Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Review of a 36-Month Risk Evaluation and Mitigation Strategy (REMS) Assessment Report

Date:	June 29, 2016
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Therapeutic Class:	Extended-Release and Long-Acting opioid analgesics (ER/LA)
Submission Dates:	July 7-13, 2015

Drug Name	Application Type/ Number	Applicant/ Sponsor	eCTD sequence #	SDN	Submission Date
BELBUCA (buprenorphine)	NDA 207932	Endo	approved after submittal date		
BUTRANS (buprenorphine)	NDA 021306	Purdue	142	357	7/8/2015
DURAGESIC (Fentanyl Transdermal	NDA 019813	Janssen	131	795	7/7/2015
fentanyl	ANDA 077449	Aveva	26	98	7/9/2015
fentanyl	ANDA 077154	Mallinkrodt	62	125	7/9/2015
fentanyl	ANDA 076258	Mylan Techno	50	213	7/9/2015

Drug Name	Application Type/ Number	Applicant/ Sponsor	eCTD sequence #	SDN	Submission Date
fentanyl	ANDA 077775	Noven	99	112	7/9/2015
fentanyl	ANDA 077062	Par	50	130	7/8/2015
fentanyl	ANDA 076709	Watson	No Submission		
ZOHYDRO ER (hydrocodone bitartrate)	NDA 202880	Zogenix	74	173	7/13/2015
HYSINGLA ER (hydrocodone bitartrate)	NDA 206627	Purdue	48	70	7/8/2015
EXALGO (hydromorphone hydrochloride)	NDA 021217	Mallinkrodt	153	429	7/9/2015
hydromorphone hydrochloride	NDA 202144	Actavis	No Submission		
hydromorphone hydrochloride	NDA 204278	Paddock	No Submission		
DOLOPHINE (methadone hydrochloride)	NDA 006134	Roxane	41	155	7/8/2015
methadone hydrochloride	ANDA 203502	Aurolife Pharma	approved after submittal date		
methadone hydrochloride	ANDA 090065	CorePharma	approved after submittal date		
methadone hydrochloride	ANDA 040517	Mallinkrodt	38	81	7/9/2015
methadone hydrochloride	ANDA 087393	Roxane	33	111	7/9/2015
methadone hydrochloride	ANDA 089897	Roxane	30	125	7/9/2015
methadone hydrochloride	ANDA 087997	Roxane	31	88	7/9/2015
methadone hydrochloride	ANDA 040241	Sandoz	No Submission		
methadone hydrochloride	ANDA 090635	ThePharma Network	34	38	7/9/2015
methadone hydrochloride	ANDA 090707	VistaPharm	29	43	7/9/2015
METHADOSE (methadone hydrochloride)	ANDA 040050	Mallinkrodt	37	103	7/9/2015
EMBEDA (morphine sulfate and naltrexone hydrochloride	NDA 022321	Alpharma	132	278	7/9/2015
KADIAN (morphine sulfate)	NDA 020616	Watson	56	579	7/9/2015
MORPHABOND (morphine sulfate)	NDA 206544	Inspirion Delivery Technologies	approved after submittal date		
morphine sulfate	ANDA 203849	Actavis	No Submission		
morphine sulfate	ANDA 79040	Actavis	No Submission		
morphine sulfate	ANDA 076412	Mallinkrodt	39	120	7/9/2015
morphine sulfate	ANDA 76438	Mallinkrodt	37	82	7/9/2015
morphine sulfate	ANDA 200824	Mylan	47	50	7/9/2015
morphine sulfate	ANDA 77855	Nesher	No Submission		

Drug Name	Application Type/ Number	Applicant/ Sponsor	eCTD sequence #	SDN	Submission Date
morphine sulfate extended-release	ANDA 203602	Novel Labs, Inc.	approved after submittal date		
morphine sulfate	ANDA 76720	Nesher	No Submission		
morphine sulfate	ANDA 76733	Nesher	No Submission		
morphine sulfate	ANDA 200812	Par	41	54	7/8/2015
morphine sulfate	ANDA 078761	Ranbaxy	31	54	7/9/2015
morphine sulfate	ANDA 074769	Rhodes	No Submission		
morphine sulfate	ANDA 074862	Rhodes	No Submission		
morphine sulfate	ANDA 202718	Teva	30	31	7/9/2015
morphine sulfate	ANDA 202104	Upsher-Smith	4	40	7/9/2015
morphine sulfate	ANDA 075295	Vintage	45	151	7/9/2015
MS CONTIN (morphine sulfate)	NDA 019516	Purdue	60	459	7/8/2015
OXYCONTIN (oxycodone hydrochloride	NDA 022272	Purdue	256	345	7/8/2015
TARGENIQ ER (oxycodone HCl and naloxone HCl)	NDA 205777	Purdue	63	64	7/8/2015
OPANA ER (oxymorphone hydrochloride) (old)	NDA 021610	Endo	74	511	7/9/2015
OPANA ER (oxymorphone hydrochloride) (new)	NDA 201655	Endo	130	250	7/9/2015
oxymorphone hydrochloride	ANDA 079046	Actavis	No Submission		
oxymorphone hydrochloride	ANDA 079087	Impax	39	117	7/8/2015
oxymorphone hydrochloride	ANDA 202946	Mallinkrodt	25	31	7/9/2015
oxymorphone hydrochloride	ANDA 200792	Par	30	32	7/8/2015
oxymorphone hydrochloride	ANDA 200822	Roxane	36	45	7/8/2015
oxymorphone hydrochloride	ANDA 203506	Sun	17	18	7/9/2015
NUCYNTA ER (tapentadol)	NDA 200533	Janssen	141	381	7/9/2015

1 Executive Summary

This review includes an analysis of five elements of the 36-month Extended-Release and Long-Acting (ER/LA) Risk Evaluation and Mitigation Strategy (REMS) assessment report (elements 1, 2, 3a & b, 4 and 8) as well providing an overall evaluation of all elements of the assessment report. This assessment report was submitted by the ER/LA Opioid Analgesic Applicant holders, also known as the REMS Program Committee (RPC), and is the fourth assessment report since approval of the ER/LA REMS on July 9, 2012, and the first assessment report to address a specific numeric goal for REMS-compliant training. The findings from this assessment were presented and discussed at the May 3-4, 2016 Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC). A number of recommendations for modifications to the program were provided by the Advisory Committee and the Agency is considering how best to proceed in making these changes. The reviewer comments and recommendations in this review, however, represent the Agency's review of the 36 month ER/LA Opioid analgesic REMS Assessment; any recommendations should be considered as interim recommendations as we continue to determine our next steps.

The goal of the ER/LA Opioid Analgesic 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 interest include addiction, unintentional overdose, and death.

The primary intervention of this REMS is prescriber training (assessment element 1) made available through accredited continuing education (CE) programs funded by the RPC. The training is based upon the FDA blueprint for Prescriber Education for Extended-Release and Long-Acting Opioids. The goal of this training is to sufficiently inform prescribers such that serious adverse outcomes (such as addiction, unintentional overdose, and death) will be reduced by reducing inappropriate prescribing, misuse and abuse. Prescribers are not required to take the training in order to prescribe ER/LA opioid analgesics. A total of 37,512 ER/LA opioid analgesic prescribers have completed RPC-supported REMS-compliant training, which represents 47% of the milestone of 80,000 which was to be achieved by March 1, 2015. While the prescriber milestone wasn't met, over 100,000 health professionals overall have taken the RPC-funded training. Potential factors that may have an impact on why the goal of 80,000 prescriber-completers has not been achieved include: 1) how "prescribers" are defined, and 2) the large number of competing CE programs. To-date, the RPC has issued four Requests for Applications (RFAs) and has awarded funding for over 500 REMS-compliant CE programs through 19 grants to accredited CE providers. Thus the RPC has made significant strides in making REMS-compliant training available. The RPC should continue to explore other means of increasing awareness of the REMS-compliant trainings. Regarding the RPC's audits of CE Activities, 9 of the 29 audit reports had issues related to disclosure of financial relationships.

Two prescriber surveys were included in this evaluation (assessment elements 3a & b). In the survey conducted as a follow-up to the 2013 baseline prescriber survey conducted in 2013 ("follow-up survey"), across all key risk messages, completing a CE activity significantly increased the likelihood of answering questions correctly. The second survey (long-term evaluation survey) of prescribers included in this assessment, surveyed prescribers 6-12 months following participation in a REMS training. The results of this survey demonstrated that since participating in a REMS-compliant activity, respondents reported more often conducting appropriate prescriber behaviors (i.e. counseling on risks and side effects, using tools to screen patients for risk or misuse and abuse, completing a Patient-Prescriber Agreement). In

addition, findings of surveys of patients (assessment element 4) submitted in this assessment, show similar knowledge to that found in the 24-month assessment, and respondents showed a good understanding ER/LA opioid analgesics risks. However, across all surveys, respondents were not representative of the general population of prescribers and patients that use ER/LA opioid analgesics, so one main concern with the three surveys is generalizing their results to the targeted population of interest. Those choosing to take the CE may differ from the ER/LA opioid analgesic prescriber population in general. The two prescriber surveys are convenience samples of the targeted population of ER/LA opioid analgesic prescribers. The patient survey is also a convenience sample of the targeted patients who were prescribed ER/LA opioid analgesics. The 36-month REMS assessment report did not provide comparisons of the characteristics of the survey respondents to those of the targeted population for each of the surveys. Thus, it is impossible to assess whether or how the results of these surveys can be generalized to the population. The FDA statistical review recommended that future survey analyses: (1) compare characteristics of survey participants to its target population for each survey; and (2) propose methods to standardize the results of each survey to its targeted population. The RPC should submit a concept paper for alternate study designs for evaluation of prescriber and patient knowledge.

According to the Division of Epidemiology II (DEPI II) review[1], the surveillance studies (assessment element 5) suggest encouraging downward trends in some, but not all, clinical outcomes; however, they do not indicate whether the REMS itself is contributing to these changes. The submitted surveillance studies may provide some useful contextual information but are unable to show whether the ER/LA Opioid Analgesic REMS is making progress toward the goal of reducing serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of these drugs. Nor do the studies demonstrate that the REMS is failing to achieve its goals. Overall, each of the surveillance studies had considerable methodological limitations. The RPC should be encouraged to explore methods to conduct a more robust examination of the outcomes of interest in prescribers that undertook training in comparison to those that did not take the training. that .

The DEPI II review[2] of drug use patterns and prescribing behaviors (assessment elements 6 and 7) concludes that although significant decreases were noted in ER/LA opioid analgesic prescriptions, the clinical significance of these changes is unclear. In addition, the noted decreases began prior to l REMS implementation and are largely driven by decreases in oxycodone ER prescriptions. Data sources that can compare the prescribing activity of trained versus non-trained prescribers as well as the appropriateness of the prescribing are needed to fully assess the impact of the REMS on utilization of these products as well as prescribing patterns.

Patient access was evaluated using patients identified as having been dispensed prescriptions for ER/LA opioid analgesics and their responses to a specific survey, however this information alone cannot

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[1] May 19, 2016 DEPI (J. McAninch) Epidemiology: Review of Post-marketing Studies included in the 36-month REMS Assessment Report

[2] DEPI II's Review of 36th Month Assessment of the Risk Evaluation and Mitigation Strategy for the in the FDA Briefing Document for the May 3-4, 2016 Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) regarding the ER/LA REMS (Backgrounder pages 217-249)

definitively assess whether the REMS has had an effect on this metric. The RPC should submit a concept paper for an alternate approach to evaluating the impact of the REMS on patient access.

Findings from the 36th Month ER/LA Opioid Analgesics REMS Assessment show mixed results that make it difficult to draw conclusions regarding the success of the program. While a relatively large number of healthcare providers overall have taken the voluntary CE training, the proportion of targeted prescribers who actually took the voluntary training is consistent with participation rates for other REMS with voluntary training. The hope was that CE credits, awarded as part of the training, would incentivize targeted prescribers to take the REMS - compliant CE training, and completion of training would lead to safe and responsible ER/LA opioid prescribing and patient counseling on the risks, safe use, and safe storage of ER/LA opioid analgesics. Though we are encouraged by the uptake of the ER/LA Opioid Analgesics REMS training by both the targeted prescribers as well as other HCPs, it is likely too early to see widespread impact of this training on prescriber behavior and subsequent impact on the adverse events of interest (addiction, unintentional overdose, and death). Also confounding the evaluation of impact of the ER/LA Opioid Analgesics REMS are the multiple competing educational programs offered by other federal agencies and requirements for pain and/or opioid education by individual states, and other interventions put in place during the same time period in different parts of the country.

2 Introduction

The 36-month ER/LA Opioid Analgesic REMS assessment report was submitted by the REMS Program Companies (RPC) on July 7-13th, 2015 for ER/LA Opioid Analgesics (referred to in this document as ER/LA REMS) to determine if the assessment is complete and if the goals of the REMS are being met. This REMS assessment report covers the period from May 11, 2014 through May 9, 2015. The elements are as follows:

Assessment Element 1: Assessment of how many prescribers of ER/LA opioid analgesics have successfully completed the training. Specify performance goals for the number of prescribers trained by time.

Assessment Element 2: Independent audit of the quality of the content of the educational materials used by the CE Providers to provide the education. The audit should evaluate the quality of the content against the content approved by FDA as part of the REMS, as well as against the ACCME's and other accrediting bodies' standards for commercial support.

Assessment Element 3a: Prescriber Survey (Follow-up 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: Prescriber Survey Long-term Evaluation

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 setting

Assessment Element 6: Evaluation of drug utilization patterns

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: Evaluation of Patient Access

This review includes an analysis of elements 1, 2, 3a & b, 4 and 8 as well providing an overall summary evaluation of all elements of the assessment report. DEPI II conducted in-depth analyses[3] [4] of elements 5, 6, and 7. DB7 conducted statistical reviews[5] [6]of elements 3a, 3b, 4, 5, 6, and 7.

3 Review Materials

The following is a list of materials informing this review:

- March 28, 2014 DRISK (J. Ju) review of Review of Proposed Methodology and Survey Instruments
- May 13, 2015 response from the RPC to an April 9, 2015 IR from the FDA (regarding patient access)
- July 7 – 13, 2015 36-month REMS Assessment Report from the RPC
- July 23, 2015 36-month REMS Assessment Report Errata from the RPC
- August 4, 2015 response from the RPC to a July 21, 2015 IR from FDA (re: prescriber training completer totals)
- August 14, 2015 response from the RPC to an August 4, 2015 IR from FDA (re: prescriber training completer totals)
- September 21, 2015 response from the RPC to a September 4, 2015 IR from FDA (re: patient survey)
- September 25, 2015 response from the RPC to a September 4, 2015 IR from FDA (re: patient survey)
- September 28, 2015 Amended 36-month REMS Assessment Report from the RPC

[3] May 19, 2016 DEPI (J. McAninch) Epidemiology: Review of Post-marketing Studies included in the 36-month REMS Assessment Report

[4] DEPI II's Review of 36th Month Assessment of the Risk Evaluation and Mitigation Strategy for the in the FDA Briefing Document for the May 3-4, 2016 Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) regarding the ER/LA REMS (Backgrounder pages 217-249)

[5] December 11, 2015 DB7 (J-Y Lee & Y-H Hsueh) Statistical Review and Evaluation of a REMS Assessment

[6] December 11, 2015 DB7 (Y-H Hsueh) Statistical Review and Evaluation of REMS Knowledge Surveys

- October 26, 2015 response from the RPC to an October 22, 2015 IR from FDA (re: prescriber training completer totals)
- November 13, 2015 response from the RPC to a November 10, 2015 IR from FDA (re: identity of accrediting bodies)
- December 11, 2015 DB7 (J-Y Lee & Y-H Hsueh) Statistical Review and Evaluation of a REMS Assessment
- December 11, 2015 DB7 (Y-H Hsueh) Statistical Review and Evaluation of REMS Knowledge Surveys
- DEPI II's Review of 36th Month Assessment of the Risk Evaluation and Mitigation Strategy for the in the FDA Briefing Document for the May 3-4, 2016 Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) regarding the ER/LA REMS (Backgrounder pages 217-249)
- May 19, 2016 DEPI (J. McAninch) Epidemiology: Review of Post-marketing Studies included in the 36-month REMS Assessment Report.

4 REVIEW RESULTS

4.1 Assessment Element 1 - Prescriber Training

This assessment element states:

> *Documentation of the number of prescribers of ER/LA opioids who have completed REMS-compliant training. Performance goals based on the 2011 estimate that 320,000 prescribers are active prescribers of ER/LA opioids (prescribers who have prescribed an ER/LA opioid within the last 12 months), are as follows:*
>
> - *Within two years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of active prescribers) are to have been trained*

The REMS Supporting Document (SD) states that a secondary outcome measure will be the number of prescribers who have completed some but not all portions of a training activity. The SD also states that an independent non-industry party is to produce the report (compiled from all accredited CE providers) of the number of prescribers who have taken the training by profession type and by other characteristics.

4.1.1 RPC Data for Prescriber Training

REMS compliant-training is characterized as: 1) training offered by an accredited CE provider to licensed prescribers; 2) includes all elements of the FDA Blueprint; 3) includes a knowledge assessment of all of the sections of the Blueprint, and 4) is subject to independent audit.

While the ER/LA REMS was approved on July 9, 2012, the first RPC-supported REMS-compliant CE activity was launched on February 28, 2013. This REMS represents the first time that accredited CE has been used to fulfill a REMS training requirement. "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 analgesic prescription in the past year*." Completion of an activity is defined as "*prescribers that have completed all components of an educational activity including instruction, assessment of learning, and potentially evaluation*."[7]

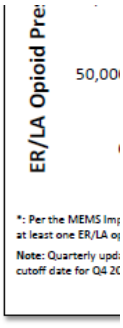
[7] These criteria were determined based on prescribers' self-attestation.

The data cut-off for this current 36-month report was February 28, 2015, which represents the 2-year mark and the first training milestone of 80,000 prescribers completing REMS-compliant training. The previous assessment report indicated that 20,345 ER/LA opioid analgesics prescribers completed RPC-supported REMS-compliant training (February 28, 2013 – February 28, 2014). During this reporting period (March 1, 2014- February 28, 2015), data from the RPC's October 26, 2015 response to an FDA information request) an additional 17,707 prescribers completed the training. The overall total number of ER/LA opioid analgesic prescribers completing REMS-compliant is **37,512**, a total which represents 47% of the 2 –year goal of 80,000. The RPC states that any additional prescriber completer totals which result following resolution will be included in the 48-Month Report.

On October 26th 2015, in response to an FDA information request, the RPC provided updated data regarding the number of CE training participants, completers, and ER/LA prescriber completers current as of 2/28/15. The RPC emphasizes that while CE providers collect these data, the data are not required for reporting to accreditors and thus RPC-funded CE providers provide these data informally. However, the RPC was able to provide these informal, unaudited data in Figure 1 below which displays the cumulative number of participants, completers, and ER/LA prescriber completers. Data presented is based on the definitions below. It should be noted that the completers and ER/LA prescriber completers are subsets of the total number of participants.

- Participant- an individual who at the time of data reporting had only partially completed the CE activity
- Completer- an individual that has completed all components of an educational activity and meets the criteria for passing
- ER/LA prescriber completer- A clinician registered with the DEA to prescribe Schedule II and/or III controlled substances and has written at least one ER/LA prescription in the past year, has completed all components of an educational activity, and meets the criteria for passing.

Figure 1: Cumulative Number of Participants, Completers, and ER/LA Prescriber Completers Reported Directly from RPC-supported CE Providers (from 10/26/15 IR response)



Source: October 26, 2015 RPC response to an October 22, 2015 FDA Information Request

Figure 1 reveals that as of May 28, 2015, only 53% of healthcare providers (HCPs) who start a REMS-compliant CE program actually complete the activity. Of these completers, only 38% self-identify as ER/LA prescribers. Additionally, the RPC reports that CE providers indicate that approximately 60% of HCPs completing REMS-compliant CE have stated that they had not written a prescription for an ER/LA opioid analgesic in the past year and thus cannot be counted toward the REMS completer goal.

The majority of ER/LA prescribers completers (N=38,370) were physicians (approximately 67%). The remaining prescribers were advanced practice nurses (approximately 24%), physician assistants (approximately 7%) and "other" (approximately 3%). For those prescribers for whom a practice area was reported (N= 11,184), 66.4% were primary care physicians, 21% were "non-pain specialists" and 12.6% were pain specialists.

Regarding REMS-compliant CE education activities, cumulatively, 507 of these have been launched. Of these, 253 were available during this reporting period. A total of 220 activities were presented as live training, 32 were internet-based enduring programs and one program was in the form of print materials. All activities were accredited by at least 1 of 6 National Accrediting Bodies.[8] A description of all REMS-compliant CE activities available March 1, 2014 to February 28, 2015, arranged by grantee, is provided in **Table 1** below (reproduced directly from the RPC report's Table 4):

[8] Accreditation Council for Continuing Medical Education (ACCME); American Academy of Family Physicians (AAFP); American Osteopathic Association (AOA); Accreditation Council for Pharmacy Education (ACPE); American Nurses Credentialing Center (ANCC); and American Academy of Physician Assistants (AAPA)

Table 1: RPC-Supported REMS-compliant Continuing Education Activities Available During the Reporting Period (March 1, 2014- February 28, 2015)

Dannemiller,	
TOTAL	

[1] The table is
first activity.

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

There have been 18 non-RPC supported CE activities reported to ACCME (or other accreditors), with 1,747 prescriber completers. These 18 activities were "self-identified" as REMS-compliant by the CE provider. As reported previously by the RPC, the RPC itself cannot directly verify that non-RPC supported activities are REMS-compliant. Thus these prescribers are not included in the total number of prescriber completers reported in assessment element 2. The RPC reports that one non-RPC supported CE (presumably based upon the FDA Blueprint) was evaluated. The CD program, entitled *Safe Prescribing for Pain*, was mapped to the educational items contained within the FDA Blueprint. The evaluation revealed that 39% of the FDA Blueprint educational content was covered by this CE activity.

Each year, the RPC issues a Request for Applications (RFA) to secure, support and make available REMS CE programs that train HCPs on the ER/LA REMS FDA Blueprint. Since 2012, the RPC has issued 4 RFAs and awarded funding to support over 500 REMS-compliant activities through 19 grants to accredited CE providers and their 100+ educational partners. The RPC receives feedback from the CE Community,

including CE providers and the Conjoint Committee for Continuing Education (CCCE) prior to each RFA cycle. On March 10, 2015, the RPC issued two RFAs that were designed to ensure that a broad spectrum of REMS CE activities would be available to HCPs for 2016 and 2017. One of these, RFA 050315, asks proposers to detail novel educational initiatives that will increase the reach, attraction, and engagement of ER/LA opioid analgesic prescribers to increase their participation in and completion of REMS CE. It is hoped that the applicant will propose educational modalities and/or partnerships that are likely to yield more completers that prescribe ER/LA opioid analgesics.

