be necessary.

- The sponsor-developed system could be changed. Since FDA has direct authority over the sponsor, if FDA finds that the system developed by the manufacturers is not satisfactory, FDA can require that it be modified.

- The system could be incorporated into existing systems. A sponsor-developed automated system could be incorporated into existing systems already familiar to pharmacists and healthcare providers. Foremost among these would be the pharmacist's pharmacy practice management system. If a sponsor-developed implementation system works seamlessly with this system, the REMS could operate without disrupting the workflow of the pharmacist and without requiring significant training of the healthcare practitioners on the procedural components of the REMS.

- Many stakeholders are in favor of this approach. In particular, stakeholders in the pharmacy setting such as the American Pharmacists Association and the National Association of Chain Drug Stores have supported the notion of a sponsor-developed system that taps into the existing claims processing and pharmacy practice management systems.

- The system could be made compatible with other REMS and additional REMS elements. A well-designed REMS system could be expanded to include additional products and elements to

[7] The National Community Pharmacists Association, Academy of Managed Care Pharmacy, American Society of Pain Educators, American Pharmacists Association, and CVS Caremark all requested that the REMS be compatible with existing pharmacy practice management systems.

assure safe use if necessary. This is in contrast to industry's proposed DEA system, which would apply only to prescriber certification for drugs scheduled under the Controlled Substances Act.

- The system could automatically verify prescriber certification prior to dispensing and incorporate "hard stops." These hard stops make it difficult or impossible for a pharmacist to dispense the drug to a patient who has not received a prescription from a certified prescriber. This contrasts with the DEA system in which prescribing by non-certified prescribers may be detected only after the drug is dispensed, and only through the concerted efforts of law enforcement officers.

Sponsor-developed systems also have some drawbacks:

- A sponsor-developed pharmacy system could only incorporate the drugs produced by the sponsors. If FDA wished to verify that *all* prescribers of Schedule II opioids have taken the training, FDA will need to require a REMS for all of those opioids and ask the manufacturers of these drugs to work collaboratively on what would be a very large and complicated system.
- The system could be costly for the sponsors to implement. Given the unprecedented size of the opioid REMS, developing and implementing such a system could prove expensive for opioid manufacturers.
- The system would have to be well-designed to meet FDA needs. Many of the advantages of a sponsor-developed automated system are contingent on the sponsor implementing a system that is designed to work with existing pharmacy systems and that adequately assures safe use.

CONCLUSIONS

The WG recommends against adoption of the DEA system. The workgroup feels that the current REMS framework, in which the sponsor develops the REMS system, is more likely to assure safe use and minimize the burden on the healthcare delivery system. In addition, should the DEA system prove to have shortcomings, it will be difficult to modify.

Instead, the WG recommends that FDA ask relevant sponsors to develop a system that allows for automatic verification of safe use conditions, with the stipulation that the system meet several requirements, including the following:

- The system must ensure safe use. FDA should ask the sponsor to create as system that includes "hard stops" and careful auditing to ensure that only certified prescribers are dispensing the drug.
- The system must minimize the burden on the healthcare delivery system. The sponsor-developed system should be compatible with other REMS, and should work within existing systems. The more mundane procedural components of the REMS should be simplified or automated when possible.
- The system should be compatible with established distribution, procurement, and dispensing systems. The sponsor should use existing pharmacy management systems and allow for the transmission of REMS information using established communication standards. The REMS should also incorporate an open framework that allows a variety of distributors, systems vendors, pharmacies, and prescribers to participate, and that is flexible enough to make possible the addition of further elements to assure safe use if they are deemed necessary in the future.

Opioid REMS Working Group
Access Working Group

June 2010[1]

Access Working Group Members
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BACKGROUND

In early 2009, FDA sent letters to manufacturers of certain opioid drug products, indicating that these drugs will be required to have a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drugs continue to outweigh the risks. FDA explained that the REMS would include elements to assure safe use to make certain that prescribers, dispensers, and patients are aware of and understand the risks and appropriate use of these products. FDA also stated that, with limited exceptions, the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires generic and innovator products to use a single shared system to implement the elements to assure safe use. The affected opioid drugs include long-acting and extended-release brand name and generic products and are formulated with the active ingredients fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.

FDA is mindful of provisions in FDAAA that require elements to assure safe use to be, among other things, commensurate with the specific serious risk listed in the labeling of the drug, not unduly burdensome on patient access to the drug, and designed to be compatible with established distribution, procurement, and dispensing systems.

To obtain public input on how best to design a REMS for this class of drugs, FDA held a series of meetings with relevant stakeholders (May 4 and 5, 2009; May 27 and 28, 2009; December 4, 2009) and opened a public docket to receive public comments on relevant issues. Meeting minutes of the May 4 and 5 stakeholder meetings, and transcripts of the May 27 and 28, and December 4 meetings are in the docket and on FDA's Web site.[2] FDA plans to provide an additional opportunity for public input before finalizing the elements of the REMS.

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[1] The WG formulated its recommendations in January 2010; this report has been finalized in preparation for the July 2010 Advisory Committee meeting.
[2] See http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm.
[*] Division of Anesthesia and Analgesia Products
[**] Office of Surveillance and Epidemiology
[^] Controlled Substance Staff

Following the meetings, FDA formed an Opioid REMS Steering Committee, a multidisciplinary team from throughout the Center for Drug Evaluation and Research. To thoroughly analyze the substantial public and stakeholder input received on the development of the REMS and to conduct additional research, the Steering Committee formed seven[3] work groups to focus on the various aspects of an opioid REMS and the effects of possible components of the REMS on use.

Following their analysis, the work groups were asked to provide recommendations to the Steering Committee for consideration as it develops options for what should be included in the REMS. The seven work groups addressed the following areas:

- Scope of an opioid REMS
- Prescriber education
- Pharmacist education
- Patient education
- Pharmacy systems
- Effect of possible restrictions on patient access to pain medication
- Metrics

This is the report and recommendations from the Access Working Group (WG).

GOAL OF THE ACCESS WORKING GROUP

In 2009, when FDA announced that a REMS for opioid manufacturers of long-acting and extended-release (LA/ER) opioids would be required, the possible elements of the planned REMS included:

- A Medication Guide, with patient-directed labeling
- Requirement that prescribers are trained and certified with regard to safe and proper prescribing
- Requirement that dispensers are trained and certified on proper opioid dispensing and safe use
- A system to implement the training and certification requirements
- A timetable for periodic assessment of the REMS

The Access Working Group (WG) was charged with evaluating how opioids are provided and determining whether elements in a REMS could adversely or inappropriately affect access to opioids by certain patients or practitioners, or within certain settings, including:

- Long-term care or assisted living facilities
- Hospices
- Hospitals (inpatient and outpatient settings)
- Special populations (e.g., pediatric patients)
- Prescribers who also dispense opioids
- Medical residents (i.e., physicians in training)
- Outlying (rural) areas
- Urban (inner city) areas
- Veterinarians

[3] In addition, an eighth working group was created to handle external communications about the REMS. That working group was not involved in the review of comments and did not create a report.

The Access WG also considered concerns raised in submissions to the docket opened to receive input on the planned opioid REMS, namely, concerns about the potential adverse effects of an opioid patient registry as well as potential limitations on opioid access if the planned opioid REMS included restrictive requirements for distributors.

SUMMARY OF ISSUES OF CONCERN/CHALLENGES

The WG had a number of concerns as summarized here. A REMS with the elements proposed in 2009 would effect restrictions on treatment, based on certain patient characteristics. Also, the need for training or certification of prescribers and dispensers under the REMS could subject practitioners to additional requirements beyond existing licensure and DEA registration.

Although proper patient selection and assurance of adequate prescriber and dispenser knowledge of the risks and proper use of opioids are important and reasonable objectives, steps to ensure these objectives could result in reduced prescribing of LA/ER opioids by practitioners, causing unintentional negative effects on patient pain management. The requirements under the REMS could also bring additional time and financial costs to the healthcare system as a result of having to institute new systems to monitor for proper and safe opioid use.

In addition, very limited scientific data are available on the effect of risk management programs or restrictive regulations on access or drug availability. The few studies that have been done show that it is difficult to distinguish the effect of a specific restriction (e.g., mandatory prescriber certification) on access. This is usually because restrictive programs often have multiple components. Also, it is difficult to distinguish the effect of a restrictive program from the effect of other concurrent factors (e.g., high-profile media reporting of potential adverse effects or release of a newer and better therapy for the same indication).

The limited data do suggest that restrictions on drug prescribing and/or dispensing can lead to decreased use. What is difficult to determine is whether decreased use reflects a transition towards more appropriate use of the product, or a transition from use in general for reasons related to the restriction (e.g., fear, increased burden). There are also limited data on issues related to access to opioid medications based on either certain settings or by certain populations.

SUMMARY OF RECOMMENDATIONS

The recommendations proposed by the Access WG are intended to assist with the development of a REMS that balances the need for proper pain management with the need to reduce serious adverse consequences related to using long-acting opioids. The following recommendations are broken out by specific issue. In the sections that follow, we discuss each issue in more detail, providing the Access WG's analysis, including a discussion of advantages and disadvantages of a specific step, when appropriate.

Stringency or Restrictiveness of the Proposed Opioid REMS

- As FDA moves forward with proposing the opioid REMS, the Agency should be mindful that the requirements placed on sponsors, healthcare practitioners, and patients are unambiguous, are consistent with the overall purpose of the REMS, and are not arbitrary or without reasonable scientific or legal basis.

- As FDA moves forward with proposing the opioid REMS, the Agency should be mindful that the REMS may result in decreased use of the opioids covered under the REMS. This decrease may be an unintended negative consequence of the additional restrictions regarding use by patients and prescribers, or may reflect shifts to more appropriate prescribing by knowledgeable prescribers.

Healthcare Setting Issues

- The opioid REMS should exempt the hospital setting (i.e., inpatient and emergency department) from certain requirements if they are included in the final REMS, specifically certification of the healthcare institution or the hospital pharmacy, and education of patients about the risks and proper use of sustained-release and long-acting opioids.

- If certification or training is required for healthcare practitioners under the proposed REMS, the program should include periodic training of nursing home staff engaged in managing, dispensing, and administering opioids. Nursing home staff might benefit from periodic training on appropriate tracking, use, and disposal of controlled substances.

- No special allowances for pharmacies or practitioners in rural or urban (inner-city) areas are indicated under a REMS.

- Education under a REMS about the risks and proper use of opioid analgesics is recommended for healthcare practitioners in both urban and rural areas.

Healthcare Practitioner Issues

- The opioid REMS should create strong incentives for training prescribers about the risks and proper use of sustained-release and long-acting opioids. Training of prescribers should not be mandatory under the REMS.

- The opioid REMS should not include requirements or exemptions for veterinarians or veterinary practices.

- The opioid REMS should not adversely affect medical residents' ability to prescribe sustained-release and long-acting opioids.

Patient Issues

- The opioid REMS should not require a patient–practitioner agreement (PPA), as it is traditionally known. A PPA should also not be required for patients in inpatient settings (e.g., hospices, hospitals) or for patients in the emergency department setting.

- The opioid REMS should include patient education on the risks, proper use, and storage/disposal of their opioid medications.

- The opioid REMS should not include a patient registry.

- The REMS should not include exemptions for special or select patient populations, such as pediatric patients, sickle-cell patients, or cancer patients. Similarly, the REMS should not include requirements that unnecessarily impede access to opioids by those patients.

- If included in the final opioid REMS, a Patient-Caregiver-Practitioner "agreement" or plan for care with opioids should be used in the in-home hospice setting. The agreement should include clear training on use and administration of opioids as well as storage and disposal, with periodic updates.

Dispenser (Pharmacist) Issues

- The opioid REMS should not mandate training or certification of pharmacies or pharmacists.

- The opioid REMS should not interfere with the lawful access to Schedule II opioids via mail (i.e., dispensing of sustained-release and long-acting opioids by mail order pharmacies).

Distributor Issues

- The opioid REMS should not require certification of wholesale distributors of the opioid drugs covered under the REMS.

DETAILED DISCUSSION OF SPECIFIC ISSUES

This section summarizes the analysis performed by the Access WG members on the following specific issues.

- Overall stringency of an opioid REMS
- Effect of drug restrictions on medical practice
- Opioids in the hospital (inpatient and emergency department) setting
- Access in hospices and nursing homes
- Access in rural and urban areas
- Access and veterinary practices
- Access and residents in training
- Patient registries
- Access and the patient–practitioner agreement (PPA)
- Access and mailing of schedule II opioids
- Access and wholesale distributors

When appropriate, a variety of options were considered and advantages and disadvantages considered.

Overall Stringency of an Opioid REMS

In 2000, the Pain & Policy Studies Group (PPSG) at the University of Wisconsin began evaluating the impact of state policies governing the medical use of opioid medications, specifically investigating the

effect of such policies on the appropriate use of opioids as well as their potential for hindering patient access to opioids. The PPSG has developed criteria for statutes, regulations, policies, and guidelines, which are used to identify provisions that have the potential to enhance or impede pain management.[4] These criteria are listed in Table 1, below. The Access WG reviewed the PPSG criteria and those considered meaningful for the proposed opioid REMS are **bolded** and *italicized*. Specifically, the Access WG considered whether certain of the potential opioid REMS elements outlined in 2009 might impede pain management.

As described above, when FDA announced that a REMS would be required for LA/ER opioids, one of the goals was to ensure proper patient selection for treatment. To achieve this, the potential REMS would have to include the requirement for treatment based on certain patient characteristics, as well as the need for training or certification of prescribers *in appropriate prescribing*. Such a REMS would, therefore, have subjected practitioners to additional prescription requirements beyond medical licensure and DEA registration.

Although proper patient selection and assurance of adequate prescriber knowledge of the risks and proper use of opioids are important and reasonable objectives, steps to strengthen these could have unintentional negative effects on patient pain management.

[4] *Achieving balance in state pain policy: A report card (July 2008).* Pain & Policy Studies Group, University of Wisconsin (www.painpolicy.wisc.edu).

Table 1: Pain & Policy Studies Group Criteria for Evaluating Statutes, Regulations, Policies, and Guidelines for their Potential to Enhance or Impede Pain Management[5]

Positive Provisions: criteria that identify policy language with the potential to enhance pain management

1. Controlled substances are recognized as necessary for the public health
2. Pain management is recognized as part of general medical practice
3. Medical use of opioids is recognized as legitimate professional practice
4. Pain management is encouraged
5. Practitioners' concerns about regulatory scrutiny are addressed
6. Prescription amount alone is recognized as insufficient to determine the legitimacy of prescribing
7. Physical dependence or analgesic tolerance are not confused with "addiction"
8. Other provisions that may enhance pain management
    - Category A: Issues related to healthcare professionals
    - Category B: Issues related to patients
    - Category C: Regulatory or policy issues

Negative Provisions: criteria that identify policy language with the potential to impede pain management

9. Opioids are considered a treatment of last resort
10. Medical use of opioids is implied to be outside legitimate professional practice
11. Physical dependence or analgesic tolerance are confused with "addiction"
12. ***Medical decisions are restricted***
    - ***Category A: Restrictions based on patient characteristics***
    - Category B: Mandated consultation
    - Category C: Restrictions regarding quantity prescribed or dispensed
    - Category D: Undue prescription limitations
13. Length of prescription validity is restricted
14. ***Practitioners are subject to additional prescription requirements***
15. Other provisions that may impede pain management
16. ***Provisions that are ambiguous***
    - ***Category A: Arbitrary standards for legitimate prescribing***
    - ***Category B: Unclear intent leading to possible misinterpretation***
    - ***Category C: Conflicting (or inconsistent) policies or provisions***

The ***Access WG recommends*** that as FDA moves forward with proposing the opioid REMS, the Agency should be mindful that requirements imposed on sponsors, healthcare practitioners, and patients should be unambiguous, consistent with the overall purpose of the REMS, and not be arbitrary or without reasonable scientific or legal basis.

[5] *Achieving balance in state pain policy: A report card (July 2008).* Pain & Policy Studies Group, University of Wisconsin (www.painpolicy.wisc.edu).

Effect of Drug Restrictions on Medical Practice

The Access WG examined the available literature to assess the effect on medical practice of restrictions on the availability of certain drugs. Specifically, the Access WG assessed whether restrictions have the effect of shifting medical practice away from the use of those drugs (i.e., decreasing the availability of those drugs to patients). For this assessment, the Access WG evaluated Isotretinoin, Ticosyn (dofetilide), Betapace AF (stotalol), and Lotronex (alosetron). With the exception of Betapace AF, all of these products have some kind of restriction on their use.

Isotretinoin

Isotretinoin is approved for the treatment of severe recalcitrant nodular acne. However, it can cause fetal birth defects during pregnancy. In April 2002, the SMART risk management program was implemented for isotretinoin with the goal of preventing pregnancy in females of childbearing potential who were taking isotretinoin. In the 4th quarter of 2002 (i.e., after SMART was initiated), generic versions of isotretinoin were approved, each with its own risk management plan. The Access WG reviewed an article[6] that reported on a study of prescription drug dispensing patterns for isotretinoin (new prescriptions and refills), comparing patterns from April 2001 to March 2002 to those from April 2002 to March 2003. The study found that the total number of prescriptions (including generics) decreased 23% after SMART was initiated. Also, the number of refills decreased (from 15.8% to 2.4%). However, the percentage of prescriptions written by dermatologists remained essentially the same (76% before and 80% after), as did the percentage of prescriptions written for *severe acne* and the percentage of prescriptions written for different patient age groups. This article suggests that the SMART program was associated with a decrease in use of the drug. *Of note*: factors such as publicity about psychiatric effects of isotretinoin may also have been at play in discouraging patients from using a product.

The data sources used for the study did not allow for examination of the number of patients prescribed isotretinoin, or for evaluation of proper use of the drug. Also, the study did not evaluate whether the number (or percentage) of prescribers decreased after institution of the SMART program. To find out more, the Access WG contacted FDA's Office of Surveillance and Epidemiology staff, who examined drug use data and determined that the number of prescribers of isotretinoin products had decreased by 27% between year 2004 and 2008, following the institution of the latest risk management program for isotretinoin, iPLEDGE. Other factors that could have led to this were not explored.

Tikosyn (dofetilide) and Betapace AF (sotalol)

Tikosyn (dofetilide) is an oral anti-arrhythmic approved in 2002 for conversion of atrial fibrillation and atrial flutter and maintenance of sinus rhythm in patients with these conditions. Data showed that Tikosyn is associated with dose- and concentration-dependent incidence of QT prolongation and Torsades de Pointe, a cardiac arrhythmia that is usually fatal. When Tykosin was approved, it was approved with a risk management plan (RMP).

Under the Tykosin RMP:

- There is mandatory physician education.
- The drug can only be prescribed by a trained physician.

[6] *Pharmacoepidemiology and Drug Safety*, 2005; 14:615-618.

- Administration of drug is initiated in the hospital only.
- There is mandatory testing of the patient's serum creatinine, potassium, magnesium; QTc interval.
- The starting dose based on patient's creatinine clearance CLcr.
- An ECG must be taken 2–3 hours after each dose.
- Concomitant use of certain drugs must be avoided.

Shortly after the approval of Tikosyn, Betapace AF (sotalol) was approved for maintenance of sinus rhythm in patients with atrial fibrillation and atrial flutter, two types of cardiac arrhythmias. Although Betapace was a new sotalol product, it was not a new molecular entity. Sotalol had already been marketed for treatment of ventricular arrhythmias. Notably, sotalol had been approved without an RMP.

Although Betapace AF has risks similar to Tikosyn, an RMP was not required at the time of approval because of the considerable previous experience with sotalol. However, Betapace AF has labeling language similar to Tikosyn.

A study in the American Heart Journal[7] included a chart review of 167 patients treated with Tikosyn (n=47) or Betapace AF (n=117) to evaluate if a mandated RMP increased compliance with dosing and monitoring recommendations. This was a single-center study preformed at a site that had a standardized order form for Tykosin (but not Betapace). Patients in the Tikosyn group were more likely than patients in the Betapace AF group to have had their drug prescribed by a physician who had completed the required educational program and had the requisite laboratory and ECG testing performed. Overall, there were no differences in terms of outcomes (e.g., deaths, rhythm at discharge, discontinuation of treatment) between patients treated with Tikosyn (which has an RMP) compared to patients treated with Betapace AF (which does not have an RMP). However, the study showed better adherence to dosing and monitoring recommendations for Tikosyn vs. Betapace AF.

The smaller number of patients treated with Tikosyn may indicate that physicians are unwilling to prescribe the drug because of the restrictions/constraints. However, the standardized order form for Ticosyn may have enhanced adherence to labeling instructions. Additionally, patients in the Betapace AF group were generally cared for by a non-cardiologist, which may explain some of the differences detected. Also, physicians have previous experience with Betapace AF, and several may have deviated from the labeled recommendations of use.

Lotronex (alosetron)

Lotronex was approved in February 2000 for diarrhea-predominant irritable bowel syndrome (IBS) in women. Sales of Lotronex were $54 million between February and October 2000.[8] Lotronex was withdrawn from the market by the sponsor in November 2000 because of serious gastrointestinal (GI) events, including fatal ischemic colitis. However, at an FDA Advisory Committee meeting in April 2002, the Advisory Committee recommended that Lotronex be returned to the market because it believed the potential benefits outweighed the risks in certain patients.

[7] *American Heart Journal* 2003 (Nov); 146: 894-901.
[8] *Am J health Syst Pharm* 2004; 61:1210-1212.

In October 2002, the drug was reintroduced with a RMP. The goal of the RMP was to limit use to women with severe IBS. The components of the Lotronex RMP include:

- Physician attestation form including:
  - The conditions under which Lotronex should be prescribed
  - Requirement for physicians to affirm that they can diagnose and treat IBS, ischemic colitis, and other complications of Lotronex
- Requirement for physicians to enroll in the Lotronex prescribing program
- Special stickers on prescriptions (to show physician enrollment)
- Physician–patient agreement

The impact of the Lotronex RMP was assessed between October 2002 and December 2003.[9] The assessment found that use had declined. Of an estimated 3.9 million patients who were possible candidates for therapy, 10,000 patients received 30,000 prescriptions. Of the 5,053 enrolled physicians, half actually wrote a prescription. The sales of Lotronex were $5.9 million during that period.

Perceptions of the RMP may have contributed to the reduced use. Physician perceptions of the RMP were that the RMP transferred liability from sponsor to physician; that the attestation form is offensive ("affront" to professional training); and that the attestation is an unnecessary duplication of the licensing process. Patient perceptions were reportedly that the new labeling (about risks) is frightening and that the patient–practitioner agreement made them hesitant to take the treatment, since an agreement is generally not required for other kinds of therapies[10].

Factors other than the RMP may explain the changed patterns in use of Lotronex. For example, prior to reintroduction to the market, Lotronex received a lot of negative media attention. Also, withdrawal from the market for safety reasons could have contributed to physician and patient reluctance to use Lotronex.

Following review of data on the three examples previously discussed, the Access WG reached the following preliminary conclusions on the effects of restrictions on medical practice and patient access to medications:

1. Data are scarce on impact of restrictive programs on patient access. Evaluations of use of drug are generally based on number/percentage of prescriptions (not a direct measurement of number of treated patients)
2. Nevertheless, it appears that when first introduced, restrictions on use of products can result in reduced/low use of a product because of:
   a. Physician fears (liability; workload burden)
   b. Patients (*exaggerated* risks)
   c. Physician, patient, dispenser lack of familiarity with procedures

   OR
   d. Shift to appropriate use (proper patient selection)

   But there are no data on whether prescriptions are being given to the *appropriate* patients.

[9] *Am J Health Syst Pharm* 2004; 61:1210-1212.
[10] *Am J Health Syst Pharm* 2004; 61:1210-1212.

3. It is difficult to rule out *other* confounders (i.e., other prevention mechanisms that may have occurred, such as health advisories, significant publicity); or there may be other concerning risks associated with the drug (e.g., depression as with isotretinoin).

The ***Access WG recommends*** that as FDA moves forward with proposing the opioid REMS, the Agency be mindful that the REMS may result in decreased use of the opioids covered under the REMS. This decrease may be an unintended negative consequence of the additional restrictions regarding use, or may reflect shifts to more appropriate prescribing by knowledgeable prescribers.

Opioids in the Hospital (Inpatient and Emergency Department) Setting

Access to and use of opioids within the hospital setting is heavily regulated and monitored by state and accreditation bodies. There is efficient provision of product to patients directly by (or overseen by) licensed and DEA-registered healthcare practitioners.[11] In the inpatient hospital setting, there is also significant monitoring of patients and tracking of opioid products in that setting using electronic monitoring systems, as well as secure storage units.

Basic hospital standards are regulated under the Center for Medicare & Medicaid Services (CMS) conditions of participation. Hospitals must comply with these requirements to be eligible for reimbursement for patients covered by Medicare. Under 42 CFR 482.25,[12] several of the conditions of participation for pharmaceutical services include:

- Drugs and biologicals not specifically prescribed for a specific time or number of doses must automatically be stopped after a reasonable time that is predetermined by the medical staff.
- Drug administration errors, adverse drug reactions, and incompatibilities must be immediately reported to the attending physician and, if appropriate, to the hospital-wide quality assurance program.
- Abuses and losses of controlled substances must be reported, in accordance with applicable Federal and state laws, to the individual responsible for the pharmaceutical service, and to the chief executive officer, as appropriate.
- Information relating to drug interactions and information about drug therapy, side effects, toxicology, dosage, indications for use, and routes of administration must be available to the professional staff.

In the hospital setting, to obtain schedule II drugs, hospital pharmacists must complete DEA Form 222, the Controlled Substances Ordering Form, or the electronic Controlled Substance Ordering System (CSOS). [13] Copies 1 and 2 of the form are sent to the supplier. When the pharmacy receives its shipment of the medicine, the pharmacist counts and verifies the contents of the shipment and immediately reports discrepancies or damaged items to the supplier, as per normal pharmacy procedures. The pharmacist secures and updates all newly received controlled substances into its general inventory. The 3rd copy of the DEA Form 222 is updated with the number of commercial or bulk containers received and the date on which the containers are received. DEA Forms 222 must be maintained separately from all other records and they must be kept available for inspection by DEA for two years.

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[11] DEA Practitioner's Manual: http://www.deadiversion.usdoj.gov/pubs/manuals/pract/pract_manual012508.pdf.
[12] 21 CFR 1300, http://www.deadiversion.usdoj.gov/faq/dea222.htm.
[13] DEA Form 222 is a paper-based form requisitioned directly from the DEA that is filled out in triplicate.

Inpatient setting

In the inpatient setting, opioid drugs are prescribed and dispensed as follows: the prescriber writes an order for a drug, and the order is sent to the pharmacy. The product is kept in secure storage until it is dispensed to the patient and administered by a nurse. In this setting, there is significant tracking of products and patient monitoring and, therefore, relatively low risk of overdose or abuse. Nevertheless, adverse events due to improper prescribing do occur.

