Title: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Twelve-Month FDA Assessment Report

Document Number: Version 1

Product Name: All Extended-Release (ER) and Long-Acting (LA) Opioid Analgesic Products

Companies: REMS Program Companies (RPC)

Date: 28 June 2013

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LIST OF ABBREVIATIONS

AAFP	American Academy of Family Physicians
AAHPM	American Academy of Hospice and Palliative Medicine
AANP	American Association of Nurse Practitioners
ACCME®	Accreditation Council for Continuing Medical Education
AE	Adverse Event
AGS	American Geriatrics Society
AMA	American Medical Association
ANCC	American Nurses Credentialing Center
AOA	American Osteopathic Association
ASAM	American Society of Addiction Medicine
BPS	Baseline Prescriber Survey
BUSM	Boston University School of Medicine
CAFP	California Academy of Family Physicians
CE	Continuing Education
CME/CE	Continuing Medical Education/Continuing Education
CMS	Council of Medical Specialty Societies
DDRP	Dear DEA-Registered Prescriber
DEA	Drug Enforcement Administration
DO	Doctor of Osteopathy
DPOLB	Dear Professional Organization/Licensing Board
ER	Extended-Release
ET	Eastern Time
ETASU	Elements to Assure Safe Use
FAQs	Frequently Asked Questions
FDA	Food and Drug Administration
FSMB	Federation of State Medical Boards
GMS	Grant Management System
HCP	Healthcare Professional
KAB	Knowledge, Attitudes, and Behavior
LA	Long-Acting
LOA	Letter of Agreement
MAOIs	Monoamine oxidase inhibitors

MD	Medical Doctor
MEMS	Medical Education and Metrics Standards
NDA/ANDA	NewDrug Application/Abbreviated New Drug Application
NP	Nurse Practitioner
NPHF	Nurse Practitioner Healthcare Foundation
PA	Physician Assistant
PCD	Patient Counseling Document
DPOLB	Dear Professional Organization/Licensing Board
POMAF	Pennsylvania Osteopathic Medical Association Foundation
PPA	Patient Prescriber Agreement
REMS	Risk Evaluation and Mitigation Strategy
RFA	Request for Applications
RPC	REMS Program Companies
US	United States
USPS	United States Postal Service

1. EXECUTIVE SUMMARY

The Food and Drug Administration (FDA) has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for all Extended-Release and Long-Acting (ER/LA) opioid analgesic drug products to ensure that their benefits outweigh their risks, especially with regard to specific adverse outcomes. The goal of the ER/LA Opioid Analgesics REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications.

This Twelve-Month FDA Assessment Report is the second Report since approval of the ER/LA Opioid Analgesics REMS on July 9, 2012. It includes updates on:

- Assessment Element 1: Prescribers who have successfully completed REMS-compliant training, which launched on February 28, 2013;
- Assessment Element 2: Independent audits of Continuing Medical Education/Continuing Education (CME/CE) activities;
- Assessment Element 3a: Evaluation of ER/LA opioid analgesic prescribers' understanding of key risks by use of a voluntary Baseline Prescriber Survey (BPS).

This Report also includes status updates on the functional components of the REMS including the distribution of the Dear DEA-Registered Prescriber (DDRP) Letter 2 and Dear Professional Organization/Licensing Board (DPOLB) Letter 2, the Patient Counseling Document (PCD), and the REMS Call Center.

The key accomplishments in the past 12 months include planning, constructing, and deploying the infrastructure to support REMS-compliant CME/CE activities, the establishment of comparative data on ER/LA prescribers' understanding of key risk messages via the BPS, and the establishment and maintenance of all ongoing REMS functional and operational components.

The first REMS-compliant CME/CE supported by the REMS Program Companies (RPC) launched on February 28, 2013. Two of the five series of REMS-compliant activities selected for support in 2013 by the RPC had begun their programs by the data collection cutoff for this reporting period, May 10, 2013. Nine REMS-compliant educational activities, out of the total of more than 274 supported by the RPC to date, constituted the activities that were launched between February 28 and May 4, 2013. Eight unique CME/CE Providers presented the nine activities. The activities were accredited by five different National Accrediting Bodies.

A total of 1,147 ER/LA opioid prescribers completed the education and assessment requirements for REMS-compliant training between February 28, 2013 and May 10, 2013. Of these, 856 (74.6%) ER/LA opioid prescribers completed REMS-compliant RPC-supported training through live activities and 291 (25.3%) participated in internet-based activities. The majority of the prescribers completing the training during this period were physicians. Of the total number of prescribers completing REMS-compliant, RPC-supported education activities, 73.7% were physicians, 21.9% were advanced practice nurses, 3.3% were physician assistants, and approximately 1% were podiatrists (N = 3), pharmacists (N = 2), dentists (N = 2) or prescribers describing their profession as "other" (N = 5). Practice type data was collected on 65.6% (753) of ER/LA opioid prescribers in this reporting period, and 65.9% of these (N = 496) were in primary care practices, 20.8% (N = 157) were non-pain specialists, and 13.2% (N = 100) were pain specialists.

The Request for Applications for the next cycle of CME/CE accredited REMS-compliant activities was disseminated via posting on the RPC website and GMS on May 21, 2013. Grant applicants are required to submit RFA proposals by July 16, 2013, and details of the grant awards will be included in the Two-Year FDA Assessment Report.

The RPC elected to conduct a BPS to measure prescriber awareness and understanding of REMS safety messages and receipt of REMS materials, as well as self-reported behaviors and practices early in the development of the REMS. The survey included a total of 54 key risk message items based on the key risk messages outlined in the FDA Blueprint and 24 items related to the requirements of the REMS and receipt of the educational materials. Survey questions were pre-tested prior to finalizing the questionnaire and launching the survey.

A total of 605 prescribers completed the survey. The modal score of the knowledge items scored correctly was 83%. The majority (64.8% of 54) of questions/items had correct scores for more than 80% of participants, indicating a reasonably high level of knowledge.

Prescribers were asked about their awareness, receipt, and review of educational materials associated with the ER/LA Opioid REMS. The proportion of prescribers who were aware of the DDRP Letter was 27.3% (165 prescribers), and 115 prescribers (89.8% of those aware) reported reading it. One-third of prescribers (N = 195, 32.2%) were aware of the PCD, and 97 prescribers (16%) were aware of the ER/LA Opioid Analgesics REMS website (www.er-la-opioidrems.com). These levels of awareness existed despite all DEA-registered prescribers having been sent DDRP Letters 1 and 2. Approximately half of the survey respondents (N = 266, 44.0%) indicated they were aware of the Medication Guide and 188 (87.4% of 266) read the Medication Guide for the opioid analgesic they prescribe.

Concerning the functional components of the ER/LA Opioid Analgesics REMS, a second DDRP letter (DDRP Letter 2) was used to announce availability of ER/LA Opioid Analgesic REMS CME/CE opportunities no later than 30 days before the first REMS-compliant prescriber training was offered. The target audience for the letter was all DEA-registered prescribers, regardless of discipline/degree. The letter was distributed electronically by e-mail or facsimile or via United States Postal Service (USPS). Letters were sent to all 1,342,173 unique prescribers in the DEA list of Prescribers on the DEA master registration file. To further ensure that prescribers are aware of ER/LA Opioid Analgesic REMS-related CME/CE opportunities, the RPC distributed a letter to relevant Learned Societies and Professional Associations (DPOLB Letter 2) on January 24, 2013. Overall, 326 professional organizations and healthcare professional licensing boards were sent the DPOLB Letter 2. Of the 326 letters sent, one was returned as undeliverable.

During this reporting period, (November 9, 2012 to May 10, 2013), the PCD has been downloaded 1,920 times. The PCD was also included as an attachment in DDRP Letter 2 and DPOLB Letter 2 communications (electronic and hardcopy). As part of the REMS, a portal was designed for prescribers to order copies of the PCD via an online order form or by fax. For the reporting period, 241 total PCD orders (226 online, 13 fax, 2 phone), equating to 584 pads, were successfully fulfilled.

The ER/LA Opioid Analgesics REMS Program established a centralized Call Center, which became operational on July 23, 2012. The primary purpose of the Call Center is to provide REMS Program support to consumers and Healthcare Professionals (HCPs). The most frequently asked question (37.6%) was “about completing the CME/CE programs in order to prescribe

ER/LA opioids." The second most frequently asked question (12.2%) concerned "where training programs would be offered." The third most frequently asked question (10.6%) was "how prescribers are defined in the ER/LA opioid program." Since the launch of the centralized Call Center, on average, 10 calls per week have been received (with the exception of the first two weeks immediately following two large mailings).

The ongoing evaluation and modification to the design of the program is an important operating principle in this single shared REMS program. One modification that the RPC is recommending after collecting and evaluating data over the past year of operation is decommissioning the centralized Call Center due to the low call volume. In addition to low call volume, almost all (95.3%) of the questions received are covered by frequently asked questions readily available on the ER/LA Opioid Analgesics REMS website. If decommissioning is approved by FDA and a live agent is required, the RPC's existing call centers will be utilized. The RPC views this efficiency as a way to enhance sustainability, provide the flexibility needed to make continuing improvements, and ensure resources are properly allocated.

In summary, significant progress has been made in initiating and implementing the REMS. All requirements of the REMS up to this point in time have been met. Future activities will focus on meeting the requirements for the next year of the REMS and in working to continue to improve the management of the risks of prescription opioid analgesics through the collective efforts of RPC initiatives.

2. BACKGROUND

In April 2011, in accordance with section 505-1 of the Federal Food Drug and Cosmetic Act, the FDA determined that a REMS was necessary for all ER/LA opioid analgesic drug products to ensure that their benefits outweigh their risks, especially with regard to specific adverse outcomes. The goal of the ER/LA Opioid Analgesics REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of particular interest include addiction, unintentional overdose, and death. In the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, the FDA determined that a single shared system should be used to implement this REMS.

The New Drug Application/Abbreviated New Drug Application (NDA/ANDA) holders of branded and generic drug products meeting the following requirements are obligated to participate in the ER/LA Opioid Analgesics REMS: extended-release, oral-dosage formulations containing hydromorphone, morphine, oxycodone, oxymorphone, and tapentadol; transdermal delivery systems containing fentanyl or buprenorphine; and methadone formulations that are indicated for use as analgesics.

Pharmaceutical companies subject to this REMS (the REMS Program Companies, or RPC) worked together to implement a REMS for all ER/LA opioid analgesic drug products. The RPC was actively involved in providing input to FDA during the development of the ER/LA Opioid Analgesics REMS. The ER/LA Opioid Analgesics REMS provides a structure for all of the companies of the RPC to implement risk evaluation and mitigation activities across all ER/LA opioid analgesics in a uniform manner. The REMS was approved by FDA on July 9, 2012 (http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm).

The elements of the REMS include Medication Guides, Elements to Assure Safe Use (ETASU) and a Timetable for Submission of Assessments. Under the REMS, the NDA/ANDA holders must do the following:

- Ensure that training is available to prescribers who prescribe the ER/LA opioid analgesics
- Provide to prescribers information that the prescriber can use to educate patients about the risks of ER/LA opioid analgesics and their safe use, storage, and disposal
- Inform prescribers of the existence of the ER/LA Opioid Analgesics REMS and the need to successfully complete the necessary training

Training will be considered "REMS-compliant training" under this REMS if:

- Training provided by (CME/CE) Providers is offered by an accredited Provider to licensed prescribers,
- It includes all elements of the FDA Blueprint for Prescriber Education for ER/LA Opioid Analgesics ("FDA Blueprint"),
- It includes a post-course knowledge assessment of all of the sections of the FDA Blueprint, and
- It is subject to independent audit to confirm that conditions of the REMS training have been met.

As part of the REMS, performance goals were established for availability of the REMS-compliant training. These goals are:

- Not later than March 1, 2013, the first REMS-compliant training will be made available.
- Within two years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of the 320,000 active prescribers in 2011) will have been trained.
- Within three years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of the 320,000 active prescribers in 2011) will have been trained.
- Within four years from the time the first REMS-compliant training becomes available, 192,000 prescribers (based on 60% of the 320,000 active prescribers in 2011) will have been trained.

The REMS includes a plan to inform prescribers and potential prescribers identified via the Drug Enforcement Administration (DEA) registration database about the REMS and the need to complete the necessary training. The primary communication methods to disseminate this information include DDRP Letters and DPOLB Letters. Performance goals established for these communications are:

- DDRP Letter 1 will be sent not later than 60 days after the initial approval of this REMS
- DDRP Letter 2 will be sent not later than 30 days before the first prescriber REMS-compliant training required by the REMS is offered by Providers
- At least annually from the date of initial approval of the REMS, the DEA Registration Database will be reviewed and Prescriber Letter 3 will be sent to all newly DEA-registered prescribers who are registered to prescribe Schedule II and III drugs
- DPOLB Letter 1 will be sent not later than 60 days after REMS approval
- DPOLB Letter 2 will be sent not later than 30 days before the first prescriber REMS-compliant training is available

Educational materials must be developed for prescribers to use in educating their patients. The REMS includes Patient Counseling Document (PCD) on ER/LA Opioid Analgesics and Medication Guides. These materials must be accessible to prescribers; the RPC has developed an ER/LA Opioid Analgesics REMS website and has established a Call Center to provide easy access to these materials. Performance goals regarding information availability include:

- An interim single toll-free number Call Center must be implemented no later than July 23, 2012, and a fully operational centralized Call Center must be implemented no later than 90 calendar days after the approval of the REMS (by October 21, 2012)

A critical aspect of the REMS is assessment of the effectiveness of the program in meeting its goals. The FDA has indicated eight key areas for assessment as well as evaluation of the functional components of the REMS implementation. These elements are shown in Table 1.

TABLE 1: FDA-REQUIRED REMS ASSESSMENTS

FDA REQUIREMENTS
Evaluation of Functional Components **Dates when the following were initiated:** • REMS Website • Dear DEA-Registered Prescriber Letter • Dear Professional Organizations, Licensing Boards, and Medical Societies Letter • Call Center
Assessment Element 1: Assessment of how many prescribers of ER/LA opioids have successfully completed the training. Specify performance goals for number of prescribers trained by time.
Assessment Element 2: Independent audit of the quality of the content of the educational materials used by the CME/CE Providers to provide the education. The audit should evaluate the quality of the content against the content approved by the FDA as part of the REMS, as well as against the Accreditation Council for Continuing Medical Education (ACCME®'s) and other accrediting bodies' standards for commercial support.
Assessment Element 3a: Prescriber survey Evaluation of healthcare professional (HCP) awareness and understanding of the serious risks associated with these products (e.g., through surveys of HCPs) and specification of measures that would be taken to increase awareness if surveys of HCPs indicate that HCP awareness is not adequate.
Assessment Element 3b: Long-term evaluation grants
Assessment Element 4: Patient survey Evaluation of patients' understanding of the serious risks of these products.
Assessment Element 5: Surveillance monitoring for misuse, abuse, overdose, addiction, death and any intervention to be taken resulting from signals of these metrics, including information for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency rooms, addiction treatment centers, poison control call centers). As much as possible, the information should be drug-specific.
Assessment Element 6: Evaluation of drug utilization patterns (IMS data)
Assessment Element 7: Evaluation of changes in prescribing behavior Evaluation of changes in prescribing behavior of prescribers, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills.
Assessment Element 8: Monitoring patterns of prescribing to identify changes in access to ER/LA opioid analgesics

REMS assessments will be submitted to the FDA at six months and twelve months after REMS approval and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. This report is the second (twelve month) assessment of the ER/LA Opioid Analgesics REMS, covering the time period from November 10, 2012 through May 10, 2013. The report cutoff is 60 days prior to submission of the report to the FDA (July 9, 2013). This report includes an evaluation of the REMS Functional Components cited in Table 1 and describes the progress that has been made toward addressing the eight key assessments. The time frame for addressing the eight key assessments and the types of evaluation metrics to be used are shown in Table 2.

TABLE 2: INDIVIDUAL ASSESSMENTS REQUIRED FOR ASSESSMENT REPORTS AND ASSESSMENT REPORT VENDOR ACTIVITIES

INDIVIDUAL ASSESSMENT ELEMENTS	KEY ACTIVITIES[1]				
	ASSESSMENT REPORT #1 (JAN 9, 2013)	ASSESSMENT REPORT #2 (JULY 9, 2013)	ASSESSMENT REPORT #3 (JULY 9, 2014)	ASSESSMENT REPORT #4 (JULY 9, 2015)	SUBSEQUENT REPORTS (ANNUALLY)
Functional Components Assessment	Dates, Call Centers FAQs	Dates, Call Centers FAQs	- -		-
Assessment Element 1 Prescribers successfully completing training	Grant reports	# of Prescribers trained; estimate of future trained	# of Prescribers trained; estimate of future trained	Target:80,000 Prescribers (Feb 28, 2015)	Target:160,000 Prescribers (Feb 28, 2016) 192,000 Prescribers (Feb 28, 2017)
Assessment Element 2 Independent audit of CME/CE activities	- -		√	√	√
Assessment Element 3a[2] Evaluation of prescriber understanding (i.e., Prescriber Survey)	-	Qualitative Research and Baseline Survey	-	√	Per FDA Request
Assessment Element 3b: Long-term Evaluation Grants Grants to CME/CE organizations to assess prescribers' knowledge/practice changes 6-12 months after REMS-compliant training	# of proposals and grants, list of grantees, date of training and evaluation	# of proposals and grants, list of grantees, date of training and evaluation	# of proposals and grants, list of grantees, date of training and evaluation	# of proposals and grants, list of grantees, date of training and evaluation	Per FDA Request
Assessment Element 4 Evaluation of patient understanding (i.e., Patient Survey)	- -		√	√	Per FDA Request

TABLE 2: INDIVIDUAL ASSESSMENTS REQUIRED FOR ASSESSMENT REPORTS AND ASSESSMENT REPORT VENDOR ACTIVITIES

INDIVIDUAL ASSESSMENT ELEMENTS	KEY ACTIVITIES[1]				
	ASSESSMENT REPORT #1 (JAN 9, 2013)	ASSESSMENT REPORT #2 (JULY 9, 2013)	ASSESSMENT REPORT #3 (JULY 9, 2014)	ASSESSMENT REPORT #4 (JULY 9, 2015)	SUBSEQUENT REPORTS (ANNUALLY)
Assessment Element 5 Surveillance monitoring for misuse, abuse, overdose, addiction, death and intervention taken	-	-	√	√	√
Assessment Element 6 Evaluation of drug utilization patterns (IMS data, claims data)	-	-	√	√	√
Assessment Element 7 Evaluation of changes in prescribing behavior	-	-	√	√	√
Assessment Element 8 Changes in access to ER/LA opioid analgesics	-	-	√	√	√

[1] Checkmark indicates that reporting on this individual Assessment Element is required for this Assessment Report.

[2] Assessment 3a was not a requirement for inclusion in the Six-Month FDA Assessment Report

3. REMS ASSESSMENT RESULTS

3.1. Assessment Element 1 – Prescribers Who Have Successfully Completed Training

A key component following the implementation of REMS-compliant CME/CE activities is the assessment of the extent to which the training is effective in meeting the aims of the ER/LA Opioid Analgesics REMS. To assess the impact of the training, the RPC established and implemented a plan to measure the reach of the REMS-compliant, RPC-supported educational activities, as measured by the number of prescribers who successfully complete the training, and other metrics related to the educational activities and the participating prescriber audiences. The following is an overview of the assessment strategy employed to evaluate the REMS-compliant education supported by the RPC, as well as the metrics associated with the educational activities achieved as of the Twelve-Month FDA Assessment Report data cutoff on May 10, 2013.

3.1.1. Assessment Overview

The ER/LA Opioid Analgesics REMS represents the first time that certified CME/CE has been used to fulfill a REMS training requirement. Therefore, a multitude of systems and processes needed to be developed and implemented in conjunction with the National CME/CE Accrediting Bodies, CME/CE Provider Organizations, and other key REMS stakeholders to enable provision of REMS-compliant CME/CE, as well as data collection, aggregation, reporting, and independent audits to occur.

Recognizing the importance of collaboration with the CME/CE communities, yet mindful of adhering to the standards for commercial support to ensure independence in CME/CE activities, the RPC established a CE Sub-team to focus on this critical aspect of the REMS. Members of the CE Sub-team began interacting with the National Accrediting Bodies in 2010 and continued to work with these organizations to obtain input/feedback during the course of the development and implementation of the REMS.

3.1.2. REMS Continuing Education Stakeholders

Upon approval of the REMS on July 9, 2012, the RPC, with the National Accrediting Bodies and other key CME/CE stakeholder groups, promptly moved forward to formalize plans for initiation, tracking, reporting, and auditing REMS-compliant CME/CE activities. A list of the major CME/CE stakeholders that the RPC has worked with to-date to develop and implement the REMS training/education requirement is outlined in Table 3.

TABLE 3: HIGH-LEVEL DESCRIPTION OF REMS CONTINUING EDUCATION STAKEHOLDER ORGANIZATIONS

CME/CE STAKEHOLDER	HIGH-LEVEL DESCRIPTION
National CME/CE Provider Organizations	• Represent various groups of CME/CE Providers that may conduct REMS CME/CE, including RPC-supported activities. • Fielded surveys prior to final REMS approval to assess CME/CE Provider awareness of REMS and to gauge potential interest of CME/CE Providers in providing REMS CME/CE. • Represent accredited Providers on the MedBiquitous Working Group to ensure the Medical Education and Metrics Standards (MEMS) 2.0 Specifications that serve as the basis for uniform REMS CME/CE data reporting are appropriate/feasible from the CME/CE Provider's standpoint. • Provide input/feedback on operational aspects of REMS CME/CE to RPC via participation in live meetings, teleconferences, and webinars. • Assist in broadly communicating information on the REMS to groups of CME/CE Providers.
National CME/CE Accrediting Bodies	• Interface with CME/CE Providers and RPC to ensure that REMS-compliant CME/CE activities are conducted in accordance with the established standards for commercially supported accredited CME/CE. • Act as independent auditors of REMS-compliant CME/CE activities to ensure independent audit requirements described in Section I.B.1.d. of the REMS are met and documented. • Act as primary data collectors for REMS-compliant CME/CE data; collect data from CME/CE Providers and report it to the CME/CE Data Aggregation Vendor contracted by RPC. • Participate in the MedBiquitous Working Group to ensure that the MEMS 2.0 specifications that serve as the basis for uniform REMS CME/CE data reporting are appropriate/feasible from the Accrediting Body's standpoint.
National Professional Societies	• Important stakeholders who have participated in both FDA and RPC REMS planning discussions to provide clinical and patient safety-related input/feedback. • Assist in raising REMS awareness and disseminating information about REMS CME/CE through well-established communication networks. • Participate in independent and collaborative initiatives to engage their members in completing REMS-compliant CME/CE.

TABLE 3: HIGH-LEVEL DESCRIPTION OF REMS CONTINUING EDUCATION STAKEHOLDER ORGANIZATIONS

CME/CE STAKEHOLDER	HIGH-LEVEL DESCRIPTION
CMSS (Council of Medical Specialty Societies)	• United consortium of medical specialty organizations working to improve US healthcare through policy, accreditation, and broad-reaching medical education initiatives. • Key stakeholder committed to encouraging its 700,000 physician members to complete REMS-compliant CME/CE. • Actively engaged in fostering effective REMS communication and collaboration among regulatory agencies, policy makers, the CME/CE community, and industry.
Conjoint Committee on Continuing Medical Education	• Sixteen national organizations spanning the spectrum of medical education and practice; the Committee's focus is on identifying ways for CME to help improve US healthcare. • Providing integral input, feedback, and assistance in successfully operationalizing REMS CME/CE, which has been identified by the Conjoint Committee as a priority initiative.
MedBiquitous Consortium (MedBiquitous)	• Develops and updates nationally recognized, ANSI-accredited information technology standards for healthcare education and quality improvement. • Creator/owner of the MEMS that underlay a uniform system of CME/CE data collection, aggregation, and reporting.

3.1.3. REMS Continuing Education Development Process

A graphic illustration of the RPC's major CME/CE-related milestones can be seen in Figure 1. A synopsis of the CME/CE-related system and process development necessitated by the REMS is provided below.

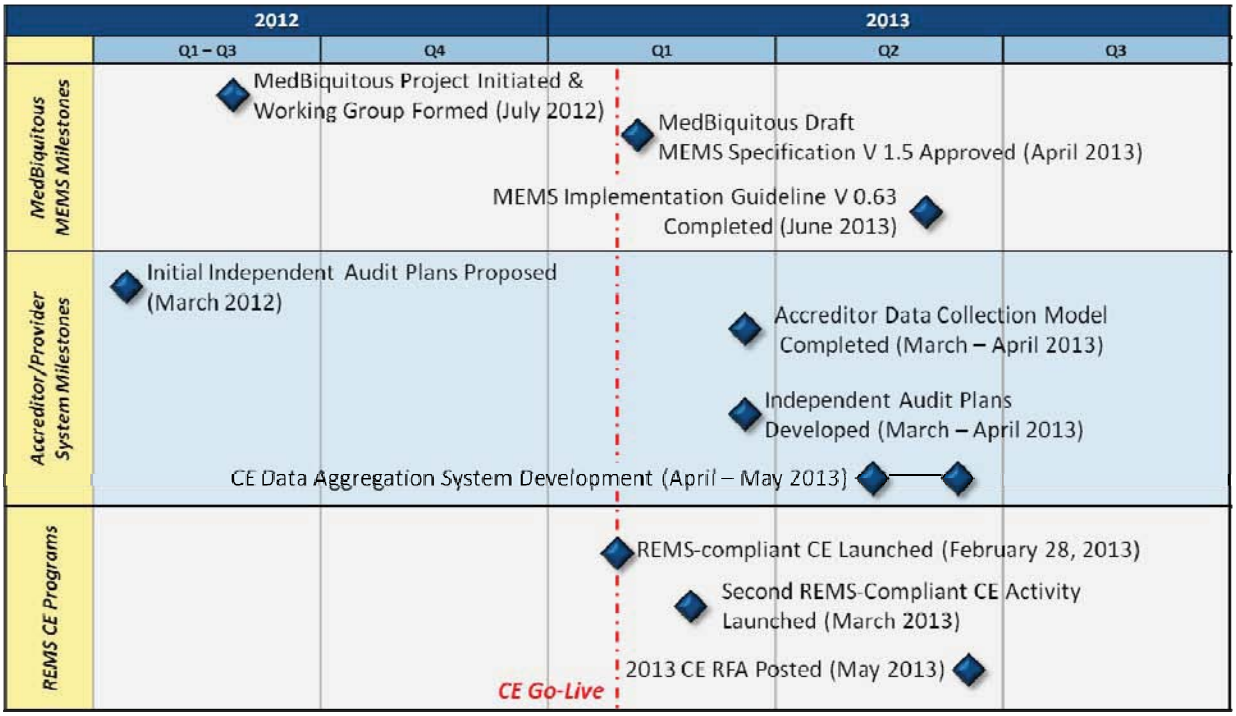
In early 2012, the RPC initiated discussions with National Accrediting Bodies to identify approaches to CME/CE data collection/aggregation and independent audits, which could be conducted in a manner accordant with the Accreditors' standards for commercially supported CME/CE.

Cognizant of the need for a standardized approach to REMS CME/CE data collection/aggregation, the RPC contacted the MedBiquitous Consortium, a developer of information technology standards for education and quality improvement. By mid-year, the MedBiquitous Working Group, consisting of representatives from the National CME/CE Accrediting Bodies, National CME/CE Provider Organizations, Professional Societies/other invited experts, RPC, and the Agency, was formed. This group worked to revise the Medical Education Metrics Specifications (MEMS) to provide a data structure that allows for collection and analysis of CME/CE data in order to fully meet the Agency requirements for the ER/LA Opioid Analgesics REMS. As of June 2013, the MedBiquitous Working Group was in the final stage of completing a revised set of MEMS specifications. The working draft of the specifications is posted at http://medbiq.org/working_groups/metrics/index.html.[1]

[1] Following review by the MedBiquitous Standards Committee, public review, and balloting, the specifications will be considered final and the revised MEMS 2.0 standards will be posted to the site.

These specifications underlay the process for collecting REMS-compliant CME/CE data and reporting it to the CME/CE Data Aggregation Vendor contracted by the RPC. This process was created by the CME/CE Accrediting Bodies in collaboration with the MedBiquitous Working Group and has been accepted by the RPC. CME/CE Providers who received early award grants were invited to participate in the MedBiquitous Working Group to ensure seamless exchange of data beginning with the first REMS-compliant CME/CE activity. With the completion of the working draft of the MEMS specification revisions, National Accrediting Bodies are now fully equipped to communicate directly with REMS CME/CE Providers and the CME/CE Data Aggregation Vendor in order to facilitate ongoing CME/CE data collection and reporting. See Section 3.1.7 for the CME/CE data associated with the first REMS-compliant CME/CE activities.

Figure 1: RPC Major Continuing Education-Related Milestones



3.1.4. Data Collection Processes

The CME/CE Data Aggregation Vendor has collected the CME/CE data from Accrediting Bodies for this Assessment Report, which focuses on the number of prescribers who successfully completed ER/LA Opioid REMS-compliant CME/CE activities through the end of the data collection period for CME/CE metrics for the Twelve-Month FDA Assessment Report, which was May 10, 2013. (Note: While only RPC-supported REMS-compliant CME/CE was available at the time of preparing this report, in the future, Accrediting Bodies may report data for both RPC-supported and non-RPC supported REMS-compliant CME/CE.)

The scope of this report section includes CME/CE data collected from REMS-compliant, RPC-supported activities.

3.1.5. Requirements for Assessment

As part of the REMS performance goals for the availability of training, RPC was to ensure that REMS-compliant training was made available to Prescribers of ER/LA Opioid Analgesics no later than March 1, 2013.

In order for REMS-compliant educational activities to be made available, it was first necessary for the RPC to prepare and disseminate Request for Applications (RFA) to support accredited independent CME/CE, receive and review the applications, and to award the grants for CME/CE activity development and implementation. Prior to the submission of the Six-Month FDA Assessment Report, two RFAs were issued and one grant was awarded to the Trustees of Boston University. This grant met the REMS requirement that the first REMS-compliant training would be available no later than March 1, 2013. Data are provided in this reporting period on additional grants that were awarded after the data cutoff date for the Six-Month FDA Assessment Report.

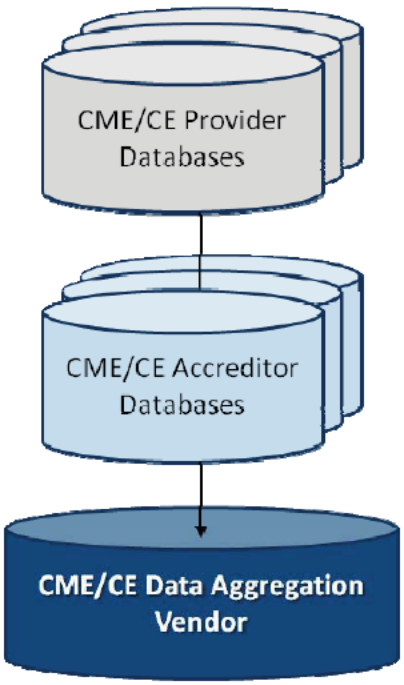
Data are also provided in this report on the number of REMS-compliant RPC-supported training activities that became available after March 1, 2013. Additionally, the number of prescribers of ER/LA opioid analgesics who completed the CME/CE associated with these activities is also provided through the end of the data collection period for CME/CE metrics, which was May 10, 2013 for this Twelve-Month FDA Assessment Report.

3.1.6. Data Collection and Analysis Method for Prescriber Education

The CME/CE Data Aggregation Vendor received CME/CE participant data from National Accrediting Bodies of CME/CE activities. The Accrediting Bodies compiled aggregate data on completers of REMS-compliant CME/CE activities conducted by independent CME/CE Provider Organizations. These data include REMS-compliant RPC-supported CME/CE activities, and may in the future include non-RPC-supported REMS CME/CE activities. The CME/CE Data Aggregation Vendor compiled the aggregated CME/CE data from the Accrediting Bodies into a single database, produced summary tables and graphs, and composed summaries of the findings from the aggregated CME/CE data for submission to FDA as part of the REMS assessment report.

As depicted in Figure 2, CME/CE data were provided by CME/CE Provider Organizations to Accrediting Bodies' databases and to the CME/CE Data Aggregation Vendor.

Figure 2: Continuing Education Data Flow Diagram



3.1.7. Available REMS-Compliant Training

3.1.7.1. Dates of Availability of REMS-Compliant Training

The first REMS-compliant CME/CE supported by the RPC launched on February 28, 2013. A description of all REMS-compliant CME/CE activities available since this date is provided in Table 4.

TABLE 4: REMS-COMPLIANT CONTINUING EDUCATION AVAILABLE BEGINNING FEBRUARY 28, 2013

GRANTEE	PARTNER ORGANIZATIONS	DATE OR PROJECTED DATE OF CME/CE AVAILABILITY	ACTIVITY TYPE	ESTIMATED TOTAL ACTIVITIES PLANNED	ESTIMATED ER/LA OPIOID PRESCRIBERS TO BE TRAINED (ESTIMATED COMPLETERS)
Trustees of Boston University	Federation of State Medical Boards (FSMB), and CMSS, comprised of 38 national medical societies	February 28, 2013	Multiple formats including web-based and live regional and local activities	112+	(b) (4)
	Title: SCOPE of Pain: Safe and Competent Opioid Prescribing Education Description: National program intended to improve the knowledge, competence, and performance of a multidisciplinary, inter-professional audience of HCPs (physicians, nurse practitioners, and physician assistants). Executed in conjunction with the FSMB (comprising 70 state medical boards), CMSS (comprising 38 professional societies), and ExtendMed, a web-based CME partner.				

