Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management
Division of Risk Management (DRISK)

Review of 12-month Risk Evaluation and Mitigation Strategy (REMS) Assessment Report

Date: August 30, 2013

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Drug Name(s): See table below

Therapeutic Class: Extended-Release and Long-Acting opioid analgesic products

OSE RCM #: 2013-1614

Drug Name	Dosage and Route	Application Type/Number	Applicant\ Sponsor	TSI #
AVINZA (morphine sulfate)	extended-release capsules	NDA 021260	King	466
BUTRANS (buprenorphine)	transdermal system	NDA 021306	Purdue	466 880
DOLOPHINE (methadone hydrochloride)	tablets	NDA 006134	Roxane	466 254
Methadone	oral solution	ANDA 087997	Roxane	--
Methadone	oral solution	ANDA 087393	Roxane	--
Methadone	oral concentrate	ANDA 089897	Roxane	--

DURAGESIC (Fentanyl Transdermal System)	transdermal system	NDA 019813	Ortho-McNeil	466 392 255
EMBEDA (morphine sulfate and naltrexone hydrochloride	extended-release capsules	NDA 022321	Alpharma/King	466 1083 1135
EXALGO (hydromorphone HCl)	extended-release capsules	NDA 021217	Mallinkrodt	466
KADIAN (morphine sulfate)	extended- release capsules	NDA 020616	Actavis	466
MS CONTIN (morphine sulfate)	controlled-release tablets	NDA 019516	Purdue	466
NUCYNTA ER (tapentadol)	extended-release oral tablets	NDA 200533	Ortho-McNeil	466 926
OPANA ER (oxymorphone hydrochloride)	extended-release oral tablets	NDA 201655	Endo	466
OPANA ER (oxymorphone hydrochloride)	extended- release oral tablets	NDA 021610	Endo	466
OXYCONTIN (oxycodone hydrochloride	controlled-release tablets	NDA 020553	Purdue	466 1136
OXYCONTIN (oxycodone hydrochloride	controlled-release tablets	NDA 022272	Purdue	466 1072

1 INTRODUCTION

This memorandum provides a review and comments to the Division of Analgesia, Anesthesia, and Addiction Products (DAAAP) from the Division of Risk Management (DRISK) in response to the Risk Evaluation and Mitigation Strategy (REMS) 12-month assessment report for Extended- Release/Long-Acting (ER/LA) opioid analgesic drug products. The aim of a DRISK REMS assessment review is to determine (1) whether the report is complete, and (2) whether the REMS is meeting the goals.

2 BACKGROUND

ER/LA opioid analgesic medicines 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, MS Contin, Nucynta ER, Opana ER, Oxycontin ER, Palladone, and generic versions of any of these brands.

On April 19, 2011, the Food and Drug Administration (FDA) notified manufacturers of ER/LA opioid analgesics that a class-wide, single shared REMS was required. The sponsors of the ER/LA opioid analgesics formed an industry working group called the REMS Program Companies (RPC) to prepare the REMS proposal for FDA approval and to operationalize the REMS program once approved. On July 9, 2012, the single-shared ER/LA opioid analgesics REMS was approved.

The goal of the ER/LA opioid analgesics REMS program 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.

REMS elements include a Medication Guide, Elements to Assure Safe Use (ETASU) (training will be made available to healthcare providers who prescribe ER/LA opioid analgesics), and a timetable for submission of assessments of the REMS at 6 months and 12 months after the initial approval date of the REMS, and annually thereafter. The first prescriber training was to be available by March 1, 2013.

The primary communication methods to disseminate the REMS and REMS-compliant training to prescribers include Dear DEA Registered Prescriber (DDRP) letters and Letters to Professional Organizations and Licensing Boards (POLB). Performance goals established for these communications are:

- DDRP letter 1 will be sent not later than 60 days after the initial approval of the REMS
- DDRP letter 2 will be sent out not later than 30 days before the first prescriber REMS-compliant training
- At least annually from the date of initial approval of the REMS, the DEA registration database will be reviewed and DDRP letter 3 will be sent to all newly DEA registered prescribers
- POLB letter 1 will be sent not later than 60 days after REMS approval
- POLB letter 2 will be sent no later than 30 days before the first prescriber REMS-compliant training is available

- 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.