Emergency Department setting

Approximately 11% of patients who come to an emergency department (ED) have chronic pain as their presenting complaint. The primary reason for seeking care in the ED is lack of a primary healthcare practitioner from whom the patient can obtain care and possibly a new or refilled prescription for pain medication. Treated patients receive opioid prescriptions from prescribers who are licensed and registered with the DEA (medical residents would not yet have met these criteria).

In a survey of healthcare practitioners about barriers to treating chronic pain in the ED,[14] time limitations were most commonly cited as obstacles when assessing and managing patients with chronic pain in the ED. Physicians responding to the survey reported that they did not have time to obtain a full patient history, address psychosocial or other issues, or work out how the proper chronic analgesic dose for the patient.

In the same survey, the following were rated as ***not*** high potential barriers to providing opioid treatment:

- Lack of or existing opioid contract
- Fear of diversion of the opioid by the patient
- History of recurrent visits to the ED for pain treatment (i.e., *frequent flyers*)

Another article[15] found that the staff in EDs generally do not have access to prescription monitoring program (PMP) databases. As such, healthcare practitioners are unable to check that patients are *appropriate* for opioid treatment. The article also stated that in general, ED treatment of a patient with chronic pain involves prescribing a few (20-30) pills of a *short-acting* Schedule III opioid (e.g. hydrocodone, codeine). This prescription is intended to act as a bridging dose until the patient can see his or her primary care practitioner and perhaps receive treatment with a long-acting or sustained-release opioid.

To expand its information about prescription of LA/ER opioids in the emergency setting, the Access WG asked FDA's Division of Epidemiology (DEPI) in the Office of Surveillance and Epidemiology to provide data on dispensed prescriptions, detailing the proportions of extended-release versus immediate-release opioids written by prescribing physician specialty (e.g. ED, internists/general practitioners, pediatricians, geriatricians, and anesthesiologists) for morphine, hydromorphone, oxycodone, and oxymorphone products. DEPI measured outpatient drug utilization from the SDI, Vector One®: National (VONA) database.[16] DEPI found that:[17]

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[14] Pain Med 2008; 9(8): 1073-1-80.

[15] Pain Med 2008; 9(8): 1073-1-80.

[16] SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

- During the 2004–2008 period, a total of 93 million prescriptions were written for the selected opioids and dispensed in outpatient retail pharmacy settings
- During the 2004–2008 period, 1-2% of prescriptions for the selected opioids were written by ED physicians. In 2008, ED physicians accounted for 1.9% of prescriptions for the selected opioids.
- Oxycodone accounted for ~65% of the total share of the prescriptions for the selected opioids that were written by ED physicians. This was followed by hydromorphone, morphine, and oxymorphone with 24%, 10%, and 1% of the total market share, respectively.
- Immediate-release oxycodone products accounted for the majority (~72%) of oxycodone prescriptions written by ED physicians. Extended-release oxycodone products accounted for ~28% of oxycodone prescriptions written by ED physicians.

The Access WG could not find data on the extent of mis-prescribing, misuse, and abuse of opioids obtained in the ED setting.

The overall impression from the available literature and DEPI data is that in the inpatient and ED hospital settings, time constraints and logistical factors limit the extent to which practitioners can employ certain strategies intended to ensure proper patient selection and safe use of prescribed medicines, such as checking that the patient has an opioid contract with a healthcare practitioner, checking patient databases to verify that the patient is an appropriate candidate for opioid treatment, or providing safe use information to each patient.

Because patients do not self-administer drugs and may not be in a condition to comprehend educational information, patient education would not go far to mitigate medication errors in the ED setting. In addition, emergency healthcare professionals are in close proximity after a drug is administered. Therefore, in the case of an adverse drug effect, healthcare professionals will be able to quickly provide care to the patient. Because of the high level of oversight in the inpatient setting, a REMS requirement for patient education would not contribute to improved safety, but could instead cause delays in drug administration. If, however, a patient will be prescribed a long-acting opioid product upon discharge from the hospital, the patient could receive education about proper use of the drug at that time.

Because EDs account for a very small fraction of the prescriptions written for sustained-release and long-acting opioids, and mis-prescribing, abuse, and misuse of opioids obtained in the ED appears to be comparatively low, the Access WG believes that targeted restrictions for ED prescribers do not appear indicated.

The ***Access WG recommends*** that the proposed opioid REMS exempt the hospital setting (inpatient and ED) from certain potential REMS requirements, including certification of the healthcare institution. Also, the Access WG recommends that education of inpatient and emergency department patients about the risks and proper use of LA/ER opioids not be required under the proposed REMS.

Opioid Access and Hospices and Nursing Homes

In addition to proper prescribing, the focus of a proposed opioid REMS would be to reduce misuse (i.e., incorrect prescribing and administration) of LA/ER opioids, as well as abuse of opioids (i.e., taking a drug for non-medical purposes).

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[17] SDI, Vector One®: National. Extracted 11-8-2009. Source File: VONA 2009-1504 Opioid REMS ER IR 11-9-09.xls.

Hospices and nursing homes are inpatient care units that are subject to overarching Federal regulations, addressing their facilities, patients, and drug management systems. Federal regulations require hospices (42 CFR part 418) and nursing homes (42 CFR part 483) to store controlled substances in secured areas (i.e. locked up). State regulations, governing the specifics of facility management, provide additional regulations. The Center for Medicaid & Medicare Services (CMS) oversight is also involved if either Medicare or Medicaid reimbursements are to be paid; facilities are subject to CMS sanctions if they are not compliant with state and Federal laws. Despite this regulation, situations vary greatly from hospice, to nursing home, to home hospice and nursing situations.

Hospices

Specialized training of physicians in hospices (palliative care physicians), considerable Federal and state oversight (47 states and DC have pain policies Alaska, Delaware Illinois and Indiana do not),[18] [19] and guidelines and oversight imposed by accrediting bodies and overarching organizations (see WHO guidelines see AAHPM website) make hospices a special situation when considering additional REMS requirements. This is reflected in the fact that no reports could be found in peer reviewed literature citing misuse and abuse of opioids in the hospice setting.

When compared to oversight in nursing homes, regulatory oversight of hospices appears to be more stringent. A large number of guidelines and rules apply to all hospices (see American Academy of Hospice Management Web site for guidelines[20]).

- Licensed prescribers must prescribe the opioid and the prescriber cannot add refills to the prescription. Most states allow for 30, 60, or 90 day prescriptions. "Licensed prescribers" include physicians, but, in some states, also include nurse practitioners.
- All records of drugs prescribed, procured dispensed, and administered must be accurate and current.
- A licensed pharmacist must provide consultation on all aspects of the provision of pharmaceutical care.
- Faxed prescriptions are allowed for patients in long-term care facilities or for those who are receiving hospice care (even if at home).
- The hospice must have a written plan for tracking, collecting, and disposing of controlled substances within a patient's home.
- Patients and family must be educated in the use, disposal, and potential dangers of controlled substances.[21]
- Hospices must inform the patient and family of their policies regarding tracking and disposing of controlled substances.
- Each patient must have a physician-written plan of care that includes pain management.

[18] Federation of State Medical Boards of the United States. *Model Policy for the Use of Controlled Substances for the Treatment of Pain*. 2004. Available at: http://www.painpolicy.wisc.edu/domestic/model04.pdf Accessed February 16, 2008.

[19] Stokowski, LA. Laws and Regulations Affecting Opioid Prescribing. 2008. from Medscape Neurology and Neurosurgery located at http://cme.medscape.com/viewarticle/572102?src=mp&spon=26&uac=20842SK.

[20] See http://www.aahpm.org/pdf/guidelinesforopioids.pdf.

[21] Typically, particularly in the outpatient hospice setting, there will be a Patient-Caregiver–Practitioner Agreement that includes mandatory training in opioid storage, administration, and disposal, as well as agreement to allow only the patient to receive the drug. The Agreement includes a regular refresher for both the patient and caregiver.

- Drugs are stored in secure areas, and disposal is in compliance with hospice policy and state and Federal regulations.
- When state law permits, nurses may see, treat, and write orders for patients.

Abundant training and educational materials are available on prescribing and administering opioids to hospice patients.

Hospice facilities give paliative care at the end-of-life. In this setting, care is provided to terminally ill patients by professionals with specialized training in the risks and use of opioid products. In-home hospice settings, a Patient-Caregiver-Practitioner Agreement is usually employed. The Agreement should includes clear instructions on use and administration of opioids as well as storage and disposal guidelines. Because in-home hospice care involves less highly trained medical oversight, [22] additional training of family member(s) who care for a patient could reduce misuse through misunderstanding and potentially abuse and diversion.

Despite concerns about the quality of in-home hospice caregiver education (e.g., quality can depend on a variety of issues[23]), imposition of additional restrictions on opioid use in the hospice setting may be unduly burdensome to patients and may be unnecessary in this setting.

The ***Access WG recommends*** that in-patient hospices be exempted from proposed opioid REMS requirements, especially from requirements to train or certify of healthcare practitioners, develop and use patient-practitioner agreements, and certify hospice pharmacies. In-home hospice care settings could benefit from training of the caregiver in the use of opioid medications. However, such a program would best be a voluntary program because the tracking of the satisfactory conduct of training poses challenges. (It would be important to test the training program to see if it is effective for caregivers in learning how to better manage opioids.)

Nursing Homes

In contrast to hospice settings, nursing homes (NH) have been known to have high staff turnover, and comparatively less oversight at the state level because of the number of nursing homes. There are also scattered reports of misuse,[24] abuse (diversion),[25] and error[26] involving opioid drugs in the NH setting. Thus, nursing homes might need some form of additional oversight.

Federal regulations state that in the NH setting, at sites receiving Medicare or Medicaid benefits, a licensed consultant pharmacist must be employed to oversee all drug procurement processes (accurate acquiring, receiving, dispensing and administering) for the nursing home.[27] Under the regulations, nursing homes can choose the pharmacy(ies) that they use and NH residents in some states also have

[22] Lau, DT et al. Family caregiver skills in medication management for hospice patients: a qualitative study to define a construct. 2009 *J of Gerontology* vol 64B (6).
[23] Ibid.
[24] Dosa, DM et al. Frequency of long-acting opioid analgesic initiation in opioid naïve nursing home residents. 2009. *J Pain and Symptom Management* 11 1-7.
[25] Martin, C. Controlled substance issues in long term care. 2008. *Journal of the American Society of Consultant Pharmacists* 23(9) 654-64.
[26] Barber, ND et al, Care homes' use of medicine study: prevalence, causes and potential harm of medication errors in care homes for older people. 2009. *Qual Safe Health Care* 18 341-46.
[27] 42 Code of Federal Regulations Section 483.

the right to choose the pharmacy that supplies their medicines, might have to do with insurance reimbursement and thus presents an access issue if the patient must choose a pharmacy for which his or her carrier does not reimburse. Federal regulations stipulate that a licensed prescriber must prescribe drugs to NH residents.

State oversight of nursing home care can and does vary. Individual states determine which practitioner or caregiver can administer drugs to a NH resident, and there is great variability depending on the state. With regard to opioids, in some states, there is strict regulation and training of those who can administer controlled drugs; in other states, the oversight is less strict regarding the training and competencies of those administering opioids.

A recent GAO report delved into this problem by evaluating 136 CMS-chosen poorly performing NHs. Poor performance was determined based on inappropriate pain management and other aspects of quality care. Overall, the study showed that NHs do not have the necessary level of Federal and state oversight to consistently be in compliance with the CMS regulations, but that non-compliance is most likely at the NH staff level.[28] "Staff" should be interpreted to mean anyone who is in the employ of a NH and who works in the care of patients or has action in dispensing, administering, handling, or prescribing opioids.[29]

Despite evidence of efficacy and safety of opioid use for the treatment of pain in the elderly, fear of patient dependence and addiction, shared by both patients and physicians, remains a significant barrier to access to proper pain management. In one study, 70% of NH residents with chronic pain were treated with short-acting pain medications. Pain management was considered to be suboptimal in most cases.[30] Despite this, there do not appear to be many reports of patients abusing their opioid medications. Controlled substances are to be kept secured (Federal and state regulations), thus preventing residents from having no general access to these drugs — and misuse would not occur at their level. No reports were found of NH residents abusing opioids, and only a handful of reports were found of misuse and diversion of opioids by staff.[31] There are reports of inadequate pain management in the elderly and in NH patients, based on improper knowledge about the proper and safe use of opioids for chronic pain in these patients. In fact, lawsuits are on the books about patients who received inadequate pain management from physicians — in a case in California, the family of a 72-year-old mesothelioma patient won a suit against a doctor after the patient's death.[32] There are also reports of

[28] Nursing Homes CMS's special focus facility methodology should better target the most poorly performing homes which tended to be chain affiliated and for profit. *GAO Report*. August 2009.

[29] Martin, C., Controlled substance issues in long term care. 2008. *Journal of the American Society of Consultant Pharmacists* 23(9) 654-64. See also martin, CM. Controlled substances in long-term care pharmacy: part 2. 2008. *Journal of the American Society of Consultant Pharmacists* 23(10) 742-56.

[30] Reisman, M. The Problem of Pain Management in Nursing Homes. 2007 P&T 32(9) 494-95; [*physician and patient perceptions of opioids can cause under treatment of pain*].

[31] Controlled substance issues in long term care. Martin, C., 2008. *Journal of the American Society of Consultant Pharmacists* 23(9) 654-64.

[32] Shapiro, DW. (Editor) Professional Liability Newsletter. Vol 33 (6).

misuse of long-acting opioids in opioid naïve residents.[33] Given this reporting of under management of pain,[34] a cautious approach is appropriate when implementing any REMS requirements in this setting.

In the case of NHs, staff bear the responsibility for appropriately prescribing, dispensing, administering, and tracking drugs. When considering additional restrictions or requirements in a proposed REMS, additional and continuing training of NH staff should be considered. However, some caveats should also be considered. Training could be difficult to enact, especially among NH staff who comprise a varied group including any number of highly skilled members (e.g., pharmacists, nurses, physician assistants PAs) and less skilled members (e.g., technicians, care practitioners, volunteers). In addition, although training could benefit staff management and administration of opioids, it might not affect access to opioids per se, and it could negatively affect staffing and cause staff loss (NHs already have rapid staff turnover[35]). Appropriate training programs could also be difficult to develop,[36] implement, track, and confirm program adherence. Therefore, staff training could be important to conduct under the REMS, but implementation and continued education might be a problem if staff is not stable.

The ***Access WG recommends*** that FDA use caution when deciding how opioids REMS will be applied to NH. A very restrictive REMS could result in the reluctance of healthcare practitioners to use long-acting opioids to treat chronic pain in the elderly, thus adversely affecting these patients' pain management, particularly in NH settings. Any REMS developed should require periodic training of NH staff engaged in managing, dispensing, and administering opioids. NH staff might also benefit from periodic training on appropriate tracking, use, and disposal of controlled substances.

Opioid Access in Rural and Urban areas

Data are limited when it comes to assessing access to opioids in rural versus in urban areas. However, opioid access in rural areas appears to be reduced when compared to urban areas. Prior to a study carried out by Washington state,[37] only two population-based studies of opioid availability had been conducted in the United States: one in New York City and one in Michigan. The New York City study concluded that pharmacies in predominately nonwhite neighborhoods do not stock sufficient medications to treat patients with severe pain.[38] The Michigan study found that pharmacies in minority zip codes were 52 times less likely to carry sufficient opioids than pharmacies in white zip codes.[39] The Washington state study reported that responding pharmacies had a broad supply of both short-and long-acting opioids in rural and urban areas: 98.6% of the pharmacies stocked acetaminophen with

[33] Dosa, DM et al. Frequency of long acting opioid analgesic initiation in opioid naïve nursing home residents. 2009 *J Pain and Symptom Management* 11 1-7. See also Martin, C. Controlled substance issues in long term care. 2008. *Journal of the American Society of Consultant Pharmacists* 23(9) 654-64.

[34] Reisman, M. The Problem of Pain Management in Nursing Homes. 2007 32(9) 494-95; [*physician and patient perceptions of opioids can cause under treatment of pain*]

[35] Ibid.

[36] For example, what type of training should staff receive if they administer versus prescribe opioids?

[37] Mayer, J., Kirlin, B., Rehm, C. & Loeser, J. (2008). Opioid Availability in Outpatient Pharmacies in Washington State. *Clinical Journal of Pain,* 24, 120-123.

[38] Morrison, S., Wallenstein, S., Natale, D., Senzel, R & Huang, L. (2000). "We Don't Carry That"- Failure of Pharmacies in Predominately Nonwhite Neighborhoods to Stock Opioid Analgesics*. The New England Journal of Medicine*, 342, 1023-1026.

[39] Green, Carmen R., Ndao-Brumblay, S. Kady, West, Brady (2005). Differences in Prescription Opioid Analgesic Availability: Comparing Minority and White Pharmacies Across Michigan. *The Journal of Pain*, Vol. 6, 689-699.

hydrocodone, and 96% stocked sustained release OxyContin. Hydromorphone and codeine were the only opioids that were carried by fewer than 90% of pharmacies. The study showed that pharmacies in areas with a high percentage of non-white residents or residents below the poverty level were more likely to have reduced access to opioids, but the differences were negligible.

Overall, available literature shows that the majority of rural consumers have pharmacy access within 15 to 20 miles. SK&A Healthcare Information Services, Inc. analyzed U.S. pharmacy access in 2007.[40] Pharmacies studied included chain drug stores, independently owned drug stores, supermarket pharmacies, and pharmacies operated by mass merchandisers. Based on the analysis, urban consumers have access to 30 competing independent[41] pharmacies within 2 miles, and rural consumers have access to 14 competing independent pharmacies within 15 miles. Suburban consumers have access to 7 competing independent pharmacies within 5 miles. Telepharmacy[42] offers pharmacy services to communities that cannot support their own pharmacy.[43]

A search of the literature noted additional, often geographically related barriers to effective pain management: [44,45,46]

- Physician reluctance to prescribe opioid medication especially in rural areas
- Healthcare practitioner's lack of knowledge about prescribing opioids, especially in rural areas
- Regulatory oversight/sanctions
- Inadequate access to healthcare due to financial burden, especially for the rural elderly
- Lack of insurance, especially in rural areas
- Less access to pain specialists and practitioners in rural areas
- Lack of objective measurements of pain
- Opioids not stocked in pharmacies in some rural and urban ("inner city") pharmacies due to low demand, fear of theft, and fear of state and Federal penalties and monitoring.

Education of healthcare practitioners regarding opioids could address and reduce some of these barriers, e.g., physician reluctance to prescribe opioid medication especially in rural areas, healthcare practitioner's lack of knowledge about prescribing opioids, especially in practitioners in rural areas, and lack of objective measurements of pain. Such education may be more difficult in rural areas, however,

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[40] SK&A Healthcare Information Solutions report, (2007). *Consumer Access to Pharmacies in the United States*. Prepared for Pharmaceutical Care Management Association.

[41] An independent pharmacy is a retail pharmacy that is not directly affiliated with any chain pharmacy, such as CVS/pharmacy, Walgreens or Eckerd.

[42] *Telepharmacy* is a process by which pharmacists working from a home or central pharmacy location use electronic information and communication technology processes to adjudicate prescriptions and then transmit them to pharmacists registered pharmacy technicians working in stores in remote or rural locations who then deliver medications to customers. Remote areas also make use of mail order pharmacies.

[43] McEllistrem-Evenson, A. (2009*). Pharmacy and Prescription Drugs Frequently Asked Questions*. Retrieved October 23, 2009, from Rural Assistance Center: http://www.raconline.org/info_guides/pharmacy/pharmacyfaq.php

[44] Remster, E and Marx T. (2008). Barriers to Managing Chronic Pain: A Pilot of Prescriber Perceptions in Rural Appalachia. *Journal of Pain and Symptom Management,* 36, issue 3, e1-e2.

[45] The National Advisory Committee on Rural Health and Human Services (2006). The 2006 report to the Secretary: Rural Health and Human Service Issues.

[46] Morrison, S., Wallenstein, S., Natale, D., Senzel, R & Huang, L. (2000). "We Don't Carry That"- *Failure of Pharmacies in Predominately Nonwhite Neighborhoods to Stock Opioid Analgesics. The New England Journal of Medicine*, 342, 1023-1026.

if practitioners have less time or less computer access. If additional education requirements are considered too burdensome and cause participants in rural or inner-city areas to *opt out* of prescribing long-acting or sustained release opioids, pain patients in those areas would be at a higher risk of not being treated effectively. Professional organizations that advocate for rural health may be able to promote education for practitioners in rural areas.[41]

In 2005, the Center for Studying Health System Changes noted that with the exception of localized areas where access and quality problems persist, overall access and quality of healthcare in rural areas compares favorably to that in urban areas, except for mental health. Although lower incomes and lack of insurance coverage in rural areas do result in greater demand side access problems, little evidence was found, apart from the mental health area, that a lower supply of practitioners affected patient access to healthcare.[47]

The ***Access WG recommends*** that no special allowances be made for pharmacies or practitioners in rural or urban (inner-city) areas in any proposed opioid REMS. Education about the risks and proper use of opioid analgesics is recommended for healthcare practitioners in all areas.

Opioid Access and Veterinary Practice

For its evaluation of access to opioids within the veterinary health system and the potential impact of a proposed opioid REMS on veterinary health practices, the Access WG considered the information submitted to the docket and to the Interagency Committee for Drug Control (ICDC) by the American Veterinary Medical Association,[48,49] information provided by the Center for Veterinary Medicine (CVM), and information provided by the Drug Enforcement Administration (DEA).

In a December 8, 2009, teleconference, the DEA reported that the number of veterinarians registered with the DEA represent approximately 5% of the total number of practitioners registered. As of 2009, there were 1.1 million practitioners (e.g. MDs, DOs, and DDSs) registered in the United States including 58,170 veterinarians. In addition, there were 1,537 animal shelters and 347 euthanasia technicians registered with the DEA. These are considered *mid-level* practitioners who, depending on state laws and regulations, may prescribe and/or administer opioid products.

Under the U.S. Food, Drug, and Cosmetic Act (FDCA), veterinarians can prescribe drugs approved for human use to their animal patients. The relationship with their patients (the animal) and the animal's owner is analogous to the relationship between a pediatrician (other physician, dentist), a child, and the parent or legal guardian. Veterinarians also meet the definition of a health prescriber under the Controlled Substances Act (CSA). Veterinarians are subject to the requirements set under the CSA for prescribing, administering, and dispensing controlled substances. Although veterinarians can use opioids for-in office procedures, opioid products can be dispensed for use outside of the office (e.g., at the animal owner's home or farm). In such cases, the opioid would be prescribed for the animal, and

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[47] Reschovsky, J. Staiti, A. (2005). *Access and Quality of Medical Care in Urban and Rural Areas*. Center for Studying Health System Change. Abstracts Academy Health Meeting, 3021.

[48] Docket N0. FDA-2009-N-0143- American Veterinary Medical Association, June 30, 2009.

[49] American Veterinary Medical Association, September 10, 2009. Letter to the Interagency Committee for Drug Control.

the drug would be dispensed by a local pharmacy directly to the pet owner. Opioid products dispensed by veterinarians include fentanyl patches, oxycodone, and morphine and liquid methadone.

FDA's Center for Veterinary Medicine (CVM) has the authority to approve drugs for animal use. Under 21 CFR 514(c), animal drugs are subject to the same evaluation of their potential for abuse as drugs approved for human use. In a teleconference with the Access WG, representatives from CVM reported that it has very few opioid products approved under Section 512 of FDCA. The majority of opioid products used in the veterinary health system are those approved for human use (i.e., drugs approved under Section 505 of FDCA).

CVM also reported to the Access WG that currently only one veterinary product is on the market under a risk minimization and restricted distribution program. This product, ProHeart 6 (moxidectin) Sustained Release Injectable for Dogs,[50] is a heartworm preventive medicine used in dogs. The product was voluntarily recalled in September 2004, after CVM expressed concerns about reports of serious adverse events that included seizures, liver failure, and death. The sponsor reintroduced the product to the market in June 2008, under the risk minimization and restricted distribution program. [51] This program includes veterinarian training, pet owner education and consent forms, and specific requirements for the purchase and administration of the product. Veterinarians who wish to purchase the product must complete a Web-based training program and register with the sponsor prior to obtaining the product. Veterinarians who purchase ProHeart 6 are also required to provide pet owners with a client information sheet, as well as obtain a signed informed consent form from the pet owner before the product is administered. Representatives from CVM concurred with the sponsor's decision to return ProHeart 6 to the U.S. veterinary market under a risk minimization and restricted distribution program.

CVM representatives also explained that, in the opinion of their legal staff, a REMS for a drug approved under section 505 of the FDCA would not apply to veterinarians under Section 907 of FDAAA. The representatives explained that they rely in large measure on the DEA and scheduling requirements to govern veterinarian use of human opioid products. However, if a manufacturer of a human opioid product required adherence by veterinarians to certain restrictions, that could well be acceptable (the representatives cited their experience with the thalidomide and isotretinoin RMP as examples of a similar situation).[52]

Major issues for consideration by the Access WG were the proportion of opioids prescribed or used by veterinarians, as well as the extent to which opioids are misused or abused within the veterinary health system. The Access WG could not find data to assess the volume of opioid medications used by veterinarians or to estimate the levels of misuse and abuse of opioids by veterinarians.

The Federal controlled substances laws are designed to work together with state controlled substance laws. Toward this same goal, DEA works in close cooperation with state professional licensing boards and state and local law enforcement officials to ensure that pharmaceutical controlled substances are

[50] The marketing application number is NADA 141-189.

[51] Proheart 6 Risk Minimization and Restricted Distribution Program; http://www.proheart6dvm.com/.

[52] It is FDA's position that, under section 907 of FDAAA, veterinarians practicing in the context of a veterinarian–client patient relationship are not subject to the requirements of a REMS. If the Agency determines that limits on veterinarians access to certain drugs is necessary, the Agency has authority under Section 512(a)(5) of the Act to put in place regulations governing the extra label use of drugs approved for human use.

prescribed, administered, and dispensed for legitimate medical purposes in accordance with Federal and state laws. Within this cooperative framework, the majority of investigations into possible violations of the controlled substances laws are carried out by state authorities. However, DEA also conducts investigations into possible violations of Federal law as circumstances warrant. In this area, DEA reported to the Access WG that for the 2007 to 2009 period, 31 investigations involving veterinarians were initiated, and 16 of those cases were completed. Most of the cases involved the use of a veterinarian's DEA license number by someone other than the veterinarian and abuse of drugs by the practicing veterinarian. DEA also reported that these cases, which are small in scale, are investigated at the state level.

The CVM representatives stated that veterinary practices typically purchase opioids in bulk for their inpatients (e.g., for use after surgery) and will then administer drug from that stock. As such, the veterinary practice functions as both a prescriber and dispenser of opioids. For the most part, use of drugs (including opioids) is recorded in the patient's medical chart. There is no common or universal tracking system for use of opioids, thus prescriptions are not tracked in the veterinary pharmacy in the same way as opioid prescriptions for human patients.

