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 the fifth (48 month, May 11, 2014 through May 9, 2015) Risk Evaluation and Mitigation Strategy (REMS) Consolidated Assessment Report for Extended-Release and Long-Acting (ER/LA) opioid analgesic products

Date: **August 10, 2017**

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Therapeutic Class: Extended-Release and Long-Acting opioid analgesic (ER/LA) products

Submission Dates: **September 7-9, 2016**

Drug Name	Application Type/ Number	Applicant/ Sponsor	SDN	eCTD sequence #	Submission Date
BELBUCA (buprenorphine)	NDA 207932	Endo	96	44	9/8/2016
BUTRANS (buprenorphine transdermal [TD])	NDA 21306	Purdue	415	162	9/8/2016
DURAGESIC (Fentanyl TD)	NDA 19813	Janssen	826	160	9/9/2016
fentanyl TD	ANDA 76709	Actavis	product approved just before submission date		
fentanyl TD	ANDA 77449	Aveva	109	37	9/9/2016
fentanyl TD	ANDA 77154	Mallinkrodt	150	79	9/7/2016
fentanyl TD	ANDA 76258	Mylan	239	60	9/8/2016

Drug Name	Application Type/ Number	Applicant/ Sponsor	SDN	eCTD sequence #	Submission Date
fentanyl TD	ANDA 77775	Noven	ANDA withdrawn		
fentanyl TD	ANDA 77062	Par	154	70	9/9/2016
ZOHYDRO ER (hydrocodone bitartrate)	NDA 202880	Pernix Ireland Pain	237	107	9/8/2016
HYSINGLA ER (hydrocodone bitartrate)	NDA 206627	Purdue	147	81	9/8/2016
VANTRALA ER (hydrocodone bitartrate)	NDA 207975	Teva	product not approved before submission date		
hydrocodone bitartrate ER	ANDA 206952	Actavis	product approved just before submission date		
EXALGO (hydromorphone hydrochloride ER)	NDA 21217	Mallinkrodt	453	171	9/9/2016
hydromorphone hydrochloride ER	ANDA 202144	Actavis	product not approved before submission date		
hydromorphone hydrochloride ER	ANDA 205629	Osmotica	product not approved before submission date		
hydromorphone hydrochloride ER	ANDA 204278	Paddock	no submission		
DOLOPHINE (methadone hydrochloride)	NDA 06134	Roxane	171	57	9/8/2016
methadone hydrochloride	ANDA 203502	Aurolife Pharma	no submission		
methadone hydrochloride	ANDA 90065	CorePharma	35	32	9/8/2016
methadone hydrochloride	ANDA 40517	Mallinkrodt	99	54	9/7/2016
methadone hydrochloride	ANDA 87393	Roxane	124	46	9/9/2016
methadone hydrochloride	ANDA 89897	Roxane	135	40	9/8/2016
methadone hydrochloride	ANDA 87997	Roxane	100	43	9/9/2016
methadone hydrochloride	ANDA 40241	Sandoz	no submission		
methadone hydrochloride	ANDA 90635	The Pharma Network	46	42	9/9/2016
methadone hydrochloride	ANDA 90707	VistaPharm	55	41	9/8/2016
METHADOSE (methadone hydrochloride)	ANDA 40050	Mallinkrodt	111	50	9/7/2016
ARYMO ER (morphine sulfate ER)	NDA 208603	Eaglet	product not approved before submission date		
AVINZA (morphine sulfate ER)	NDA 21260	King	no submission		
EMBEDA (morphine sulfate and naltrexone hydrochloride ER	NDA 22321	Alpharma	345	166	9/9/2016
KADIAN (morphine sulfate ER)	NDA 20616	Allergan	599	74	9/9/2016
MORPHABOND (morphine sulfate ER)	NDA 206544	Inspirion Delivery Technologies	product approved shortly before submission date		
MS CONTIN (morphine sulfate ER)	NDA 19516	Purdue	477	76	9/8/2016
morphine sulfate ER	ANDA 203849	Actavis	no submission		
morphine sulfate ER	ANDA 79040	Actavis	no submission		
morphine sulfate ER	ANDA 91357	CorePharma	22	21	9/8/2016
morphine sulfate ER	ANDA 200411	Impax	33	33	9/7/2016
morphine sulfate ER	ANDA 76412	Mallinkrodt	139	56	9/7/2016
morphine sulfate ER	ANDA 76438	Mallinkrodt	101	54	9/7/2016
morphine sulfate ER	ANDA 205386	Mayne Pharma	product not approved before submission date		
morphine sulfate ER	ANDA 200824	Mylan	58	55	9/8/2016