The RPC states that they had expected that the goal of 80,000 ER/LA opioid analgesic prescribers could be exceeded based on their projection of 165,000 prescribers that could be reached by the CE Providers receiving funding. However, the RPC states that CE providers have informed them that it is considerably more challenging than expected to attract ER/LA opioid analgesic prescribers to participate in REMS-compliant activities and to keep them engaged through completion of the full activity and assessment. The RPC has identified three predominant challenges in getting prescribers to complete the trainings:

1. **Lack of awareness of the REMS and the importance of completing ER/LA opioid analgesic REMS-compliant CE:** A survey done by CO*RE in November and December 2013 (8 months after the launch of the first REMS-compliant CE activity) demonstrated that 41% of the 2,629 respondents were unaware of the FDA ER/LA REMS. The RPC has received the following additional information:
    a. The term “REMS” itself is not meaningful to prescribers;
    b. There is considerable ambiguity given the variability in clinician-related requirements from one REMS to another;
    c. Prescribers may find it difficult to distinguish between those that are and are not REMS-compliant;
    d. Prescribers who complete non-REMS compliant CE (such as those required for state licensure) are unlikely to complete REMS-compliant CE since prescribers may consider it redundant; and
    e. Prescribers may not complete REMS-compliant CE as they may think they already know the material.

2. **Education is not tailored to the adult professional learner:** the length of activities and the associated time commitment for completion, coupled with no accommodation for demonstration of prior knowledge or competency impacts prescriber willingness to complete REMS-compliant CE.

    The RPC has indicated based on feedback from REMS CE providers, accrediting bodies, the CCCE, and from learners that the rigidity and extent of content of the FDA Blueprint is not conducive to the type of education that is engaging to adult learners.

3. **Available opioid education competes with REMS-Compliant CE:** there are many non-REMS-compliant (hence non-RPC funded) CE activities regarding opioid available to clinicians, both online and in live settings that may potentially dilute the audience of ER/LA opioid analgesic prescribers who may complete the REMS-compliant CE activities (such as those that fulfill state-mandated licensure requirements; or endorsed by prominent, non-industry-related organizations such as NIDA, the Office of National Drug Control Policy (ONDCP), the Substance Abuse and Mental Health Services Administration (SAMHSA), etc.; or cover opioid risk management within the broader context of appropriate pain management). The RPC has conducted a keyword search to determine the number of non-RPC funded CE activities that may be returned if a prescriber attempted to search for CE activities related to opioids, controlled substances, pain management or another similar search term.

A total of 150 non-RPC-funded accredited CE activities related to opioid analgesics were reviewed and categorized. Key findings were:

a. 87% of the activities were "Non-REMS Opioid-Related CE"
b. 34% of these "Non-REMS Opioid Related CE" activities were endorsed developed, or funded by federal agencies such as NIDA, ONDCP, SAMHSA, and National Institute of Neurological Disorders and Stroke (NINDS)
c. 8% of the activities were identified by the CE Provider as "FDA Blueprint-Compliant"
d. A significant percentage met state-mandated CE requirements for license renewal. These included:
    - 100% (12 out of 12) of those non-RPC funded CE activities identified by the CE Provider as "FDA Blueprint-Compliant"
    - 38% of the "Non-REMS Opioid-Related CE activities"

In response to these identified challenges, the RPC states that they are implementing a REMS awareness campaign and have selected an awareness campaign vendor. This effort is to include ongoing communication with RPC-supported CE Providers to gain insights into challenges encountered in providing REMS-compliant CE and potential ways to increase awareness and prescriber completers. Part of this effort is to assess the desired look and feel for REMS-awareness materials, what the materials should convey, and potential suggestions for how the REMS awareness materials could be used. The RPC is considering a logo and tagline.

4.1.2 **Reviewer Comments**

1. A total of 37,512 ER/LA opioid analgesic prescribers have completed RPC-supported REMS-compliant training which represents 47% of the 2 year milestone of 80,000 for this report. However as of May 28, 2015, over 100,000 health professionals (this total includes the 37,512 aforementioned prescribers) have taken the RPC-funded training, There are likely a number of factors as to why the goal of 80,000 ER/LA prescriber-completers has not been achieved:
    a. The definition of "Prescribers" is "*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 analgesic prescription in the past year*." Thus this definition excludes prescribers who have only recently registered with the DEA as well as institutional prescribers.
    b. The RPC points out and the FDA is aware that there are a number of competing opioid educational programs (both private and governmental) for prescribers to choose from. In addition, the RPC also points out that 41% of prescribers in a survey done 8 months after the launch of the first REMS-compliant CE activity were unaware of this REMS.

2. To-date, the RPC has issued 4 RFAs and has awarded funding for over 500 REMS-compliant CEs through 19 grants to accredited CE providers. Thus the RPC has made significant strides in making REMS-compliant training available. However, the FDA should encourage the RPC to
    a. continue to explore ways to raise awareness about the availability of the ER/LA Opioid Analgesic REMS-compliant training programs; and
    b. Explore with the CE providers ways to capture the reasons why prescribers initiate a training but fail to complete it.

4.2 Assessment Element 2 – Audits of CE Activities

This assessment element states:

> *The results of an independent audit of the quality of the content of the educational materials used by the CE providers to provide the REMS-compliant training. Audits must be conducted on a random sample of at least 10% of the training funded under the ER/LA Opioid REMS, and a random sample of REMS-compliant training not funded under the ER/LA Opioid REMS that will be counted as REMS-compliant training for purposes of meeting the milestones in item 2 above and must evaluate:*
>
> *a. whether the content of the training covers all elements of the FDA "blueprint" approved as part of the REMS;*
> *b. whether the post-course knowledge assessment measures knowledge of all sections of the FDA "blueprint"; and*
> *c. whether the training was conducted in accordance with the Accreditation Council for Continuing Medication Education (ACCME) standards for CE or appropriate standards for accreditation bodies.*

The REMS SD states that the training should also be assessed as to whether or not the content is free from promotional material and that accreditation bodies of CE providers would be considered independent of the RPC and would be eligible to conduct the audits.

4.2.1 RPC Data for CE Audits

The RPC has audits conducted by parties that are independent of the NDA/ANDA holders and acceptable to various CE accrediting bodies. The audits evaluate whether:

- the content is factually correct;
- the training covers all sections of the FDA Blueprint;
- the post-course knowledge assessment measures knowledge of all sections of the FDA Blueprint; and
- the training was conducted in accordance with the standards for CE of the ACCME or other accrediting bodies; is independent of the pharmaceutical industry's influence; and the content is free from promotional material.

The CE activity audits are based on a random sample of at least 10% of the RPC-supported, REMS-compliant CE activities (and REMS-compliant training not funded by the RPC but that will be counted towards meeting the REMS performance goals).

Five nationally recognized accrediting bodies that have submitted independent audit reports are shown in Table 2 below (a reproduction of an RPC table).

Table 2: SUMMARY OF INDEPENDENT AUDIT REPORTS

AOA
TOTAL

American Academy of Family Physicians (AAFP); American Association of Nurse Practitioners (AANP); Accreditation Council for Continuing Medical Education (ACCME); American Nurses Credentialing Center (ANCC); and American Osteopathic Association (AOA).

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

Of the 29 audit reports received, 20 (69%) met the criteria for REMS-compliant CE. Nine of the 29 audit reports had issues related to disclosure of financial relationships. Of the 9:

- seven did not disclose relevant financial information;
- eight of the nine did not provide evidence that disclosure of either relevant financial information or of no financial relationships was made to learners prior to the beginning of the activity;
- six did not meet either financial disclosure requirement (noted above).

The RPC has reviewed the documentation for these 9 ACCME audit reports and views the issues as important but not impacting content. The RPC is following up with each provider to ensure appropriate remediation in a timely manner.

The RPC states that CE providers are informed that they are now required to submit activities for audit *prior to launch* so that any observations can be remediated prior to the program being available to the public. However, the RPC also admits that this is not possible for programs that were created and launched prior to implementation of the audit process. Regardless, the RPC requires CE providers to provide documentation of remedial actions taken to address any non-compliance observations (i.e., identify why the issue occurred, what procedures have been put in place to safeguard a repeat occurrence, and communicate with the CE provider a 'demonstration of compliance is a requirement for RPC-supported activities."

The 36-month assessment report did not include any information regarding audit results of non-RPC-funded REMS-compliant training. However, audits of these non-RPC-funded programs are required only

if these participants are to contribute to the total numbers trained. The RPC has indicated that they have no authority to audit programs that are not funded by them or unless they are requested by the other funder(s) to audit the programs.

4.2.2 **Reviewer Comments**

The FDA should encourage the RPC to in turn encourage their grantees to ensure that financial information regarding the authors of the REMS-compliant training is disclosed, and that the disclosure should be done prior to the beginning of the activity.

4.3 Assessment Element 3: Prescriber Surveys

This assessment element states:

Evaluation of Prescriber Understanding:

a. *The results of an evaluation of ER/LA opioid prescribers' awareness and understanding of the serious risks associated with these products and their awareness of appropriate prescribing practices for ER/LA opioids, comparing the awareness and understanding of prescribers who have taken the REMS-compliant training with those who have not taken such training. This evaluation may include, for example, surveys of healthcare providers.*
b. *The results of any long-term evaluation of prescribers of ER/LA opioid analgesics who have taken ER/LA Opioid REMS-funded training to determine these prescribers' knowledge retention and practice changes 6 months to 1 year after they completed the REMS-compliant training*.

4.3.1 **Assessment Element 3a – Follow-Up Prescriber Survey**

This survey of prescribers is a follow-up to the baseline prescriber survey. The baseline prescriber survey was conducted with 605 prescribers, who prescribed at least one ER/LA opioid analgesic in the last year as identified by the IMS XPonent database and who had not completed the REMS-compliant training, between February 8, 2013 and April 17, 2013. The results of the baseline survey were reported in the 12-month REMS assessment.

This follow-up survey was conducted two years post-launch of the REMS compliant CE in order to compare prescribers that took the REMS complaint CE training with prescribers that did not take the training. The assessment report states "The objectives of the follow-up prescriber survey are to: 1) assess the prescribers' understanding of the serious risks associated with the use of the ER/LA opioid analgesics and how to prescribe ER/LA opioid analgesics appropriately according to the six domains of the FDA Blueprint, 2) assess ER/LA prescribers' opioid prescribing behavior and practice, including questions from the five domains from the FDA Blueprint, where applicable and feasible, and 3) to assess prescribers familiarity with general and product-specific drug information concerning ER/LA opioid analgesics.

The FDA Blueprint includes six core messages for prescribers. Prescribers should:

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

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

The follow-up prescriber survey was pretested in 24 ER/LA opioid analgesic prescribers to assess comprehension and interpretation of the survey questions related to the key risk messages and to identify whether question or response options may be misunderstood. Findings and recommendations were incorporated into the final survey. User acceptance testing (UAT) was also conducted to test that the survey had been developed according to the user requirements and the protocol. Follow-up formal testing then occurred to ensure the system was compliant with the requirements.

Results

The follow-up prescriber survey was conducted between February and April 2015. Prescribers were eligible to participate if they had prescribed an ER/LA opioid analgesic at least once in the year prior to the survey. A total of 993 prescribers responded to the survey invitation. Of those 612 prescribers completed the survey (99% by internet and 1% via paper). Over half of the survey respondents were recruited from IMS data (n=311; 51%) and the remaining participants were invited by CE providers (n=301; 49%). Approximately 60% of respondents reported that they completed a REMS-compliant continuing education (CE). Of the prescribers surveyed, 70% prescribed Oxycontin ER, 69% prescribed fentanyl patch, 68% prescribed MS Contin, 53% prescribed Duragesic, and 51% prescribed morphine sulfate ER. Eight-one percent (81%) of respondents were transdermal patch prescribers, 49% were methadone prescribers, and 96% were oral ER/LA opioid analgesic prescribers. Over half of respondents were male (54%). Almost half of respondents were Doctors of Medicine (MD) (48%), followed by physician assistants (22%) and nurse practitioners (21%). Approximately 34% of MDs and Doctors of Osteopathy (DO) had been practicing medicine for over 15 years.

Survey respondents were more likely to have prescribed ER/LA opioid analgesics in the past month, were more likely to come from the west, and were more likely to have a specialty of pain management (22% survey vs. 1% IMS database) than those in the overall population of ER/LA opioid analgesic prescribers. It should be noted that the population of overall ER/LA opioid analgesic prescribers for this comparison was extracted from IMS in December of 2014, and includes 420,154 prescribers, which is 100,000 more ER/LA opioid analgesic prescribers than the FDA estimates that were used to determine the training targets of 320,000. We are awaiting further description from the RPC of the database used for this analysis (see Table 3 below).

Table 3: Description of Survey Participants

	Baseline (n=605)	**36-Month Survey (n=612)**
Gender	Male: 407 (67%) Female: 197 (33%)	Male: 333 (54%) Female: 274 (45%) Prefer not to answer: 5 (1%)
Medical Degree	MD: 284 (47%) DO: 18 (3%) Nurse Practitioner: 142 (24%) Advanced Practice Nurse:1 (1%) Physician Assistant: 154 (26%)	MD: 292 (48%) DO: 36 (6%) Nurse Practitioner: 127 (21%) Advanced Practice Nurse: 23 (4%) Physician Assistant: 134 (22%)
Specialty	General Practice: 307 (51%) Pain Medicine: 55 (9%) Internal Medicine: 51 (8%)	General Practice: 307 (51%) Pain Medicine: 55 (9%) Internal Medicine: 51 (8%)

Table 3: Description of Survey Participants		
	Baseline (n=605)	**36-Month Survey (n=612)**
	Orthopedics: 44 (7%) Oncology: 42 (7%) Rheumatology: 23 (4%) Neurology: 18 (3%) Anesthesiology: 9 (2%) Hospice/Palliative Care: 9 (2%) Other: 47 (8%)	Orthopedics: 44 (7%) Oncology: 42 (7%) Rheumatology: 23 (4%) Neurology: 18 (3%) Anesthesiology: 9 (2%) Hospice/Palliative Care: 9 (2%) Other: 47 (8%)

4.3.2 **Reviewer's comments:**

1. Respondents that were recruited from IMS data were assumed to not have taken a REMS compliant CE activity. Sixty percent (60%) of all respondents reported completing a REMS-complaint CE activity although only 49% of respondents were recruited from CE providers. There is no way to be certain that respondents categorized as IMS respondents did not take a REMS compliant CE training.
2. Some CE providers did not record how many invitations were sent out so a response rate is not provided. For future assessments, the CE providers should keep track of and report the number of invitations sent.
3. There is no information provided about how many CE providers participated in respondent recruitment and from how many CE providers the current respondents were recruited from. This information should be provided for the current and future assessments.
4. We recognize that there is overlap between some of the messages included in the Blueprint. After reconsideration of the current categorizations, we recommend changes to the key risk message categories.

The survey contained questions addressing six key risk messages: 1) patients should be assessed for treatment with ER/LA opioid analgesic therapy, 2) prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics, 3) management of ongoing therapy with ER/LA opioid analgesics opioid analgesics is important, 4) the importance of counseling patients and caregivers about the safe use of ER/LA opioid analgesics, 5) prescribers must be familiar with general drug information concerning ER/LA opioid analgesics, and 6) prescribers must be familiar with product-specific drug information concerning ER/LA opioid analgesics.

Key risk message 1: Patients should be assessed for treatment with ER/LA opioid analgesic therapy

This key risk message included questions about how prescribers assess patients for treatment including understanding risks of overdose, when to refer high-risk patients, and opioid tolerance criteria. (See *Table 4 below*)

- Respondents were aware of some of the important risks to consider when evaluating patients for treatment with ER/LA opioid analgesics including: the patient's current opioid tolerance level, respiratory depression, interactions with other medications, inadvertent exposure to children, and a personal history of past or current alcohol or drug abuse and knew to refer a patient at high risk for drug abuse to a pain management specialist. Respondents were also aware that a patient with a history of substance abuse can be prescribed an opioid and that a

personal history of psychiatric disorders and a family history of illicit drug use or alcohol abuse were risk factors for opioid abuse.

- For all questions, CE provider respondents had a higher knowledge score than IMS data respondents although the differences were not significant.
- Overall, 85% of respondents met or exceed the 80% threshold (5 out of 6 questions correct.

Table 4: Prescriber Understanding of Key Risk Message 1: Patients Should Be Assessed for Treatment with ER/LA Opioid Analgesics

Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (N=612)**
A patient with a history of substance abuse must not be prescribed an ER/LA opioid analgesic	True: 38 (13%) **False: 258 (86%)** Don't Know: 5 (2%)	True: 50 (16%) **False: 249 (80%)** Don't Know: 12 (4%)	True: 88 (14%) **False: 507 (83%)** Don't Know: 17 (3%)
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: 289 (96%)** False: 10 (3%) Don't Know: 2 (1%)	**True: 298 (96%)** False: 10 (3%) Don't Know: 3 (1%)	**True: 587 (96%)** False: 20 (3%) Don't Know: 5 (1%)
When evaluating patients for treatment with ER/LA opioid analgesics, which of the following are important risks to consider?	The patient's current opioid tolerance: 0 (0%) Respiratory depression, particularly in elderly or debilitated patients: 5 (2%) Interactions with other medications the patient may be taking: 2 (1%) Inadvertent exposure, especially in children present in the home: 1 (<1%) **All of the above: 293 (97%)** None of the above: 0 (0%) I don't know: 0 (0%)	The patient's current opioid tolerance: 9 (3%) Respiratory depression, particularly in elderly or debilitated patients: 5 (2%) Interactions with other medications the patient may be taking: 5 (2%) Inadvertent exposure, especially in children present in the home: 1 (<1%) **All of the above: 291 (94%)** None of the above: 0 (0%) I don't know: 1 (<1%)	The patient's current opioid tolerance: 9 (1.5%) Respiratory depression, particularly in elderly or debilitated patients: 10 (2%) Interactions with other medications the patient may be taking: 7 (1%) Inadvertent exposure, especially in children present in the home: 2 (<1%) **All of the above: 584 (95%)** None of the above: 0 (0%) I don't know: 0 (0%)
Which of the following are risk factors for opioid abuse?	**A personal history of psychiatric disorders: 257 (85%)** **A personal history of**	**A personal history of psychiatric disorders: 263 (85%)** **A personal history of**	**A personal history of psychiatric disorders: 520 (85%)** **A personal history of**

Table 4: Prescriber Understanding of Key Risk Message 1: Patients Should Be Assessed for Treatment with ER/LA Opioid Analgesics			
Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (N=612)**
	past or current alcohol or drug abuse: 299 (99%) **A family history of illicit drug use or alcohol abuse: 256 (85%)** A family history of hypercholesterolemia: 32 (11%) None of the above: 2 (<1%) I don't know: 1 (<1%)	**past or current alcohol or drug abuse: 307 (99%)** **A family history of illicit drug use or alcohol abuse: 269 (86.5%)** A family history of hypercholesterolemia: 43 (14%) None of the above: 0 (0%) I don't know: 1 (<1%)	**past or current alcohol or drug abuse: 606 (99%)** **A family history of illicit drug use or alcohol abuse: 525 (86%)** A family history of hypercholesterolemia: 75 (12%) None of the above: 2 (<1%) I don't know: 1 (<1%)

Key risk message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA Opioid Analgesics

This key risk message included questions to assess prescriber knowledge about dose selection, individualizing dosage, and the basics of pain management (See *Table 5 below*).

- The majority of respondents were aware of certain factors to consider when selecting an initial dose of an ER/LA opioid analgesic including: the patient's degree of opioid experience (99%), concurrent medication (99.5%), and general medical status of the patient (100%). Only 65% of respondents correctly answered that the patient's family history of mental illness did not need to be considered.
- For the question, which should prescribers do when initiating a patient on ER/LA opioid analgesics, 88% correctly answered titrate doses based on efficacy and tolerability while only 75% correctly answered consider a rescue medication for breakthrough pain.
- Eighty-five percent (85.5%) of respondents correctly answered that with methadone, the peak of respiratory depression can occur later and can persist longer than the analgesic effects.
- Most respondents were aware of the correct indication for ER/LA opioid analgesics with 86% correctly identifying chronic non-cancer pain. Twenty-nine percent (29%) of respondents incorrectly chose breakthrough pain from cancer.
- The majority of respondents were aware of federal regulations for writing a prescription for an ER/LA opioid analgesic: 88% were aware that refills are not allowed, 96% aware that refills cannot be phoned in, and 92% aware that prescriptions cannot be faxed.
- Fewer respondents correctly answered questions related to dosing and conversion:
    - 75% of respondents reported that conversion of patients to or from methadone using equianalgesic tables can result in overdose and death (81% CE provider respondents

versus 68.5% IMS respondents). High prescribers of oral ER/LA opioid analgesics had higher knowledge scores than low prescribers (80% vs. 70%).[9]

- Only 43.5% of respondents identified the recommended way to convert an opioid-tolerant patient safely from a parenteral opioid to an oral ER opioid analgesic by starting with 50% of an equianalgesic dose. High prescribers of transdermal patches and methadone were more knowledgeable (54% and 59%) than low prescribers (38% and 43%). In addition, high prescribers of oral ER/LA opioid analgesics were more likely to get this question correct as compared to low prescribers (51% vs. 39%).

- Only 61% were aware that there are no federal limits on quantities of ER/LA opioid analgesics dispensed via prescription (62% IMS respondents versus 59% CE provider respondents).
- In general, CE provider respondents had higher knowledge scores than IMS respondents.
- Overall, 60% of respondents met or exceed the 80% threshold (12 out of 15 questions correct.

Table 5: Prescribers Understanding of Key Risk Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics

Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (N=612)**
For methadone, the peak of respiratory depression can occur later and can persist longer than the analgesic effects.	**True: 270 (90%)** False: 10 (3%) Don't Know: 21 (7%)	**True: 253 (81%)** False: 13 (4%) Don't Know: 45 (14.5%)	**True: 523 (85.5%)** False: 23 (4%) Don't Know: 66 (11%)
Conversion of patients to or from methadone using equianalgesic tables can result in overdose and death	**True: 244 (81%)** False: 31 (10%) Don't Know: 26 (9%)	**True: 213 (68.5%)** False: 38 (12%) Don't Know: 36 (12%)	**True: 457 (75%)** False: 69 (11%) Don't Know: 86 (14%)
What is the recommended way to convert safely 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 the lowest available dose: 17 (6%) Start with 25% of an equianalgesic dose: 61 (20%) **Start with 50% of an equianalgesic dose: 143 (47.5%)** Start with an equianalgesic dose: 54 (18%) I don't know: 26 (9%)	Start with the lowest available dose: 20 (6%) Start with 25% of an equianalgesic dose: 71 (23%) **Start with 50% of an equianalgesic dose: 123 (39.5%)** Start with an equianalgesic dose: 61 (20%) I don't know: 36 (12%)	Start with the lowest available dose: 37 (6%) Start with 25% of an equianalgesic dose: 132 (22%) **Start with 50% of an equianalgesic dose: 266 (43.5%)** Start with an equianalgesic dose: 115 (19%) I don't know: 62 (10%)
Which of the following should	**Consider a rescue**	**Consider a rescue**	**Consider a rescue**

[9] High/low prescribers were defined as a response to the question "On average, how many times in the past month have you prescribed ER/LA opioids?" High equals prescribed 11 or more times in the past month. Low equals prescribed 0 to 10 times.