Although one could argue that the lack of systematic study of the extent of misuse and abuse of opioids in the veterinary setting suggests a more cautious approach when considering additional restrictions and requirements under a possible REMS, it seems that imposition of training, certification, or other requirements would interfere with access to opioids within the practice of veterinary medicine without providing useful benefits. Veterinarians comprise a small percentage of the opioid prescribers and frequency of misuse/abuse of opioids within the veterinary health system is low. As currently interpreted, Section 907 of FDAAA would not affect the ability of veterinarians to use the opioids, and in general, veterinarians have tended to comply with restrictions imposed by RMPs for other products with serious risks.

The ***Access WG recommends*** that any proposed opioid REMS not include requirements or exemptions specifically for veterinarians.

Opioid Access and Residents in Training

The Access WG was asked to explore whether residents in training should be subject to requirements under a proposed opioid REMS. Most residents (including residents in medical and surgical specialties) receive training in pain management in medical school and receive further training throughout their residencies. Internal medicine and family medicine residents treat many chronic pain patients during their training. Deficiencies in this training, however, have been documented. In recent years, medical schools and residency training programs appear to be modifying their curriculums to address these deficiencies.

Although they are in training programs, medical residents do not have to obtain a DEA license to prescribe opiate medications. Practitioners (e.g., interns, residents, staff physicians, mid-level practitioners) who are agents or employees of a hospital or other institution may administer, dispense, or prescribe controlled substances under the registration of the hospital or other institution in which they are employed, provided that:

- The dispensing, administering, or prescribing is in the usual course of professional practice.
- Practitioners are authorized to do so by the state in which they practice.

- The hospital or institution has verified that the practitioner is permitted to dispense, administer, or prescribe controlled substances within the state.
- The practitioner acts only within the scope of employment in the hospital or institution.
- The hospital or institution authorizes the practitioner to dispense or prescribe under its registration and assigns a specific internal code number for each practitioner so authorized.

A list of internal codes and the corresponding individual practitioners is to be kept current by the hospital or other institution. This list is to be made available at all times to other registrants and law enforcement agencies upon request for the purpose of verifying the authority of the prescribing individual practitioner.

Although most medical schools include pain management and palliative care in the required course curriculum,[53] residency programs have documented deficiencies in resident training for chronic pain management. A survey of one medical residency noted that their residents lack confidence (preparation fair or poor) in the management of chronic pain.[54] Another internal medicine program analyzed a resident questionnaire and performed a chart review.[55] Again, residents reported a lack of confidence in managing chronic pain patients and reported treating these patients less rewarding than other chronic disease states such as diabetes. The chart review documented that more than 80% of the time residents use medication agreements, document the pain diagnosis, and score, they documented illicit drug use and legal history less than 40% of the time, and only 18% had urine drug screens. Thirty-eight percent of these residents reported being threatened by patients over pain medicine prescriptions. Another training program has documented improvement in resident skills for chronic pain by having workshops that use standardized simulated patients for instruction.[56]

Given this situation, an argument could be made that residents are a prime audience for an opioid REMS because the residency is a prime time for training and the resident could be trained according to the opioid REMS right from the beginning. The resident, by definition, is being supervised by attending physicians who would have to fulfill the opioid REMS training requirements. The training physicians would pass the REMS training onto the residents under their supervision, although such training may best be carried out during medical and osteopathic school, as well as during postgraduate training.[57]

If the REMS has additional requirements related to opioid prescribing, especially if costs are associated with them, residents might opt out of obtaining a DEA registration. Any physician training required in the opioid REMS could be made available to the residents on a voluntary basis and at no cost.

The ***Access WG recommends*** that the proposed opioid REMS not specifically include medical residents. The Agency should collaborate with the accrediting organizations that oversee medical and osteopathic graduate education and the prerequisite education obtained before residency training in medical and

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[53] American Association of Medical Colleges (AAMC) Curriculum Survey, 2008, http://services.aamc.org/currdir/section2/2008hottopics.pdf.

[54] Teaching and Learning in Medicine. 2007; 19:101-105.

[55] *J Opioid Manag*. 2008;4:201-211.

[56] *Pain*. 2007; 8:152-160.

[57] The training of residents is overseen by the ACGME (Accreditation Council for Graduate Medical Education). This council defines the core content for a resident training program and then ensures that the program requirements are met. For osteopathic physicians, the American Osteopathic Association Council on Postdoctoral Training oversees these programs.

osteopathic schools. The Safe Use Initiative may provide a mechanism for this collaboration. Residents should be able to voluntarily participate at no cost in any opioid REMS training that becomes available to healthcare practitioners.

Patient Registries

The purpose of patient registries is generally to systematically and prospectively capture adverse outcomes in a specific population. Most of the existing risk management plans that include patient registries are for medical conditions with small patient populations or for capturing significant and serious adverse effects of treatment (e.g., teratogenicity). It is estimated that there are over 70 million patients in the United States with chronic pain. As such, a patient registry for this population would be extremely large and possibly the first of such a size and would require tremendous effort and resources to establish and maintain. In addition, there may be stigma associated with such a registry.

Patient advocacy groups, such as the American Pain Foundation, state that negative connotations or stigma would be associated with an opioid registry where patients may feel unnecessarily targeted or fear potential adverse consequences of participating in a registry and avoid seeking proper treatment for pain.

On the other hand, the absence of a mandatory patient registry decreases the assurance that each legitimate patient receiving an opioid is accounted for. Also, without a patient registry, we lose a data collection tool that could be used to analyze the impact of the REMS implementation. Finally, a patient registry may provide more opportunities for patient education and drug monitoring.

The FDA has not evaluated the effects of patient registries, including their impact on access to drug treatment, patients' refusal to participate in a registry, or the impact on prescribing rates for products that have a patient registry. For example, the iPLEDGE program showed that although there was an observed decrease in the number of prescribers and prescriptions since the launch of the risk management plan, no analysis has been conducted to determine if this decrease may be due to concerns about adverse events with isotretinoin rather than issues with the patient registry or drug access. The creation, maintenance, and implementation of a patient registry could become a burden on the healthcare system, given the large numbers of patients needing to be enrolled. There is no clear evidence of benefit of having a patient registry to address the goals of the class opioid REMS, including misuse, overdose, and abuse.

The ***Access WG recommends*** that an opioid REMS not include a patient registry. A required patient registry may hinder access to needed LA/ER opioids for appropriate patients with pain, and may not contribute to the planned REMS' goal of reducing drug misuse, overdose, and abuse.

Opioid Access and the Patient-Practitioner Agreement (PPA)

Patient–practitioner agreements (PPAs), occasionally referred to as Action Plans, are contracts between healthcare practitioners and their patients that educate and outline the responsibilities and rules for each party related to the treatment of the patient's condition. PPAs have had some use in two other chronic disease states, including asthma and COPD that require self medication adjustments. The use of PPAs has been especially endorsed by specialists in chronic pain management with opioids. A PPA usually addresses the proper use, dosing, administration, storage, and disposal of a medicine. The PPA in the opioid context usually communicates the risks from misuse, abuse, diversion, and overdose of opioid

medications. The PPA may require that the patient obtain his or her opioid medication from only one physician and one pharmacist and may require that the patient agree to random urine drug screens.

PPAs have come into common use by practitioners who treat chronic pain. The Federation of State Medical Boards recommends their use. In addition, some state legislatures have mandated their use in state regulations. The list of specialty societies that endorse the use of PPAs is extensive. Pain specialty societies, such as the American Pain Society and the American Academy of Pain Medicine, recommend the use of PPAs.[58] Their recommendation 2 regarding PPAs states:

> Informed consent and opioid management plans: When starting COT (Chronic Opioid Therapy), informed consent should be obtained. A continuing discussion with the patient regarding COT should include goals, expectations, potential risks, and alternatives to COT (strong recommendation, low-quality evidence).[59] 2.1 Clinicians may consider using a written COT management plan to document patient and clinician responsibilities and expectations and assist in patient education (weak recommendation, low-quality evidence).

The American Academy of Pain Management provides a model consent form on their Web site.[60] The American Society of Interventional Pain Physicians (ASIPP) has also published guidelines recommending the use of the PPA that include a sample consent form. [61]

The American Academy of Family Physicians has developed a CME Monograph on the treatment of chronic pain. "Balancing clinical and risk management consideration for chronic pain patients on opioid therapy."[62] The document calls for a written treatment plan or agreement with informed consent. The monograph references the American Academy of Pain Medicine (AAPM) model form noted above. One of the authors reports that of the patients to whom he/she provides information sheets outlining the risks and benefits 50% decline opioid therapy. The National Pain Education Council Web site also recommends the AAPM consent form.

Another government agency also recommends written opioid treatment agreements (see the Veterans Administration/Department of Defense clinical practice guideline for the management of opioid therapy for chronic pain). Some states have endorsed the use of PPAs.[63] The Federation of State Medical Boards published in 2004 a Model Policy for the Use of Controlled Substances for the Treatment of Pain.[64]

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[58] *J Pain* 2009;10:113-130.

[59] In general, a strong recommendation was based on the American Pain Society and the American Academy of Pain Medicine expert panel's assessment that "potential benefits of following the recommendation clearly outweigh potential harms and burdens." A weak rating was based on "more closely balanced benefits to harms or burdens, or weaker evidence." To grade the quality of a body of evidence that supports a recommendation, the expert panel considered the type, number, size, and quality of studies; strength of associations or effects; and consistency of results among studies.

[60] http://www.painmed.org/pdf/opioid_consent_form.pdf.

[61] *Pain Physician* 2003;6:233-257.

[62] Young SS et al. "Balancing clinical and risk management consideration for chronic pain patients on opioid therapy.'' CME Monograph. American Academy of Family Physicians. http://www.aafp.org/online/etc/medialib/aafp_org/documents/news_pubs/mono/painmono/chronicpain.Par.0001.File.tmp/painmono.pdf

[63] http://www.medsch.wisc.edu/painpolicy/domestic/states/VA/vambguid.htm

[64] See http://www.fsmb.org/pdf/2004_grpol_Controlled_Substances.pdf

PPAs or action plans have been used in other chronic disease states, such as asthma and COPD,[65] although scientific evaluation of benefit has not been documented. The plans reportedly help with medication management. COPD action plans yield positive outcomes on self management by improving the use of antibiotics and steroids. Access, however, is not an issue for these chronically used medications.

The use of a primary care action plan has been considered for cardiovascular health.[66] Half of the patients in a negotiation session with their practitioner made a behavior change that they agreed to do. The reported benefit was that the patient-physician spent time on an important issue that usually would not be addressed.

Despite the many recommendations to use opioid PPAs, little research is available that has evaluated the effect of PPAs. Most publications focus on analyzing substance abuse by those who have signed the forms. Manichikanti performed random urine drug screens among patients and found 16% with substance abuse (3% cocaine and 13% marijuana).[67] In a later report, 500 patients were prospectively followed for adherence monitoring.[68] Five percent of the patients violate the agreement by obtaining opioids from a second physician while 4% obtained them from illegal sources. Another academic teaching clinic reported on its five-year experience.[69] Thirty-seven percent of patients with PPAs discontinued (20% voluntarily and 17% for substance abuse). Another report describes patient satisfaction with the use of a pain management contract. This was a small survey of 20 patients of whom 8 (40%) had aberrant behaviors that might represent violations of the contract.[70] A few reports document that some patients refuse to sign the PPAs. Those patients that do sign often voluntarily terminate them. Random urine drug screens document that many patients violate the PPAs. The literature does not fully address the reasons for these refusals, terminations or violations, or what these patients subsequently do. Hariharahan noted that 66 patients refused, as they sought to enroll 500 patients. In the AAFP monograph, one author noted that about 50% of the patients do not want to sign the PPA. The reports do not address the reasons for these refusals and what these patients subsequently do.

Reviews about opioid contracts do not address patient access or physician prescribing patterns. The focus is on use, objectives, and ethical considerations.[71][72] There is little factual data about the impact of PPAs on patient access and the potential change in physician prescribing patterns. PPAs have not been systematically studied to evaluate patient comprehension or retention, nor which healthcare practitioner (physician, pharmacist, or other educator) is the best at reviewing this information. Clearly some patients refuse to sign, but we do not know what they do next and the impact on the patient-physician relationship. The published literature, therefore, raises doubts about the effectiveness of PPAs. They may negatively affect the patient–physician relationship, especially mutual trust. Clearly, many patients refuse to sign and terminate relationships based upon having to sign a PPA. Some patients report being stigmatized, as no other chronic disease state currently requires patients to sign a

[65] *Am J Health-Syst Pharm*. 2006;63(supp3):514-21.)
[66] *J Am Board Fam Med* 2006;19:224-31.
[67] *Pain Physician* 2003;6:173-178.)
[68] *Pain Physician* 2006;9:57-60.
[69] *JGIM* 2007;22:485-490.)
[70] I*HS Prim Care Provid*. 2005;30:299-305.
[71] *Am J Med 2*006;119:292-296
[72] *Clinical Journal of Pain* 2002;18(supp 4):S70-5.

contract for care. Research has not been done to analyze if PPAs might be beneficial for one demographic group versus another. (e.g., a young male with chronic low back pain versus an elderly patient with osteoarthritis).

In addition, PPAs are time consuming and potentially burdensome. Reviews and reports note concerns that physicians have about the time commitment of a PPA and also their fear of law enforcement and medical malpractice issues that deter them from prescribing opioids for chronic pain, but these concerns have not been quantified. It is likely that a busy physician practice site would delegate the signing of the PPA to office staff. If reimbursement is not provided for this service, financial burden would also be incurred. Tracking for the presence of a PPA adds further complexity, as a new system to perform this task would need to be created.

On the other hand, PPAs may represent an opportunity for patient and possibly practitioner education. Reviewing and signing a PPA would require patient and practitioner face-to-face time to discuss and review the addition of opioids to the pain management plan. This would take approximately 15 to 30 minutes in a patient–physician encounter. This discussion would emphasize the proper storage and disposal of opioids, as well as the importance of not sharing opioids. PPAs also could be standardized for all patients. Of course, other patient healthcare interactions could provide this education. For example, a pharmacist is well suited to provide this education. And if reimbursement is provided, this may be a welcomed addition to the pharmacist–patient relationship. Other educators and educational tools also warrant further study. Studies have not determined whether a patient retains opiate education more readily from a physician, pharmacist, or other educator.

Despite the widespread recommendations for use of PPAs in guideline documents, rigorous scientific evaluation of their use has not been performed. Some unstudied elements include what should be in the PPA, and what is the patient retention of the information. Also, research has not been performed that delineates the positive or negative impact of these contracts on patient access to opioids, practitioner prescribing of opioids, patient education, or the patient-physician relationship.

The ***Access WG recommends*** that an opioid REMS not require a patient–practitioner agreement (PPA) at this time. However, we recommend additional research to study their impact. The Agency should endorse the study of PPAs. These studies should evaluate different education techniques by different practitioners to determine what tools and methods work best. In addition, the impact on the patient-practitioner relationship needs to be understood. The lessons learned may advance chronic opioid management and that of other chronic disease states.

If the Agency does not require use of a PPA under the REMS, it might be perceived as counter to a growing consensus to use them. If PPAs are later demonstrated through research to have positive outcomes, this could lead to improvements in the PPA and the process. (Alternatively, another education tool might be found to be more effective.)

Currently, there are no approved REMS drugs that include PPAs or Action Plans. There are, however, REMS that include “patient acknowledgement” forms in which patients acknowledge that they have been advised of the risks and benefits of treatment. The Agency has an opportunity to call for research to advance the science of PPAs and Action Plans. Patient practitioner contract science is in its infancy and its study should be promoted as methods and benefits once fully understood might then be applied to opioid pain management and other chronic disease states.

Opioid Access and Mailing of Schedule II Opioids

Mailing controlled substances to patients by pharmacies after receipt of a legitimate prescription does not provide an exemption to the general Controlled Substances Act (CSA) prohibition against distributing controlled substances. The CSA tightly regulates the manufacture, importation and exportation, prescribing, and dispensing of Schedule II substances. Schedule II controlled substances require a written prescription that must be signed by the practitioner. While some states and many insurance carriers limit the quantity of controlled substance dispensed to a 30-day supply, there are no specific Federal limits on quantities of drugs dispensed via a prescription. For Schedule II controlled substances, an oral order is only permitted in an emergency situation. The refilling of a prescription for a controlled substance listed in Schedule II is prohibited. DEA has revised its regulations regarding the issuance of multiple prescriptions for Schedule II controlled substances. Under the new regulation, which became effective December 19, 2007, an individual practitioner may issue multiple prescriptions authorizing a patient to receive a total of up to a 90-day supply of a Schedule II controlled substance provided that certain conditions are met.[73]

Mailing controlled substances is allowed within the United States. The U.S. Postal Service imposes certain restrictions and establishes standards for mailing controlled substances. The first Postal Service restriction that must be adhered to is that it is unlawful to mail a controlled substance that cannot otherwise be lawfully distributed. If distribution of the controlled substance is otherwise lawful, it may be mailed, as long as certain packaging standards are met.[74] Mail order pharmacies, such as Medco, ship Schedule II substances via 2-day air carrier and require a signature upon receipt to ensure that the medications have been received.[75] The Access WG could not locate any information regarding the volume of Schedule II opioids dispensed through mail order.

Mail delivery might be the only viable way for homebound patients or patients in rural or underserved areas to access their opioid medication. Limiting or removing the opportunity for mailing of opioid drugs under the REMS could limit access for numerous patients and practitioners. Therefore, the ***Access WG recommends*** that the proposed opioid REMS not interfere with the lawful access to Schedule II opioids via mail. Patient education programs might have to be adapted to accommodate mail orders.

Opioid Access and Wholesale Distributors

In its submission to the docket for the proposed opioid REMs, Covance, a drug development services organization, recommended that FDA not require certification of distributors under an opioid REMS. That is, the opioid REMS should not require that distributors receive specialized certification to distribute the opioids covered under the REMS.

A *wholesale distributor* is defined as anyone engaged in the wholesale distribution of prescription drugs, including manufacturers, repackers, own label distributors, jobbers, private-label distributors, brokers,

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[73] Practitioner's manual. Section V - Valid Prescription Requirements. Schedule II Substances. See http://www.deadiversion.usdoj.gov/pubs/manuals/pract/section5.htm.

[74] Mailing Standards of the United States Postal Service Domestic Mail Manual. 600-Basic Standards for All Mailing Services. 6001- Mailability. http://pe.usps.com/text/dmm300/601.htm.

[75] Medco Health. http://www.medcohealth.com/medco/corporate/home.jsp.

warehouses (including manufacturers' and distributors' warehouses), manufacturer's exclusive distributors, authorized distributors of record, drug wholesalers or distributors, independent wholesale drug traders, specialty wholesale distributors, third party logistics distributors, and chain pharmacy warehouses that conduct wholesale distribution.

There are many Federal and state requirements for drug distributors of opioids already in existence. According to the Prescription Drug Marketing Act of 1987, no person or entity may engage in the wholesale distribution of human prescription drugs in any state unless the person or entity is licensed by that state in accordance with guidelines set forth in FDA regulations that establish minimum standards, terms, and conditions. In addition, wholesale distributors that are not the manufacturer or an authorized distributor of record must provide to the recipient of the drugs a written statement commonly referred to as a pedigree that identifies each prior sale, purchase, or trade of the drugs.

According to DEA regulations, all wholesale distributors who deal with controlled substances must register with the appropriate state controlled substance authority and with the DEA and must comply with all applicable state, local, and DEA regulations. Every wholesale distributor in a state who engages in wholesale distribution of prescription drugs in interstate commerce must be licensed by the state licensing authority.

Although absence of distributor certification decreases the assurance that opioids will be sent from the manufacturer to the appropriate wholesale distributors (and subsequently from the distributors to the appropriate pharmacies), diversion issues lie outside the scope of any REMS for opioid drug products.

Therefore, the ***Access WG recommends*** that the opioid REMS not require certification of wholesale distributors of opioid drugs. The Access WG believes that requiring certification of wholesale distributors of opioid drugs is not necessary given the strict and complex Federal and state requirements for distributors already in existence. Rather than creating new requirements that would create additional burden on the wholesale distributors without the evidence of a defined benefit, we recommend that existing regulations be enforced.

Conclusion

A REMS for LA/ER opioids that has the elements proposed in 2009 would effect restrictions on treatment, based on certain patient characteristics. Also, the need for training or certification of prescribers and dispensers under such a REMS could subject practitioners to additional requirements beyond existing licensure and DEA registration. The requirements under that kind of REMS could also incur additional time and financial costs to the healthcare system, as a result of having to institute new systems to monitor for proper and safe opioid use. The Access Working Group evaluated how opioids are provided to determine whether and how certain REMS elements could adversely or inappropriately affect access to opioids by certain patients or practitioners, or within certain settings.

The WG found that very limited scientific data are available on the effect of risk management programs or restrictive regulations on access or drug availability. The few studies that have been done show that it is difficult to distinguish the effect of a specific restriction on access. This is usually because restrictive programs often have multiple components. Also, it is difficult to distinguish the effect of a restrictive program from the effect of other concurrent factors. Nevertheless, data do suggest that restrictions on

drug prescribing and/or dispensing can lead to decreased use. What is difficult to determine is whether decreased use reflects a transition towards more appropriate use of the product, or a transition from use in general for reasons related to the restriction (e.g., fear, increased burden).

Based on its evaluation of available data and medical literature the Access WG recommends that:

- The REMS for LA/ER opioids should strongly incentivize training of healthcare providers in the risks and proper use of these products. Training of healthcare providers should not be mandated by the REMS. The REMS should not include requirements or exemptions specifically for veterinarians or verterinary practices or medical residents.
- If the REMS for LA/ER opioids includes certification of healthcare institutions or pharmacies, hospitals (both the inpatient and emergency department settings), hospices, and nursing homes should be exempted from such requirements.
- Because there is reasonable access to healthcare providers and pharmacies in rural and urban (i.e., inner-city) areas, no special allowances should be made under the REMS for pharmacies or healthcare providers in those areas.
- The REMS for LA/ER opioids should include patient education on the risks, proper use, and storage/disposal of their opioid medications. However, a "traditional" patient-provider agreement is not necessary under the REMS. Additionally, the REMS should not include a patient registry as a requirement for treatment.
- The REMS for LA/ER opioids should not specify exemptions for select or special populations, such as patients with cancer or those with sickle-cell disease. This is because by not including certification requirements for hospitals and hospices, or requiring a patient registry under the REMS, these patient populations will not be subject to REMS restrictions.
- The REMS for LA/ER opioids should not require training certification of pharmacies and pharmacists, or of wholesale distributors. This is because in the absence of required training for opioid prescribers and of a patient registry, there is no need for training of pharmacists in assessment of whether a prescriber is eligible to write a prescription or a patient is eligible to receive the medication. Similarly, if pharmacies are not certified, there is no need for certification of distributors since there would be no reason for distributors to check that they are delivering the drugs only to eligible pharmacies.
- The REMS for LA/ER should not affect the lawful access to Schedule II opioids through the mail.

In summary, the Access WG recommends that the REMS for LA/ER opioids comprise the following elements:

- Medication Guide
- Healthcare provider training, that is, made available to prescribers, but is not mandatory in order for them to be able to prescribe opioids

Risk Evaluation and Mitigation Strategy for Opioid Analgesics
Final Report of the Patient Education Working Group

June 2010[1]

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BACKGROUND

In early 2009, FDA sent letters to manufacturers of certain opioid drug products, indicating that these drugs will be required to have a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drugs continue to outweigh the risks. FDA explained that the REMS would include elements to assure safe use to make certain that prescribers, dispensers, and patients are aware of and understand the risks and appropriate use of these products. FDA also stated that, with limited exceptions, the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires generic and innovator products to use a single shared system to implement the elements to assure safe use. The affected opioid drugs include long-acting and extended-release brand name and generic products and are formulated with the active ingredients fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.

FDA is mindful of provisions in FDAAA that require elements to assure safe use to be, among other things, commensurate with the specific serious risk listed in the labeling of the drug, not unduly burdensome on patient access to the drug, and designed to be compatible with established distribution, procurement, and dispensing systems.

To obtain public input on how best to design a REMS for this class of drugs, FDA held a series of meetings with relevant stakeholders (May 4 and 5, 2009; May 27 and 28, 2009; December 4, 2009) and opened a public docket to receive public comments on relevant issues. Meeting minutes of the May 4 and 5 stakeholder meetings, and transcripts of the May 27 and 28, and December 4 meetings are in the docket and on FDA's Web site.[2] FDA plans to provide an additional opportunity for public input before finalizing the elements of the REMS.

[1] The conclusions in this report were formulated in December, 2009, and the report was completed in June, 2010.
[2] See http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm.

Following the meetings, FDA formed an Opioid REMS Steering Committee, a multidisciplinary team from throughout the Center for Drug Evaluation and Research. To thoroughly analyze the substantial public and stakeholder input received on the development of the REMS and to conduct additional research, the Steering Committee formed seven[3] work groups to focus on the various aspects of an opioid REMS and the effects of possible components of the REMS on use.

Following their analysis, the work groups were asked to provide recommendations to the Steering Committee for consideration as it develops options for what should be included in the REMS. The seven work groups addressed the following areas:

- Scope of an opioid REMS
- Prescriber education
- Pharmacist education
- Patient education
- Pharmacy systems
- Effect of possible restrictions on patient access to pain medication
- Metrics

This is the report and recommendations from the Patient Education Working Group.

Goal of the Working Group

The Patient Education Working Group (WG) was charged with evaluating whether the Agency should require a patient education component, as part of the REMS for opioid analgesics, to reduce their risks while ensuring that patients with a legitimate need for these drugs continue to have appropriate access.[4] The purpose of this component would be to help patients develop a better understanding of how to use opioid products by providing them with information, through multiple channels, on the safe use of long-acting and sustained-release opioid products.

Summary of Recommendations

The WG recommends that two elements be included within the REMS framework:

- A pain treatment agreement
- A patient education handout

In addition, the WG recommends that a Web site be developed as part of the Safe Use Initiative to make available to patients and prescribers educational materials about the use of opioid products, including information from the Pain Treatment Agreement and Patient Education Handout. These elements will provide information about safe use of long-acting and sustained-release opioid products to patients

[3] In addition, an eighth working group was created to handle external communications about the REMS. That working group was not involved in the review of comments and did not create a report.

[4] Miaskowski, C. The use of risk-management approaches to protect patients with cancer-related pain and their healthcare providers. *Oncology Nursing Forum*, 2008, 35 (6), Supplement: 20-24. Miaskowski notes the risk for under treatment as well as risk for abuse or addiction, and the need for a balanced perspective.

through multiple channels—printed materials, in-person education with the prescriber, and on-line—and important messages will be repeated.