TABLE 4: REMS-COMPLIANT CONTINUING EDUCATION AVAILABLE BEGINNING FEBRUARY 28, 2013

GRANTEE	PARTNER ORGANIZATIONS	DATE OR PROJECTED DATE OF CME/CE AVAILABILITY	ACTIVITY TYPE	ESTIMATED TOTAL ACTIVITIES PLANNED	ESTIMATED ER/LA OPIOID PRESCRIBERS TO BE TRAINED (ESTIMATED COMPLETERS)
California Academy of Family Physicians for CO*RE (Collaborative for REMS Education)	10 Partner Organizations in cooperation with >50 professional and state medical societies	March 13, 2013	Multiple formats including live national, regional and state level activities; on-line activities and curriculum resources	137+	(b) (4)
	Title: CO*RE REMS Initiative: A Collaborative Solution to the ER/LA Opioid Public Health Crisis Description: National program with educational units corresponding to the FDA Blueprint. In addition to the live and on-line activities, CO*RE curriculum resources such as videos, demonstrations, cases, tools, and references will be available to all learners.				
Association for Hospital Medical Education (AHME)	Teaching institutions	July 1, 2013	Multiple formats including live activities, online activities and online resource center	20	(b) (4)
	Title: AHME Collaborative for REMS Education Description: AHME will provide 20 block grants to teaching institutions to provide REMS-compliant training to hospital-based HCPs, including Medical Doctors (MD) and Doctors of Osteopathy (DO) (including residents and fellows), Nurse Practitioners (NP) and Physician Assistants (PA), and medical students. The series of educational activities will utilize the evidence-based, fully FDA REMS-compliant CO*RE curriculum and resources, as well as standardized evaluation activities developed by CO*RE.				
Utah Medical Association Foundation	8 Utah-based governmental and professional organizations	October 1, 2013	Web-based video with interactive options between instructor/learners	1	(b) (4)
	Title: Utah Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Educational Programming Project Description: Provide prescribers with best practice information and patient educational materials that will enable them to ensure that the benefits of such therapies outweigh the risks and that they prescribe in a manner that is appropriate to the patient's diagnosis.				

TABLE 4: REMS-COMPLIANT CONTINUING EDUCATION AVAILABLE BEGINNING FEBRUARY 28, 2013

GRANTEE	PARTNER ORGANIZATIONS	DATE OR PROJECTED DATE OF CME/CE AVAILABILITY	ACTIVITY TYPE	ESTIMATED TOTAL ACTIVITIES PLANNED	ESTIMATED ER/LA OPIOID PRESCRIBERS TO BE TRAINED (ESTIMATED COMPLETERS)
American College of Physicians, Inc.	Pri-Med	June 15, 2013	Multiple formats including live national symposia, online interactive, and online resource center	4	(b) (4)
	Title: SAFE Opioid Prescribing: Strategies. Assessment. Fundamentals. Education. Description: Series of 3 live, plenary session symposia held in regions with high concentrations of ER/LA opioid prescribers; on-line interactive modules; online REMS Resource Center.				

3.1.7.2. Prescribers Completing REMS-Compliant Training

Nine REMS-compliant education activities supported by the RPC were launched between February 28 and May 4, 2013. Eight unique CME/CE Provider Organizations presented the nine activities. The activities received accreditation from five different National Accrediting Bodies; American Academy of Family Physicians (AAFP) accredited four of the activities and ACCME accredited five activities, with three activities receiving dual accreditation. Eight of the activities were presented as live training activities and one activity was presented in an internet-based format. Data on the prescribers completing the training was collected from the activity launch through the May 10, 2013 cutoff date for this Twelve-Month FDA Assessment Report. During that period, 1,147 prescribers completed the training. The majority of the prescribers completing the training during this period are physicians, and most prescriber completers of the education are in primary care practice. The following sections provide additional detail on the training activities and the prescribers successfully completing the RPC-supported REMS-compliant education.

3.1.7.3. Prescribers Completing REMS-Compliant RPC-Supported Training

Table 5 presents an overview of the REMS-compliant, RPC-supported education activities, organized by start date of the activities, and including information on the CME/CE Provider Organization and Accrediting Body for each activity, as well as the format and the total number of prescribers who completed each respective activity. Table 6 provides the organization names associated with each acronym in Table 5.

TABLE 5: PRESCRIBERS COMPLETING REMS-COMPLIANT RPC-SUPPORTED TRAINING

ACCREDITED CME/CE PROVIDER	ACCREDITING BODY	TITLE OF ACTIVITY	ACTIVITY START DATE	ACTIVITY FORMAT	TOTAL # ER/LA PRESCRIBERS COMPLETING ACTIVITY AS OF 05/10/2013[1]
BUSM	AAFP and ACCME	SCOPE of Pain: Safe and Competent Opioid Prescribing Education	February 28, 2013	Internet-based	(b) (4)
AAHPM	ACCME	Opioid REMS—Prescriber Education That Is Relevant, Case Based, and Addresses the Tough Issues	March 13, 2013	Live training	
AANP	AANP	ER/LA Opioid REMS: Achieving Safe Use While Improving Patient Care	April 17, 2013	Live training	
NPHF	ANCC	Understanding the Pharmacology of Addiction & Prescription Drug Abuse	April 17, 2013	Live training	
CAFP	AAFP	ER/LA Opioid REMS: Achieving Safe Use While Improving Patient Care	April 20, 2013	Live training	
ASAM	AAFP and ACCME	ASAM 44th Annual Medical-Scientific Conference—Medical Topics in Addiction Medicine for Primary Care Physicians	April 25, 2013	Live training	
AGS	ACCME	Opioid REMS—Prescriber Education That Is Relevant, Case Based, and Addresses the Tough Issues	May 2, 2013	Live training	
POMAF	AOA	ER/LA Opioid REMS: Achieving Safe Use While Improving Patient Care	May 2, 2013	Live training	
CAFP	AAFP and ACCME	ER/LA Opioid REMS: Achieving Safe Use While Improving Patient Care	May 4, 2013	Live training	

[1]Per the MEMS Implementation Guidelines, "Prescribers" are defined as "clinicians who are registered with the DEA to prescribe Schedule II and/or III controlled substances and have written at least one ER/LA opioid prescriptions in the past year." Completion of an activity is defined as "Prescribers that have completed all components of an educational activity and met the education provider's criteria for passing. Components of an educational activity include instruction, assessment of learning, and potentially evaluation."

TABLE 6: ACCREDITING BODY AND ACCREDITED PROVIDER NAME AND ACRONYM

ORGANIZATION ACRONYM	ORGANIZATION NAME
AAFP	American Academy of Family Physicians
AAHPM	American Academy of Hospice and Palliative Medicine
AANP	American Association of Nurse Practitioners
ACCME	Accreditation Council for Continuing Medical Education
AGS	American Geriatrics Society
ANCC	American Nurses Credentialing Center
AOA	American Osteopathic Association
ASAM	American Society of Addiction Medicine
BUSM	Boston University School of Medicine
CAFP	California Academy of Family Physicians
NPHF	Nurse Practitioner Healthcare Foundation
POMAF	Pennsylvania Osteopathic Medical Association Foundation

3.1.7.3.1. Number of Prescribers Completing REMS-Compliant Training

A total of 1,147 prescribers completed the education and assessment requirements for REMS-compliant training between the launch of the first activity, February 28, 2013, and the date of the data collection cutoff for this reporting period, May 10, 2013. Per the REMS, a secondary outcome measure will be the number of prescribers who have completed some but not all necessary portions of a training activity as a diagnostic for interpreting completion rates. This measure will be evaluated in future FDA Assessment Reports.

3.1.7.3.2. Prescribers Completing Training by Training Format Types

As presented in Figure 3 and Table 7 of the nine activities, eight activities were presented as live training activities, and 856 prescribers completed REMS-compliant RPC-supported training through these live activities, which represents 74.6% (N = 856) of the total number of prescribers completing training. The remaining 25.3% (N = 291) of prescribers completing training participated in internet-based activities.

Figure 3: Prescribers Completing REMS-Compliant RPC-Supported Training by Training Format Type

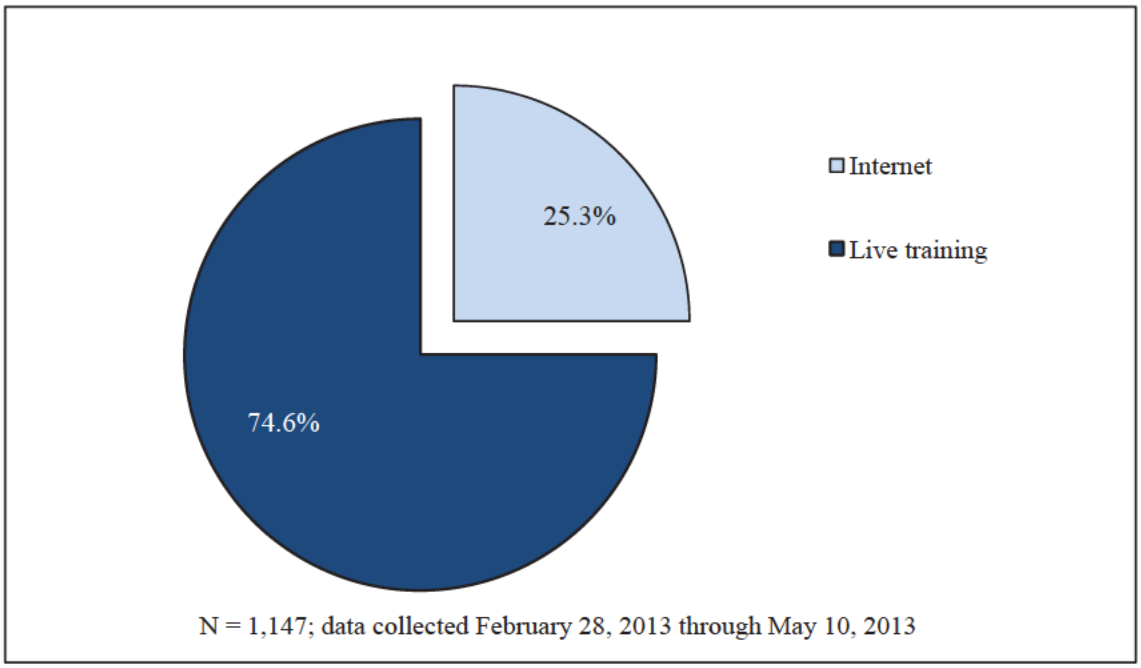


TABLE 7: REMS-COMPLIANT RPC-SUPPORTED TRAINING BY FORMAT TYPE

TRAINING FORMAT TYPE	# PRESCRIBERS COMPLETING TRAINING BY TRAINING FORMAT TYPE (N = 1,147)	RELATIVE % OF TOTAL PRESCRIBERS COMPLETING TRAINING BY TRAINING FORMAT TYPE
Live training	856	74.6
Internet-based	291	25.3
Total	1147	100

3.1.7.3.3. Characteristics of Prescribers Completing Training

Of the total number of prescribers completing REMS-compliant, RPC-supported education activities, almost three-quarters of the completers (N = 846, 73.7%) are physicians, as presented in Figure 4 and Table 8. Of the prescribers completing the training, 21.9% (N = 251) are advanced practice nurses and 3.3% (N = 38) are physician assistants, while approximately 1% of the remaining prescriber completers of the education are podiatrists (N = 3), pharmacists (N = 2), dentists (N = 2) or prescribers describing their profession as "other" (N = 5).

Figure 4: Prescribers Completing Training by Profession

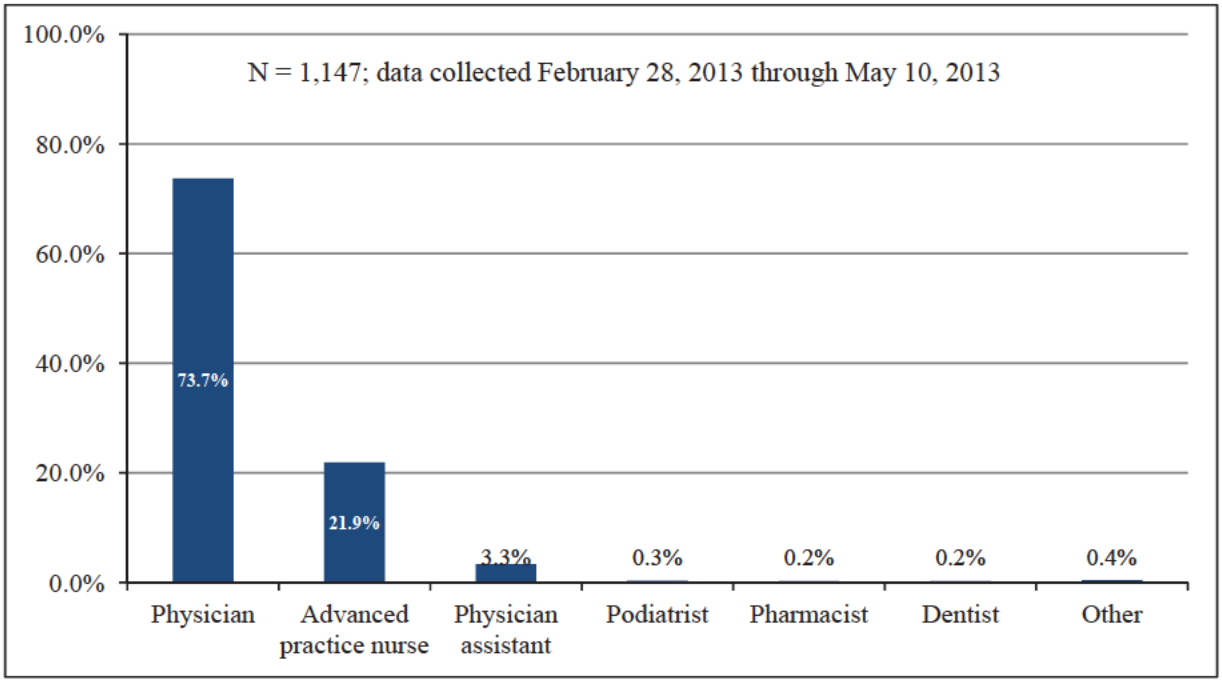


TABLE 8: TRAINING BY PROFESSION

PROFESSION OF PRESCRIBERS	# PRESCRIBERS COMPLETING TRAINING BY PROFESSION (N = 1,147)	RELATIVE % OF TOTAL PRESCRIBERS COMPLETING TRAINING BY PROFESSION
Physician	846	73.7
Advanced Practice Nurse	251	21.9
Physician Assistants	38	3.3
Podiatrists	3	0.26
Pharmacist	2	0.17
Dentist	2	0.17
Other	5	0.44
Total	1147	100

Below, Figure 5 and Table 9 provide data according to the practice type, or the clinical practice focus of the prescriber. Practice type was an optional category of metrics captured for those prescribers completing the REMS-compliant training. Practice type data was collected on 753 prescribers in this reporting period, which represents two-thirds (65.6%) of all prescribers completing the REMS training. Of the prescribers for whom this data is available, two-thirds (N = 496, 65.8%) are in primary care practices, approximately one-fifth (N = 157, 20.8%) are non-pain specialists, and the remaining 13.2% (N = 100) are pain specialists.

Figure 5: Prescribers Completing REMS-Compliant RPC-Supported Training by Practice Type

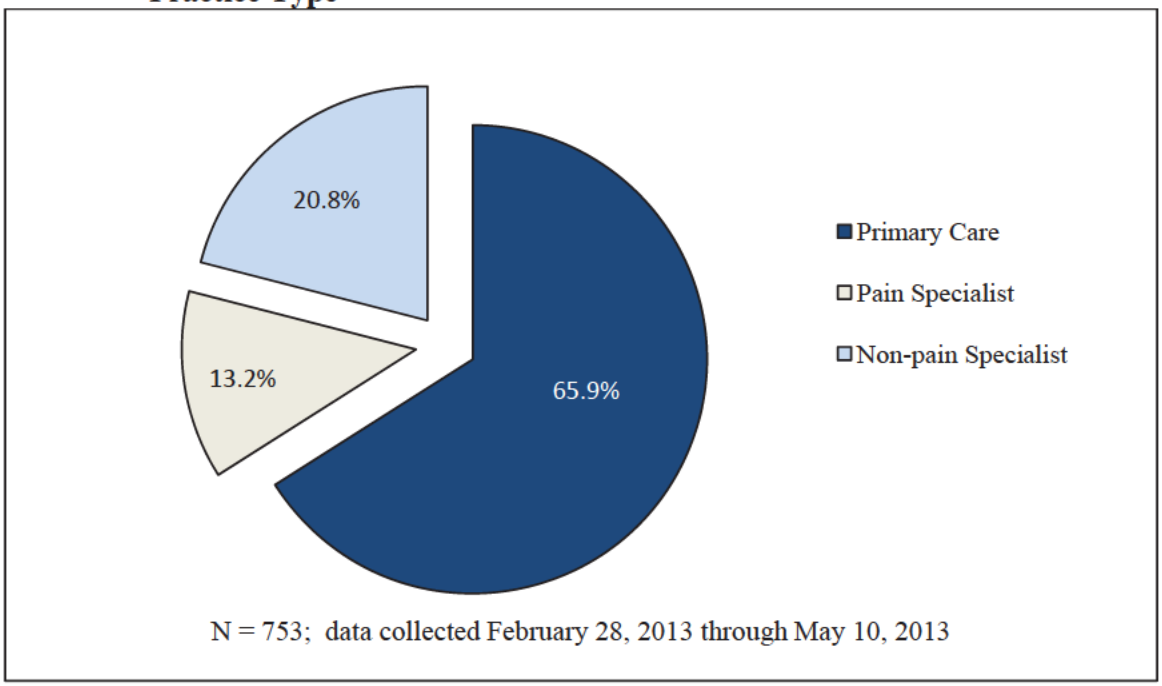


TABLE 9: TRAINING BY PRACTICE TYPE

PRACTICE TYPE OF PRESCRIBERS	# PRESCRIBERS COMPLETING TRAINING BY PRACTICE TYPE (N = 753)	RELATIVE % OF TOTAL PRESCRIBERS COMPLETING TRAINING BY PRACTICE TYPE
Primary Care	496	65.9
Non-Pain Specialist	157	20.8
Pain Specialist	100	13.2
Total	753	100

3.1.8. New Grant Request for Applications

The 2013 REMS-compliant accredited CME/CE RFA (RFA 030513) was disseminated via posting on the RPC website and GMS on May 21, 2013. RPC assured broad awareness of the RFA through mass e-mail dissemination to Accrediting Bodies, organizations representing accredited Providers, CME/CE Providers, and other CME/CE stakeholders. Additionally, the RPC hosted two informational webinars, one directed toward National Provider Organizations (held May 7, 2013) and one directed toward CME/CE Providers (held June 13, 2013). By actively involving National Provider Organizations and accredited Providers early in the RFA cycle, the RPC has sought to optimize awareness of, and the number/quality of responses to, the 2013 RFA. The full text of RFA 030513 can be found in Appendix F.

Grant applicants will submit all RFA proposals for consideration in the 2013 RPC grant cycle by 5:00 p.m. Eastern Time (ET) on July 16, 2013. The RFA specifies that grant proposals should include a number of critical components intended to inform RPC's selection of those grant applications most likely to achieve the REMS goals. These key factors include:

- Collaboration with organizations whose constituents comprise the primary REMS education audiences
- Thorough program overview including details of how the full FDA Blueprint will be integrated into the activity
- Details on performance of the activity assessments to test knowledge across all sections of the FDA Blueprint
- Broad geographic coverage and innovative learning formats to meet learner preferences and timing/practice needs
- Attestation that proposed activities are fully compliant with all applicable standards of the primary Accrediting Body, as well as other relevant standards, guidelines, and requirements as they apply to the conduct of independent medical education

A comprehensive list of grant request submission requirements can be found in Section 4 of the RFA in Appendix F.

The 2013 RFA includes several modifications from the 2012 RFA:

- More explicitly requires that potential Providers map the FDA Blueprint directly into their educational activity outline
- Provides a template for structuring the content of proposals to facilitate better comparison of the merits of proposed activities
- Greater emphasis on the incorporation of adult learning principles and instructional design to optimize both the acquisition of knowledge and its application in practice
- An optional component of the RFA provides the opportunity for Providers and Provider Organizations to submit pilot proposals that incorporate organizational change initiatives aimed at further supporting the adoption of what individual clinicians learn from the REMS-compliant CME/CE by incorporating the principles of implementation science which focus on the system in which prescribing and patient care occurs
- Includes further specific guidelines around timing of the educational activities, organization, and budget of grant proposals

3.1.9. Conclusion

The 2013 REMS-compliant accredited CME/CE RFA was disseminated on May 21, 2013. The RPC assured awareness of the RFA through multiple avenues including mass e-mails and hosting of two informational webinars, one for CME/CE Provider Organizations and one for CME/CE Providers themselves. Final grant applications for the RPC's 2013 grant review cycle will be submitted by July 16, 2013 for RPC consideration. As with the 2012 RFAs, RPC has taken steps to ensure that the emphasis for CME/CE applications in 2013 will be on REMS compliance including content focused on the full FDA Blueprint and integration of the requisite activity assessment covering all six sections of the Blueprint. To optimize the reach of the activity and the number of prescribers completing REMS-compliant CME/CE, the RPC has emphasized in the RFA and webinars the importance of strong collaborations and broad geographic coverage.

3.2. Assessment Element 2 – Independent Audit of Continuing Education Activities

While reporting on Assessment Element 2, Independent Audit of CME/CE activities is not required until the Assessment Report due in July 2014, the RPC recognizes the importance of this element and is providing a synopsis of the processes established to date.

The goal of the independent audits is to evaluate whether the REMS-compliant CME/CE activities supported by RPC adequately and accurately cover the content of the FDA Blueprint and meet the standards for commercially supported independent education of the ACCME and other Accrediting Bodies.

Specifically, the independent audits will:

- Be conducted by the National CME/CE Accrediting Bodies on at least 10% of the CME/CE funded by RPC under the ER/LA Opioid Analgesics REMS
- Evaluate whether the CME/CE covers all elements of the FDA Blueprint approved as part of the REMS
- Evaluate whether the CME/CE assessment measures knowledge of all sections of the FDA Blueprint
- Evaluate whether the CME/CE was conducted in accordance with the standards for CME of the ACCME or of another CE Accrediting Body appropriate to the prescribers' medical specialty or healthcare profession
- Verify that content of the activity reflects current evidence-based information and that the content of the FDA Blueprint is represented accurately.

In accordance with these requirements, the RPC has been working with the National CME/CE Accrediting Bodies to develop processes for independently auditing the quality of the content of the REMS educational activities/materials. These processes must be developed and implemented in a manner that is compatible with each respective Accrediting Body's infrastructure and systems and as such, it has been necessary to work with each individually to establish processes that meet the REMS Independent Audit requirements.

Since the vast majority of CME/CE activities in the United States (US) are accredited by the ACCME, the RPC focused its initial efforts on working with ACCME to develop a process for independent audits which could subsequently be used, with minor modifications as necessary, as a model for audits by other Accrediting Bodies.

The operational logistics for the independent audit process (Assessment Element 2) are as follows:

1. Following approval of an RPC-supported educational grant, a Letter of Agreement (LOA) is sent through the Grant Management System (GMS) to the CME/CE Provider of Record for the grant. The LOA contains standard language for assuring that the RPC-supported CME/CE activity meets the requirements for commercially supported independent education of the ACCME® and other Accrediting Bodies. In addition, the LOA includes a REMS-specific Addendum stipulating the independent audit requirements, confirming the Provider's agreement to participate in the audit if selected by the Accrediting Body, and obtaining the CME/CE Provider's permission for the Accrediting Body to report the REMS-compliant activity data, including independent audit results, to the RPC.

2. Following execution of the LOA/LOA Addendum, the CME/CE Provider will submit pertinent information on the activity, including start date, to the Accrediting Body to facilitate advance planning for the audits.
3. The Accrediting Body(ies) will audit at least 10% of RPC-supported CME/CE. Upon notification of an audit by the Accrediting Body, the CME/CE Provider will submit materials covering the planning, content and presentation of the activity to the Accrediting Body at least 45 days prior to the activity start date. As such, it is intended that the audits will occur prior to the time that the educational activity/material is encountered by any learners.
4. The Accrediting Body will conduct its review to verify that the CME/CE activity meets the REMS-compliant CME/CE criteria specified above. Any questions or issues will be addressed in accordance with the Accrediting Body's standards and processes.
5. The Accrediting Body will provide written documentation of the independent audit results to the RPC.
6. Any expenses incurred in association with the independent audit are covered as part of RPC grant support.

Having established this process with ACCME as a model for the independent audits, the RPC subsequently initiated discussions with the AAFP, which is anticipated to be another major Accreditor of the REMS-compliant CME/CE. The AAFP has agreed to a similar process as the ACCME model described above. RPC will next confirm processes with the remaining Accrediting Bodies, and will report upon those, as well as the audit results, in the Three-Year FDA Assessment Report.

Since all REMS-compliant activities to date have been RPC-supported, the RPC has focused its efforts on establishing processes for auditing these activities. Processes for independent audit of non-RPC-supported activities have not yet been determined.

3.3. Assessment Element 3a – Evaluation of Prescriber Understanding

The REMS Assessment Plan specifies that an evaluation of HCPs' awareness and understanding of the serious risks of ER/LA Opioid Analgesics will be included in the Three-Year FDA Assessment Report. While not a requirement of the REMS, the RPC elected to conduct a Baseline Prescriber Survey (BPS), with results to be included in this Twelve-Month FDA Assessment Report. The BPS was a cross-sectional Knowledge, Attitudes, and Behavior (KAB) survey intended to measure prescriber awareness and understanding, as well as self-reported behaviors and practices, prior to the availability of REMS-compliant training, thereby facilitating the evaluation of changes attributable to the REMS.

The BPS and the Three-Year Prescriber Survey will use the same core survey instrument with additional questions or modifications based on activities that occur during rollout of the REMS-compliant CME/CE activities. The surveys each include unique samples of randomly selected active prescribers of ER/LA opioids (active prescribers are considered to be those prescribers who have prescribed at least one ER/LA opioid in the last year, as identified by the IMS Xponent® database). Both surveys will measure comprehension of proper patient selection, general ER/LA opioid analgesic use, dosing and administration requirements for ER/LA products, and prescribers' self-reported practices for patient counseling. The surveys will also assess prescriber-reported ease of patient access to ER/LA opioids for general medical reasons.

The survey and protocol were developed by the RPC with assistance from the BPS Survey Vendor, a company with extensive experience in REMS and REMS Assessments.

The survey protocol containing the detailed methods and survey instrument to be used for the BPS and Three-Year Prescriber Surveys was submitted for FDA review on October 31, 2012.

3.3.1. Baseline Prescriber Survey

3.3.1.1. Baseline Prescriber Survey Design and Methods

The BPS was a cross-sectional survey self-administered through a secure website. This internet-based survey documented the level of knowledge and assessed the attitudes and behavior of prescribers around the key risk messages that are communicated in the REMS-compliant CME/CE activities as outlined in the FDA Blueprint. There were a total of 54 key risk message items, 8 demographic questions, and 24 items related to the requirements of the REMS and receipt of the educational materials. This survey was conducted among a sample of prescribers of ER/LA Opioid Analgesics, whose eligibility was determined via screening questions at the beginning of the survey. The survey questionnaire and protocol are included in Appendix E.

3.3.1.1.1. Qualitative Pre-Testing of the Baseline Prescriber Survey

Survey questions were pre-tested prior to finalizing the questionnaire and launching the survey. This activity occurred during the FDA review period. Cognitive debriefing interviews were conducted with active prescribers of ER/LA opioids to assess comprehension and interpretation for a subset of the survey questions related to key risk messages and to identify whether questions or response options may be misunderstood. The research was qualitative and exploratory in nature to identify themes and concepts in the respondent's "own voice" rather than those imposed by researchers or decision makers.

Prescribers were recruited using a prescriber list from a national pharmacy prescription database and represented a mix of medical specialties and practice settings. Prescriber eligibility for the qualitative research was determined based on criteria such as prescribing ER/LA opioid analgesics, treating patients at least 75% of their time, and having been in medical practice for at least five years. A total of 24 ER/LA opioid analgesics prescribers were recruited and participated in individual in-depth telephone interviews conducted by a single trained moderator. Each interview was approximately 60 minutes in duration.

During the one-on-one telephone interviews, participants reviewed a sample of the questions and response sets in the draft survey instrument. At the time qualitative pre-testing was conducted, the BPS included 25 key risk message survey items. Prescribers were asked to evaluate a subset of the key risk message survey questions so that they could read, select an answer, provide a rationale for their answer selection, and then discuss in detail their interpretation of the questions.

Feedback was obtained by asking a series of probing questions designed to evaluate each section of the survey. The feedback collected allowed for the identification of terms, questions, and topics for clarification and revision based on areas of confusion and miscomprehension of the survey.

Findings and recommendations from the qualitative research were reviewed by the RPC and incorporated into the BPS.

3.3.1.1.2. Baseline Prescriber Survey Administration

The BPS was launched on February 8, 2013, prior to the availability of the first REMS-compliant CME/CE activity on February 28, 2013. Upon survey launch, 12,000 invitations were mailed, via US postal service, to active prescribers of ER/LA opioids. Invitations were issued by facsimile to a second sample of 6,847 prescribers on February 25, 2013. In order to recruit the targeted sample size of 600 for the BPS, the survey recruitment period extended until April 17, 2013. An additional 8,674 and 7,138 invitations were issued via fax on April 15 and 16, respectively. In total, 34,659 invitations were issued. Reminder e-mails and faxes were sent between February 18 and March 20, 2013. Prescribers may have received more than one reminder letter.

3.3.1.1.2. Baseline Prescriber Survey Analysis

Questions in the survey were developed with the understanding that different respondents interpret and understand questions differently. For this reason, there are some key concepts that are measured with more than one question. The data are reported as descriptive statistics for the survey administration, study population, and KAB questions. A frequency distribution of correct responses to each question is presented. The analysis for a key risk message evaluates the percentage of prescribers who chose the correct response(s) to each individual question/item defined as a key risk message. The specific correct response to each question/item is provided in Tables 12 – 16 below. The questions were grouped according to five key risk messages:

- Key Risk Message 1: Patients should be assessed for treatment with ER/LA opioid analgesic therapy.
- Key Risk Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- Key Risk Message 3: Management of ongoing therapy with ER/LA opioid analgesics is important.
- Key Risk Message 4: It is important to counsel patients and caregivers about the safe use of ER/LA opioid analgesics.
- Key Risk Message 5: Prescribers must be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

The number of invitations issued to prescribers, the number of prescribers screened for participation, the number of prescribers eligible for participation, and the number of eligible prescribers who completed the survey are reported in Table 10. Also reported is an analysis of time to complete the survey (Figure 6).

The survey included questions to characterize the demographics and ER/LA opioid prescribing patterns of the respondents. Descriptive statistics for these characteristics are provided in Table 11 and Table 14.

In addition, prescriber awareness, receipt, and review of educational materials associated with the ER/LA Opioid Analgesic REMS, specifically, the Medication Guide(s), DDRP, PCD, and website, were explored and are discussed in Section 3.3.1.3.3.

Some analyses in this report are stratified by time period; there will be additional analyses of data collected in these two time periods in the final BPS survey report.

3.3.1.3. Baseline Prescriber Survey Results

A total of 710 prescribers agreed to participate in this survey. Of the 672 (94.6%) prescribers who met the eligibility criteria, 605 (90%) completed the survey.

Although the intent of the BPS was to measure prescriber understanding prior to availability of REMS-compliant CME/CE activities, survey recruitment efforts were not completed until after the CME/CE activities were launched. Prior to the first REMS-compliant CME/CE activity on February 28, 2013, there were 314 prescribers who completed the survey and an additional 291 prescribers completed the survey on or after that date.

All prescribers provided consent to participate in the survey. Further prescriber eligibility was determined based on the responses to questions regarding associations with RPC companies, FDA, and the BPS Survey Vendor; as well as having prescribed ER/LA opioid analgesics at least once in the last 12 months. Prescribers referred to as completers are defined as having met the eligibility criteria and answered all survey questions.

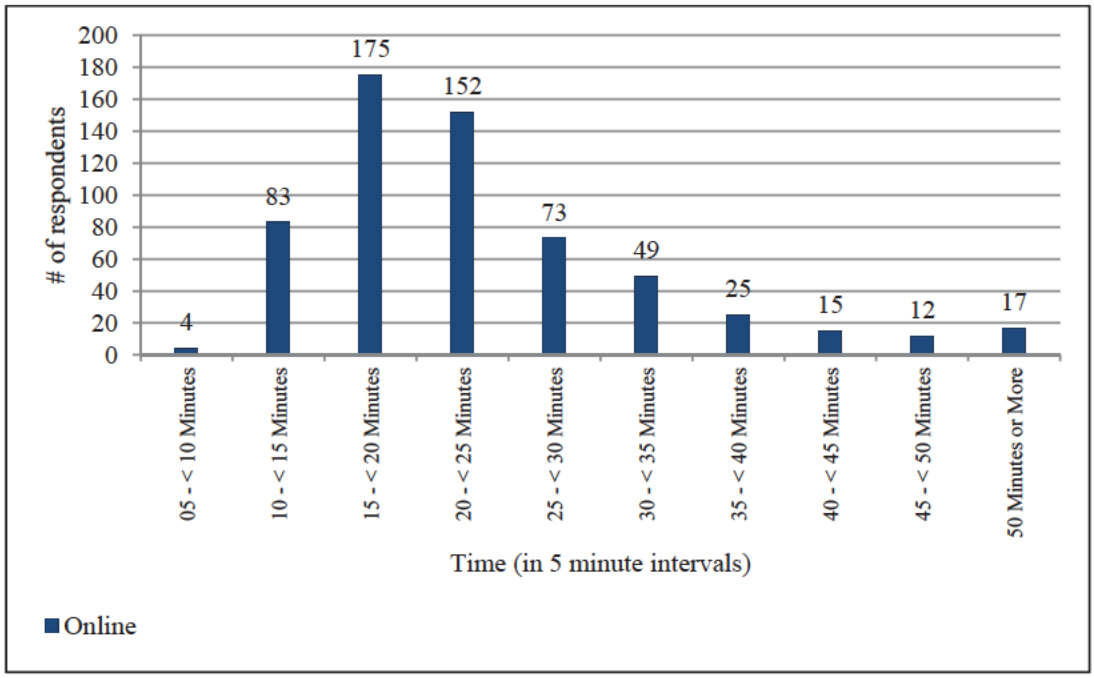
TABLE 10: ELIGIBILITY CRITERIA OF SURVEY RESPONDENTS

SURVEY ADMINISTRATION STATISTICS	N
Number of invitations issued to prescribers	34,659
Number of prescribers expressing interest in participating	710
Number declining to participate[1]	0
Number with personal or family associations with RPC companies, FDA, or United BioSource Corporation[1]	8
Number with no ER/LA opioid prescribing in last 12 months[1]	30
Number of prescribers eligible to take the survey	672
Number of prescribers who completed the survey	605

[1] Prescribers may have multiple exclusion criteria

The survey was administered online, via a secure website, and on average took 21.1 minutes to complete with a range of 8 to 74 minutes as depicted in Figure 6

Figure 6: Time to Complete Survey



3.3.1.3.1. Demographic and Respondent Characteristics

The majority of respondents were male (N = 407, 67.3%). The distribution of respondents by geographic region is shown in (Table 11); the largest numbers of participants were from the West and Central regions. A comparison of these data with the geographic distribution of all ER/LA opioid analgesic prescribers as indicated in IMS Xponent® data indicates that the proportion of prescribers who completed the survey within each geographic region was similar to the total number of ER/LA opioid prescribers in each geographic region.