Drug Name	Application Type/ Number	Applicant/ Sponsor	SDN	eCTD sequence #	Submission Date
morphine sulfate ER	ANDA 77855	Nesher	no submission		
morphine sulfate ER	ANDA 76720	Nesher	no submission		
morphine sulfate ER	ANDA 76733	Nesher	no submission		
morphine sulfate ER	ANDA 203602	Novel Labs	19	17	9/8/2016
morphine sulfate ER	ANDA 200812	Par	68	55	9/9/2016
morphine sulfate ER	ANDA 74769	Rhodes	no submission		
morphine sulfate ER	ANDA 074862	Rhodes	no submission		
morphine sulfate ER	ANDA 78761	Sun	66	44	9/9/2016
morphine sulfate ER	ANDA 205634	Sun	11	10	9/8/2016
morphine sulfate ER	ANDA 202718	Teva	43	42	9/9/2016
morphine sulfate ER	ANDA 202104	Upsher-Smith	54	17	9/8/2016
morphine sulfate ER	ANDA 75295	Vintage	166	59	9/8/2016
OXYCONTIN (oxycodone hydrochloride ER)	NDA 22272	Purdue	412	294	9/8/2016
TARGENIQ ER (oxycodone HCl and naloxone HCl)	NDA 205777	Purdue	93	93	9/8/2016
TROXYCA ER (oxycodone hydrochloride and naloxone hydrochloride)	NDA 207621	Pfizer	55	54	9/9/2016
XTAMPZA (oxycodone ER)	NDA 208090	Collegium	111	69	9/9/2016
OPANA ER (oxymorphone hydrochloride) (old)	NDA 021610	Endo	525	88	9/8/2016
OPANA ER (oxymorphone hydrochloride) (new)	NDA 201655	Endo	306	160	9/8/2016
oxymorphone hydrochloride	ANDA 079046	Actavis	no submission		
oxymorphone hydrochloride	ANDA 079087	Impax	134	56	9/7/2016
oxymorphone hydrochloride	ANDA 202946	Mallinkrodt	45	41	9/7/2016
oxymorphone hydrochloride	ANDA 200792	Par	no submission		
oxymorphone hydrochloride	ANDA 200822	Roxane	62	53	9/9/2016
oxymorphone hydrochloride	ANDA 203506	Sun	no submission		
NUCYNTA ER (tapentadol)	NDA 200533	Depomed	416	158	9/14/2016

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1 EXECUTIVE SUMMARY

This review evaluates the forty-eight (48) month risk evaluation and mitigation strategy (REMS) Assessment Report for the extended-release/long-acting opioid analgesics (ER/LA) REMS and is the fifth report since approval of the REMS on July 9, 2012. It includes information on all 8 elements as delineated in the ER/LA REMS Assessment Plan contained in the July 9, 2012 approval letter. This assessment report includes data on the number of prescribers who have completed the voluntary continuing education (CE) training, the results of an audit of the CE training, prescriber surveys, a patient survey, various surveillance data, and drug utilization data.

The goal of this REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to these pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

- As of February 29, 2016, 66,881 ER/LA **prescribers completed accredited REMS-compliant CE activities**, representing 42% of the goal total (160,000). Thus while the goal of 160,000 prescriber completers as not been met, over 326,000 healthcare professionals began the training and nearly 160,000 completed the training but 57.5% did not meet the specific criteria for a prescriber completer.
- Since 2012, the RPC has issued 6 Requests for Applications (RFAs) and awarded funding to support 783 **REMS-compliant CE** through 28 grants to accredited CE Providers and the CE Provider's 100+ educational partners. Of these 783 REMS-compliant CE activities, 278 were available during this reporting period. A total of 212 activities were presented as live training, 65 were internet-based enduring programs, and one program was performance improvement (e.g., an activity that evaluated improvements in prescriber behaviors using patient data). All activities were accredited by at least one of six National Accrediting Bodies
- The RPC submitted two prescriber surveys: follow-up prescriber survey and long-term evaluation survey in order to assess prescriber knowledge of the FDA Blueprint and retention of that knowledge and a patient survey to assess patient's knowledge of the risks of ER/LA opioid analgesics. In considering these finding it is important to note that these surveys have a number of limitations including: the use of convenience samples, low response rates, and other factors which may affect the generalizability and comparability of the survey results to the overall populations of healthcare providers who prescribe ER/LA opioid analgesics, prescriber who have taken a REMS-compliant CE training, and patients who have been prescribed ER/LA opioid analgesics.
    - Results from the **Follow-up Prescriber Survey** show that surveyed respondents were knowledgeable about the assessment, management, and counseling requirements for patients being considered for treatment or currently being treated with an ER/LA. Respondents were less knowledgeable about initiation, modification, and discontinuation of therapy, and general and product specific information for ER/LAs. The comparison of prescribers that are recruited from IMS data versus prescribers that are recruited from CE providers does not accomplish the original goal of the survey: to compare prescribers that completed training to prescribers that did not complete training since IMS respondents also self-reported completion of REMS