These materials should help create a better understanding by patients of how to use opioid products safely, including the importance of taking opioid analgesics only as directed, the need for secure storage and disposal, and an awareness of possible serious adverse events, including death.

Summary of Issues / Concerns

The WG reviewed comments and suggestions FDA has received at meetings and in documents submitted to the public docket concerning the need for more patient education, including proper use, storage, and disposal of opioid analgesics.[5] The annual National Survey on Drug Use and Health (NSDUH), sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA), was also studied by the WG. NSDUH is the primary source of information on the use of illicit drugs, alcohol, and tobacco in the civilian, non-institutionalized population of the United States aged 12 years old or older. The 2008 survey found that among persons aged 12 or older in 2007 to 2008 who used pain relievers non-medically in the past 12 months, 55.9% got the drug they most recently used from a friend or relative for free and 81.7% reported that the friend or relative had obtained the drugs from just one doctor.[6] The WG determined that these results support the need for educating patients about the serious adverse events of these drugs and demonstrate that sharing these drugs can have fatal outcomes. These survey results, research outcomes, and comments submitted to the docket were analyzed by the WG and used to assist in the development of patient education elements for the proposed REMS for opioid analgesics.

The WG believes that including a *Pain Treatment Agreement* (PTA) would provide a mechanism to clearly establish boundaries around the use of opioid analgesics. However, implementing a PTA as part of the opioid REMS would be problematic because of the time burden for prescribers who treat large numbers of pain patients and the difficulty in verifying and enforcing the use of a PTA in the absence of a patient registry. Yet research has demonstrated the positive effects of PTAs,[7] and the WG believes that the benefits of using a PTA outweigh the burdens. The additional time spent properly informing the patient up front will lead to better-educated patients who understand the seriousness of misusing and sharing these drugs.

Additionally, the WG believes that including a *Patient Education Handout* as part of the opioid REMS offers many benefits. However, obstacles that could limit the tool's effectiveness need to be considered (e.g., the burden for healthcare prescribers of reviewing the handout with the large number of patients that are prescribed opioid analgesics). The absence of a patient a registry, which would make it difficult

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[5] Inciardi, JA, Surrattt, HL, Cicero, TJ, and Beard, RA. Prescription opioid abuse and diversion in an urban community: the results of an ultra-rapid assessment. *Pain Medicine*, 2009, 10 (3): 537-548. Inciardi, et al., found that patient education appears appropriate in the areas of safeguarding medications, disposal of unused medications, and understanding the consequences of manipulating physicians and selling their medications.

[6] Substance Abuse and Mental Health Services Administration. (2009). *Results from the 2008 National Survey on Drug Use and Health: National Findings.* (Office of Applied Studies, NSDUH Series H-36, HHS Publication No. SMA 09-4434). Rockville, MD.

[7] Johnson, KE, et al. Evaluation of a chronic pain policy at a rural Indian health service clinic. *The IHS Primary Care Provider,* 2005; 30(12): 299-305; and Doleys, DM and Rickman, L. Other benefits of an opioid agreement. *Journal of Pain and Symptom Management,* 2003; 25(5): 402-403.

to verify and enforce whether a healthcare prescriber reviewed the handout with a patient, is another concern, as is funding, should healthcare professionals be expected to print the handout.

The recommended *Federal Web site* would serve as a one-stop shop for neutral, consistent, FDA-approved information and more detailed messages than would be included in the handout and PTA documents. The WG believes that the Web site would be valuable because it would allow patients to view regularly updated material at their own pace and in the privacy of their own home. However, the Web site presents two challenges:

- Because it would not be part of the opioid REMS, FDA and/or its partners would need to fund its development and maintenance, which may be expensive.
- Not all patients have access to a computer or the Internet,[8] or they may not be comfortable accessing health information in this manner.

Nevertheless, the WG believes that even with major resource requirements for the Web site, it should be included as part of its multi-channel approach to patient education.

The WG recommends using a multi-channel, iterative, messaging approach because it would provide the greatest potential in reaching patients. One method is not always effective for every audience and, as noted by the Industry Working Group (IWG), adults need to hear a message multiple times before it is learned.[9] In addition, independent of the methods employed, the WG strongly urges that messages be tested before and periodically after the start of the opioid REMS to ensure that the right message is being communicated. Messages can be edited as new information becomes known about the safe use of opioid analgesics.

Detailed Discussion of Specific Issues

The WG recommends two REMS elements to assure safe use: the *Pain Treatment Agreement* (PTA) and a *Patient Education Handout,* and one component as part of the Safe Use Initiative—the Federal Web site. The WG's perspectives, thoughts, and concerns are discussed in detail in the following sections.

Pain Treatment Agreement

The Pain Treatment Agreement (PTA) is a document that could be standardized for all opioid REMS products, defining the responsibilities of the prescriber and patient regarding the opioid analgesic prescription. The PTA is similar to a Prescriber-Patient Agreement (PPA), except for the fact that PPAs include monitoring and the PTA will not. As envisioned by the WG, the sponsor would develop this additional plain-language patient education document at an acceptable reading level and in multiple languages and Braille. The PTA would include action statements derived from the messages about safe use of opioid analgesics, misuse of opioid analgesics, and general messages. An example of an active

[8] More than 80% of Americans have a computer in their homes, and of those, almost 92% have Internet access. See Nielson Company, The Home Technology Report. December 2008, accessed on 1/4/10 from http://blog.nielsen.com/nielsenwire/wp-content/uploads/2009/03/overview-of-home-internet-access-in-the-us-jan-6.pdf.

[9] Marsha Stanton of King Pharmaceuticals, IWG participant at the FDA, December 4, 2009, meeting transcript, page 122.

action statement the PTA would employ would be, "I agree to not share, sell, or in any way provide my medication to any other person." The PTA would be used with all pain patients except for those treated in in-patient facilities, such as hospitals, hospices, and nursing homes. The PTA would be a REMS Element to Assure Safe Use.

To facilitate prescriber adherence, prescriber education would have to include the importance of reviewing the PTA with patients, setting a functional goal with patients when appropriate (see below), signing the agreement, and obtaining patients' signatures on the agreement. The PTA would be pretested to ensure intended messages are accurate and understood.[10]

The value of the PTA is that it goes beyond the Patient Education Handout as an educational tool. It would compel the prescriber and the patient to pay special attention to the requirements to which they are agreeing by signing the document. This accountability of prescribers and patients was supported by some stakeholders (i.e., the American Society of Health System Pharmacists and Rienzi & Rienzi Communications). Additionally, a PTA could help standardize communication between prescribers and their patients when the opioid REMS is rolled out and would serve as a mechanism to clearly establish boundaries around the use of opioid analgesics.

The WG also considered some of the drawbacks of using a PTA. It would place additional burden on prescribers and patients. Review of the PTA would be a time burden for prescribers and patients, especially for prescribers who treat large numbers of pain patients. Moreover, signing a PTA would not necessarily mean that patients will abide by the agreement and not misuse or share the opioid drugs. Finally, as mentioned with the Patient Education Handout, without a patient registry, which may not be feasible given the numbers of patients taking the affected products, with it would be difficult to verify and enforce the use of a PTA.

Despite these drawbacks, the WG believes that the benefits outweigh the burdens. The burden to patients and physicians as more time is spent properly educating the patient up front would lead to better educated patients who understand the seriousness of misusing and sharing these drugs. The positive effects of PTAs have been demonstrated by research[11] and confirmed by the opinions of officials in the Department of Veterans Affairs (VA)[12] and the Industry Working Group. Finally, the Utah Department of Health uses a PTA for its pain patients, and although it has not evaluated it, the prescribers believe their PTA is worth using.[13]

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[10] Meeting with Nicholas Reuter, Senior Public Health Advisor, Center for Substance Abuse Treatment (CSAT)/Division of Pharmacologic Therapies (DPT); and Robert Lubran, Director, CSAT/DPT, SAMHSA, September 22, 2009. There is a need to pretest all patient tools to determine if the right message is being communicated.

[11] Johnson, KE, et al. Evaluation of a chronic pain policy at a rural Indian health service clinic. *The IHS Primary Care Provider,* 2005; 30(12): 299-305; and Doleys, DM and Rickman, L. Other benefits of an opioid agreement. *Journal of Pain and Symptom Management,* 2003; 25(5): 402-403.

[12] Telephone interview with Robert M. Kerns, National Coordinator for Pain Management, Veterans Health Administration, Department of Veterans Affairs, October 19, 2009.

[13] Telephone interview with Erin Johnson, Program Manager, Prescription Pain Medication, Utah Department of Health, November 16, 2009.

Functional Goals

An optional feature of the PTA would be for the prescriber and patient to develop a functional goal and timeframe related to treatment of the patient's chronic pain with opioid analgesics.[14] A functional goal would be developed for something that the patient wants to do but can do no longer because of his or her pain. An example of a functional goal might be the patient once again will be able to walk to the mailbox without assistance by the second week of treatment. If the functional goal is not met within the timeframe, the prescriber and patient would review and update the treatment agreement and set a new target date to meet the goal. Therefore, the PTA would be reviewed with the patient at each functional goal target date. The prescriber and patient would both sign the PTA with the original filed in the patient's medical records, with a copy given to the patient. If no functional goal is set, the PTA should be reviewed and signed every 6 months.

Patient Education Handout

As envisioned by the WG, the Patient Education Handout would be a single-paged, standardized document that is developed by the sponsor, approved by FDA, and written in plain language at an acceptable reading level. The handout messages, outlined below, would include information on the safe use and misuse of opioid analgesics.

<u>Examples of communication messages about safe use of opioid analgesics:</u>

- Pain management is important
- Reason that drug has been prescribed
- Information about the drug (e.g., active ingredients, narcotic)
- Dosing instructions (e.g., take only as directed)
- Potential side effects (e.g., drowsiness, dizziness, and risk of addiction, unintentional overdose, opioid tolerance, or death)
- Symptoms of overdose and message that overdose can lead to death if not properly treated
- With signs of overdose, call 911
- Warnings (e.g., there is potential for abuse or misuse, do not change dosing on your own, do not drink alcohol while taking this drug, extra caution is necessary if taken with sleeping, anti-anxiety, antihistamine, and tranquilizing medication as well as with other pain medication)
- Information on addiction treatment

<u>Examples of communication messages about misuse of opioid analgesics:</u>

- Information about secure storage of opioid analgesics
- Sharing of opioid analgesics is illegal
- Information about safe disposal of unused opioid analgesics

<u>Examples of communication general messages:</u>

[14] Telephone interview with Erin Johnson, Program Manager, Prescription Pain Medication, Utah Department of Health, November 16, 2009. Prescribers in Utah are encouraged to develop functional goals with pain patients as a way, if possible, to ensure that patients' concerns are met. Although functional goals are not widely used by prescribers, many therapists, including physical therapists, use functional goals to determine success with the treatment.

- Patients should talk to their healthcare prescriber or pharmacist for more information
- Patients can ask for information written for healthcare prescribers
- Link to Web site
- Explain all components of the opioid analgesics REMS, including any exceptions, such as if the patient's signature is required to obtain the prescription and the patient is incapacitated, then a caregiver can sign for the prescription

This handout would be printed in multiple languages and in Braille and pretested to ensure intended messages are accurate and understood.[15] The sponsor would create the handout, which would include Web site links and telephone numbers to additional resources. The handout would be a REMS Element to Assure Safe Use.

The Patient Education Handout would be reviewed by the prescriber with the patient and caregivers at each visit for the prescription. The prescriber would review the handout and answer questions that the patient may have concerning the prescription. To facilitate prescribers' adherence to this REMS element, the prescriber education needs to include the importance of distributing and reviewing the handout with patients and caregivers. After the prescriber visit, a trained healthcare provider, such as a registered nurse, would summarize the key points of the handout with the patient and ask if the patient has any questions. Therefore, the handout would be reviewed with the patient and caregivers twice at each visit.

The WG believes that the Patient Education Handout would serve as the universal document to educate patients about the prescribed opioid analgesic, minimizing confusion from multiple documents by eliminating multiple drug information documents. Many stakeholders supported the handout, including CVS Caremark and the National Association of Chain Drug Stores, as does the Industry Working Group. Review of the handout by the prescriber and a trained healthcare professional at every prescriber visit would provide consistent messages, which would increase the knowledge and retention by patients, as well as raise awareness of risks. Moreover, as just one aspect of a multi-channel patient education strategy, this practice would contribute to the strategy of having various methods of patient education, which research has shown to be successful.[16]

The information provided in the Patient Education Handout would relay information to the patient about the opioid analgesic prescribed and how to secure the medication to minimize contact with other household members. Educational discussions between prescriber and patient would provide an opportunity to determine the patient's ability to store the medication securely. In addition, prescriber communication with the patient is important and has been found to be positively correlated with patient adherence to treatment.[17] Last, the handout would serve as a mechanism to make the patient aware of the possible risks of abuse and misuse associated with opioid analgesics.

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[15] Meeting with Nicholas Reuter, Senior Public Health Advisor, Center for Substance Abuse Treatment (CSAT)/Division of Pharmacologic Therapies (DPT); and Robert Lubran, Director, CSAT/DPT, SAMHSA, September 22, 2009. There is a need to pretest all patient tools to determine whether the right message is being communicated.

[16] Syrjala, KL, et al. Patient training in cancer pain management using integrated print and video materials: A multisite randomized controlled trial. *Pain,* 2008; 135: 175-186.

[17] Zolnierik, HK and DiMatteo, MR. Physician communication and patient adherence to treatment: a meta-analysis, *Medical Care*, 2009; 47(8): 826-834.

Despite the many benefits of having a Patient Education Handout, some obstacles could arise that may limit the tool's effectiveness. First, reviewing the handout with the patient is a time-intensive activity; and given the large number of patients that are prescribed opioid analgesics, it could be a burden for healthcare prescribers.

The WG has identified other challenges to including this document in the REMS. For example, in the absence of a patient registry, it would be difficult to verify and enforce whether a healthcare prescriber reviewed the document with a patient. Also, if healthcare professionals are expected to print the Patient Education Handout, funding may be an issue. The WG considered requiring the pharmacist to review the handout with the patient, but was concerned that this would be impractical because it would require a costly change to the practice of pharmacy to implement such activities.[18]

Even with disadvantages to including a Patient Education Handout, the tool's obstacles and limitations do not significantly reduce its utility. The handout would still be a useful patient educational instrument.

Federal Web site

The Federal Web site that the WG recommends be developed would provide stand-alone education and training about all opioid analgesics affected by the opioid REMS, as part of the Safe Use Initiative, launched by FDA in 2010.[19] The Web site would serve as an educational resource for patients and caregivers as well as for prescribers, pharmacists, and the public.

The Federal Web site would provide comprehensive, detailed information on the safe use of opioid analgesics, misuse of opioid analgesics, and general messages that provide more detail than what will be found in the Patient Education Handout and the PTA documents. Much of the content would be crafted into interactive education for patients, as well as training for healthcare professionals. The Web site also would provide information on addiction treatment, which is not included in either the Patient Education Handout or the PTA. The Web site would be tested for usability and accuracy of message, and modified as needed.

The Federal Web site would serve as a one-stop shop for neutral, consistent information approved by FDA. From the WG perspective, a Web site is valuable because it allows patients to view material at their own pace and in the privacy of their own home, and information on the Web site can be updated as it changes. A Web site would facilitate patient health literacy, which can create an understanding to minimize abuse, misuse, and sharing of opioid analgesics, and should be included as a component of the multi-method approach to patient education. Research[20] and State experience[21] (i.e., Utah's state Web site) demonstrate patient education from a Web site can be successful. The development of a Web site is supported by the American Society of Clinical Oncology.

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[18] Resnick, DB, Ranelli, PL, and Resnik, SP. The conflict between ethics and business in community pharmacy: what about patient counseling? *Journal of Business Ethics,* 2000, 28: 179-186.

[19] See FDA's Safe Use Web site at http://www.fda.gov/Drugs/DrugSafety/ucm187806.htm.

[20] Syrjala, KL, et al. Patient training in cancer pain management using integrated print and video materials: A multisite randomized controlled trial. *Pain,* 2008; 135: 175-186.

[21] Review of State Web sites with patient education regarding prescription drug abuse.

The WG identified two key issues related to developing a Federal Web site. First, because the Web site will not be part of the opioid REMS, the FDA and/or its partners would need to fund its development and maintenance, which may be expensive. Second, not all patients have access to a computer or the Internet,[22] or they may not be comfortable accessing health information in this manner. Even with the Web site's major resource requirements, the WG recommends it should be included as part of the multi-method approach to patient education.

The WG has identified three options for funding the development and maintenance of the Federal Web site: (1) FDA and federal partners, (2) Sponsors who hold approved applications for opioid analgesics, and (3) public-private partnerships such as the partnership between the National Institutes of Health (NIH) and Friends of the National Library of Medicine (NLM). However, more research is required to determine the costs and viability of each option. Due to time constraints, the WG was only able to discuss these options from a very high level perspective.

- FDA and federal partners

  FDA could develop the content along with potential partnering agencies, including the Centers for Disease Control and Prevention (CDC), NIH, and the Substance Abuse and Mental Health Services Administration (SAMHSA). The different Federal partners would share the costs. This option would enhance working relationships between FDA and Federal partners in this joint effort. With the Federal partners controlling the Web site, it may be viewed as a trusted source of information.

- Sponsors holding approved applications for an opioid analgesics

  The sponsors holding approved applications for opioid analgesics could develop and maintain the Web site. FDA would monitor the Web site for accuracy of content. This option would greatly reduce startup and maintenance costs of the Web site for FDA, requiring resources for monitoring purposes only. However, information may be perceived by patients as being more favorable to the manufacturer.

- Public-private partnerships

  FDA could solicit a public-private partnership through a memorandum of understanding (MOU) with a well respected health information Web site (e.g., WebMD) to host an opioid REMS Webpage. Although the current MOU with WebMD may not be an appropriate mechanism for this partnership, it provides a precedent for such collaboration. This type of public-private partnership would greatly minimize any initial or maintenance funding that FDA would need to provide because the agency mainly would be contributing the content. Using a private health information Web site will also draw more viewers to the opioid REMS Web page due to its established customer base and name

[22] More than 80% of Americans have a computer in their homes, and of those, almost 92% have Internet access. See Nielson Company, The Home Technology Report. December 2008, accessed on 1/4/10 from http://blog.nielsen.com/nielsenwire/wp-content/uploads/2009/03/overview-of-home-internet-access-in-the-us-jan-6.pdf.

recognition.[23] Many consumers and healthcare professionals view Web sites such as WebMD and Medscape as reputable sources of information.

Another example of a public-private partnership is the partnership among NIH components, including the National Library of Medicine (NLM), the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute of Neurological Disorders and Stroke (NINDS), and the Friends of NLM.

NLM could be the host of the Federal Web site, with the funding coming from institutes conducting work on pain treatments (NLM, NCI, NIDA, and NINDS), as well as from Friends of NLM, a not-for-profit private entity formed in 1986 to support the NLM. NLM already has a following of healthcare professionals on its Medline/PubMed/DailyMed sites and consumers on its MedlinePlus site. MedlinePlus has a page dedicated to information on pain, with some information translated into 15 languages. NLM has experience with educating the public about important issues and has created more than 165 video tutorials.

Alternative Options

The WG considered four alternative options to enhance patient education. The options were found to be untenable for a variety of reasons, including being too costly or requiring a patient registry, which is not considered to be feasible because of the number of patients taking long-acting and extended release opioids. [24] The WG considered all options from the standpoint of the sponsor, the prescriber, the patient, and the public.

- Use of Inflexxion's Web site

The WG considered use of an existing Web site managed by Inflexxion.[25] The Web site provides on-demand training and post-tests focused on the safe use of opioids for back pain, migraine pain, and cancer pain. The Web site has additional plans with NIH funding to develop sections containing information on arthritis pain, neuropathic pain, and fibromyalgia pain. Spanish-language versions of some offerings on the site are already under development. The site also offers personal stories and shared knowledge sections are offered on this site as well.

The advantage of this Web site is that it is already in place and functioning. The possibility of continued funding from the NIH exists to offset costs. This option would be a one stop shop for consistent prescription information. Patients could view the Web site in the privacy of their home, decreasing the stigma that many feel about opioid use. Consistent information at the fingertips of the public could greatly increase public awareness and mitigate risk.

[23] The FDA and WebMD partnership was launched in December 2008, with the goal to reach consumers with important safety information. Since the launch, over 150,000 consumers have accessed the FDA destination on WebMD for health and wellness information on issues, ranging from egg safety to contact lens safety to medicine safety. FDA's consumer information is also available through *WebMD the Magazine*, distributed ten times a year and reaching an additional 11 million consumers with each issue.

[24] The PEWG did not consider a patient registry because of the unprecedented large number of patients taking the opioid analgesics that require a REMS and concerns regarding patients' privacy.

[25] Inflexxion's Web site is www.painaction.com.

FDA's lack of control over the information presented on the Web site is a disadvantage. The public and industry as a whole may view the use of the Inflexxion site as favoritism to a particular vendor. Sponsors' buy-in may be difficult to achieve as they would lack control over the information presented about their products.

- No Sharing Stickers

The WG considered the addition of "No Sharing" stickers on medication packaging. The pharmacist would add the stickers at the point of dispersion of the medication. "No Sharing" stickers would remind patients to not share their medication. These types of stickers have been used with other medications with REMS, such as isotretinoin. Unfortunately, research provides no evidence that the "No Sharing" stickers actually deter unwanted behavior. Medication bottles are often already covered with other types of stickers making it difficult for patients to see the dosing instructions. Sponsors and pharmacies may feel overburdened with the sticker cost and the time it takes to place them on every opioid medication leaving the pharmacy.

- Patient Quizzes

The WG also considered use of quizzes to verify patient knowledge and understanding of the safe use of opioid analgesics. After the patient receives the prescription, he or she, or a caregiver if the patient was unable to do it, would have to pass a quiz on the Federal Web site. Once the patient has passed the quiz, this information would go on the Web site so the pharmacist can verify that the patient understands the medication before dispensing the prescription. The patient would be required to complete a new quiz with each new prescription refill. Multiple quiz versions would be available. The option would require a patient registry and a prescription monitoring program with a mechanism for pharmacists to verify completion of the required quiz. The option would include outpatients only, which would exclude in-patient hospice and hospitalized patients.

The quiz and the database itself would enable prescribers and pharmacists to determine if the patient receives and understands the education provided to them about opioid use. FDA would receive feedback on the education provided, which would be consistent across the entire patient population. Repetition of the quiz with each prescription would increase retained knowledge. However, multiple obvious disadvantages exist within this option. A Federal Web site would have to be available for the quizzing to take place. A patient registry would be required adding to the stigma that is already associated with opioid use, and a registry is believed to be infeasible because of the numbers of patients affected. Many patients may not have the stamina to complete the quiz. It would be difficult to determine whether patients actually took the quiz. Caregivers would be required to take the quiz if the patients were at home and unable to take it themselves. Language barriers exist that could not be appropriately mitigated on a Federal Web site. Individuals without Internet access would be unable to take the quiz, and could be deprived of access to needed medications.

- Pain Management Program

The Pain Management Program could be a sponsor-run system that enroll patients in the program and create specific educational messages for each patient. For example, if a patient lives with

teenagers, information would be sent to the patient concerning deaths from misuse of opioids and thus the need for secured storage of the drug. Two methods of enrollment could be used: opt-in, where patients are asked if they want to participate in the program; and opt-out, where patients are automatically enrolled and need to request not to participate. The Pain Management Program would be based on the disease management programs that insurance companies use to help keep patients well and thus save the insurance companies money. However, without a patient registry, this option would be difficult to implement and enforce.

CONCLUSIONS

The WG recommends that the REMS require sponsors to develop a pain treatment agreement and a patient education handout that can be used by prescribers to educate patients about the risks and appropriate use of long-acting and extended release opioids.

In addition, the WG recommends that a Web site be developed as part of the Safe Use Initiative to make available to patients and prescribers educational materials about the use of opioid products, including information from the Pain Treatment Agreement and Patient Education Handout.

These materials should help create a better understanding by patients of how to use opioid products safely, including the importance of taking opioid analgesics only as directed, the need for secure storage and disposal, and an awareness of possible serious adverse events, including death.

Risk Evaluation and Mitigation Strategy for Opioid Analgesics
Final Report of the Pharmacist Education Working Group

June 2010[1]

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BACKGROUND

In early 2009, FDA sent letters to manufacturers of certain opioid drug products, indicating that these drugs will be required to have a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drugs continue to outweigh the risks. FDA explained that the REMS would include elements to assure safe use to make certain that prescribers, dispensers, and patients are aware of and understand the risks and appropriate use of these products. FDA also stated that, with limited exceptions, the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires generic and innovator products to use a single shared system to implement the elements to assure safe use. The affected opioid drugs include long-acting and extended-release (LA/ER) brand name and generic products and are formulated with the active ingredients fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.

FDA is mindful of provisions in FDAAA that require elements to assure safe use to be, among other things, commensurate with the specific serious risk listed in the labeling of the drug, not unduly burdensome on patient access to the drug, and designed to be compatible with established distribution, procurement, and dispensing systems.

To obtain public input on how best to design a REMS for this class of drugs, FDA held a series of meetings with relevant stakeholders (May 4 and 5, 2009; May 27 and 28, 2009; December 4, 2009) and opened a public docket to receive public comments on relevant issues. Meeting minutes of the May 4 and 5 stakeholder meetings, and transcripts of the May 27 and 28, and December 4 meetings are in the docket and on FDA's Web site.[2] FDA plans to provide an additional opportunity for public input before finalizing the elements of the REMS.

Following the meetings, FDA formed an Opioid REMS Steering Committee, a multidisciplinary team from throughout the Center for Drug Evaluation and Research. To thoroughly analyze the substantial public and stakeholder input received on the development of the REMS and to conduct additional research, the Steering Committee formed seven[3] work groups to focus on the various aspects of an opioid REMS and the effects of possible components of the REMS on use.

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[1] The conclusions in this report were formulated in December 2009, and the report was completed in June 2010.
[2] See http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm.
[3] In addition, an eighth working group was created to handle external communications about the REMS. That working group was not involved in the review of comments and did not create a report.

Following their analysis, the work groups were asked to provide recommendations to the Steering Committee for consideration as it develops options for what should be included in the REMS. The seven work groups addressed the following areas:

- Scope of an opioid REMS
- Prescriber education
- Pharmacist education
- Patient education
- Pharmacy systems
- Effect of possible restrictions on patient access to pain medication
- Metrics

This is the report and recommendations from the Pharmacist Education Working Group.