TABLE 11: SURVEY PARTICIPANTS AND ALL ER/LA OPIOID ANALGESIC PRESCRIBERS BY GEOGRAPHIC REGION

GEOGRAPHIC REGION[1]	ELIGIBLE PRESCRIBERSCOMPLETING SURVEY N = 605		ALL PRESCRIBERS WHO HAVE PRESCRIBED AN ER/LA OPIOID WITHIN THE LAST 12 MONTHS[2] N = (b) (4)	
	N	%	N	%
Northeast	81	13.4	(b) (4)	
East	126	20.8		
Central	151	25.0		
South	84	13.9		
West	163	26.9		
US territories	0	0		

TABLE 11: SURVEY PARTICIPANTS AND ALL ER/LA OPIOID ANALGESIC PRESCRIBERS BY GEOGRAPHIC REGION

GEOGRAPHIC REGION[1]	ELIGIBLE PRESCRIBERSCOMPLETING SURVEY N = 605		ALL PRESCRIBERS WHO HAVE PRESCRIBED AN ER/LA OPIOID WITHIN THE LAST 12 MONTHS[2] N = (b) (4)	
	N	%	N	%
Prefer not to answer	0	0		
Total	605	100	(b) (4)	

[1] Northeast includes CT, DC, MA, ME, MD, NH, RI, and VT. East includes DE, NJ, NY, and PA. Central includes AR, IA, IN, IL, KS, KY, MI, MN, MO, ND, NE, OH, OK, SD, TN, WI, and WV. South includes AL, FL, GA, LA, MS, NC, SC, TX, and VA. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. US Territories includes American Samoa, Guam, Northern Mariana Islands, Puerto Rico, and US Virgin Islands.

[2] IMS Xponent® extracted May 2012 through April 2013

The number of survey completers by healthcare degree and medical specialty are shown in Table 12 and Table 13, respectively. The largest number of respondents reported a healthcare degree of MD (N = 284, 46.9%); one-quarter of the respondents were physician assistants (N = 154, 25.5%) and nurse practitioners made up most of the remaining respondents (N = 142, 23.5%). MD was also the most frequent healthcare degree of prescribers in the IMS Xponent® data (May 2012 through April 2013). The most common medical specialties among survey respondents were General Practice (N = 307, 50.7%) and Pain Medicine (N = 55, 9.1%). Similarly, the IMS Xponent® data (May 2012 through April 2013) reflected a high number of ER/LA opioid prescribers associated with General Practice (N = (b) (4)) and Internal Medicine (N = (b) (4) %) specialties.

TABLE 12: SURVEY PARTICIPANTS AND ALL ER/LA OPIOID ANALGESIC PRESCRIBERS BY HEALTHCARE DEGREE

HEALTHCARE DEGREE	ELIGIBLE PRESCRIBERS COMPLETING SURVEY N = 605		ALL PRESCRIBERS WHO HAVE PRESCRIBED AN ER/LA OPIOID WITHIN THE LAST 12 MONTHS[1] N = (b) (4)	
	N	%	N	%
Medical Doctor	284	46.9	(b) (4)	
Doctor of Osteopathy	18	3.0		
Nurse Practitioner	142	23.5		
Advanced Practice Nurse	7	1.2		
Physician Assistant	154	25.5		
Podiatrist				

TABLE 12: SURVEY PARTICIPANTS AND ALL ER/LA OPIOID ANALGESIC PRESCRIBERS BY HEALTHCARE DEGREE

HEALTHCARE DEGREE	ELIGIBLE PRESCRIBERS COMPLETING SURVEY		ALL PRESCRIBERS WHO HAVE PRESCRIBED AN ER/LA OPIOID WITHIN THE LAST 12 MONTHS[1]	
	N = 605		N = (b) (4)	
	N	%	N (b) (4)	%
Veterinarian				
Dentists				
Optometrists				
Unknown				
Total	605	100		

[1] IMS Xponent® extracted May 2012 through April 2013

TABLE 13: SURVEY PARTICIPANTS AND ALL ER/LA OPIOID ANALGESIC PRESCRIBERS BY MEDICAL SPECIALTY

MEDICAL SPECIALTY	ELIGIBLE PRESCRIBERS COMPLETING SURVEY N = 605		ALL PRESCRIBERS WHO HAVE PRESCRIBED AN ER/LA OPIOID WITHIN THE LAST 12 MONTHS[1] N = (b) (4)	
	N	%	N (b) (4)	%
General Practice	307	50.7		
Oncology	42	6.9		
Neurology	18	3.0		
Anesthesiology	9	1.5		
Rheumatology	23	3.8		
Orthopedics	44	7.3		
Hospice/Palliative Care	9	1.5		
Internal Medicine	51	8.4		
Pain Medicine	55	9.1		
Other	47	7.8		
Total	605	100		

[1] IMS Xponent® extracted May 2012 through April 2013

TABLE 14: SURVEY PARTICIPANTS AND ALL ER/LA OPIOID ANALGESIC PRESCRIBERS BY MONTHLY PRESCRIBING OF ER/LA OPIOID ANALGESICS

NUMBER OF TIMES PER MONTH PRESCRIBING ER/LA OPIOID ANALGESICS IN PAST 3 MONTHS	ELIGIBLE PRESCRIBERS COMPLETING SURVEY N = 605		ALL PRESCRIBERS WHO HAVE PRESCRIBED AN ER/LA OPIOID WITHIN THE LAST 3 MONTHS[1] N = (b) (4)	
	N	%	N	%
1 time	61	10.1	(b) (4)	
2 – 3 times	107	17.7		
4 – 5 times	82	13.6		
6 – 7 times	50	8.3		
8 – 9 times	42	6.9		
10 or more times	253	41.8		
I don't remember	10	1.7		
No prescriptions in the last 3 months (but at least 1 prescription in the last 12 months)	Not Applicable	Not Applicable		
Total	605	100		

[1] IMS Xponent® extracted May 2012 through April 2013

Of the respondents with an MD or DO degree, most (N = 294, 97.4%) had practiced medicine for more than 15 years. Few respondents were in practice less than 15 years. Less than 1% of the respondents reported being in practice for 0 – 5 years and 4 (1.3%) had been in practice for 11 – 15 years (Table 15). A comparison to IMS Xponent® data was not possible since this data source does not provide years of medical practice.

TABLE 15: YEARS OF MEDICAL PRACTICE AFTER POST-GRADUATE EDUCATION (MD AND DO DEGREES ONLY)

YEARS OF MEDICAL PRACTICE	ELIGIBLE PRESCRIBERS COMPLETING SURVEY N = 302	
	N	%
Less than 3 years	2	0.6
3 – 5 years	1	0.3
6 – 10 years	0	0
11 – 15 years	4	1.3
More than 15 years	294	97.4
Prefer not to answer	1	0.3
Total	302	100

Among prescribers completing the survey, the three most commonly prescribed ER/LA opioids were Duragesic® or the generic equivalent (fentanyl transdermal) ER/LA medicine (N = 433, 71.6%) of prescribers), followed by OxyContin® (N = 428, 70.7%) and MS Contin® (N = 415, 68.5%) (Table 16).

TABLE 16: TYPE OF ER/LA OPIOID ANALGESIC PRESCRIBED IN LAST SIX MONTHS

TYPE OF ER/LA OPIOID ANALGESIC PRESCRIBED IN THE LAST SIX MONTHS	ELIGIBLE PRESCRIBERS N = 605[1]	
	N	%
TRANSDERMAL PATCH		
Duragesic® or generic (fentanyl transdermal)	433	71.6
Butrans®	183	30.2
METHADONE		
Dolophine® or generic (methadone)	97	16.0
Methadose™ or generic (methadone hydrochloride)	138	22.8
Methadone hydrochloride Intensol™ oral concentrate	21	3.5
Methadone hydrochloride Oral Solution	35	5.8
ORAL PRODUCTS		
Avinza® or generic (morphine)	122	20.2
Embeda®	8	1.3
Exalgo®	65	10.7
Kadian®	124	20.5
MS Contin®	415	68.6
Nucynta® ER	172	28.4
Opana® ER or generic (oxymorphone hydrochloride)	166	27.4
Oxycontin®	428	70.7
Palladone®	2	0.3
Morphine sulfate extended-release tablets	285	47.1
Oxycodone hydrocodone extended-release tablets	293	48.4
All of the above	0	0.0
None of the above	4	0.7

[1] More than one response can be selected so percentages may not sum to 100%.

3.3.1.3.2. Key Risk Messages

Survey respondents were asked to complete questions about the safe use of the ER/LA opioid analgesics.

Figure 7 shows the distribution of correct scores for the 54 safe use questions/items. The majority of questions/items (N = 35, 64.8%) had correct scores for more than 80% of

participants, indicating a reasonably high level of knowledge. However, 40 prescribers (6.9%) scored below 70%, demonstrating a moderately low level of knowledge. Figure 7 shows the distribution of questions/items ranked by score. The corresponding questions and correct answers ranked by score are shown in Table 17.

Figure 7: Distribution of Correct Scores for the 54 Knowledge Questions/Items among Prescribers in the Survey

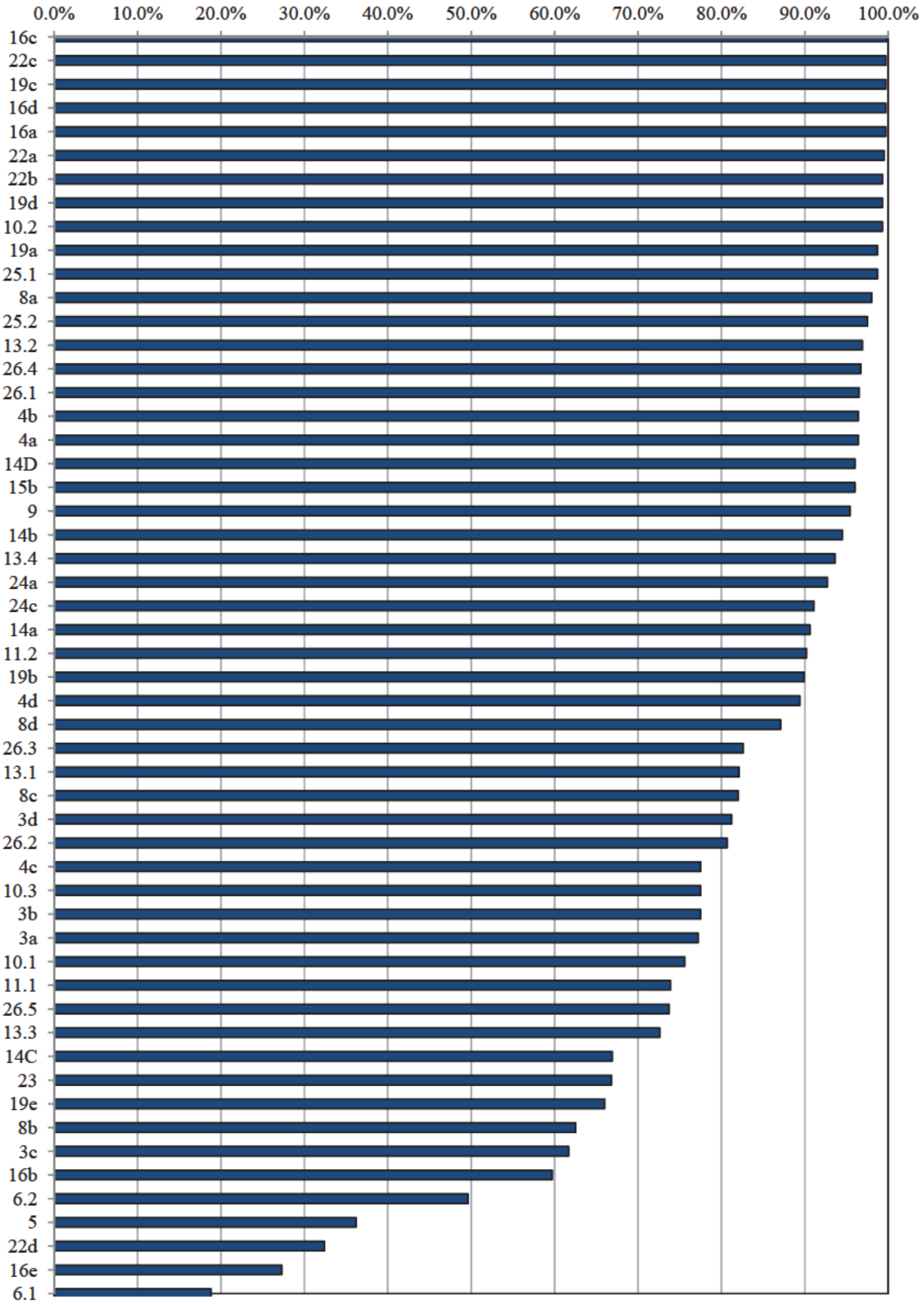


TABLE 17: INDIVIDUAL KEY RISK MESSAGE QUESTION/ITEMS AND CORRECT ANSWERS ORDERED BY SCORE

QUESTION #	QUESTION/ITEMS AND CORRECT ANSWERS	SCORE (%)
16c	How should prescribers reassess patients maintained on ER/LA opioid analgesics during follow-up visits? (Evaluate pain control and functional improvement – True)	99.8
19.3	Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Alcohol – Yes)	99.7
16a	How should prescribers reassess patients maintained on ER/LA opioid analgesics during follow-up visits? (Periodically assess the continued need for opioid analgesics – True)	99.7
16d	How should prescribers reassess patients maintained on ER/LA opioid analgesics during follow-up visits? (Evaluate for changes in the patient's medical condition – True)	99.7
22c	Which of the following are important factors to consider when selecting an initial dose of an ER/LA opioid analgesic? (General medical status of the patient – Yes)	99.7
22a	Which of the following are important factors to consider when selecting an initial dose of an ER/LA opioid analgesic? (The patient's degree of opioid experience – Yes)	99.5
10.2	Which of the following are risk factors for opioid abuse? Please select all that apply. (A personal history of past or current alcohol or drug abuse)	99.3
19.3	Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Illegal drugs – Yes)	99.3
22b	Which of the following are important factors to consider when selecting an initial dose of an ER/LA opioid analgesic? (Concurrent medication – Yes)	99.3
19.1	Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Sedative hypnotics – Yes)	98.7
25.1	When counseling patients about the safe use of ER/LA opioid analgesics, prescribers should inform patients of the following. Please select all that apply. (The importance of adhering to a dosage regimen as prescribed)	98.7
8a	Central nervous system depressants can have a potentiating effect on the sedation and respiratory depression caused by opioids. (True)	98.0
25.2	When counseling patients about the safe use of ER/LA opioid analgesics, prescribers should inform patients of the following. Please select all that apply. (It is illegal to sell or give away ER/LA opioid analgesics)	97.5
13.2	Which of the following are the warning signs and symptoms of respiratory depression from ER/LA opioid analgesics? Please select all that apply. (Decreased rate of respiration)	96.9
26.4	How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Please select all that apply. (Periodically re-evaluate therapy)	96.7
26.1	How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Please select all that apply. (Document any "drug seeking" behavior)	96.5
4a	After thorough clinical evaluation, it is appropriate for prescribers to refer a patient at high risk for drug abuse to a pain management specialist. (True)	96.4
4b	It is not necessary to re-evaluate a patient's underlying medical condition if the clinical presentation changes over time. (False)	96.4

TABLE 17: INDIVIDUAL KEY RISK MESSAGE QUESTION/ITEMS AND CORRECT ANSWERS ORDERED BY SCORE

QUESTION #	QUESTION/ITEMS AND CORRECT ANSWERS	SCORE (%)
14d	PPAs may include commitments regarding follow-up visits, monitoring for misuse, and safeguarding the medication. (True)	96.0
15b	A patient should not cut an extended release tablet in half to reduce the dose. (True)	96.0
9	When evaluating patients for treatment with ER/LA opioid analgesics, which of the following are important risks to consider? (All of the above)	95.4
14b	PPAs can include information about treatment goals, risks, and safe use of the ER/LA opioid. (True)	94.5
13.4	Which of the following are the warning signs and symptoms of respiratory depression from ER/LA opioid analgesics? Please select all that apply. (Profound sedation)	93.6
24a	When starting a patient who is currently taking a sedative on an ER/LA opioid analgesic, reduce the dose of one or both. (True)	92.7
24c	Patients who are not opioid tolerant can initiate opioid therapy with any type of ER/LA opioid analgesic. (False)	91.1
14a	PPAs are signed by both prescriber and patient at the time an opioid is initially prescribed. (True)	90.6
11.2	Which of the following should prescribers do when initiating a patient on ER/LA opioid analgesics? Please select all that apply. (Titrate doses based on efficacy and tolerability)	90.2
19.2	Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Anxiolytics – Yes)	89.9
4d	Chewing a solid, oral dosage form of an ER/LA opioid analgesic can result in rapid release and absorption of a potentially fatal dose of opioid. (True)	89.4
8d	Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids. (True)	87.1
26.3	How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Please select all that apply. (Use drug testing for both screening and confirmatory tests)	82.6
13.1	Which of the following are the warning signs and symptoms of respiratory depression from ER/LA opioid analgesics? Please select all that apply. (Reduced urge to breathe)	82.1
8c	Monoamine oxidase inhibitors (MAOIs) are the preferred antidepressants for use with ER/LA opioid analgesics. (False)	82.0
3d	Some opioids can increase the QTc interval. (True)	81.2
26.2	How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Please select all that apply. (Utilize state Prescription Drug Monitoring Programs)	80.7
10.3	Which of the following are risk factors for opioid abuse? Please select all that apply. (A family history of illicit drug use or alcohol abuse)	77.5
4c	ER/LA opioid analgesic transdermal patches that have a matrix formulation may be cut prior to use. (False)	77.5

TABLE 17: INDIVIDUAL KEY RISK MESSAGE QUESTION/ITEMS AND CORRECT ANSWERS ORDERED BY SCORE

QUESTION #	QUESTION/ITEMS AND CORRECT ANSWERS	SCORE (%)
3b	A patient with the history of substance abuse must not be prescribed ER/LA Opioid Analgesic. (False)	77.5
3a	For methadone, the peak of respiratory depression can occur later and can persist longer than the analgesic effects. (True)	77.2
10.1	Which of the following are risk factors for opioid abuse? Please select all that apply. (A personal history of psychiatric disorders)	75.4
11.1	Which of the following should prescribers do when initiating a patient on ER/LA opioid analgesics? Please select all that apply. (Consider a rescue medication for breakthrough pain)	73.9
26.5	How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Please select all that apply. (Perform medication reconciliation by counting leftover drug supplies)	73.7
13.3	Which of the following are the warning signs and symptoms of respiratory depression from ER/LA opioid analgesics? Please select all that apply. ("Sighing" pattern of breathing)	72.6
14c	PPAs are a legal requirement. (False)	66.9
23	What should be done if a patient treated with a transdermal opioid develops a high fever? (Monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary)	66.8
19.4	Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Caffeine – No)	66.0
8b	Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol. (True)	62.5
3c	Conversion of patients to or from methadone using equianalgesic tables can result in overdose and death. (True)	61.7
16b	How should prescribers reassess patients maintained on ER/LA opioid analgesics during follow-up visits? (Perform a comprehensive physical examination at each visit (False)	59.7
6.2	Patients considered opioid-tolerant are those. Please select all that apply. (Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer)	49.6
5	What is the recommended way to safely convert an opioid-tolerant patient from a parenteral opioid, such as morphine or meperidine, to an oral extended-release opioid, such as oxycodone or oxymorphone? (Start with 50% of an equianalgesic dose)	36.2
22d	Which of the following are important factors to consider when selecting an initial dose of an ER/LA opioid analgesic? (The patient's family history of mental illness (No)	32.4
16e	Systematically perform drug screening for all patients. (False)	27.3
6.1	Patients considered opioid-tolerant are those. Please select all that apply. Who are taking 25 mcg/hour transdermal fentanyl for at least 7 days	18.8

There were 11 (21%) questions/items that had levels of understanding of less than 70% (Table 18). Of these 11 questions/items, four (36.3%) of the incorrect answers were related to Key Risk Message 5, six incorrect responses were associated with Key Risk Messages 2 and 3 and one incorrect response was associated with Key Risk Message 4. There were no scores of less than 70% for question/items associated with Key Risk Message 1.

TABLE 18: SURVEY QUESTIONS/ITEMS WITH SCORES LESS THAN 70% CORRECT WITHIN EACH KEY RISK MESSAGE

QUESTION/ITEM AND CORRECT ANSWER	SCORE (%)
Key Risk Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.	
3c. Conversion of patients to or from methadone using equianalgesic tables can result in overdose and death. (True)	61.7
5. What is the recommended way to safely convert an opioid-tolerant patient from a parenteral opioid, such as morphine or meperidine, to an oral extended-release opioid, such as oxycodone or oxymorphone? (Start with 50% of an equianalgesic dose)	36.2
22d. Which of the following are important factors to consider when selecting an initial dose of an ER/LA opioid analgesic? The patient's family history of mental illness (No)	32.4
Key Risk Message 3: Management of ongoing therapy with ER/LA opioid analgesics is important.	
16b. How should prescribers reassess patients maintained on ER/LA opioid analgesics during follow-up visits? - Perform a comprehensive physical examination at each visit (False)	59.7
16e. How should prescribers reassess patients maintained on ER/LA opioid analgesics during follow-up visits? Systematically perform drug screening for all patients (False)	27.3
14c. PPAs are a legal requirement. (False)	66.9
Key Risk Message 4: It is important to counsel patients and caregivers about the safe use of ER/LA opioid analgesics.	
19.4. Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Caffeine – No)	66.0
Key Risk Message 5: Prescribers must be familiar with general and product-specific drug information concerning ER/LA opioid analgesics	
23. What should be done if a patient treated with a transdermal opioid develops a high fever? Please select the best response. (Monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary)	66.8
8b. Please select True, False, or I don't know for each of the following statements about drug-drug interaction profiles for ER/LA opioid analgesics. Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol. (True)	62.5
6.2. Patients considered opioid-tolerant are those (Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer)	49.6
6.1. Patients considered opioid-tolerant are those (Who are taking 25 mcg/hour transdermal fentanyl for at least 7 days)	18.8

Tables 19 through 23 show the responses to each of the 5 key risk messages and the associated key risk message questions/items.

TABLE 19: CORRECT SCORES FOR QUESTIONS ADDRESSING KEY RISK MESSAGE 1

KEY RISK MESSAGE 1: PATIENTS SHOULD BE ASSESSED FOR TREATMENT WITH ER/LA OPIOID ANALGESIC THERAPY.			
QUESTION #	QUESTION/ITEMS AND CORRECTANSWERS	N	%
3b	A patient with a history of substance abuse must not be prescribed an ER/LA opioid analgesic. (False)	469	77.5
4a	After thorough clinical evaluation, it is appropriate for prescribers to refer a patient at high risk for drug abuse to a pain management specialist. (True)	583	96.4
9	When evaluating patients for treatment with ER/LA opioid analgesics, which of the following are important risks to consider? (All of the above)	577	95.4
10.1	Which of the following are risk factors for opioid abuse? Please select all that apply. (A personal history of psychiatric disorders)	456	75.4
10.2	Which of the following are risk factors for opioid abuse? Please select all that apply. (A personal history of past or current alcohol or drug abuse)	601	99.3
10.3	Which of the following are risk factors for opioid abuse? Please select all that apply. (A family history of illicit drug use or alcohol abuse)	469	77.5

TABLE 20: CORRECT SCORES FOR QUESTIONS ADDRESSING KEY RISK MESSAGE 2

KEY RISK MESSAGE 2: PRESCRIBERS MUST BE FAMILIAR WITH HOW TO INITIATE THERAPY, MODIFY DOSE, AND DISCONTINUE USE OF ER/LA OPIOID ANALGESICS.			
QUESTION #	QUESTION/ITEMS AND CORRECTANSWERS	N	%
3a	For methadone, the peak of respiratory depression can occur later and can persist longer than the analgesic effects. (True)	467	77.2
3c	Conversion of patients to or from methadone using equianalgesic tables can result in overdose and death. (True)	373	61.7
5	What is the recommended way to safely convert an opioid-tolerant patient from a parenteral opioid, such as morphine or meperidine, to an oral extended-release opioid, such as oxycodone or oxymorphone? (Start with 50% of an equianalgesic dose)	219	36.2
11.1	Which of the following should prescribers do when initiating a patient on ER/LA opioid analgesics? Please select all that apply. (Consider a rescue medication for breakthrough pain)	447	73.9
11.2	Which of the following should prescribers do when initiating a patient on ER/LA opioid analgesics? Please select all that apply. (Titrate doses based on efficacy and tolerability)	546	90.2
22a	The patient's degree of opioid experience (Yes)	602	99.5
22b	Concurrent medication (Yes)	601	99.3
22c	General medical status of the patient (Yes)	603	99.7
22d	The patient's family history of mental illness (No)	196	32.4

TABLE 21: CORRECT SCORES FOR QUESTIONS ADDRESSING KEY RISK MESSAGE 3

KEY RISK MESSAGE 3: MANAGEMENT OF ONGOING THERAPY WITH ER/LA OPIOID ANALGESICS IS IMPORTANT.			
QUESTION #	QUESTION/ITEMS AND CORRECTANSWERS	N	%
4b	It is not necessary to re-evaluate a patient's underlying medical condition if the clinical presentation changes over time. (False)	583	96.4
14a	PPAs are signed by both prescriber and patient at the time an opioid is initially prescribed. (True)	548	90.6
14b	PPAs can include information about treatment goals, risks, and safe use of the ER/LA opioid. (True)	572	94.5
14c	PPAs are a legal requirement. (False)	405	66.9
14d	PPAs may include commitments regarding follow-up visits, monitoring for misuse, and safeguarding the medication. (True)	581	96.0
16a	Periodically assess the continued need for opioid analgesics (True)	603	99.7
16b	Perform a comprehensive physical examination at each visit (False)	361	59.7
16c	Evaluate pain control and functional improvement (True)	604	99.8
16d	Evaluate for changes in the patient's medical condition (True)	603	99.7
16e	Systematically perform drug screening for all patients (False)	165	27.3
26.1	How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Please select all that apply. (Document any "drug seeking" behavior)	584	96.5
26.2	How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Please select all that apply. (Utilize state Prescription Drug Monitoring Programs)	488	80.7
26.3	How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Please select all that apply. (Use drug testing for both screening and confirmatory tests)	500	82.6
26.4	How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Please select all that apply. (Periodically re-evaluate therapy)	585	96.7
26.5	How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Please select all that apply. (Perform medication reconciliation by counting leftover drug supplies)	446	73.7

TABLE 22: CORRECT SCORES FOR QUESTIONS ADDRESSING KEY RISK MESSAGE 4

KEY RISK MESSAGE 4: IT IS IMPORTANT TO COUNSEL PATIENTS AND CAREGIVERS ABOUT THE SAFE USE OF ER/LA OPIOID ANALGESICS.			
QUESTION #	QUESTION/ITEMS AND CORRECTANSWERS	N	%
4c	ER/LA opioid analgesic transdermal patches that have a matrix formulation may be cut prior to use. (False)	469	77.5
4d	Chewing a solid, oral dosage form of an ER/LA opioid analgesic can result in rapid release and absorption of a potentially fatal dose of opioid. (True)	541	89.4

TABLE 22: CORRECT SCORES FOR QUESTIONS ADDRESSING KEY RISK MESSAGE 4

KEY RISK MESSAGE 4: IT IS IMPORTANT TO COUNSEL PATIENTS AND CAREGIVERS ABOUT THE SAFE USE OF ER/LA OPIOID ANALGESICS.			
QUESTION #	**QUESTION/ITEMS AND CORRECTANSWERS**	**N**	**%**
13.1	Which of the following are the warning signs and symptoms of respiratory depression from ER/LA opioid analgesics? Please select all that apply. (Reduced urge to breathe)	497	82.1
13.2	Which of the following are the warning signs and symptoms of respiratory depression from ER/LA opioid analgesics? Please select all that apply (Decreased rate of respiration)	586	96.9
13.3	Which of the following are the warning signs and symptoms of respiratory depression from ER/LA opioid analgesics? Please select all that apply ("Sighing" pattern of breathing)	439	72.6
13.4	Which of the following are the warning signs and symptoms of respiratory depression from ER/LA opioid analgesics? Please select all that apply (Profound sedation)	566	93.6
15b	A patient should not cut an extended release tablet in half to reduce the dose. (True)	581	96.0
19.1	Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Sedative hypnotics – Yes)	597	98.7
19.2	Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Anxiolytics – Yes)	544	89.9
19.3	Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Alcohol – Yes)	603	99.7
19.3	Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Illegal drugs – Yes)	601	99.3
19.4	Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? (Caffeine – No)	399	66.0
25.1	When counseling patients about the safe use of ER/LA opioid analgesics, prescribers should inform patients of the following. Please select all that apply. (The importance of adhering to a dosage regimen as prescribed)	597	98.7
25.2	When counseling patients about the safe use of ER/LA opioid analgesics, prescribers should inform patients of the following. Please select all that apply. (It is illegal to sell or give away ER/LA opioid analgesics)	590	97.5

TABLE 23: CORRECT SCORES FOR QUESTIONS ADDRESSING KEY RISK MESSAGE 5

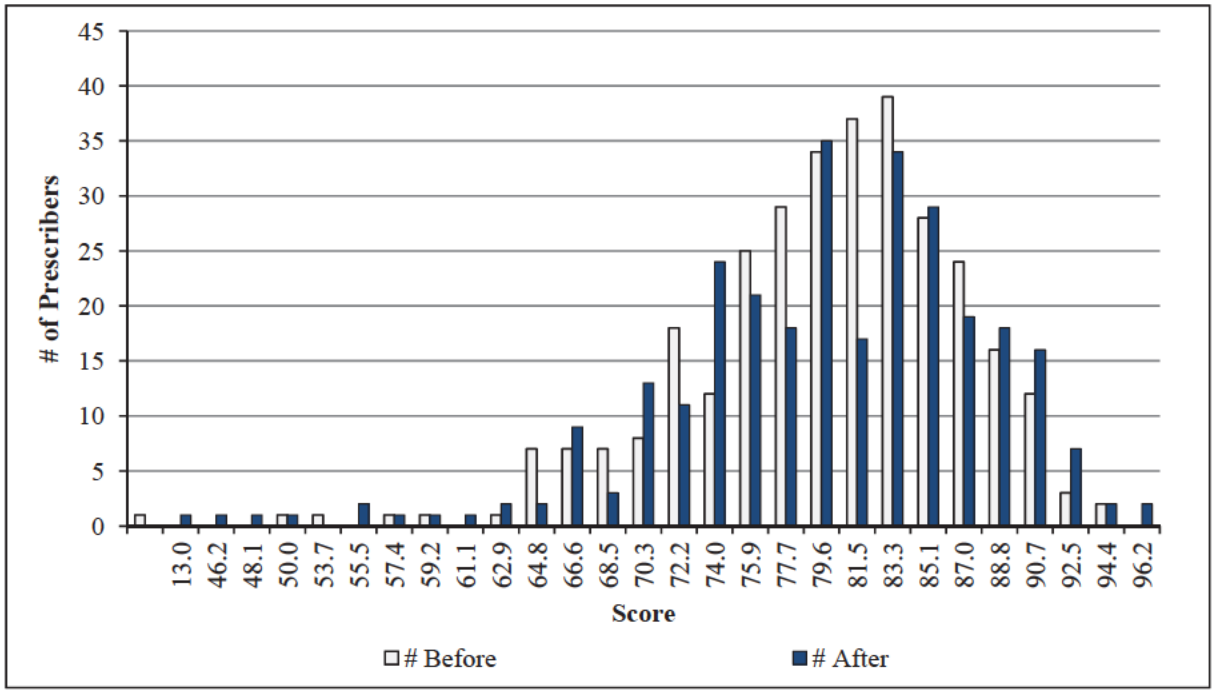
KEY RISK MESSAGE 5: PRESCRIBERS MUST BE FAMILIAR WITH GENERAL AND PRODUCT-SPECIFIC DRUG INFORMATION CONCERNING ER/LA OPIOID ANALGESICS.			
QUESTION #	**QUESTION/ITEMS AND CORRECTANSWERS**	**N**	**%**
3d	Some opioids can increase the QTc interval. (True)	491	81.2
6.1	Patients considered opioid-tolerant are those (please select all that apply): Who are taking 25 mcg/hour transdermal fentanyl for at least 7 days	114	18.8
6.2	Patients considered opioid-tolerant are those please select all that apply: (Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer)	300	49.6

TABLE 23: CORRECT SCORES FOR QUESTIONS ADDRESSING KEY RISK MESSAGE 5

KEY RISK MESSAGE 5: PRESCRIBERS MUST BE FAMILIAR WITH GENERAL AND PRODUCT-SPECIFIC DRUG INFORMATION CONCERNING ER/LA OPIOID ANALGESICS.			
8a	Central nervous system depressants can have a potentiating effect on the sedation and respiratory depression caused by opioids. (True)	593	98.0
8b	Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol. (True)	378	62.5
8c	Monoamine oxidase inhibitors (MAOIs) are the preferred antidepressants for use with ER/LA opioid analgesics. (False)	496	82.0
8d	Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids. (True)	527	87.1
23	What should be done if a patient treated with a transdermal opioid develops a high fever? (Monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary)	404	66.8
24a	When starting a patient who is currently taking a sedative on an ER/LA opioid analgesic, reduce the dose of one or both. (True)	561	92.7
24c	Patients who are not opioid tolerant can initiate opioid therapy with any type of ER/LA opioid analgesic. (False)	551	91.1

Because the survey was open beyond February 27, 2013, an analysis was done comparing the scores stratified by those who completed the survey before and after the launch of the REMS-compliant CME/CE activities on February 28, 2013. (Since the survey had not been planned to extend beyond March 1, 2013, there was not a question in the survey as to whether the respondent had accessed any CME/CE activity so the date of the CME/CE program launch was used as a surrogate for having received REMS education.). Total scores for the 54 key risk message questions/items were transformed into a percentage correct score across the 54 questions/items for each respondent, e.g., 50 correct items out of 54 total items = a total score of 92.6%. Figure 8 shows the key risk message scores for respondents who completed the survey before February 28, 2013 and scores for respondents who completed the survey on or after February 28, 2013. The pattern suggests that most respondents scored between 70% and 90% on the key risk message questions/items, regardless of the time period in which they completed the survey.