As part of the REMS, performance goals for the REMS compliant training 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 Assessment Plan includes the followings:

- An assessment of the number of prescribers who have completed REMS-compliant training (first due in 12 month assessment then annually thereafter)
- A summary of independent audits of training (first due: year 2)
- Evaluation of healthcare provider understanding of the training information using surveys (first due: year 3)
- Evaluation of patient understanding of the safe use of ER/LA opioids using surveys (first due: year 2)
- Surveillance of abuse, misuse, overdose, addiction, and death from ER/LA opioids (first due: year 2)
- Evaluation of drug utilization patterns (first due: year 2)
- Evaluation of prescribing behaviors (first due: year 2)
- Monitoring patterns of prescribing that suggest changes in patient access to ER/LA opioids (first due: year 2).

The 6-month assessment of the ER/LA opioid analgesics REMS, covering the time period from July 9, 2012 through November 9, 2012, was submitted on December 21, 2012. That report included an evaluation of the REMS functional components (REMS website, DDRP letter, POLB letter, and call center), and described the progress that has been made toward addressing the eight key assessments. FDA's review concluded that the 6-month assessment report was complete and that all ER/LA opioid analgesic REMS requirements had been met or exceeded for the 6-month assessment period.

3 MATERIAL REVIEWED

- July 9, 2012, ER/LA opioid analgesics REMS and REMS approval letter
- January 11, 2013, DRISK's review (J. Ju) of baseline prescriber survey methodology
- February 14, 2013, DRISK's review (J. Ju) of the 6-month ER/LA opioid analgesics REMS assessment
- July 2, 2013, ER/LA opioid analgesics 12-month REMS assessment report

4 RESULTS

4.1 Functional Components

4.1.1 Dear DEA-Registered Prescriber Letter 2 (DDRP letter 2)

From the DEA Master Registrant file, 1,342,173 unique DEA-registered prescribers and 15,561 hospitals and pharmacies were identified as of December 31, 2012. DDRP letter 2 was used to announce availability of ER/LA opioid REMS-related CME opportunities. The goal was to send this letter no later than 30 days before the first prescriber REMS-compliant training was offered.

- Electronic distribution of the letter by email or facsimile was initiated on January 22, 2013 (6 days prior to the indicated deadline), and completed on January 28, 2013.
    - Number of letters sent by e-mail: 256,093
    - Number of letters sent by facsimile: 226,206
    - Number of letters undeliverable: 66,370
    - Number of letters opened: Unable to know
- Mailing of the DDRP letter 2 via the USPS mails was initiated on January 22, 2013 and completed on January 28, 2013.
    - Number of letters mailed: 832,669
    - Number of letters undeliverable: 27,205 (2%)
- DDRP letter 2 was posted on the ER/LA REMS website on February 6, 2013

Reviewer comments:

The distribution of the DDRP letter 2 met the performance goal that this letter be sent out no later than 30 days prior to the start of CME activities.

4.1.2 Dear Professional Organization/Licensing Board Letter 2 (DPOLB letter 2)

On January 24, 2013, 34 days before the start of the CME activities, DPOLB 2 was sent to a total of 326 relevant professional organizations and licensing boards by USPS, notifying these organizations of the REMS-compliant CME training.

- Number of letters mailed: 326
- Number of letters undeliverable: 1
- Number of letters opened: Unable to know

Reviewer comments:

The distribution of the DPOLB letter 2 met the performance goal that this letter be sent out no later than 30 days prior to the start of CME activities.

4.1.3 Call Center

A centralized call center became operational on July 23, 2012 with the operation hours on Monday-Friday from 8 a.m. to 8 p.m. ET. The primary purpose of the call center is to provide REMS program support to consumers and HCPs. The call center's responsibilities include the following:

- Provide responses to ER/LA opioid analgesics REMS-related questions
- Provide a single copy of patient counseling document (PCD) and any REMS program letter (DDRP and DPOLB letter) upon request
- Provide directions for obtaining ER/LA opioid analgesics REMS materials (MG, Prescribing Information, and PCD pads)

- Warm transfer calls when possible, or forward documented reports to the appropriate company if a potential adverse event or product quality concern is identified or is 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

A total of 268 calls were received in the 6-month reporting period and 473 calls were received during the 12-month reporting period. Most questions were posed by prescribers and pharmacists. The call center volume was highest during the two weeks immediately following the mailing of DDRP letter 2. Excluding the two-week period after the mailing were distributed, the call center consistently averages approximately 10 calls per week.