compliant training. In addition, since the information is self-reported there is no way to know for certain if the completed CE activity was REMS compliant. The RPC provided a concept paper which proposed an epidemiologic study to examine changes in prescribing behavior and patient outcomes, comparing providers who have received the REMS training to those who have not. We recommend the elimination of this survey for future assessments to be replaced by the proposed concept paper#1 study.

- The **Long-Term Evaluation Prescriber Survey** shows that surveyed respondents were knowledgeable about management and counseling requirements for patients being considered for treatment or currently being treated with ER/LAs. Respondents were less knowledgeable about assessment of patients, initiation and modification of treatment, and general and product specific information for ER/LAs. 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/LAs, instructing patients to keep ER/LAs away from children, informing patients that it is illegal to share, sell, or give-away ER/LAs, using tools to screen patients for risk of misuse or abuse, completing a Patient Prescriber Agreement (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, patient non-compliance, and patients continuing to identify new drug-seeking behaviors that were not addressed in the training activity.
- **Patient Survey** respondents had a high understanding of the key risk messages. 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 (92%) but only 33% of respondents received the PCD in the last 12 months. Most respondents reported satisfaction with access to ER/LAs (83%). Patient-reported frequency of appropriate prescriber behaviors was low. Results were similar to the survey results from the previous assessments. As in the previous survey, the survey respondents were not representative of the patient population dispensed these products. The RPC utilized different databases to recruit Medicare patients and Medicaid patients but the sample size was small. In addition, caregivers were allowed to participate but only 13 completed the survey. Future surveys should use a sample of patients who are more representative of the overall population of patients prescribed ER/LA opioid analgesics.

- The Division of Epidemiology II's (DEPI) review of the submitted **surveillance data** suggests that the incidence of Opioid Overdose and Poisoning (OOP) ED visits and hospitalizations may have decreased, especially in prevalent ER/LA opioid analgesic users; however, these observed decreases are likely not attributable only to the REMS. The state medical examiner data submitted by the REMS Program Companies (RPC) indicate that opioid overdose death trends vary considerably across states, and indicate that a larger

number of states' data need to be examined so as to be able to monitor overdose death trends. While surveillance data can be valuable for understanding national trends in prescribing patterns and adverse outcomes of interest, these data do not inform the question of whether this REMS is having the desired impact on prescribing or abuse-related outcomes. Concept Paper #1 ("*Evaluation of the Impact of the REMS on Prescribing Practices and Patient Outcomes and Prescriber and Patient Knowledge*"**)** that was submitted in the 48-month Assessment Report has promise for providing valuable information about the impact of the REMS CE training on prescriber behavior and patient outcomes. RPC is now asked to submit a full protocol and Statistical Analysis Plan (SAP) for this study. In addition, the RPC is also asked to explore new data sources for assessing trends in the incidence of prescription opioid overdose-related ED visits and hospitalizations. Additional suggestions for enhancement of the RPC's surveillance data submissions are also provided, including limited analyses of Poison Center Data, Medical Examiner data from additional states, as well as additional years of Monitoring the Future data.

- The percentage of opioid non-tolerant patients prescribed ER/LAs in the post-REMS period ranged from 26.0% to 79.6%. However, utilizing only the primary definition for opioid tolerance (as described in the study by *Willy et al*[1]) likely results in underestimation for patients considered "opioid tolerant", and thus the RPC is asked to modify its criteria for determining opioid tolerance.
- The RPC's early refill methodology is inadequate to address whether or not the REMS has impacted inappropriate prescribing, misuse, or abuse of ER/LAs Switch data will not be requested for future assessments.
- Although the RPC has provided data on the percentage of switches from ER/LA products to IR opioids, reasons for are needed so as to be able to meaningfully interpret these data. Early refill data will not be requested for future assessments.

As communicated following the review of the 36 month REMS assessment, it is not possible to determine whether or not the REMS is meeting its goal since the surveillance data do not inform the question of whether this REMS is having the desired impact on prescribing or abuse-related outcomes.