Figure 8: Evaluation of Differences in Total Scores among Survey Respondents Who Completed the Survey before versus after the Launch of the REMS-Compliant Continuing Education



3.3.1.3.3. Awareness and Use of REMS Educational Materials

Prescribers were asked about their awareness, receipt, and review of educational materials associated with the ER/LA Opioid REMS, specifically, the Medication Guide(s), DDRP, PCD, and ER/LA Opioid Analgesics REMS website (www.er-la-opioidrems.com) (Table 24).

Approximately half of the survey respondents (N = 266, 44.0%) indicated they were aware of the Medication Guide. Of those, 188 (87.4%) respondents indicated that they read the Medication Guide for the opioid analgesic they prescribe. For those who were aware of the Medication Guide, many learned of it from a sales representative (N = 150, 56.4%).

When asked about the Dear DEA-Registered Prescriber Letter, 165 prescribers (27.3%) indicated they were aware of the DDRP Letter, and of those who were aware and acknowledged receipt of the letter, 115 prescribers (89.8%) reported reading it.

One-third of prescribers (N = 195, 32.2%) were aware of the PCD prior to taking the survey, and 97 prescribers (16%) were aware of the ER/LA Opioid Analgesics REMS website (www.er-la-opioidrems.com). These levels of awareness existed in spite of all DEA-registered prescribers having been sent the Dear DEA-Registered Prescriber Letter 1 and 2.

Some respondents (N = 161, 26.6%) reported having questions about the Medication Guide(s), Dear DEA-Registered Prescriber Letter, PCD, or ER/LA Opioid Analgesics REMS website. These prescribers were directed to the REMS Call Center for information.

TABLE 24: AWARENESS RECEIPT AND READING OF REMS EDUCATIONAL MATERIALS

	MEDICATION GUIDE		DEAR DEA-REGISTERED PRESCRIBER LETTER (DDRP)		PATIENT COUNSELING DOCUMENT (PCD)		ER/LA OPIOID ANALGESICs REMS WEBSITE	
	N/Denominator	%	N/Denominator	%	N/Denominator	%	N/Denominator	%
Awareness	266/605	44.0	165/605	27.3	195/605	32.2	97/605	16.0
Receive/Have Access[1]	215/266	80.8	128/165	77.6	149/195	76.4	88/97	90.7
Read[2]	188/215	87.4	115/165	89.8	133/149	89.3	58/88	65.9

[1] Because of survey skip logic, denominator is prescribers who were aware of the education materials.

[2] Because of survey skip logic, denominator is prescribers who received or had access to the education materials.

Respondents indicated that they most commonly became aware of the Medication Guide through a sales representative (N = 150, 56.4%) (Table 25). The majority of the respondents reported the mailing as the source of awareness for the DDRP. Conferences and mailings were the two highest reported sources for awareness of the PCD (N = 68, 34.9%) and (N = 71, 36.4%) respectively.

TABLE 25: SOURCES OF PRESCRIBERS' AWARENESS OF REMS EDUCATION MATERIALS

	MEDICATION GUIDE		DEAR DEA-REGISTERED PRESCRIBER (DDRP)		PATIENT COUNSELING DOCUMENT (PCD)		ER/LA OPIOID ANALGESIC WEBSITE	
	N = 266[1]	%	N = 165[1]	%	N = 195[1]	%	N = 97[1]	%
Mailing	88	33.1	123	74.5	71	36.4	39	40.2
E-mail	40	15	25	15.2	31	15.9	26	26.8
Online download	43	16.2	15	9.1	23	11.8	18	18.6
Sales Representative	150	56.4	40	24.2	76	39	40	41.2
Pharmacy	53	19.9	14	8.5	28	14.4	9	9.3
Conference	99	37.2	24	14.5	68	34.9	25	25.8
Other	29	10.9	18	10.9	20	10.3	7	7.2
I don't Know	17	6.4	2	1.2	13	6.7	3	3.1
No	339		440		410		508	

[1]Denominator is respondents who were aware of the tool

Similarly, respondents reported the Sales Representative as the most common source for receipt of the Medication Guide (N = 125, 58.1%) (Table 26). And, like awareness, the most common

source for receipt of the DDRP letter was via mail (N = 104, 81.3%). The highest reported source for receipt of the PCD was via mail (N = 57, 38.3%).

TABLE 26: SOURCES OF PRESCRIBERS' RECEIPT OF REMS EDUCATIONAL MATERIALS

	MEDICATION GUIDE		DEAR DEA-REGISTERED PRESCRIBER (DDRP)		PATIENT COUNSELING DOCUMENT (PCD)	
	N = 215[1]	%	N = 128[1]	%	N = 149[1]	%
Mailing	75	34.9	104	81.3	57	38.3
E-mail	33	15.3	22	17.2	27	18.1
Online download	85	33.5	15	11.7	40	26.8
Sales Representative	125	58.1	27	21.7	55	36.9
Pharmacy	46	21.4	7	5.5	21	14.1
Conference	41	19.1	8	6.3	44	29.5
Other	13	6.0	10	7.8	15	10.1
I don't know	390		477		456	

[1]Denominator includes only respondents who reported receipt of the tool.

3.3.1.4. Prescriber Behaviors

Prescribers were asked to indicate the practices they followed when treating patients with ER/LA opioid analgesics (Table 27). The most frequently reported behavior was with respect to warning patients not to break, chew, or crush their oral ER/LA opioid, as it could result in an overdose (N = 528, 87.3%).

Table 28 shows the responses to survey questions regarding the frequency of following specific safe use behaviors. 91 respondents (15.0%) reported 'always' using the PCD when treating patients with ER/LA opioid analgesics while 226 (37.4%) reported never using the PCD when treating patients with ER/LA opioid analgesics.

More than half of respondents reported always cautioning patients about important risks including overdose and respiratory depression 330 (54.5%).

With respect to advising patients, 199 (32.9%) of respondents reported that they 'always' advise patients on how to safely taper an ER/LA opioid when discontinuing and 18 (3.0%) reported they 'never' discuss this with patients. The majority (528, 87.3%) respondents reported that they warn patients not to break, chew, or crush their oral ER/LA opioid.

Notably, only 208 (34.4%) survey respondents regularly instruct patients on the importance and how to safely dispose of unused opioids while 173 (28.6%) rarely do and 37 (6.1%) reported never doing so.

Finally, the majority of prescribers indicated they always or regularly (N = 400, 66.1%) complete a Patient Prescriber Agreement (PPA) or patient contract at the time an ER/LA opioid is first prescribed, while 89 (14.7%) reported never completing a patient contract/agreement.

TABLE 27: PRESCRIBER BEHAVIORS REGARDING SAFE USE

WHICH OF THE FOLLOWING DO YOU DO WITH PATIENTS WHEN PRESCRIBING AN ER/LA OPIOID ANALGESIC? PLEASE SELECT ALL THAT APPLY.	RESPONSE N = 605	
	N	%
Use the *Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids* when discussing the proper use of opioids with my patient	262	43.3
Advise patients how to safely taper their ER/LA opioid dose when discontinuing	414	68.4
Explain what patients should do if they miss a dose of their ER/LA opioid analgesic	426	70.4
Warn patients not to break, chew or crush their oral ER/LA opioid, as it could result in an overdose	528	87.3
None of the above	23	3.8

TABLE 28: FREQUENCY OF SAFE USE BEHAVIORS BY PRESCRIBERS

HOW FREQUENTLY DO YOU PERFORM THE FOLLOWING ACTIVITIES WHEN TREATING PATIENTS WITH ER/LA OPIOID ANALGESICS?	RESPONSE N = 605									
	ALWAYS		REGULARLY		RARELY		NEVER		I DON'T KNOW	
	N	%	N	%	N	%	N	%	N	%
Use the *Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids* for discussion with patients	91	15.0	125	20.7	137	22.6	226	37.4	26	4.3
Caution patients about important risks, including overdose and respiratory depression	330	54.5	238	39.3	32	5.3	3	0.5	2	0.3
Discuss with patients how to safely taper their ER/LA opioid analgesic if it is no longer needed	199	32.9	280	46.3	103	17.0	18	3.0	5	0.8
Counsel patients on the most common side effects from opioid use	328	54.2	261	43.1	13	2.1	2	0.3	1	0.2
Instruct patients about the importance and how to safely dispose of their unused opioids	178	29.4	208	34.4	173	28.6	37	6.1	9	1.5
Use structured interview tools or other screening tools to assess patients' risk of abuse or misuse of their medications when managing patients using ER/LA opioids	109	18.0	189	31.2	176	29.1	123	20.3	8	1.3
Complete a Patient Prescriber Agreement (PPA) or patient contract at the time an ER/LA opioid is first prescribed	236	39.0	164	27.1	112	18.5	89	14.7	4	0.7
Perform urine drug tests	60	9.9	255	42.1	191	31.6	93	15.4	6	1.0
Reassess the need for opioids	330	54.5	266	44.0	5	0.8	2	0.3	2	0.3

3.3.2. Conclusion

A baseline survey of active prescribers of ER/LA opioids was undertaken to measure knowledge, attitudes, and behaviors associated with the prescribing of ER/LA opioid analgesics and the risks associated with their use. Although intended to measure knowledge and understanding prior to the availability of the REMS-compliant CME/CE activities, the BPS survey included respondents who completed the survey after the launch date of the first REMS-compliant CME/CE activity. Scores for those completing before and after this date were high in both groups, with most respondents having a summary score of between 70% and 90%. The analyses of responses to questions defining each of the five key risk messages demonstrated that most

prescribers were well informed about the risks and safe use criteria associated with ER/LA Opioid Analgesics. The majority (79%) of the key risk message questions/items were answered correctly (correctly being defined as a score of above 70%). The most common themes of the questions answered incorrectly were related to opioid tolerance and conversion.

In terms of awareness of REMS educational materials, 165 prescribers (27.3%) indicated they were aware of the DDRP Letter, and of those who were aware and acknowledged receipt of the letter, 115 prescribers (89.8%) reported reading it. Approximately half of the survey respondents (N = 266, 44.0%) indicated they were aware of the Medication Guide. Of those, 188 (87.4%) respondents indicated that they read the Medication Guide for the opioid analgesic they prescribe. One-third of prescribers (N = 195, 32.2%) were aware of the PCD prior to taking the survey, and 97 prescribers (16%) were aware of the ER/LA Opioid Analgesics REMS website (www.er-la-opioidrems.com). These levels of awareness were reported despite all DEA-registered prescribers having been sent the DDRP Letters 1 and 2.

A detailed report of the BPS assessment is currently in development and will include analyses stratified by the pre- and post-CME/CE launch periods. Additional analyses will be offered as they become available.

3.4. Assessment Element 3b – Long-Term Evaluation Grants

A RFA will be issued to solicit applications for CME/CE Providers or CME/CE outcomes organizations that have the capability to conduct long-term evaluations. The RFA will be for activities to evaluate prescribers of ER/LA opioids who have completed their CME/CE training to assess knowledge retention and practice changes six months to one year after completing the REMS-compliant training.

Since the long-term evaluation activities will not begin until six to twelve months after learners complete REMS CME/CE training, and since the first REMS-compliant CME/CE launched just two months prior to the Twelve-Month FDA Assessment Report data lock, the details of the long-term evaluation process were in development at the time of this report. Detailed information will be provided in the Two-Year FDA Assessment Report.

3.5. Functional Components

3.5.1. Dear DEA-Registered Prescriber Letter 2 (DDRP Letter 2)

A series of DDRP Letters was planned as part of the prescriber outreach for the REMS. The first DDRP letter announced the approval of the ER/LA Opioid Analgesic REMS. During this reporting period, a second DDRP letter, (DDRP Letter 2) was used to announce availability of ER/LA Opioid Analgesic REMS-related CME/CE opportunities. The goal was to send this letter no later than 30 days before the first prescriber REMS-compliant training was offered. The target audience for the letter was all DEA-registered prescribers, regardless of discipline/degree. The REMS Communication Vendor that distributed the first DDRP letter delivered this second letter to the targeted audience using the same methods as it had for delivery of DDRP Letter 1. The letter was distributed electronically by e-mail or facsimile or via USPS. The REMS Communication Vendor used its proprietary database of HCPs who have "opted in" to receive electronic communications on drug safety alerts and REMS Communication Letters. The database of opt-in prescribers was matched to the list of DEA-registered prescribers to identify prescribers in the opt-in database to receive electronic communications. Prescribers on the DEA master registration file (DEA file), but not on the REMS Communication Vendor opt-in list,

received the letter through USPS mail. Addresses for mailing the letters were obtained from the DEA list or from matching the DEA list to the American Medical Association (AMA) list of physicians. In cases where the electronic communication was undeliverable, the prescribers were sent a letter by direct mail to the address indicated on the DEA or AMA file within 30 days after sending the electronic communication.

A process of identifying unique prescribers within the DEA file was conducted. After removal of duplicate registrations, registrations with address errors, and records from deceased registrants, the target registrant audience for receipt of the DDRP Letter 2, as of December 31, 2012, totaled 1,342,173. Letters were sent to all prescribers in this data file.

There is currently no reliable method for tracking accurate volumes of unopened/unread e-mails. Industry standard e-mail exchange services/programs (e.g., Microsoft Exchange, Unix Sendmail) have limited ability to accurately track and report when an e-mail is opened or read. An affirmative action on the part of the recipient (i.e., downloading images or clicking on a hyperlink) is required to enable tracking of opening rates. It is not possible to know when an e-mail is read in the absence of these actions. In addition, many e-mail programs/services block images and hyperlinks by default as protection against spam and virus attacks. As well, many recipients do not download images as a matter of common practice for the same reasons. Finally, when the critical safety information for DDRP Letters and other REMS communications is embedded within the body of the communication, the recipient may choose to read some or all of it in a preview pane without ever downloading images or clicking on any hyperlinks. As a result, it is not currently possible to accurately know when the content of an e-mail is read.

Electronic (e-mail and facsimile) communications for DDPR Letter 2 were initiated on January 22, 2013, 6 days prior to the indicated deadline. Mailing of hardcopy communications was initiated on January 22, 2013. The sending of DDRP Letter 2 by all routes was completed on January 28, 2013. Letter 2 was posted on the ERLA Opioid Analgesics REMS website on February 6, 2013.

Table 29 shows the number of registrants in the DEA master registration file, as well as the final number of registrants targeted. A total of 256,093 letters were sent by e-mail, 226,206 by fax, and 832,669 by USPS. Of these, 27,205 (2%) were returned.

TABLE 29: DDRP LETTER 2 COMMUNICATION SUMMARY (TOTAL DELIVERED)

ROW	CATEGORY	DEA REGISTRATIONS OR REGISTRANTS	PERCENT OF TARGETED REGISTRANTS
1	DEA Master Registration File, as of December 31, 2012	1,451,325	
2	Deceased + Duplicates + Address Errors + B	- 56,319	
3	Unique Registrants Targeted	1,342,173	
4	Unique Registrants Reached	1,314,968	98.0
4a	by e-mail	256,093	19.5
4b	by facsimile	226,206	17.2
4c	by USPS	832,669	63.3

Row 1 = total *registrations* of all Business Activity codes (NB: an entity may have more than one registration)

Row 2 = sum of registrations for deceased registrants, duplicate registrations, registrations with address errors, and Business Activity Code B (employed residents, physicians, nurse practitioners, etc. who may not have individual registrations)

Row 3 = the number of unique registrants attempted to reach

Row 4 = the number and percent of unique registrants eventually reached

Rows 4a – c = the number and percent of unique registrants reached by communication route

Attempts at electronic communication of DDRP Letter 2 resulted in 66,370 being undeliverable. These were then sent via USPS in hardcopy form.

In addition, the Communication Vendor attempted to send hard copy DDRP Letter 2 by USPS to all hospital and pharmacy registrants (N = 15,561), of which 15,468 (99.4%) were delivered.

3.5.1.1. Conclusion

The performance goal was successfully met for ensuring that DDRP Letter 2 was sent no later than 30 days prior to the start of CME/CE activities. Of the 1.34 million prescribers that were targeted, 98.0% of DDRP Letter 2 were successfully delivered.

3.5.2. Dear Professional Organization/Licensing Board Letter 2 (DPOLB Letter 2)

To further ensure that prescribers are aware of ER/LA Opioid Analgesic REMS-related CME/CE opportunities, the RPC distributed a letter to relevant Learned Societies and Professional Associations (DPOLB Letter 2) on January 24, 2013, 34 days prior to the start of CME/CE activities. The recipients of this letter included the leadership of organizations shown in Table 30.

TABLE 30: LEARNED SOCIETIES AND PROFESSIONAL ASSOCIATIONS RECEIVING DPOLB LETTER 2

LEARNED SOCIETIES AND PROFESSIONAL ASSOCIATIONS		
American Academy of Addiction Psychiatry	American Board of Medical Specialties	American Osteopathic Association of Addiction Medicine
American Academy of Family Physicians	American Board of Orofacial Pain	American Pain Society
American Academy of Hospice and Palliative Medicine	American College of Emergency Physicians	American Society of Addiction Medicine
American Academy of Neurology	American College of Nurse Practitioners	American Society for Pain Management Nursing
American Association of Nurse Practitioners	American College of Osteopathic Family Physicians	American Society of Pain Educators
American Academy of Nursing	American College of Physicians	Association of American Medical Colleges
American Academy of Orofacial Pain	American College of Rheumatology	Hospice and Palliative Nurses Association
American Academy of Pain Management	American Dental Association	National Association of Managed Care Physicians
American Academy of Pain Medicine	American Dental Education Association	National Association of State Controlled Substances Authorities
American Academy of Physical Medicine and Rehabilitation	American Medical Association	National Commission on Certification of Physician Assistants
American Academy of Physician Assistants	American Medical Directors Association	National Hospice and Palliative Care Organization
American Association of Colleges of Osteopathic Medicine	American Nurses Association	Society of Emergency Medicine Physician Assistants
American Association of Colleges of Nursing	American Nurses Credentialing Center	
American Association of Poison Control Centers	American Osteopathic Association	

A similar letter was sent to the following Licensing Boards on January 24, 2013, 34 days prior to the start of CME/CE activities:

- State Licensing Boards of:
  - Medicine (allopathic and osteopathic)
  - Nursing
  - Dentistry
- Associations of State Licensing Boards:
  - Federation of State Medical Boards
  - National Council of State Boards of Nursing
  - American Association of Dental Boards

The RPC also included additional state medical and osteopathic societies to the distribution list for DPOLB Letter 2. The Communication Vendor researched the information for these societies and their contact information (http://www.ama-assn.org/ama/pub/about-ama/our-people/the-

federation-medicine/state-medical-society-websites.page and http://www.osteopathic.org/inside-aoa/about/affiliates/Pages/state-osteopathic-medical-associations.aspx). These additional societies are all engaged in activities, including training, aimed at reducing the misuse and abuse of opioid analgesics and will further reinforce the objectives of ER/LA Opioid Analgesics REMS training by distributing the DPLOB Letter 2 to their members. All letters were sent via USPS. There was one returned letter.

Overall, 326 professional organizations and healthcare professional licensing boards were targeted to receive a version of DPOLB Letter 2, notifying these organizations of the REMS-compliant CME/CE opportunities (Table 31). Of the 326 letters sent, one was returned. The DPOLB Letter 2 sent to the South Dakota Osteopathic Association was returned as undelivered. The REMS Communication Vendor sourced on the internet for an alternate address for this organization and was unable to find one. In addition, the REMS Communication Vendor contacted the organization via phone using a phone number sourced on the internet and received no response.

TABLE 31: DPOLB LETTER 2 COMMUNICATION SUMMARY

COMMUNICATIONS TO PROFESSIONAL ORGANIZATIONS AND LEARNED SOCIETIES	
Targeted Professional Organizations and State Licensing Boards	326
Electronic Notifications Delivered	0
Hardcopy Notifications Sent	326
Total Notifications Sent	**326**
Returned Mail	1
Total Successful Notifications Delivered	**325**

3.5.2.1. Conclusion

The performance goal that DPOLB Letter 2 was to be sent no later than 30 days prior to the start of CME/CE activities was successfully met. Letters were successfully delivered to all but one of the 326 targeted professional organizations and licensing boards.

3.5.3. Patient Counseling Document (PCD)

The PCD on ER/LA Opioid Analgesics is a tool to facilitate important discussions between prescribers and patients for whom an ER/LA opioid analgesic is being prescribed. The PCD contains important safety information about the drug products covered by the REMS. Key messages outlined in the PCD include the importance of taking ER/LA opioid analgesics exactly as prescribed, the need to store ER/LA opioid analgesics safely and securely—out of the reach of children, pets, and household acquaintances—to avoid risks from unintended exposure, the importance of not sharing these medications, even if someone has the same symptoms as the patient, and the proper methods of disposal of unneeded ER/LA opioid analgesics. Additionally, the PCD has been translated into Spanish.

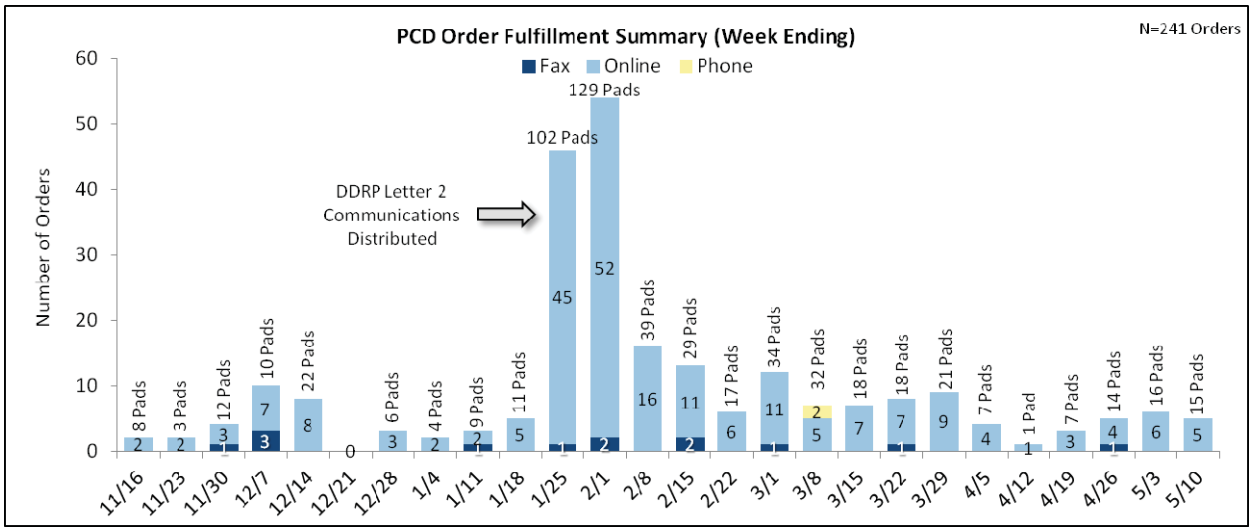
A PDF version of the PCD was posted on the website on July 23, 2012 (website launch). During this reporting period, from November 9, 2012 to May 10, 2013, the PCD has been downloaded 1,920 times. In this same time period, one order for a copy of the PCD was fulfilled by the ER/LA Opioid Analgesics REMS Call Center.

The PCD (Appendix D) was also included as an attachment in DDRP Letter 2 (Appendix B) and DPOLB Letter 2 (Appendix C) communications (electronic and hardcopy) and is provided in the appendix of this report for reference.

As part of the REMS, a portal was designed for prescribers to order copies of the PCD via an online order form or by fax. The fax order form is available on the portal. Larger orders (more than 3 PCD pads) can be requested by phone.

From November 9, 2012 to May 10, 2013, 241 total PCD orders (226 online, 13 fax, 2 phone), equating to 584 pads, were successfully fulfilled. The highest number of requests followed the issuance of the DDRP Letter 2 (Figure 9). The PCD Portal Vendor collects and batches orders for pick-up and packing from inventoried materials once per week on Fridays. Orders received prior to 5:00 p.m. (Central Time) on Thursday ship on the following Friday of each week.

Figure 9: PCD Order Fulfillment through PCD Portal during This Reporting Period, November 10, 2012 – May 10, 2013 (N = 241 Orders)



3.5.3.1. Conclusion

The PCD continues to be readily accessible to all stakeholders through multiple modalities.

3.5.4. REMS Call Center

The ER/LA Opioid Analgesics REMS Program established a centralized Call Center, which became operational on July 23, 2012. The primary purpose of the Call Center is to provide REMS Program support to consumers and HCPs. The Call Center is staffed by qualified and trained Call Center agents.

The Call Center agent responsibilities include, but are not limited to, the following:

- Provide responses to ER/LA Opioid Analgesics REMS-related questions
- Provide a single copy of PCD and any REMS Program Letter (DDRP and DPOLB Letter) upon request
- Provide directions for obtaining ER/LA Opioid Analgesics REMS materials (such as Medication Guides, US Prescribing Information, and PCD Pads (see Section 3.5.3)
- Warm transfer calls when possible, or forward documented reports to the appropriate company if a potential adverse event (AE) or product quality concern is identified or if there is a medical information question
- Assist in navigating the ER/LA Opioid Analgesics REMS website
- Facilitate issue resolution of any reported problems and inquiries not covered by an existing frequently asked question (FAQ)

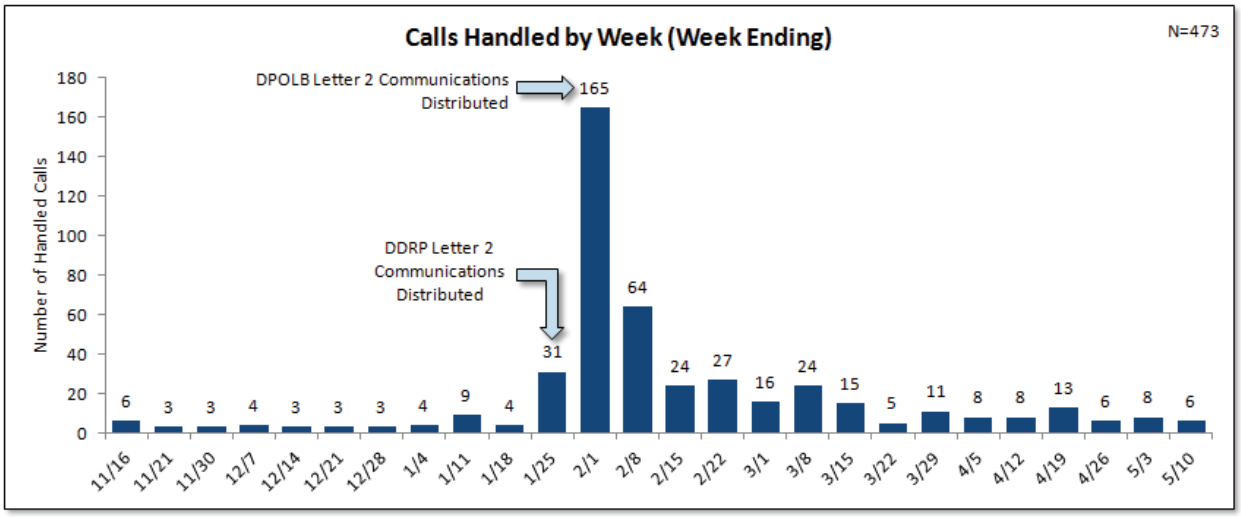
The Call Center has access to all REMS materials and the ER/LA Opioid REMS website. In addition, the Call Center staff has access to a controlled list of FAQs and RPC-approved responses.

The ER/LA Opioid REMS Program Call Center hours of operation are Monday – Friday, 8:00 a.m. to 8:00 p.m. ET. Callers outside of these hours are instructed to leave a message that will be addressed by the Call Center or the appropriate company, if necessary.

Weekly Call Center reports are provided on Friday mornings. As such, the data provided for the Call Center include data one day prior to the 60-day data lock (for this reporting period the data cutoff date was Thursday, May 9, 2013). Since the Six-Month FDA Report 60-day data lock (November 8, 2012), the call center has received a total of 473 calls. The average length of a call is 3:13 minutes.

Figure 10 shows the Call Center weekly call volume. The Call Center volume was highest during the two weeks immediately following mailing of DDRP Letter 2. Excluding the two-week period after the mailings were distributed, the Call Center consistently averages approximately ten calls per week.

Figure 10: Call Center Weekly Call Volume for This Reporting Period, November 9, 2012 – May 9, 2013 (N = 473)



Source: REMS Call Center Summary Report (November 9, 2012 – May 9, 2013)

A report of abandoned calls was assessed to ensure that this was not the cause of the consistently low call volume. During call center business hours, there were a total of 14 abandoned calls in this reporting period.

The primary focus of the shared Call Center is to answer REMS-related questions; however, the RPC instituted multiple processes to handle potential AE and product complaint reports that may be received by the Call Center. From November 9, 2012 – May 9, 2013 there have been two potential AE reports received through the Call Center, which were transferred to the appropriate member company.

TABLE 32: TOP 25 FAQS UTILIZED FROM NOVEMBER 9, 2012 – MAY 9, 2013

FAQ	UTILIZATIONS
Are there mandatory components associated with the REMS program that I must complete (e.g., program enrollment, training), to allow me to continue prescribing ER/LA opioid analgesics to my patients?	206
Where and how is the education/training offered?	67
How are "Prescribers" defined in the ER/LA Opioid Analgesics REMS program?	58
Is it really okay to flush my unused opioid pain medicine down the toilet?	16
What is a REMS program and what is this REMS program?	15
When will this REMS program education/training be available?	9
What pain medicines are included in this REMS program?	9
How many CME/CE credits will a Healthcare Professional receive for completing the REMS education/training and how long will it take to complete?	7
How much will the education/training cost to participate?	7
How can I find out more about the REMS-compliant education/training and when it becomes available?	6
Will pharmacists be required to complete education/training, enrollment, or verification to dispense these opioid analgesic products?	4
What are the components of this REMS program?	4
Are there components of this REMS program that impact inpatient or long-term care pharmacy practice?	3
Did this REMS program impact the Medication Guides?	3
Who is funding the REMS-compliant education/training?	3
Who are you?	3
Are there components of this REMS program that impact outpatient or mail-order pharmacy practice?	2
Is there someone specific to contact if I should have questions about the grant application/process?	2
Where can I go to access additional copies of the Patient Counseling Document (PCD)?	2
What happens if I do NOT participate in REMS-compliant education/training?	2
What extended-release/long-acting (ER/LA) opioid analgesics are involved in this REMS program?	2
What are the goals of this REMS program?	2

TABLE 32: TOP 25 FAQS UTILIZED FROM NOVEMBER 9, 2012 – MAY 9, 2013

FAQ	UTILIZATIONS
Am I required to provide the "Instructions for Use" with the Medication Guide?	2
How can I be sure I complete REMS-compliant education/training and not just any training – is it currently available?	2
What REMS materials are available and how can I access them?	2

Summary of Frequently Asked Questions (FAQs)

A review of the top 25 frequently asked questions (FAQs) available for the Call Center Specialists to answer incoming inquiries revealed that the top three questions received by the Call Center accounted for 60.4% of the questions asked.

- The most frequently asked question (37.6%) was "about completing the CME/CE programs in order to prescribe ER/LA opioids." This most frequently asked question was consistent with the Six-Month FDA Assessment Report.
- The second most frequently asked question (12.2%) concerned "where training programs would be offered."
- The third most frequently asked question (10.6%) was "how prescribers are defined in the ER/LA opioid program."

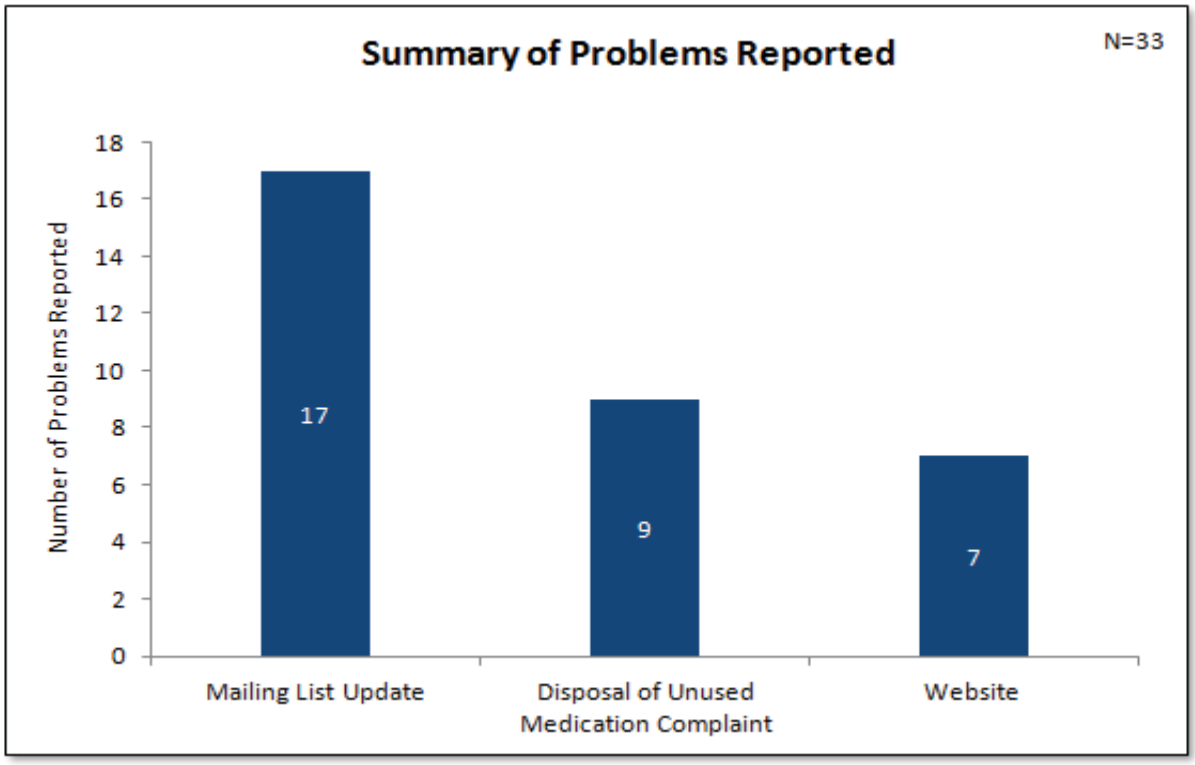
The first and third most asked questions were consistent within the top questions asked in the Six-Month FDA Assessment Report.

Other frequent questions, (total 40 questions or 7.3%) were "disposal of narcotics down the toilet", "what is a REMS program?", and "when will REMS training be available?"

After implementation of the CME/CE activities beginning on February 28, 2013, there was a reduction in the number of questions concerning the grant process and CME/CE Provider questions compared to the number reported in the Six-Month FDA Assessment Report.