A summary of frequently asked questions between November 9, 2012 and May 9, 2013 were summarized in Table 1.

Table 1. Top 25 FAQs Utilized From November 9, 2012 –May 9, 2013

FAQ	6-Month	12-Month
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?	50	206
How are "Prescribers" defined in the ER/LA Opioid Analgesics REMS Program?	22	58
Will pharmacists be required to complete education/training, enrollment, or verification to dispense these opioid analgesic products?	15	4
When will this REMS Program education/training be available?	13	9
Is it really okay to flush my unused opioid pain medicine down the toilet?	13	16
Are there components of this REMS Program that impact outpatient or mail-order pharmacy practice?	12	2
How can I find out more about the REMS-compliant education/training and when it becomes available?	11	6
Is there someone specific to contact if I should have questions about the grant application/process?	10	2
What is a REMS Program and what is this REMS Program?	7	15
Are there components of this REMS Program that impact inpatient or long-term care	7	3
Where can I go to access additional copies of the Patient Counseling Document?	5	2
What happens if I do NOT participate in REMS-compliant education/training?	5	2
Who is funding the REMS-compliant education/training?	5	3
Did this REMS Program impact the Medication Guides?	4	3

What extended-release/long-acting (ER/LA) opioid analgesics are involved in this REMS Program?	4	2
Where and how is the education/training offered?		67
What pain medicines are included in this REMS program?		9
How many CME/CE credit will a healthcare professional receive for completing the REMS education/training and how long will it take to complete?		7
What are the components of this REMS program?		4
Who are you?		3
What are the goals of this REMS program?		2
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
Who can submit a grant application to support independent, accredited ER/LA Opioid Analgesics REMS prescriber education/training?	7	
Does this REMS Program require pharmacists to counsel patients on the safe use of ER/LA opioid analgesics?	7	
If I am a CE provider, what is the process for applying for grant monies?	6	
What pain medicines are included in this REMS Program?	5	
How can pharmacists obtain the product-specific Medication Guides?	5	
What if I have previously completed a/an [opioid, TIRF1, Butrans, Embeda, Exalgo, Opana, OxyContin] REMS training, do I still need to complete additional education/training for the REMS Program?	4	
How do I find the Website/Access this/Troubleshoot that?	3	
Can you tell me more about the safety education/training intended for prescribers, such as myself?	3	
What areas of education are contained in the FDA's ER/LA Opioid Analgesics REMS 'Blueprint'?	3	

Since November 9, 2012, there were 33 calls that could be classified as "reports of problems". The followings are the three types of problems that were reported:

- 17 requests to have the mailing list updated or corrected. As a result, all appropriate and possible changes to the mailing lists were made by the REMS Communication Vendor.
- 9 complaints were received regarding the unused medication disposal information stated in the PCD: "Do flush unused medication down the toilet". The RPC continues to monitor any

complaints of this nature. Considerations of other methods of disposal, such as, certified drug take-back programs that may be available in the community, has been modified to the FAQ.
- 7 reports were received that the website malfunctioned. The website vendor resolved the website malfunction reports and access issues.

RPC requests that FDA consider removing or revising the requirement for a centralized call center. The followings are the rationales provided by the RPC:

- On average, the call center handles only 10 calls per week
- 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.
- There were only 21 abandoned calls since the call center has been in place and this factor has been eliminated as an explanation for the consistently low call volume.
- The ER/LA REMS website remains the most consistently used and informative element of the REMS.
- The ER/LA REMS website remains an efficient, effective method of connecting stakeholders to important safety information, REMS communications, FAQs, and CME/CE.
- The ER/LA REMS website contains readily accessible contact information for RPC member companies and links so specific products' prescribing information and Medication Guide.
- Stakeholders may contact the Grants Management Vendor by e-mail via the website for targeted or technical CME/CE questions.
- The RPC has developed new FAQs and enhanced existing FAQs for all stakeholders

RPC proposed an alternative to decommissioning the call center, which is to replace the current call center structure with an interactive voice mail/message retrieval system. The followings are the rational for this alternative approach:

- Call volume has been consistently low
- An interactive system would allow callers to select information based on prompts specific to the stakeholder without any hold time.
- 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.
- The interactive system could direct callers to the website.
- Product-specific questions or potential AE or product complaints could continue to be directed to the appropriate member company for processing.