Table 5: Prescribers Understanding of Key Risk Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics			
Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (N=612)**
prescribers do when initiating a patient on ER/LA opioid analgesics?	**medication for break-through pain: 228 (76%)** **Titrate doses based on efficacy and tolerability: 271 (90%)** Start with the highest recommended dose of the ER/LA and decrease the dose depending on tolerability: 0 (0%) If switching from another opioid, convert to an equianalgesic dose: 142 (47%) None of the above: 4 (1%) I don't know: 2 (1%)	**medication for break-through pain: 231 (74%)** **Titrate doses based on efficacy and tolerability: 268 (86%)** Start with the highest recommended dose of the ER/LA and decrease the dose depending on tolerability: 2 (1%) If switching from another opioid, convert to an equianalgesic dose: 171 (55%) None of the above: 9 (3%) I don't know: 2 (1%)	**medication for break-through pain: 459 (75%)** **Titrate doses based on efficacy and tolerability: 539 (88%)** Start with the highest recommended dose of the ER/LA and decrease the dose depending on tolerability: 2 (<1%) If switching from another opioid, convert to an equianalgesic dose: 313 (51%) None of the above: 13 (2%) I don't know: 4 (1%)
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: 297 (99%)** No: 4 (1%) I don't know: 0 (0%)	**Yes: 307 (99%)** No: 4 (1%) I don't know: 0 (0%)	**Yes: 604 (99%)** No: 8 (1%) I don't know: 0 (0%)
Concurrent medication	**Yes: 299 (99%)** No: 1 (<1%) I don't know: 1 (<1%)	**Yes: 310 (100%)** No: 1 (<1%) I don't know: 0 (0%)	**Yes: 609 (99.5%)** No: 2 (<1%) I don't know: 1 (<1%)
General medical status of the patient	**Yes: 300 (100%)** No: 1 (<1%) I don't know: 0 (0%)	**Yes: 311 (100%)** No: 0 (0%) I don't know: 0 (0%)	**Yes: 611 (100%)** No: 1 (<1%) I don't know: 0 (0%)
The patient's family history of mental illness	Yes: 197 (65%) **No: 88 (29%)** I don't know: 16 (5%)	Yes: 199 (64%) **No: 92 (30%)** I don't know: 20 (6%)	Yes: 396 (65%) **No: 180 (29%)** I don't know: 36 (6%)
For which of the following conditions are ER/LA opioid analgesics indicated?	Acute or postoperative pain: 43 (14%) As needed for	Acute or postoperative pain: 53 (17%) As needed for headache or migraine	Acute or postoperative pain: 96 (16%) As needed for

Table 5: Prescribers Understanding of Key Risk Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics			
Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (N=612)**
	headache or migraine pain: 11 (4%) Dental abscess pain: 14 (5%) Breakthrough pain from cancer: 74 (25%) **Chronic non-cancer pain: 260 (86%)** None of the above: 28 (9%) I don't know: 0 (0%)	pain: 14 (4.5%) Dental abscess pain: 17 (5.5%) Breakthrough pain from cancer: 106 (34%) **Chronic non-cancer pain: 268 (86%)** None of the above: 23 (7%) I don't know: 1 (<1%)	headache or migraine pain: 25 (4%) Dental abscess pain: 31 (5%) Breakthrough pain from cancer: 180 (29%) **Chronic non-cancer pain: 528 (86%)** None of the above: 51 (8%) I don't know: 1 (<1%)
Federal regulations stipulate which of the following when writing a prescription for an ER/LA opioid?			
Refills are not allowed for Schedule II products	**True: 272 (90%)** False: 23 (8%) I don't know: 6 (2%)	**True: 272 (87.5%)** False: 36 (12%) I don't know: 3 (1%)	**True: 544 (89%)** False: 59 (10%) I don't know: 9 (1.5%)
There are specific federal limits to quantities of ER/LA opioids dispensed via a prescription.	True: 178 (59%) **False: 93 (31%)** I don't know: 30 (10%)	True: 194 (62%) **False: 78 (25%)** I don't know: 39 (12.5%)	True: 372 (61%) **False: 171 (28%)** I don't know: 69 (11%)
Refills for an ER/LA opioid prescription can be phoned into a pharmacy.	True: 8 (3%) **False: 291 (97%)** I don't know: 2 (1%)	True: 12 (4%) **False: 298 (96%)** I don't know: 1 (<1%)	True: 20 (3%) **False: 589 (96%)** I don't know: 3 (<1%)
Any prescription for a Schedule II product can be faxed to the pharmacy.	True: 18 (6%) **False: 277 (92%)** I don't know: 6 (2%)	True: 14 (4.5%) **False: 288 (93%)** I don't know: 9 (3%)	True: 32 (5%) **False: 565 (92%)** I don't know: 15 (2.5%)
Fatal respiratory depression may occur, with the highest risk at initiation and when the dose is increased.	**True: 284 (94%)** False: 12 (4%) I don't know: 5 (2%)	**True: 282 (91%)** False: 13 (4%) I don't know: 16 (5%)	**True: 566 (92.5%)** False: 25 (4%) I don't know: 21 (3%)

Key Risk Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics

This key risk message included questions to assess whether prescribers establish goals for therapy and monitor adherence to them, periodically evaluate pain control, outcomes, side effects, and quality of

life, and prescriber awareness of the Patient Prescriber Agreements (PPAs) and knowledge about managing adverse events and referral sources (See *Table 6 below*).

- The majority of respondents were aware of the PPA, what it includes, its purpose, and when it should be signed. Twenty-four percent (24%) of respondents incorrectly thought that the PPA was a legal requirement.
- Most respondents correctly chose false to it is unnecessary to re-evaluate a patient's underlying medical condition if the clinical presentation changes over time (96%).
- Respondents were aware that a prescriber should reassess patients on ER/LA opioid analgesics during follow-up visits by periodically assessing the continued need for opioid analgesics (99%), evaluating pain control and functional improvement (99.8%), and evaluating changes in the patient's medical condition (99%). Respondents were less aware that a comprehensive physical exam did not have to be performed at each visit (54%) or that drug screening should not be systematically performed for all patients (20%).
- Most respondents were aware of the appropriate ways to monitor patient adherence in regards to misuse and abuse:
    - Document drug seeking behaviors (97.5%)
    - Utilize state Prescription Drug Monitoring Programs (95%)
    - Use drug testing for both screening and confirmatory tests (94%)
    - Periodically re-evaluate therapy (97%)
    - Perform medication reconciliation by counting leftover drug supplies (87%).
- In general, most CE provider respondents had slightly higher knowledge scores across all questions with the exception of awareness that a comprehensive physical exam did not have to be performed at each visit (51.5% CE provider respondents versus 56% IMS respondents).
- Overall, 91% of respondents met or exceed the 80% threshold (12 out of 15 questions correct.

Table 6: Prescribers' Understanding of Key Risk Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics is Important

Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (N=612)**
It is not necessary to re-evaluate a patient's underlying medical condition if the clinical presentation changes over time.	True: 10 (3%) **False: 290 (96%)** Don't Know: 1 (<1%)	True: 14 (4.5%) **False: 297 (95.5%)** Don't Know: 0 (0%)	True: 24 (4%) **False: 587 (96%)** Don't Know: 1 (<1%)
PPAs are signed by both prescriber and patient at the same time an opioid is initially prescribed.	**True: 288 (96%)** False: 9 (3%) Don't Know: 4 (1%)	**True: 293 (91%)** False: 10 (3%) Don't Know: 8 (3%)	**True: 581 (95%)** False: 19 (3%) Don't Know: 12 (2%)
PPAs can include information about treatment goals, risks, and safe use of the ER/LA opioid.	**True: 293 (97%)** False: 4 (1%) Don't Know: 4 (1%)	**True: 302 (97%)** False: 4 (1%) Don't Know: 5 (2%)	**True: 595 (97%)** False: 8 (1%) Don't Know: 9 (1.5%)
PPAs are a legal requirement.	True: 70 (23%) **False: 193 (64%)** Don't Know: 38 (13%)	True: 77 (25%) **False: 191 (61%)** Don't Know: 43	True: 147 (14%) **False: 384 (63%)** Don't Know: 81

Table 6: Prescribers' Understanding of Key Risk Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics is Important			
Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (N=612)**
		(14%)	(13%)
PPAs may include commitments regarding follow-up visits, monitoring for misuse, and safeguarding the medication.	**True: 297 (99%)** False: 2 (1%) Don't Know: 2 (1%)	**True: 308 (99%)** False: 0 (0%) Don't Know: 3 (1%)	**True: 605 (99%)** False: 2 (<1%) Don't Know: 5 (1%)
How should prescribers reassess patients maintained on ER/LA opioid analgesics during follow-up visits?			
Periodically assess the continued need for opioid analgesics	**True: 300 (100%)** False: 1 (<1%) Don't Know: 0 (0%)	**True: 309 (99%)** False: 2 (1%) Don't Know: 0 (0%)	**True: 609 (99.5%)** False: 3 (<1%) Don't Know: 0 (0%)
Perform a comprehensive physical examination at each visit	True: 155 (51.5%) **False: 141 (47%)** Don't Know: 5 (2%)	True: 173 (56%) **False: 132 (42%)** Don't Know: 6 (2%)	True: 328 (54%) **False: 273 (45%)** Don't Know: 11 (2%)
Evaluate pain control and functional improvement	**True: 300 (100%)** False: 1 (<1%) Don't Know: 0 (0%)	**True: 311 (100%)** False: 0 (0%) Don't Know: 0 (0%)	**True: 611 (100%)** False: 1 (<1%) Don't Know: 0 (0%)
Evaluate for changes in the patient's medical condition	**True: 299 (99%)** False: 2 (1%) Don't Know: 0 (0%)	**True: 309 (99%)** False: 2 (1%) Don't Know: 0 (0%)	**True: 608 (99%)** False: 4 (1%) Don't Know: 0 (0%)
Systematically perform drug screening for all patients	True: 236 (78%) **False: 56 (19%)** Don't Know: 9 (3%)	True: 234 (75%) **False: 67 (21.5%)** Don't Know: 10 (3%)	True: 470 (77%) **False: 123 (20%)** Don't Know: 19 (3%)
How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse?	**Document any drug seeking behaviors: 294 (98%)** **Utilize state Prescription Drug Monitoring Program: 291 (97%)** **Use drug testing for both screening and confirmatory tests: 288 (96%)** Perform laboratory testing for serum	**Document any drug seeking behaviors: 303 (97%)** **Utilize state Prescription Drug Monitoring Program: 290 (93%)** **Use drug testing for both screening and confirmatory tests: 285 (92%)** Perform laboratory testing for serum	**Document any drug seeking behaviors: 597 (97.5%)** **Utilize state Prescription Drug Monitoring Program: 581 (95%)** **Use drug testing for both screening and confirmatory tests: 573 (94%)**

Table 6: Prescribers' Understanding of Key Risk Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics is Important			
Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (N=612)**
	triglycerides: 46 (15%) **Periodically re-evaluate therapy: 292 (97%)** **Perform medication reconciliation by counting leftover drug supplies: 271 (90%)** None of the above: 0 (0%) I don't know: 1 (<1%)	triglycerides: 65 (21%) **Periodically re-evaluate therapy: 303 (97%)** **Perform medication reconciliation by counting leftover drug supplies: 264 (85%)** None of the above: 0 (0%) I don't know: 1 (<1%)	Perform laboratory testing for serum triglycerides: 111 (18%) **Periodically re-evaluate therapy: 595 (97%)** **Perform medication reconciliation by counting leftover drug supplies: 535 (87%)** None of the above: 0 (0%) I don't know: 2 (<1%)

Key Risk Message 4: It is Important to Counsel Patients and Caregivers about the Safe Use of ER/LA Opioid Analgesics

This key risk message included questions to assess prescriber knowledge about safe use of the ER/LA opioid analgesics (See *Table 7 below*).

- The majority of respondents were aware of the signs and symptoms of respiratory depression such as reduced urge to breathe (91%), decreased rate of respiration (98%), sighing patterns of breathing (84%), and profound sedation (94%). Respondents were also aware that the most common long-term side effect of ER/LA opioid analgesics was constipation (89%).
- Respondents were aware of medications that could potentiate the risks of serious overdose and death when taken along with ER/LA opioid analgesics including sedative hypnotics (99%) or alcohol (99%).
- Respondents knew that an extended release tablet should not be cut in half to reduce the dose (94%) and that chewing a solid, oral dosage form of an ER/LA opioid analgesic could result in absorption of a fatal dose of opioid (89%). Respondents were less aware that transdermal patches with a matrix formulation should not be cut prior to use (75%).
- The majority of respondents knew that patients should be counseled about the importance of adhering to a dosage regimen as prescribed (99%) and that it is illegal to sell or give away ER/LA opioid analgesics (98.5%).
- CE provider respondent's knowledge scores were slightly higher than IMS respondents for most questions except awareness of constipation as the most common long-term side effect (IMS respondents 89% versus 87% CE provider respondents).

- High prescribers of methadone were more aware that caffeine does not potentiate the risk of overdose and death as compared to low prescribers (78% vs. 60%).
- Overall, 94% of respondents met or exceed the 80% threshold (12 out of 15 questions correct.

Table 7: Prescribers' Understanding of Key Risk Message 4: The Importance of Counseling Patients and Caregivers about Safe Use			
Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (N=612)**
ER/LA opioid analgesic transdermal patches that have a matrix formulation may be cut prior to use.	True: 30 (10%) **False: 223 (74%)** Don't Know: 48 (16%)	True: 33 (11%) **False: 237 (76%)** Don't Know: 41 (13%)	True: 63 (10%) **False: 460 (75%)** Don't Know: 89 (14.5%)
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: 276 (92%)** False: 15 (5%) Don't Know: 10 (3%)	**True: 267 (86%)** False: 20 (10%) Don't Know: 14 (4.5%)	**True: 543 (89%)** False: 45 (7%) Don't Know: 24 (4%)
Which of the following are warning signs and symptoms of respiratory depression from ER/LA opioid analgesics?	**Reduced urge to breathe: 276 (92%)** **Decreased rate of respiration: 297 (99%)** **Signing pattern of breathing: 253 (84%)** **Profound sedation: 284 (94%)**	**Reduced urge to breathe: 283 (91%)** **Decreased rate of respiration: 302 (97%)** **Signing pattern of breathing: 261 (84%)** **Profound sedation: 294 (94.5%)**	**Reduced urge to breathe: 559 (91%)** **Decreased rate of respiration: 599 (98%)** **Signing pattern of breathing: 514 (84%)** **Profound sedation: 578 (94%)**
A patient should be told not cut an extended release tablet in half to reduce the dose.	**True: 284 (94%)** False: 16 (5%0 Don't Know: 1 (<1%)	**True: 291 (94%)** False: 15 (5%) Don't Know: 5 (2%)	**True: 575 (94%)** False: 31 (5%) Don't Know: 6 (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: 300 (100%)** No: 1 (<1%) I don't know: 0 (0%)	**Yes: 304 (98%)** No: 2 (1%) I don't know: 5 (2%)	**Yes: 604 (99%)** No: 3 (<1%) I don't know: 5 (1%)
Anxiolytics	**Yes: 286 (95%)** No: 5 (2%) I don't know: 10 (3%)	**Yes: 283 (91%)** No: 10 (3%) I don't know: 18 (6%)	**Yes: 569 (93%)** No: 15 (2.5%) I don't know: 28 (5%)
Alcohol	**Yes: 300 (100%)** No: 1 (<1%) I don't know: 1 (<1%)	**Yes: 310 (100%)** No: 1 (<1%) I don't know: 1 (<1%)	**Yes: 610 (100%)** No: 1 (<1%) I don't know: 1 (<1%)
Illegal drugs	**Yes: 300 (100%)**	**Yes: 309 (99%)**	**Yes: 609 (99.5%)**

Table 7: Prescribers' Understanding of Key Risk Message 4: The Importance of Counseling Patients and Caregivers about Safe Use			
Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (N=612)**
	No: 0 (0%) I don't know: 1 (<1%)	No: 0 (0%) I don't know: 2 (1%)	No: 0 (0%) I don't know: 3 <1%)
Caffeine	Yes: 30 (10%) **No: 220 (73%)** I don't know: 51 (17%)	Yes: 45 (14.5%) **No: 197 (63%)** I don't know: 69 (22%)	Yes: 75 (12%) **No: 417 (68%)** I don't know: 120 (20%)
When counseling patients about the safe use of ER/LA opioid analgesics, prescribers should inform patients of the following	**The importance of adhering to a dosage regimen as prescribed: 298 (99%)** **It is illegal to sell or give away ER/LA opioid analgesics: 298 (99%)**	**The importance of adhering to a dosage regimen as prescribed: 307 (99%)** **It is illegal to sell or give away ER/LA opioid analgesics: 305 (98%)**	**The importance of adhering to a dosage regimen as prescribed: 605 (99%)** **It is illegal to sell or give away ER/LA opioid analgesics: 603 (98.5%)**
The most common long-term side effect of ER/LA opioid analgesics is constipation.	**True: 261 (87%)** False: 30 (10%) I don't know: 10 (3%)	**True: 278 (89%)** False: 26 (8%) I don't know: 7 (2%)	**True: 539 (88%)** False: 56 (9%) I don't know: 17 (3%)

Key Risk Message 5: **Prescribers Must be Familiar with General Drug Information Concerning ER/LA Opioid Analgesics**

This key risk message included questions to assess prescriber knowledge of general characteristics of ER/LA opioid analgesics including side effects, drug-drug interactions, definition of opioid-tolerant patients, and dosing (See *Table 8 below*).

- Eighty-nine percent (89%) of respondents were aware that some opioids can increase QTc interval.
- Most respondents were aware that central nervous system depressants can have a potentiating effect on sedation and respiratory depression caused by opioids (98%), that MAOIs are not the preferred antidepressant for use with ER/LA opioid analgesics (81%), and that 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 (92.5%).
- Most respondents (93%) knew that when starting a patient who is taking a sedative on ER/LA opioid analgesics, that the dose of one or both should be reduced. Respondents were also aware that all ER/LA opioid analgesics do not reach steady plasma concentration at the same time (95%).
- Only 72% of respondents were aware that some ER opioid formulations may rapidly release opioids when exposed to alcohol although awareness of CE provider respondents was significantly higher (82% CE provider respondents versus 63% IMS respondents).

- Similarly, only 78% of respondents correctly answered false to patients that were not opioid tolerant can initiate opioid therapy with any type of ER/LA opioid analgesic although awareness of CE provider respondents was significantly higher (82% CE provider respondents versus 74% IMS respondents).
- Only 55% of respondent were aware that if a patient using a transdermal opioid develops a high fever that the patient should be monitored closely for side effects and the dose of the patch should be reduce if necessary.
- In general, CE provider respondents had statistically significantly higher knowledge scores than IMS respondents across almost all questions.
- Overall, 77.5% of respondents met or exceeded the 80% threshold (answered 9 out of 11 questions correctly).

Table 8: Prescribers' Understanding of Key Risk Message 5: Prescribers Must be Familiar with General Drug Information Concerning ER/LA Opioid Analgesics

Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (N=612)**
Some opioids can increase the QTc interval	**True: 491 (81%)** False: 19 (1%) Don't Know: 95 (16%)	**True: 491 (81%)** False: 19 (1%) Don't Know: 95 (16%)	**True: 549 (90%)** False: 16 (3%) Don't Know: 47 (8%)
Central nervous system depressants can have a potentiating effect on the sedation and respiratory depression caused by opioids	**True: 593 (98%)** False: 2 (<1%) Don't Know: 10 (2%)	**True: 593 (98%)** False: 2 (<1%) Don't Know: 10 (2%)	**True: 602 (98%)** False: 4 (1%) Don't Know: 6 (1%)
Some ER opioid formulations may rapidly release opioid (dose dump) when exposed to alcohol.	**True: 378 (62%)** False: 25 (4%) Don't Know: 202 (33%)	**True: 378 (62%)** False: 25 (4%) Don't Know: 202 (33%)	**True: 441 (72%)** False: 27 (4%) Don't Know: 144 (23.5%)
Monoamine oxidase inhibitors (MAOIs) are the preferred antidepressants for use with ER/LA opioid analgesics.	True: 11 (2%) **False: 496 (82%)** Don't Know: 98 (16%)	True: 11 (2%) **False: 496 (82%)** Don't Know: 98 (16%)	True: 21 (3%) **False: 496 (81%)** Don't Know: 95 (15.5%)
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%)** False: 13 (2%) Don't Know: 65 (11%)	**True: 527 (87%)** False: 13 (2%) Don't Know: 65 (11%)	**True: 566 (92.5%)** False: 8 (1%) Don't Know: 38 (6%)
What should be done if a patient treated with a transdermal opioid develops a high fever?	Remove the patch until the fever is below 102: 143 (24%) Switch the patient to another ER/LA: 54 (9%) **Monitor the patient**	Remove the patch until the fever is below 102: 143 (24%) Switch the patient to another ER/LA:	Remove the patch until the fever is below 102: 138 (22.5%) Switch the patient to another ER/LA:

Table 8: Prescribers' Understanding of Key Risk Message 5: Prescribers Must be Familiar with General Drug Information Concerning ER/LA Opioid Analgesics			
Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (N=612)**
	closely for opioid side effects and reduce the dose of the patch if necessary: 404 (67%) Move the patch to another location in the body: 4 (<1%) I don't know: 94 (15%)	54 (9%) **Monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary: 404 (67%)** Move the patch to another location in the body: 4 (<1%) I don't know: 94 (15%)	42 (7%) **Monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary: 334 (55%)** Move the patch to another location in the body: 4 (1%) I don't know: 94 (15%)
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 (93%)** False: 28 (5%) Don't Know: 16 (3%)	**True: 561 (93%)** False: 28 (5%) Don't Know: 16 (3%)	**True: 568 (93%)** False: 18 (3%) Don't Know: 26 (4%)
Patients who are not opioid tolerant can initiate opioid therapy with any type of ER/LA opioid analgesic	True: 194 (32%) **False: 354 (59%)** Don't Know: 57 (9%)	True: 194 (32%) **False: 354 (59%)** Don't Know: 57 (9%)	True: 103 (17%) **False: 479 (78%)** Don't Know: 30 (5%)
All ER/LA opioids reach steady state plasma concentration at the same time.	True: 8 (1%) **False: 568 (94%)** Don't Know: 29 (5%)	True: 8 (1%) **False: 568 (94%)** Don't Know: 29 (5%)	True: 11 (2%) **False: 583 (95%)** Don't Know: 18 (3%)
The Controlled Substance Act includes ER/LA opioids because of the potential risk for abuse.	**True: 546 (90%)** False: 14 (2%) Don't Know: 45 (7%)	**True: 546 (90%)** False: 14 (2%) Don't Know: 45 (7%)	**True: 558 (91%)** False: 17 (3%) Don't Know: 17 (3%)
The underlying pharmacokinetic and pharmacodynamic mechanisms are the same for all ER/LA opioids.	True: 25 (4%) **False: 538 (89%)** Don't Know: 42 (7%)	True: 25 (4%) **False: 538 (89%)** Don't Know: 42 (7%)	True: 37 (6%) **False: 558 (91%)** Don't Know: 17 (3%)

Key Risk Message 6: **Prescribers Must be Familiar with Product-Specific Drug Information Concerning ER/LA Opioid Analgesics**

This key risk message included questions to assess prescriber knowledge of product-specific characteristics of ER/LA opioid analgesics including side effects, drug-drug interactions, definition of opioid-tolerant patients, and dosing (See *Table 9 below*).