Problems Reported and Resolutions

Figure 11: Summary of Problems Reported in This Reporting Period, November 9, 2012 – May 9, 2013 (N = 33)



Source: REMS Assessment Problems Reported (November 9, 2012 – May 9, 2013)

Since November 9, 2012, there were 33 calls that could be classified as "reports of problems." These calls were focused on the following problems:

Mailing List Update

Issue: Mailing List Update

There were 17 requests to have the mailing list updated or corrected. One caller wanted to know why she had not received the mailing as she was a certified prescriber, but refused to provide further information.

Resolution: All appropriate and possible changes to the mailing lists were made by the REMS Communication Vendor.

Disposal of Unused Medication Complaint

Issue: Disposal of unused medication down the toilet complaint

Nine complaints were received regarding the unused medication disposal information stated in the PCD. The statement currently reads: "Do flush unused medication down the toilet"

- Several complainants stated this was against their state law or EPA regulation.
- Complainants did not agree with this statement.

Resolution: The RPC continues to monitor any complaints of this nature. Additionally, an FAQ on this topic has been modified to include consideration of other methods of disposal such as certified drug take-back programs that may be available in the community.

Website

Issue: Malfunction/Access of Website

Seven reports were received that the website malfunctioned. Of these, there was one report of discrepant data between the FDA-approved risk evaluation and mitigation strategies webpage and the ER/LA Opioid Analgesics REMS website, and one report that Internet Explorer 10 is not compatible with viewing the Products page on the ER/LA Opioid Analgesics REMS website.

Resolution: The five website malfunction reports and access issues were resolved with the Website Vendor. The one report of discrepant data was evaluated and it was noted that the product listing on the FDA Website was updated on April 25, 2013; however discrepancies still exist.

The single report regarding Internet Explorer 10 not being compatible was evaluated. At the time of the report, Internet Explorer 10 was used by approximately 1% of visitors to the ER/LA Opioid Analgesics REMS website. When Internet Explorer 10 usage increases to at least 10% of the visitors to the ER/LA Opioid Analgesics REMS website, it will be considered an officially supported browser and any functionality issues will be addressed at that time. Figure 11 depicts the three categories of calls related to reports of problems.

ER/LA Opioid Analgesics REMS Questions versus Product-Specific Questions

Since November 9, 2012, the ER/LA Opioid Analgesics REMS Call Center received a total of 473 calls. Most calls related to one or more already prepared FAQs, with a total of 448 questions asked. There were 427 general REMS-related questions, and 21 product-specific questions. Of the 21 product-specific questions asked, all calls were successfully transferred to the appropriate RPC member company. Two of these calls included questions about potential AEs, which were transferred to the appropriate RPC member companies. There were a small number of calls that were not related to an FAQ or to REMS-related questions (Table 33).

Table 33 shows the number of REMS-related questions received by stakeholder type. Most questions were posed by prescribers and pharmacists. This pattern for prescribers is consistent with the Six-Month FDA Report, whereas the number of pharmacist calls has surpassed the number of CME/CE Stakeholder calls in this report compared with the Six-Month FDA Assessment Report.

TABLE 33: SUMMARY OF GENERAL REMS QUESTIONS AND PRODUCT-SPECIFIC QUESTIONS BY STAKEHOLDERS IN THIS REPORTING PERIOD, NOVEMBER 9, 2012 – MAY 9, 2013

STAKEHOLDER	# GENERAL REMS QUESTIONS N = 427		# PRODUCT-SPECIFIC QUESTIONS N = 21	
	N	%	N	%
Prescriber	322	75.4%	2	9.5%
Pharmacist	28	6.5%	8	38.0%

TABLE 33: SUMMARY OF GENERAL REMS QUESTIONS AND PRODUCT-SPECIFIC QUESTIONS BY STAKEHOLDERS IN THIS REPORTING PERIOD, NOVEMBER 9, 2012 – MAY 9, 2013

STAKEHOLDER	# GENERAL REMS QUESTIONS N = 427		# PRODUCT-SPECIFIC QUESTIONS N = 21	
	N	%	N	%
Patient/Consumer/Caregiver	15	3.5%	10	47.6%
CME/CE Stakeholders[1]	14	3.2%	0	
Distributor	0		0	
All Other Stakeholders[2]	48	11.2%	1	4.7%

[1]Refers to all CME/CE stakeholders (e.g., Accredited CME/CE Provider, Accreditor, Non-Accredited Medical Education Partner, etc.)

[2]Refers to all stakeholders that did not fall into the categories above (e.g., veterinarian, animal control, pharmaceutical representative)

Source: REMS Assessment REMS Questions versus Product-Specific Questions Report (November 9, 2012 – May 9, 2013)

3.5.4.1. Conclusion

The established performance goals regarding the Call Center were that an interim single toll-free number Call Center must be implemented no later than July 23, 2012, and a fully operational centralized Call Center must be implemented no later than 90 calendar days after approval of the REMS (October 21, 2012). The RPC exceeded this goal, as the fully functional centralized Call Center was fully operational as of July 23, 2012.

The data from the Call Center indicate that:

- The total number of calls received has been substantially low (ten calls per week), with peaks only following the dissemination of the DDRP and DPOLB letters.
- Almost all (95.3%) questions received were covered by FAQs that are readily available on the ER/LA Opioid Analgesics REMS website.
- Of the 1.34M prescribers sent the DDRP letter, the Call Center received only 67 inquiries about access to REMS-compliant training.
- As noted from the questions received, the majority of callers are prescribers (72.3%). However, all stakeholders, including patients (5.6%), are able to have their inquiries addressed via RPC member companies' customer service call centers.

3.5.4.2. Call Center Considerations for FDA

As noted in a recent communication to the FDA, the RPC requests that FDA consider removing or revising the requirement for a centralized Call Center. As previously stated in the Six-Month FDA Assessment Report, call volume and content have been reviewed since the inception of the

REMS Call Center. Based on this review, RPC's primary recommendation is decommissioning the Call Center.

The rationale for this request follows:

- On average, the Call Center handles only 10 calls per week (two calls/business day) since the centralized call center has been in place, with the exception of the first two weeks immediately following the mailing of the DDRP and DPOLB letters.
- In the event that a caller needs assistance, the RPC member companies' customer service call centers are well equipped to handle both REMS-related questions and their respective product-specific questions.
- Since the centralized Call Center has been in place, there have been just 21 abandoned calls, and this factor has been eliminated as an explanation for the consistently low call volume.
- The ER/LA Opioid Analgesics REMS website remains the most consistently used and informative element of the REMS, available 24 hours a day and 7 days a week. The website is fully functional and there has been no down-time to date.
- The ER/LA Opioid Analgesics REMS website remains an efficient, effective method of connecting stakeholders to important safety information, REMS communications, FAQs, and CME/CE.
- The ER/LA Opioid Analgesics REMS website contains readily accessible contact information for RPC member companies and links to specific products' prescribing information and Medication Guides.
- Stakeholders may contact the Grants Management Vendor by e-mail via the website for targeted or technical CME/CE questions, and the Grants Management Vendor will respond to questions by e-mail or telephone.
- In addition to the FAQs that were anticipated prior to the website 'go-live' date, the RPC has developed new FAQs, particularly in regard to CME/CE Grants and CME/CE offerings and has enhanced existing FAQs for all stakeholders. The current list of FAQs presented on the website presents a robust amount of information and responds to the common (and not so common) inquiries. The RPC continues to assess and modify FAQs as needed.

3.5.4.3. Alternative Call Center Consideration for FDA

As stated above, the ER/LA Opioid Analgesics REMS website and RPC member companies' customer service call centers provide more than adequate back-up coverage for the centralized Call Center. An alternative to decommissioning the Call Center is to replace the current Call Center structure with an interactive voice mail/message retrieval system.

The rational for this alternative request follows:

- Call volume was highest during the first two weeks immediately following mailing of DDRP and DPOLB letter communications (July 30, 2012 – August 10, 2012 and January 28, 2013 – February 8, 2013) and is consistently low otherwise, averaging 10 calls per week since the centralized Call Center has been in place.
- An interactive system would allow callers to select information based on prompts specific to the stakeholder without any hold time. In addition, the prompts would highlight the most frequently used FAQs as determined by the Call Center data collection to date.
- An interactive system is available 24 hours a day, 7 days a week.
- Messages could be returned by the following business day, and targeted information could be prepared and provided in response to specific questions.
- This interactive system could also direct callers to the website, a comprehensive source of information and an easily accessible point of contact for focused CME/CE questions and links that is also available 24 hours a day, 7 days a week.
- Product-specific questions or potential AE/product complaints could continue to be directed to the appropriate member company for processing.

As stated in a recent communication to the FDA, RPC understands that our request for consideration of decommissioning the Call Center and the alternative proposal requires FDA approval, proper vendor notification, updates to the website, and potential regulatory action.

4. CONCLUSION

The RPC continues to work as a consortium to ensure that the benefits of ER/LA opioid analgesic drug products outweigh their risks. The education of prescribers is a cornerstone of the ER/LA Opioid Analgesics REMS. As frontline stakeholders, prescribers play a unique and essential role in appropriately providing patients essential relief from pain while maintaining a high level of vigilance for such risks as addiction, unintentional overdose, and death. Accordingly, the design and build of the REMS has focused on the education of prescribers; this early period in the REMS has been accomplished through the collective efforts of disparate NDA/ANDA holders, the CME/CE community, professional and patient organizations, and the FDA with mutual focus on the goal of improving public health and patient safety as relates to ER/LA opioid analgesic drug products' availability and use.

This Twelve-Month FDA Report describes major areas of REMS accomplishments that have been completed by the end of the current reporting period (May 10, 2013). One of the significant activities was building the infrastructure to support REMS-compliant CME/CE activities that meet the goal of the FDA Blueprint while maintaining independence from the RPC. The ER/LA Opioid Analgesics REMS represents the first time that certified CME/CE has been used to fulfill a REMS training requirement. A second major accomplishment was the establishment of

comparative data to assess the baseline level of knowledge among ER/LA opioid analgesic prescribers. The results will serve as a benchmark against which prescriber gains in knowledge can be measured after participation in the CME/CE activities.

4.1. Infrastructure Construction and Completion

Preparation for CME/CE activities for REMS-compliant training began in 2010 and was completed by the RPC during this reporting period, achieving the REMS goal of having CME/CE available to ER/LA opioid analgesic prescribers by March 1, 2013. This major accomplishment required significant coordination, collaboration, and agreement among the diverse, independent organizations that are involved in accrediting or delivering CME/CE activities. An important foundation for creating the appropriate infrastructure was the revision of the Medical Education and Metrics Standards (MEMS) to establish a uniform data standard for collection and analysis of CME/CE data. This was accomplished over many months by the MedBiquitous Working Group which included representatives from the CME/CE Accrediting Bodies, National CME/CE Provider Organizations, Professional Societies, MedBiquitous, early REMS CME/CE providers, the FDA, and the RPC. The first REMS-compliant CME/CE program consists of a multi-modal (web-based and live) program which became available on February 28, 2013. Between that time and May 4, 2013, five other REMS-compliant CME/CE activities supported by the RPC have launched.

The availability of the ER/LA Opioid Analgesics REMS-compliant CME/CE opportunities was widely communicated to DEA-registered prescribers. Following in the footsteps of other successful public health initiatives, active communication to the affected community was given top priority. Specifically, letters were successfully delivered to 1,314,968 prescribers, as well as to 40 societies and professional associations, and to 325 Professional Organizations and State Licensing Boards. As a result, despite the substantial time required for an individual prescriber to successfully complete education on the full FDA Blueprint and the knowledge assessment, 1,147 prescribers completed the training in the ten-week time period between the launch of the first CME/CE activity and the end of this reporting period. Most of these prescribers completed the training in person (N = 856, 74.6%), while 291 prescribers (25.3%) completed the training online.

A new RFA was disseminated during this reporting period to further expand the number of CME/CE activities available to prescribers; in this RFA cycle, the RPC partnered with National Provider Organizations and accredited Providers to optimize awareness and increase the number of applications. Grant applications in responses to the RFA are due on July 16, 2013, and will be described in the Two-Year FDA Assessment Report.

4.2. Establishment of Comparative Data

The RPC successfully designed and conducted a Baseline Prescriber Survey (BPS) in this time period to evaluate ER/LA prescribers' understanding of the key risk messages in the FDA Blueprint prior to the widespread availability of the REMS-compliant CME/CE activities. As with most observational studies, high-quality comparator data is of critical importance. These baseline results will be compared with the results of the survey to be administered in 2014 for inclusion in the Four-Year Assessment Report in 2015. Overall the BPS found a high level of knowledge around many of the key risk messages covered in the survey. Lower levels of understanding (< 70%) were found for 21% (N = 11) of questions, primarily as relates to opioid

tolerance and conversion. Data from the BPS will be further analyzed over the coming months to gain further insight.

4.3. Operations

The operational aspects of the ER/LA Opioid Analgesics REMS continued to function effectively during this time period. The Call Center received and handled a small number of calls (with a peak volume around the issuance of the DDRP letter), and FAQs continued to be developed to provide consistent, comprehensive responses. The RPC is requesting FDA consideration of an alternate plan for handling this small volume of requests.

The next Assessment Report will build upon the elements reported on in this report as the number of available REMS-compliant CME/CE activities grows and more prescribers are trained in the important aspects of risk minimization of ER/LA opioid analgesic products.

5. APPENDIX

Appendix A: Glossary

Accredited provider:	An institution or organization that is accredited to provide certified continuing education activities for licensed health care professionals [a]
Ashfield Healthcare	REMS Call Center Vendor
Call Center Subteam	The team responsible for selection and oversight of the vendor operating the centralized Call Center for the ER/LA Opioid Analgesics REMS, including development and ongoing operations.
Cenveo	PCD Portal Vendor
Certified continuing education activity	An educational event or intervention offered by an accredited provider to licensed health care professionals that is based upon identified needs, has a purpose or objectives, and is evaluated to assure the needs are met[a]
CE Outcomes	CE Data Aggregation Reporting Vendor
Continuing Education Subteam	The team responsible for design and implementation of CE activities for the REMS Program (eg, grant management system, review process).
Dentist	Dental public health, endodontics, general dentistry, oral and maxillofacial pathology, oral and maxillofacial radiology, oral and maxillofacial surgery, orthodontics and dentofacial orthopedics, pediatric dentistry, periodontics and prosthodontics[b]
ER/LA opioid prescriber	An individual clinician who is registered with the DEA to prescribe schedule 2 and/or 3 controlled substances and has written at least one ER/LA opioid script in the past year[b]
Extended-Release/Long-Acting (ER/LA) opioid analgesics	Certain opioid drug products indicated for use as analgesics that comprise two distinct subsets – those products that have a duration of action that is inherently, or pharmacologically, longer-acting than most other opioid analgesic drug substances, and those products embodying modified-release formulations that are specifically designed to provide a longer duration of action than immediate-release formulations containing the same opioid drug substances. The long-acting/extended-release opioid analgesics currently include a) extended-release, solid, oral dosage forms containing hydromorphone, morphine, oxycodone, tapentadol, and oxymorphone, plus the fentanyl-containing and buprenorphine-containing transdermal delivery systems (collectively, the modified-release formulations that are pharmaceutically-long-acting opioid analgesics), and b) methadone tablets or liquid, which are not formulated in extended-release dosage forms (collectively, the pharmacologically-long-acting opioid analgesics)[a]
FDA Blueprint	A document entitled, "FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics," approved as

	part of this REMS that contains core messages to be conveyed to prescribers in the training about the risks and appropriate prescribing practices for the safe use of ER/LA opioids[a]
McKesson	REMS Website Vendor
MedBiquitous Consortium	CE Data Collection Standards Vendor
Metrics Subteam	The team responsible for designing and implementing the metrics Assessment Reports in accordance with FDA requirements.
NDA/ANDA holder	A pharmaceutical company that has authorization to market a drug product that is subject to the ER/LA Opioid Analgesics REMS[a]
Non-pain specialist	A specialist or subspecialist that does not specialize in the evaluation and treatment of patient pain[b]
Pain specialist	A specialist whose practice predominately involves the evaluation and treatment of patient pain[b]
PDRN	REMS Communication Vendor
Polaris	GMS Portal Vendor
	CE Data Aggregation System Vendor
Practice type	A description of the clinician's practice by broad category [b]
Prescriber	A licensed healthcare professional that is authorized to write prescriptions for medications or medical devices. Prescribers are required to be registered with the federal Drug Enforcement Administration to write prescriptions for medicines containing controlled substances. In some jurisdictions, a separate registration with a state controlled substances authority is also required for prescribing those medicines.[a]
Prescribers successfully completing	FDA REMS defined ER/LA opioid prescribers that have completed all components of na educational activity and met the education provider's criteria for passing. Components of an education al activity include instruction, assessment of learning, and potentially evaluation[b]
	Profession: Professions inclusive of all those eligible to prescribe ER/LA opioids- physicians, advanced practice nurse, pharmacists, dentist, optometrist, physician assistant, podiatrist, other[b]
Primary care:	A clinician serving as a first contact and providing continuing care to the patient. Primary care clinicians may coordinate specialist care for the patient.[b]
Profession	Professions inclusive of all those eligible to prescribe ER/LA opioids- physicians, advanced practice nurse, pharmacists, dentist, optometrist, physician assistant, podiatrist, other [(b)]
Project Management Office	The hub of the REMS Program execution including: 1) program management for ER/LA Opioid Analgesics REMS Program, 2)

	procurement of suppliers, and 3) implementation and ongoing operational support services for the approved REMS Program.
Related activities	Activity is related to the REMS regulation but does not meet all requirements set out for CE activities by the REMS regulation[c]
REMS Program Companies (RPC)	Companies with approved ANDAs/NDAs for ER/LA opioid analgesics. The RPC is the program's governing body with overall responsibility for supervision and direction of the program.
REMS Program Companies (RPC)	The consortium of NDA/ANDA holders of branded and generic long-acting and extended-release opioid analgesic drug products that was formed for the express purpose of creating a single shared REMS for those products[a]
REMS-compliant training	Training will be considered "REMS-compliant training" if 1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioids ("FDA Blueprint"), 3) it includes a post-course knowledge assessment of all of the sections of the FDA Blueprint, and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met.[a]
UBC:	Baseline Prescriber Survey Vendor Umbrella MetricsVendor
RPC Oversight Committee	An appointed number of RPC member companies selected by the entire RPC responsible for day-to-day operations of the ER/LA Opioid Analgesics REMS.
Schedule 2 and 3 registered prescriber:	An individual clinician who is registered with the DEA to prescribe Schedule 2 and/or 3 controlled substances[b]
Schedule 2 and 3 registered prescribers successfully completing:	Schedule 2 or 3 registered prescribers that have completed all components of an educational activity and met the education provider's criteria for passing. Components of an educational activity include instruction, assessment of learning, and potentially evaluation[b]
Sponsor	A term used by the continuing education community to refer to accredited providers of certified continuing education activities[a]
Successfully completing	Completing all components of an educational activity and meeting the education provider's criteria for passing. Components of an educational activity include instruction, assessment of learning, and potentially evaluation[b]
Technology Subteam	The team responsible for providing oversight and subject-matter expertise on the ER/LA Opioid Analgesics REMS Website and other

Technology Subteam	The team responsible for providing oversight and subject-matter expertise on the ER/LA Opioid Analgesics REMS Website and other technology related items, eg Call Center, metrics database
Title	The title of the CE activity[c]

Sources:

(a) Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Supporting Document

(b) Medical Education Metrics definition- MedBiquitous website http://www.medbiq.org/mems/definitions

(c) Medical Education Metrics Implementation Guidelines for REMS CE Data Exchange 4/26/13

Appendix B: Dear DEA-Registered Prescriber (DDRP) Letter

Subject:	**Availability of Risk Evaluation and Mitigation Strategy (REMS)-compliant training under the REMS for all extended-release/long-acting opioid analgesic drug products.**

FDA-Required REMS Program for Serious Drug Risks

Dear **DEA**-Registered Prescriber:

Extended-release and long-acting (ER/LA) opioid analgesics[1] are approved for the management of chronic moderate-to-severe pain in the U.S., and can be safe and effective in appropriately selected patients when used as directed. However, opioid analgesics are also associated with serious risks and are at the center of a major public health crisis of increased misuse, abuse, addiction, overdose, and death. The U.S. Food and Drug Administration (FDA) determined that a Risk Evaluation and Mitigation Strategy (REMS) was necessary to ensure that the benefits of ER/LA opioid analgesics continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

Several months ago, you received a letter announcing the REMS for all ER/LA opioid analgesic drug products, which explained that the principal components of this REMS are:

a) Prescriber training on all ER/LA opioid analgesics,
b) the *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD), and
c) a unique Medication Guide for each ER/LA opioid analgesic drug product.

REMS-compliant Training Programs

The purpose of this letter is to provide notification of the upcoming availability of REMS-compliant training on ER/LA opioid analgesics – provided at a nominal to no cost to prescribers. REMS-compliant training is a critical component of the ER/LA Opioid Analgesics REMS program and constitutes essential safety education for prescribers. *REMS-compliant training* will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.

REMS-compliant training will focus on the safe prescribing of ER/LA opioid analgesics. The FDA developed core messages to be communicated to prescribers in the FDA Blueprint, which will be used by accredited CE providers to design and deliver REMS-compliant training courses. The FDA Blueprint is available at

http://www fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf

The core messages include:

[1] **The branded and generic drug products subject to this REMS include *all***: a) extended-release, oral-dosage forms containing: hydromorphone, morphine, oxycodone, oxymorphone, or tapentadol; b) fentanyl and buprenorphine-containing transdermal delivery systems; ***and*** c) methadone tablets and solutions that are indicated for use as analgesics.

- Understand how to assess patients and determine which may be appropriate for treatment with ER/LA opioid analgesics.
- Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- Be knowledgeable about how to manage and monitor ongoing therapy with ER/LA opioid analgesics.
- Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

REMS-compliant training for prescribers also includes information on weighing the benefits and risks of opioid therapy and how to recognize evidence of, and the potential for, opioid misuse, abuse, addiction, and overdose. REMS-compliant training may also be offered by academic institutions or learned societies independent of REMS-related funding. We encourage you to successfully complete REMS-compliant training from an accredited CE provider to improve your ability to prescribe these medications more safely.

Prescriber Action

Under the REMS, you are **strongly encouraged** to do **all** of the following:

- **Train (Educate Yourself) -** Complete REMS-compliant training on the ER/LA opioid analgesics offered by an accredited provider of continuing education (CE) for your discipline.

- **Counsel Your Patients –** Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time you prescribe these medicines. Use the enclosed *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD) to facilitate these discussions.

- **Emphasize Patient and Caregiver Understanding of the Medication Guide -** Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as information may have changed.

- **Consider Using Other Tools -** In addition to the PCD, there are other publicly-available tools to improve patient, household, and community safety when using ER/LA opioids, as well as compliance with conditions of treatment, including Patient-Prescriber Agreements (PPAs) and risk assessment instruments.

A listing of REMS-compliant training funded under this REMS appears on www.ER-LA-opioidREMS.com.

The Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics (PCD)

Enclosed with this letter is the Patient Counseling Document that was developed under the REMS for ER/LA opioid analgesics to assist you in having important conversations with patients for whom you select an ER/LA opioid analgesic. It contains important safety information common to the drug products subject to this REMS and includes space for you to write additional information to help your patients use their specific ER/LA

opioid analgesic safely. The PCD should be provided to the patient or their caregiver at the time of prescribing. Patients and their caregivers should be counseled on:

- the importance of taking these medicines exactly as you prescribe them,
- the need to store ER/LA opioid analgesics safely and securely – out of the reach of children, pets, and household members – to avoid risks from unintended exposure,
- the importance of not sharing these medications, even if someone has the same symptoms as the patient, *and*
- the proper methods of disposal of unneeded ER/LA opioid analgesics.

You can re-order or print additional copies of the PCD from www.ER-LA-opioidREMS.com.

Adverse Event Reporting

To report all suspected adverse reactions associated with the use of the ER/LA opioid analgesics, contact:

- the pharmaceutical company that markets the specific product, or
- the FDA MedWatch program:
  - by phone at 1-800-FDA-1088 (1-800-332-1088) or
  - online at www.fda.gov/medwatch/report.htm

More information about this REMS can be obtained at: www.ER-LA-opioidREMS.com or by calling the ER/LA Opioid Analgesic REMS Call Center at 1-800-503-0784.

Sincerely,

The ER/LA Opioid Analgesic Companies

Appendix C: Professional Organization/Licensing Board (POLB) Letter

Subject:	**Availability of Risk Evaluation and Mitigation (REMS)-compliant training under the REMS for all extended-release/long-acting opioid analgesic drug products.**

FDA-Required REMS Program for Serious Drug Risks

Dear **<Professional Organization/Licensing Board>**:

Extended-release and long-acting (ER/LA) opioid analgesics[2] are approved for the management of chronic moderate-to-severe pain in the U.S., and can be safe and effective in appropriately selected patients when used as directed. However, opioid analgesics are also associated with serious risks and are at the center of a major public health crisis of increased misuse, abuse, addiction, overdose, and death. The U.S. Food and Drug Administration (FDA) determined that a Risk Evaluation and Mitigation Strategy (REMS) was necessary to ensure that the benefits of ER/LA opioid analgesics continue to outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

Several months ago, you received a letter announcing the REMS for all ER/LA opioid analgesic drug products, which explained that the principal components of this REMS are:

d) Prescriber training on all ER/LA opioid analgesics,
e) the *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD), and
f) a unique Medication Guide for each ER/LA opioid analgesic drug product.

REMS-compliant Training Programs

The purpose of this letter is to provide notification of the upcoming availability of REMS-compliant training on ER/LA opioid analgesics – provided at a nominal to no cost to prescribers. REMS-compliant training is a critical component of the ER/LA Opioid Analgesics REMS program and constitutes essential safety education for prescribers. *REMS-compliant training* will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.

REMS-compliant training will focus on the safe prescribing of ER/LA opioid analgesics. The FDA developed core messages to be communicated to prescribers in the FDA Blueprint, which will be used by accredited CE providers to design and deliver REMS-compliant training courses. The FDA Blueprint is available at http://www fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf

The core messages include:

[2] **The branded and generic drug products subject to this REMS include *all***: a) extended-release, oral-dosage forms containing: hydromorphone, morphine, oxycodone, oxymorphone, or tapentadol; b) fentanyl and buprenorphine-containing transdermal delivery systems; ***and*** c) methadone tablets and solutions that are indicated for use as analgesics.

- Understand how to assess patients and determine which may be appropriate for treatment with ER/LA opioid analgesics.
- Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
- Be knowledgeable about how to manage and monitor ongoing therapy with ER/LA opioid analgesics.
- Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.
- Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

REMS-compliant training for prescribers also includes information on weighing the benefits and risks of opioid therapy and how to recognize evidence of, and the potential for, opioid misuse, abuse, addiction, and overdose. REMS-compliant training may also be offered by academic institutions or learned societies independent of REMS-related funding. We encourage you to successfully complete REMS-compliant training from an accredited CE provider to improve your ability to prescribe these medications more safely.

Requested Action

We ask you to encourage your <members/licensees> to successfully complete REMS-compliant training to improve their ability to prescribe these medications more safely. Under the REMS, prescribers are **strongly encouraged** to do **all** of the following:

- **Train (Educate Themselves) -** Complete REMS-compliant training offered by an accredited provider of continuing education (CE) for their discipline.

- **Counsel Their Patients –** Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time you prescribe these medicines. Use the enclosed *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD) to facilitate these discussions. Prescribers can re-order or print additional copies of the PCD from www.ER-LA-opioidREMS.com.

- **Emphasize Patient and Caregiver Understanding of the Medication Guide -** Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as information may have changed.

- **Consider Using Other Tools -** In addition to the PCD, there are other publicly-available tools to improve patient, household, and community safety when using ER/LA opioids, as well as compliance with conditions of treatment, including Patient-Prescriber Agreements (PPAs) and risk assessment instruments.

A listing of REMS-compliant training funded under this REMS appears on www.ER-LA-opioidREMS.com.

Adverse Event Reporting

To report all suspected adverse reactions associated with the use of the ER/LA opioid analgesics, contact:

- the pharmaceutical company that markets the specific product, or
- the FDA MedWatch program:
  - by phone at 1-800-FDA-1088 (1-800-332-1088) or
  - online at www.fda.gov/medwatch/report.htm

More information about this REMS can be obtained at: www.ER-LA-opioidREMS.com or by calling the ER/LA Opioid Analgesic REMS Call Center at 1-800-503-0784.

Sincerely,

The ER/LA Opioid Analgesic Companies

Appendix D: Patient Counseling Document

Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics
Patient Name:
The DOs and DON'Ts of Extended-Release / Long - Acting Opioid Analgesics
DO: • Read the **Medication Guide** • Take your medicine exactly as prescribed • Store your medicine away from children and in a safe place • Flush unused medicine down the toilet • Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
Call 911 or your local emergency service right away if: • You take too much medicine • You have trouble breathing, or shortness of breath • A child has taken this medicine
Talk to your healthcare provider: • If the dose you are taking does not control your pain • About any side effects you may be having • About all the medicines you take, including over-the-counter medicines, vitamins, and dietary supplements
DON'T: • **Do not** give your medicine to others • **Do not** take medicine unless it was prescribed for you • **Do not** stop taking your medicine without talking to your healthcare provider • **Do not** break, chew, crush, dissolve, or inject your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider. • **Do not** drink alcohol while taking this medicine
For additional information on your medicine go to: **dailymed.nlm.nih.gov**

Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics
Patient Name:
Patient Specific Information
Take this card with you every time you see your healthcare provider and tell him/her: • Your complete medical and family history, including any history of substance abuse or mental illness • The cause, severity, and nature of your pain • Your treatment goals • All the medicines you take, including over-the-counter (non-prescription) medicines, vitamins, and dietary supplements • Any side effects you may be having **Take your opioid pain medicine exactly as prescribed by your healthcare provider.**

Appendix E: Baseline Prescriber Survey

PROTOCOL TITLE:	**Quantitative Testing of Prescriber Knowledge, Attitudes, and Behavior about Extended-Release (ER) and Long-Acting (LA) Opioid Analgesic Products Safety and Use Information**
SPONSOR:	**REMS Program Companies (RPC)**

VERSION: 5.0

DATE: 06FEB2013

APPROVED:

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LIST OF APPENDICES

1. LIST OF ABBREVIATIONS

CE Continuing	Education
DEA	Drug Enforcement Administration
EDC	Electronic Data Capture
ER Extended-R	elease
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
FPI	Full Prescribing Information
HCP Healthcare	Provider
HIPAA	Health Insurance Portability and Accountability Act
KAB	Knowledge, Attitudes and Behavior
IWG	Industry Working Group
LA Long-Acting	
REMS Risk	Evaluation and Mitigation Strategy
RPA	REMS Program Agreement
RPC	REMS Program Companies
SERP	Safety Event Reporting Plan
UBC	United BioSource Corporation

2. BACKGROUND

Extended-release (ER) and long-acting (LA) opioid analgesic medicines (ER/LA opioid analgesics) containing buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxymorphone, and tapentadol are indicated for the management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The ER/LA opioid analgesics include Avinza®, Butrans®, Dolophine®, Duragesic®, Embeda®, EXALGO®, Kadian®, Methadose™, MS Contin®, Nucynta® ER, Opana® ER, Oxycontin® ER, Palladone®, and generic versions of any of these brands. The manufacturers of these products are members of the REMS Program Companies (RPC).

On April 19, 2011, The Food and Drug Administration (FDA) notified manufacturers of extended release/long acting (ER/LA) opioids that the manufacturers were required to submit a proposal for a class-wide, single shared Risk Evaluation and Mitigation Strategy (REMS) The goal of the REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death. To accomplish this goal, representatives from the manufacturers of ER/LA opioids began working together as the Industry Working Group (IWG) to prepare the REMS proposal for FDA approval and, once approved, to operationalize the REMS program. Since that time, the IWG has signed a REMS Program Agreement (RPA); the collective name for the companies signing this agreement was changed to the RPC. What was originally known as the IWG will be referred to in this document as the RPC. The ER/LA Opioid Analgesics REMS was approved by the FDA on July 9, 2012.

The ER/LA Opioid Analgesic REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), and a Timetable for Submission of Assessments of the REMS. A key REMS component is "REMS-compliant training," which will be provided by accredited continuing education (CE) providers, including all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint").

The FDA Blueprint for Prescriber Education (FDA Blueprint, see Appendix A) describes the knowledge and practice domains that need to be covered by REMS compliant CE activities.

FDA Blueprint consists of the following five domains:

a) how to assess patients for treatment with ER/LA opioids;
b) how and when to initiate therapy, modify dose, and discontinue use of ER/LA opioids;
c) how to manage ongoing therapy with ER/LA opioids;
d) how to counsel patients and caregivers about the safe use of ER/LA opioids, including proper storage and disposal;
e) general and product specific drug information concerning ER/LA opioids;

The FDA-approved plan to evaluate the ER/LA Opioid Analgesics REMS has eight (8) components. One important component of the ER/LA Opioid Analgesics REMS assessment is the conduct of quantitative evaluation surveys to assess prescribers' understanding and

knowledge of the safe use and appropriate prescribing of ER/LA opioid analgesics as described in the ER/LA Opioid Analgesics REMS educational materials, FDA Blueprint, and Full Prescribing Information (FPI) of each product. The evaluation will include a baseline assessment of prescriber understanding of the products' risks prior to the implementation of REMS-compliant CE programs and a follow-up evaluation of prescriber understanding of the products' risks and the REMS program requirements after the introduction of the CE programs. The baseline survey results will be compared to results from the post-REMS prescriber survey in order to assess changes in prescriber knowledge and behavior after the ER/LA Opioid Analgesics REMS implementation. The post-REMS survey may include additional questions about information in the CE material. This protocol will describe the administration of the baseline and post-REMS surveys that will be conducted among active prescribers who prescribed an ER/LA opioid at least once in the year prior to survey administration.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

REMS Assessment Reports will be submitted to the FDA at 6 months and 12 months after the initial approval date of the ER/LA Opioid Analgesics REMS, and annually thereafter. The baseline prescriber survey will be conducted prior to implementation of CE activities, with survey data collection completed by February 28, 2013. CE activities are anticipated to begin in March 1, 2013. A follow-up prescriber survey will be implemented, with results to be reported to the FDA at 3 years after ER/LA Opioid Analgesics REMS approval.