Reviewer comments:
The performance of the call center is acceptable.

There is a value to maintain the call center because:
1) new questions will be posed as program rolls out
2) call volume increased in the 12-month assessment period compared to the 6-month period

3) the baseline survey results showed that only 16% of survey respondents were aware of the ER/LA opioid analgesics REMS website
4) the baseline survey results showed that 161 (27%) survey participants reported having questions about the Medication Guide, DDRP letter, PCD, or ER/LA opioid REMS website.

The proposal to replace the current call center with an interactive voice mail/message retrieval system seems acceptable. However, there will be limitations, such as, inability to reach the caller when returning the call in the next business day.

4.1.4 Patient Counseling Document (PCD)

During this reporting period between November 9, 2012 and May 10, 2013, the PCD has been downloaded 1,920 times. One order for a copy of the PCD was fulfilled by the ER/LA REMS call center. Additionally, 241 PCD orders equating to 584 pads were received and shipped. The sponsor stated that the PCD would continue to be readily accessible to all stakeholders through multiple modalities.

Reviewer comments:
The accessibility of PCD is acceptable.

4.2 Assessment 1- Prescribers Training

The 2013 REMS-compliant accredited CME/CE RFA was disseminated via posting on the RPC website and Grants Management Specialist (GMS) on May 21, 2013. RPC assured broad awareness of this RFA through mass e-mail dissemination to various stakeholders. Two informational webinars were hosted by RPC on May 7 and June 13, 2013. Grant applicants will submit all RFA proposals for consideration in the 2013 grant cycle by 5 p.m. ET on July 16, 2013.

The first REMS-compliant CME/CE training supported by the RPC was launched on February 28, 2013. Table 2 provided a description of all REMS-compliant CME/CE activities offered by grantees since the 6-month report.

Table 2. REMS-compliant CE 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.

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.				

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.

Nine REMS-compliant education activities supported by RPC were launched between February 28 and May 4, 2013. Eight unique CME/CE provider organizations presented the nine activities. These activities received accreditation from five different National Accrediting Bodies. Eight of the activities were presented as live training activities and one activity was presented in an internet-based format.

From the activity launch through May 10, 2013, a total of 1,147 prescribers completed the training. Among those, 856 (74.6%) prescribers completed the training through live activities and 291 (25.3%) completed training via internet-based activities. The majority of the prescribers completing the training during this period were physicians (n=846, 73.7%). Of the prescribers completing the training, 21.9% (n=251) were advanced practice nurses and 3.3% (n=38) were physician assistants. Approximately 1% of the remaining prescribers completers of the training were podiatrists (n=3), pharmacist (n=2), dentist (n=2), and other (n=5). Practice type data was collected on 753 prescribers. Of these prescribers for whom these data is available, 496 (65.8%) were in primary care practice, 20.8% (n=157) were non-pain specialists, and the remaining 13.2% (n=100) were pain specialists. Table 3 presents an overview of the REMS-compliant, RPC-supported education activities.

Table 3. Prescribers completing the REMS-compliant, RPC-supported education activities

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	

					(b) (4)
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] "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."

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

Reviewer comments:
The date of CE availability of February 28, 2013 met the established performance goal of the first REMS-compliant training becoming available by March 1, 2013. The number of prescribers completing the REMS-compliant training as of the data cutoff for this report is too low to allow

adequate evaluation of uptake of the training. The RPC and grantees should develop strategies to increase the number of prescribers completing the training.

4.3 Assessment 2- Independent Audit of CE Activities

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. Initial efforts has been focused 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. This evaluation will be provided in the two-year assessment report.

Reviewer comments:
The progress in this assessment is appropriate.