[1] "*Candidate Metrics for Evaluating the Impact of Prescriber Education on the Safe Use of Extended-Release/Long-Acting (ER/LA) Opioid Analgesics, Pain Medicine 2014; Sep;15(9):1558-68*

1.1. List of Abbreviations

LIST OF ABBREVIATIONS	
AAFP	American Academy of Family Physicians
AANP	American Association of Nurse Practitioners
ACCME	Accreditation Council for Continuing Medical Education
ANCC	American Nurses Credentialing Center
AOA	American Osteopathic Association
ASI-MV	Addiction Severity Index – Multimedia Version
CCCE	Conjoint Committee on Continuing Education
CDER	Center for Drug Evaluation and Research
CE	Continuing Education
CHAT	Comprehensive Health Assessment for Teens
CME	Continuing Medical Education
CO*RE	Collaborative for REMS Education
CS	College Survey Program
DAAAP	Division of Anesthetics, Analgesia and Addiction Products
DDRP	Dear DEA-Registered Prescriber
DEA	Drug Enforcement Administration
DEPI	Division of Epidemiology
DPV	Division of Pharmacovigilance
DRISK	Division of Risk Management
ED	Emergency department
ER	Extended-Release

ER/LA	Extended-Release and Long-Acting opioid analgesics
ETASU	Elements to Assure Safe use
FDA	Food and Drug Administration
HCP	Healthcare Professional
HIRD	HealthCore Integrated Research Database
IR	Information Request
IR opioids	immediate-release opioids
LOA	Letter of Agreement
LRx	IMS Health, LifeLink™ patient-level longitudinal prescription
LTE	Long-Term Evaluation
MG	Medication Guide
MTF	Monitoring the Future
NAVIPPRO	National Addictions Vigilance Intervention and Prevention Program
NIDA	the National Institute on Drug Abuse
NIH	National Institutes of Health
NP	Nurse Practitioner
NPA	IMS Health, National Prescription Audit™
NSDUH	National Survey on Drug Use and Health
OB	Office of Biometrics
OOP	opioid overdoses and poisonings
OSE	Office of Surveillance and Epidemiology
OTP	Opioid Treatment Program
PA	Physician's Assistant
PC	Poison Center
PCD	Patient Counseling Document
PCP	primary care
PDMP	Prescription Drug Monitoring Program
PPA	Patient Prescriber Agreement
RADARS	Researched Abuse, Diversion and Addiction-Related Surveillance
REMS	Risk Evaluation and Mitigation Strategy
RFA	Request for Application
RFP	Request for Proposal
RPC	REMS Program Companies
SAMHSA	Substance Abuse and Mental Health Services Administration
SD	Supporting Document
SKIP	Survey of Key Informants' Patients Program
TC	Treatment Center Program
TDS	transdermal systems
US	United States
USPS	United States Postal Service

2 INTRODUCTION

This review evaluates the 48-month risk evaluation and mitigation strategy (REMS) assessment report submitted by the REMS Program Companies (RPC) on September 7-14th, 2016 for Extended-Release and Long-acting Opioid Analgesics (referred to in this document as **ER/LAs)** REMS to determine if the report is complete and if the goals of the REMS are being met. This REMS Assessment Report covers the period from May 9, 2015 through May 6, 2016.

3 BACKGROUND

Extended-Release/Long-Acting Opioid Analgesics (**ER/LAs**) are opioid drug products indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.This class of products comprises two distinct subsets: 1) products that have a duration of action that is pharmacologically longer-acting than most other opioid analgesic drug substances; and 2) and modified-release formulations that provide a longer duration of action. Thus, ER/LA products include: a) methadone tablets or liquid; and b) extended-release, solid, oral dosage forms containing hydrocodone, hydromorphone, morphine, oxycodone, tapentadol, and oxymorphone, and the fentanyl-containing and buprenorphine-containing transdermal delivery systems. The misuse and abuse of these drugs have resulted in a serious public health crisis of addiction, overdose, and death[2]

In accordance with section 505-1 of the Federal Food Drug and Cosmetic Act, the FDA determined that a REMS was necessary for all ER/LA products to ensure that their benefits outweigh their risks, especially with regard to specific adverse outcomes of concern which include addiction, unintentional overdose, and death. In addition, to minimize burden on the healthcare delivery system, the FDA determined that a shared system should be used to implement this REMS. Thus on April 19, 2011, the FDA notified manufacturers of ER/LAs that a class-wide, shared REMS was required. The sponsors of the ER/LA formed an industry working group called the **REMS Program Companies (RPC)** to prepare the REMS proposal for FDA approval and to operationalize the REMS program once approved. On July 9, 2012, FDA approved a class shared system REMS for ER/LA opioid analgesics.