- Respondents were less aware of what patient was considered opioid tolerant with only 36% correctly selecting patients who are taking 25 mcg/hour transdermal fentanyl for at least 7 days as tolerant (IMS respondents 37% versus 35% CE provider respondents) and 69% selecting patients who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer (IMS respondents 67% versus 71% CE provider respondents).
- Seventy-seven percent (77%) of respondents were aware that for some ER/LA opioid analgesic products, patients must be opioid tolerant before using certain strengths or daily doses. Only a little over half (51%) of respondents correctly answered that patients must be opioid tolerant before using any strength of transdermal fentanyl or ER hydromorphone. High prescribers of methadone had higher knowledge scores than low prescribers (60% vs. 43%).
- Only 69% of respondents correctly selected that transdermal opioids should not be disposed of by cutting into small pieces and throwing them in the trash. Only 46% of respondents correctly advised patients experiencing back pain and being treated with a transdermal opioid to not soak in a hot tub since heat can affect absorption of the opioid.
- CE provider respondent's knowledge scores were higher than IMS respondents for most questions except knowledge that patients who are taking 25 mcg/hour transdermal fentanyl for at least 7 days are opioid-tolerant (IMS respondents 37% versus 35% CE provider respondents).
- Overall, only 28% of respondents met or exceeded the 80% threshold (answered 5 out of 6 questions correctly).

Table 9: Prescribers' Understanding of Key Risk Message 6: Prescribers Must be Familiar with Product-Specific Drug Information Concerning ER/LA Opioid Analgesics

Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (N=612)**
Patients considered opioid-tolerant are those:	**Who are taking 25 mcg/hour transdermal fentanyl for at least 7 days: 106 (35%)** Who are not currently taking opioid therapy, but have no known intolerance or hypersensitivity to the drug fentanyl: 23 (8%) **Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer: 215 (71%)** None of the above: 66 (22%) I don't know: 14 (5%)	**Who are taking 25 mcg/hour transdermal fentanyl for at least 7 days: 114 (37%)** Who are not currently taking opioid therapy, but have no known intolerance or hypersensitivity to the drug fentanyl: 41 (13%) **Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer: 207 (67%)** None of the above: 71 (23%) I don't know: 22 (7%)	**Who are taking 25 mcg/hour transdermal fentanyl for at least 7 days: 220 (36%)** Who are not currently taking opioid therapy, but have no known intolerance or hypersensitivity to the drug fentanyl: 64 (10.5%) **Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer: 422 (69%)** None of the above: 137 (22%) I don't know: 36 (6%)
Patients must be opioid	**True: 168 (56%)**	**True: 142 (46%)**	**True: 310 (51%)**

Table 9: Prescribers' Understanding of Key Risk Message 6: Prescribers Must be Familiar with Product-Specific Drug Information Concerning ER/LA Opioid Analgesics			
Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (N=612)**
tolerant before using any strength of transdermal fentanyl or ER hydromorphone.	False: 116 (38.5%) Don't Know: 17 (6%)	False: 150 (48%) Don't Know: 19 (6%)	False: 266 (43.5%) Don't Know: 36 (6%)
For some ER products, patients must be opioid tolerant before using certain strengths or certain daily doses.	**True: 237 (79%)** False: 48 (16%) Don't Know: 16 (5%)	**True: 234 (75%)** False: 55 (18%) Don't Know: 22 (7%)	**True: 471 (77%)** False: 103 (17%) Don't Know: 38 (6%)
Dispose of transdermal patches by cutting into small pieces and throwing in the trash	True: 50 (17%) **False: 219 (73%)** Don't Know: 32 (11%)	True: 58 (19%) **False: 202 (65%)** Don't Know: 51 (16%)	True: 108 (18%) **False: 421 (69%)** Don't Know: 83 (14%)
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?	It is acceptable to soak in the hot tub for less than half an hour: 9 (3%) He should cover the patch with an occlusive dressing if entering the hot tub: 31 (10%) He must remove the patch while soaking in the hot tub: 79 (26%) **Do not soak in the hot tub since heat can affect the absorption of the opioid: 142 (47%)** None of the above: 11 (4%) I don't know: 29 (10%)	It is acceptable to soak in the hot tub for less than half an hour: 13 (4%) He should cover the patch with an occlusive dressing if entering the hot tub: 52 (17%) He must remove the patch while soaking in the hot tub: 57 (18%) **Do not soak in the hot tub since heat can affect the absorption of the opioid: 138 (44%)** None of the above: 11 (3.5%) I don't know: 40 (13%)	It is acceptable to soak in the hot tub for less than half an hour: 22 (4%) He should cover the patch with an occlusive dressing if entering the hot tub: 83 (14%) He must remove the patch while soaking in the hot tub: 136 (22%) **Do not soak in the hot tub since heat can affect the absorption of the opioid: 280 (46%)** None of the above: 22 (4%) I don't know: 69 (11%)

Educational Materials Questions:

Out of the 612 prescribers:

- 60% were aware of the Medication Guide (67% CE provider respondents; 53% IMS respondents); The main source of awareness for CE provider respondents was conferences (40%) followed by online download (32.5%) and sales representative (28%). The main source of awareness for IMS respondents was sales representatives (60%) followed by mailings (33%) and conferences (32.5%).

- 37% were aware of the Dear DEA Registered Prescriber Letter (44.5% CE provider respondents; 30% IMS respondents); the main source of awareness for both CE provider respondents and IMS respondents was mailing followed by email.
- 43% were aware of the Patient Counseling Document (53.5% CE provider respondents; 33% IMS respondents); the main source of awareness for CE provider respondents was conferences (42%) followed by online download (32.5%). The main source of awareness for IMS respondents was sales representatives (35%) followed by conferences (33%).
- 30% were aware of the ER/LA REMS website (49.5% CE provider respondents; 30% IMS respondents); the main source of awareness for CE provider respondents was email (35%) followed by conferences (34%). The main source of awareness for IMS respondents was sales representatives (32%) followed by email (30%).
- 55% were aware of the availability of REMS-compliant activities (71% CE provider respondents; 39% IMS respondents).

Prescriber Behavior Questions:

These questions assessed prescriber-patient communication related to safe use of ER/LA opioid analgesics, evaluation of potential abuse or misuse of the medications, ease of patient-access to ER/LA opioid analgesics, and impact of the FDA-required REMS on access to ER/LA opioid analgesics (see *Table 10 below*).

- Respondents were asked about obstacles to patient access to prescription opioids for pain control medical needs in the past month. The top obstacles reported were: insurance coverage (74%), insurance authorizations and approvals (72%) and patient's ability to pay (55%).
- Respondents were asked about the current level of access to ER/LA opioid analgesics for patients that are indicated to take them. Over half of respondents (52.5%) though the ease of access was about right. Twenty-five percent (25%) of respondents thought access was too difficult and 15% reported access as too easy. IMS respondents were more likely to report that access was too difficult as compared to CE provider respondents (29% versus 22%).
- Respondents were asked about the impact of the REMS on patient access to ER/LA opioid analgesics. Overall, 38% of respondents felt that the REMS made access more difficult while 37% of respondents reported that there was no impact. CE provider respondents were more likely to report no impact as compared to IMS respondents (41% versus 33%).
- Respondents were asked how the types of medications they prescribe have changed since the implementation of the REMS in July 2012. Overall, while almost half reported no change (48% overall; 44% CE provider respondents vs. 51% IMS respondents); 23% of respondents reported they have limited which ER/LA opioid analgesic they prescribe, 22.5% reported prescribing more non-opioid medications, and 18% reported prescribing fewer ER/LA opioid analgesics. Twenty-seven percent of CE provider respondents reported prescribing more non-opioid medications since the implementation of the REMS compared to 18% of IMS respondents. In addition, 11% of CE provider respondents reported prescribing more immediate release opioids since the implementation of the REMS compared to 6% of IMS respondents.
- Respondents reported on what activities they do when prescribing an ER/LA opioid analgesic. While most respondents reported warning patients not to break, chew, or crush their oral ER/LA opioid (92.5%), explaining what to do if a dose is missed (85.5%), and advising patient how to safely taper their dose when discontinuing (84%). A smaller percentage of respondents (64%) reported that they use the patient counseling document (PCD) for discussions with patients. CE provider respondents were more likely to report using the PCD than IMS respondents (70% vs. 58%).

- Respondents also reported on how frequently they perform certain activities when prescribing ER/LA opioid analgesics. Respondents self -reported a high frequency of appropriate behaviors reporting that they always or regularly: caution patients about important risks (95.5%) and common side effects (98%), discuss how to safely taper the ER/LA opioid analgesic if it is no longer needed (82%), counsel to keep ER/LA opioid analgesics away from children (89%), and instruct patients that it is illegal to sell, share, or give away ER/LA opioid analgesics (86.5%). Fewer respondents reported always or regularly using the PCD with patients (49.5%; CE provider respondents 54% vs. IMS respondent 44%), instructing patients on how to dispose of unused ER/LA opioid analgesics, and discussed with patients what to do if a dose is missed (76%).
- Respondents also reported on how frequently they perform certain activities when treating patients with ER/LA opioid analgesics. Respondents self -reported that they always or regularly reassess the need for opioid analgesics during treatment (99%). Fewer respondents reported that they always or regularly: use structured interview tools or screening tools to assess patients risk of abuse or misuse (66%), perform urine drug tests (71%), or complete a patient-prescriber agreement (PPA) or patient contract when the ER/LA opioid analgesic is first prescribed (76.5%).

Table 10: Prescriber-Reported Behaviors When Prescribing ER/LA Opioid Analgesics

Question	36 Month Survey n (%)		
	CE Providers Respondents (n=301)	IMS Data Respondents (n=311)	Total (n=612)
How frequently do you perform the following activities when treating patients with ER/LA opioid analgesics?			
Used the patient counseling document (PCD) on ER/LA opioids for discussions with patients	Always: 73 (24%) Regularly: 91 (30%) Rarely: 53 (18%) Never: 80 (27%) Don't know: 4 (1%)	Always: 60 (19%) Regularly: 77 (25%) Rarely: 64 (21%) Never: 99 (32%) Don't know: 11 (3.5%)	Always: 133 (22%) Regularly: 168 (27.5%) Rarely: 117 (19%) Never: 179 (29%) Don't know: 15 (2.5%)
Cautioned about important risks, including overdose and respiratory depression	Always: 180 (60%) Regularly: 112 (37%) Rarely: 6 (2%) Never: 2 (1%) Don't know: 1 (<1%)	Always: 189 (61%) Regularly: 105 (34%) Rarely: 16 (5%) Never: 0 (0%) Don't know: 1 (<1%)	Always: 369 (60%) Regularly: 217 (35.5%) Rarely: 22 (4%) Never: 2 (<1%) Don't know: 2 (<1%)
Discussed how to safely taper their ER/LA opioid analgesics if it is no longer needed	Always: 101 (34%) Regularly: 142 (47%) Rarely: 49 (16%) Never: 6 (2%) Don't know: 3 (1%)	Always: 118 (38%) Regularly: 138 (44%) Rarely: 48 (15%) Never: 5 (2%) Don't know: 2 (1%)	Always: 219 (36%) Regularly: 280 (46%) Rarely: 97 (16%) Never: 11 (2%) Don't know: 5 (1%)
Counsel patients on the most common side effects from opioid use	Always: 186 (62%) Regularly: 110 (36.5%) Rarely: 3 (1%) Never: 2 (1%) Don't know: 0 (0%)	Always: 175 (56%) Regularly: 128 (41%) Rarely: 7 (2%) Never: 0 (0%) Don't know: 1 (<1%)	Always: 361 (59%) Regularly: 238 (39%) Rarely: 10 (2%) Never: 2 (<1%) Don't know: 1 (<1%)
Instruct patients about the importance and how to safely dispose	Always: 114 (38%) Regularly: 103 (34%) Rarely: 68 (23%)	Always: 116 (37%) Regularly: 108 (35%) Rarely: 71 (23%)	Always: 230 (38%) Regularly: 211 (34.5%) Rarely: 139 (23%)

Table 10: Prescriber-Reported Behaviors When Prescribing ER/LA Opioid Analgesics			
Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (n=612)**
How frequently do you perform the following activities when treating patients with ER/LA opioid analgesics?			
of their unused opioids	Never: 15 (5%) Don't know: 1 (<1%)	Never: 13 (4%) Don't know: 3 (1%)	Never: 28 (5%) Don't know: 4 (1%)
Counsel patients on the importance of keeping ER/LA opioid analgesics safe and away from children.	Always: 173 (57.5%) Regularly: 90 (30%) Rarely: 32 (11%) Never: 5 (2%) Don't know: 1 (<1%)	Always: 182 (58.5%) Regularly: 100 (32%) Rarely: 23 (7%) Never: 4 (1%) Don't know: 2 (1%)	Always: 355 (58%) Regularly: 190 (31%) Rarely: 55 (9%) Never: 9 (1.5%) Don't know: 3 (<1%)
Instruct patients that it is illegal to sell, share, or give away ER/LA opioid analgesics.	Always: 172 (57%) Regularly: 89 (30%) Rarely: 32 (11%) Never: 8 (3%) Don't know: 0 (0%)	Always: 180 (58%) Regularly: 89 (29%) Rarely: 31 (10%) Never: 10 (3%) Don't know: 1 (<1%)	Always: 352 (57.5%) Regularly: 178 (29%) Rarely: 63(10%) Never: 18 (3%) Don't know: 1 (<1%)
Discuss with patients what to do if a dose if missed.	Always: 96 (32%) Regularly: 127 (42%) Rarely: 68 (23%) Never: 8 (3%) Don't know: 2 (1%)	Always: 86 (28%) Regularly: 156 (50%) Rarely: 59 (19%) Never: 8 (3%) Don't know: 2 (1%)	Always: 182 (30%) Regularly: 283 (46%) Rarely: 127 (21%) Never: 16 (3%) Don't know: 4 (1%)
Which of the following do you do with patients when prescribing an ER/LA opioid analgesic?	Use the PCD for discussions with patients: 211 (70%) Advise patients how to safely taper their ER/LA opioid dose when discontinuing: 250 (83%) Explain what patients should do if they miss a dose of their ER/LA opioid analgesic: 261 (87%) Warn patients not to break, chew or crush their oral ER/LA opioid: 281: (93%) None of the above: 12 (4%)	Use the PCD for discussions with patients: 180 (58%) Advise patients how to safely taper their ER/LA opioid dose when discontinuing: 264 (85%) Explain what patients should do if they miss a dose of their ER/LA opioid analgesic: 262 (84%) Warn patients not to break, chew or crush their oral ER/LA opioid: 285 (92%) None of the above: 11 (3.5%)	Use the PCD for discussions with patients: 391 (64%) Advise patients how to safely taper their ER/LA opioid dose when discontinuing: 514 (84%) Explain what patients should do if they miss a dose of their ER/LA opioid analgesic: 523 (85.5%) Warn patients not to break, chew or crush their oral ER/LA opioid: 566 (92.5%) None of the above: 23 (4%)
Use structured interview tools or other screening tools to assess patients' risk of abuse or misuse of	Always: 83 (28%) Regularly: 124 (41%) Rarely: 66 (22%) Never: 27 (9%) Don't know: 1 (<1%)	Always: 88 (28%) Regularly: 107 (34%) Rarely: 73 (23.5%) Never: 39 (12.5%) Don't know: 4 (1%)	Always: 171 (28%) Regularly: 231 (38%) Rarely: 139 (23%) Never: 66 (11%) Don't know: 5 (1%)

Table 10: Prescriber-Reported Behaviors When Prescribing ER/LA Opioid Analgesics			
Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (n=612)**
How frequently do you perform the following activities when treating patients with ER/LA opioid analgesics?			
their medications when managing patients using ER/LA opioids			
Complete a PPA or patient contract at the time an ER/LA opioid is first prescribed.	Always: 151 (50%) Regularly: 79 (26%) Rarely: 34 (11%) Never: 34 (11%) Don't know: 3 (1%)	Always: 166 (53%) Regularly: 71 (23%) Rarely: 38 (12%) Never: 34 (11%) Don't know: 4 (1%)	Always: 317 (52%) Regularly: 150 (24.5%) Rarely: 72 (12%) Never: 68 (11%) Don't know: 5 (1%)
Perform urine drug tests	Always: 55 (18%) Regularly: 157 (52%) Rarely: 65 (22%) Never: 23 (8%) Don't know: 1 (<1%)	Always: 67 (21.5%) Regularly: 154 (49.5%) Rarely: 64 (21%) Never: 24 (8%) Don't know: 2 (1%)	Always: 122 (20%) Regularly: 311 (51%) Rarely: 129 (21%) Never: 47 (8%) Don't know: 3 (<1%)
Reassess the need for opioids	Always: 182 (60.5%) Regularly: 113 (37.5%) Rarely: 5 (2%) Never: 1 (<1%) Don't know: N/A	Always: 190 (61%) Regularly: 119 (38%) Rarely: 2 (1%) Never: 0 (0%) Don't know: N/A	Always: 372 (61%) Regularly: 232 (38%) Rarely: 7 (1%) Never: 1 (<1%) Don't know: N/A
In your opinion, what have the obstacles been to patient access to prescription opioids in the past month?	Insurance coverage: 205 (68%) Insurance authorizations and approvals: 201 (67%) Patients' ability to pay: 159 (53%) Stigma regarding opioids: 98 (33%) Pharmacy authorization: 69 (23%) Pharmacy stocking issues: 102 (34%) Physicians do not want to prescribe ER/LAs because they do not wish to complete REMS training: 63 (21%) Patients are afraid to take ER/LAs because of risk warnings: 71 (24%) Legal liability or malpractice concerns:	Insurance coverage: 247 (79%) Insurance authorizations and approvals: 238 (76.5%) Patients' ability to pay: 177 (57%) Stigma regarding opioids: 78 (25%) Pharmacy authorization: 90 (29%) Pharmacy stocking issues: 140 (45%) Physicians do not want to prescribe ER/LAs because they do not wish to complete REMS training: 63 (20%) Patients are afraid to take ER/LAs because of risk warnings: 74 (24%) Legal liability or malpractice concerns:	Insurance coverage: 452 (74%) Insurance authorizations and approvals: 439 (72%) Patients' ability to pay: 336 (55%) Stigma regarding opioids: 176 (29%) Pharmacy authorization: 159 (26%) Pharmacy stocking issues: 242 (39.5%) Physicians do not want to prescribe ER/LA because they do not wish to complete REMS training: 126 (21%) Patients are afraid to take ER/LAs because of risk warnings: 145 (24%) Legal liability or malpractice concerns:

Table 10: Prescriber-Reported Behaviors When Prescribing ER/LA Opioid Analgesics			
Question	**36 Month Survey n (%)**		
	CE Providers Respondents (n=301)	**IMS Data Respondents (n=311)**	**Total (n=612)**
How frequently do you perform the following activities when treating patients with ER/LA opioid analgesics?			
	134 (44.5%) Other: 21 (7%) I don't know: 11 (4%)	91 (29%) Other: 5 (2%) I don't know: 3 (1%)	225 (37%) Other: 26 (4%) I don't know: 14 (2%)
Do you think the current level of access to ER/LA opioid analgesics for patients who are indicated to take them is:	Too easy: 51 (17%) Too difficult: 65 (22%) About right: 158 (52.5%) I don't know: 27 (9%)	Too easy: 40 (13%) Too difficult: 90 (29%) About right: 163 (52%) I don't know: 18 (6%)	Too easy: 91 (15%) Too difficult: 155 (25%) About right: 321 (52.5%) I don't know: 45 (7%)
What impact does the FDA-required 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: 110 (36.5%) It makes it easier for patients to get opioids: 12 (4%) It doesn't have any impact on patient access to opioids: 124 (41%) I don't know: 55 (18%)	It makes it more difficult for patients to get opioids: 123 (39.5%) It makes it easier for patients to get opioids: 4 (1%) It doesn't have any impact on patient access to opioids: 103 (33%) I don't know: 81 (26%)	It makes it more difficult for patients to get opioids: 233 (38%) It makes it easier for patients to get opioids: 16 (3%) It doesn't have any impact on patient access to opioids: 227 (37%) I don't know: 136 (22%)
Since implementation of the REMS in July 2012, how have the types of medications you prescribed changed?	I have prescribed more ER/LA opioids: 33 (11%) I have prescribed fewer ER/LA opioids: 57 (19%) I have prescribed more immediate release opioids: 34 (11%) I prescribed more non-opioid medications: 81 (27%) I have limited which ER/LA opioid analgesics I prescribe: 70 (23%) Other: 3 (1%) I have not changed the types of medication I prescribe: 133 (44%)	I have prescribed more ER/LA opioids: 31 (10%) I have prescribed fewer ER/LA opioids: 54 (17%) I have prescribed more immediate release opioids: 20 (6%) I prescribed more non-opioid medications: 57 (18%) I have limited which ER/LA opioid analgesics I prescribe: 73 (23.5%) Other: 2 (1%) I have not changed the types of medication I prescribe: 159 (51%)	I have prescribed more ER/LA opioids: 64 (10.5%) I have prescribed fewer ER/LA opioids: 11 (18%) I have prescribed more immediate release opioids: 54 (9%) I prescribed more non-opioid medications: 138 (22.5%) I have limited which ER/LA opioid analgesics I prescribe: 143 (23%) Other: 5 (1%) I have not changed the types of medication I prescribe: 292 (48%)

4.3.3 **Overall Reviewer's Comments on Follow-up Prescriber Survey**

Overall, respondents were knowledgeable about the assessment, management, and counseling requirements for patients being considered for treatment or currently being treated with an ER/LA opioid analgesic. Respondents were less knowledgeable about initiation, modification, and discontinuation of therapy, and general and product specific information for ER/LA opioid analgesics.

In general, CE provider respondents were more likely to answer questions correctly as compared to IMS respondents. While 60% of all respondents reported that they did complete a CE activity, there is no way to know if the completed CE activity was REMS compliant. Respondents that reported completion of a CE activity also had higher knowledge scores than respondents that reported not completing a CE activity. High volume prescribers were also more likely to answer questions correctly across almost all key risk messages.

Compared to the baseline survey, overall response rates to 44 items improved, 17 remained the same, and 4 items decreased. Overall, awareness of REMS materials was low: 60% aware of the Medication Guide, 37% aware of the Dear DEA Prescriber Letter, 43% aware of the Patient Counseling Document, and 30% aware of the REMS website. The top sources for REMS materials for CE provider respondents was conferences and online download compared to sales representatives and conferences for IMS respondents. In general, respondents reported a high frequency of appropriate prescriber behaviors such as always or regularly counseling on risks and side effects, instructing patients to keep ER/LA opioid analgesic medications away from children, informing patients that it is illegal to share, sell, or give-away ER/LA opioid analgesics, and reassessing the need for opioid analgesics. Respondents were less likely to always or regularly use the PCD, instruct patients on how to dispose of unused medication, use tools to screen patients for risk of misuse or abuse, perform urine drug tests, and complete Patient Prescriber Agreements.

In terms of access, respondents reported that the main barriers to patient access to prescription opioids analgesics are insurance coverage and insurance authorizations and approvals. While more than half of respondents thought patients' access to ER/LA opioid analgesics were about right, at least 25% thought the current level of access was too difficult. Overall, respondents reported the REMS made it more difficult for patients to get opioid analgesics (38%) followed closely by no impact (37%). IMS respondents were more likely to report that the REMS made access more difficult as compared to CE provider respondents (39.5% vs. 36.5%). While almost half of respondents reported no changes in the types of medications prescribed since implementation of the REMS (48%), 23% reported limiting which ER/LA opioid analgesics they prescribe and prescribing more non-opioid medications.