4.4 Assessment 3a- Evaluation of Prescriber Understanding

An evaluation of prescribers' understanding of the serious risks of ER/LA opioid analgesics will be included in the three-year assessment report.

While not a requirement of the REMS, the RPC has elected to conduct a baseline prescriber survey to measure prescriber understanding and behaviors prior to the availability of REMS-compliant training. Qualitative pre-testing was conducted in December 2012. The baseline prescriber survey and the future prescriber surveys 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 baseline prescriber survey was a cross-sectional survey self-administered through a secure website. It was launched on February 8, 2013, prior to the availability of the first REMS-compliant CME/CE activity on February 28, 2013. Invitations were mailed via USPS and faxed to active prescribers of ER/LA opioids. To reach the targeted sample size of 600 prescribers, the survey recruitment period was extended until April 17, 2013. A total of 710 prescribers agreed to participate in the survey and 672 prescribers met the eligibility criteria. Among the 605 prescribers who completed the survey, 314 prescribers completed the survey prior to the first REMS-compliant CME/CE activity on February 28, 2013, and an additional 291 prescribers completed the survey on or after that date.

4.4.1 Survey Participants

The majority of survey respondents were male (n=407, 67.3%). The distribution of respondents by geographic region was similar to the total number of ER/LA opioid prescribers. Compared to all prescribers who have prescribed an ER/LA opioid within the last 12 months, fewer survey participants were medical doctor (46.9% vs. 73.05%) or doctor of osteopathy (3% vs. 8.42%), more survey participants were nurse practioner (23.5% vs. 8.39%), or physician assistant (25.5% vs. 6.92%). Of the respondents with and MD or DO degree, most (n=294, 97.4%) had practiced medicine for more than 15 years. Table 4 below compares the survey participants with all ER/LA opioid analgesic prescribers by healthcare degree. Table 5 compares the survey participants with all ER/LA opioid analgesic prescribers by medical specialty.

Table 4. Survey participants compared with 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	%
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				
Veterinarian				
Dentists				
Optometrists				
Unknown				
Total	605	100		

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

Table 5. Survey participants compared with 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	%
General Practice	307	50.7	(b) (4)	
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		

			(b) (4)
Pain Medicine	55	9.1	
Other	47	7.8	
Total	605	100	

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

4.4.2 Survey Results on Key Risk Messages

The following tables 6-10 provided survey results to the five key risk messages that assessed in the baseline prescriber survey.

Table 6. 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 7. 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 8. 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 9. 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
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 10. 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
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	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

An analysis was done comparing the scores stratified by those who completed the survey before and after the launch of the first REMS-compliant CME/CE activities on February 28, 2013. The 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. The key risk message scores for respondents who completed the survey before or after February 28, 2013 were similar. Most respondents scored between 70% and 90% on the key risk messages.

4.4.3 Survey Results on REMS Educational Materials

Approximately half of the survey respondents (44%) indicated that they were aware of the Medication Guide; 27.3% indicated that they were aware of the DDRP letter; and 32.2% were aware of the PCD, and 16% were aware of the ER/LA opioid analgesics REMS website prior to taking the survey. Some survey participants (n=161, 26.6%) reported having questions about the Medication Guide, DDRP letter, PCD, or ER/LA opioid REMS website.

Table 11. 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.

4.4.4 Survey Results on Prescriber Behaviors

Prescribers were asked to indicate the practices they followed when treating patients with ER/LA opioid analgesics. Table 12 showed the prescriber behaviors regarding safe use of ER/LA opioid analgesics. Table 13 showed the survey responses to survey questions regarding the frequency of following specific safe use behaviors.

Table 12. Prescriber behaviors regarding safe use of ER/LA opioid analgesics

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 13. Frequency of prescribers' safe use behaviors

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

Reviewer comments:

The under-representation of medical doctor and doctor of osteopathy and over-representation of nurse practitioner and physician assistant in the baseline prescriber survey may have biased the survey results towards higher or lower knowledge rates which may lead to lower or larger intervention effects by comparing the post-training prescriber knowledge rate with the baseline prescriber knowledge rate. In order to examine whether medical doctor and doctor of osteopathy perform differently than nurse practitioner and physician assistant, stratified analysis of knowledge rates by these four categories of medical degrees should be conducted in future surveys.