The ER/LA REMS is part of a broader multi-agency Federal effort (including the National Institute of Health, Centers for Disease Control and Prevention, and the Office of National Drug Control Policy, amongst others) to address the growing problem of prescription drug abuse and misuse. The REMS provides safety measures intended to reduce risks and improve the safe use of ER/LAs, while continuing to provide access to these medications for patients in pain.

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2 https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/MisuseofPrescriptionPainRelievers/ucm2007101.htm

3.1. REMS Elements

The **Goal** of this REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

The REMS Elements include:

- **Medication Guide (MG)**
- **Elements to Assure Safe Use**: NDA/ANDA holders must ensure that training is available to prescribers who prescribe ER/LAs. Training will be considered "REMS-compliant training" under this REMS if: 1) it, for training provided by Continuing Education (CE) providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"), 3) it includes a knowledge assessment of all of the sections of the FDA Blueprint, and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met. The NDA/ANDA holders must inform prescribers of the existence of the ER/LA REMS and the importance of successfully completing the voluntary training.

  At least annually from the date of initial approval of the REMS, the DEA Registration Database will be reviewed and a Prescriber Letter will be sent to all newly DEA-registered prescribers who are registered to prescribe Schedule II and III drugs to inform them of the existence of the REMS, provide them the Patient Counseling Document (PCD), and notify them of the availability of the REMS-compliant training and how to find REMS-compliant courses.
- **Implementation System**
- **Timetable for Assessment Reports:** REMS assessments were submitted to the FDA at 6 months and 12 months after the initial approval date of the REMS (July 9, 2012), and annually thereafter.

See **Appendix Section 10.1** for the current Assessment Plan.

3.2. FINDINGS FROM PREVIOUS REMS ASSESSMENTS

The 36-month assessment report for ER/LA REMS was reviewed on June 29, 2016. The assessment was complete. The FDA's July 7, 2016 36-month REMS Assessment Acknowledgement Letter comments to the RPC can be found in **Appendix Section 10.2**. These comments indicated to the RPC the FDA's view that the epidemiologic surveillance data submitted were not capable of evaluating the impact of the REMS continuing education (CE) activities on prescriber behavior or adverse patient outcomes. Additionally, at the May 2016 Advisory Committee (AC), committee members not only concurred with the FDA's assessment but also agreed that a more rigorous study should be explored to directly evaluate the effect of REMS CE activities on prescribing behavior and patient outcomes. Thus, following the AC, FDA requested that the RPC submit a concept paper proposing a study that would assess changes in prescribing behavior and patient outcomes among

providers who have or have not participated in a REMS CE activity. As part of the 48-month REMS assessment, the RPC has submitted such a concept paper.

3.4. REMS MODIFICATIONS

The most recent REMS modification was approved on May 26, 2017, and was REMS modification to conform to the safety labeling changes approved December 16, 2016.

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4. REVIEW METHODS AND MATERIALS

- July 9, 2012 DAAAP (J. Racoosin) Supplement/REMS approval for ER/LA opioid analgesics Letter
- March 28, 2014 DRISK (J. Ju) review of Review of Proposed Methodology and Survey Instruments
- May 19, 2016 DEPI (J. McAninch & A. Secora) Epidemiology Review of Post-Marketing Studies
- July 7, 2016, REMS Assessment Acknowledgement Letter (J. Racoosin)
- September 7-14, 2016 48-Month REMS Assessment Report Submission
- September 30, 2016 Supplement #26 Approval/REMS Modification Letter (S. Hertz)
- List of ER/LA Opioid Analgesic REMS products at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=17 (accessed January 23, 2017)
- February 7, 2017 Review (J. McAninch, YH Hsueh) of Submitted Concept Paper (comments conveyed to the RPC on February 10, 2017 via an email from OSE's W. Brown).
- March 9, 2017 DB7 Review (YH. Hsueh) Statistical Review and Evaluation Consult Memorandum for 48-Month REMS Assessment Report
- April 3, 2017 DEPI Memo (J. McAninch and J. Wong) Review of 48-month epidemiology and drug utilization surveillance data
- April 28, 2017 RPC response to an April 18, 2017 FDA Information Request
- May 26, 2017 Supplement and REMS Modification Approval Letter

5. REVIEW RESULTS

5.1. ELEMENT 1 – PRESCRIBER LETTER

This first REMS Assessment element states that the RPC is to report:
"*Documentation of the dissemination of Prescriber Letter 3:*

a. number of prescriber letters electronically sent, received, undeliverable, and opened; and
b. *number of prescriber letters mailed and undeliverable*."