GOAL OF THE WORKING GROUP

The Pharmacist Education Working Group (WG) was charged with evaluating whether the Agency should require pharmacist education or pharmacist certification to dispense opioid products to patients as part of the REMS. The purpose of the certifications would be to ensure that pharmacists are educated about the risks of these products and that they understand the importance of counseling patients on the safe and appropriate use of these prescription medications. Certification of pharmacists as an element to assure safe use (ETASU) of an LA/ER opioid REMS could include some or all of the following requirements: pharmacists have a thorough understanding of the risks and benefits associated with these drug products; have special training on how to administer the products; agree to fill prescriptions for and dispense these drugs only after receiving prior authorization; agree to fill prescriptions for and dispense these products only within specified timeframes; and agree to only fill prescriptions from enrolled prescribers; agree to counsel patients on the safe and appropriate use of opioids.

SUMMARY OF RECOMMENDATIONS

The Pharmacist Education Working Group recommends that the REMS for LA/ER opioids not require pharmacist education or pharmacist certification. No additional training or regulatory oversight is warranted for pharmacists beyond that which already exists within the pharmacy profession. The WG also recommends against mandatory pharmacist counseling of patients.

SUMMARY OF ISSUES AND CONCERNS

The WG focused its work on three specific issues:

- Whether the REMS should require pharmacist education and certification.
- Whether a REMS that requires pharmacist training and certification should also require mandatory patient counseling
- Whether if such training were to be required as part of an opioid REMS, industry or someone else should provide training to pharmacists

Because the WG does not believe that additional pharmacist training and certification would mitigate risks in the use of SR/LA opioids, the WG recommends no additional training or regulatory oversight for pharmacists beyond what already exists as part of professional training. Opioid products are heavily regulated by the Drug Enforcement Agency (DEA) and pharmacies require special pharmacy licensure to

stock them, strict inventory control, special storage, and special order forms, among other things. Current federal and state laws, as well as regulations from other agencies, provide more than adequate oversight and guidelines for dispensing and managing opioid drug products. Additionally, new prescriptions must be written each time the products are dispensed.

Pharmacists already are knowledgeable about the risks associated with controlled substances, including LA/ER opioids, and it remains unclear whether pharmacists contribute to the problem of inappropriate patient selection, abuse, misuse, and addiction. They are already required to identify any therapeutic problem and use their professional judgment on a daily basis, as this is recognized as a standard of pharmacy practice. With most REMS programs, pharmacists have the responsibility for dispensing Medication Guides to patients. In some circumstances, they are also required to comply with certain procedural requirements, such as verifying prescriber eligibility to prescribe certain products.

Were a requirement for pharmacist training to be imposed, it would be difficult to determine who should provide the training, although industry would be best positioned to provide it.

The WG considered whether if the REMS required pharmacist education and certification, it should also require patient counseling. Concerns were raised that the current pharmacy systems, especially those in the retail settings, would not be conducive to interventions such as patient counseling under a REMS, although pharmacists would be involved in routine interventions, such as conducting drug use reviews and providing patient counseling for any prescription product that they dispense. Additionally, current pharmacy systems are not designed to enable pharmacists to ensure that the right prescription was written by the prescriber for the right patient under the right conditions (i.e., opioid tolerant) — although there are efforts under way by several pharmacy organizations to change the business model for pharmacies and move towards a patient care-based model that would include pharmacists as an integral part of the healthcare system and allow for patient counseling.

In sum, when the requirements for pharmacist education or pharmacist certification are viewed within the context of the regulatory constraints already placed on pharmacists, it appears that additional requirements would not be warranted**.**

DETAILED DISCUSSION OF SPECIFIC ISSUES

After considering the issues and the advantages and disadvantages of several options, the Pharmacist Education WG concluded that the REMS for LA/ER opioid products should not require pharmacist education and certification. The following paragraphs outline the WG's thinking on the issues, including on the benefits and drawbacks of certification, patient counseling, and industry provided training.

Requiring Pharmacist Education and Certification in the Opioid REMS

Despite the many positive efforts on the part of FDA in recent years through additional labeling requirements, collaboration with its partner federal agencies, and increased communication with physicians and patients, in many instances, prescribers, dispensers, and patients remain under-informed about the risks associated with these products. However, to be able to stock and dispense opioid drug products, pharmacies and pharmacists are already heavily regulated (e.g., by the DEA, state, and local governments). Requiring another layer of regulation for dispensing and stocking LA/ER opioids or mandatory certification could create unanticipated consequences, the most significant of which might be a reluctance to stock and dispense these products. As LA/ER opioids (oxycodone, oxymorphone, hydromorphone, fentanyl, methadone) comprise only a small fraction of the total prescription market

(0.5% dispensed in retail settings over the past three years), pharmacists might simply refuse to stock the LA/ER opioids.[4] Community pharmacies/pharmacists are already afraid of being victimized by criminals for certain drugs that are highly desired for abuse and diversion. *The Journal of Law, Medicine & Ethics* stated that some pharmacists are reluctant to stock these drugs, thus restricting patient access.[5] A published survey in the *Journal of the American Pharmacists Association* reported that 46% of pharmacists viewed diversion and abuse of prescription opioids as a problem in their community.[6] A REMS requirement at the pharmacy level would only provide another disincentive to stocking prescription opioids.

A review of federal legislation affecting pharmacy practice published in *Pharmacy Times*[7] stated that the main goal of every federal law that affects the practice of pharmacy is to protect the health, safety, and welfare of the patient from the potential risk of drug use or misuse. Federal and state laws and DEA regulations have imposed very tight regulations (e.g., the Controlled Substances Act, the Corresponding Responsibility Rule), which govern distribution and dispensing of these products. Under the Corresponding Responsibility Rule, DEA regulations provide guidance for pharmacists to use their professional judgment to screen for suspicious prescriptions and prevent their diversion and to ensure the therapeutic appropriateness of the prescribed opioid analgesics. This guidance explains the pharmacist's duty to the patient beyond technical accuracy in order processing. Based on published surveys, the majority of pharmacists (87%) already are able to distinguish legitimate prescriptions for opioids from non-legitimate scripts.

Additionally, an article published in *the Journal of Law, Medicine & Ethics* in 2001[8] stated that "The DEA admits that over-regulation of these drugs would interfere with effective therapy and do more harm than good." Pharmacy certification requiring the pharmacist-in-charge (PIC) to ensure that all pharmacy staff (i.e., full time, part-time and floater pharmacists) receive training in the REMS program and are compliant with the program requirements would create substantial additional responsibility and liability for pharmacists.

Imposing interventions in the pharmacy setting would very likely be burdensome on the healthcare system while providing uncertain benefit. The WG concluded that if the other initial REMS interventions prove insufficiently effective, interventions at the pharmacy level could be considered at a later time.

Mandatory Patient Counseling

There are data to support the positive impact pharmacists provide in patient counseling upon discharge from the hospital. Benefits include a reduced rate of preventable adverse events, hospitalizations, ED visits, and primary care visits. A study published by Arch Intern Med (2006) showed the intervention group that received pharmacist counseling upon discharge from the hospital and a follow-up phone call had a lower rate of preventable adverse events compared to the control group (1% vs 11%, P=0.01).[9] Also, the rate of

[4] CDER-OSE/DEPI-consult Nov 2009.
[5] Brushwood D. From confrontation to collaboration: collegial accountability and the expanding role of pharmacist in the management of chronic pain. *Journal of Law, Medicine & Ethics*, 2001 (29):60-93.
[6] Pharmaceutical care in chain pharmacies, *JAPhA*2001; 41.
[7] Dusen V V, Spies A. A review of federal legislation affecting pharmacy practice. *Pharmacy Times*, 2006, ACPE.
[8] Brushwood D. From confrontation to collaboration: collegial accountability and the expanding role of pharmacist in the management of chronic pain. *Journal of Law, Medicine & Ethics.* 2001 (29):60-93.
[9] Schnipper J, Kirwin J, Cotugno M, et al. Role of pharmacist counseling in preventing adverse drug events after hospitalization. *Arch Intern Med*. 2006; 166:565-571.

preventable, medication-related emergency department (ED) visits or hospital re-admissions was lower in the intervention group compared to the control group (1% vs 8%, P=0.03).[10]

Other literature provides support for the concept that when pharmacists are trained and used to their full professional capacity, including providing face-to-face patient counseling, they play a critical role in improving patient outcomes with chronic diseases and ultimately, public health in their communities. A study published by the Journal of the American Pharmacists Association(JAPhA) (2003) showed that when trained pharmacists provided face-to-face counseling to diabetes patients in Asheville N.C , patient adherence to four behaviors targeted by diabetes care guidelines improved significantly (patients monitoring A1c by 18%, foot exam by 43% , using ACEI by 38% and self-testing blood sugar by 92%).[11] With this PCS program, the employers made the program part of their health plan benefit. A second study published by JAPhA (2006) also showed that when trained pharmacists provided patient counseling under community-based medication therapy management (MTM) for asthmatic patients (N=207), it had both positive clinical and economic outcomes that continued for a five-year period. Emergency department visits decreased from 9.9% to 1.3%, and hospitalization from 4% to 1.9%.[12] In 2008, a third study published by the same journal showed that trained pharmacists providing scheduled face-to-face patient counseling under community-based MTMs for patients (N=620) with chronic cardiovascular diseases, hypertension and hyperlipidemia also had both positive clinical and economic outcomes over a six-year period: the percentage of patients who achieved targeted blood pressure increased from 0.25 to 67.4%; the percentage of patients who reached LDL cholesterol goal increased from 49.9% to 74.6%; the rate of cardiovascular (CV) events decreased by half during study period (77/1,000 persons vs 38/1,000 person-years).[13] Overall, the number of CV events per year ranged from 0 to 5 during the historical period; the number decreased to 0–2 CV events per year during the study period. The emergency visits and hospitalizations decreased overall by 54% during the study period (P<0.0001).

The Comprehensive Drug Abuse Prevention and Control Act of 1970 (Pub L .No. 91-513), known as the Controlled Substance Act (CSA), lays out requirements for pharmacists for dispensing controlled substances, and regulations at 21 CFR 1306.04 discuss corresponding responsibilities that instruct pharmacists as to their expected conduct. In addition, case law (see discussion of *McLaughlin v. Hook SuperX* that follows) has demonstrated that a pharmacist also has the legal duty to intervene to inform the prescriber of a patient's overuse and educate the patient on potential dependence and addiction through patient counseling. Failure to perform these duties and ensure therapeutic appropriateness of the prescription has resulted in lawsuits brought against pharmacists.

This focus on patient counseling is, to a large extent, the result of the Omnibus Budget Reconciliation Act of 1990 (OBRA '90). The U.S. Congress enacted the OBRA '90 Act, on November 5, 1990.[14] This legislation contains 13 titles addressing a variety of areas. The act requires the states to improve understanding of medications by Medicaid beneficiaries for whom they were prescribed and dispensed.[15] In short, the

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[10] Ibid.

[11] Cranor C, Bunting B, and Christenson D. The Ashville project: long-term clinical and economic outcomes of a community pharmacy diabetes care program. *JAPhA.* 2003; 43 (2): 173-184.

[12] Bunting B, and Cranor C. The Asheville project: long –term clinical, humanistic, and economic outcomes of a community-based medication therapy management program for asthma. *JAPhA*. 2006; 46 (2): 133-147.

[13] Bunting B, Smith B, and Sutherland S. The Asheville project: clinical and economic outcomes of a community–based long term medication therapy management program for hypertension and dyslipidemia. *J Am Pharm Assoc*, 2008; 48:23-31.

[14] Reiss B, Hall G. Guide to Federal Pharmacy Law, 6th edition. Boynton Beach, Apothecary Press, 2008. OBRA 90 and Patient Counseling, 133-137.

[15] Vivian J and Fink J. OBRA '90 at Sweet Sixteen: A Retrospective Review. *U.S. Pharmacist*. 2008; 33(3):59-65.

framers of OBRA '90 are counting on the strength of Drug Use Review (DUR) to ensure quality care and reduce medical costs within State Medicaid programs. OBRA '90 requirements, in support of state Medicaid recipients, make pharmacists responsible for the following, effective January 1, 1993: 1) Prospective Drug Use Review (PDUR), 2) patient counseling, 3) maintaining proper patient records**.** The information that is required to be discussed with the patient during counseling is: (1) name and description of the medication, (2) dosage form, dosage, route of administration, and duration of drug therapy, (3) special directions and precautions for preparation, administration, and use by the patient, (4) common side effects or adverse effects or interactions and therapeutic contraindication that may be encountered, (5) proper storage, (6) action taken in the event of a missed dose.[16] The pharmacist is also expected to perform prospective drug use reviews (PDURs) to identify any drug therapy issues, such as therapeutic duplication, clinical misuse, or abuse of medications. The PDURs are part of pharmacy standard practice. Currently, in about 90% of the states, OBRA '90 requirements apply to all patients.[17]

The WG was concerned that an additional education and certification requirement for pharmacists could potentially increase liability for pharmacists. Especially in the retail setting, pharmacists do not have access to patients' clinical data and would not be able to determine whether or not a patient is opioid tolerant. The pharmacist is at greater risk legally should a patient experience an adverse event about which the pharmacist had knowledge and failed to inform him or her. A malpractice law suit could be brought against a pharmacist if a patient believes that a "negligent" pharmacist has caused injury. As in the case of *McLaughlin v. Hook SuperX* published in the *The Journal of Law, Medicine & Ethics*,[18] pharmacists and the pharmacy were determined liable for failing to notify the prescriber that the patient was overusing the prescribed pain medication, propoxyphene, and for not warning the patient that she or he could become physically dependent. The court ruled that the pharmacist's duty to the patient goes beyond technical accuracy in order processing and includes promoting patient safety. The three factors on which the court based its ruling were: (1) the relationship between pharmacists and patients; (2) the expectation of harm to the patient when an overuse of opioid analgesics occurs and a pharmacist intervention is not undertaken; and (3) public considerations.

To protect themselves from liability, pharmacists might resort to more aggressive behavior in questioning patients in at attempt to verify the legitimacy of these prescriptions. And such behavior could result in job loss from patient complaints and dissatisfaction as demonstrated in overzealous prescription screening in the case of *Ryan vs. Dan's Food Stores*, published in *Pharmacy Times* (2006).[19] In this case, a pharmacist (plaintiff) was terminated from his job by his employer because of numerous complaints by patients. The pharmacist was aggressive in questioning patients with controlled substance prescriptions, suggesting that they were invalid. Occasionally, he simply refused to dispense them by telling patients he was out-of-stock. The pharmacist referred to the Corresponding Responsibilities Rule to support his action and stated he was doing what the law required of him. The court ruled against him, saying that "the rule only prohibits pharmacists from knowingly filling suspect prescriptions. It does not mandate or even authorize a pharmacist to question every prescription or to conduct an investigation to determine whether an otherwise factually valid prescription has been issued other than in the usual course of the doctor's practice."

Furthermore, it appears that patient counseling under OBRA '90 has not been enforced and OBRA '90 has not achieved the desired outcome. JAPhA (2001) and Drug Topics (2007) cited several barriers as contributing to OBRA '90's lack of success, including but not limited to, lack of time,

[16] Ibid.
[17] Ibid.
[18] Ibid.
[19] Dusen V Vand Spies A. A review of federal legislation affecting pharmacy practice. *Pharmacy Times,* 2006. ACPE.

absence of a private area for counseling and no reimbursement or recognition for "extra work."[20] One could argue that it did not succeed because there was no consideration of how to fit the requirement into the pharmacy workflow or business model.

Mandatory patient counseling of 4 million patients who receive about 20-30 million prescriptions for LA/ER opioids annually is not feasible within the current system and would create a significant burden in the pharmacy setting. Success in imposing this requirement would require enforcement and incentives to prevent pharmacies from refusing to stock and dispense these products due to the increased burden.

The responsibilities of pharmacists have changed over time, but the practice setting has remained the same. By imposing another mandatory counseling requirement on the pharmacist, pharmacies may opt out and not even stock these products to avoid this REMS requirement. Requiring pharmacists to selectively interact with patients who are receiving LA/ER opioids could further stigmatize patients with chronic pain. Additionally, the lack of privacy at pharmacy counters could worsen the problem.

Implementing Training Programs

The WG considered who might provide pharmacist training, were it to be required in the opioid REMS. In general, the consensus of the WG was that the pharmaceutical industry would be best positioned to provide training.

A 2004 FDA survey of more than 2,000 pharmacists revealed that only 70% of respondents were familiar with the term "Medication Guide" and only 30% of those were aware of federal requirement to distribute the leaflets.[21] Additionally, from anecdotal evidence we know that some pharmacists are not aware of currently approved REMS program requirements for pharmacists, such as the requirement to dispense Medication Guides, or verify patient or prescriber eligibility.

The industry might be best positioned to provide information about the REMS via training. For example, industry could distribute information on the available training materials to all pharmacies receiving their products; industry could also provide a multi-media approach to the training (e.g., computer based, written material to fax, postcards).

Despite the need to improve pharmacy training, an effort to provide it to all pharmacists may not be viable since LA/ER opioids are primarily dispensed in retail settings, whose pharmacy systems are not designed to track information such as verification of training.

Additional Considerations

During its deliberations, the Pharmacist WG considered whether mandating continuing pharmacist education on *chronic pain management* (linked to licensure renewal) would help improve patient counseling. It is critical that pharmacists receive proper training and education on all aspects of pain management therapy if they were to play a more active role in counseling and educating patients.

Based on surveys, pharmacists do not receive adequate education in this area through pharmacy school. In a study published by JAPhA, (2003), 21 of 28 respondents (75%) believed that "too little" emphasis was being given to the topic of pain management. All surveyed instructors complained about the lack of

[20] Pharmaceutical care in chain pharmacies, *JAPhA* , 2001; 41.
[21] *J Am Pharm Assoc*. 48:4: Jul/Aug 2008.

complete texts on pain management for pharmacists. The study concluded that while pain management was included in the curricula of all 28 schools of pharmacy, it was generally covered in a fragmented manner.[22] In a survey published in Psychoactive Drugs (2006), 67.5% of pharmacists reported participating in two hours or less of addiction/substance abuse education in pharmacy school. About 29% reported having received no addiction education.[23] Another survey published by JAPhA (2001) showed that pharmacists' knowledge of and attitudes toward opioid pain medications in relation to federal and state policies are mixed: 12% of the participants reported their knowledge about opioids and pain management was poor and 38% reported fair; 5% of responders said their knowledge about controlled substance requirements was poor and 28% fair; 87% responded that they recognized legitimate and non-legitimate prescriptions and only 13% responded no. The study concluded that pharmacists need continuing education programs focusing on pain, opioid analgesics, the characteristics and risk of addiction, federal and state controlled substances and pharmacy policies and the use of controlled substances for pain management.[24] The set goals for LA/ER opioid REMS may best be achieved through prevention, patient education/counseling and disease management interventions.

Although OBRA'90 required that an offer to counsel the patient be made, it was not until the practice was established under pharmaceutical care services (PCS) or Medicare Part D, Medication Therapy Management (MTM) that scheduled, face-to-face patient counseling was provided by trained pharmacists with reimbursements.

Although counseling could be a good idea, the current pharmacy workflow or business model is not structured to allow for counseling of 4 million patients per year. However, if FDA's initial efforts to develop and implement opioids REMS are not as successful as hoped, the option of mandatory education through ACPE plus patient counseling could be reconsidered. Such an effort could align well with the changes being sought by the National Association of Board of Pharmacy (NABP) in the pharmacy setting to allow for counseling on a more routine basis. The NABP stated that there is an effort to transition the current pharmacy practice model from business to a patient focus.[25] NABP is piloting an accreditation program that will focus on patient outcomes with two major medication providers with live data available in the first quarter in 2010. NABP also stated that chronic pain management and opioid use could be easily incorporated in an accreditation program.[26]

Many organizations[27] have endorsed pharmacist education through established and multiple providers of Accreditation Council for Pharmacy Education (ACPE) for several reasons. These organizations believe that pharmacy education should be provided by entities such as national, state, or local pharmacy associations or schools of pharmacy, which are experts in developing pharmacy-specific training and certification programs. They believe that providers of continuing pharmacy education (CPE) should be accredited by the ACPE and accessible through multiple CE providers. They also believe that it is the individual pharmacist's responsibility and should, therefore, be linked to CE for license renewal. NABP is developing a CE monitoring and tracking system in conjunction with ACPE to give each pharmacist his or her own record of CE, using a NABP number. NABP has the infrastructure but still needs to notify the ACPE for implementation in early 2010.

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[22] Rubina Mand Singh S, and Wyant L. . Pain Management Content in Curricula of U.S. Schools of Pharmacy. *J Am Pharm Assoc*. 2003; 43(1).
[23] Ibid.
[24] Rubina M. Singh, S and Wyant L .Pain Management Content in Curricula of U.S. Schools of Pharmacy. *J Am Pharm Assoc*. 2003; 43(1).
[25] Telephone interview with Carmen Catizone, Executive Director/Secretary, NABP, November 9, 2009.
[26] Ibid.
[27] ASHP, APhA, NCPA, NACDS, CVS/CAREMARK, WALGREEN, and IWG.

Although pharmacist responsibilities have increased over time, pharmacy practice sites have remained the same. With an increasing workload, pharmacists face challenges in fulfilling their responsibilities, both product- and patient-oriented.[28] Also, the pharmacist-to-technician ratio does not afford pharmacists the extra time required for the proposed pharmacist–patient interaction.

CONCLUSIONS

After considering various options, the Pharmacist Education Working Group recommends that the REMS for LA/ER opioids not require pharmacist education or pharmacist certification. No additional training or regulatory oversight should be required as part of the REMS for pharmacists beyond that which already exists within the pharmacy profession. The Working Group also recommends against requiring mandatory pharmacist counseling of patients, although if FDA's initial efforts to develop and implement opioids REMS are not as successful as hoped, the option of mandatory education through ACPE plus patient counseling could be reconsidered.

[28] Brushwood D. From confrontation to collaboration: collegial accountability and the expanding role of pharmacist in the management of chronic pain. *Journal of Law, Medicine & Ethics.* 2001 (29):60-93.

Risk Evaluation and Mitigation Strategy for Opioid Analgesics
Final Report of the Metrics Working Group

June 2010[1]

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BACKGROUND

In early 2009, FDA sent letters to manufacturers of certain opioid drug products, indicating that these drugs will be required to have a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of the drugs continue to outweigh the risks. FDA explained that the REMS would include elements to assure safe use to make certain that prescribers, dispensers, and patients are aware of and understand the risks and appropriate use of these products. FDA also stated that, with limited exceptions, the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires generic and innovator products to use a single shared system to implement the elements to assure safe use. The affected opioid drugs include long-acting and extended-release (LA/SR) brand name and generic products and are formulated with the active ingredients fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone.

FDA is mindful of provisions in FDAAA that require elements to assure safe use to be, among other things, commensurate with the specific serious risk listed in the labeling of the drug, not unduly burdensome on patient access to the drug, and designed to be compatible with established distribution, procurement, and dispensing systems.

To obtain public input on how best to design a REMS for this class of drugs, FDA held a series of meetings with relevant stakeholders (May 4 and 5, 2009; May 27 and 28, 2009; December 4, 2009) and opened a public docket to receive public comments on relevant issues. Meeting minutes of the May 4 and 5 stakeholder meetings, and transcripts of the May 27 and 28, and December 4 meetings are in the docket and on FDA's Web site.[2] FDA plans to provide an additional opportunity for public input before finalizing the elements of the REMS.

[1] The WG formulated its recommendations in January 2010; this report has been finalized in preparation for the July 2010 Advisory Committee meeting.
[2] See http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm.

Following the meetings, FDA formed an Opioid REMS Steering Committee, a multidisciplinary team from throughout the Center for Drug Evaluation and Research. To thoroughly analyze the substantial public and stakeholder input received on the development of the REMS and to conduct additional research, the Steering Committee formed seven[3] work groups to focus on the various aspects of an opioid REMS and the effects of possible components of the REMS on use.

Following their analysis, the work groups were asked to provide recommendations to the Steering Committee for consideration as it develops options for what should be included in the REMS. The seven work groups addressed the following areas:

- Scope of an opioid REMS
- Prescriber education
- Pharmacist education
- Patient education
- Pharmacy systems
- Effect of possible restrictions on patient access to pain medication
- Metrics

This is the report and recommendations from the Metrics Working Group.

Goal of the Working Group

The Opioid Metrics Working Group (WG) was charged with identifying the metrics that would be used to evaluate the opioid REMS and then exploring the possible databases that would provide the relevant data. A tentative evaluation strategy was developed. To do this, the WG reviewed information submitted to the docket, particularly the comments of the Industry Working Group, which included a number of possible databases that might be used to evaluate the REMS. The WG also contacted managers of a number of the potential databases to learn about the strengths and limitations of each source. In addition, the WG initiated discussions with a number of Federal partners to explore possible collaborations.

Summary of Recommendations

The Metrics Working Group proposes seven recommendations regarding the metrics for evaluating of the opioid REMS. These recommendations should ensure a comprehensive evaluation of the REMS.

- Establish measurable goals for the opioid REMS. Specific, measureable goals are needed to guide the evaluation of the opioid REMS.
- Use multiple metrics and data sources to measure the impact of the REMS. Using multiple metrics will enable FDA to measure multiple facets of the opioid problem and compensate for the limitations of individual data sources.

[3] In addition, an eighth working group was created to handle external communications about the REMS. That working group was not involved in the review of comments and did not create a report.

- Create new data sources or methods to measure certain components of the REMS. Existing databases are insufficient for measuring the impact of the REMS. Sponsors and FDA will need to develop new methods and data sources to collect relevant data, including surveys and, potentially, surveillance systems. Surveys can measure the knowledge of patients and prescribers to ensure that educational efforts are having the desired effect.
- Measure the effect of the REMS on outcomes related to both extended release products and all opioids. Many existing data sources do not distinguish between extended release/long acting (SR/LA) opioids and immediate release, and many do not distinguish between different opioid molecules (e.g., hydrocodone and oxycodone), so that measuring the effect of the REMS on the covered subset of opioids may be difficult. We think it will be equally important to measure the effect of the REMS on all opioids to help us evaluate the level of the *balloon effect* in which misuse, abuse, and improper prescribing of opioids may shift from SR/LA opioids to immediate release products.
- Establish baseline metrics to determine the degree to which the REMS changes knowledge, behaviors, and health outcomes. Baseline measures at the time the opioid REMS is approved and as additional elements of the REMS are introduced will be needed. The required assessment schedule should be adjusted accordingly.
- Account for confounders. Other initiatives and trends that may affect outcomes of interest, including policy changes, state and regional initiatives, product introductions, manufacturing changes, and public information campaigns associated with opioids need to be monitored.
- Establish working definitions for outcomes of interest. Definitions of abuse, misuse, and other key outcomes must be in place.

Summary of Issues and Concerns

The WG acknowledges that there are many challenges associated with the evaluation of a multi-drug REMS that has multiple components. In addition, there will be a number of confounders that will limit the conclusions that can be drawn from the assessment, such as the implementation of state and local efforts to address prescription drug abuse.