The baseline prescriber survey results demonstrated that most prescribers were informed about the risks and safe use conditions associated with ER/LA opioid analgesics. The majority (79%) of the key risk message questions/items were answered correctly. The most common themes of the questions/items answered incorrectly were related to opioid tolerance and conversion.

Responses to the survey questions regarding prescribers' behavior regarding safe use of ER/LA opioid analgesic products showed there is a need to improve prescribers' behavior to use the PCD when discussing the proper use of opioids with patients, to advise patients how to safely taper ER/LA opioid dose when discontinuing, and to explain what patients should do if they miss a dose of their ER/LA opioids.

In order to understand better prescribers' and patients' understanding of each domain of key risk messages, frequency distribution of the number and percentage of survey participants who got 0, 1, 2, etc., correct responses across the total number of items for each given key risk message should be provided for future prescriber and patient surveys.

The findings from the baseline prescriber survey that 161(27%) survey participants reported having questions about the Medication Guide, DDRP letter, PCD, or ER/LA opioid REMS website and only 16% were aware of the ER/LA opioid analgesics REMS website support the decision to maintain the REMS call center or replace it with an alternative consumer service system.

4.5 Assessment 3b- Long-term Evaluation Grants

An RFA will be issued to solicit applications for special grants to CE providers who also agree to conduct long-term evaluation of prescribers who have completed REMS-compliant training to determine their knowledge retention and practice changes six months to one year after completing the training. Since this long-term evaluation will not begin until 6 to 12 months after REMS training, the details of the evaluation grants were in development at the time of this report.

Reviewer comments:
None.

4.6 Assessment 4- Patient Survey

An evaluation of patients' understanding of the serious risks of ER/LA opioid analgesics will be included in the two-year assessment report.

4.7 Assessment 5- Surveillance Monitoring for Misuse, Abuse, Overdose, Addiction, Death, and Intervention Taken

To be provided in future assessment reports starting from year two.

4.8 Assessment 6- Evaluation of Drug Utilization Patterns

To be provided in future assessment reports starting from year two.

4.9 Assessment item 7- Evaluation of Changes in Prescribing Behavior

To be provided in future assessment reports starting from year two.

4.10 Assessment item 8- Changes in Access to ER/LA Opioid Analgesics

To be provided in future assessment reports starting from year two.

4.11 Applicant's overall assessment of whether the REMS is meeting the goals

The applicant stated in this report that the operational aspects of the ER/LA opioid analgesics REMS continued to function effectively during this time period.

5 CONCLUSION

This assessment report is complete and addresses all issues relevant to 12-month assessment outlined in the approved REMS assessment plan.

We conclude that all ER/LA opioid analgesic REMS requirements have been met for the 12-month assessment period.

7 RECOMMENDATIONS

On August 28, 2013, DRISK, DAAAP, and the Office of Compliance met to discuss the conclusion based on the data in the assessment report. There was consensus that the 12-month assessment report was complete and the REMS goals were met for the 12-month assessment period. The review team also agreed that the sponsors' request to replace the centralized call center with an interactive voice mail/message retrieval system was reasonable recognizing that there would be limitations associated with the proposed voice mail/message retrieval system. We recommend that the applicants be sent a REMS complete with comments letter.

Please send the following comments to the applicants:

- *We acknowledge that the REMS-compliant training just began in March, but also note that the number of prescribers completing the REMS-compliant training as of the data cutoff for this report is low. You should develop and provide plans to increase the number of prescribers completing the training so that the performance goals for the REMS compliant training may be met.*

- *Your request to replace the centralized call center with an interactive voice mail/message retrieval system is reasonable.*

- *In future prescriber surveys, conduct a stratified analysis of the knowledge rates of the key risk messages by survey participants' medical degrees of medical doctor, doctor of osteopathy, nurse practitioner, and physician assistant, and by prescribers' medical specialties.*

- *In future prescriber and patient surveys, provide frequency distribution of the number and percentage of survey participants who got 0, 1, 2, etc., correct responses across the total number of items for each given key risk message.*

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/s/

JING JU
08/30/2013

MARY E WILLY
08/30/2013
I concur