In the Follow-up Prescriber survey, it is not clear if the respondents identified as not having taken REMS-compliant training (recruited from IMS Data) in actuality did not take REMS-compliant training. This raises concerns because without that information, it cannot be determined whether the results provided represent an accurate comparison of the knowledge of prescribers who had taken and had not taken REMS-compliant training. In addition, the populations identified as having taken REMS training and those not having taken the REMS training were also very different from each other in other ways that could have impacted the results. (e.g., health profession , specialty).

Another concern with the Follow-up Prescriber survey is generalizing results to the targeted population of interest. Those choosing to take the CE may differ from the ER/LA opioid analgesic prescriber population in general. This survey was a convenience sample of the targeted population of ER/LA opioid analgesic prescribers. The 36-month REMS assessment report did not provide comparisons of the characteristics of the survey respondents to those of the targeted population for each of the surveys. Thus, it is impossible to assess whether or how the results of these surveys can be generalized to the

population. The FDA statistical review recommended that future survey analyses: (1) compare characteristics of survey participants to its target population for each survey; and (2) propose methods to standardize the results of each survey to its targeted population.

4.3.4 **Assessment Element 4b –Long-Term Evaluation Survey**

The purpose of the long-term evaluation (LTE) prescriber survey is to evaluate knowledge about prescribing ER/LA opioid analgesics, completion of the REMS processes, and to assess changes in behavior, prescribing, and patient assessment practices for prescribers who completed a continuing education (CE) activity within the past 6 to 12 months. The specific objectives include: 1) to assess the understanding of ER/LA opioid analgesic prescribers of the serious risks associated with the use of the ER/LA opioid analgesics and how to prescribe ER/LA opioid analgesics appropriately according to the six domains of the FDA Blueprint; 2) to assess understanding of whether the CE activities impacted prescribers' self-reported opioid prescribing behavior and practice; 3) to assess understanding of whether ER/LA opioid analgesic prescribers have encountered any barriers to applying knowledge gained in CE activities; and 4) to assess understanding of whether ER/LA opioid analgesics prescribers found completion of REMS-compliant training to be manageable or experienced obstacles to completion, including the time and/or effort required being overly burdensome.

The survey contained questions about the six core blueprint messages:

- Core Blueprint Message 1: Patients should be assessed for treatment with ER/LA opioid analgesic therapy;
- Core Blueprint Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics;
- Core Blueprint Message 3: Management of ongoing therapy with ER/LA opioid analgesics is important;
- Core Blueprint Message 4: It is important to counsel patients and caregivers about the safe use of ER/LA opioid analgesics.
- Core Blueprint Message 5: Prescribers must be familiar with general drug information concerning ER/LA opioid analgesics.
- Core Blueprint Message 6: Prescribers must be familiar with product-specific drug information concerning ER/LA opioid analgesics.

The LTE survey was qualitatively pre-tested with 16 ER/LA opioid analgesic prescribers that had completed any CE activity within the past year to assess comprehension and interpretation of questions.

Results

The LTE prescriber survey was conducted between February 17, 2015 and April 27, 2015. Prescribers were recruited using a subset of CE providers who sent invitation letters to all prescribers who completed a CE activity in the designated timeframe. Data on the number of invitations sent was not reported. A total of 546 prescribers responded to the invitation, 485 agreed to participate, 361 were eligible, and 328 completed the survey for a completion rate of 60%. Most participants completed the survey by internet (99%) while 1% completed it by paper.

Over half of respondents were male (55.5%), MDs (59.5%), and had been in clinical practice for more than 15 years (60%). The main specialty reported was pain management (28%) followed by other (16%), general practice/family medicine (11.5%), and hospice/palliative care (11.5%). Almost half of

prescribers reported prescribing ER/LA opioid analgesics on average between less than 5 to 10 times per month (47.5%). The most commonly prescribed ER/LA were Oxycontin ER (71%), MS Contin (68%), Fentanyl (67%), and Duragesic (55%).

To assess changes in prescribing patterns, respondents were asked how many times, if any, if they considered prescribing an ER/LA opioid analgesic in the past 3 months but decided not to and if so, why. Over half of respondents (55.5%) reported that they considered prescribing on average 2-7 times in the past three months, but ultimately decided not to. The main reasons reported for deciding not to prescribe included I am selecting my patients differently based on assessment (55%) and I changed to prescribing more non-opioid medications (45%).

The survey contained questions about the six blueprint messages: 1) patients should be assessed for treatment with ER/LA opioid analgesics, 2) prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics, 3) management of ongoing therapy with ER/LA opioid analgesics, 4) the importance of counseling patients and caregivers about the safe use of ER/LA opioid analgesics, 5) prescribers must be familiar with general drug information concerning ER/LA opioid analgesics, and 6) prescribers must be familiar with product-specific drug information concerning ER/LA opioid analgesics.

4.3.5 **Reviewers Comments**

1. There is no information provided about how many CE providers participated in respondent recruitment and from how many CE providers the current respondents were recruited from. This information should be provided for the current and future assessments.
2. We recognize that there is overlap between some of the messages included in the Blueprint. After reconsideration of the current categorizations, we recommend changes to the key risk message categories.

Blueprint Message 1: Patients should be assessed for treatment with ER/LA opioid analgesic therapy

This domain included questions about how prescribers assess patients when they are considering treatment with ER/LA opioid analgesics including considering the risks of overdose and abuse, knowing when to appropriately refer high-risk patients to pain management specialists, and understanding opioid tolerance criteria (*see Table 11*).

- Respondents were aware of the risk factors for opioid abuse and were aware that prescribers should refer patients at high risk for drug abuse to a pain management specialist.
- Respondents were less aware of risk factors for opioid abuse (such as age, gender, and cigarette smoking) when presented with a case. Overall, most respondents were aware of steps to take to further assess possible abuse.
- There were 6 questions in this risk message with 17 correct responses. Overall, 14% of respondents answered all 6 questions correctly, 34% answered 5 correctly, and 30% answered 4 correctly.
- Forty-eight percent (48%) of respondents met or exceeded the 80% threshold (5 out of 6 questions correct).

Table 11: Prescriber Understanding of Blueprint Message 1: Patients Should Be Assessed for Treatment with ER/LA Opioid Analgesics Therapy

Question	36 Month (n=328) n (%)
A patient with a history of substance abuse must not be prescribed an ER/LA opioid	True: 29 (9%) **False: 293 (89%)**

Table 11: Prescriber Understanding of Blueprint Message 1: Patients Should Be Assessed for Treatment with ER/LA Opioid Analgesics Therapy	
Question	**36 Month (n=328) n (%)**
	I don't know: 6 (2%)
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: 319 (97%)** False: 7 (2%) I don't know: 2 (1%)
Which of the following are risk factors for opioid abuse?	**A personal history of psychiatric disorders: 280 (85%)** **A personal history of past or current alcohol or drug abuse: 324 (99%)** A family history of hypercholesterolemia: 24 (7%) **A family history of illicit drug use or alcohol abuse: 290 (88%)** None of the above: 0 (0%) I don't know: 0 (0%)
Case Elliott: Elliot is a thin, anxious 27-year-old man who is new to the area and comes to see you at 3:50 PM on Friday with a complaint of chronic left knee pain from a skiing accident 3 years ago. He says he is currently taking Oxycontin® ER 40 mg tablets every 12 hours. He wants only oxycodone ER and oxycodone IR for "rescue". He has had 3 knee surgeries in the last 4 years and persistent trouble walking since the last surgery 12 months ago. He has had a number of non-medication therapies but says that only oxycodone ER works and that he is allergic to acetaminophen and NSAIDs. On physical examination of the knee, you note no erythema, swelling, or bruising. Surgical scars are present. His left quadriceps has signs of atrophy compared to the right side. There is limited range of motion (flexion less than 90 degrees) and pain on flexion of the left knee. On further questioning, Elliot admits to smoking cigarettes and drinking 1-2 beers every couple of days. He denies seeing other healthcare professionals for pain management. He also denies using therapeutic or recreational marijuana.	
Which of the following factors in Elliot's history raise your assessment of his risk for opioid abuse and misuse?	**27 years old: 162 (49%)** **Male gender: 138 (42%)** Chronic left knee pain from skiing accident: 66 (20%) **Request for specific drugs: 314 (96%)** **Cigarette smoking: 177 (54%)** I don't know: 1 (<1%)
Which of the following would be useful in further assessing possible abuse?	**Ask for contact information for his primary physician: 291 (89%)** **Ask Elliott to provide a urine sample for drug screen: 298 (91%)** **Ask Elliott about his family's use of drugs and alcohol: 280 (85%)** **Check the state prescription monitoring program database for Elliott's prescription history (where available): 324 (99%)**

Table 11: Prescriber Understanding of Blueprint Message 1: Patients Should Be Assessed for Treatment with ER/LA Opioid Analgesics Therapy	
Question	**36 Month (n=328) n (%)**
	Use a risk assessment tool, such as the ORT (Opioid Risk Tool) to find out about mood swings, use of illegal substances, or history of legal problems: 314 (96%) I don't know: 1 (<1%)
Case Warren: Warren is a 67-year-old man with moderately severe degenerative lumbar disc disease, spinal stenosis, chronic back pain, and history of a back injury as a teenager. Up until the last 3 months, Warren has been successful in managing his pain with therapeutic exercises and NSAIDs, but he started having more pain after some vigorous hiking. He has curtailed his activities because of pain on slow walking and standing. He has no history of smoking, excessive alcohol intake, chronic depression, or legal problems.	
Which of the following would be important steps prior to starting Warren on a trial of ER/LA opioid analgesic medication?	**Obtain a comprehensive urine drug screen: 235 (72%)** Get a full psychiatric evaluation: 53 (16%) **Complete a comprehensive pain history and physical examination: 320 (98%)** **Obtain a signed Patient Prescriber agreement for opioids: 290 (88%)** Check for police records: 24 (7%) **I don't know: 2 (1%)**

Blueprint Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics

This key risk message included questions to assess prescriber knowledge about dose selection, individualizing dosage, and the basics of pain management (See *Table 12 below*).

- Overall, most respondents were aware of the correct indication for ER/LA opioid analgesics; chronic non-cancer pain (85%). Thirty percent of respondents incorrectly selected breakthrough pain from cancer as a possible indication.
- Respondents were less aware of steps prescribers should take when initiating a patient on ER/LA including considering a rescue medication for break-through pain (76.5%) and titrating doses based on efficacy and tolerability (78%).
- There were 7 questions in this risk message with 9 correct responses. Overall, 4% of respondents answered all 7 questions correctly, 25% answered 6 correctly, and 33% answered 5 correctly.
- Twenty-nine percent (29%) of respondents met or exceeded the 80% threshold (6 out of 7 correct responses).

Table 12: Prescribers Understanding of Blueprint Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioids	
Question	**36 Month (n=328) n (%)**
For methadone, the peak of respiratory depression can occur later and can persist longer	**True: 286 (87%)** False: 10 (3%)

Table 12: Prescribers Understanding of Blueprint Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioids	
Question	**36 Month (n=328) n (%)**
than the analgesic effects.	I don't know: 32 (10%)
Conversion of patients to or from methadone using equianalgesic tables can result in overdose and death.	**True: 243 (74%)** False: 51 (15.5%) I don't know: 34 (10%)
Which of the following should prescribers do when initiating a patient on ER/LA opioid analgesics?	Start with the highest recommended dose of the ER/LA opioid analgesic and decrease the dose depending on tolerability: 2 (1%) **Consider a rescue medication for breakthrough pain: 251 (76.5%)** If switching from an immediate-release opioid, convert to an equianalgesic dose: 186 (57%) **Titrate doses based on efficacy and tolerability as indicated in the product label: 255 (78%)** None of the above: 12 (4%) I don't know: 1 (<1%)
For which of the following conditions are ER/LA opioid analgesics indicated?	Acute or postoperative pain: 64 (19.5%) As needed for headache or migraine pain: 13 (4%) Dental abscess pain: 27 (8%) Breakthrough pain from cancer: 100 (30.5%) **Chronic non-cancer pain: 280 (85%)** None of the above: 28 (8.5%) I don't know: 0 (0%)
Fatal respiratory depression may occur with the highest risk at initiation and when the dose is increased.	**True: 312 (95%)** False: 9 (3%) I don't know: 7 (2%)
Case Nancy: Nancy is a 35-year-old woman with chronic back pain from a motor vehicle accident in 2004. She tells you she was recently diagnosed with familial Long QT syndrome after several fainting spells. She has no known allergies and is currently taking NSAIDs for her back pain, but the pain is not well-controlled. She is in your office for help with her pain.	
You decide to give Nancy a 5-day trial of immediate-release oxycodone, 5 mg every 6 hours and 1 extra 5 mg dose at bedtime (25 mg/day total). During that time, her pain was not well controlled and she frequently had breakthrough pain. She says she does not like taking a lot of pills. Starting which of the following would be appropriate (select all that apply):	**Avinza® (morphine sulfate ER), 45 mg once a day: 92 (28%)** Duragesic® (fentanyl transdermal system), one (1) 12 mg patch every 3 days: 176 (54%) Oxycontin® ER (oxycodone hydrochloride), 60 mg once a day: 47 (14%) **Nucynta® ER (tapentadol), 50 mg twice a day: 90 (27%)** I don't know: 30 (9%)
In managing Nancy's treatment, you decide to rotate her medication to oxymorphone ER. The	Start her on a 24-hour dose of 12.5 mg oxymorphone ER (new opioid) based on the

Table 12: Prescribers Understanding of Blueprint Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioids	
Question	**36 Month (n=328) n (%)**
equianalgesic table indicates that the equianalgesic dose for oral oxycodone 25 mg/per day (current opioid) is 12.5 mg per day oral oxymorphone ER (new opioid). The most prudent course of action is (select the one best response):	table: 72 (22%) **Reduce the starting dose of oxymorphone ER (new opioid) by 25% to 50%: 192 (58.5%)** Taper her from the oxycodone before starting oxymorphone ER: 4 (1%) Keep increasing the dose of oxycodone to establish pain control before rotating her to oxymorphone ER: 18 (5.5%) Rotate her medication from immediate release-oxycodone, 5 mg every 6 hours and 1 extra 5 mg dose at bedtime (25 mg/day total), to oxymorphone ER: 31 (9.5%) I don't know: 11 (3%)

Blueprint Message 3: Management of ongoing therapy with ER/LA opioid analgesics is important.

This message included questions to assess whether prescribers establish goals for therapy and monitor adherence to them, periodically evaluate pain control, outcomes, side effects, and quality of life, and prescriber awareness of the Patient Prescriber Agreements (PPAs) and knowledge about managing adverse events and referral sources (See *Table 13*).

- Overall, most respondents were aware of how prescribers should monitor patient adherence.
- There were 6 questions in this risk message with 14 correct responses. Overall, 32% of respondents answered all 6 questions correctly, 36% answered 5 correctly, and 20% answered 4 correctly.
- Sixty-seven percent (67%) of respondents met or exceeded the 80% threshold (5 out of 6 correct responses).

Table 13: Prescribers' Understanding of Blueprint Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics is Important	
Question	**36 Month (n=328) n (%)**
How should prescribers monitor patient adherence to the treatment plan, especially with regard to misuse and abuse? Select all that apply.	**Document any "drug seeking" behavior: 319 (97%)** **Utilize state Prescription Drug Monitoring Programs: 322 (98%)** **Use urine drug testing for both screening and confirmatory tests: 316 (96%)** Perform laboratory testing for serum triglycerides: 66 (20%) **Periodically re-evaluate therapy: 322 (98%)** **Perform medication reconciliation by counting leftover drug supplies: 305 (93%)**

Table 13: Prescribers' Understanding of Blueprint Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics is Important	
Question	**36 Month (n=328) n (%)**
	None of the above: 0 (0%) I don't know: 2 (1%)
Case Elliott: Elliot is a thin, anxious 27-year-old man who is new to the area and comes to see you at 3:50PM on Friday with a complaint of chronic left knee pain from a skiing accident 3 years ago. He says he is currently taking Oxycontin® ER 40 mg tablets every 12 hours. He wants only oxycodone ER and oxycodone IR for "rescue". He has had 3 knee surgeries in the last 4 years and persistent trouble walking since the last surgery 12 months ago. He has had a number of non-medication therapies but says that only oxycodone ER works and that he is allergic to acetaminophen and NSAIDs. On physical examination of the knee, you note no erythema, swelling, or bruising. Surgical scars are present. His left quadriceps has signs of atrophy compared to the right side. There is limited range of motion (flexion less than 90 degrees) and pain on flexion of the left knee. On further questioning, Elliot admits to smoking cigarettes and drinking 1-2 beers every couple of days. He denies seeing other healthcare professionals for pain management. He also denies using therapeutic or recreational marijuana.	
You find out that Elliot has received 9 prescriptions for opioids from 4 different physicians, using 5 pharmacies in the past 3 months; some insurance paid for, some he paid for with cash. The urine drug screen is positive for THC, hydromorphone, and oxycodone metabolites. The best option would be to (select all that apply):	Write for a 4-day supply of ER and IR oxycodone, to last until you contact his previous prescriber on Monday: 24 (7%) **Not write a prescription today, as he lied about prescribers and drug use. His possible untreated addiction or abuse prevents you from addressing his pain. Refer to a pain management physician with addiction expertise: 299 (91%)** Write 30-day prescriptions for ER and IR oxycodone while you get his prior medical records, obtain functional testing of his left leg and review test results: 5 (1.5%) Report him to the police as he is obviously diverting drug to pay for marijuana: 14 (4%) I don't know: 3 (1%)
Case Roberta: Roberta is a 71-year-old retired, executive legal secretary. She has osteoarthritis in both knees, with incapacitating pain, but she does not want total knee replacement. She has used hydrocodone/acetaminophen 3 times a day for two years with good pain control and function. She is a non-smoker, no history of excessive alcohol intake or driving while intoxicated or of substance misuse. She signed a treatment agreement and consent form for treatment with ER/LA opioid analgesics. Her urine drug screen is consistent with prescribed hydrocodone. On physical exam, you note swelling and tenderness to palpation of her knees bilaterally with decreased range of motion. Your state's Prescription Drug Monitoring Program reports that Roberta received two identical prescriptions from another prescriber during the past 2 months.	

Table 13: Prescribers' Understanding of Blueprint Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics is Important	
Question	**36 Month (n=328) n (%)**
When shown the report, Roberta admits diverting one of the prescriptions to her son, who also has chronic back pain.	
Which of the following would be the most appropriate step? Select the one best response.	Ask her to bring her son in at her next clinic visit to counsel them both: 86 (26%) **Tell her you will not prescribe ER/LA opioid analgesics for her: 204 (62%)** Call the other physician to complain: 3 (1%) Report this as a felony for dispensing opioids without a license: 13 (4%) I don't know: 22 (7%)
Case Danielle: Danielle is a 46-year-old woman with history of crush injury to the right foot and ankle after a bookcase fell on her at work about 2 years ago. She developed a subsequent complex regional pain syndrome with pain, numbness, and joint stiffness, but reports good pain control with regular use of hydrocodone 7.5 mg three times a day and occasional NSAIDs. She says she is not using other medications. She also reports symptom relief and increased joint mobility with physical therapy. She has a signed Opiate Treatment Agreement on file and has kept all her quarterly appointments over the past 18 months. She is in the office for a routine check-up and evaluation for continued opioid treatment.	
With this patient without clinical evidence of addictive illness, interim management at each office visit would include (select all that apply):	Assessment of the continued need for ER/LA opioid analgesics: 303 (92%) Comprehensive physical examination and full laboratory work-up at each visit: 90 (27%) Pain control and functional improvement evaluation: 319 (97%) Asking about changes in medications or the patient's medical condition: 316 (96%) Not doing a urine drug screen: 49 (15%) Checking the state Prescription Monitoring Program database for prescription history (where available): 283 (86%) I don't know: 1 (<1%)
Danielle's urine drug screen comes back strongly positive for cocaine metabolites and negative for hydrocodone metabolites. When confronted, she admits to using cocaine, but says it was several weeks ago and requests another screen on the spot, which gives the same results. Finding only cocaine metabolites in the urine drug screen of two separate samples, without metabolites of the prescribed opioid suggests which of the following? Select the one best response.	Lab error: 3 (1%) Infrequent "recreational use" of cocaine: 10 (3%) **Diversion of prescribed opioid: 281 (86%)** Need for in-depth psychodynamic in-office counseling sessions: 25 (8%) I don't know: 9 (3%)

Table 13: Prescribers' Understanding of Blueprint Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics is Important	
Question	**36 Month (n=328) n (%)**
Case Lynette: Lynette is a married 58-year-old woman with ovarian cancer, who lives with her husband and two cats. Her disease is stable based on recent imaging and CA 125 assay results. She has had stable pain control for 9 months with hydromorphone ER (EXALGO®) 12 mg QD. She comes to the office each month for renewal of her EXALGO® prescription; however, for the past 2 months, she has asked for renewal 5 days early, as she ran out of medication. When questioned at her office visit, she says she did not realize that she was requesting refills early and does not recall using more medication than prescribed. She reports no change in her pain control and says her current regimen is still effective. She is alert, oriented to person, place and time, and behaves appropriately. When you query your state's Prescription Monitoring Program, you do not find evidence that she has seen other doctors or filled multiple prescriptions for opioids.	
Which of the following steps are most appropriate? (select all that apply):	**Collect a sample for urine drug screen: 262 (80%)** Refuse to give her a refill until the date when her prescription would have been used up: 100 (30.5%) **Ask where she keeps her medications and how she secures them: 310 (94.5%)** Consider rotating her to another opioid: 84 (26%) I don't know: 1 (<1%)

Blueprint Message 4: It is important to counsel patients and caregivers about the safe use of ER/LA opioid analgesics.

This key risk message included questions to assess prescriber knowledge about safe use of the ER/LA opioids (See *Table 14*).

- Most respondents were aware of drugs and other substances that can potentiate the risk of a serious overdose and death. Respondents were also aware of instructions to give patients when starting ER/LA opioid analgesic including not to drink alcohol.
- There were 10 questions in this risk message with 13 correct responses. Overall, 45% of respondents answered all 10 questions correctly, 36% answered 9 correctly, and 13% answered 8 correctly.
- Ninety-four percent (94%) of respondents met or exceeded the 80% threshold (8 out of 10 correct responses).