During this reporting period, the third Dear DEA-Registered Prescriber (DDRP) letter (DDRP Letter 3) was sent to newly DEA-registered Schedule II and III prescribers (regardless of discipline/degree), to announce the existence of the ER/LA REMS and availability of ER/LA REMS-related CE training. The REMS communication vendor used its proprietary database of healthcare professionals (HCPs) who have "opted in" to receive electronic communications on drug

safety alerts and REMS Communication Letters. The database of opt-in prescribers was matched to the list of DEA-registered prescribers to identify prescribers in the opt-in database to receive electronic communications. In cases where the electronic communication was undeliverable, prescribers were sent a letter by direct mail within 30 days after sending the electronic communication. Prescribers not opting in for electronic communications received the letter through the US Postal Service (USPS) mail. The target registrant audience for receipt of the annual distribution of DDRP Letter 3, as of June 19, 2015, totaled 74,724 (73,847 unique registered prescribers and 877 hospitals/clinics). Of the total 73,847 unique registered prescribers, the RPC states that 73,172 were individual registered prescribers (i.e., unique individual practitioners or mid-level practitioners who have prescribing authority).

Electronic (e-mail and facsimile) distribution of DDRP Letter 3 was initiated on July 1, 2015 while mailing of hardcopy DDRP Letter 3 was initiated on July 8, 2015. The distribution of DDRP Letter 3 by all routes was completed by September 2, 2015. Of the 73,172 individual registered prescribers targeted, 69,216 registrants were reached, of which 67,100 were delivered by USPS (3,008 undeliverable), 2,016 letters by email (117 potentially not delivered), and 100 by fax (31 potentially not delivered). The RPC states that there is currently no reliable method for tracking accurate volumes of unopened/unread e-mails. Information about the posting of DDRP Letter 3 to the web was not provided in the report

Of the 856 hospitals/clinic registrants, 815 (95%) DDRP Letter 3s were delivered.

5.1.1. Reviewer Comments

1. In subsequent assessment reports, the RPC should more fully explain the difference between the "unique registered prescribers" (73,847 in this report), and "individual registered prescribers" (73,172 in this report) in their calculations for the distribution of DDRP Letter 3. In addition, in subsequent reports the RPC should explain why the number of hospitals targeted (877 in this report) differs from the number of hospitals for which distribution of DDRP Letter 3 was attempted (856 in this report).

5.2. ELEMENT 2 - 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;
- Within three years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of active prescribers) are to have been trained;
- Within four years from the time the first REMS-compliant training becomes available, 192,000 prescribers (based on 60% 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 necessary portions of a training activity as a

diagnostic for interpreting completion rates. An additional outcome measure will be the number and profession of non-prescribers who have completed REMS-compliant CE training but are not counted towards the goals. The SD also states that an independent non-industry party is to produce the report (compiled from all accredited providers) of the number of prescribers who have taken the training by profession type and by other characteristics.

5.2.1. Background

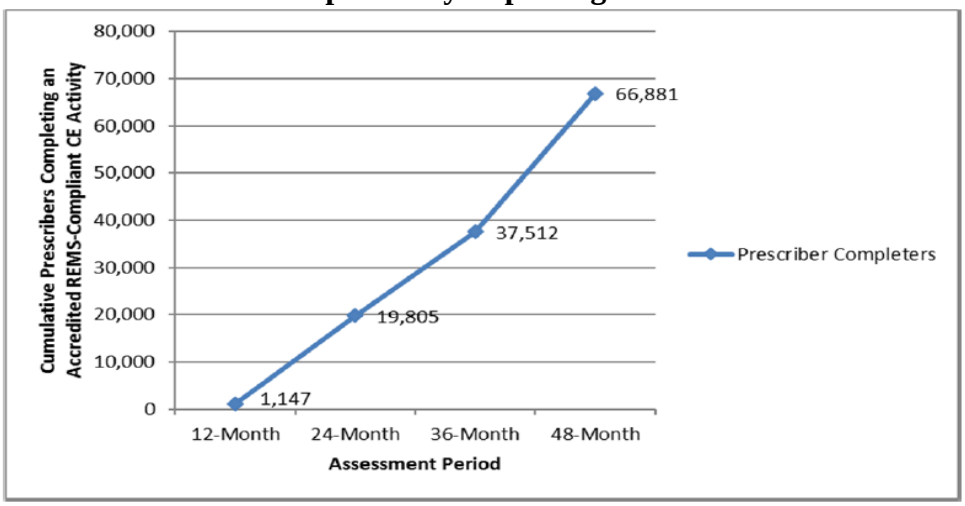
While the ER/LA REMS was approved on July 9, 2012, the first RPC-supported REMS-compliant CE activity was launched on February 28, 2013. This REMS represents the first time that accredited CE has been used to fulfill a REMS training requirement. "Prescribers" are defined as "*clinicians who are registered 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*."