Sponsors are responsible for the collection of data, but the WG recognizes that an active collaboration with FDA will be needed. FDA is also exploring potential collaborations with our Federal partners at the Substance Abuse and Mental Health Services Administration (SAMHSA), the Centers for Disease Control and Prevention (CDC), the Centers for Medicare & Medicaid Services (CMS), Department of Defense (DoD), and the Veterans Administration as part of the overall opioid REMS evaluation.

Detailed Discussion of Specific Issues

The abuse of prescription opioids is a considerable public health problem. In 2007, an estimated 5.2 million persons, aged 12 years or older, reported using prescription pain relievers non-

medically in the past month.[4] Use of these drugs is associated with a high number of hospitalizations and deaths: there were 13,755 deaths from opioids in 2006[5] and 420,000 emergency room visits for misuse and abuse.[6]

Prescribers of opioids play a role in the widespread misuse of these drugs. Research has found that a significant percentage of persons reporting nonmedical use of pain relievers obtained their drug from their doctor or from family or friends, rather than through illicit means.[7] A recent study that investigated the source of abused prescription drugs reported that prescribers often are a source of abused prescription drugs and recommended that prescribers receive training on the safe prescribing of opioids.[8]

To facilitate the safe use of opioids, FDA proposed the development of an opioid REMS to ensure that the benefits of these drugs continue to outweigh certain risks. As part of the development of the REMS, the opioid REMS steering committee identified the goal for the program:

> *Reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of sustained-release (SR) and long-acting (LA) opioids while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.*
>
> *This will be accomplished by educating prescribers in appropriate patient selection, dosing, and patient monitoring, and by educating patients in the safe use, storage, and disposal of opioids.*

Setting the Stage for Measuring Effects

The development of a REMS should start with the identification of the risks to be minimized and relevant outcome goals for the REMS. Goals should be as specific as possible and measureable. The final goals developed for the opioid REMS should address specific risks that have been identified with opioids and focus on patients and prescribers. The evaluation of whether the goals have been met will require evaluating certain knowledge, behavior, and outcome metrics.

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[4] Substance Abuse and Mental Health Services Administration, Office of Applied Studies. (February 5, 2009). *The NSDUH report: trends in nonmedical use of prescription pain relievers: 2002 to 2007*. Rockville, MD.

[5] Warner M, Chen LH, Makuc DM. Increase in fatal poisonings involving opioid analgesics in the US, 199902006. NCHS Data Brief, 2009; no 22.

[6] Substance Abuse and Mental Health Services Administration. Office of Applied Studies, Drug Abuse Warning Network. Detailed tables: national estimates of drug-related emergency department visits 2004-2008. Accessed March 11, 2010 http://dawninfor.samsha.gov/data.

[7] Substance Abuse and Mental Health Services Administration. (2009). Results from the 2008 National Survey on Drug Use and Health: National Findings (Office of Applied Studies, NSDUH Series H-36, HHS Publication No. SMA 09-4434)

[8] Inciardi JA, Surratt HL, Cicero TJ, Beard RA. Prescription opioid abuse and diversion in an urban community: the results of an *ultra*-rapid assessment. Pain Med; 2009: 10: 537-548.

The opioid REMS is designed to address a complex and multifaceted problem, and no single data source can provide timely, complete, and drug-specific data on even a single aspect of the problem. Therefore, the metrics working group suggests using multiple databases to evaluate whether the REMS is meeting its goals. Using multiple databases will enable FDA to address the complexity of the opioid problem and to compensate for the weaknesses of individual databases.

A number of key measures of behavior are not found in any existing databases (e.g., measures of safe storage and disposal, safe use, decreased inappropriate prescribing). The WG, therefore suggests that FDA work with sponsors and Federal partners to develop new data sources, including surveys, focus groups, and, perhaps, surveillance systems or other new methods for analyzing existing data to enable us to learn more about how well the REMS is working.

The WG also believes that the outcomes of the opioid REMS should be measured for all opioids, not just SR and LA opioids. Although it is desirable to measure outcomes related to individual opioid products, this may not always be feasible; most databases do not distinguish between SR/LA opioids and immediate release (IR) opioids, and many do not even distinguish between individual molecules (e.g., hydrocodone and oxycodone). FDA may wish to ask CDC and SAMHSA to modify their existing data collection instruments to include a method for identifying SR/LA opioids, although such a modification will take several years to implement. Regardless of whether this change is made, measuring the effect of the opioid REMS on all opioids, not just SR/LA opioids, will enable FDA to determine whether the REMS focus on SR/LA opioids will decrease the number of adverse events from all opioids despite its potential to shift some of the abuse, misuse, and mis-prescribing to IR opioids. Also, since the drugs with which FDA is concerned are a subset of "all opioids," if there is a decrease in adverse outcomes in all opioids, it may be possible to conclude that the REMS is working.

The WG believes that we should establish baseline metrics prior to the implementation of the REMS. Tracking and accounting for other trends and initiatives that may affect the outcomes of interest will help FDA determine whether any changes in opioid-related adverse events can be attributed to the REMS. These other trends and initiatives could include policy changes, state and regional initiatives, product introductions, manufacturing changes, and public information campaigns associated with opioids.

Finally, the WG supports the public communication of all working definitions for the outcomes of interest, including opioid misuse, abuse, addiction, and unintentional overdose, as many of these terms do not have a single scientifically accepted definition. The Industry Working Group has suggested that consensus definitions be developed in a public forum, but for the purposes of the opioid REMS the WG does not believe such a forum is necessary.

Proposed Data Sources and Metrics

The diagram below provides a broad overview of the types of data that should be collected to measure the effect of the opioid REMS. These data needs align with the overall goal of the opioid REMS described previously. Since this goal is to be achieved through the education of prescribers and patients, the following should be measured:

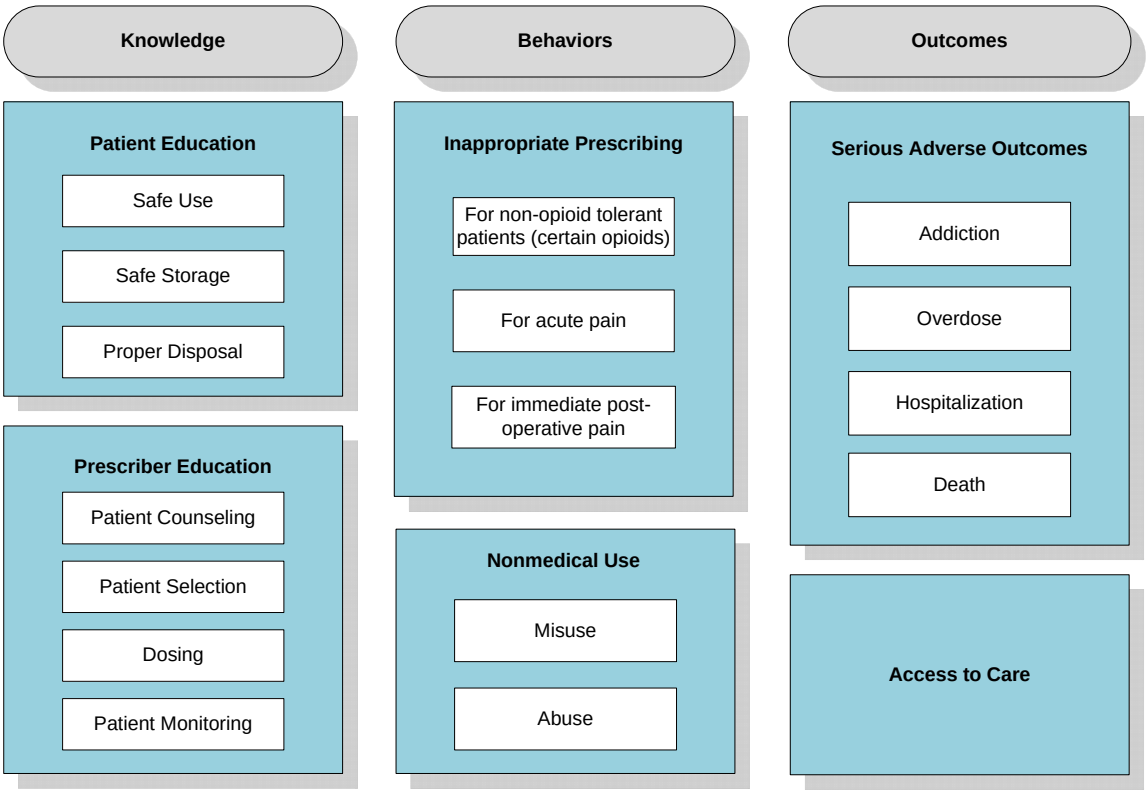
- Whether the REMS increased prescriber and patient knowledge
- The behaviors that we intend to reduce through the REMS, including nonmedical use of opioids and inappropriate prescribing of opioids
- The adverse events of interest

As we evaluate the effectiveness of the REMS in reducing serious adverse events, we should track the effect of the REMS on access to care to ensure that patients likely to benefit from SR/LA opioids continue to receive them.

Certain behaviors that we hope to reduce through the REMS have not been included in the diagram as we do not believe it will be feasible to measure them at this time. These behaviors include prescribing for "as needed" (prn) pain treatment and for mild pain. In some cases, however, FDA or the sponsors may be able to develop new data collection instruments to capture the excluded information for future REMS evaluations.

Diagram: Metrics Data Needs

To measure the effect of the REMS on health outcomes, data should be collected in the following areas:



Proposed Metrics

Process

The WG expects that the opioid REMS will have some type of patient and prescriber education program. Depending on the final program, a system will need to be in place to collect training data. The sponsors will need to develop a system for collecting these data.

The opioid REMS will seek to reduce serious adverse outcomes related to opioids by educating prescribers and patients on the safe use of these drugs. Educational efforts can be evaluated using surveys and tests of prescriber and patient knowledge, although these surveys will not be able to measure whether patients or prescribers change their behavior.

Knowledge

- Prescriber Education

If prescribers are required to receive training prior to being able to prescribe opioids, they can be given tests both before and immediately after the training to determine how the educational program has affected their knowledge of opioid prescribing. Additional surveys can be conducted some time after the prescribers have completed the training to determine whether they have retained what they have learned.

- Patient Education

Patient surveys can be conducted to determine whether patients understand how to use opioids safely and how to properly store and dispose of opioids. In addition, the sponsors should measure how reliably and frequently educational materials and messages reach patients.

Behaviors

Prescriber and patient behaviors are difficult to measure, as doing so requires tracking and monitoring the actions of individual physicians and patients. In addition, it is particularly difficult to determine when a change in behavior is a result of a REMS. Nevertheless, measuring behaviors is valuable in helping to determine which interventions are most effective, and whether our understanding of the opioid problem is complete.

Inappropriate Prescribing

Without the ability to directly observe physician behavior, it is difficult to identify when inappropriate prescribing of SR/LA opioids has occurred. This is particularly challenging in the case of opioids, which are used in a variety of contexts and for which appropriate treatment requires a nuanced understanding of the patient and his or her condition. Nevertheless, using existing data from healthcare claims and other data systems, it may be possible to identify certain forms of inappropriate prescribing without the need to directly observe physician behavior. This includes cases when certain opioids[9] intended for opioid-tolerant patients are used in opioid-naïve patients, and when opioids are used for acute pain, including immediate post-operative pain. Other metrics that may serve as proxies for changes in prescribing behavior are being explored with Federal partners.

Nonmedical Use

Nonmedical use of opioids includes both misuse and abuse of opioids (see "Definitions" sections). Nonmedical use is measured annually in the National Survey on Drug Use and Health (NSDUH http://oas.samhsa.gov/nsduh.htm). The survey, however, is unable to determine why nonmedical use has occurred; it does not ask patients whether an opioid was used inappropriately for analgesic purposes or purely for its psychoactive effects. Monitoring the Future provides data about school-attending adolescents and young adults regarding the use of

[9] Based on the labeling, the following drugs require use in opioid tolerant patients: oxycodone ER, 60mg and 80mg; hydromorphone ER, all doses; and morphine/naltrexone, 100mg/4mg. Opioid tolerance is defined as: at least 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromoprhone/day, 25 mg oral oxymorphone/day or an equianalgesic dose of another opioid for one week or longer.

opioids without a prescription and might be another valuable data source (www.monitoringthefuture.org).

Outcomes

Adverse Events

- Unintentional Overdose

The National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project and the American Association of Poison Control Centers (AAPCC) each collect national data on unintentional overdoses. NEISS-CADES data are collected from emergency department (ED) visits and AAPCC 's National Poison Data System (NPDS) data are collected from calls made to poison control centers across the country (www.aapcc.org). Data collected from these databases will help determine whether there has been a change in prescribing behavior (fewer medication errors) and patient behavior (increased proper use of drug, as well as safe storage and disposal).

- Emergency Departments visits

ED visits due to opioid misuse and abuse can be measured using SAMHSA's Drug Abuse Warning Network (DAWN https://dawninfo.samhsa.gov/default.asp). Data made available through DAWN are updated frequently to allow for the tracking of emerging trends in misuse/abuse-related adverse events. Although there are other national databases that collect information on medical services delivered by Emergency Departments, each have limitations. AHRQ's National Emergency Department Sample (NEDS) and CDC's National Hospital Ambulatory Medical Care Survey– Emergency Department (NHAMCS-ED) sample use ICD-9 codes to identify adverse drug effect/poisoning, which do not allow us to identify the specific opioids responsible for the ED visit. Both databases are unable to provide timely data. The working group therefore recommends the use of DAWN data to track emerging trends in opioid-related ED visits. Other databases may be used to validate the trends identified in DAWN.

- Addiction

Although addiction is not directly measured in any population-level databases, the prevalence of addiction can be estimated using SAMHSA's Treatment Episode Data Set (TEDS), which tracks how often patients are admitted to an addiction treatment program for prescription opioid abuse (http://www.oas.samhsa.gov/dasis.htm#teds2). Privately run surveillance systems, such as Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS), and the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO), also collect information on treatment center admissions.

- Deaths

The most comprehensive source of death data is the Vital Statistics data collected by the Centers for Disease Control and Prevention's National Center for Health Statistics (NCHS)

through the National Vital Statistics System, which captures information on the causes and circumstances of all U.S. deaths (http://www.cdc.gov/nchs/deaths.htm). Unfortunately, as mentioned previously, with the exception of methadone, the Vital Statistics data do not identify the specific prescription opioid responsible for the death, nor do they distinguish between short and long-acting opioids.

Access to Care

Many patient groups are concerned that any REMS intervention will further limit access to care with prescription opioids for legitimate chronic pain patients. The measurement of access to care is complicated by the fact that one must disassociate a drop in inappropriate use, which is the goal of the REMS, from a drop in appropriate use, which could occur as a consequence of restricted access to care and would be undesirable.

A particularly valuable public data source to measure access to care is the Agency for Health Research and Quality's (AHRQ) Medical Expenditure Panel Survey (MEPS http://www.meps.ahrq.gov/mepsweb/). The survey asks patients specific questions about access to care that can help determine where gaps in access may exist. Possible access to care measures include (1) the number of prescribers who had prescribed SA/LA opioids in the past but do not prescribe the drugs after the opioid REMS is approved; (2) measures of patient proximity to physicians who prescribe SA/LA opioids, for example, the number of prescribing physicians per xxx square miles; (3) the number/percentage of moderate/severe chronic pain patients who could not get a prescription because their healthcare provider refused to provide services and/or the patient did not know where to get care and/or the patient had problems getting to the doctor's office; and (4) the number/percentage of patients with chronic severe/moderate pain who discussed the condition with their doctor and are not receiving prescription opioids. These questions are not opioid-specific, but an analysis can focus on patients who are prescribed SA/LA opioids. Comparisons might be made between patients prescribed SA/LA opioids for different indications to help determine whether their use of opioids is in fact appropriate.

Another measure available for evaluation is the number of physicians who opt out of participation in a REMS, along with characteristics of the patient populations they serve. However, if the opioid REMS does not include mandatory educational requirements, this metric will not be useful in assessing access to care.

Proposed Data Sources

There are a number of data sources that might be used as part of the evaluation of the opioid REMS. Many of the databases are sponsored by the Federal government. The Federal data are well established and generally have large, representative samples, but they are made public with a delay of up to 2.5 years, so reliance on them would significantly postpone the evaluation of the REMS. On the other hand, this limitation is often not present with data from private vendors who may also be particularly amenable to quickly updating their survey instruments to reflect the needs of data users. Whatever the benefits of private data, FDA, and therefore this WG, is not in a position to recommend specific vendors. However, we acknowledge that sponsors may have other data sources they can tap into.

The following is a list of the databases recommended by the WG and a brief description of their strengths and limitations.

Table 1: Databases, Strengths and Limitations

METRIC	DATABASE	STRENGTHS	LIMITATIONS
PROCESS MEASURES OF COMPLIANCE WITH TRAINING	To be developed by Sponsors	Important to know the rate of compliance with training	May be difficult to identify trained prescribers
KNOWLEDGE PROPORTION OF PRESCRIBERS AND PATIENTS WITH UNDERSTANDING OF RISK	Surveys	Provide prescriber- and patient-level information	Will require private contractors; there are no Federal data sources that provide this information
INAPPROPRIATE PRESCRIBING: 1. NUMBER (RATIO) OF PRESCRIPTIONS TO NON-OPIOID TOLERANT PATIENTS 2.NUMBER (RATIO) OF PRESCRIPTIONS TO IMMEDIATE POST-OPERATIVE CARE/LESS INVASIVE SURGERY	Prescription claims databases	Provide timely information for specific drugs	Without review of medical records cannot be sure that analysis is valid
NUMBER (RATIO) IDENTIFIED WITH **NON-MEDICAL USE AND ABUSE** IN VARIOUS SETTINGS	NSDUH "Monitoring the Future" Survey Commercial surveillance systems (eg. RADARS, NAVIPPRO)	Provide class specific (some drug-specific information) information; nationally representative Provide class specific (some drug-specific information) information; but some unique data sources and may be more	Some of these data are not as timely as would like; not all data are available to public; data not available for a subset of the proposed REMS drugs Not all nationally representative

		timely	
NUMBER (RATIO) OF IDENTIFIED **UNINTENTIONAL OVERDOSES** FROM OPIOIDS	NEISS-CADES AAPCC (NPDS)	Provide class specific (some drug-specific information) information; nationally representative	Data are not as timely as would like; not all data are available to public
NUMBER (RATE) OF ED VISITS FOR MISUSE AND ABUSE	DAWN	Provide class specific (some drug-specific information) information; nationally representative	Data are not as timely as would like; not all data are available to public
ADDICTION NUMBER (RATIO) OF ADMISSIONS TO TREATMENT PROGRAMS	TEDS Commercial surveillance systems (eg. RADARS, NAVIPPRO)	Provide class specific (some drug-specific information) information; nationally representative See above	Data are not as timely as would like; not all data are available to public
NUMBER (RATIO) OF IDENTIFIED **DEATHS** FROM OPIODS	National Vital Statistics	Provide class specific information; nationally representative	Data are not as timely as would like
ACCESS CHANGE IN ACCESS TO OPIOIDS	MEPS	Includes questions regarding access to care problems and the reasons for them; can account for drug taken, severity and cause of pain	Data are not as timely as would like; data reflect access to care for any drug taken by the patient

Definitions

Definitions of the outcomes of interest are crucial. A number of stakeholders mentioned the need to have valid, clear definitions of the events of interest. Further discussion will be needed, but the WG supports use of the definitions that follow.

Inappropriate prescribing of extended-release and long-acting opioids: Inappropriate prescribing of LR and LA opioids includes the following behaviors: prescribing for mild pain or pain that is not expected to last for an extended period of time, prescribing for as needed (PRN) use, prescribing to non-opioid tolerant patients (for certain drugs), prescribing for immediate post-operative pain, and prescribing to patients with acute pain. Inappropriate prescribing may also include prescribing to patients who are already taking other extended-release opioids.

Misuse: Misuse is the use of a drug outside label directions or in a way other than prescribed or directed by a healthcare practitioner. This definition includes patients using a drug for a different condition than that for which the drug is prescribed, patients taking more drug than prescribed or at different dosing intervals, and individuals using a drug not prescribed for them although for therapeutic purposes

Abuse: Abuse is the nonmedical use of a drug, repeatedly, or even sporadically, for the positive psychoactive effects it produces

Addiction: Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. This definition of addiction has been accepted by the American Academy of Pain Medicine, the American Pain Society and the American Society of Addiction Medicine. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) equates *addiction* to *drug dependence.* However, the use of the term *drug dependence* is confusing because it sounds like physical dependence, which means something totally different. Physical dependence represents the physiologic adaptation to the continuous presence of certain drugs in the body. For example, a person could become physically dependent on the effects of a drug use for lowering blood pressure.

Overdose: For the purposes of the evaluation of the opioid REMS, *overdose* should be defined as an unintentional exposure to a medically unsafe dose of an opioid. This definition includes overdoses that result from a therapeutic error, such as an unintentional exposure to the wrong dose, wrong person, or wrong substance. Overdose may also include an exposure that results from the intentional exposure to an improper dose of an opioid for reasons other than the pursuit of a psychotropic or euphoric effect.

Identification of Specific Drugs

Analysis of each outcome of interest may focus on all SR/LA opioids or specific drugs in the class. Many of the data sources do not provide drug-specific information. For example, the International Classification of Diseases, 9th revision (ICD-9) codes used in some databases has

the category poisoning by analgesics, antipyretics, and antireheumatics (965). Under that code there is a code for methadone (965.02) and another code for other opioids (965.09). Other data sources provide drug-specific information, but may not specify if the drug is short-acting or long-acting.

Strengths and Limitations of Commonly Used Denominator Sources

The evaluation of certain elements of the opioid REMS requires a numerator (the events of interest), but also a denominator. None of the databases under consideration provide denominator data, but there are a number of different denominators that can be used. Each has strengths and limitations

Table 2: Denominators — Sources, Strengths, and Limitations

DENOMINATOR	**STRENGTHS**	**LIMITATIONS**
POPULATION	Readily available	Assumes uniform exposure
TOTAL NUMBER OF RX	Readily available Easily understood	Does not allow for adjustment by dosage strength and size of prescription
TOTAL NUMBER OF UNIQUE PATIENTS FILLING PRESCRIPTIONS	Readily available Easily understood	Does not allow for dosage form and size of Rx adjustment, and provides limited information on chronic *vs*. acute use.
KG DISTRIBUTED	Readily available	Does not allow for potency, rates for high potency drugs will be overestimated
DELIVERY UNITS (TABLETS, ML, PATCHES, ETC)	Provides a closer estimate of drug availability	Does not provide for dosage strength adjustment

Conclusions

The opioid REMS provides an opportunity to address prescription drug abuse. To determine the effectiveness of the REMS, the program must be carefully evaluated based on a measurable set of goals. The WG has developed a list of recommendations and reviewed a number of databases that might be used to assist in this evaluation. Evaluation efforts will require collaboration between the sponsors and FDA. FDA has already begun to collaborate with a number of Federal partners to explore novel ways to evaluate the opioid REMS program, with the goal of obtaining relevant information in a timely fashion.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	June 18, 2010
To:	Bob Rappaport, MD, Division Director, Division of Anesthesia and Analgesia Products, Office of New Drugs II
Through:	Solomon Iyasu, M.D., MPH, Director, Division of Epidemiology, Office of Surveillance and Epidemiology
From:	Laura Governale, Pharm.D, MBA, Drug Utilization Data Analysis Team Leader Tracy Pham, Pharm.D., Drug Utilization Data Analyst, Division of Epidemiology Office of Surveillance and Epidemiology
Subject:	Extended-Release/Long-Acting and Immediate-Release Opioid Utilization Trends, 2000-2009
OSE RCM #:	2010-1198

6-22-10

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This document contains proprietary drug use data obtained by FDA under contract. The drug use data in this review have been cleared for public release.

Table of Contents

EXECUTIVE SUMMARY

Nearly three-quarters of all extended-release (ER) and long-acting (LA) opioid sales distribution from manufacturers to wholesalers are directed toward outpatient retail pharmacy settings. Opioids constitute approximately 6-7% of the entire outpatient retail dispensed prescription market between years 2000 through 2009. Of these, the vast majority of dispensed prescriptions for opioid products are for immediate-release (IR) products. In year 2009, ER and LA opioids accounted for approximately 23 million dispensed prescriptions (9% of 257 million opioid prescriptions) and nearly 4 million unique patients in the outpatient retail pharmacy setting. Patients aged 50-59 years had the highest proportion of use (27%), followed by patients aged 40-49 years (22%) and patients aged 60-69 years (17%). ER oxycodone prescriptions accounted for approximately a third of all ER/LA opioid prescriptions whereas ER morphine and fentanyl, and methadone products each accounted for approximately 20%. The top 5 prescribing specialties of ER/long acting opioids were general practice (27%), internal medicine (17%), anesthesiology (14%), physical medicine and rehabilitation (9%), and nurse practitioners (6%). For IR products, the top 5 prescribing specialties were general practice (27%), internal medicine (15%), dentistry (8%), orthopedic surgery (7%), and emergency medicine (5%). At 28 days, ER/LA opioids had the longest mean days of therapy per prescription, compared to 21 days for IR single-ingredient opioids, and 14 days for IR combination and buprenorphine products. The most common diagnoses associated with the use of ER/LA opioids in year 2009 were "diseases of the musculoskeletal system and connective tissue" which include arthritic conditions (55%), followed by "headaches and nerve pain" (14%), and "neoplasms" (11%). For IR opioid products, the most common diagnoses associated with use were "diseases of the musculoskeletal system and connective tissue" (30%), and "fractures, sprains, contusions and injuries" (17-26%).

1 INTRODUCTION

In preparation for the upcoming Opioid Risk Evaluation and Mitigation Strategy (REMS) Advisory Committee Meeting on July 22-23, 2010, this review summarizes the outpatient opioid utilization trends for LA/ ER and IR (IR) opioid products in the U.S. for years 2000 through 2009.

2 BACKGROUND

On July 22-23, 2010, the Anesthetic and Life Support Drugs and Drug Safety and Risk Management committees will be convened to provide advice on an FDA proposal to require a REMS for the class of LA and ER opioid drug products. The affected products include LA and ER formulations of fentanyl, hydromorphone, methadone, oxycodone, and oxymorphone. To understand utilization patterns and assess the potential impact of REMS requirements on this class of drugs, this review summarizes the outpatient opioid utilization trends for LA/ER and IR opioid products in the U.S. for years 2000 through 2009.

3 METHODS AND MATERIAL

3.1 DATA SOURCES

Proprietary drug use databases licensed by the Agency were analyzed by DEPI drug utilization analysts (see ***Appendix 2*** for full database descriptions).

The IMS Health, IMS National Sales Perspective™ database was used to determine the primary settings of use for ER and IR opioid products for year 2009. Outpatient drug utilization was measured from SDI, Vector One®: National (VONA). From these data sources, the estimates of the total annual number of prescriptions dispensed were obtained for all opioid products used for pain (excluding cough medicines) from year 2000 - 2009. We also obtained the number of dispensed prescriptions stratified by the prescribing specialties for ER and IR opioid products as well as the mean days of therapy per prescription for these products for year 2009. In addition, the number of patients receiving a dispensed prescription for an ER opioid product in the outpatient setting was obtained from the SDI, Total Patient Tracker database for years 2002 through 2009. Diagnosis associated with the use of ER and IR opioids were obtained from the SDI, Physician Drug and Diagnosis Audit for year 2009.