Table 14: Prescribers' Understanding of Blueprint Message 4: The Importance of Counseling Patients and Caregivers about Safe Use of ER/LA opioid analgesics.	
Question	**36 Month (n=328) n (%)**
ER/LA opioid analgesic transdermal patches may be cut prior to use.	True: 18 (5.5%) **False: 302 (92%)** I don't know: 8 (2%)
A patient should be told not to cut an extended	**True: 299 (91%)**

Table 14: Prescribers' Understanding of Blueprint Message 4: The Importance of Counseling Patients and Caregivers about Safe Use of ER/LA opioid analgesics.	
Question	**36 Month (n=328) n (%)**
release tablet in half to reduce the dose.	False: 27 (8%) I don't know: 2 (1%)
Which of the following can potentiate the risk of a serious overdose or death when taken with an ER/LA opioid analgesic? Select Yes, No, or I don't know for each of the following options.	
Sedative hypnotics	**Yes: 327 (99.7%)** No: 0 (0%) I don't know: 1 (<1%)
Anxiolytics	**Yes: 317 (97%)** No: 4 (1%) I don't know: 7 (2%)
Alcohol	**Yes: 327 (99.7%)** No: 1 (<1%) I don't know: 0 (0%)
Illegal drugs	**Yes: 328 (100%)** No: 0 (0%) I don't know: 0 (0%)
Caffeine	**Yes: 30 (9%)** No: 238 (73%) I don't know: 60 (18%)
Case Nancy: Nancy is a 35-year-old woman with chronic back pain from a motor vehicle accident in 2004. She tells you she was recently diagnosed with familial Long QT syndrome after several fainting spells. She has no known allergies and is currently taking NSAIDs for her back pain, but the pain is not well-controlled. She is in your office for help with her pain.	
When you initiate the oxymorphone ER, which of the following instructions do you need to give Nancy? Select all that apply.	Take oxymorphone ER tablets whole with enough water to swallow them: 277 (84.5%) For a smaller dose, cut the tablet in half: 9 (3%) Throw away the leftover oxycodone in the trash: 29 (9%) Don't drink alcohol while taking the oxymorphone ER: 314 (96%) Store the tablets in the bathroom medicine cabinet: 31 (9.5%) I don't know: 3 (1%)
Case Lynette: Lynette is a married 58-year-old woman with ovarian cancer, who lives with her husband and two cats. Her disease is stable based on recent imaging and CA 125 assay results. She has had stable pain control for 9 months with hydromorphone ER (EXALGO®) 12 mg QD. She comes to	

Table 14: Prescribers' Understanding of Blueprint Message 4: The Importance of Counseling Patients and Caregivers about Safe Use of ER/LA opioid analgesics.	
Question	**36 Month (n=328) n (%)**
the office each month for renewal of her EXALGO® prescription; however, for the past 2 months, she has asked for renewal 5 days early, as she ran out of medication. When questioned at her office visit, she says she did not realize that she was requesting refills early and does not recall using more medication than prescribed. She reports no change in her pain control and says her current regimen is still effective. She is alert, oriented to person, place and time, and behaves appropriately. When you query your state's Prescription Monitoring Program, you do not find evidence that she has seen other doctors or filled multiple prescriptions for opioids.	
Lynette reports that she keeps her medications at home in her purse or desk drawer, which is unlocked. On further questioning about her household, she mentions that her neighbor's teenage son has been helping her with her cat boxes for the last four months. Which of the following would be the most appropriate step(s)? Select all that apply.	Only prescribe 2 weeks of hydromorphone ER at a time and ask her to bring in her prescription bottles for pill counts at each visit: 176 (54%) **Stress the safety concerns when ER/LA opioid analgesics are taken by someone for whom they are not prescribed: 312 (95%)** **Recommend storing medication in a safe and secure place away from children, family members, and visitors: 322 (98%)** Tell her that if she cannot safeguard her medications, you will consider an alternative treatment plan and therapy: 244 (74%) I don't know: 1 (<1%)
Case Fred: Fred is an 89-year-old obese man with severe lumbar disc degeneration treated for over 10 years with daily acetaminophen/oxycodone 5/325 mg every 6 hours. He has significantly increased back and leg pain after sliding off his chair onto the floor. The pain keeps him awake at night and now he wants "something that works better." You complete a thorough physical examination and abuse risk evaluation. You decide to start Fred on a trial of a daily ER/LA opioid analgesic.	
Which of the following statements are appropriate patient education and counseling information for you to give him (select all that apply):	What to do for a missed dose: Double up with the missed tablet to keep pain under control: 37 (11%) **The treatment goal: Control the pain so he can sleep at night and walk with assistance during the day; evaluate with physical examination and information from wife and family: 309 (94%)** **Discuss the risks of long-term opioid use**

Table 14: Prescribers' Understanding of Blueprint Message 4: The Importance of Counseling Patients and Caregivers about Safe Use of ER/LA opioid analgesics.	
Question	**36 Month (n=328) n (%)**
	including constipation and Fred or his caregivers should let you know if he has any bowel issues: 311 (95%) Avoid discussing addiction potential, respiratory depression, and death with such an elderly patient or his caregivers: 12 (4%) Discontinuing treatment: Just stopping ER/LA opioid analgesics is OK if you are not addicted: 7 (2%) I don't know: 2 (1%)

Blueprint Message 5: Prescribers must be familiar with general drug information concerning ER/LA opioid analgesics.

This key risk message included questions to assess prescriber knowledge of general characteristics of ER/LA opioid analgesics including side effects, drug-drug interactions, definition of opioid-tolerant patients, and dosing (See *Table 15 below*).

- There were 7 questions in this risk message. Overall, 28% of respondents answered all 7 questions correctly, 39% answered 6 correctly, and 24% answered 5 correctly.
- Sixty-eight percent (68%) of respondents met or exceeded the 80% threshold (6 out of 7 correct responses).

Table 15: Prescribers' Understanding of Blueprint Message Key Risk Message 5: Prescribers must be familiar with general drug information concerning ER/LA opioid analgesics.	
Question	**36 Month (n=328) n (%)**
Central nervous system depressants, such as benzodiazepines, can have a potentiating effect on the sedation and respiratory depression caused by opioids.	**True: 326 (99%)** False: 0 (0%) I don't know: 2 (1%)
Some ER opioid formulations may rapidly release opioid (dose dump) when taken with alcohol.	**True: 267 (81%)** False: 24 (7%) I don't know: 37 (11%)
Monoamine oxidase inhibitors (MAOIs) are the preferred antidepressants for use with ER/LA opioid analgesics.	True: 8 (2%) **False: 288 (88%)** I don't know: 32 (10%)
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: 311 (95%)** False: 4 (1%) I don't know: 13 (4%)
What should be done if a patient treated with a transdermal opioid develops a high fever? Select the one best response.	Remove the patch until the fever is below 102F: 76 (23%) Switch the patient to another ER/LA opioid

Table 15: Prescribers' Understanding of Blueprint Message Key Risk Message 5: Prescribers must be familiar with general drug information concerning ER/LA opioid analgesics.	
Question	**36 Month (n=328) n (%)**
	analgesic: 34 (10%) **Monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary: 169 (51.5%)** Move the patch to another location on the body: 3 (1%) I don't know: 46 (14%)
When initiating an ER/LA opioid analgesic in a patient who is currently taking a sedative, reduce the dose of the opioid and/or sedative.	**True: 314 (96%)** False: 10 (3%) I don't know: 4 (1%)
Patients who are not opioid tolerant can initiate opioid therapy with any type of ER/LA opioid analgesic.	True: 72 (22%) **False: 245 (75%)** I don't know: 11 (3%)

Blueprint Message 6: Prescribers must be familiar with product-specific drug information concerning ER/LA opioid analgesics.

This key risk message included questions to assess prescriber knowledge of product-specific characteristics of ER/LA opioid analgesics including side effects, drug-drug interactions, definition of opioid-tolerant patients, and dosing (See *Table 16 below*).

- Respondents were less aware of product-specific drug information. Respondents were less aware of what patients were considered opioid-tolerant, how to properly dispose of transdermal patches, and which specific opioid to prescribe when presented with a case scenario.
- There were 3 questions in this risk message with 5 correct responses. Overall, 8% of respondents answered all 3 questions correctly, 34.5% answered 2 correctly, and 40% answered 1 correctly.
- Eight percent (8%) of respondents met or exceeded the 80% threshold (3 correct responses).

Table 16: Prescribers' Understanding of Blueprint Message Key Risk Message 6: Prescribers must be familiar with product specific drug information concerning ER/LA opioid analgesics.	
Question	**36 Month (n=328) n (%)**
Patients considered opioid-tolerant are those (select all that apply):	**Who are using 25 mcg/hour transdermal fentanyl for at least 7 days: 132 (40%)** Who are not currently taking opioid therapy, but have no known intolerance or hypersensitivity to the drug fentanyl: 27 (8%) **Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer: 240 (73%)** None of the above: 69 (21%)

Table 16: Prescribers' Understanding of Blueprint Message Key Risk Message 6: Prescribers must be familiar with product specific drug information concerning ER/LA opioid analgesics.	
Question	**36 Month (n=328) n (%)**
	I don't know: 11 (3%)
Dispose of transdermal patches by cutting into small pieces and throwing in the trash.	True: 67 (20%) **False: 229 (70%)** I don't know: 32 (10%)
Case Nancy: Nancy is a 35-year-old woman with chronic back pain from a motor vehicle accident in 2004. She tells you she was recently diagnosed with familial Long QT syndrome after several fainting spells. She has no known allergies and is currently taking NSAIDs for her back pain, but the pain is not well-controlled. She is in your office for help with her pain.	
Which of the following opioids should be avoided for her pain management? Select all that apply.	**Butrans® (buprenorphine transdermal system): 112 (34%)** Avinza® (morphine sulfate ER): 59 (18%) EXALGO® (hydromorphone hydrochloride): 51 (15.5%) **Dolophine® (methadone hydrochloride): 221 (67%)** None of the above: 21 (6%) I don't know: 41 (12.5%)

Prescriber Behavior Questions:

- These questions assessed changes in prescribing practices, behaviors, and opinions after participating in a REMS-compliant CE activity (see *Table 17 below*).
- Respondents reported on how frequently they perform certain activities when treating patients with ER/LA opioid analgesics since their participation in the REMS-compliant CE activity. Respondents self-reported that since completion of a CE-activity, they more often caution patients about important risks, including overdose and respiratory depressions (65%), counsel patients on the importance of keeping ER/LA opioid analgesics safe and away from children (56%), instruct patient that it is illegal to sell, share, or give away ER/LA opioid analgesics (53%), counsel patient on the most common side effects from opioid use (50%), instruct patients about the importance of and how to safely dispose of their unused opioids (49%), discuss with patients how to safely taper their ER/LA opioid analgesics if it is no longer needed (45%), discuss with patients what to do if a dose is missed (41%), and use the PCD for discussions with patients (39%). Respondents also reported that they more often reassess the need for opioids (65%), check the state Prescription Monitoring Program database for prescription history (64%), use structured interview tools or screening tools to assess patient's risk of abuse or misuse (50%), perform urine drug tests (49%), or complete a patient-prescriber agreement (PPA) or patient contract when the ER/LA opioid analgesics is first prescribed (48%).
- Respondents were asked about barriers to implementing information learned at the CE activities. The top barriers included: insufficient time during the clinical encounter to address all of the treatment considerations (63%), patient non-compliance with dose reconciliation efforts (57%), and patients continue to identify new ways of drug-seeking behavior not currently addressed in the REMS-compliant CE for ER/LA opioid analgesics (48%).
- Respondents were asked how their prescribing behaviors have changed since participation in a REMS-complaint CE activity. Overall, while over half reported no change (56%); 22% of respondents reported prescribing ER/LA opioid analgesics less often and 19% reported prescribing ER/LA opioid analgesics more often.
- Respondents were asked how the types of medications they prescribe have changed since participation in a REMS–compliant CE activity. Thirty-eight percent (38%) of respondents

reported prescribing more non-opioid medications and 23% of respondents reported limiting which ER/LA opioid analgesics they prescribe. Thirty-two percent (32%) of respondents reported no change in the types of medications they prescribe.

Table 17: Prescriber-Reported Behaviors When Prescribing ER/LA Opioid Analgesics	
Question	**36 Month (n=328) n (%)**
Based on your participation in recent REMS-compliant CE for ER/LA opioid analgesics, indicate if you engage in any of these behaviors more often, less often, or about the same.	
Used the patient counseling document (PCD) on ER/LA opioids for discussions with patients	More often: 129 (39%) About the same: 122 (37%) Less often: 3 (1%) Never: 69 (21%) Don't know: 5 (1.5%)
Cautioned about important risks, including overdose and respiratory depression	More often: 213 (65%) About the same: 114 (35%) Less often: 1 (<1%) Never: 0 (0%) Don't know: 0 (0%)
Discuss with patients how to safely taper their ER/LA opioid analgesic if it is no longer needed	More often: 147 (45%) About the same: 171 (52%) Less often: 7 (2%) Never: 3 (1%) Don't know: 0 (0%)
Counsel patients on the most common side effects from opioid use	More often: 165 (50%) About the same: 160 (49%) Less often: 2 (1%) Never: 0 (0%) Don't know: 1 (<1%)
Instruct patients about the importance of and how to safely dispose of their unused opioids	More often: 162 (49%) About the same: 145 (44%) Less often: 8 (2%) Never: 12 (4%) Don't know: 1 (<1%)
Counsel patients on the importance of keeping ER/LA opioid analgesics safe and away from children.	More often: 183 (56%) About the same: 137 (42%) Less often: 6 (2%) Never: 2 (1%) Don't know: 0 (0%)
Instruct patients that it is illegal to sell, share, or give away ER/LA opioid analgesics.	More often: 173 (53%) About the same: 149 (45%) Less often: 2 (1%) Never: 4 (1%) Don't know: 0 (0%)
Discuss with patients what to do if a dose if missed.	More often: 134 (41%) About the same: 180 (55%) Less often: 9 (3%) Never: 4 (1%)

Table 17: Prescriber-Reported Behaviors When Prescribing ER/LA Opioid Analgesics	
Question	**36 Month (n=328) n (%)**
	Don't know: 1 (<1%)
Based on your participation in recent REMS-compliant CE for ER/LA opioid analgesics, indicate if you engage in any of these behaviors more often, less often, or about the same.	
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 opioid analgesics	More often: 163 (50%) About the same: 138 (42%) Less often: 6 (2%) Never: 20 (6%) Don't know: 1 (<1%)
Complete a PPA or patient contract at the time an ER/LA opioid analgesic is first prescribed.	More often: 156 (48%) About the same: 146 (44.5%) Less often: 7 (2%) Never: 18 (5.5%) Don't know: 1 (<1%)
Perform urine drug screens	More often: 161 (49%) About the same: 136 (41.5%) Less often: 5 (1.5%) Never: 26 (8%) Don't know: 0 (0%)
Reassess the need for opioids	More often: 213 (65%) About the same: 114 (35%) Less often: 1 (<1%) Never: 0 (0%) Don't know: 0 (0%)
Check the state Prescription Monitoring Program database for prescription history (where available)	More often: 209 (64%) About the same: 98 (30%) Less often: 3 (1%) Never: 16 (5%) Don't know: 2 (1%)
Select from the list below the barriers that you've encountered in your ability to apply the information that you gained in the REMS-compliant CE for ER/LA opioid analgesics	Insufficient time during the clinical encounter to address all of the treatment considerations: 207 (63%) Patient non-compliance with dose reconciliation efforts: 188 (57%) Patients continue to identify new ways of drug seeking behavior not currently addressed in the REMS-compliant CE for ER/LA opioid analgesics: 156 (48%) Challenges communicating safe storage considerations to patients: 65 (20%) Difficulty getting patients to sign treatment agreement forms: 49 (15%) No barriers were encountered: 44 (13%) Other: 5 (1.5%)
Since you have participated in a REMS-compliant CE for ER/LA opioid analgesics,	I have prescribed more ER/LA opioid analgesics: 58 (18%)

Table 17: Prescriber-Reported Behaviors When Prescribing ER/LA Opioid Analgesics	
Question	**36 Month (n=328) n (%)**
how have the types of medications you prescribed changed?	I have prescribed fewer ER/LA opioid analgesics: 43 (13%) I have prescribed more immediate release opioids: 27 (8%) I prescribed more non-opioid medications: 126 (38%) I have limited which ER/LA opioid analgesics I prescribe: 77 (23.5%) Other: 7 (2%) I have not changed the types of medication I prescribe: 106 (32%)
Since you have participated in a REMS-compliant CE for ER/LA opioid analgesics, how has your prescribing behavior changed?	I write ER/LA opioid analgesic prescriptions more often: 61 (19%) I write ER/LA opioid analgesic prescriptions less often: 72 (22%) Other: 11 (3%) There has been no change in my prescribing behavior related to ER/LA opioid analgesics: 184 (56%)

4.3.6 **Reviewer's comments on Long-term Prescriber Survey**

Overall, respondents were knowledgeable about management and counseling requirements for patients being considered for treatment or currently being treated with ER/LA opioid analgesics. Respondents were less knowledgeable about assessment of patients, initiation and modification of treatment, and general and product specific information for ER/LA opioid analgesics. Since participating in a REMS-compliant activity, respondents reported more often conducting appropriate prescriber behaviors such as counseling on risks and side effects, instructing patients how to safely dispose of unused ER/LA opioid analgesics, instructing patients to keep ER/LA opioid analgesics medications away from children, informing patients that it is illegal to share, sell, or give-away ER/LA opioid analgesics, using tools to screen patients for risk of misuse or abuse, completing a PPA, performing urine drug screens, checking the state prescription monitoring program database, and reassessing the need for opioids. Respondents reported that the main barriers to applying information learned from the REMS-compliant CE activities were insufficient time to address all of the treatment considerations (63%), patient non-compliance (57%), and patients continuing to identify new drug-seeking behaviors that were not addressed in the training activity (48%).

While over half of respondents reported no changes in prescribing behaviors since participating in the CE activity, 22% reported writing prescriptions for ER/LA opioid analgesics less often and 19% reported writing more ER/LA opioid analgesics prescriptions. Thirty-eight percent (38%) of respondents reported prescribing more non-opioid medications since the CE activity while 23% reported limiting which ER/LA opioid analgesics they prescribe. Thirty-two percent (32%) of respondents reported no changes in the types of medications prescribed since the CE activity.

One main concern with the survey is generalizing results to the targeted population of interest. Those choosing to take the CE may differ from the ER/LA opioid analgesic prescriber population in general. This survey was a convenience sample of the targeted population of ER/LA opioid analgesic prescribers.

The 36-month REMS assessment report did not provide comparisons of the characteristics of the survey respondents to those of the targeted population for each of the surveys. Thus, it is impossible to assess whether or how the results of these surveys can be generalized to the population. The FDA statistical review recommended that future survey analyses: (1) compare characteristics of survey participants to its target population for each survey; and (2) propose methods to standardize the results of each survey to its targeted population.

4.4 Assessment Element 4: Patient Survey

This assessment element states:

> *Evaluation of Patient Understanding: The results of an evaluation of patients' understanding of the serious risks of these products and their understanding of how to use these products safely.*

The purpose of the patient surveys was to assess patient knowledge of the safe use of ER/LA opioid analgesics products following implementation of the REMS. The survey also included questions about patient-reported prescriber behaviors including appropriate screening and counseling.

Comments about the 24-month patient survey were sent to the RPC on February 13, 2015. The response was that the comments were sent too late to be incorporated into the 36-month assessment report but would be considered for the next assessment. Comments included using an alternative recruitment source to supplement the database used that includes patients on Medicaid and Medicare; the inclusion of caregivers as survey participants; revisions to the survey questions; the possibility of a sub-study focusing on new users; and making the opioid drug lists consistent across the survey.

The 36-month patient survey was conducted between September 1, 2013 and August 31, 2014. The patient survey was pretested in 21 patients prescribed ER/LA opioid analgesics to identify any limitations with the survey instrument and survey process prior to the 12 month assessment report submission. Patients were identified from medical and pharmacy claims in the HealthCore Integrated Research Database (HIRD). This database contains longitudinal claims data from commercially-insured patients in the US (14 health plans). Patients were eligible to participate if they currently active HIRD members and adults age 18 or older who filled at least one prescription for an ER/LA opioid analgesics between September 1, 2013 and August 31, 2014. Patients were excluded if they were contacted for the 24-month survey, failed to validate date of birth or name; did not fill a prescription in the 12 months prior to the survey; were employed as a physician, employed or family member employed with survey vendor, RPC, or FDA; or unsure of the opioid or class prescribed. Approximately 11,500 patients were eligible to complete the survey. A total of 2,441 patients were contacted via mail or telephone. Out of those, 272 were excluded during screening leaving 2,169 contacted patients. A total of 423 patients completed the survey for a response rate of 17% among the contacted respondents: 268 users of oral, non-methadone opioids; 101 patch users; 54 methadone users.

According to patient reports, most patients were between the ages of 35-64 (83%); female (60%); used oral drugs that were not methadone only (65%); Caucasian (94%); married (68%); and used ER/LA opioid analgesics for arthritis, arthropathies, osteoarthritis, and musculoskeletal pain (86%). Over half of patients (56%) had an annual income of $50,000 or more and half were college or community college/technical school graduates or completed graduate school (50%). Most patients had used an ER/LA opioid analgesic before the most recent prescription (83%). Almost half were prescribed the ER/LA opioid analgesic by a pain specialist (42%) other specialists (30%), and primary care providers (25%). The most commonly used drugs as reported by survey respondents were: Oxycodone (39%) and

Morphine (15%). Only 16% of respondents were new users and 56% of respondents reported 12 months or more since they were first prescribed the ER/LA opioid analgesics.

The survey contained questions about four key domains of interest: 1) patients' understanding of the serious risks of ER/LA opioid analgesics, 2) receipt and comprehension of the Medication Guide (MG) and patient counseling document (PCD), 3) perceived access and satisfaction of access to pain medications, and 4) patient-reported frequency of appropriate prescriber behaviors, including appropriate screening and counseling about ER/LA opioid analgesics.

Domain 1: Patients' understanding of the serious risks of ER/LA opioid analgesics.

This domain included questions about the five key risk messages: 1) The patient understands the serious risks associated with the use of their ER/LA opioid analgesics; 2) The patient knows what to do if they take too much drug; 3) The patient understands the need to store the drug in a safe place, 4) The patient knows they should not share the drug with anyone; and 5) The patient understands how to use the drug safely.

Key risk message 1: The patient understands the serious risks associated with the use of their ER/LA opioid analgesic. This key risk message included questions about the risks and side effects associated with the use of ER/LA opioid analgesics. (See *Table 18 below*)

- Respondents' understanding of this key risk message was high. Eighty-one percent of participants were aware that ER/LA opioid analgesics can cause dizziness, lightheadedness, and sleepiness. Ninety-three percent of participants were aware of the problems that overdoses can cause (i.e. breathing problems, slow breathing that can lead to death).
- Overall, 77% of respondents answered both questions correctly for this risk message; 21% answered 1 of 2 correctly and 3% answered both incorrectly.

Table 18: Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics
Key Risk Message 1: The patient understands the serious risks associated with the use of their ER/LA opioid analgesic

Question	**24-Month (n=413)** **N (%)**	**36-Month (n=423)** **N (%)**
Overdose may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death.	Correct: 386 (94%) Incorrect: 10 (2%) Don't Know: 16 (4%)	Correct: 394 (93%) Incorrect: 13(3%) Don't Know: 15 (4%) No Response: 1 (<1%)
ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy.	Correct: 345 (84%) Incorrect: 46 (11%) Don't Know: 21 (5%)	Correct: 342 (81%) Incorrect: 49 (12%) Don't Know: 32 (8%)

Key risk message 2: The patient knows what to do if they too much drug (See *Table 19 below*).

- Respondent's understanding was high. The majority of respondents (88%) knew to seek emergency medical help for overdose, even if the patient felt fine and knew to seek emergency help if experienced side effects such as trouble breathing, chest pain, or swelling of their face, tongue, or throat (97%).
- Overall, 87% of respondents answered both questions correctly for this risk message.