3. OBJECTIVES OF THE EVALUATION SURVEY

The goals of the baseline survey are to estimate, among prescribers who prescribed an ER/LA opioid analgesic, baseline knowledge about prescribing ER/LA opioids and information on their ER/LA opioid prescribing behavior and practice prior to implementation of the REMS program. Some of the particular points this survey will address include prescribers' comprehension of proper patient selection, general ER/LA opioid use, the potential risks associated with use of ER/LA opioid analgesics, dosing and administration requirements, and compliance with counseling patients.

The goals of the post-REMS survey are similar, and will evaluate the change in understanding from the baseline assessment. The post-REMS survey may also include questions derived from the CE material.

The specific objectives for the surveys are as follows:

- To assess the understanding of ER/LA opioid prescribers of the serious risks associated with the use of the ER/LA opioids and how to prescribe ER/LA opioids appropriately, including the five domains of the FDA Blueprint.

- To assess ER/LA opioid prescribers' opioid prescribing behavior and practice, including questions from the five domains from the FDA Blueprint, where applicable and feasible.

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of prescribers around the key information and risk messages communicated through the REMS and outlined in the FDA Blueprint. The survey will also collect data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

4. METHODS

The survey was designed in collaboration between RPC and United BioSource Corporation (UBC) and will be administered by UBC.

4.1 Survey Design

This survey will be conducted among a sample of prescribers identified via the IMS prescription database. Respondents who participate in the first wave of the ER/LA opioid analgesic REMS survey will not be eligible to participate in subsequent survey waves.

The survey will be self-administered online through a secure website. The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes

4.1.1 Qualitative Testing of the Survey

The purpose of qualitative testing is to obtain feedback on the Knowledge, Attitudes, and Behavior (KAB) questionnaire from healthcare providers (HCPs) who have written prescriptions for ER/LA opioid analgesics. Cognitive debriefing interviews will be conducted with HCPs to assess prescriber comprehension and interpretation for a subset of the full Prescriber KAB survey questions, and to identify whether questions or response options might be misunderstood. The research will be qualitative or exploratory in nature to identify themes and concepts in the respondent's "own voice" rather than those imposed by researchers or decision makers. The research will occur in conjunction with protocol and questionnaire submission to the FDA.

A total of twenty-four (24) HCPs will be recruited and scheduled for in-depth telephone interviews, approximately sixty (60) minutes in duration. Prescribers will be recruited using a prescriber list provided by the sponsor, and will represent a mix of medical specialties and practice settings. To participate in the research, HCPs must prescribe ER/LA opioid analgesics to patients. HCPs will receive $200 for their participation in the research, as compensation for their time.

During the one-on-one phone interviews, HCPs will review a sample of the questions and response sets in the draft survey instrument. Feedback will be gathered by asking a series of probing questions designed to evaluate each section of the survey. The feedback collected will

help to identify terms, questions, and topics for clarification and revision based on areas of confusion and miscomprehension of the Prescriber KAB survey.

Findings and recommendations from qualitative research will be included in the first KAB Assessment Report.

4.1.2 Questions on REMS Goals

The KAB questionnaire is made up of multiple-choice, close-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options). These will evaluate current knowledge, attitudes, and behavior regarding the key risk messages.

Questions will be presented in two formats:

- Statements or questions asking the respondent to indicate whether a statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use "yes" or "no" as potential response options); and

- Statements or questions asking the respondent to choose from a defined list of possible statements or answers.

Questionnaires will be analyzed to determine prescriber understanding of each key risk message.

For statements or questions that use "true" or "yes" vs. "false" or "no" response options, the desired response for key risk messages is generally "true" or "yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix B).

Key Risk Message 1: Patients should be assessed for treatment with ER/LA opioid analgesic therapy.		
Question No.	**Question Desired**	**response**
	Please select True, False, or I don't know for each of the following statements about ER/LA opioid analgesics.	
3b	A patient with a history of substance abuse must not be prescribed an ER/LA opioid analgesic.	**FALSE**
4a	After thorough clinical evaluation, it is appropriate for prescribers to refer a patient at high risk for drug abuse to a pain management specialist.	**TRUE**
9	When evaluating patients for treatment with ER/LA opioid analgesics, which of the following are important risks to consider? Please select the one best response.	**ALL OF THE ABOVE**
10	Which of the following are risk factors for opioid abuse? Please select all that apply.	**A personal history of psychiatric disorders** **A personal history of past or current alcohol or drug abuse** **A family history of illicit drug use or alcohol abuse**

Key Risk Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.		
Question No.	**Question Desired**	**response**
	Please select True, False, or I don't know for each of the following statements about ER/LA opioid analgesics.	
3a	For methadone, the peak of respiratory depression can occur later and can persist longer than the analgesic effects.	**TRUE**
3c	Conversion of patients to or from methadone using equianalgesic tables can result in overdose and death.	**TRUE**
5	What is the recommended way to safely convert an opioid-tolerant patient from a parenteral opioid, such as morphine or meperidine, to an oral extended-release opioid, such as oxycodone or oxymorphone? Please select the best response.	**START WITH 50% OF AN EQUIANALGESIC DOSE**
11	Which of the following should prescribers do when initiating a patient on ER/LA opioid analgesics? Please select all that apply.	**Consider a rescue medication for break-through pain** **Titrate doses based on efficacy and tolerability**
22	Which of the following are important factors to consider when selecting an initial dose of an ER/LA opioid analgesic? Please indicate Yes, No, or I don't know for each of the following options.	
22a	The patient's degree of opioid experience	**YES**
22b	Concurrent medication	**YES**
22c	General medical status of the patient	**YES**
22d	The patient's family history of mental illness	**NO**

Key Risk Message 3: Management of ongoing therapy with ER/LA opioid analgesics is important.		
Question No.	**Question Desired**	**response**
	Please select True, False, or I don't know for each of the following statements about ER/LA opioid analgesics.	
4b	It is not necessary to re-evaluate a patient's underlying medical condition if the clinical presentation changes over time.	**FALSE**
14	Please answer True, False, or I don't know for each of the following statements about the use of Patient Prescriber Agreements (PPAs).	
	PPAs are signed by both prescriber and patient at the time an opioid is initially prescribed.	**TRUE**
	PPAs can include information about treatment goals, risks, and safe use of the ER/LA opioid.	**TRUE**
	PPAs are a legal requirement.	**FALSE**
	PPAs may include commitments regarding follow-up visits, monitoring for misuse, and safeguarding the medication.	**TRUE**
16	How should prescribers reassess patients maintained on ER/LA opioid analgesics during follow-up visits? Please answer True, False, or I don't know for each of the following statements.	
16a	Periodically assess the continued need for opioid analgesics	**TRUE**
16b	Perform a comprehensive physical examination at each visit	**FALSE**
16c	Evaluate pain control and functional improvement	**TRUE**
16d	Evaluate for changes in the patient's medical condition	**TRUE**
16e	Systematically perform drug screening for all patients	**FALSE**
26	How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Please select all that apply.	**Document any "drug seeking" behavior** **Utilize state Prescription Drug Monitoring Programs** **Use drug testing for both screening and confirmatory tests** **Periodically re-evaluate therapy** **Perform medication reconciliation by counting leftover drug supplies**

Key Risk Message 4: It is important to counsel patients and caregivers about the safe use of ER/LA opioid analgesics.		
Question No.	**Question Desired**	**response**
	Please select True, False, or I don't know for each of the following statements about ER/LA opioid analgesics.	
4c	ER/LA opioid analgesic transdermal patches that have a matrix formulation may be cut prior to use.	**FALSE**
4d	Chewing a solid, oral dosage form of an ER/LA opioid analgesic can result in rapid release and absorption of a potentially fatal dose of opioid.	**TRUE**
13	Which of the following are the warning signs and symptoms of respiratory depression from ER/LA opioid analgesics? Please select all that apply.	**Reduced urge to breathe** **Decreased rate of respiration** **"Sighing" pattern of breathing** **Profound sedation**
	Please select True, False, or I don't know for each of the following statements about ER/LA opioid analgesics.	
15b	A patient should not cut an extended release tablet in half to reduce the dose.	**TRUE**
19	Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? Please answer Yes, No, or I don't know for each of the following options.	
	Sedative hypnotics	**YES**
	Anxiolytics	**YES**
	Alcohol	**YES**
	Illegal drugs	**YES**
	Caffeine	**NO**
25	When counseling patients about the safe use of ER/LA opioid analgesics, prescribers should inform patients of the following: (please select all that apply):	**The importance of adhering to a dosage regimen as prescribed** **It is illegal to sell or give away ER/LA opioid analgesics**

Key Risk Message 5: Prescribers must be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.		
Question No.	**Question Desired**	**response**
	Please select True, False, or I don't know for each of the following statements about ER/LA opioid analgesics.	
3d	Some opioids can increase the QTc interval.	**TRUE**
6	Patients considered opioid-tolerant are those (please select all that apply):	**Who are taking 25 mcg/hour transdermal fentanyl for at least 7 days** **Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer**
8	Please select True, False, or I don't know for each of the following statements about drug-drug interaction profiles for ER/LA opioid analgesics.	
8a	Central nervous system depressants can have a potentiating effect on the sedation and respiratory depression caused by opioids.	**TRUE**
8b	Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol.	**TRUE**
8c	Monoamine oxidase inhibitors (MAOIs) are the preferred antidepressants for use with ER/LA opioid analgesics.	**FALSE**
8d	Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids.	**TRUE**
23	What should be done if a patient treated with a transdermal opioid develops a high fever? Please select the best response.	**Monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary**
	Please select True, False, or I don't know for each of the following statements about ER/LA opioid analgesics.	
24a	When starting a patient who is currently taking a sedative on an ER/LA opioid analgesic, reduce the dose of one or both.	**TRUE**

Key Risk Message 5: Prescribers must be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.		
24c	Patients who are not opioid tolerant can initiate opioid therapy with any type of ER/LA opioid analgesic.	**FALSE**

4.1.3 Additional Questions

Additional questions will be asked about the requirements of the ER/LA Opioid Analgesics REMS Program and receipt and understanding of the ER/LA opioid analgesics educational materials. Links will be provided in the survey to view an outline of each educational material, including the Medication Guide, Dear DEA-Registered Prescriber Letter, Patient Counseling Document, and the ER/LA REMS Website, as a point of reference for respondents. The text of each document will not be visible. Respondents will be directed to the RPC Call Center telephone number should they have questions about ER/LA opioid analgesics or need copies of any of the materials/documents mentioned in the survey. The survey will also ask questions about prescriber behaviors. Demographic information will be collected at the end of the survey.

4.2 Participant Recruitment

RPC will provide IMS lists of current prescribers for each of the three product formulation categories to be sampled (transdermal patch, methadone, and oral products), in order to assess formulation-specific risk and safe use awareness.

Recruitment for the baseline and post-REMS surveys will be samples of HCPs who have prescribed an ER/LA opioid at least once in the year prior to the survey administration (prescribers for the post-REMS survey will include samples of prescribers who have and have not completed a REMS-compliant CE course). For each survey administration, a UBC statistician will select a random sample from each formulation group stratified by medical specialty (Specialists, General Practice and Primary Care Physicians, and Non-MD Prescribers; detailed definitions are outlined in Section 7.1.1), prescribing level, and geographic regions of the US (based on prescriber location as reported in the IMS lists). Attempts will be made to stratify the sample into three groups based on level of prescribing: top two deciles, middle two deciles, and bottom two deciles for each of the three formulations.

Given an assumed 10% response rate, each sample will include over 2000 prescribers in order to achieve approximately 200 (+/- 50) completed surveys in that category (transdermal, methadone, oral products). Since the samples are not independent, i.e., one prescriber may prescribe all three formulations, the statistician will oversample by 25% in each group. UBC will then match the names in each sample to remove duplicates. The first 2000 names in each group will be invited to participate in the survey. A smaller back-up sample will be selected in a similar manner if additional respondents are required.

The text of the written invitation to prescribers for both the baseline and post-REMS surveys can be found in Appendix C. If the required number of completed surveys is not achieved within the expected timeframe of approximately ten (10) days after the first mailing, a second mail or e-mail invitation will be sent to non-respondents from the original sample with subsequent fax

and/or e-mail follow-up to maximize participation. The distribution within the mailing to the second sample will be adjusted in accordance with the allocation by formulation category and medical specialty in the original sample. If these efforts do not result in the required number of surveys within each category within two to three weeks, then a new sample of prescribers will be randomly selected. Once the required number of prescribers has completed the survey, the remaining prescribers who log onto the UBC Electronic Data Capture (EDC) Survey System will be told that the quota has been reached and thanked for their interest.

All respondents who complete the survey and provide their contact information will be mailed a $125 payment card (honorarium) to thank them for their participation, except for prescribers who practice in Vermont, Massachusetts, or Minnesota. Participants will be informed that prescribers from these states will not receive compensation for their participation. The mailing will include a Thank You Letter, the payment card, a copy of the Select FPI, and a copy of the correct answers to key risk message questions.

4.2.1 Measures to Minimize Bias in the Sample

The sample of healthcare providers who are invited to participate in each of the surveys will be a stratified random sample of all active prescribers who have prescribed an ER/LA opioid at least once in the year prior to survey administration. The sample of participating prescribers will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of prescribers for participation. The number of completed surveys will include 200 +/- 50 respondents in each formulation stratum (transdermal patch, methadone, and oral products), and the overall sample will include Specialists, General Practice and Primary Care Physicians, and Non-MD Prescribers with prescribers invited in proportion to their representation in the overall prescribing population. Where possible, samples will include prescribers from different deciles, as described in Section 4.2; however, no quotas will be established by prescribing level.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the online survey. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 600 healthcare providers who are registered to prescribe Schedule II and III drugs is proposed for the baseline survey. A similar sample size is assumed for the post-REMS survey as well. The size of each of the samples was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*. A sample of 600 completed surveys will allow estimation of the comprehension rate for each risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 600 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Precision of Estimated Rates of Understanding with a Sample Size of 600

(2-sided 95% Confidence Interval)

Estimated Rate	Estimated Confidence Interval	
50% 45.9%		54.1%
55% 50.9%		59.0%
60% 56.0%		63.9%
65% 61.0%		68.8%
70% 66.2%		73.6%
75% 71.3%		78.4%
80% 76.6%		83.1%
85% 81.9%		87.8%
90% 87.3%		92.3%
95% 92.9%		96.6%

5.1.2 Comparison between Two Subgroups in the Survey

A sample size of at least 600 prescribers in each survey will provide a margin of error of 8% or less around an estimated difference of ten or more percentage points between two subgroups at the 95% confidence level, as shown in the bottom two rows of Table 2 below.

Minimum Precision (95% Confidence Limits) Associated with the Percentage Difference between Two Subgroups Answering a Survey Item Correctly in the Survey

Sample Size		Percentage Answering Correctly				
Subgroup 1	Subgroup 2	Subgroup 1	Subgroup 2	Difference in Percentage Answering Correctly	Lower 95% Confidence Limit	Upper 95% Confidence Limit
100	100	50%	55%	5%	-9.8%	19.8%
100	100	50%	60%	10%	-4.7%	24.7%
200	200	50%	55%	5%	-0.53%	15.3%
200	200	50%	60%	10%	-0.02%	20.2%
300	300	50%	55%	5%	-3.3%	13.3%
300	300	50%	60%	10%	1.7%	18.3%

Note: Precision calculated using PASS 2008 software, confidence intervals for two proportions using differences, chi-square (Yates) formula.

Stratum-specific estimates (transdermal patch, methadone, and oral products) will necessarily have lower statistical precision.

5.1.3 Eligibility Criteria

Healthcare providers who prescribe ER/LA opioid analgesics and have prescribed an ER/LA opioid at least once in the year prior to each survey administration are eligible to participate in the survey.

6. SURVEY PROCESS

The surveys will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm prescriber eligibility. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, the respondent is immediately notified with a "thank you" message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

An Internet-based survey system will be used for conducting the KAB surveys. The survey invitation directs the prescriber to a secured website to complete screening questions. The Internet survey will be convenient for respondents since they can complete the questionnaire at any convenient time and location during the specified time period.

The data entry system used for survey administration has been validated and is secure for receiving and storing survey data. An Internet-based data repository will be used to store survey data and other relevant program information. The system is 21 CFR Part 11 and HIPAA compliant. Prescriber-identifying information will be stored separately from survey data.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from each survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. The data from the sample population will be reported using frequency distributions of responses to all questions.

The following will be reported as part of this analysis:

- The number of invitations issued to prescribers
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents who complete the survey

- Representativeness of prescribers based on geography
- Description of survey participants, including:
  - Medical degree of respondent: MD, DO, NP/APN, PA
  - Medical specialty (neurologists, anesthesiologists, rheumatologists, orthopedics, oncologists, hospice/palliative care providers; general practice and primary care physicians)
  - Years of professional experience
  - Geographic region of practice
  - Number of times ER/LA opioid analgesics were prescribed in the last 12 months
  - Types of ER/LA opioid analgesics prescribed (transdermal patch, methadone, and oral products)

7.1.1 Description of Primary Analyses

Primary analyses are done for all key risk messages. The primary analysis for a key risk message evaluates the rate for each correct response to each individual question/item defined by the key risk message. The specific correct response to each question/item is identified in the body of the key risk message table.

Data from the baseline and post-REMS surveys will be used to report:

i. Counts and percentages with 95% CIs of prescribers who understand and/or practice key components comprising each of the five domains outlined in the FDA Blueprint as detailed in Appendix A.

These counts and percentages will be calculated separately:

1. for high and low prescribers of each of the types of ER/LA opioids (i.e., transdermal patches, methadone, oral products);
2. by categories of prescribers (e.g., Physicians; Nurse Practitioners and Advanced Practice Nurses; Physicians' Assistants);
3. by medical specialty (Specialists, General Practice and Primary Care Physicians, and non-MD Prescribers)
4. by prescribers' geographic region;
5. by prescribers' sex.

Counts and percentages will be calculated separately for physicians who are Specialists, General Practice and Primary Care Physicians, and Non-MD Prescribers. Specialty designations (e.g., American Medical Association specialty codes) will be used to distinguish between the Specialist/General Practice and Primary Care Physicians groups. The individual specialty designations for the Specialist group will include: neurologists, anesthesiologists, rheumatologists, orthopedics, oncologists, and hospice and palliative care prescribers. A second

group will be classified as General Practice and Primary Care Physicians. Non-MDs will include nurse practitioners, advanced practice nurses and physicians' assistants.

In the event there are sufficient surveys (at least 20), certain sub-populations may be analyzed. Other exploratory analyses may be performed.

7.1.2 Description of Secondary Analyses

Secondary analyses are done only for those key risk messages that contain multiple questions/items. The secondary analysis entails a frequency distribution of the number of respondents who got 0, 1, etc. correct responses across the total number of items for the given key risk message.

7.1.3 Comparison of Baseline and Post-REMS Survey

The baseline survey results will be compared to results from the post-REMS prescriber survey in order to assess changes in prescriber knowledge and behavior after the ER/LA Opioid Analgesics REMS implementation.

Further details on the analyses of both the baseline and post-REMS surveys are included in the Survey Analysis Plan (SAP).

7.1.4 Analysis Population

The analysis population will be based on eligible prescribers who completed the survey.

8. SAFETY EVENT REPORTING

The term 'Safety Event' is defined as any information reported by a survey respondent that meets the criteria of an Adverse Event, Product Complaint, or Medical Information Requests. While it is not the intention of the survey to solicit information that meets the criteria of a Safety Event, it is possible that a respondent may spontaneously report information that meets these criteria in free text fields of the survey. The questionnaires will be monitored for any comments recorded in the free text fields. Information on all reports that may constitute an adverse event or other safety event will be forwarded to the RPC Call Center as described in the Safety Event Reporting Plan (SERP).

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The EDC system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail the $125 payment card, a Thank You Letter, the correct responses to key risk messages, and the Select FPI after the survey is completed. Respondent contact information is also needed when necessary to comply with a

federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions.

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to prescribe ER/LA opioid analgesics.

Appendix A FDA Blueprint

Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics

Why Prescriber Education is Important

Health care professionals who prescribe extended-release (ER) and long-acting (LA) opioid analgesics (hereafter referred to as ER/LA opioid analgesics) are in a key position to balance the benefits of prescribing ER/LA opioid analgesics to treat pain against the risks of serious adverse outcomes including addiction, unintentional overdose, and death. Opioid misuse and abuse, resulting in injury and death, has emerged as a major public health problem.

- Based on the 2010 National Survey on Drug Use and Health, public health experts estimate more than 35 million Americans age 12 and older used an opioid analgesic for non-medical use some time in their life—an increase from about 30 million in 2002.[1]
- In 2009, there were nearly 343,000 emergency department visits involving nonmedical use of opioid analgesics.[2]
- In 2008, nearly 36,500 Americans died from drug poisonings, and of these, nearly 14,800 deaths involved opioid analgesics.[3]
- Improper use of any opioid can result in serious side effects including overdose and death, and this risk can be greater with ER/LA opioid analgesics.

Appropriate prescribing practices and patient education are important steps to help address this public health problem. Health care professionals who prescribe ER/LA opioid analgesics have a responsibility to help ensure the safe and effective use of these drug products.

The expected results of the prescriber education in this REMS are that the prescribers will:

a. Understand how to assess patients for treatment with ER/LA opioid analgesics.
b. Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.
c. Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics.
d. Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal.

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[1] Substance Abuse and Mental Health Services Administration. 2011. *Results from the 2010 National Survey on Drug Use and Health: Detailed Table*, Table 7.1.a. Rockville, MD. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/tabs/Sect7peTabs1to45.htm#Tab7.1A. Accessed on March 30, 2012.

[2] Substance Abuse and Mental Health Services Administration. 2011. *Drug Abuse Warning Network, 2009: National Estimates of Drug-Related Emergency Department Visits*, Table 19. Rockville, MD. http://www.samhsa.gov/data/2k11/DAWN/2k9DAWNED/HTML/DAWN2k9ED.htm#Tab19. Accessed on March 30, 2012

[3] Warner M, Chen LH, Makuc DM, Anderson RN, and Miniño AM. 2011. Drug Poisoning Deaths in the United States, 1980–2008, in U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, *NCHS Data Brief*, *No 81*. December 2011. Hyattsville, MD. http://www.cdc.gov/nchs/data/databriefs/db81.pdf. Accessed on March 30, 2012.

e. Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics.

I. Assessing Patients for Treatment with ER/LA Opioid Analgesic Therapy

a. Prescribers should consider risks involved with ER/LA opioid analgesics and balance these against potential benefits. Risks include:
   i. Overdose with ER/LA formulations, as most dosage units contain more opioid than immediate-release formulations.
   ii. Abuse by patient or household contacts.
   iii. Misuse and addiction.
   iv. Physical dependence and tolerance.
   v. Interactions with other medications and substances (See table in Section VI for specific information).
   vi. Inadvertent exposure by household contacts, especially children.

b. Prescribers should assess each patient's risk of abuse, including substance use and psychiatric history. Prescribers should:
   i. Obtain a complete history and conduct a complete physical examination, including assessment of family history of substance abuse and psychiatric disorders, as well as special considerations for the elderly and children.
      - A history of substance abuse does not prohibit treatment with ER/LA opioid analgesics but may require additional monitoring and expert consultation.
   ii. Be knowledgeable about risk factors for opioid abuse.
   iii. Understand and appropriately use screening tools for addiction or abuse to help assess potential risks associated with chronic opioid therapy and to help manage patients using ER/LA opioid analgesics (e.g., structured interview tools).
   iv. Adequately document all patient interactions and treatment plans.

c. Prescribers should understand when to appropriately refer high risk patients to pain management specialists.

d. Prescribers should understand opioid tolerance criteria as defined in the product labeling.
   - Prescribers should know which products and which doses are indicated for use only in opioid tolerant patients. (See table in Section VI for specific information).

II. Initiating Therapy, Modifying Dosing, and Discontinuing Use of ER/LA Opioid Analgesics

a. Prescribers should have awareness of federal and state regulations on opioid prescribing.

b. Prescribers should be aware that:
   i. Dose selection is critical, particularly when initiating therapy in opioid non-tolerant patients.
   ii. Some ER/LA opioid analgesics are only appropriate for opioid-tolerant patients.
   iii. Dosage should be individualized in every case.
   iv. Titration should be based on efficacy and tolerability.

c. Prescribers should be knowledgeable about when and how to supplement pain management with immediate-release analgesics, opioids and non-opioids.

d. Prescribers should be knowledgeable about converting patients from immediate-release to

ER/LA opioid products and from one ER/LA opioid product to another ER/LA opioid product.

e. Prescribers should understand the concept of incomplete cross-tolerance when converting patients from one opioid to another.
f. Prescribers should understand the concepts and limitations of equianalgesic dosing and follow patients closely during all periods of dose adjustments.
g. Prescribers should understand the warning signs and symptoms of significant respiratory depression from opioids.
h. Prescribers should understand that tapering the opioid dose is necessary to safely discontinue treatment with ER/LA opioid analgesics when therapy is no longer needed.

III. Managing Therapy with ER/LA Opioid Analgesics

a. Prescribers should establish analgesic and functional goals for therapy and periodically evaluate pain control, functional outcomes, side-effect frequency and intensity, and health-related quality of life.
b. Prescribers should be aware of the existence of Patient Prescriber Agreements (PPAs).
    i. PPAs are documents signed by both prescriber and patient at the time an opioid is prescribed.
    ii. PPAs can help ensure patients and caregivers understand the goals of treatment, the risks, and how to use the medications safely.
    iii. PPAs can include commitments to return for follow-up visits, to comply with appropriate monitoring (such as random drug testing), and to safeguard the medication.
c. Prescribers should monitor patient adherence to the treatment plan, especially with regard to misuse and abuse by:
    i. Recognizing, documenting, and addressing aberrant drug-related behavior.
    ii. Utilizing state Prescription Drug Monitoring Programs, where practical, to identify behaviors that may represent abuse.
    iii. Understanding the utility and interpretation of drug testing (e.g., screening and confirmatory tests), and using it as indicated.
    iv. Screening and referring for substance abuse treatment as indicated.
    v. Performing medication reconciliation as indicated.
d. Prescribers should understand how to anticipate and manage adverse events associated with ER/LA opioid analgesics.
e. Prescribers treating patients with ER/LA opioid analgesics should periodically assess benefits and side effects of these drugs, and the continued need for opioid analgesics.
f. Prescribers should understand the need for reevaluation of patient's underlying medical condition if the clinical presentation changes over time.
g. Prescribers should be familiar with referral sources for the treatment of abuse or addiction that may arise from the use of ER/LA opioid analgesics.

IV. Counseling Patients and Caregivers about the Safe Use of ER/LA Opioid Analgesics

a. Prescribers should use the Patient Counseling Document as part of the discussion when prescribing opioid analgesics.
b. Prescribers should explain product-specific information about the prescribed ER/LA opioid analgesic.
c. Prescribers should explain how to take the ER/LA opioid analgesic as prescribed.
d. Prescribers should explain the importance of adherence to dosing regimen, how to handle missed doses, and to contact their prescriber should pain not be controlled.
e. Prescribers should inform patients and caregivers to read the specific ER/LA opioid analgesic Medication Guide they receive from the pharmacy.
f. Prescribers should warn patients that under no circumstances should an oral ER/LA opioid analgesic be broken, chewed or crushed, and patches should not be cut or torn prior to use, as this may lead to rapid release of the ER/LA opioid analgesic causing overdose and death. When a patient cannot swallow a capsule whole, prescribers should refer to the product labeling to determine if it is appropriate to sprinkle the contents of a capsule on applesauce or administer via a feeding tube.
g. Prescribers should caution patients that the use of other CNS depressants such as sedative-hypnotics and anxiolytics, alcohol, or illegal drugs with ER/LA opioid analgesics can cause overdose and death. Patients should be instructed to only use other CNS depressants, including other opioids, under the instruction of their prescriber.
h. Prescribers should instruct patients to tell all of their doctors about all medications they are taking.
i. Prescribers should warn patients not to abruptly discontinue or reduce their ER/LA opioid analgesic and discuss how to safely taper the dose when discontinuing.
j. Prescribers should caution patients that ER/LA opioid analgesics can cause serious side effects that can lead to death. Prescribers should counsel patients and caregivers on the risk factors, signs, and symptoms of overdose and opioid-induced respiratory depression, gastrointestinal obstruction, and allergic reactions.
k. Prescribers should counsel patients and caregivers on the most common side effects of ER/LA opioid analgesics, and about the risk of falls, working with heavy machinery, and driving.
l. Patients should call their prescriber for information about managing side effects.
m. Prescribers should explain that sharing ER/LA opioid analgesics with others may cause them to have serious side effects including death, and that selling or giving away ER/LA opioid analgesics is against the law.
n. Prescribers should counsel patients to store their ER/LA opioid analgesic in a safe and secure place away from children, family members, household visitors, and pets.
o. Prescribers should warn patients that ER/LA opioid analgesics must be protected from theft.
p. Prescribers should counsel patients to dispose of any ER/LA opioid analgesics when no longer needed and to read the product-specific disposal information included with the ER/LA opioid analgesic product.
q. Prescribers should counsel patients and caregivers to inform them about side effects.

r. Adverse events should be reported to the FDA at 1-800-FDA-1088 or via http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082725.pdf.

V. General Drug Information for ER/LA Opioid Analgesic Products

Prescribers should be knowledgeable about general characteristics, toxicities, and drug interactions for ER/LA opioid analgesic products. For example,

a. ER/LA opioid analgesic products are scheduled under the Controlled Substances Act and can be misused and abused.
b. Respiratory depression is the most important serious adverse effect of opioids as it can be immediately life-threatening.
c. Constipation is the most common long-term side effect and should be anticipated.
d. Drug-drug interaction profiles vary among the products. Knowledge of particular opioid-drug interactions, and the underlying pharmacokinetic and pharmacodynamic mechanisms, allows for the safer administration of opioid analgesics.
    i. Central nervous system depressants (alcohol, sedatives, hypnotics, tranquilizers, tricyclic antidepressants) can have a potentiating effect on the sedation and respiratory depression caused by opioids.
    ii. Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol. Some drug levels may increase without dose dumping when exposed to alcohol. See individual product labeling.
    iii. Using opioids with monoamine oxidase inhibitors (MAOIs) may result in possible increase in respiratory depression. Using certain opioids with MAOIs may cause serotonin syndrome.
    iv. Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone (ADH).
    v. Some opioids (methadone, buprenorphine) can prolong the QTc interval.
    vi. Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids. (See table in Section VI for specific information).

e. Tolerance to sedating and respiratory-depressant effects of opioids is critical to the safe use of certain products, certain dosage unit strengths, or certain doses of some products.
    i. Patients must be opioid tolerant before using any strength of
        - Transdermal fentanyl, or
        - ER hydromorphone.
    ii. For other ER products, patients must be opioid tolerant before using
        - Certain strengths, or
        - Certain daily doses.
    iii. See table in Section VI for specific information.
f. ER/LA opioid analgesic tablets must be swallowed whole. ER/LA opioid analgesic capsules should be swallowed intact or when necessary, the pellets from some capsules can be sprinkled on applesauce and swallowed without chewing.
g. For transdermal products, external heat, fever, and exertion can increase absorption of the

opioid, leading to fatal overdose. Transdermal products with metal foil backings are not safe for use in MRIs.

VI. Specific Drug Information for ER/LA Opioid Analgesic Products

Prescribers should be knowledgeable about specific characteristics of the ER/LA opioid analgesic products they prescribe, including the drug substance, formulation, strength, dosing interval, key instructions, specific information about conversion between products where available, specific drug interactions, use in opioid-tolerant patients, product-specific safety concerns, and relative potency to morphine. The attached table is a reference. For detailed information, prescribers can refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Avinza (morphine sulfate ER capsules) **Butrans** (buprenorphine transdermal system) **Dolophine** (methadone HCl tablets) **Duragesic** (fentanyl transdermal system) **Embeda** (morphine sulfate ER-naltrexone capsules) **Exalgo** (hydromorphone HCl ER tablets) **Kadian** (morphine sulfate ER capsules) **MS Contin** (morphine sulfate CR tablets) **Nucynta ER** (tapentadol HCl ER tablets) **Opana ER** (oxymorphone HCl ER tablets) **OxyContin** (oxycodone HCl CR tablets)	
Dosing Interval	▪ Refer to individual product information.
Key Instructions	▪ Individually titrate to a dose that provides adequate analgesia and minimizes adverse reactions. ▪ The times required to reach steady-state plasma concentrations are product specific; refer to product information for titration interval. ▪ Continually reevaluate to assess the maintenance of pain control and the emergence of adverse reactions. ▪ During chronic therapy, especially for non-cancer-related pain, periodically reassess the continued need for opioids. ▪ If pain increases, attempt to identify the source, while adjusting the dose. ▪ When an ER/LA opioid analgesic is no longer required, gradually titrate downward to prevent signs and symptoms of withdrawal in the physically-dependent patient. **Do not abruptly discontinue these products.** ▪ Limitations of usage: • Not for use as an as-needed analgesic. • Not for mild pain or pain not expected to persist for an extended duration. • Not for use in treating acute pain. ▪ Solid oral dosage forms: • Swallow tablets and capsules whole: crushing, chewing, breaking, cutting or dissolving may result in rapid release and absorption of a potentially fatal dose of opioid.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	• Some capsules can be opened and pellets sprinkled on applesauce for patients who can reliably swallow without chewing and used immediately. See individual product information. • Exposure of some products to alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of opioid. • Dispose of unused product by flushing down the toilet. ▪ Transdermal dosage forms: • Avoid exposure to external heat. Patients with fever must be monitored for signs or symptoms of increased opioid exposure. • Location of application must be rotated. • Prepare skin by clipping, not shaving hair, and washing area only with water. ▪ See individual product information for the following: • Dosage reduction for hepatic or renal impairment.
Drug Interactions Common to the Class	▪ Concurrent use with other central nervous system depressants (sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, other tranquilizers, and alcohol) can increase the risk of respiratory depression, hypotension, profound sedation, or coma. Reduce the initial dose of one or both agents. ▪ Partial agonists and mixed agonist/antagonist analgesics (i.e., buprenorphine, pentazocine, nalbuphine and butorphanol) may reduce the analgesic effect or precipitate withdrawal symptoms. Avoid concurrent use. ▪ Opioids may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiration depression. ▪ Concurrent use with anticholinergic medication increases the risk of urinary retention and severe constipation, which may lead to paralytic ileus.
Use in Opioid-Tolerant Patients	▪ See individual product information for which products: • Have strengths or total daily doses only for use in opioid-tolerant patients. • Are only for use in opioid-tolerant patients at all strengths.
Contraindications	▪ Significant respiratory depression ▪ Acute or severe asthma in an unmonitored setting or in the absence of resuscitative equipment ▪ Known or suspected paralytic ileus ▪ Hypersensitivity (e.g., anaphylaxis) See individual product information for additional contraindications.
Relative Potency To	▪ **These are intended as general guides.** ▪ Follow conversion instructions in individual product information.