3.2 PRODUCTS INCLUDED

All non-injectable opioid products were grouped into the following categories for this review. Except for hydrocodone and buprenorphine products, Schedule III – IV opioids were classified as weak opioids; Schedule II opioids were classified as potent opioids.

- **ER Opioids:** oxycodone, morphine, fentanyl transdermal, hydromorphone, oxymorphone, methadone
- **IR Opioids:**
    - **Single-Ingredient Potent**: oxycodone, morphine, fentanyl, hydromorphone, oxymorphone, meperidine, levorphanol
    - **Single-Ingredient Weak**: tramadol, propoxyphene, butorphanol, codeine
    - **Hydrocodone**: hydrocodone/acetaminophen, hydrocodone/ibuprofen, hydrocodone other combinations
    - **Combination Potent**: oxycodone/acetaminophen, oxycodone/aspirin, oxycodone/ibuprofen, meperidine combo
    - **Combination Weak**: propoxyphene combo, codeine combo, tramadol/acetaminophen, dihydrocodeine combo
    - **Buprenorphine**: buprenorphine/naloxone, buprenorphine

4 RESULTS

4.1 SALES DISTRIBUTION OF ER AND IR OPIOIDS

In year 2009, the primary distribution setting for most IR single-ingredient and combination opioid products (roughly 60% or more of sales distribution) was outpatient retail pharmacies except for IR single-ingredient morphine and IR combination codeine products which were primarily distributed to non-retail settings of care.[1] For ER opioid products, the outpatient retail pharmacy setting accounted for approximately 76% of sales distribution for year 2009.[2]

[1] IMS Health, IMS National Sales Perspectives™, Year 2009, Extracted 6/10. File: NSPC 2010-1198 IR Opioid Channels 6-7-10 1006iro2.xls

[2] IMS Health, IMS National Sales Perspectives™, Year 2009, Extracted 6/10. File: NSPC 2010-1198 ER Opioid Channels 6-7-10 1006ero1.xls

4.2 OUTPATIENT DISPENSED PRESCRIPTIONS FOR ER AND IR OPIOIDS (TABLE 1 AND FIGURES 1 - 3)

Opioids constitute approximately 6-7% of the entire outpatient retail dispensed prescription market between years 2000 through 2009. In year 2000, approximately 174.1 million (6%) of the total number of all retail prescriptions (2.9 billion prescriptions) on the U.S. market were dispensed for opioids. Of this total number of dispensed prescriptions for opioids, around 9.3 million ER opioid prescriptions (5% of all opioids) and 164.8 million IR opioid prescriptions (95% of all opioids) were dispensed. Oxycodone containing products (5.5 million prescriptions, 59%) was most commonly dispensed in the ER opioid group, followed by ER fentanyl products (1.7 million prescriptions, 19%). Hydrocodone containing products (78 million prescriptions, 47%) was most commonly dispensed in the IR opioid group. Same trends were observed for other years, 2001 to 2009.

In year 2009, approximately 257 million prescriptions for opioids were dispensed, a 48% increase from year 2000. The data also showed an increase in the total number of dispensed prescriptions for ER (23 million prescriptions, 146% increase from year 2000) and IR (234 million prescriptions, 42% increase from year 2000) opioids. The market share of the dispensed prescriptions for ER opioids slightly increased (5% to 9%) whereas the market share of the dispensed prescriptions for IR opioids slightly declined (95% to 91%) over the years. ER oxycodone continued to be the market leader among ER opioids with nearly 34% of the market, followed by ER morphine, fentanyl transdermal products, methadone, and oxymorphone with approximately 23%, 22%, 19%, and 3% of the ER opioid market, respectively.

Among the IR opioid products, hydrocodone continued to be the market leader with approximately 123 million dispensed prescriptions (53%) in year 2009. IR potent opioids accounted for nearly 20% of the IR market with the combination potent opioids (14% of IR) holding a larger share compared to the single-ingredient potent opioids (6% of IR). The absolute number of dispensed prescriptions and market share increased for all IR opioid classes, except for the combination weak opioids which decreased by approximately 37% from year 2000 to 2009.

4.3 NUMBER OF PATIENTS RECEIVING ER OPIOIDS (TABLES 2 AND 3)

Trends for patient data were similar to prescription data. Approximately 2.7 million unique patients received a dispensed prescription for an ER/LA opioid from outpatient retail pharmacies in year 2002. The number of unique patients continued to increase up to 3.9 million in year 2008; an increase of approximately 46%. In year 2009, the number slightly declined to approximately 3.8 million (3% decline from previous year).

We also examined age and sex distribution for patients receiving ER/LA opioid products for year 2009. Female patients accounted for a slight majority in use with approximately 55%. Patients aged 50-59 years had the highest proportion of use (27%), followed by patients aged 40-49 years old (22%) and patients aged 60-69 years old (17%). Patients aged 19 years and younger accounted for less than 1% of the total number of patients receiving ER/LA opioid products during year 2009.

4.4 TOP 10 PRESCRIBERS (FIGURES 4-1 AND 4-2)

Data collected for year 2009 showed that the majority of dispensed prescriptions for IR and ER/LA opioids in the U.S. were prescribed by general practice/family medicine/osteopathic

specialists accounting for approximately 27% each of ER and IR prescription share. Internal medicine specialists were the second largest group in the top 5 groups of prescribers who commonly prescribed IR and ER/LA opioids with 15% and 17% of prescription share, respectively.

Dentists (8%), orthopedic surgeons (7%) and emergency medicine specialists (5%) were among the top 5 groups of prescribers who prescribed IR opioids. Following the top 5 groups of prescribers were physician assistants (4%), nurse practitioners (3.5%), anesthesiologists (3%) and physical medicine and rehabilitation specialists (3%).

For ER/LA opioids, anesthesiologists (14%), physical medicine and rehabilitation specialists (9%), and nurse practioners (6%) were among the top 5 groups of prescribers. Physician assistants (4%), neurologists (3%), orthopedic surgeons (2%) and hematologists (2%) were in the top 10 groups of prescribers.

4.5 MEAN DAYS OF THERAPY PER PRESCRIPTION (TABLE 4)

The mean days of therapy per prescription increased for all opioids throughout the study period. LA/ER opioids had the greatest mean days of therapy per prescription, ranging from 23 days to 28 days per prescription between year 2000 and 2009. IR single-ingredient opioids, weak or potent, had average therapy days per prescription ranging from 13 days to 21 days per prescription. Combination opioids (hydrocodones, weak and potent opioid combinations) and buprenorphine products had the shortest duration of therapy days per prescription, ranging from 8 to 14 days of therapy per prescription.

4.6 INDICATIONS FOR USE ER AND IR OPIOIDS Y2009 (TABLE 5)

We also obtained the most common diagnoses associated with the use of ER/LA opioids and IR single-ingredient and combination opioids for year 2009. "Diseases of the musculoskeletal system and connective tissue" (ICD-9 codes 710-739) were the most common diagnoses associated with the use of all groups of opioid agents analyzed; IR opioids accounted for approximately 30% of use mentions each for single-ingredient and combination opioids, and ER/LA opioids accounted for approximately 55% of total use mentions for diagnoses related to these conditions. For IR single-ingredient and combination opioid products, conditions related to "fractures, sprains, contusions and injuries" (ICD-9 codes 800-999) were the second most common diagnoses associated with the use of single-ingredient and combination IR opioid products with approximately 26% and 17% of total diagnosis mentions, respectively. Pain conditions related to "neoplasms" (ICD-9 code 140-239) and "headaches and nerve pain" (ICD-9 code 337-356) accounted for approximately 3-6.5% and 4-5.5%, respectively, for IR opioid products.

For ER/LA opioids, following "diseases of the musculoskeletal system and connective tissue" (ICD-9 codes 710-739), conditions related to "headaches and nerve pain" (ICD-9 code 337-359) and "neoplasms" (ICD-9 code 140-239) accounted for approximately 14% and 11% of diagnosis mentions, respectively. Diagnoses related to "fractures, sprains, contusions and injuries" (ICD-9 codes 800-999) accounted for approximately 6% of the diagnoses associated with the use of ER/LA opioids.

5 DISCUSSION

Although we could not tease out chronic versus acute pain conditions with our current data resources, the results of the diagnoses data showed that the majority of use ER/LA opioid

products were associated with “diseases of the musculoskeletal system and connective tissue” (ICD-9 codes 710-739) which include arthritic conditions and back pain. Furthermore, our analysis of mean days of therapy per dispensed opioid prescription attempted to show that ER/LA opioid products were used for longer duration of use.

This analysis did not include concurrent use of opioid products nor were any switching analyses conducted to show severity of pain conditions. Further analysis using longitudinal patient-level data could shed further light on duration of use as well as concurrent use and switching among opioid products.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that opioid products are distributed primarily to the outpatient setting. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these outpatient retail pharmacy channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

SDI uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

Indications for use were obtained using SDI’s PDDA, a monthly survey of 3,200 office based physicians. Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, PDDA data are best used to identify the typical uses for the products in clinical practice, and the VONA outpatient prescription data to evaluate trends over time.

Unique patient counts may not be added across time periods due to the possibility of double counting those patients who are receiving treatment over multiple periods in the study. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

6 CONCLUSIONS

Approximately 3.8 million patients, annually, in the outpatient setting may be affected by the Agency’s proposed REMS on ER/LA opioid products. The highest proportion of prescription use was among females, and among patients aged 50-59 years old. Nearly half of prescriptions for ER/LA opioid products are prescribed by primary care physicians. ER/LA opioids had longer mean days of therapy per dispensed opioid prescription than IR opioids, and were used more commonly for conditions that are often associated with chronic pain. Further analysis using longitudinal patient-level data could shed further light on duration of use as well as concurrent use and switching among opioid products.

APPENDIX 1: TABLES AND FIGURES

Table 1

Total number of prescriptions dispensed for long-acting/extended-release and immediate-release opioids from U.S. outpatient retail pharmacies, years 2000 - 2009

	2000		2001		2002		2003		2004		2005		2006		2007		2008		2009	
	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*	Retail TRxs	*Share*
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
TOTAL Rx MARKET	**2,855,144,332**	***100.0%***	**2,978,357,535**	***100.0%***	**3,038,392,408**	***100.0%***	**3,083,900,360**	***100.0%***	**3,116,207,146**	***100.0%***	**3,192,994,078**	***100.0%***	**3,309,218,914**	***100.0%***	**3,457,595,826**	***100.0%***	**3,549,815,441**	***100.0%***	**3,573,135,166**	***100.0%***
All Opioids	**174,147,208**	***6.1%***	**182,937,580**	***6.1%***	**187,510,683**	***6.2%***	**194,644,109**	***6.3%***	**204,535,438**	***6.6%***	**217,208,836**	***6.8%***	**230,434,358**	***7.0%***	**245,215,276**	***7.1%***	**256,710,049**	***7.2%***	**256,950,776**	***7.2%***
ER Opioids	**9,308,446**	***5.3%***	**11,602,226**	***6.3%***	**12,696,768**	***6.8%***	**14,717,961**	***7.6%***	**15,971,019**	***7.8%***	**17,353,890**	***8.0%***	**19,355,379**	***8.4%***	**21,305,847**	***8.7%***	**22,864,082**	***8.9%***	**22,912,032**	***8.9%***
oxycodone hcl	5,462,496	*58.7%*	6,558,762	*56.5%*	6,225,475	*49.0%*	6,595,324	*44.8%*	6,303,494	*39.5%*	6,427,090	*37.0%*	6,960,034	*36.0%*	7,541,029	*35.4%*	7,816,692	*34.2%*	7,732,612	*33.7%*
morphine sulfate	1,260,460	*13.5%*	1,513,568	*13.0%*	1,885,013	*14.8%*	2,229,712	*15.1%*	2,776,301	*17.4%*	3,212,774	*18.5%*	3,728,745	*19.3%*	4,194,588	*19.7%*	4,830,637	*21.1%*	5,151,090	*22.5%*
fentanyl	1,729,950	*18.6%*	2,334,775	*20.1%*	2,965,311	*23.4%*	3,723,901	*25.3%*	4,113,876	*25.8%*	4,295,141	*24.8%*	4,734,610	*24.5%*	5,195,507	*24.4%*	5,378,501	*23.5%*	5,041,724	*22.0%*
methadone hydrochloride	855,540	*9.2%*	1,195,121	*10.3%*	1,620,969	*12.8%*	2,169,024	*14.7%*	2,777,348	*17.4%*	3,418,885	*19.7%*	3,911,818	*20.2%*	4,180,449	*19.6%*	4,438,687	*19.4%*	4,416,468	*19.3%*
oxymorphone hydrochloride	--	--	--	--	--	--	--	--	--	--	--	--	20,172	*0.1%*	194,274	*0.9%*	399,565	*1.7%*	570,138	*2.5%*
IR Opioids	**164,838,762**	***94.7%***	**171,335,354**	***93.7%***	**174,813,915**	***93.2%***	**179,926,148**	***92.4%***	**188,564,419**	***92.2%***	**199,854,946**	***92.0%***	**211,078,979**	***91.6%***	**223,909,429**	***91.3%***	**233,845,967**	***91.1%***	**234,038,744**	***91.1%***
Hydrocodone	**78,194,168**	***47.4%***	**83,831,501**	***48.9%***	**87,634,344**	***50.1%***	**92,194,126**	***51.2%***	**98,756,771**	***52.4%***	**106,480,945**	***53.3%***	**114,138,052**	***54.1%***	**120,970,989**	***54.0%***	**124,550,235**	***53.3%***	**123,106,090**	***52.6%***
HCD/APAP	74,985,314	*95.9%*	80,491,856	*96.0%*	86,080,964	*98.2%*	90,890,399	*98.6%*	96,571,250	*97.8%*	104,199,282	*97.9%*	111,749,993	*97.9%*	118,944,225	*98.3%*	122,732,399	*98.5%*	121,651,340	*98.8%*
HCD/Ibuprofen	3,200,730	*4.1%*	3,333,704	*4.0%*	1,548,672	*1.8%*	1,303,119	*1.4%*	2,185,436	*2.2%*	2,281,643	*2.1%*	2,388,046	*2.1%*	2,026,758	*1.7%*	1,817,833	*1.5%*	1,454,747	*1.2%*
HCD Others	8,124	*0.0%*	5,941	*0.0%*	4,708	*0.0%*	608	*0.0%*	85	*0.0%*	20	--	13	--	6	--	3	--	3	--
Combo Weak	**53,224,242**	***32.3%***	**51,836,763**	***30.3%***	**51,239,938**	***29.3%***	**49,476,800**	***27.5%***	**47,438,247**	***25.2%***	**45,576,505**	***22.8%***	**42,638,998**	***20.2%***	**40,367,332**	***18.0%***	**37,957,562**	***16.2%***	**33,346,529**	***14.2%***
Propoxyphene Combo	28,864,001	*54.2%*	28,210,013	*54.4%*	26,341,824	*51.4%*	25,316,268	*51.2%*	24,357,299	*51.3%*	23,448,884	*51.4%*	22,526,685	*52.8%*	21,770,749	*53.9%*	20,756,025	*54.7%*	17,821,760	*53.4%*
Codeine Combo	23,337,531	*43.8%*	22,229,662	*42.9%*	19,909,223	*38.9%*	18,264,650	*36.9%*	16,966,969	*35.8%*	15,970,970	*35.0%*	15,006,149	*35.2%*	14,289,620	*35.4%*	13,585,267	*35.8%*	12,521,828	*37.6%*
Tramadol/APAP	--	--	377,132	*0.7%*	3,999,607	*7.8%*	4,973,488	*10.1%*	5,337,060	*11.3%*	5,508,583	*12.1%*	4,531,861	*10.6%*	3,800,854	*9.4%*	3,226,083	*8.5%*	2,715,243	*8.1%*
Pentazocine combo	817,633	*1.5%*	739,376	*1.4%*	656,811	*1.3%*	567,342	*1.1%*	491,516	*1.0%*	457,323	*1.0%*	420,104	*1.0%*	387,139	*1.0%*	307,040	*0.8%*	230,845	*0.7%*
Dihydrocod Combo	205,077	*0.4%*	280,580	*0.5%*	332,473	*0.6%*	355,052	*0.7%*	285,403	*0.6%*	190,745	*0.4%*	154,199	*0.4%*	118,970	*0.3%*	83,147	*0.2%*	56,853	*0.2%*
Combo Potent	**16,831,658**	***10.2%***	**18,206,240**	***10.6%***	**19,509,205**	***11.2%***	**21,184,177**	***11.8%***	**22,996,820**	***12.2%***	**25,387,211**	***12.7%***	**27,397,963**	***13.0%***	**29,716,811**	***13.3%***	**31,669,772**	***13.5%***	**32,623,967**	***13.9%***
oxycodone hcl/acetaminophen	15,268,297	*90.7%*	16,724,007	*91.9%*	18,024,972	*92.4%*	19,834,590	*93.6%*	21,728,517	*94.5%*	24,022,441	*94.6%*	26,090,286	*95.2%*	28,606,963	*96.3%*	30,717,242	*97.0%*	32,400,150	*99.3%*
Oxycodone/ASA	581,195	*3.5%*	506,951	*2.8%*	454,481	*2.3%*	384,745	*1.8%*	321,567	*1.4%*	288,516	*1.1%*	221,173	*0.8%*	199,548	*0.7%*	170,931	*0.5%*	140,370	*0.4%*
Meperidine Combo	982,166	*5.8%*	975,282	*5.4%*	1,029,752	*5.3%*	964,842	*4.6%*	946,736	*4.1%*	933,027	*3.7%*	917,111	*3.3%*	858,494	*2.9%*	753,218	*2.4%*	63,173	*0.2%*
Oxycodone/Ibuprofen	--	--	--	--	--	--	--	--	--	--	143,227	*0.6%*	169,393	*0.6%*	51,806	*0.2%*	28,381	*0.1%*	20,275	*0.1%*
SS Weak	**13,287,530**	***8.1%***	**13,575,258**	***7.9%***	**11,891,843**	***6.8%***	**11,727,264**	***6.5%***	**13,036,228**	***6.9%***	**14,851,425**	***7.4%***	**17,914,300**	***8.5%***	**21,009,495**	***9.4%***	**23,719,761**	***10.1%***	**25,467,781**	***10.9%***
Tramadol	11,463,131	*86.3%*	11,931,297	*87.9%*	10,346,607	*87.0%*	10,358,743	*88.3%*	11,759,242	*90.2%*	13,645,288	*91.9%*	16,764,373	*93.6%*	19,901,515	*94.7%*	22,649,662	*95.5%*	24,497,386	*96.2%*
Propoxyphene	793,537	*6.0%*	752,626	*5.5%*	709,196	*6.0%*	626,811	*5.3%*	598,960	*4.6%*	573,089	*3.9%*	571,851	*3.2%*	556,922	*2.7%*	538,454	*2.3%*	476,493	*1.9%*
Butorphanol	945,686	*7.1%*	803,115	*5.9%*	754,121	*6.3%*	654,528	*5.6%*	587,951	*4.5%*	541,930	*3.6%*	492,253	*2.7%*	461,988	*2.2%*	441,878	*1.9%*	405,497	*1.6%*
Codeine	85,170	*0.6%*	88,219	*0.6%*	81,919	*0.7%*	87,182	*0.7%*	90,075	*0.7%*	91,118	*0.6%*	85,823	*0.5%*	89,070	*0.4%*	89,767	*0.4%*	88,405	*0.3%*
Pentazocine	6	--	1	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
SS Potent	**3,270,658**	***2.0%***	**3,845,683**	***2.2%***	**4,491,046**	***2.6%***	**5,226,509**	***2.9%***	**6,019,769**	***3.2%***	**6,970,706**	***3.5%***	**7,922,677**	***3.8%***	**9,744,807**	***4.4%***	**12,190,207**	***5.2%***	**13,753,546**	***5.9%***
Oxycodone	1,198,726	*36.7%*	1,655,964	*43.1%*	1,966,794	*43.8%*	2,404,416	*46.0%*	2,915,730	*48.4%*	3,615,921	*51.9%*	4,393,662	*55.5%*	5,886,252	*60.4%*	8,010,875	*65.7%*	9,239,631	*67.2%*
Hydromorphone	508,297	*15.5%*	572,687	*14.9%*	710,854	*15.8%*	834,453	*16.0%*	984,800	*16.4%*	1,220,586	*17.5%*	1,398,626	*17.7%*	1,628,568	*16.7%*	1,878,458	*15.4%*	2,181,637	*15.9%*
Morphine	736,624	*22.5%*	782,606	*20.4%*	914,885	*20.4%*	1,056,234	*20.2%*	1,180,538	*19.6%*	1,182,501	*17.0%*	1,198,926	*15.1%*	1,307,634	*13.4%*	1,431,594	*11.7%*	1,303,404	*9.5%*
Meperidine	796,215	*24.3%*	764,050	*19.9%*	742,124	*16.5%*	676,711	*12.9%*	607,278	*10.1%*	586,262	*8.4%*	554,761	*7.0%*	505,545	*5.2%*	448,499	*3.7%*	616,568	*4.5%*
Fentanyl	22,907	*0.7%*	64,010	*1.7%*	151,554	*3.4%*	249,568	*4.8%*	324,295	*5.4%*	356,817	*5.1%*	359,106	*4.5%*	344,667	*3.5%*	300,834	*2.5%*	247,622	*1.8%*
Oxymorphone	727	*0.0%*	65	*0.0%*	7	*0.0%*	2	--	2	--	--	--	8,229	*0.1%*	62,102	*0.6%*	109,115	*0.9%*	153,815	*1.1%*
Levorphanol	7,162	*0.2%*	6,301	*0.2%*	4,828	*0.1%*	5,125	*0.1%*	7,126	*0.1%*	8,619	*0.1%*	9,367	*0.1%*	10,039	*0.1%*	10,832	*0.1%*	10,870	*0.1%*
Buprenorphines	**30,506**	***0.0%***	**39,909**	***0.0%***	**47,539**	***0.0%***	**117,272**	***0.1%***	**316,584**	***0.2%***	**588,154**	***0.3%***	**1,066,989**	***0.5%***	**2,099,995**	***0.9%***	**3,758,430**	***1.6%***	**5,740,831**	***2.5%***
buprenorphine hcl/naloxone hc	--	--	--	--	--	--	63,359	*54.0%*	239,123	*75.5%*	491,116	*83.5%*	935,809	*87.7%*	1,887,941	*89.9%*	3,438,529	*91.5%*	5,311,312	*92.5%*
Buprenorphine	30,506	*100.0%*	39,909	*100.0%*	47,539	*100.0%*	53,913	*46.0%*	77,461	*24.5%*	97,038	*16.5%*	131,180	*12.3%*	212,054	*10.1%*	319,901	*8.5%*	429,518	*7.5%*

SDI, Vector One®: National. Years 2000 - 2009. Extracted June 2010.