Table 19: Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics: Key Risk Message 2: The patient knows what to do if they take too much drug.		
Question	**24-Month (n=413) N (%)**	**36-Month (n=423) N (%)**
Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fine.	Correct: 363 (88%) Incorrect: 22 (5%) Don't Know: 26 (6%)	Correct: 374 (88%) Incorrect: 38 (9%) Don't Know: 10 (2%) No Response: 1 (<1%)
Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics.	Correct: 400 (97%) Incorrect: 10 (2%) Don't Know: <5 (1%)	Correct: 412 (97%) Incorrect: 8 (2%) Don't Know: 3 (1%)

Key risk message 3: The patient understands the need to store the drug in a safe place (See *Table 20 below*).

- The majority of respondents knew that unused ER/LA opioid analgesics should not be thrown in the trash (93%) and that a child could die if they take or use ER/LA opioid analgesics (93%).
- Only 71% of respondents were aware the ER/LA opioid analgesics should not be stored in the medicine cabinet with other medications in the household.
- Overall, 62% of respondents answered all three questions correctly and 33% answered 2 out of the 3 correctly.

Table 20: Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics Key Risk Message 3: The patient understands the need to store the drug in a safe place.		
Question	**24-Month (n=413) N (%)**	**36-Month (n=423) N (%)**
Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household.	Correct: 271 (66%) Incorrect: 96 (23%) Don't Know: 46 (11%)	Correct: 300 (71%) Incorrect: 90 (21%) Don't Know: 33 (8%)
Do not throw away any unused ER/LA opioid analgesics in the trash.	Correct: 375 (91%) Incorrect: 22 (5%) Don't Know: 16 (4%)	Correct: 393 (93%) Incorrect: 21 (5%) Don't Know: 9 (2%)
A child could die if they take or use the respondent's ER/LA opioid analgesics.	Correct: 384 (93%) Incorrect: 14 (3%) Don't Know: 15 (4%)	Correct: 393 (93%) Incorrect: 17 (4%) Don't Know: 13 (3%)

Key risk message 4: The patient knows they should not share the drug with anyone (See *Table 21 below*).

- There was a very high understanding of this key risk message. The majority of respondents were aware that ER/LA opioid analgesics should not be given to other people with the same condition (98%) and selling or giving away ER/LA opioid analgesics was against the law (98%).
- Overall, 96% of respondents answered both questions correctly.

Table 21: Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics Key Risk Message 4: The patient knows they should not share the drug with anyone.

Question	24-Month (n=413) N (%)	36-Month (n=423) N (%)
Do not give ER/LA opioid analgesics to other people who have the same condition as you.	Correct: 406 (98%) Incorrect: 6 (1%) Don't Know: <5 (1%)	Correct: 415 (98%) Incorrect: 6 (1%) Don't Know: 2 (<1%)
Selling or giving ER/LA opioid analgesics is against the law.	Correct: 402 (97%) Incorrect: 11 (3%) Don't Know: 0 (0%)	Correct: 413 (98%) Incorrect: 9 (2%) Don't Know: 1 (<1%)

Key risk message 5: The patient understands how to use the drug safely (See *Table 22 below*).

- There was a high level of understanding for some questions. Most respondents knew that they should talk to their healthcare provider before stopping ER/LA opioid analgesics (84%), they should talk to their healthcare provider if the current dose doesn't control their pain (96%), they should inform their healthcare provider about all other medications being used (93%), that it is not okay to drink alcohol while using ER/LA opioid analgesics (93%), they should inform their healthcare provider about a history of drug or alcohol abuse or mental health problems (90%), and they should inform their healthcare provider about over the counter medications and vitamins or supplements (87%).
- There was a lower level of understanding in terms of awareness that patients should read the medication guide every time a prescription is filled (55%) and that it is okay to drink caffeine while using ER/LA opioid analgesics (49%).
- Overall, 16% of respondents answered all eight questions correctly; 40% answered 7 out of 8 correctly, and 26% answered 6 out of 8 correctly.
- The majority of oral non-methadone user respondents (n=268; 93%) were aware that they should not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed. Seventy-six percent of oral user respondents (76%) were aware that ER/LA opioid analgesics should not be split or crushed if the respondent is having trouble swallowing.
- Most patch user respondents (n=101; 91%) were aware that the patches should not be cut in half to use less medication. A lower percentage of patch user respondents were aware that they should inform their healthcare provider of any fever (70%) and not to use a hot tub or sauna while using ER/LA opioid analgesics if pain persists (77%)
- Seventy-one percent (71%) of non-methadone oral drug users answered both of the cohort specific questions correctly. Responses were split between patch users with 48% of respondents answering all three questions correctly and 44% answering 2 out of 3 correctly.

Table 22: Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics
Key Risk Message 5: The patient understands how to use the drug safely

Question	24-Month (n=413) N (%)	36-Month (n=423) N (%)
Talk to a healthcare provider prior to stopping ER/LA opioid analgesics	Correct: 346 (84%) Incorrect: 49 (12%) Don't Know: 18 (4%)	Correct: 357 (84%) Incorrect: 50 (12%) Don't Know: 16 (4%)
Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control your pain.	Correct: 389 (94%) Incorrect: 18 (4%) Don't Know: 6 (1%)	Correct: 405 (96%) Incorrect: 10 (2%) Don't Know: 7 (<1%) No Response: 1 (<1%)

Table 22: Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics Key Risk Message 5: The patient understands how to use the drug safely		
Question	**24-Month (n=413) N (%)**	**36-Month (n=423) N (%)**
It is not okay to drink alcohol while taking or using ER/LA opioid analgesics.	Correct: 385 (93%) Incorrect: 12 (3%) Don't Know: 16 (4%)	Correct: 394 (93%) Incorrect: 16 (4%) Don't Know: 12 (3%) No Response: 1 (<1%)
Read the attached MG every time an ER/LA opioid analgesic prescription is filled.	Correct: 231 (56%) Incorrect: 145 (35%) Don't Know: 37 (9%)	Correct: 232 (55%) Incorrect: 136 (32%) Don't Know: 55 (13%)
Inform healthcare providers about all the other medications being used.	Correct: 398 (96%) Incorrect: 13 (3%) Don't Know: <5 (1%)	Correct: 394 (93%) Incorrect: 26 (6%) Don't Know: 3 (1%)
Inform healthcare providers about any history of abuse of street or prescription drugs, alcohol addiction, or mental health problems.	Correct: 375 (91%) Incorrect: 28 (7%) Don't Know: 10 (2%)	Correct: 382 (90%) Incorrect: 30 (7%) Don't Know: 10 (2%) No Response: 1 (<1%)
Inform healthcare providers about over the counter medicines, vitamins, and dietary supplements.	Correct: 368 (89%) Incorrect: 38 (9%) Don't Know: 7 (2%)	Correct: 369 (87%) Incorrect: 42 (10%) Don't Know: 10 (2%) No Response: 2 (<1%)
It is okay to drink caffeine while using ER/LA opioid analgesics.	Correct: 202 (49%) Incorrect: 60 (15%) Don't Know: 148 (36%)	Correct: 207 (49%) Incorrect: 85 (20%) Don't Know: 131 (31%)
ER/LA opioid analgesics should not be split or crushed if the respondent is having trouble swallowing their medication. (*only for non-methadone oral drug users)	Correct: 206 (77%) Incorrect: 23 (9%) Don't Know: 37 (14%)	Correct: 204 (76%) Incorrect: 34 (13%) Don't Know: 30 (11%)
Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed. (only for non-methadone oral drug users)	Correct: 244 (92%) Incorrect: 15 (6%) Don't Know: 5 (2%)	Correct: 248 (93%) Incorrect: 14 (5%) Don't Know: 6 (2%)
Inform healthcare providers of any fever (*only for patch and no methadone users)	Correct: 74 (73%) Incorrect: 14 (14%) Don't Know: 14 (14%)	Correct: 71 (70%) Incorrect: 20 (20%) Don't Know: 10 (10%)
Do not use a hot tub or sauna while using ER/LA opioid analgesics is pain persists (*only for patch and no methadone users)	Correct: 84 (82%) Incorrect: 8 (8%) Don't Know: 10 (10%)	Correct: 78 (77%) Incorrect: 10 (10%) Don't Know: 12 (12%)
Do not cut ER/LA opioid analgesics patches in half to use less medicine. (only for patch and no methadone users)	Correct: 84 (82%) Incorrect: 7 (7%) Don't Know: 11 (11%)	Correct: 91 (90%) Incorrect: 6 (6%) Don't Know: 4 (4%)

Domain 2: Receipt and comprehension of the Medication Guide (MG) and Patient Counseling Document (PCD)

There were 14 questions that accessed patient receipt and comprehension of the Medication Guide and PCD (See *Table 23 below*). Most respondents reported receiving the Medication Guide from their

pharmacists with their last fill (94%) while 95% of respondents received the Medication Guide from their pharmacist in the last 12 months. Of the respondents that received the Medication Guide, 89% read all with each pharmacy fill (14%) or read all (65%) of the Medication Guide at least once. The majority of respondents that read the Medication Guide (94%) understood all or most of the information. Respondents that received the Medication Guide were less likely to be first-time users (29% vs 16%). The main source of the Medication Guide was the pharmacist (95%). For respondents that reported receiving the Medication Guide from a source other than a pharmacist, these sources included their HCP, the internet, another HCP, and somewhere else.

Only 38% of respondents reported receiving the PCD from their healthcare provider when the ER/LA opioid analgesic was first prescribed and only 32% of respondents reported receiving the patient counseling document in the last 12 months. Only 26% reported that their HCP referenced the PCD in the past 12 months. Of the respondents that received the PCD, 75% understood all or most of the information.

Table 23: Patient-Reported Receipt and Comprehension of the Medication Guide and Patient-Counseling Document

Question	24-Month (n=413) N (%)	36-Month (n=423) N (%)
Medication Guide (MG) Questions		
Received MG from pharmacist with the last ER/LA opioid analgesic prescription fill	Yes: 373 (90%) No: 21 (5%) Not sure: 19 (5%) Refused: 0 (0%)	Yes: 396 (94%) No: 8 (2%) Not sure: 19 (4%) Refused: 0 (0%)
Received MG from pharmacist in the last 12 months	Yes: 374 (91%) No: 23 (6%) Not sure: 16 (4%) Refused: 0 (0%)	Yes: 400 (95%) No: 9 (2%) Not sure: 14 (3%) Refused: 0 (0%)
Received MG from non-pharmacist in the last 12 months	Yes: 53 (13%) No: 337 (82%) Not sure: 23 (6%) Refused: 0 (0%)	Yes: 48 (11%) No: 359 (85%) Not sure: 16 (4%) Refused: 0 (0%)
Read MG	Never read any: 14 (3%) Read some, at least once: 64 (16%) Read all, at least once: 274 (66%) Read all, with each pharmacy fill: 61 (15%) Refused: 0 (0%)	Never read any: 13 (3%) Read some, at least once: 75 (18%) Read all, at least once: 274 (65%) Read all, with each pharmacy fill: 61 (14%) Refused: 0 (0%)
Offer to explain MG	Yes: 267 (65%) No: 128 (31%) Not sure: 18 (4%) Refused: 0 (0%)	Yes: 269 (64%) No: 140 (33%) Not sure: 14 (3%) Refused: 0 (0%)
Accepted offer to explain MG	Yes: 147 (55%) No: 119 (45%)	Yes: 137 (51%) No: 131 (49%)

Table 23: Patient-Reported Receipt and Comprehension of the Medication Guide and Patient-Counseling Document		
Question	**24-Month (n=413) N (%)**	**36-Month (n=423) N (%)**
	Not sure: 1 (<1%) Refused: 0 (0%)	Not sure: <5 (<1%) Refused: 0 (0%)
Usefulness of the information in the MG	Not useful at all: 6 (1%) Not very useful: 15 (4%) Somewhat useful: 164 (40%) Very useful: 224 (55%) Refused: 0 (0%)	Not useful at all: 6 (1%) Not very useful: 9 (2%) Somewhat useful: 164 (39%) Very useful: 243 (58%) Refused: 0 (0%)
Understanding of the information in the MG	Did not understand it at all: <5 (1%) Understood some of the information: 6 (1%) Understood about half of the information: 11 (3%) Understood most of the information: 137 (33%) Understood all of the information: 251 (61%) Refused: <5 (1%)	Did not understand it at all: <5 (<1%) Understood some of the information: <5 (<1%) Understood about half of the information: 18 (4%) Understood most of the information: 163 (39%) Understood all of the information: 234 (55%) Refused: 0 (0%)
Patient Counseling Document (PCD) Questions		
Received PCD from healthcare provider when first prescribed the current ER/LA opioid analgesic	Yes: 155 (38%) No: 135 (33%) Not sure: 123 (30%) Refused: 0 (0%)	Yes: 160 (38%) No: 138 (33%) Not sure: 125 (30%) Refused: 0 (0%)
Received PCD from healthcare provider when prescribed the current ER/LA opioid analgesic in the last 12 months	Yes: 111 (27%) No: 207 (50%) Not sure: 95(23%) Refused: 0 (0%)	Yes: 135 (32%) No: 200 (47%) Not sure: 88 (21%) Refused: 0 (0%)
Healthcare provider referred to or discussed PCD when prescribing the current ER/LA opioid analgesic in the last 12 months	Yes: 109 (26%) No: 206 (50%) Not sure: 98 (24%) Refused: 0 (0%)	Yes: 111 (26%) No: 212 (50%) Not sure: 100 (24%) Refused: 0 (0%)
Understanding of the information discussed from the PCD	Did not understand it at all: 23 (8%) Understood some of the information: 5 (2%) Understood about half of the information: 11 (4%) Understood most of the information: 64 (21%) Understood all of the information: 169 (56%)	Did not understand it at all: 33 (10%) Understood some of the information: <5 (<1%) Understood about half of the information: 16 (5%) Understood most of the information: 90 (28%) Understood all of the information: 150 (47%)

Table 23: Patient-Reported Receipt and Comprehension of the Medication Guide and Patient-Counseling Document		
Question	**24-Month (n=413) N (%)**	**36-Month (n=423) N (%)**
	Refused: 32 (11%)	Refused: 24 (8%)

Domain 3: Perceived access and satisfaction with access to pain medications

Five survey items assessed patient's perceived access to treatment and satisfaction with access to pain medications (See *Table 24*). In terms of perceived access, 71% agreed they were able to get a prescription when needed. Thirty-five percent (35%) of respondents felt they had to go to their HCP too often when ER/LA opioid analgesics were needed.

Most respondents reported satisfaction with their access to ER/LA opioid analgesics. The majority were satisfied with their ability to get a prescription (83%), with their access to ER/LA opioid analgesics (78%), and with their ability to get ER/LA opioid analgesics from the pharmacy (80%).

Table 24: Patients' Perceived Access to Treatment and Satisfaction with Access		
Question	**24-Month (n=413) N (%)**	**36-Month (n=423) N (%)**
Able to get a prescription for ER/LA opioid analgesics through my healthcare provider when needed for pain	Agreed: 302 (73%) Disagreed: 62 (15%) Neither agreed not disagreed: 49 (12%)	Agreed: 300 (71%) Disagreed: 79 (19%) Neither agreed not disagreed: 44 (10%)
Satisfied with ability to get a prescription for ER/LA opioid analgesics	Agreed: 329 (80%) Disagreed: 46 (11%) Neither agreed not disagreed: 37 (9%) No response: 1(<1%)	Agreed: 349 (83%) Disagreed: 41 (10%) Neither agreed not disagreed: 33 (8%)
Satisfied with access to ER/LA opioid analgesics	Agreed: 336 (81%) Disagreed: 38 (9%) Neither agreed not disagreed: 38 (9%) No response: 1 (1%)	Agreed: 329 (78%) Disagreed: 54 (13%) Neither agreed not disagreed: 40 (9%)
Does not have to go to healthcare provider too often when more ER/LA opioid analgesics are needed	Agreed: 223 (54%) Disagreed: 122 (30%) Neither agreed not disagreed: 68 (16%)	Agreed: 227 (54%) Disagreed: 147 (35%) Neither agreed not disagreed: 48 (11%) No response: 1 (<1%)
Satisfied with ability to get ER/LA opioid analgesics from a pharmacy	Agreed: 326 (79%) Disagreed: 52 (13%) Neither agreed not disagreed: 35 (8%)	Agreed: 337 (80%) Disagreed: 61 (14%) Neither agreed not disagreed: 25 (6%)

Domain 4: Patient-reported frequency of appropriate prescriber behaviors, including appropriate screening and counseling about ER/LA opioid analgesics

Survey items assessed patient-reported frequency of appropriate prescriber behaviors (see *Table 25*). The majority of respondents agreed that their HCP asked about medical history when prescribing (93%),

talked about how much medication to take or use when prescribing (92%), and discussed opioid choice including the benefits and risks associated with opioid therapy and important safety information (76%). Patient-reported responses were low for other appropriate prescriber behaviors. Sixty-four percent (64%) of respondents reported that their HCP discussed what to do if a dose was missed. A little over half of respondents reported that their HCP talked about what to do with extra medication when prescribing (56%) and discussed how to safely discontinue the current ER/LA opioid analgesics (57%). Respondents reported that their HCP always or regularly used the PCD for discussion (26%), cautioned about the risks associated with use (54%), discussed how to safely discontinue (39%), counseled on common side effects (50%), instructed about the importance of and how to safely dispose of unused medication (38%), instructed to keep medication away from children (52%), and instructed not to share medication (60%). Respondents reported that their HCP never used the PCD for discussion (29%), discussed how to safely discontinue (27%), instructed about the importance and how to safely dispose of any unused ER/LA opioid analgesics (29%), instructed to keep medication away from children (22%), and instructed not to share medication (20%).

Table 25: Patient-Reported Frequency of Appropriate Prescriber Behaviors

Question	**24-Month (n=413)** **N (%)**	**36-Month (n=423)** **N (%)**
Used the patient counseling document (PCD) on ER/LA opioid analgesics for discussion	Always: 64 (15%) Regularly: 33 (8%) Sometimes: 68 (16%) Rarely: 44 (11%) Never: 129 (31%) Don't know: 74 (18%) No response: 1 (1%)	Always: 59 (14%) Regularly: 52 (12%) Sometimes: 72 (17%) Rarely: 45 (11%) Never: 122 (29%) Don't know: 72 (17%) No response: 1 (<1%)
Cautioned about important risks associated with ER/LA opioid analgesics, including overdose or taking too much	Always: 131 (32%) Regularly: 83 (20%) Sometimes: 72 (17%) Rarely: 43 (10%) Never: 63 (15%) Don't know: 20 (5%) No response: 1 (1%)	Always: 138 (33%) Regularly: 88 (21%) Sometimes: 86 (20%) Rarely: 41 (10%) Never: 64 (15%) Don't know: 6 (1%)
Discussed how to safely discontinue ER/LA opioid analgesics if they are no longer needed	Always: 97 (23%) Regularly: 60 (15%) Sometimes: 72 (17%) Rarely: 43 (10%) Never: 111 (27%) Don't know: 29 (7%) No response: 1 (1%)	Always: 91 (22%) Regularly: 73 (17%) Sometimes: 82 (19%) Rarely: 43 (10%) Never: 115 (27%) Don't know: 17 (4%) No response: 2 (<1%)
Counseled on the most common side effects from using ER/LA opioid analgesics	Always: 120 (29%) Regularly: 87 (21%) Sometimes: 96 (23%) Rarely: 46 (11%) Never: 48 (12%) Don't know: 16 (4%)	Always: 109 (26%) Regularly: 103 (24%) Sometimes: 105 (25%) Rarely: 45 (11%) Never: 55 (13%) Don't know: 6 (1%)
Instructed about the importance and how to safely dispose of any unused	Always: 87 (21%) Regularly: 52 (13%)	Always: 95 (22%) Regularly: 69 (16%)

Table 25: Patient-Reported Frequency of Appropriate Prescriber Behaviors		
Question	**24-Month (n=413) N (%)**	**36-Month (n=423) N (%)**
ER/LA opioid analgesics	Sometimes: 60 (15%) Rarely: 35 (8%) Never: 144 (35%) Don't know: 35 (8%)	Sometimes: 70 (17%) Rarely: 49 (12%) Never: 123 (29%) Don't know: 15 (4%) No response: 2 (<1%)
Instructed about keeping ER/LA opioid analgesics safe and away from children	Always: 140 (34%) Regularly: 61 (15%) Sometimes: 52 (12%) Rarely: 41 (10%) Never: 98 (24%) Don't know: 20 (5%) No response: 1 (<1%)	Always: 156 (37%) Regularly: 64 (15%) Sometimes: 59 (14%) Rarely: 43 (10%) Never: 94 (22%) Don't know: 7 (2%)
Instructed not to share ER/LA opioid analgesics with anyone else	Always: 166 (40%) Regularly: 59 (14%) Sometimes: 39 (9%) Rarely: 32 (8%) Never: 99 (24%) Don't know: 18 (4%)	Always: 173 (41%) Regularly: 82 (19%) Sometimes: 49 (12%) Rarely: 31 (7%) Never: 84 (20%) Don't know: 4 (1%)
Healthcare provider asked about medical history when prescribing ER/LA opioid analgesics*	Agreed: 385 (93%) Disagreed: 14 (3%) Neither agreed not disagreed: 14 (3%)	Agreed: 392 (93%) Disagreed: 25 (6%) Neither agreed not disagreed: 6 (1%)
Healthcare provider talked about how much medication to take or use when ER/LA opioid analgesics were prescribed*	Agreed: 393 (95%) Disagreed: 13 (3%) Neither agreed not disagreed: 7 (2%)	Agreed: 391 (92%) Disagreed: 20 (5%) Neither agreed not disagreed: 12 (3%)
Healthcare provider talked about what to do with extra medication when ER/LA opioid analgesics were prescribed*	Agreed: 218 (53%) Disagreed: 143 (35%) Neither agreed not disagreed: 49 (12%) No response: 1 (<1%)	Agreed: 238 (56%) Disagreed: 136 (32%) Neither agreed not disagreed: 48 (11%) No response: 1 (<1%)
Healthcare provider discussed opioid choice, including the benefits and risks associated with opioid therapy, and important safety information when prescribing the current ER/LA opioid analgesic in the last 12 months*	Yes: 321 (78%) No: 78 (19%) Not sure: 14 (3%) Refused: 0 (0%)	Yes: 321 (76%) No: 86 (20%) Not sure: 16 (4%) Refused: 0 (0%)
Healthcare provider discussed how to safely discontinue the current ER/LA opioid analgesic when it was prescribed in the last 12 months*	Yes: 221 (54%) No: 176 (43%) Not sure: 16 (4%) Refused: 0 (0%)	Yes: 243 (57%) No: 161 (38%) Not sure: 19 (4%) Refused: 0 (0%)
Healthcare provider discussed what to do if a dose was missed of the current ER/LA opioid analgesic when it was	Yes: 252 (61%) No: 138 (33%) Not sure: 23 (6%)	Yes: 269 (64%) No: 135 (32%) Not sure: 19 (4%)

Table 25: Patient-Reported Frequency of Appropriate Prescriber Behaviors		
Question	**24-Month (n=413) N (%)**	**36-Month (n=423) N (%)**
prescribed in the last 12 months*	Refused: 0 (0%)	Refused: 0 (0%)
Healthcare provider completed a Patient Prescriber Agreement (PPA) or patient contract when the current ER/LA opioid analgesic was prescribed in the last 12 months*	Yes: 191 (46%) No: 149 (36%) Not sure: 73 (18%) Refused: 0 (0%)	Yes: 225 (53%) No: 133 (31%) Not sure: 65 (15%) Refused: 0 (0%)

*Different response options across survey questions

4.4.1 **Reviewer's Comments on Patient Survey**

Overall, respondents had a high understanding of the key risk messages, though the survey respondents were not representative of the drug use population. There was a lower understanding of aspects of safe storage and using the drug safely. The majority of respondents received the Medication Guide in the last 12 months (95%) but only 32% of respondents received the PCD in the last 12 months. Most respondents reported satisfaction with access to ER/LA opioid analgesics (83%). Patient-reported frequency of appropriate prescriber behaviors was low.