Drug Information Common to the Class of Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Oral Morphine	▪ Incomplete cross-tolerance and inter-patient variability require the use of conservative dosing when converting from one opioid to another - halve the calculated comparable dose and titrate the new opioid as needed.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Avinza	Morphine Sulfate ER Capsules, 30 mg, 45 mg, 60 mg, 75 mg, 90 mg, and 120 mg
Dosing Interval	Once a day
Key Instructions	▪ Initial dose in opioid non-tolerant patients is 30 mg. ▪ Titrate using a minimum of 3-day intervals. ▪ Swallow capsule whole (do not chew, crush, or dissolve). ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing; use immediately. ▪ Maximum daily dose: 1600 mg due to risk of serious renal toxicity by excipient, fumaric acid.
Specific Drug Interactions	▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	90 mg and 120 mg capsules are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Butrans	Buprenorphine Transdermal System, 5 mcg/hr, 10 mcg/hr, 20 mcg/hr
Dosing Interval	One transdermal system every 7 days
• Key Instructions	▪ Initial dose in opioid non-tolerant patients when converting from less than 30 mg morphine equivalents, and in mild to moderate hepatic impairment - 5 mcg/hr dose. ▪ When converting from 30 mg to 80 mg morphine equivalents -

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	first taper to 30 mg morphine equivalent, then initiate with 10 mcg/hr dose. ▪ Titrate after a minimum of 72 hours prior to dose adjustment. ▪ Maximum dose: 20 mcg/hr due to risk of QTc prolongation. ▪ Application • Apply only to sites indicated in the Full Prescribing Information. • Apply to intact/non-irritated skin. • Skin may be prepped by clipping hair, washing site with water only • Rotate site of application a minimum of 3 weeks before reapplying to the same site. • Do not cut. ▪ Avoid exposure to heat. ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet.
• Specific Drug Interactions	▪ CYP3A4 Inhibitors may increase buprenorphine levels. ▪ CYP3A4 Inducers may decrease buprenorphine levels. ▪ Benzodiazepines may increase respiratory depression. ▪ Class IA and III antiarrythmics, other potentially arrhythmogenic agents, may increase risk for QTc prolongation and torsade de pointe.
• Use in Opioid-Tolerant Patients	• Butrans 10 m cg/hr and 20 m cg/hr transdermal systems are for use in opioid-tolerant patients only.
• Drug-Specific Safety Concerns	▪ QTc prolongation and torsade de pointe. ▪ Hepatotoxicity ▪ Application site skin reactions
• Relative Po tency To Oral Morphine	• Equipotency to oral morphine has not been established.
Dolophine	Methadone Hydrochloride Tablets, 5 mg and 10 mg
Dosing Interval	Every 8 to 12 hours
Key Instructions	▪ Initial dose in opioid non-tolerant patients: 2.5 to 10 mg ▪ Conversion of opioid-tolerant patients using equianalgesic tables can result in overdose and death. Use low doses according to the table in the full prescribing information. ▪ High inter-patient variability in absorption, metabolism, and

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	relative analgesic potency. ▪ Opioid detoxification or maintenance treatment shall only be provided in a federally certified opioid (addiction) treatment program (Code of Federal Regulations, Title 42, Sec 8).
Specific Drug Interactions	▪ Pharmacokinetic drug-drug interactions with methadone are complex. ▪ CYP 450 inducers may increase methadone levels. ▪ CYP 450 inhibitors may decrease methadone levels. ▪ Anti-retroviral agents have mixed effects on methadone levels. ▪ Potentially arrhythmogenic agents may increase risk for QTc prolongation and torsade de pointe. ▪ Benzodiazepines may increase respiratory depression
Use in Opioid-Tolerant Patients	Refer to full prescribing information.
Product-Specific Safety Concerns	▪ QTc prolongation and torsade de pointe. ▪ Peak respiratory depression occurs later and persists longer than analgesic effect. ▪ Clearance may increase during pregnancy. ▪ False positive urine drug screens possible.
Relative Potency To Oral Morphine	Varies depending on patient's prior opioid experience.
Duragesic	Fentanyl Transdermal System, 12, 25, 50, 75, and 100 mcg/hr
Dosing Interval	Every 72 hours (3 days)
Key Instructions	▪ Use product specific information for dose conversion from prior opioid ▪ Use 50% of the dose in mild or moderate hepatic or renal impairment, avoid use in severe hepatic or renal impairment ▪ Application • Apply to intact/non-irritated/non-irradiated skin on a flat surface. • Skin may be prepped by clipping hair, washing site with water only • Rotate site of application. • Titrate using no less than 72 hour intervals. • Do not cut. ▪ Avoid exposure to heat.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	▪ Avoid accidental contact when holding or caring for children. ▪ Dispose of used/unused patches by folding the adhesive side together and flushing down the toilet. **Specific contraindications:** ▪ Patients who are not opioid-tolerant. ▪ Management of acute or interm ittent pain, or in patients who require opioid analgesia for a short period of time. ▪ Management of post-operative pain, including use after out-patient or day surgery. ▪ Management of mild pain.
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase fentanyl exposure. ▪ CYP3A4 inducers may decrease fentanyl exposure.
Use in Opioid-Tolerant Patients	All doses of Duragesic are indicated for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	▪ Accidental exposure due to secondary exposure to unwashed/unclothed application site. ▪ Increased drug exposure with increased core body temperature or fever. ▪ Bradycardia ▪ Application site skin reactions
Relative Potency To Oral Morphine	See individual product information for conversion recommendations from prior opioid
Embeda	Morphine Sulfate ER-Naltrexone Capsules, 20 mg/0.8 mg, 30 mg/1.2 mg, 50 mg/2 mg, 60 mg/2.4 mg, 80 mg/3.2 mg, 100 mg/4 mg
Dosing Interval	Once a day or every 12 hours
Key Instructions	▪ Initial dose as first opioid: 20 mg/0.8 mg. ▪ Titrate using a minimum of 3-day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve) ▪ Crushing or chewing will release morphine, possibly resulting in fatal overdose, and naltrexone, possibly resulting in withdrawal symptoms. ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Specific Drug Interactions	▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Embeda 100 mg/4 mg capsule is for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Exalgo	Hydromorphone Hydrochloride Extended-Release Tablets, 8 mg, 12 mg or 16 mg
Dosing Interval	Once a day
Key Instructions	▪ Use the conversion ratios in the individual product information. ▪ Start patients with moderate hepatic impairment on 25% dose that would be prescribed for a patient with normal hepatic function. ▪ Start patients with moderate renal impairment on 50%, and patients with severe renal impairment on 25% of the dose that would be prescribed for a patient with normal renal function. ▪ Titrate using a minimum of 3 to 4 day intervals. ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Do not use in patients with sulfa allergy—contains sodium metabisulfite.
Specific Drug Interactions	None
Use in Opioid-Tolerant Patients	All doses of Exalgo are indicated for opioid-tolerant patients only.
Drug-Specific Adverse Reactions	Allergic manifestations to sulfa component.
Relative Potency To Oral Morphine	Approximately 5:1 oral morphine to hydromorphone oral dose ratio, use conversion recommendations in the individual product information.
Kadian	Morphine Sulfate

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
	Extended-Release Capsules, 10 mg, 20mg, 30 mg, 50 mg, 60 mg, 80 mg, 100 mg, and 200 mg
Dosing Interval	Once a day or every 12 hours
Key Instructions	▪ Product information recommends not using as first opioid. ▪ Titrate using a minimum of 2-day intervals. ▪ Swallow capsules whole (do not chew, crush, or dissolve). ▪ May open capsule and sprinkle pellets on applesauce for patients who can reliably swallow without chewing, use immediately.
Specific Drug Interactions	▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of morphine. ▪ PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	Kadian 100 mg and 200 mg capsules are for use in opioid-tolerant patients.
Product-Specific Safety Concerns	None
MS Contin	Morphine Sulfate Controlled-release Tablets, 15 mg, 30 mg, 60 mg, 100 mg, and 200 mg
Dosing Interval	Every 8 hours or every 12 hours
Key Instructions	▪ Product information recommends not using as first opioid. ▪ Titrate using a minimum of 2-day intervals. ▪ Swallow tablets whole (do not chew, crush, or dissolve).
Specific Drug Interactions	PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two-fold.
Use in Opioid-Tolerant Patients	MS Contin 100 mg and 200 mg tablet strengths are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	None
Nucynta ER	Tapentadol Extended-Release Tablets, 50 mg, 100mg, 150 mg, 200 mg, and 250 mg

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Dosing Interval	Every 12 hours
Key Instructions	▪ Use 50 mg every 12 hours as initial dose in opioid nontolerant patients ▪ Titrate by 50 mg increments using a minimum of 3-day intervals. ▪ Maximum total daily dose is 500 mg ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Take one tablet at a time and with enough water to ensure complete swallowing immediately after placing in the mouth. ▪ Dose once daily in moderate hepatic impairment with 100 mg per day maximum ▪ Avoid use in severe hepatic and renal impairment.
Specific Drug Interactions	▪ Alcoholic beverages or medications containing alcohol may result in the rapid release and absorption of a potentially fatal dose of tapentadol. ▪ Contraindicated in patients taking MAOIs.
Use in Opioid-Tolerant Patients	No product-specific considerations.
Product-Specific Safety Concerns	▪ Risk of serotonin syndrome ▪ Angioedema
Relative Potency To Oral Morphine	Equipotency to oral morphine has not been established.
Opana ER	Oxymorphone Hydrochloride ER Tablets, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, 30 mg, and 40 mg
Dosing Interval	Every 12h dosing, some may benefit from asymmetric (different dose given in AM than in PM) dosing.
Key Instructions	▪ Use 5 mg every 12 hours as initial dose in opioid non-tolerant patients and patients with mild hepatic impairment and renal impairment (creatinine clearance < 50 mL/min) and patients over 65 years of age ▪ Swallow tablets whole (do not chew, crush, or dissolve). ▪ Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth. ▪ Titrate using a minimum of 2-day intervals. ▪ Contraindicated in moderate and severe hepatic impairment.
Specific Drug	▪ Alcoholic beverages or medications containing alcohol may result in the absorption of a potentially fatal dose of oxymorphone.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Interactions	
Use in Opioid-Tolerant Patients	No product specific considerations.
Product-Specific Safety Concerns	None
Relative Potency To Oral Morphine	Approximately 3:1 oral morphine to oxymorphone oral dose ratio
OxyContin	▪ Oxycodone Hydrochloride ▪ Controlled-release Tablets, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
Dosing Interval	▪ Every 12 hours
Key Instructions	▪ Opioid-naïve patients: initiate treatment with 10 mg every 12 hours. ▪ Titrate using a minimum of 1 to 2 day intervals. ▪ Hepatic impairment: start with one third to one half the usual dosage ▪ Renal impairment (creatinine clearance <60 mL/min): start with one half the usual dosage. ▪ Consider use of other analgesics in patients who have difficulty swallowing or have underlying GI disorders that may predispose them to obstruction. Swallow tablets whole (do not chew, crush, or dissolve). ▪ Take one tablet at a time, with enough water to ensure complete swallowing immediately after placing in the mouth.
Specific Drug Interactions	▪ CYP3A4 inhibitors may increase oxycodone exposure. ▪ CYP3A4 inducers may decrease oxycodone exposure.
Use in Opioid-Tolerant Patients	▪ Single dose greater than 40 mg or total daily dose greater than 80 mg are for use in opioid-tolerant patients only.
Product-Specific Safety Concerns	▪ Choking, gagging, regurgitation, tablets stuck in the throat, difficulty swallowing the tablet. ▪ Contraindicated in patients with gastrointestinal obstruction.

Specific Drug Information for Extended-Release and Long-Acting Opioid Analgesics (ER/LA opioid analgesics)	
Relative Potency To Oral Morphine	Approximately 2:1 oral morphine to oxycodone oral dose ratio.
For detailed information, refer to prescribing information available online via DailyMed at www.dailymed.nlm.nih.gov or Drugs@FDA at www.fda.gov/drugsatfda.	

Appendix B Prescriber Questionnaire

Survey Legend

[PROGRAMMER] is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

[BEGIN ONLINE SURVEY CONTENT] and **[END SURVEY CONTENT]** are used to indicate to the programmer the beginning and end of the survey..

[TERMINATE] is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey unless different language is specified with the question.

> *Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.*

[RANDOMIZE LIST] is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as "I don't know," "Prefer not to answer" or "None of the above" will always appear at the end of the randomized responses.

[GO TO Qx] (Skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

[MULTILINE INPUT] indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines or a free-text response).

Survey Legend

[DROP-DOWN LIST INPUT WITH STATES TABLE] indicates to the programmer that the response should be a drop-down list containing the States and US territories in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

The following is used to categorize survey populations into standard geographic regions for the analysis, but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, East, Central, South, West and Other regions

Northeast includes CT, DC, MA, ME, MD, NH, RI, and VT. East includes DE, NJ, NY, and PA. Central includes AR, IA, IN, IL, KS, KY, MI, MN, MO, ND, NE, OH, OK, SD, TN, WI, and WV. South includes AL, FL, GA, LA, MS, NC, SC, TX, and VA. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes American Samoa, Guam, Northern Mariana Islands, Puerto Rico, and US Virgin Islands.

[BEGIN ONLINE SURVEY CONTENT]

[PREAMBLE 1]

Before you begin, we would like to share some important information about this research survey. The manufacturers of Extended Release (ER) and Long-Acting (LA) opioid analgesic medicines (ER/LA opioid analgesics) are conducting this survey, as required by the FDA, to assess prescribers' understanding of the safe use and prescribing of these medicines. The ER/LA opioid analgesics include Avinza®, Butrans®, Dolophine®, Duragesic®, Embeda®, EXALGO®, Kadian®, Methadose™, MS Contin®, Nucynta® ER, Opana® ER, Oxycontin® ER, Palladone®, and generic versions of any of these brands. You were invited to participate in this survey because you are a healthcare provider who may have prescribed one or more of these medicines. The manufacturers of these medicines are Apotex Inc., Endo Pharmaceuticals, Inc., Impax, Janssen Pharmaceuticals Inc., Mallinckrodt Inc. (a Covidien Company), Mylan Technologies Inc., Noven Pharmaceuticals Inc., Par Pharmaceuticals, Pfizer Inc, Purdue Pharma L.P., Ranbaxy Pharmaceuticals Inc., Rhodes Pharmaceuticals L.P., Roxane Laboratories, Inc., Sandoz Inc., The PharmaNetwork LLC, VistaPharm Inc., and Watson Laboratories Inc. The survey will take approximately 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to prescribe ER/LA opioid analgesics.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other healthcare professionals taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of ER/LA opioid analgesics. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $125 payment card for your time and participation. This compensation represents the fair market value for your services in connection with completion of the survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you.

Your name and address will be used to send you the payment card after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation. Physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

Providing a telephone number is optional. Your phone number will be used only if there are any questions about your survey responses.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of ER/LA opioid analgesics nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your personal information will not be used in a manner inconsistent with this document. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of ER/LA opioid analgesics to use your information is entirely voluntary but necessary to take part in this survey.

How to Learn More about This Survey

If you have questions about the survey, or problems with the survey, please call the Survey Coordinating Center at 1-800-497-9511. Be sure to write down this telephone number; it will not be displayed again.

If you have questions or concerns about your rights as a survey participant, or to offer your input, you may contact E&I toll free at 1-800-472-3241.

Taking the Survey

Once you have answered a question and moved on, you cannot go back and change your answer.

Thank you for your participation in this survey.

[END PREAMBLE 1]

[BEGIN ELIGIBILITY QUESTIONS]

1. Do you agree to participate in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

1a. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

   - ○ Apotex Inc. **[TERMINATE]**
   - ○ Endo Pharmaceuticals, Inc.**[TERMINATE]**
   - ○ Impax **[TERMINATE]**
   - ○ Janssen Pharmaceuticals Inc. **[TERMINATE]**
   - ○ Mallinckrodt Inc. (a Covidien Company) **[TERMINATE]**
   - ○ Mylan Technologies Inc. **[TERMINATE]**
   - ○ Noven Pharmaceuticals Inc. **[TERMINATE]**
   - ○ Par Pharmaceuticals **[TERMINATE]**
   - ○ Pfizer Inc **[TERMINATE]**
   - ○ Purdue Pharma L.P. **[TERMINATE]**
   - ○ Ranbaxy Pharmaceuticals Inc. **[TERMINATE]**
   - ○ Rhodes Pharmaceuticals L.P. **[TERMINATE]**
   - ○ Roxane Laboratories, Inc. **[TERMINATE]**
   - ○ Sandoz Inc. **[TERMINATE]**
   - ○ The PharmaNetwork LLC **[TERMINATE]**
   - ○ VistaPharm Inc. **[TERMINATE]**
   - ○ Watson Laboratories Inc. **[TERMINATE]**
   - ○ United BioSource Corporation **[TERMINATE]**

- ○ FDA **[TERMINATE]**
- ○ None of these apply **[IF SELECTED, ALL OTHER OPTIONS SHOULD BE CLEARED]**
- ○ I don't know **[TERMINATE]**
- ○ Prefer not to answer **[TERMINATE]**

2. Have you prescribed ER/LA opioid analgesics at least once within the last 12 months? The ER/LA opioid analgesics include Avinza®, Butrans®, Dolophine®, Duragesic®, Embeda®, EXALGO®, Kadian®, Methadose™, MS Contin®, Nucynta® ER, Opana® ER, Oxycontin® ER, Palladone®, and generic versions of any of these brands.

- ○ Yes
- ○ No **[TERMINATE]**
- ○ I don't remember **[TERMINATE]**

[END ELIGIBILITY QUESTIONS]

3. Please select True, False, or I don't know for each of the following statements about ER/LA opioid analgesics.

	[RANDOMIZE LIST]	True	False	I don't know
3a.	For methadone, the peak of respiratory depression can occur later and can persist longer than the analgesic effects.	○	○	○
3b.	A patient with a history of substance abuse must not be prescribed an ER/LA opioid analgesic.	○	○	○
3c.	Conversion of patients to or from methadone using equianalgesic tables can result in overdose and death.	○	○	○
3d.	Some opioids can increase the QTc interval.	○	○	○

4. Please select True, False, or I don't know for each of the following statements about ER/LA opioid analgesics.

	[RANDOMIZE LIST]	True	False	I don't know
4a.	After thorough clinical evaluation, it is appropriate for prescribers to refer a patient at high risk for drug abuse to a pain management specialist.	○	○	○
4b.	It is not necessary to re-evaluate a patient's underlying medical condition if the clinical presentation changes over time.	○	○	○
4c.	ER/LA opioid analgesic transdermal patches that have a matrix formulation may be cut prior to use.	○	○	○
4d.	Chewing a solid, oral dosage form of an ER/LA opioid analgesic can result in rapid release and absorption of a potentially fatal dose of opioid.	○	○	○

5. What is the recommended way to safely convert an opioid-tolerant patient from a parenteral opioid, such as morphine or meperidine, to an oral extended-release opioid, such as oxycodone or oxymorphone? Please select the best response.

[RANDOMIZE LIST WITH LAST OPTION ALWAYS AT BOTTOM]

- ○ Start with the lowest available dose
- ○ Start with 25% of an equianalgesic dose
- ○ Start with 50% of an equianalgesic dose
- ○ Start with an equianalgesic dose
- ○ I don't know

6. Patients considered opioid-tolerant are those (please select all that apply):

[RANDOMIZE LIST WITH LAST TWO OPTIONS ALWAYS AT BOTTOM]

- ☐ Who are taking 25 mcg/hour transdermal fentanyl for at least 7 days
- ☐ Who are not currently taking opioid therapy, but have no known intolerance or hypersensitivity to the drug fentanyl
- ☐ Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer
- ☐ None of the above **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**
- ☐ I don't know **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**

7. Which of the following do you do with patients when prescribing an ER/LA opioid analgesic? Please select all that apply.

[RANDOMIZE LIST WITH LAST OPTION ALWAYS AT BOTTOM]

- ☐ Use the **Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids** **[DISPLAY Patient Counseling Document.JPG WHEN HYPERLINK IS CLICKED]** when discussing the proper use of opioids with my patient
- ☐ Advise patients how to safely taper their ER/LA opioid dose when discontinuing
- ☐ Explain what patients should do if they miss a dose of their ER/LA opioid analgesic
- ☐ Warn patients not to break, chew or crush their oral ER/LA opioid, as it could result in an overdose
- ☐ None of the above **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**

8. Please select True, False, or I don't know for each of the following statements about drug-drug interaction profiles for ER/LA opioid analgesics.

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
8a.	Central nervous system depressants can have a potentiating effect on the sedation and respiratory depression caused by opioids.	○	○	○
8b.	Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol.	○	○	○
8c.	Monoamine oxidase inhibitors (MAOIs) are the preferred antidepressants for use with ER/LA opioid analgesics.	○	○	○
8d.	Concomitant drugs that act as inhibitors or inducers of various cytochrome P450 enzymes can result in higher or lower than expected blood levels of some opioids.	○	○	○

9. When evaluating patients for treatment with ER/LA opioid analgesics, which of the following are important risks to consider? Please select the one best response.

[RANDOMIZE LIST WITH LAST THREE OPTIONS ALWAYS AT BOTTOM]

- ○ The patient's current opioid tolerance
- ○ Respiratory depression, particularly in elderly or debilitated patients
- ○ Interactions with other medications the patient may be taking
- ○ Inadvertent exposure, especially in children present in the home
- ○ All of the above
- ○ None of the above
- ○ I don't know

10. Which of the following are risk factors for opioid abuse? Please select all that apply.

[RANDOMIZE LIST WITH LAST TWO OPTIONS ALWAYS AT BOTTOM]

- ☐ A personal history of psychiatric disorders
- ☐ A personal history of past or current alcohol or drug abuse
- ☐ A family history of hypercholesterolemia
- ☐ A family history of illicit drug use or alcohol abuse
- ☐ None of the above **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**
- ☐ I don't know **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**

11. Which of the following should prescribers do when initiating a patient on ER/LA opioid analgesics? Please select all that apply.

[RANDOMIZE LIST WITH LAST TWO OPTIONS ALWAYS AT BOTTOM]

- ☐ Start with the highest recommended dose of the ER/LA opioid and decrease the dose depending on tolerability
- ☐ Consider a rescue medication for break-through pain
- ☐ If switching from another opioid, convert to an equianalgesic dose
- ☐ Titrate doses based on efficacy and tolerability
- ☐ None of the above **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**
- ☐ I don't know **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**

12. For which of the following conditions are ER/LA opioid analgesics indicated? Please select all that apply.

[RANDOMIZE LIST WITH LAST TWO OPTIONS ALWAYS AT BOTTOM]

- ☐ Acute or postoperative pain
- ☐ As needed for headache or migraine pain
- ☐ Dental abscess pain
- ☐ Breakthrough pain from cancer
- ☐ Chronic non-cancer pain
- ☐ None of the above **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**
- ☐ I don't know **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**

13. Which of the following are the warning signs and symptoms of respiratory depression from ER/LA opioid analgesics? Please select all that apply.

[RANDOMIZE LIST]

- ☐ Reduced urge to breathe
- ☐ Decreased rate of respiration
- ☐ "Sighing" pattern of breathing
- ☐ Hypersalivation
- ☐ Sinus congestion
- ☐ Profound sedation

14. Please answer True, False, or I don't know for each of the following statements about the use of Patient Prescriber Agreements (PPAs).

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
14a.	PPAs are signed by both prescriber and patient at the time an opioid is initially prescribed.	○	○	○
14b.	PPAs can include information about treatment goals, risks, and safe use of the ER/LA opioid.	○	○	○
14c.	PPAs are a legal requirement.	○	○	○
14d.	PPAs may include commitments regarding follow-up visits, monitoring for misuse, and safeguarding the medication.	○	○	○

15. Please select True, False, or I don't know for each of the following statements about ER/LA opioid analgesics.

	[RANDOMIZE LIST]	True	False	I don't know
15a.	All ER/LA opioids reach steady state plasma concentration at the same time.	○	○	○
15b.	A patient should not cut an extended release tablet in half to reduce the dose.	○	○	○
15c.	The Controlled Substances Act includes ER/LA opioids because of the potential risk for abuse.	○	○	○
15d.	Dispose of transdermal patches by cutting into small pieces and throwing in the trash.	○	○	○
15e.	The underlying pharmacokinetic and pharmacodynamic mechanisms are the same for all ER/LA opioids.	○	○	○

16. How should prescribers reassess patients maintained on ER/LA opioid analgesics during follow-up visits? Please answer True, False, or I don't know for each of the following statements.

	[RANDOMIZE LIST]	True	False	I don't know
16a.	Periodically assess the continued need for opioid analgesics	○	○	○
16b.	Perform a comprehensive physical examination at each visit	○	○	○
16c.	Evaluate pain control and functional improvement	○	○	○
16d.	Evaluate for changes in the patient's medical condition	○	○	○
16e.	Systematically perform drug screening for all patients	○	○	○

17. How frequently do you perform the following activities when treating patients with ER/LA opioid analgesics? Please answer Always, Regularly, Rarely, Never, or I don't know.

[RANDOMIZE LIST]	Always	Regularly	Rarely	Never	I don't know
17a. Use the **Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids** **[DISPLAY Patient Counseling Document.JPG WHEN HYPERLINK IS CLICKED]** for discussions with patients	○	○	○	○	○
17b. Caution patients about important risks, including overdose and respiratory depression	○	○	○	○	○
17c. Discuss with patients how to safely taper their ER/LA opioid analgesic if it is no longer needed	○	○	○	○	○
17d. Counsel patients on the most common side effects from opioid use	○	○	○	○	○
17e. Instruct patients about the importance and how to safely dispose of their unused opioids	○	○	○	○	○

18. How frequently do you perform the following activities when treating patients with ER/LA opioid analgesics? Please answer Always, Regularly, Rarely, Never, or I don't know.

[RANDOMIZE LIST]	Always	Regularly	Rarely	Never	I don't know
18a. Use structured interview tools or other screening tools to assess patients' risk of abuse or misuse of their medications when managing patients using ER/LA opioids	○	○	○	○	○
18b. Complete a Patient Prescriber Agreement (PPA) or patient contract at the time an ER/LA opioid is first prescribed	○	○	○	○	○
18c. Perform urine drug tests	○	○	○	○	○
18d. Reassess the need for opioids	○	○	○	○	○

19. Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? Please answer Yes, No, or I don't know for each of the following options.

	[RANDOMIZE LIST]	Yes	No	I don't know
19a.	Sedative hypnotics	○	○	○
19b.	Anxiolytics	○	○	○
19c.	Alcohol	○	○	○
19d.	Illegal drugs	○	○	○
19e.	Caffeine	○	○	○

20. Federal regulations stipulate which of the following when writing a prescription for an ER/LA opioid? Please select True, False, or I don't know for each of the following options.

	[RANDOMIZE LIST]	True	False	I don't know
20a.	Refills are not allowed for Schedule II products.	○	○	○
20b.	There are specific federal limits to quantities of ER/LA opioids dispensed via a prescription.	○	○	○
20c.	Refills for an ER/LA opioid prescription can be phoned into a pharmacy.	○	○	○
20d.	Any prescription for a Schedule II product can be faxed to the pharmacy.	○	○	○

21. A patient is experiencing back pain and is being treated with a transdermal opioid product. After a fall at home, he would like to soak in a hot tub to relieve some of the muscle soreness. What is your advice? Please select the one best response.

[RANDOMIZE WITH LAST TWO OPTIONS ALWAYS AT BOTTOM]

- ○ It is acceptable to soak in the hot tub for less than half an hour.
- ○ He should cover the patch with an occlusive dressing if entering the hot tub.
- ○ He must remove the patch while soaking in the hot tub.
- ○ Do not soak in the hot tub since heat can affect the absorption of the opioid.
- ○ None of the above
- ○ I don't know

22. Which of the following are important factors to consider when selecting an initial dose of an ER/LA opioid analgesic? Please indicate Yes, No, or I don't know for each of the following options.

[RANDOMIZE LIST]	**Yes**	**No**	**I don't know**
22a. The patient's degree of opioid experience	○	○	○
22b. Concurrent medication	○	○	○
22c. General medical status of the patient	○	○	○
22d. The patient's family history of mental illness	○	○	○

23. What should be done if a patient treated with a transdermal opioid develops a high fever? Please select the best response.

[RANDOMIZE LIST]

- ○ Remove the patch until the fever is below 102°F
- ○ Switch the patient to another ER/LA opioid
- ○ Monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary
- ○ Move the patch to another location on the body

24. Please select True, False, or I don't know for each of the following statements about ER/LA opioid analgesics.

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
24a.	When starting a patient who is currently taking a sedative on an ER/LA opioid analgesic, reduce the dose of one or both.	○	○	○
24b.	Fatal respiratory depression may occur, with the highest risk at initiation and when the dose is increased.	○	○	○
24c.	Patients who are not opioid tolerant can initiate opioid therapy with any type of ER/LA opioid analgesic.	○	○	○

25. When counseling patients about the safe use of ER/LA opioid analgesics, prescribers should inform patients of the following: (please select all that apply):

[RANDOMIZE LISTWITH LAST TWO OPTIONS ALWAYS AT BOTTOM]

- ☐ The importance of adhering to a dosage regimen as prescribed
- ☐ Store ER/LA opioid analgesics in a medicine cabinet with other medications in the household
- ☐ It is illegal to sell or give away ER/LA opioid analgesics

- ☐ Dispose of unused prescription opioids by throwing them in the trash
- ☐ None of the above **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**
- ☐ I don't know **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**

26. How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Please select all that apply.

[RANDOMIZE LIST WITH LAST TWO OPTIONS ALWAYS AT BOTTOM]

- ☐ Document any "drug seeking" behavior
- ☐ Utilize state Prescription Drug Monitoring Programs
- ☐ Use drug testing for both screening and confirmatory tests
- ☐ Perform laboratory testing for serum triglycerides
- ☐ Periodically re-evaluate therapy
- ☐ Perform medication reconciliation by counting leftover drug supplies
- ☐ None of the above **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**
- ☐ I don't know **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**

[PREAMBLE 2]

The next set of questions is about the educational materials for ER/LA opioid analgesics and the Patient-Prescriber Agreement. As a reminder, the ER/LA opioid analgesics include Avinza®, Butrans®, Dolophine®, Duragesic®, Embeda®, EXALGO®, Kadian®, Methadose™, MS Contin®, Nucynta® ER, Opana® ER, Oxycontin® ER, Palladone®, and generic versions of any of these brands. If you wish to view an image of each document, please click on the document name for the appropriate link.

27. Prior to today, were you aware of the **Medication Guide(s)** **[DISPLAY Example Medication Guide.JPG WHEN HYPERLINK IS CLICKED]** for the ER/LA opioid analgesics that you prescribe?

- ○ Yes
- ○ No **[GO TO Q32]**
- ○ I don't know **[GO TO Q32]**

28. How were you made aware of the Medication Guide(s) for the ER/LA opioid analgesics that you prescribe? Please select all that apply.

- ☐ Mailing
- ☐ Email
- ☐ Online download
- ☐ Sales Representative
- ☐ Pharmacy
- ☐ Conference
- ☐ Other
- ☐ I don't know **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**

29. Did you receive or have access to the Medication Guide(s) for the ER/LA opioid analgesics that you prescribe?

- ○ Yes
- ○ No **[GO TO Q32]**
- ○ I don't know **[GO TO Q32]**

30. How did you receive or get access to the Medication Guide(s) for the ER/LA opioid analgesics that you prescribe? Please select all that apply.

- ☐ Mailing
- ☐ Email
- ☐ Online download
- ☐ Sales Representative
- ☐ Pharmacy
- ☐ Conference
- ☐ Other

31. Did you read the Medication Guide(s) for the ER/LA opioid analgesics that you prescribe?

- ○ Yes
- ○ No
- ○ I don't know

32. Prior to today, were you aware of the ER/LA Opioid Analgesics REMS **Dear DEA-Registered Prescriber Letter** **[DISPLAY Dear HCP Information.JPG WHEN HYPERLINK IS CLICKED]**?

- ○ Yes
- ○ No **[GO TO Q37]**
- ○ I don't know **[GO TO Q37]**

33. How were you made aware of the ER/LA Opioid Analgesics REMS Dear DEA-Registered Prescriber Letter? Please select all that apply.

- ☐ Mailing
- ☐ Email
- ☐ Online download
- ☐ Sales Representative
- ☐ Pharmacy
- ☐ Conference
- ☐ Other
- ☐ I don't know **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**

34. Did you receive or have access to the ER/LA Opioid Analgesics REMS Dear DEA-Registered Prescriber Letter?

- ○ Yes
- ○ No **[GO TO Q37]**
- ○ I don't know **[GO TO Q37]**

35. How did you receive or get access to the ER/LA Opioid Analgesics REMS Dear DEA-Registered Prescriber Letter? Please select all that apply.

- ☐ Mailing
- ☐ Email
- ☐ Online download
- ☐ Sales Representative
- ☐ Pharmacy
- ☐ Conference
- ☐ Other

36. Did you read the ER/LA Opioid Analgesics REMS Dear DEA-Registered Prescriber Letter?

- ○ Yes
- ○ No
- ○ I don't know

37. Prior to today, were you aware of the **Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids** **[DISPLAY Patient Counseling Document.JPG WHEN HYPERLINK IS CLICKED]**?

- ○ Yes
- ○ No **[GO TO Q42]**
- ○ I don't know **[GO TO Q42]**

38. How were you made aware of the Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids? Please select all that apply.

- ☐ Mailing
- ☐ Email
- ☐ Online download
- ☐ Sales Representative
- ☐ Pharmacy
- ☐ Conference
- ☐ Other
- ☐ I don't know **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**

39. Did you receive or have access to the Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids?

- ○ Yes
- ○ No **[GO TO Q42]**
- ○ I don't know **[GO TO Q 42]**

40. How did you receive or get access to the Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids? Please select all that apply.

- ☐ Mailing
- ☐ Email
- ☐ Online download
- ☐ Sales Representative
- ☐ Pharmacy
- ☐ Conference
- ☐ Other

41. Did you read the Patient Counseling Document (PCD) on Extended-Release/Long-Acting Opioids?

- ○ Yes
- ○ No
- ○ I don't know

42. Prior to today, were you aware of the **ER/LA Opioid Analgesics REMS website** **[DISPLAY ER_LA Opioids Website.JPG WHEN HYPERLINK IS CLICKED]**?