FIGURE 1

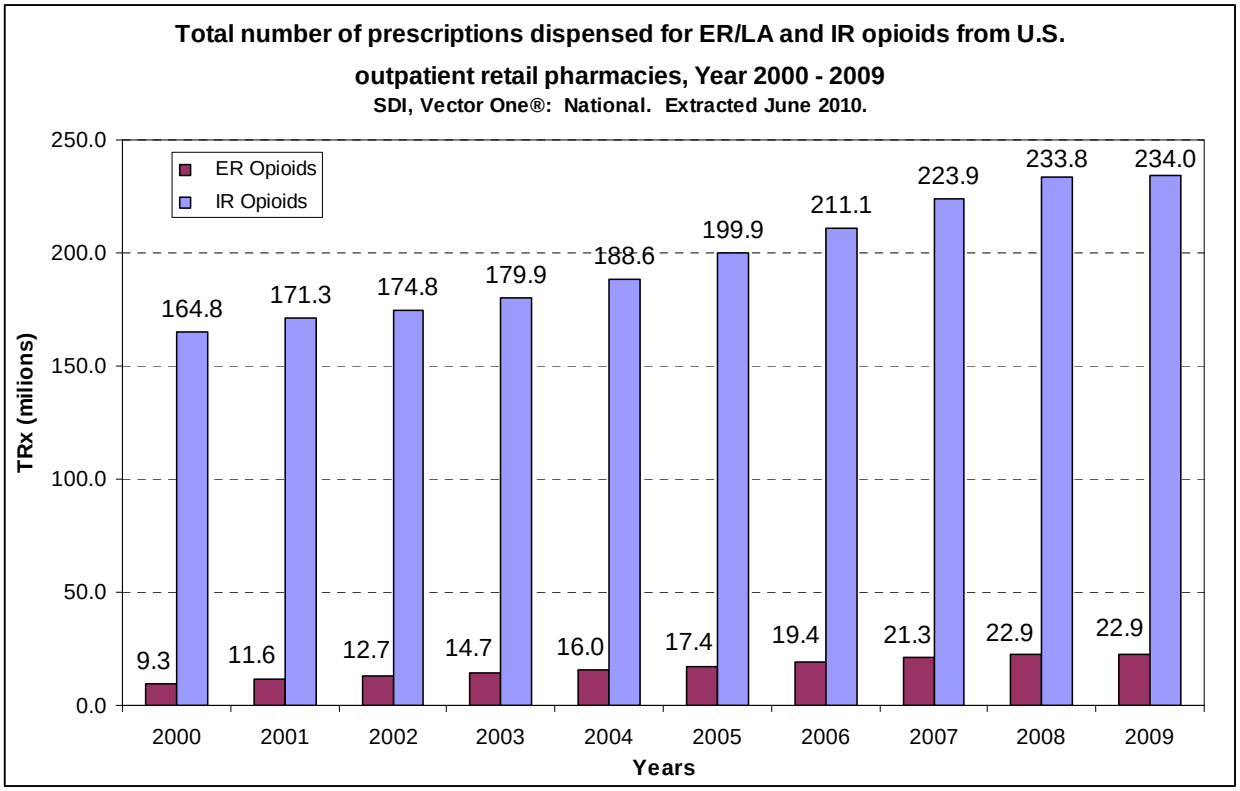
Total number of prescriptions dispensed for ER/LA and IR opioids from U.S. outpatient retail pharmacies, Year 2000 - 2009
SDI, Vector One®: National. Extracted June 2010.
ER Opioids
IR Opioids
TRx (milions)
250.0
200.0
150.0
100.0
50.0
0.0
9.3
11.6
12.7
14.7
16.0
17.4
19.4
21.3
22.9
22.9
164.8
171.3
174.8
179.9
188.6
199.9
211.1
223.9
233.8
234.0
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
Years

FIGURE 2

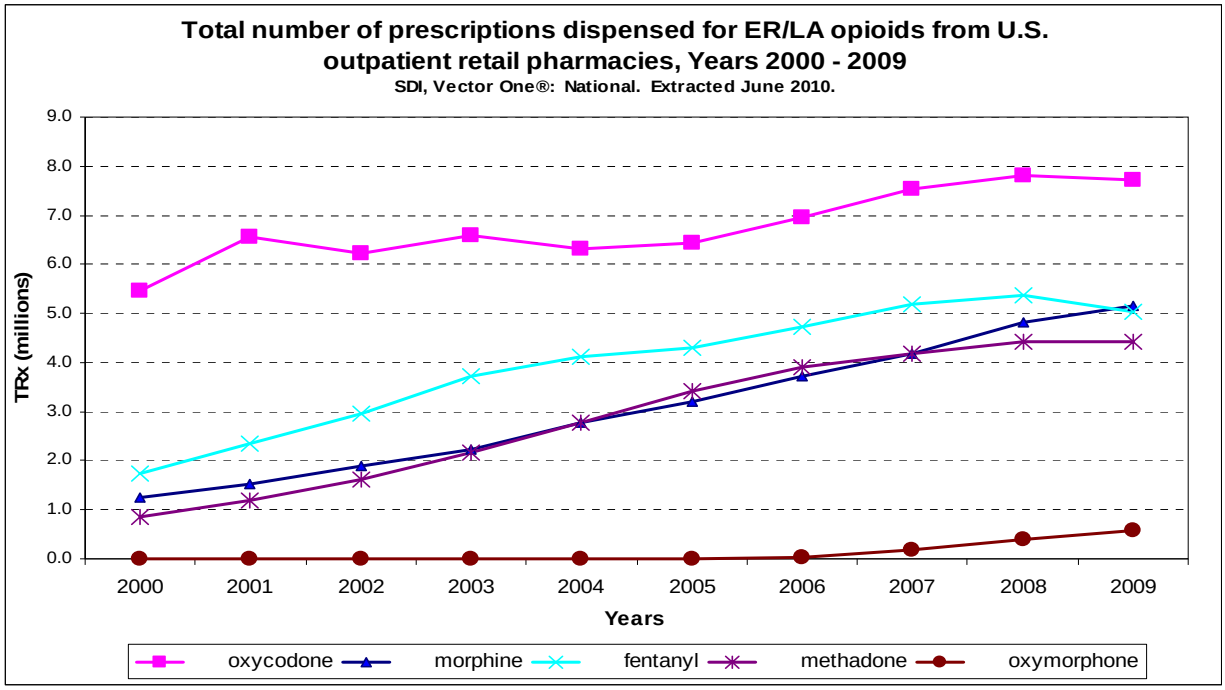

FIGURE 3

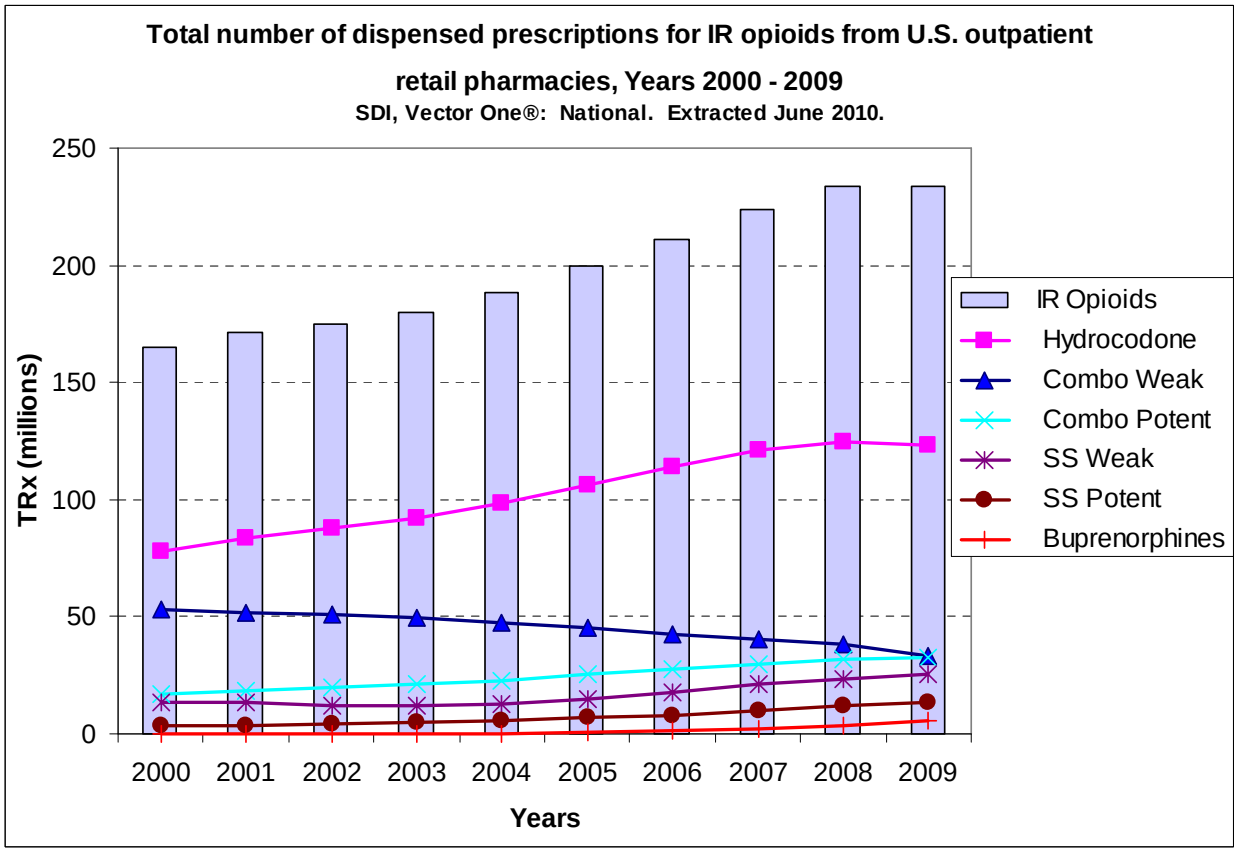

TABLE 2

Total number of unique patients receiving a dispensed prescription for a long-acting/extended-release opioid product from U.S. outpatient retail pharmacies, Years 2002 - 2009

	Years							
	2002	2003	2004	2005	2006	2007	2008	2009
Unique Patients*	**2,703,103**	**3,164,467**	**3,082,022**	**3,243,033**	**3,485,999**	**3,697,150**	**3,945,031**	**3,825,314**

*Do not add across years. Summing across years will result in double-counting and overestimates of patient counts.

SDI, Total Patient Tracker. Year 2002 - 2009. Extracted June 2010.

TABLE 3

Total number of unique patients, stratefied by age and sex, receiving a dipensed prescription for a long-acting/extended release opioid product from U.S. outpatient retail pharmacies, Year 2009

	Projected Patient		Male Patient		Female Patient		Unspecified	
	N	%	N	%	N	%	N	%
Grand Total	**3,825,314**	***100.0%***	**1,718,610**	***44.9%***	**2,091,776**	***54.7%***	**88,603**	**2.3%**
0 - 9	8,397	*0.2%*	4,271	*0.2%*	3,546	*0.2%*	967	11.5%
10 - 19	20,880	*0.6%*	11,102	*0.6%*	9,678	*0.5%*	222	1.1%
20 - 29	190,397	*5.0%*	101,239	*5.9%*	88,251	*4.2%*	3,921	2.1%
30 - 39	430,786	*11.3%*	209,583	*12.2%*	219,489	*10.5%*	9,439	2.2%
40 - 49	835,337	*21.8%*	392,393	*22.8%*	440,783	*21.1%*	13,805	1.7%
50 - 59	1,047,187	*27.4%*	506,997	*29.5%*	538,028	*25.7%*	13,696	1.3%
60 - 69	655,668	*17.1%*	290,552	*16.9%*	364,219	*17.4%*	5,213	0.8%
70 - 79	391,969	*10.3%*	148,750	*8.7%*	242,933	*11.6%*	1,923	0.5%
80+	257,215	*6.7%*	70,991	*4.1%*	185,630	*8.9%*	2,098	0.8%
UNKNOWN AGE	122,621	*3.2%*	28,033	*1.6%*	85,005	*4.1%*	37,318	30.4%

*Subtotals may not sum exactly due to rounding. Because of patients aging during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across years will result in overestimates of patient counts.

SDI, Total Patient Tracker, Year 2009, Extracted June 2010.

FIGURE 4-1

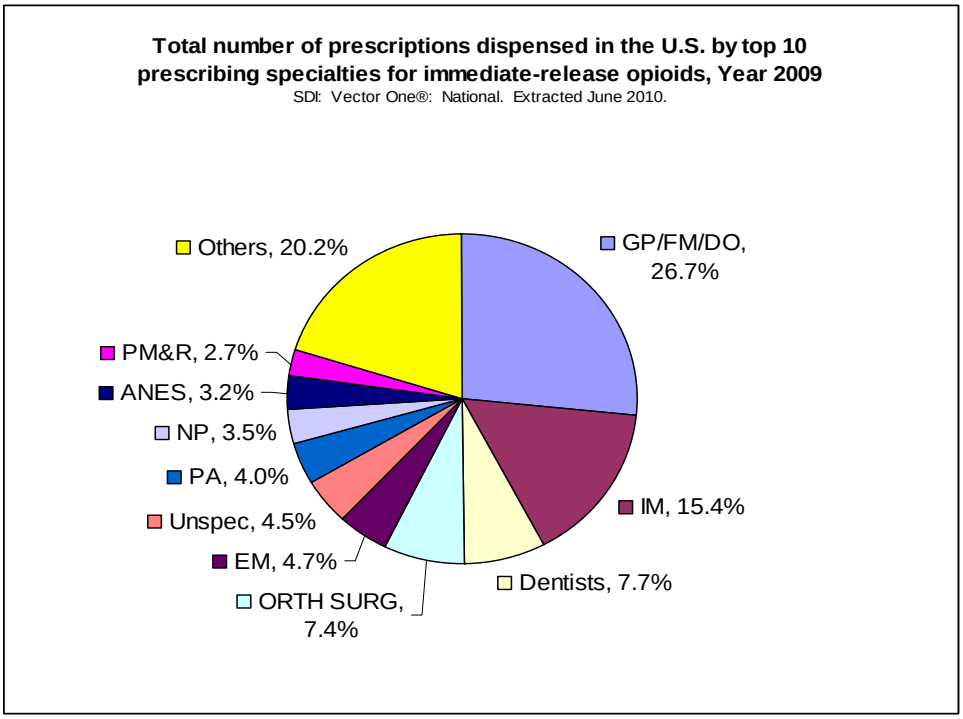

FIGURE 4-2

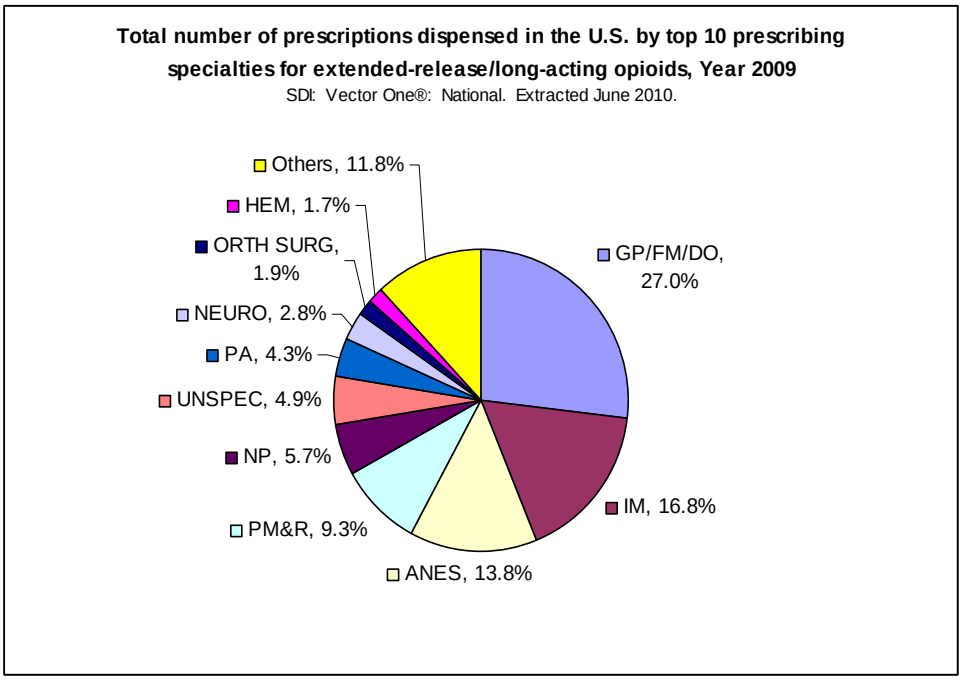

TABLE 4

Mean Days of Therapy per Dispensed Opioid Prescription, Years 2000 - 2009

	Days
ER/LA opioids	23 - 28
IR Single-Ingredient (potent and weak) opioids	13 - 21
IR Combination (potent and weak), Hydrocodones, Buprenorphines	8 - 14

SDI, Vector One®: National. Years 2000 - 2009. Extracted June 2010.

TABLE 5

Diagnoses associated with use (by grouped ICD-9 codes) for single-ingredient, combination, and extended-release/long-acting opioids as reported by office-based physicians in the U.S., Year 2009

	Year 2009					
	Single-Ingredient		Combination		ER/LA	
	N (000)	%	N (000)	%	N (000)	%
TOTAL MARKET	**64,618**	***100.0%***	**21,001**	***100.0%***	**7,094**	***100.0%***
Bacterial, Viral, Parasitic Infections (001-138)	733	*1.1%*	160	*0.8%*	78	*1.1%*
Neoplasms (140-239)	1,848	*2.9%*	1,356	*6.5%*	**809**	***11.4%***
Headaches and Nerve Pain (337-359)	2,508	*3.9%*	1,160	*5.5%*	**982**	***13.8%***
Diseases of the musculoskeletal system & connective tissue (710-739)	**19,591**	***30.3%***	**6,337**	***30.2%***	**3,928**	***55.4%***
Fever & General Symptoms (780-789)	2,665	*4.1%*	2,057	*9.8%*	175	*2.5%*
Fractures, Sprains, Contusions, Injuries (800-999)	**16,555**	***25.6%***	**3,519**	***16.8%***	407	*5.7%*
Follow up examination	4,874	*7.5%*	2,404	*11.4%*	368	*5.2%*
All Others	15,846	*24.5%*	4,002	*19.1%*	355	*5.0%*

SDI, Physician Drug and Diagnosis Audit, Year 2009, Extracted 6/10. Files: PDDA_2010-1198_opioid_REMS_ER_All_Dx3_6-8-10.xls, PDDA_2010-1198_opioid_REMS_IR_Combo_SS_Dx3_6-8-10.xls

APPENDIX 2: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI, Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI, Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

SDI Physician Drug & Diagnosis Audit (PDDA) with Pain Panel

SDI's Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

The National Survey on Drug Use and Health (NSDUH)

The National Survey on Drug Use and Health (NSDUH) is the primary source of statistical information on the use of illegal drugs, alcohol, and tobacco in the civilian, non-institutional population of the United States aged 12 or older. Conducted by the Federal Government since 1971, the survey collects data by administering questionnaires to a representative sample of the population through face-to-face interviews at the respondent's place of residence. The survey is sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA), U.S. Department of Health and Human Services, and is planned and managed by SAMHSA's Office of Applied Studies (OAS). Data collection is conducted under contract with RTI International, Research Triangle Park, North Carolina.[1]

NSDUH collects information from residents of households and non-institutional group quarters (e.g., shelters, rooming houses, dormitories) and from civilians living on military bases. The survey excludes homeless persons who do not use shelters, military personnel on active duty, and residents of institutional group quarters, such as jails and hospitals.

Since 1999, the NSDUH interview has been carried out using computer-assisted interviewing. Most of the questions are administered with audio computer-assisted self-interviewing (ACASI). ACASI is designed to provide the respondent with a highly private and confidential means of responding to questions to increase the level of honest reporting of illicit drug use and other sensitive behaviors and problems. Less sensitive items are administered by interviewers using computer-assisted personal interviewing.

In addition to questions about the use of tobacco and alcohol, the survey obtains information on nine different categories of illicit drug use:

- Marijuana
- Cocaine
- Heroin
- Hallucinogens
- Inhalants

The nonmedical use of prescription-type pain relievers, tranquilizers, stimulants, and sedatives
Hashish is included with marijuana, and crack is considered a form of cocaine. Several drugs are grouped under the hallucinogens category, including LSD, PCP, peyote, mescaline, mushrooms, and "Ecstasy" (MDMA). Inhalants include a variety of substances, such as nitrous oxide, amyl nitrite, cleaning fluids, gasoline, spray paint, other aerosol sprays, and glue. The four categories of prescription-type drugs (pain relievers, tranquilizers, stimulants, and sedatives) cover numerous pharmaceutical drugs available by prescription and drugs within these groupings that may be manufactured illegally, such as methamphetamine, which is included under stimulants. Respondents are asked to report only "nonmedical" use of these drugs, defined as use without a prescription of the individual's own or simply for the experience or feeling the drugs caused. Within the pain reliever category, specific questions about nonmedical use of OxyContin are asked. Use of over-the-counter drugs and legitimate use of prescription drugs are not included.

[1] RTI International is a trade name of Research Triangle Institute.

Questions assessing substance use disorders, based on DSM-IV criteria, are included, as are items on treatment for substance use problems. Mental health status and treatment are also covered in NSDUH.

The 2008 NSDUH employed a State-based design with an independent, multistage area probability sample within each State and the District of Columbia. The eight States with the largest population (which together account for 48 percent of the total U.S. population aged 12 or older) were designated as large sample States (California, Florida, Illinois, Michigan, New York, Ohio, Pennsylvania, and Texas). For these States, the design provided a sample sufficient to support direct State estimates. For the remaining 42 States and the District of Columbia, smaller, but adequate, samples support State estimates using small area estimation techniques. The design oversampled youths and young adults, so that each State's sample was approximately equally distributed among three age groups: 12 to 17 years, 18 to 25 years, and 26 years or older.

Nationally, 142,938 addresses were screened for the 2008 survey, and 68,736 completed interviews were obtained. The survey was conducted from January through December 2008. Weighted response rates for household screening and for interviewing were 89.0 and 74.4 percent, respectively.

Although the design of the 2002 through 2008 NSDUHs is similar to the design of the 1999 through 2001 surveys, there are important methodological differences that affect the comparability of the 2002-2008 estimates with estimates from prior surveys. In addition to the name change, each NSDUH respondent completing the interview is now given an incentive payment of $30. These changes, implemented in 2002 and continued subsequently, resulted in an improvement in the response rate, but also affected respondents' reporting of items that are the basis of prevalence measures produced each year. Comparability also may be affected by improved data collection quality control procedures that were introduced beginning in 2001 and by the incorporation of new population data from the 2000 decennial census into NSDUH sample weighting procedures**.** Analyses of the effects of these factors on NSDUH estimates have shown that 2002 and later data should not be compared with 2001 and earlier data from the survey series to assess changes over time.

A comprehensive set of tables, referred to as "detailed tables," is available through the Internet at http://www.oas.samhsa.gov. The tables are organized into sections based primarily on the topic, and most tables are provided in several parts, showing population estimates (e.g., numbers of drug users), rates (e.g., percentages of population using drugs), and standard errors of all non-suppressed estimates. Additional methodological information on NSDUH, including the questionnaire, is available electronically at the same Web address.

Annual summary reports, brief descriptive reports and in-depth analytic reports focusing on specific issues or population groups are produced by OAS. A complete listing of published reports from NSDUH and other data sources is available from OAS. Most of these reports also are available through the Internet (http://www.oas.samhsa.gov). In addition, OAS makes public use data files available to researchers through the Substance Abuse and Mental Health Data Archive (SAMHDA, 2007) at http://www.icpsr.umich.edu/SAMHDA/index.html. Currently, files are available from the 1979 to 2008 surveys. The 2009 NSDUH public use file will be available by the end of 2010.

Drug Abuse Warning Network

The Drug Abuse Warning Network (DAWN) provides information on some of the most serious medical consequences of substance use, misuse, and abuse as manifested in visits to hospital emergency departments (EDs) and in deaths investigated by medical examiners/coroners.

DAWN Emergency Department Surveillance

DAWN records substances associated with drug-related ED visits; provides a means for monitoring drug misuse and abuse patterns, trends, and the emergence of new substances; assesses some of the morbidity associated with drug misuse and abuse; and generates information for national, state, and local drug policy and program planning. DAWN is also a tool that is increasingly being used for postmarket surveillance and risk management for the pharmaceuticals regulated by the Food and Drug Administration (FDA). DAWN is the responsibility of the Office of Applied Studies, a Federal statistical unit within the Substance Abuse and Mental Health Services Administration (SAMHSA).

DAWN relies on a national probability sample of non-Federal, short-stay, general hospitals that operate 24-hour EDs. The DAWN sample is designed to produce estimates and trends for the United States overall, and for individual metropolitan areas (12 in 2008). To achieve this, the selected metropolitan areas are oversampled. The oversampled hospitals and a supplementary sample of hospitals outside those areas together capture ED visits in all 50 states and the District of Columbia. Based on data from sampled units, national estimates of drug-related ED visits for the United States are produced annually.

DAWN estimates for 2008 are based on data submitted by 231 hospitals. The overall weighted hospital response rate was 32.9% (response rates have been stable from year to year). In 2008, DAWN recorded 351,697 drug-related ED visits. Response rates for the oversampled metropolitan areas ranged from 26.8% in Houston to 83.1% in Detroit. Estimates reflect adjustments for the stratified sample design, unit nonresponse, and nonresponse within a facility. At this time, comparisons over time are available for 2004 – 2008.

To collect the data, each hospital ED that participates in DAWN has one or more trained DAWN reporters who review ED medical records retrospectively to find DAWN cases. Cases reported to DAWN include ED visits caused by or related to drug use for patients of any age. The drug use must be recent; chronic effects and history of drug abuse are not reportable. Visits related to drugs used for therapeutic purposes, as well as drug misuse and abuse, are included. Information that would directly identify a patient (such as name, address, social security number) is never collected. All data are submitted electronically over a secure connection, and automated processes review case data to identify potential errors. Statistical process control (SPC) is used on an ongoing basis to monitor visit, chart, and case counts and case type distribution from participating facilities.

For each reportable visit, demographic, visit, diagnosis, and drug characteristics are abstracted from the medical record. DAWN captures substance misuse and abuse, drug-related suicide attempts, patients who are seeking detoxification or substance abuse treatment services, underage alcohol use (whether or not another drug was involved), adverse reactions to pharmaceuticals taken as prescribed or as directed on the label, overmedication (i.e., when the prescribed or recommended dose of a prescription or over-the-counter medication or dietary supplement was exceeded), malicious poisonings (i.e., drug-facilitated assault), and accidental ingestions (i.e., when a drug was used accidentally or unknowingly).

Data tables containing annual estimates, and trends are produced on most of these types of visits, as well as the following analytic categories:

- All Drug Misuse and Abuse (all ED visits that involved an illicit drug, or alcohol, or the nonmedical use of a pharmaceutical)
- Nonmedical use of Pharmaceuticals (visits that involved the patient taking more than the prescribed dose of a prescription pharmaceutical or more than the recommended dose of an over-the-counter pharmaceutical or supplement; taking a pharmaceutical prescribed for another individual; deliberate poisoning with a pharmaceutical by another person; and documented misuse or abuse of a prescription drug, an over-the-counter pharmaceutical, or a dietary supplement)
- Illicit Drugs
- All Alcohol-Related Visits
- Underage Drinking (alcohol was involved and the patient was younger than 21 years)

The analytic categories follow a standard format and include information on patient gender, age, and race/ethnicity, the number of drugs involved, the disposition of ED visit, and characteristics of the drugs.

DAWN captures very detailed drug information. Up to 16 drugs plus alcohol can be reported for each DAWN case. Drug-related ED visits often include multiple drugs, on average, 1.6 drugs per visit. For adults, alcohol is reportable only when present with another reportable drug; for minors, alcohol is always reportable. Drug information is captured at the level of detail present in the medical record. The same drug may be reported to DAWN by brand, generic, chemical, street, or nonspecific name, depending on the completeness and specificity of information in the medical record. Training and automated rules prompt DAWN reporters to use all available documentation in the medical chart to record drugs by their most specific names (e.g., OxyContin, when documented as such, instead of oxycodone), not to record the same drug by different names (e.g., marijuana and weed), and to exclude current medications unrelated to the visit. Estimates are published at the generic level (e.g., acetaminophen-hydrocodone), for specific ingredients (e.g., dextromethorphan), or by drug category (e.g., opiates/opioids, benzodiazepines). Estimates attributed to particular brand or trade names (e.g., Concerta) are not published.

Since data for DAWN are extracted from a retrospective review of medical records, no patients, family members, or healthcare practitioners are interviewed. Off-site “satellite” EDs associated with participating hospitals are included, but other units within the hospital are not. Although each drug report has an associated indicator for whether the drug was confirmed by toxicology testing, specific laboratory findings are not recorded for DAWN cases. The source of the drug is not collected because it is so rarely available in medical records. Repeat visits by the same individual cannot be linked together. Visits due to chronic conditions associated with a history of drug abuse are explicitly excluded. Although DAWN does not collect direct identifiers, such as patient name, the content of the case data could potentially render the data individually identifiable. However, individually identifiable data are protected by Federal law from disclosure without consent.

DAWN does not measure the prevalence of drug abuse in the population, and external factors unrelated to the level of drug abuse in the population may contribute to the likelihood that a person presents to a hospital ED for a drug-related problem. For example, the availability of health insurance and/or other sources of care may influence whether an individual seeks care in an ED. Purity, experience, or other

factors related to the physiological effects of drugs may affect whether a condition occurs to give rise to an ED visit.

DAWN Mortality Surveillance

DAWN also collects data on drug-related deaths reviewed by medical examiners and coroners (ME/Cs) in selected metropolitan areas and selected states. The death investigation jurisdictions that participate in DAWN do not constitute a statistical sample of the United States; as a result, extrapolation of drug-related deaths to the nation as a whole is not possible. Because most metropolitan areas contain multiple jurisdictions, totals for a metropolitan area are possible only when every jurisdiction participates. The number of jurisdictions that participate in DAWN varies from year to year. In 2008, there were 544 participating ME/Cs who identified and reported to DAWN on all deaths referred to their offices that met the DAWN criteria for being a drug-related death. These ME/Cs represent the larger metropolitan and micropolitan areas in 36 states and, collectively, cover one third of the nation's population. In 12 states, DAWN had 100% coverage.

The case criteria and data collection procedures for drug-related deaths mirror those used in EDs. Causes and manner of death are captured, in lieu of case type and diagnoses.