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.

5.2.2. Numbers Trained

The data cut-off for this current 48-month report was February 28, 2016, which represents the 3-year mark and the first training milestone of 160,000 prescribers completing REMS-compliant training. **As of February 29, 2016**, **66,881** ER/LA prescribers have completed accredited REMS-compliant CE activities, representing 42% of the goal total (160,000); 29,369 of these 66,881 ER/LA prescribers completed accredited REMS-compliant CE activities during this reporting period (March 1, 2015 to February 29, 2016). **Figure 1** following (reproduced in its entirety from the RPC report's Figure 2) shows the cumulative number of prescribers completing an accredited REMS-compliant CE activity over four 12-month assessment periods:

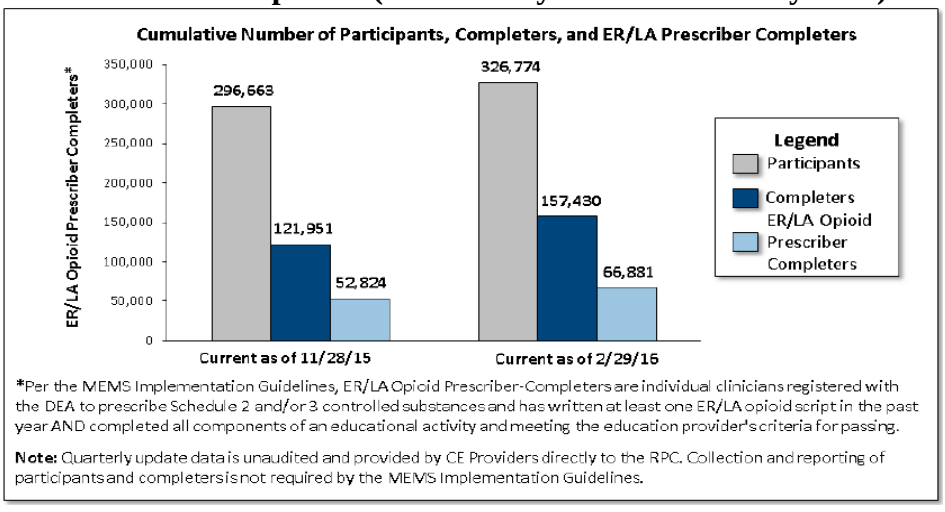
Figure 1: Cumulative Number of Accredited REMS-Compliant CE Activity Prescriber Completers by Reporting Period



In **Figure 2** (reproduced from the RPC's Figure 5), participants in the REMS-compliant activities are summarized by their status as to whether they were a Prescriber Completer, a Completer, or a Participant. The RPC defined these categories as follows:

- 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
- 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 2: Accredited REMS-Compliant Participants, Completers and ER/LA Prescriber Completers (28 February 2013-29 February 2016)