- ○ Yes
- ○ No **[GO TO Q46]**
- ○ I don't know **[GO TO Q46]**

43. How were you made aware of the ER/LA Opioid Analgesics REMS website? Please select all that apply.

- ☐ Mailing
- ☐ Email
- ☐ Internet search
- ☐ Sales Representative
- ☐ Pharmacy
- ☐ Conference
- ☐ Other
- ☐ I don't know **[SELECTING THIS OPTION WILL DESELECT ALL OTHER OPTIONS]**

44. Did you have access to the ER/LA Opioid Analgesics REMS website?

- ○ Yes
- ○ No **[GO TO Q46]**
- ○ I don't know **[GO TO Q46]**

45. Did you review the ER/LA Opioid Analgesics REMS website?

- ○ Yes
- ○ No
- ○ I don't know

46. Do you have any questions about the Medication Guide(s), Dear DEA-Registered Prescriber Letter, Patient Counseling Document, or ER/LA Opioid REMS website?

- ○ Yes
- ○ No **[GO TO Q47 - DO NOT DISPLAY PREAMBLE 3]**
- ○ I don't know **[GO TO Q47 - DO NOT DISPLAY PREAMBLE 3]**

[PREAMBLE 3]

If you have any questions about ER/LA opioid analgesics or need copies of any of the materials/documents mentioned in this survey, you can call the RPC Call Center at 1-800-503-0784.

47. On a scale of 0 to 10, how easy has it been in the past month for patients who are indicated to receive ER/LA opioids to access such an extended-release opioid (zero meaning no access and 10 meaning extremely easy to access)?

No Access	○ 0	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6	○ 7	○ 8	○ 9	○ 10	Extremely Easy Access

47a. In your opinion, what have the obstacles been to patient access to prescription opioids for pain-control medical needs in the past month? Please select all that apply.

- ☐ Insurance coverage
- ☐ Insurance authorizations and approvals
- ☐ Patients' ability to pay
- ☐ Stigma regarding opioids
- ☐ Pharmacy authorization
- ☐ Pharmacy stocking issues
- ☐ Physicians do not want to prescribe ER/LA opioids because they do not wish to complete REMS training
- ☐ Patients are afraid to take ER/LA opioids because of risk warnings
- ☐ Legal liability or malpractice concerns
- ☐ Other

47b. Ease of access can impact both risk of opioid abuse and patients who require opioids. Do you think the current level of access to ER/LA opioid analgesics for patients who are indicated to take them is:

- ○ Too easy
- ○ Too difficult
- ○ About right
- ○ I don't know

47c. In your opinion, what impact does the FDA-required Risk Evaluation and Mitigation Strategy (REMS) for ER/LA Opioid Analgesics have on the ability of patients who need opioids to get them?

- ○ It makes it more difficult for patients to get opioids
- ○ It makes it easier for patients to get opioids
- ○ It doesn't have any impact on patient access to opioids
- ○ I don't know

[DEMOGRAPHICS PREAMBLE]

There are just a few more questions to help us combine your answers with other answers we have received.

48. On average, how many times per month have you prescribed ER/LA opioid analgesics within the last 3 months?

- ○ 1 time
- ○ 2 – 3 times
- ○ 4 - 5 times
- ○ 6 – 7 times
- ○ 8 – 9 times
- ○ 10 or more times
- ○ I don't remember

49. Please select the ER/LA opioid analgesics that you have prescribed within the last 6 months. Please select all that apply.

- ☐ Avinza® or generic (morphine)
- ☐ Butrans®
- ☐ Dolophine® or generic (methadone)
- ☐ Duragesic® or generic (fentanyl transdermal)
- ☐ Embeda®
- ☐ EXALGO®
- ☐ Kadian®
- ☐ Methadose™ or generic (methadone hydrochloride)
- ☐ MS Contin®
- ☐ Nucynta® ER
- ☐ Opana® ER or generic (oxymorphone hydrochloride)
- ☐ Oxycontin® ER
- ☐ Palladone®
- ☐ Methadone hydrochloride Intensol™ oral concentrate
- ☐ Methadone hydrochloride Oral Solution
- ☐ Morphine sulphate extended-release tablets
- ☐ Oxycodone hydrocodone extended-release tablets
- ☐ All of the above **[IF SELECTED, ALL OTHER OPTIONS SHOULD BE CLEARED]**
- ☐ None of the above **[IF SELECTED, ALL OTHER OPTIONS SHOULD BE CLEARED]**

These last few questions are for demographic purposes.

50. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

51. What is your medical degree?

- ○ MD
- ○ DO
- ○ Nurse Practitioner **[GO TO Q53]**
- ○ Advanced Practice Nurse **[GO TO Q53]**
- ○ Physician Assistant **[GO TO Q53]**

52. In total, how many years have you been practicing medicine, since completing your post-graduate education?

- ○ Less than 3 years
- ○ 3 – 5 years
- ○ 6 – 10 years
- ○ 11 – 15 years
- ○ More than 15 years
- ○ Prefer not to answer

53. In which state or US territory do you practice?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" at END]

54. Are you a general practitioner or specialist?

- ○ General Practitioner **[GO TO CLOSING 1]**
- ○ Specialist

55. What is your primary medical specialty? Please select one response only.

- ○ Oncology
- ○ Neurology
- ○ Anethesiology
- ○ Rheumatology
- ○ Orthopedics
- ○ Hospice/Palliative Care
- ○ Internal Medicine
- ○ Other (please specify): _____

[CLOSING 1]

We would like to send you a $125 payment card within the next few weeks to thank you for your time, but we need your name and address to do so. If you do not provide your name and address you will not receive the payment card for your time and participation in the survey.

Do you agree to give us your name and mailing address so we can send you the payment card?

○ Yes

○ No **[SKIP TO CLOSING 2]**

FIRST NAME: _____

LAST NAME: _____

ADDRESS: **[MULTILINE INPUT]**

CITY: _____

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: _____

[CLOSING 2]

We would also like to ask for your telephone number. Providing your telephone number is optional. Your telephone number will only be used to contact you only if there are questions about your survey responses. It will not be used for any telemarketing calls or shared with anyone outside the staff of this study.

Do you want to provide your telephone number?

- ○ Yes
- ○ No **[SKIP TO CLOSING 3]**

Telephone: _____

[CLOSING 3]

That ends the survey. Thank you again for your help.

[END OF SURVEY CONTENT]

Appendix C Sample Prescriber Baseline and Post-REMS Invitation Letter

[CURR_DATE]

[PRESCRIBER NAME]

[STREET_ADDR]

[CITY], [STATE] [ZIP]

Dear [PRESCRIBER NAME]:

We are contacting you to invite you to participate in a survey being conducted by the manufacturers of Extended Release and Long-Acting (ER/LA) opioid analgesic medicines, as required by the Food and Drug Administration (FDA). The purpose of the survey is to assess prescribers' understanding of the safe and appropriate use of these medicines.

The ER/LA opioid analgesics include Avinza®, Butrans®, Dolophine®, Duragesic®, Embeda®, EXALGO®, Kadian®, Methadose™, MS Contin®, Nucynta® ER, Opana® ER, Oxycontin® ER, Palladone®, and generic versions of any of these brands. The manufacturers of ER/LA opioid analgesics include Actavis, Alza Corporation, Endo Pharmaceuticals, Inc., Impax, Janssen Pharmaceuticals, Inc., King Pharmaceuticals, Inc., Mallinckrodt (a Covidien Company), Mylan Technologies, Inc., Noven Pharmaceuticals, Inc., Pfizer Inc., Purdue Pharma L.P., Rhodes Pharmaceuticals L.P., Roxane Laboratories, Inc., Sandoz Inc., The Pharmanetwork, LLC, Vintage Pharmaceuticals, LLC, VistaPharm, Inc., and Watson Laboratories, Inc.

These manufacturers are looking for 600 prescribers to complete the survey. Eligible prescribers who complete the survey will be sent a $125 honorarium to thank them for their time. The survey will take approximately 20 minutes.

Your answers will be kept strictly confidential and will be combined with the answers from other prescribers who take this survey. Your name will not be used in the report of this survey and your contact information will only be used to send you a $125 honorarium for the time you took to complete the survey and if required to comply with a federal or state law or regulation. Physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

You are under no obligation to participate in this survey. If you are interested in participating, go to **www.ER-LA-opioidREMSsurvey.com** at your convenience within the next 7 days. You will be asked to give this unique code prior to starting the survey: **[CODE_ID]**. Please have this letter with you at the time you take the survey.

Thank you in advance for your help with this important effort.

Sincerely,

ER/LA Opioid Analgesics Team

* We recommend that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.

Appendix F: Request for (Grant) Applications (RFA)

REQUEST FOR (GRANT) APPLICATIONS (RFA)

Overview Information

Sponsoring Organization	REMS Program Companies (RPC)
RFA Title	Extended-Release and Long-Acting Opioid Analgesics: Risk Evaluation and Mitigation Strategy (REMS)
RFA Code	ER/LA ####13
RFA Goal	The goal of this RFA is to support high quality REMS-compliant Continuing Education (CE) designed to assist in ensuring that the benefits of Extended Release/Long-Acting (ER/LA) opioid analgesics outweigh the risks (in patients whose clinicians have determined ER/LA opioid analgesics to be an appropriate treatment option). The mechanism by which this is intended to occur is by educating healthcare providers on the *Food & Drug Administration (FDA) Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics* ("FDA Blueprint"), with the aim to optimize both knowledge acquisition and the translation of that knowledge into practice. Successful proposals will detail educational initiatives that ultimately assist in positively impacting safe and appropriate patient care.
RFA Elements Essential to Meet REMS Compliant CE Requirements	Educational design Proposed CE activities should take into consideration the requirements for REMS-compliant CE training: • All activities within each educational program must cover all FDA Blueprint elements contained within the six sections of the document • All activies must include a post-activity assessment that covers all six sections of the FDA Blueprint. Providers are encouraged to consider a means of integrating the assessment that increases the likelihood of learners completing it with a passing score determined by the Provider since this is a requirement for the learner to be counted toward the FDA REMS goals. • The activities are subject to independent audit by the CE Accrediting Bodies

	• The activities must be conducted in accordance with the standards for accredited CE set by the appropriate Accrediting Body(ies) FDA has set explicit definitions and goals about who the target audience is and how many will be engaged in completing REMS-compliant CE bycertain timeframes (see Section 1)
Key Dates	RFA Posted: Application Due Date: Award Notification Date:
RFA Document Parameters	Grant applicants should submit applications in MS Word.
Submission Link	Grant applications must be submitted via the Grant Management System (GMS), which will be accepting new grant applications in response to this RFP beginning on **May 21,** 2013. The GMS system may be accessed by way of the RPC website at www.ER-LA-OpioidREMS.com, via the right-hand-side link "If you are a Continuing Education Provider, click here for more information." For this specific RFA, the appropriate RFA code is **RFA 050313**.
Questions on RFA?	Please Contact Polaris Grant Coordinator: Phone - 1-800-376-9756 Email – grants@er-la-opioidrems.com

Table of Contents

Section 1: Scope of Problem and Background on ER/LA Opioid REMS

Scope of the Problem

According to the 2011 Institute of Medicine Report "*Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research,"* as many as 100 million adults in the US report having a common chronic pain condition, exceeding the number affected by heart disease, cancer, and diabetes.

The economic burden of pain to society is staggering. The IOM Report suggests that the annual health economic impact of pain represents a $560 to $635 billion burden to the US (in 2010 dollars)[i] and the morbidity and disability associated with chronic pain represents a significant public health issue. At the same time, however, the misuse and abuse of opioid analgesics, one class of medications used for managing moderate-to-severe chronic pain, has emerged as a major public health/patient safety problem.

The most recent national data available indicates that:

- At the patient health level, numerous clinical reports suggest that chronic pain remains undertreated; the percentage of patients receiving appropriate and adequate treatment has been reported to be as low as 10-25%.
- Patients with chronic pain have difficulty finding physicians who can effectively treat their pain, with nearly 50% of patients changing physicians at least once, and nearly 25% making at least three physician changes.
- Based on the 2010 National Survey on Drug Use and Health, public health experts estimate more than 35 million Americans age 12 and older used an immediate release (IR) or ER/LA opioid analgesic for non-medical use some time in their life—an increase from about 30 million in 2002.[1]
- In 2009, there were nearly 343,000 emergency department visits involving nonmedical use of opioid analgesics.[1]
- 257 million prescriptions for opioids were dispensed in 2009—a 48% increase compared with figures for 2000.[2]

ER/LA Opioid REMS and the REMS Program Companies

[1] Substance Abuse and Mental Health Services Administration. 2011. *Results from the 2010 National Survey on Drug Use and Health: Detailed Table*, Table 7.1.a. Rockville, MD. http://www.samhsa.gov/data/NSDUH/2k10NSDUH/tabs/Sect7peTabs1to45.htm#Tab7.1A. Accessed on March 30, 2012.

[2] Warner M, Chen LH, Makuc DM, Anderson RN, and Miniño AM. 2011. Drug Poisoning Deaths in the United States, 1980–2008, in U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, *NCHS Data Brief*, *No 81*. December 2011. Hyattsville, MD. http://www.cdc.gov/nchs/data/databriefs/db81.pdf. Accessed on March30, 2012.

The Extended-Release and Long-Acting (ER/LA) Opioid Analgesics REMS is designed to ensure that the benefits of ER/LA opioid analgesics outweigh the risks (in patients whose clinicians have determined ER/LA opioid analgesics to be an appropriate treatment option). The goal of this REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of extended-release or long-acting (ER/LA) opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.[3]

FDA has developed a Blueprint for Healthcare Providers Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"), which is posted on the FDA website for use by accredited CE Providers to develop the actual CE activities. (http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf)

The FDA determined that a single shared system was to be implemented for all products within this drug class. As a result, the RPC was created, being comprised of the 17 companies[4] that have ER/LA opioid products. RPC-supported REMS education will be provided through accredited continuing education (CE) activities supported by independent educational grants from these companies.[3] For a complete listing of the RPC member companies, see www.ER-LA-OpioidREMS.com

FDA Expectations of RPC-supported REMS Education and Desired Outcomes

The desired outcome of ER/LA opioid analgesic REMS-compliant CE is to increase understanding of appropriate patient assessment and prescribing practices, as well as other information which can help reduce misuse, abuse and overdose deaths associated with ER/LA opioids analgesics. Education that is focused on the expected results outlined below should result in healthcare professionals incorporating practices that assist in maintaining that the benefits of opioid analgesic medications outweight the risks.

The expected results of the education as described by the FDA in the FDA Blueprint introductory section are that prescribers of ER/LA opioid analgesics will:

- Understand how to assess patients for treatment with ER/LA opioid analgesics

[3] Adapted from the FDA Approved ER/LA Opioid Analgesics REMS document (October 2012 version). ER/LA Opioid Analgesics REMS (http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf)
[4] As of March 2013

- Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics
- Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics
- Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal
- Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics

FDA has set goals/time frames for the number of –prescribers completing REMS-compliant CE.

The first FDA-mandated CE goal[5] stipulates that 80,000 ER/LA opioid analgesic prescribers will have successfully completed REMS-compliant CE, as defined at the bottom of page 1, by Feb 28, 2015.

Subsequent goals established by FDA in the REMS are:

- ***160,000 ER/LA opioid analgesic prescribers will have successfully completed REMS-compliant CE, by Feb 28, 2016***
- ***192,000 ER/LA opioid analgesic prescribers will have successfully completed REMS-compliant CE, by Feb 28, 2017***

Definitions and Clarifications:

Definition of ER/LA opioid prescriber : « an individual clinician who is registered with the DEA, eligible to prescribe Schedule 2 and/or 3 controlled substances, and has written at least one ER/LA opioid script in the past year. » (Please see MedBiquitous website for reference : http://www.medbiq.org/mems/definitions#ER/LA_opioid_prescriber)

Note : To be counted toward these FDA REMS goals, a learner must meet the FDA ER/LA Opioid REMS definition of « prescribers successfully completing » [6] all components of an educational activity.

Definition of « prescribers successfully completing » a REMS educational activity : ER/LA opioid prescribers that have completed all components of an educational activity

[5] FDA. "Blueprint for Prescriber Education for Extended-release and Long-acting Opioid Analgesics," 2012.
[6] MedBiquitous Medical Education Metrics Definitions http://medbiq.org/mems/definitions. Accessed 3/29/13.

and met the education provider's criteria for passing. Components of an educational activity include instruction, assessment of learning, and potentially evaluation. (Please see definition of « prescribers_successfully _completing" at the MedBiquitous website : http://medbiq.org/mems/definitions The FDA Blueprint and additional information on REMS-compliant CEcan be found on the RPC website at: www.ER-LA-OpioidREMS.com.

Section 2: Funding Opportunity and Award Information

2013 RFA and Differentiating Features from 2012 RFAs

In 2012, the first two RFAs (ER/LA 010812 and 020912) were issued by the RPC. These 2012 RFA documents may be accessed by way of the RPC website at www.ER-LA-OpioidREMS.com, via the right-hand-side link "If you are a Continuing Education Provider, click here for more information" and then clicking on the link "CE Grant Management System.

This third RFA, ####13, seeks to expand the RPC's initial efforts to support education of healthcare providers on the FDA Blueprint with *two modifications.*

First, proposed educational activities must incorporate principles of adult learning and instructional design to optimize both knowledge acquisition as well as the *application and implementation* of that knowledge into routine clinical practice.

Secondly, proposals may incorporate optional activities that enhance individual adoption of what clinicians learn from the FDA Blueprint through organizational change initiatives. **While the primary focus of this RFA remains on *educating individual healthcare providers on the FDA Blueprint*, the RPC understands that individual and organizational factors simultaneously influence clinical practices and outcomes.**

Award Details

Anticipated Number of Awards	The number of submissions and their ability to address the full FDA Blueprint and assessment requirements will determine the number of grants awarded in 2013. Because of the need to engage large numbers of learners in successfully completing educational activities covering the full FDA Blueprint and passing the post-activity assessment, grant applicants are encouraged to incorporate effective co-sponsorships, partnerships and/or collaborations among organizations who have already established ongoing relationships/regular communication with the primary audience for REMS CE. (See Section 4, #5).
Award Budget	RPC understands that there will be a range of costs per learner, depending upon the specifics of the proposal. As a frame of

	reference, in 2012, the estimated cost per learner "successfully completing" education covering the full FDA Blueprint/assessment requirements ranged from $62 to $149 per person.
Award Project Period	Because of the need to report ongoing progress to FDA, the expectations are that: • The initial activity within the proposed program must begin within four months of signing the Letter of Agreement (LOA) • If an educational program contains multiple activities, all activities must start within twelve months of signing the LOA. • Any portion of a proposal with a start date more than twelve months beyond the execution of the initial LOA will require a separate grant application (although an activity that begins within twelve months of LOA execution may overlap two calendar years)
Other Award Information	To optimize the learning opportunities, the RPC intends to fund multiple grant applications from different Accredited Providers and educational partners with different, yet complementary, initiatives. Preference will be given to those grant requests that permit the RPC to support multiple high quality, diverse programs that will enable achievement of the education participation goals and outcomes as described in the FDA-approved ER/LA Opioid REMS. Grant applications will be considered that demonstrate how the proposed education will fully meet or exceed the criteria for being REMS-compliant, are cost-effective, for the scope of the proposal, and attend to the RFA Criteria outlined in Section 4. (eg, innovation, number of ER/LA opioid prescribers expected to complete fully REMS-compliant CE, etc).

Section 3: Applicant Eligibility Criteria

- ❒ The Accredited Provider who submits the grant application must serve as the Provider of Record for the activity and must be engaged in or represent healthcare professionals responsible for the delivery of patient care (e.g., Schools of Medicine, Pharmacy or Nursing, Hospitals, Medical Societies, Professional Associations, or governmental organizations).

- ❒ Applicants must be accredited to provide CE by a national accrediting body (e.g., ACCME, AAFP, AANP, AAPA, ACPE, ADA, ANCC, AOA, or equivalent accrediting body) or by an official state accrediting agency, and must demonstrate that their organization is in good standing at the time of application.

- ❒ Applicants must have demonstrated capabilities in the design and successful implementation of innovative, interactive, engaging multimodal educational activities, and effective communication skills as evidence by solid partnerships and collaborations.

Section 4: RFA Submission Information

Providers should submit RFA proposals that include *all of the following components*, and use the numbered sections to develop a response, following the outline below.

	Application Component	Description
1	**Provider of Record**	Name of Accredited Provider and person(s) responsible for this project, and contact information
2	**Partner Organizations**	Name of any partner organizations involved with the proposed education, along with roles and responsibilities, and contact information
3	**Overview of Proposed Educational Program**	A 1-2 page summary description of overall project goals, target audience, findings from needs assessment, proposed educational activities to fill gaps from needs assessment, and method for measuring outcomes.
4	**Description of Team**	• Description of methods and criteria used to select faculty, and/or individuals involved in the development and implementation of proposed educational initiatives • Description and qualifications of the members of the team responsible for implementing the project
5	**Audience(s)**	The audience for REMS CE consists of healthcare professionals involved in the care of patients with chronic moderate-to-severe pain, licensed to practice in the USA and its territories, with a DEA registration to prescribe Schedule II and III drugs. The primary audience, as defined by the FDA in the REMS, are healthcare providers who prescribe ER/LA opioid analgesics. Other audiences are also encouraged to participate in the educational activities. Within this broadly defined eligible audience, specify clearly your *target audience(s)*. Why this particular audience? What expertise do you have both reaching this audience and motivating them to complete your educational program(including passing the activity assessment)?

	Application Component	Description
6	**Geographic Coverage**	Specify geographic coverage of your educational program: • National • Regional (Multi-City, Multi-State) • State **Note: Target audiences focused on geographic regions below the state-level will be given lower priority than the aforementioned areas due to the RPC's need to meet FDA training obligations.**
7	**Needs Assessment**	If you have completed a valid and reliable needs assessment that measures gaps in knowledge from the FDA Blueprint in your target audience, please include in your proposal. If not, please specify clearly how you intend to conduct your needs assessment, how you will develop a valid and reliable method for measuring gaps in knowledge from the FDA Blueprint in your target audience, and a timeline for accomplishing the needs assessment. In addition, please explain how your needs assessment will motivate the development of the educational program you are proposing, and ideally how you will tie your needs assessment to your outcome evaluation to ensure that gaps in knowledge have been effectively closed by your program. Provide detailed description about how you measured the gaps in knowledge from the FDA Blueprint in your target audience. Indicate what measures and metrics you employed to measure gaps, and the validity and realiability of themeasures if possible. Also explain how your needs assessment links with the educational program you are proposing.

	Application Component	Description
8	**Description of Educational Program & Design** **Note: See Section 4 for details on how proposals will be reviewed and evaluated**	Narrative describing the proposed program in detail. Please include: • A detailed description of how the proposed educational program will meet all REMS-compliant CE requirements (see introductory section) • How the proposed educational program will fill the gaps in knowledge for your target audience, and how it will be linked with your needs assessment. How the overall project goals and learning objectives specifically align with the intended audience, instructional design, and architecture of the proposed activity. • A detailed description of the educational components of your program and a rationale for how they are appropriate for your target audience and link with one or more learning objectives. • How your educational program aligns with best educational practices/methods • How your education program is optimized for both knowledge acquisition and the transfer of that knowledge into clinical practice. • How your proposed program facilitates interprofessional education • An attestation that your proposed program is fully compliant with all applicable standards of your accrediting body, as well as other relevant standards, guidelines and requirements as they apply to the conduct of independent medical education • A statement that you agree to collaborate with the independent third parties (independent of RPC) conducting the FDA-required Long Term REMS Evaluations of REMS-supported CE activities 6-12 months following activity completion. **Critical Note: Ensure that the above descriptions indicate clearly how the proposed activities align with all elements of the FDA Blueprint**

	Application Component	Description
9	**Validation of Clinical Content**	Description of mechanism by which provider will validate the clinical content of proposed activities Description of an independent process for verifying that: • All elements of the FDA Blueprint are covered in the educational activity/materials to ensure completeness of content • Content of the activity reflects the most current evidence-based information and that the content of the FDA Blueprint is represented accurately • Provider has ensured fair balance and controlled for bias A process for addressing each of these items at least two months prior to the activity start date should be outlined since all REMS-compliant activities are subject to independent audit by the Accreditors, and all audit-required materials will need to be submitted to the Accreditors at least 45-XX days, as determined by the Accreditor in advance of the activity start date.

	Application Component	Description
10	**Outcome Evaluation / Knowledge Assessment**	Provide detailed description of how you intend to measure successful educational outcomes from your healthcare provider training, including the *valid and reliable measures* you intend to employ in your evaluation activities. Educational impact on healthcare professional's knowledge, competence and behavior may include attitudes, perceptions and skills. In addition to educational programs covering all elements of the FDA Blueprint, as per the FDA REMS requirements, the program must: • Include anassessment that covers all *six sections of the FDA Blueprint* and has a minimum "passing" criterion established by the Provider • Be subject to independent audit by the Accreditors to confirm that conditions of the REMS educationhave been met
11	**Marketing Plan for the Proposed CE Program**	Detail your *marketing strategy* for how the target audience will be reached, motivated to participate in your program, and be engaged to complete the entire educational program, including an assessment that meets your criteria for passing. Include steps you will take if problems arise meeting the commitments to educate the target audience that you proposed in your grant application.

	Application Component	Description
12	**Budget**	Detail budget using the template residing in the REMS Grant Management System portal. FDA has required RPC-supported CE to be provided at no cost, or at a nominal cost to the participant (e.g. a small amount to cover costs such as parking or lunch if not provided as part of activity). In keeping with the FDA's requirements, the RPC thus discourages charging a fee for RPC-supported CE. In the event the provider chooses to include a nominal registration fee, this fee should not exceed $25 per participant completing CE covering the full FDA Blueprint Explanation of rationale, efficiencies, and cost-effective approaches to both the live and enduring components, including an estimated cost per learner for both components Statement that 1. The program activities meet the accreditation/certification requirements and standards of the ACCME, AOA, AMA, AAFP or ADA CERP; 2. That no RPC member has selected or provided suggestions for any speaker involved in the program activities; and 3. The grant monies provided are for the program activity as a whole and are no meant to be a direct payment to any speaker since ultimate disbursement of the grant monies are within the control of the Provider. **Cost per learner for entire project should be calculated and provided as part of the budget.**

	Application Component	Description
13	**Timeline of Project**	Detailed project timeline for each phase and milestone. This will serve as the basis for the milestone payments in the grant as described below • Execution of Letter of Agreement: 35% • Start of First Activity and Upon Acceptance of Update Report: 25% • Mid-term of Grant Timeline and Upon Acceptance of Update Report: 30% • Completion of Last Activity and Receipt/Acceptance of Required Grant-Related Documentation: 10%
14	**Optional Organizational Change Elements**	See below for details

Optional Element of RFA

While the primary focus of this RFA remains on *educating individual clinicians on the FDA Blueprint*, the RPC understands that individual and organizational factors simultaneously influence application of learning. Therefore, an optional element of this RFA is to encourage providers to submit pilot proposals that incorporate *organizational change initiatives* aimed at further supporting the adoption of what clinicians learn from the FDA Blueprintthrough the individual healthcare provider-focused REMS CE..

Such initiatives ideally would target the organizations and environments in which patients are managed on long-term opioid therapy, or that influence this type of patient care (e.g., healthcare insititutions, medical settings, professional organizations).

If you choose to include this optional element in your proposal, please include the following:

- Overview of project
- Summary of Provider team members and qualifications
- Target audience of initiative
- Detailed description of project, including how it links to the primary healthcare professional educational program you are proposing
- How you will evaluate outcomes from the organizational change initiative

- Detailed budget for the pilot organizational change initiative, separate from your primary budget related to providing CE to individual health care professionals
- Timeline of project

Because this component of the RFA is aimed at the *organizational-level*, proposed projects will be evaluated on:

- Overall value-add to the individual healthcare provider education program
- Benefit of additional cost in relation to the potential for further advancing the application of learnings from REMS-compliant CE into clinical practice
- Potential for gaining greater insight into the importance of organizational change initiatives

While all grant applicants must meet the eligibility criteria outlined in Section 3, for proposals that include *organizational change initiatives*, such initiatives may involve additional audiences who fall outside the scope of the above criteria.

Section 5: RFA Review Information

Grant applications will be thoroughly and critically reviewed by members of the RPC Grant Review Committee and the RPC Oversight Committee. Grants will be awarded based on providers' ability to include elements in their proposals whichclearly and sufficiently address the following criteria:

Criteria	Description
Compliance	Provider meets eligibility criteria outlined in Section 3.
Alignment [7]	Includes all elements of the FDA Blueprint and presents a detailed mapping of how all elements will be covered in educational programs.
Number of ER/LA opioid prescribers fully completing the REMS-compliant CE activity	Relative to the FDA goals described on p. 6, the number of ER/LA opioid prescribers expected to have fully completed CE covering all elements of the FDA Blueprint, as well having met the education provider's criteria for « passing » an assessment which covers all six sections of the FDA Blueprint.
Qualifications of Provider and Partners	Employs effective partnerships/coalitions across professional, governmental, and/or community organizations, which can achieve broad reach and impact. Consider the inclusion of community health programs and/or patient-focused organizations.
Needs assessment [8,9,10]	Specific to the audience being trained, ensuring the content of the educational material is relevant and adapted to the needs and clinical practice circumstances of the learners.
Educational Design/methods[8,10,11,12,13,14,15]	• *Multi-method, multi-media:* Content is delivered using evidence-based methods and multiple *formats*, including, but not limited to: audio, visual, case discussions, role

[7] FDA. "Blueprint for Prescriber Education for Extended-release and Long-acting Opioid Analgesics," 2012.
[8] Bordage, G., B. Carlin, and P. E. Mazmanian. "Continuing Medical Education Effect on Physician KnowledgeEffectiveness of Continuing Medical Education: American College of Chest Physicians Evidence-Based Educational Guidelines." CHEST Journal 135, no. 3_suppl (2009): 29S–36S.
[9] Greiner, A., and Elisa Knebel. Health Professions Education: a Bridge to Quality. National Academy Press, 2003.
[10] Moore, D. E., J. S. Green, and H. A. Gallis. "Achieving Desired Results and Improved Outcomes: Integrating Planning and Assessment Throughout Learning Activities." Journal of Continuing Education in the Health Professions 29, no. 1 (2009): 1–15.
[11] Bloom, B. S. "Effects of Continuing Medical Education on Improving Physician Clinical Care and Patient Health: a Review of Systematic Reviews." International Journal of Technology Assessment in Health Care 21, no. 3 (2005): 380–385.

	plays and other features of active learning and problem-based learning approaches, to guide learners in reflection and application of new knowledge to their practice settings • Activities that are innovative / creative in nature, motivating learners to participate and complete all activities • *Multi-exposure (education sessions):* Content is delivered in digestible chunks or modules, over time, in ways that optimize learning.
Knowledge transfer[16,18]	Principles from the field of implementation science are incorporated into overall learning program to address barriers to the application of the knowledge conveyed in the program.
Interprofessional education[14,17]	Facilitates interprofessional education and educational activities, particularly for healthcare providers practicing in settings in which care is delivered by multidisciplinary teams
Valid and reliable outcome measures[14,18,19,20]	Educators should provide evidence for the validity and reliability of CE evaluation and outcome assessment methods. Preference will be given to proposals that integrate outcome assessmentsthroughout the learning program (versus waiting until the end of the entire program), to optimize learner completion rates.

[12] Chiauzzi, E., K. J. Trudeau, K. Zacharoff, and K. Bond. "Identifying Primary Care Skills and Competencies in Opioid Risk Management." Journal of Continuing Education in the Health Professions 31, no. 4 (2011): 231–240.
[13] Van Hoof, T. J., and T. P. Meehan. "Integrating Essential Components of Quality Improvement into a New Paradigm for Continuing Education." Journal of Continuing Education in the Health Professions 31, no. 3 (2011): 207–214.
[14] Institute of Medicine. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. National Academy Press, 2011.
[15] Mansouri, M., and J. Lockyer. "A Meta-analysis of Continuing Medical Education Effectiveness." Journal of Continuing Education in the Health Professions 27, no. 1 (2007): 6–15.
[16] Ratanawongsa, N., P. A. Thomas, S. S. Marinopoulos, T. Dorman, L. M. Wilson, B. H. Ashar, J. L. Magaziner, R. G. Miller, G. P. Prokopowicz, and R. Qayyum. "The Reported Validity and Reliability of Methods for Evaluating Continuing Medical Education: a Systematic Review." Academic Medicine 83, no. 3 (2008): 274–283.
[17] Sargeant, J., F. Borduas, A. Sales, D. Klein, B. Lynn, and H. Stenerson. "CPD and KT: Models Used and Opportunities for Synergy." Journal of Continuing Education in the Health Professions 31, no. 3 (2011): 167–173.
[18] Marinopoulos, S. S., T. Dorman, N. Ratanawongsa, L. M. Wilson, and B. H. Ashar. "Effectiveness of Continuing Medical Education." Evidence Reports/Technology Assessments, January 2007.
[19] Price, D. W., E. K. Miller, A. K. Rahm, N. E. Brace, and R. S. Larson. "Assessment of Barriers to Changing Practice as CME Outcomes." Journal of Continuing Education in the Health Professions 30, no. 4 (2010): 237–245.
[20] Brownson, R. C., G. A. Colditz, and E. K. Proctore (eds). Dissemination and Implementation Research in Health: Translating Science to Practice. New York: Oxford University Press, 2012.

Budget	Reasonable cost per learner given the proposed educational program (see Section 2)
Marketing Plan for CE Program	Detailed marketing strategy outlined for how target audience will be reached, motivated to participate in the educationalactivity, engaged to complete the entire educational program, including attainment of passing assessment score determined by the Provider.

References

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2. Warner M, Chen LH, Makuc DM, Anderson RN, and Miniño AM. 2011. Drug Poisoning Deaths in the United States, 1980–2008, in U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, *NCHS Data Brief*, *No 81*. December 2011. Hyattsville, MD. http://www.cdc.gov/nchs/data/databriefs/db81.pdf. Accessed on March30, 2012.
3. Adapted from the FDA Approved ER/LA Opioid Analgesics REMS document (October 2012 version)
4. There are 17 RPC member companies as of March 2013
5. FDA. "Blueprint for Prescriber Education for Extended-release and Long-acting Opioid Analgesics," 2012.
6. MedBiquitous Medical Education Metrics Definitions http://medbiq.org/mems/definitions. Accessed 3/29/13.
7. FDA. "Blueprint for Prescriber Education for Extended-release and Long-acting Opioid Analgesics," 2012.
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Additional Source Material

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