Survey results were similar to the survey results from the 24-month assessment. As in the previous survey, the survey respondents were not representative of the population of patients nationwide who need access to ER/LA opioid analgesics. The RPC reported that for subsequent surveys they will use the HealthCore Integrated Research Database for Medicare patients and a vendor that specializes in panel building for survey research to identify Medicaid patients.

FDA recommended the inclusion of caregivers in subsequent surveys. The RPC responded that the HIRD database does not allow for the inclusion of caregivers. For subsequent surveys, the RPC should use a database that will allow parents, caregivers, or legal guardians to be included.

One main concern with the survey is generalizing results to the targeted population of interest. The patient survey is a convenience sample of the targeted patients who were prescribed ER/LA opioid analgesics. The 36-month REMS assessment report did not provide comparisons of the characteristics of the survey respondents to those of the targeted population for each of the surveys. Thus, it is impossible to assess whether or how the results of these surveys can be generalized to the population. The FDA statistical review recommended that future survey analyses: (1) compare characteristics of survey participants to its target population for each survey; and (2) propose methods to standardize the results of each survey to its targeted population.

4.6. *Assessment Element 5: Surveillance*

This assessment element states**:** *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 setting*

A full review of these data can be found in the May 19, 2016 DEPI (J. McAninch) Epidemiology: Review of Post-marketing Studies included in the 36-month REMS Assessment Report. However, the cited DEPI review provides the following conclusions:

"Despite considerable methodological limitations, the data suggest encouraging downward trends in some, but not all, outcomes; however, they do not indicate whether the REMS itself is contributing to these changes. The submitted surveillance studies may provide some useful contextual information but are unable to show whether the ER/LA opioid analgesic REMS is making progress toward the goal of reducing serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of these drugs. Nor do the studies demonstrate that the REMS is failing to achieve its goals, however.

The lack of studies that directly examine associations between participation in REMS training and changes in clinical practice or patient outcomes limits the ability of these studies to evaluate the effectiveness of the REMS and guide specific changes to the program. To assess the effects of the REMS provider trainings directly, pre-post changes in prescriber behavior and/or patient outcomes for a group of providers who participate in the REMS training would need to be compared to those in a group who do not participate in the training. Conducting such a study would be challenging and resource intensive, but the feasibility of this type of investigation should be explored if more rigorous evaluation of the impact of the ER/LA opioid analgesic REMS is needed."

4.7. Assessment Elements 6 and 7: Drug Utilization and Prescribing Behavior

Assessment Element 6 states*: Evaluation of drug utilization patterns.*
Assessment Element 7 states**:** *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*.

A full review of these data can be found in DEPI II's Review of 36th Month Assessment of the Risk Evaluation and Mitigation Strategy for the in the FDA Briefing Document for the May 3-4, 2016 Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) regarding the ER/LA REMS [Backgrounder pages 217-249]). However, the cited DEPI review provides the following conclusions:

"The RPC reported a significant decrease in ER/LA opioid analgesic prescriptions dispensed and patients treated from pre-implementation to active period. However, in this large study population, small changes in study metrics can be statistically significant, but may not be clinically relevant. We (FDA) also note that the decreasing trend in the total number of ER/LA opioid analgesic prescriptions dispensed appears to have begun before the implementation of the REMS. The prescription data also show only certain ER/LA opioid analgesics decreased in utilization; the decrease in total ER/LA opioid analgesic prescriptions appears to be largely due to a decrease in prescriptions dispensed for oxycodone ER. Of note, prescriptions dispensed for morphine ER increased during the same time period. In addition, there was a decrease in the IR opioid market during the examined time, although utilization of oxycodone IR increased.

Overall, additional data sources are needed to ascertain the impact of the ER/LA REMS on patient access to ER/LA opioid therapy, as typical utilization data sources alone are insufficient. Longitudinal studies that track changes in prescribing behavior before and after REMS-compliant training by prescribers who have undergone ER/LA REMS training vs. prescribers who have not, as well as an assessment of the impact on utilization trends at the patient level should also be considered for future submissions. Secondly, information on appropriateness of use of drug

products cannot be ascertained by typical drug utilization data. The RPC would need to address this by designing studies that utilize appropriate data resources."

4.8. Assessment Element 8: Changes in Access

This Assessment Element states: *Monitoring patterns of prescribing to identify changes in access to ER/LA opioid analgesics*

As per the REMS SD, this element consists of two components:

- Changes in prescribing comparing prescribers from specialties whose prescribing is hypothesized to be relatively unaffected by the REMS (such as oncologists and hospice providers) versus those for whom the REMS could have greater impact on prescribing (e.g., dentists) using drug utilization data.
- A set of questions added to the REMS prescriber survey to assess whether prescribers perceive an impact of the ER/LA opioid analgesic REMS on access to treatment. For prescribers, survey items assess whether the REMS implementation has led to a switch in medications that they prescribe and their perception of a change in access to ER/LA opioid analgesics for patients who the prescriber judges to have a medical need. For patients, survey items assess whether patients perceive a change following implementation of the REMS in: 1) physicians' prescribing of pain medication; 2) access to medications to treat pain; and 3) satisfaction with pain treatment.

Results

Based on the Applicant holder's analysis of drug use data, the ER/LA opioid analgesics (as well as the IR opioids, and celecoxib) demonstrated statistically significant decreases in 3-month prescription volume from the pre-REMS to post-REMS period. In addition, most of the specialties assessed demonstrated statistically significant decreases in prescriptions from the Pre- to Post-REMS periods with the exception of Anesthesiologists, Nurse Practitioners, and Physicians Assistants, who demonstrated statistically significant increases.

Regarding prescribers' perceptions of patients' ability to access ER/LA opioid analgesics, the prescriber surveys revealed the following:

- Most prescribers perceived access to ER/LA opioid analgesics to be moderately easy to easy (n=383 or 62.6% of respondents chose 5 to 8 on a scale of 1 to 10);
- The perceived primary obstacles to patient access to ER/LA opioid analgesics were insurance coverage (74%) and insurance authorizations and approvals (72%);
- Both prescribers who reported taking a CE training and those who had not taken such a training thought that ease of access was "about right" for patients for whom ER/LA opioid analgesics are indicated (52.5% and 52.4%, respectively); however 38% of all respondents felt that the REMS added to the difficulty to access opioids;
- 27% of CE respondents reported prescribing more non-opioid medications since the implementation of the REMS compared to 18% of non-CE-trained respondents; 23% of all respondents also reported limiting which ER/LA they did prescribe;
- Overall, 38% of respondents felt that the REMS made access more difficult while 37% of respondents reported that there was no impact.
- 11% of prescribers who reported taking a CE training reported prescribing more IR opioids versus 6% for those who had not taken such a training.

Regarding patients' perceptions of their ability to access ER/LAs, the patient survey revealed the following:

- 71% agreed that they were able to get a prescription for an ER/LA when needed
    - However, this varied across medication types with fewer patch users (67%) and more methadone users (74%) reporting satisfaction
    - Respondents who did not understand the Medication Guide or PCD, or had only one recorded ER/LA opioid analgesic dispensing less often confirmed their access to obtain a prescription.
- Most respondents (83%) reported satisfaction with access to ER/LA opioid analgesics
    - However, only 60% of single dispensing users and 65% of respondents with a KAS (i.e., proportion of knowledge questions that a respondent answered correctly) <80% stated that they were satisfied with their ability to get a prescription when needed for ER/LAs from a healthcare provider when needed for pain.
    - Satisfaction with their ability to get a prescription was reported by 83% of respondents, and was slightly higher for methadone users (87%)
- Only 54% agreed that they did not have to go to their HCP too often when ER/LA opioid analgesics were needed

The reader is referred to DEPI II's Review of 36th Month Assessment of the Risk Evaluation and Mitigation Strategy for the in the FDA Briefing Document for the May 3-4, 2016 Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) regarding the ER/LA REMS [Backgrounder pages 217-249]) for more details regarding the methodology and results of this analysis of this assessment element.

4.8.1. Reviewers Comments

a. The utilization data provided by the RPC do not provide specific information that informs whether or not patient access has been an issue since the implementation of the ER/LA opioid REMS. Responses to specific questions from the prescriber and patients surveys are somewhat reassuring regarding patient access. Overall, however, surveys alone are not a precise tool that can quantify the extent of patient access issues or identify root causes of any access issues identified. The RPC should submit a concept paper with the September 2016 REMS assessment for an alternate approach to evaluating the impact of the REMS on patient access. This paper should address how to include individuals in pain who are determined to be appropriate candidates for ER/LA opioid analgesics, but who fail to have them prescribed and/or dispensed.

5. Conclusions

2. Prescriber CE Training:

a. Although a large number of health professionals have participated in or completed the training, the targets for prescriber training numbers have not been met. However, non-prescriber completers should not be disregarded since these may be individuals involved in communicating safe use information to patients.
b. The definition of a "Prescriber" employed by the RPC likely misses new and institutional prescribers

c. Factors limiting uptake of training include:
    i. voluntary nature of the training
    ii. the length of training (2-3 hours) may discourage taking and/or completing the training as may the lack of a "test-out" option
    iii. the RPC has uncovered sub-optimal awareness of the ER/LA REMS
    iv. the REMS training competes numerous other trainings
d. Considerations for the FDA and the RPC moving forward include:
    i. How much time should be allowed for a voluntary educational intervention to impact prescriber behavior?
    ii. How many prescribers need to be trained and how much change in clinical practice is needed to see measurable effects on outcomes?
    iii. Are the training goals/targets reasonable for a voluntary education program?
    iv. How can more training uptake and completion be encouraged?
    v. Do individuals who take a voluntary training differ from individuals who choose not to?
    vi. Is it time to consider a form of mandatory training?
    vii. Should training be tailored to specific prescriber types? For example, doe training needs differ amongst various prescriber specialties as well as between "high-volume" prescribers versus "low-volume" prescribers?
e. FDA should strongly recommend that the RPC continue to:
    i. Explore ways to raise awareness about the availability of the ER/LA Opioid Analgesic REMS-compliant training programs.
    ii. Encourage its grantees to ensure that financial information regarding the authors of the REMS-compliant training is disclosed, and that the disclosure should be done prior to the beginning of the activity; and
    iii. Explore with the CE providers ways to capture the reasons why prescribers initiate a training but fail to complete it

3. Knowledge, Attitude, and Behavior (KAB) Surveys:

a. Overall knowledge rates for most of the six areas of the FDA Blueprint were high as measured in both prescriber surveys and in the patient survey.
    i. The Follow-up Prescriber Survey indicated that those who complete CE training more frequently correctly answer survey questions
    ii. The Prescriber Long-Term Evaluation Survey indicated that those who complete CE training more often reported appropriate prescriber behaviors (e.g., providing risk counseling, screening patients for misuse/abuse)
    iii. The Patient Survey indicated an overall very good understanding of ER/LA risks
b. Survey respondents WERE not optimally representative of the general population of ER/LA prescribers and patients. In addition:
    i. There was a potential lack of comparability amongst studied groups
    ii. Limitations with all KABs typically submitted with REMS include that these are convenience samples, the participants self-select, and there is a high non-response rate amongst potential participants.
    iii. The RPC should be directed to submit a concept paper for alternate study designs for evaluation of prescriber and patient knowledge, such as those suggested at the May 3-4, 2016 Joint DSaRM/AADPAC Advisory Committee meeting. (e.g., self-control survey on probability samples, randomized

experiment, longitudinal database link to training data pre/post REMS CE training using electronic medical records or claims data).

4. **Surveillance Data:**
    a. Much of the provided surveillance indicate decreases in some of the adverse events of interest.
    b. However, these data also indicate:
        i. These decreases began to occur or had occurred before full REMS implementation
        ii. Decreases occurred in agents not subject to a REMS (IR opioids, benzodiazepines)
        iii. Numerous federal, state, local, and health system related efforts to address opioid issues
    c. Surveillance sources utilized have significant limitations (e.g. convenience sampling)
    d. It is difficult to link prescriber participation in REMS training to changes in practice or patient outcomes
    e. Thus overall it is exceedingly difficult to assess the impact of the REMS on any of the surveillance outcomes.
    f. The RPC should be directed to submit a concept paper for a study or studies that will assess the impact of the REMS by measuring changes in prescribing practices and patient outcomes (misuse, abuse, and overdose), comparing REMS-trained vs REMS-untrained prescribers. The RPC should propose methods to account for the potential confounding related to differences between prescribers who choose to take a voluntary training and those who do not. The concept paper should also propose methods for determining the appropriateness of ER/LA opioid analgesic prescribing and possible metrics for measuring changes in appropriate and inappropriate prescribing following REMS training.

5. **Drug Utilization and Prescriber Behavior Data:**
    a. From the pre-REMS to the post-REMS period, fewer prescriptions have been dispensed for ER/LA opioids, IR opioids, and other comparators studied
    b. Also, decreases were also noted in ER/LA prescriptions written by most medical specialties from the pre-REMS to post-REMS period
    c. However, the modest decreases seen from the pre-REMS to the post-REMS period should be viewed in light of the great escalation in opioid prescribing over the previous 20-25 years
    d. Decreases seen in ER/LA prescriptions appear to have started prior to full REMS implementation and driven mostly by decreases in oxycodone ER. In fact, many of the decreases began prior to full REMS implementation
    e. ER/LA to IR opioid switch data as well as early prescription fill data are difficult to interpret without additional information that can explain why either a switch or an early prescription fill occurred. For example, an early prescription fill may be due to abuse or may be due to an increased level of pain.
    f. The prescription of opioids intended for use only in *opioid-tolerant* patients to many *opioid-**non**-tolerant* patients continues. In their assessment of opioid tolerance, the RPC should not utilize a 90-day look-back period. Instead, the RPC's analysis of prescriptions to non-opioid-tolerant patients should utilize a 30-day look- back period (as noted in the paper by *Willy et al. Pain Medicine 2014; 15: 1558–1568).*

g. The RPC analysis of national trends in drug utilization should include the IR comparator products (i.e., combination oxycodone/acetaminophen, oxycodone/aspirin, oxycodone/ibuprofen, immediate-release and extended-release tramadol and tramadol/acetaminophen).

6. Patient Access:

a. To assess Patient Access, the RPC provides the following data:
   i. Drug utilization data
   ii. Responses to Patient & Prescriber Survey questions

b. Limitations of these data include:
   i. Utilization data cannot directly inform whether any impact of the REMS on patient access has occurred
   ii. Patient and prescriber responses to survey questions regarding access are somewhat reassuring; however, questions remain about the appropriateness of the survey populations
   iii. Those who could not get an ER/LA are not assessed

c. It is not possible to determine whether the REMS has impacted patient access to ER/LAs based on these data.

d. The RPC should be directed to submit a concept paper for an alternate approach to evaluating the impact of the REMS on patient access. This paper should address how to include individuals in pain who are determined to be appropriate candidates for ER/LA opioid analgesics, but who fail to have them prescribed and/or dispensed.

6. REVIEW TEAM CONCLUSION

DRISK, DPV, DEPI, OB, DAAAP, and the Office of Compliance met numerous times to discuss the assessment for the ER/LA REMS. In addition, on May 3rd and 4th, 2016, the FDA held a joint meeting of the DSaRM AC and the AADPAC to discuss these findings.

Overall, the team believes the assessment is complete but that it is difficult to determine whether the REMS is meeting its goal. FDA continues to assess the recommendations made by the joint advisory committee. The FDA and the RPC have agreed upon a 2 –month delay of the submission of the 48-month Assessment Report. As FDA continues to assess options for this REMS, the FDA is communicating the interim instructions to the RPC noted in Section 7 below.

7 RECOMMENDATIONS

This RPC's assessment report is complete in addressing the issues outlined in the approved REMS assessment plan. The findings from this assessment were presented and discussed at the May 3-4, 2016 Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC). A number of recommendations for modifications to the program were provided by the Advisory Committees and the Agency is considering how best to proceed in making these changes. The recommendations provided below should be considered as interim recommendations as we continue to determine our next steps. These recommendations were conveyed to the RPC in a teleconference on June 10, 2016.

We recommend sending the applicant an Acknowledge REMS Assessment letter with comments.

Agreed upon comments to be sent to the applicant, to be responded to in the next and subsequent assessments:

1. The FDA review team is unable to determine if the REMS is meeting its goal of reducing 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 for the following reasons:
    a. While your surveillance studies indicate that there have been decreases in some adverse safety outcomes of interest, these data also indicate that the majority of these decreases predate full REMS implementation. In addition, classes of drugs with abuse potential that are not subject to REMS have also experienced decreases in adverse safety outcomes of interest. Also, because there are numerous concurrent federal and state efforts to reduce adverse safety outcomes with opioids, the results of the assessment do not permit a determination of whether or, if so, to what extent the REMS is contributing to the reductions in adverse safety outcomes and whether the REMS is meeting its goal.
    b. The drug utilization data provided show a decrease in the volume of prescribing of ER/LA opioid analgesics. As with the surveillance data, the majority of these decreases pre-date full REMS implementation; classes of drugs with abuse potential that are not subject to REMS have also experienced decreases in dispensed prescriptions. There are many factors other than the REMS that influence prescribing trends. Furthermore, the lack of clinical context for these data precludes the ability to utilize these data to understand the impact of the ER/LA opioid analgesic REMS on *inappropriate* prescribing.
    c. The patient access data provided (utilization and survey responses) do not answer the question of whether patient access was unduly burdened by the REMS, or whether there were problems for patients appropriately prescribed opioid analgesics obtaining an ER/LA opioid analgesic.
    d. Although the survey results generally demonstrated a reasonable knowledge of the risks associated with ER/LA opioid analgesics, the populations surveyed were not representative of the full range of ER/LA opioid analgesic prescribers and patients. In the Follow-up Prescriber survey, it is not clear if the respondents identified as not having taken REMS-compliant training (recruited from IMS Data) in actuality did not take REMS-compliant training. This raises concerns because without that information, it cannot be determined whether the results provided represent an accurate comparison of the knowledge of prescribers who had taken and had not taken REMS-compliant training. In addition, the populations identified as having taken REMS training and those not having taken the REMS training were also very different from each other in other ways that could have impacted the results. (e.g., health profession , specialty)

2. Per email communication (Wendy Brown to Linda Noa, February 3, 2016), the Agency agreed to a 2-month delay in submission of the 48-month ER/LA Opioid Analgesic REMS Assessment report. The 48–month assessment report is now due on or before September 9, 2016, and should include the following:
    a. Submit the results of Assessment Elements 1, 2, 3, 4, and 5. In your report take into consideration Agency comments that were previously sent to the RPC regarding the Patient Survey (email communication, Wendy Brown to Linda Noa, January 20, 2016)

and the Follow-up Prescriber Survey and the Long-Term Evaluation Survey (email communication, Wendy Brown to Linda Noa, January 25, 2016).

b. Submit the results and analysis methods used for both prescriber surveys that were presented during the May 3-4, 2016 , Joint DSaRM and AADPAC Advisory Committee meeting, as these differ from what was provided in the 36-month assessment report as well as the RPC background document for the May 3-4, 2016, Joint Advisory Committee.
c. Assessment Element 5:
    i. Do not submit Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) or National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) data.
    ii. Submit an update on the status of outcome validation studies and National Death Index linkage in the HIRD and Medicaid studies as well as the potential for linkages between these databases and data on prescriber training completion.
    iii. Submit a report that describes trends in prescription opioid analgesic-related adverse safety outcomes of interest from 2006 through the most recent available year using data from nationally representative surveys and national-level drug overdose death data. Analyses of medical examiner overdose death data from multiple states may also be submitted.
    iv. Submit the study protocol (or detailed description of study methodology) and final results of the Pri-Med/Amazing Charts study described by Dr. Argoff at the May 3-4, 2016, Joint DSaRM and AADPAC Advisory Committee meeting.
d. Assessment Element 6:
    i. Submit an analysis of national trends in drug utilization as previously outlined (email communication Vaishali Jarral to Lisa Malandro May 6, 2014). As was stated in the communication, the analysis should include the IR comparator products (i.e., combination oxycodone/acetaminophen, oxycodone/aspirin, oxycodone/ibuprofen, immediate-release and extended-release tramadol and tramadol/acetaminophen).
e. Assessment Element 7:
    i. In your analysis of prescriptions to non-opioid tolerant patients, utilize a 30-day look- back period (in addition to the 7 day look-back) (as noted in the paper by *Willy et al. Pain Medicine 2014; 15: 1558–1568).* The 90-day look-back period in the assessment of opioid tolerance is unacceptable because the longer period may overestimate opioid tolerance. Additionally, fully describe how the percentage of opioid-non-tolerance was calculated and indicate whether this metric refers to patients or prescriptions.
f. Assessment Element 8:
    i. Do not submit the evaluation of patient access (i.e., based solely on utilization data and survey questions) that has been conducted in previous assessments. See section 3c below for additional guidance.

3. The September REMS assessment report should also include the following:
    a. *Evaluation of the impact of REMS on prescribing practices and patient outcomes*. As part of the September 2016 REMS assessment, submit a concept paper for a study or studies that will assess the impact of the REMS by measuring changes in prescribing practices and patient outcomes (misuse, abuse, and overdose), comparing REMS-trained vs REMS-untrained prescribers. Propose methods to account for the potential confounding related to differences between prescribers who choose to take a voluntary

training and those who do not. The concept paper should also propose methods for determining the appropriateness of ER/LA opioid analgesic prescribing and possible metrics for measuring changes in appropriate and inappropriate prescribing following REMS training.

b. *Evaluation of the impact of REMS on prescriber and patient knowledge.* Submit a concept paper with the September 2016 REMS assessment for alternate study designs for evaluation of prescriber and patient knowledge, such as those suggested at the May 3-4, 2016, Joint DSaRM and AADPAC Advisory Committee meeting. (e.g., self-control survey on probability samples, randomized experiment, longitudinal database link to training data pre/post REMS CE training using electronic medical records or claims data)

c. *Evaluation of the impact of REMS on patient access.* Submit a concept paper with the September 2016 REMS assessment for an alternate approach to evaluating the impact of the REMS on patient access. This paper should address how to include individuals in pain appropriately prescribed opioid analgesics who failed to procure ER/LA opioid analgesics.

4. We strongly recommend that you continue to:
    a. Explore ways to raise awareness about the availability of the ER/LA Opioid Analgesic REMS-compliant training programs.
    b. Encourage your grantees to ensure that financial information regarding the authors of the REMS-compliant training is disclosed, and that the disclosure should be done prior to the beginning of the activity; and
    c. Explore with the CE providers ways to capture the reasons why prescribers initiate a training but fail to complete it

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/s/

IGOR CERNY
06/29/2016
REMS Assessment Review

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