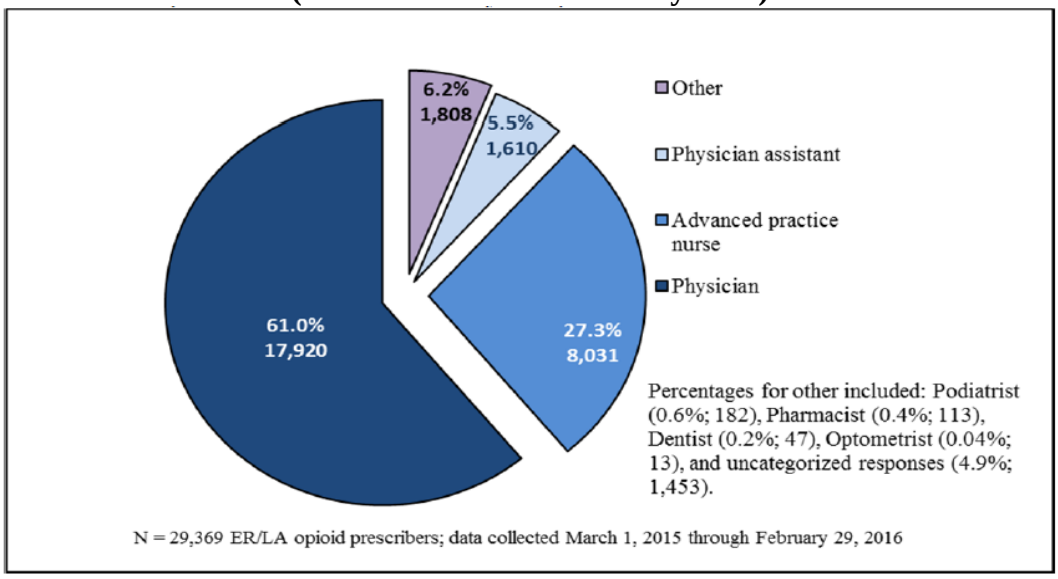


Of the 326,774 Participants, only 66,881(20.5%) were Prescriber Completers. In addition, of those that completed the REMS-compliant activity, only 42.5% (66,881/157,490) met the criteria for Prescriber Completer. Thus 57.5% of Completers were either not licensed to prescribe CII and CIII opioids and/or had not written a prescription for an ER/LA in the past year and/or did not specify if they had done so. The RPC stated at the Joint FDA Advisory Committee Meeting held in May 2016, the participant count data was 438,461 but since then have revised their figures to indicate that this total was only 326,774 as presented in this assessment report.

As in the previous assessment, the RPC reiterates that CE Providers have informed them that it is considerably more challenging than expected to attract ER/LA prescribers to participate in REMS-compliant activities and to keep them engaged through completion of the full activity and assessment. The FDA has previously requested that the RPC provide additional information about these partial completers. The RPC has replied that although they agree that additional information regarding partial completers would be useful, t not all RPC-supported CE Providers record any additional information that collection of any additional information is considered optional.

A break-down of those completing REMS-compliant CE training during this reporting period by profession is provided in **Figure 3** (taken directly from the RPC's Figure 4):

Figure 3: RPC-Supported, REMS-Compliant ER/LA Prescribers Completing Training by Profession during the Reporting Period (01 March 2015-29 February 2016)

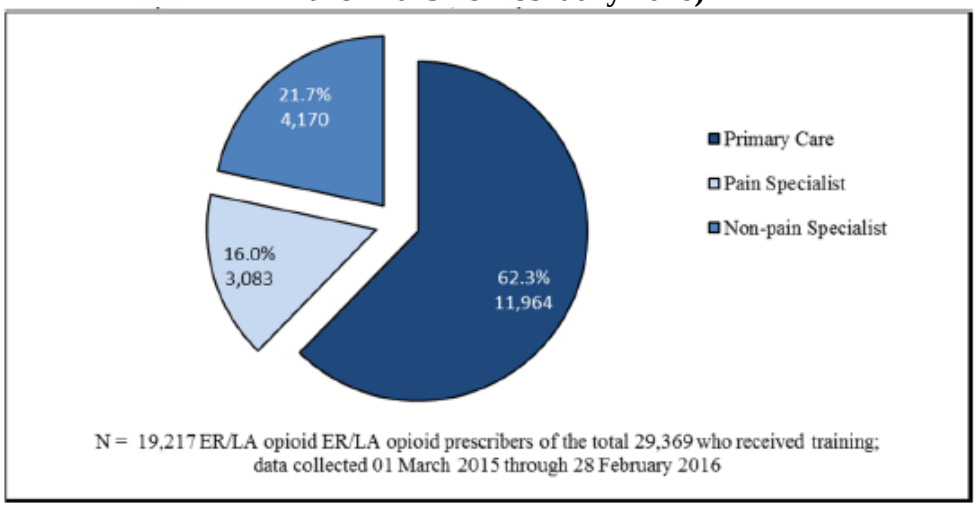


Approximately 61.0% of prescribers who completed the CE training were physicians, followed by 27.3% for Advanced Practice Nurses. The RPC's Figure 3 also notes small percentages of training completed by prescribers such as pharmacists and optometrists.

Figure 4 (taken directly from the RPC assessment report's Figure 4) provides data regarding the general practice type (primary care, pain specialist, non-pain specialist) for 19,217 of the 29,369

(65.4%) prescriber completers. Data for only 65.4% were collected since practice type was an optional category for CE providers.

Figure 4: ER/LA Prescribers Completers by Practice Type during the Reporting Period (01 March 2015-29 February 2016)



For those prescribers for whom a practice area was reported, 62.3% were primary care physicians, 21.7% were non-pain specialists, and 16.0% were pain specialists.

5.2.3. Non-RPC-supported CE

For the 24-month and 36-month FDA Assessment Reports, a total of 23 activities were reported by **non-RPC supported CE Providers** to ACCME as being accredited REMS-compliant CE activities through the Program and Activity Reporting System (PARS) database. The CE Providers for these programs indicated that they had approximately 2,047 prescriber completers.

During the current 48-month reporting period, one additional **non-RPC funded activity** was reported to ACCME as being REMS-compliant. An additional 22 activities were reported to ACCME as "REMS-related". Since collection of prescriber completer data are only mandated for RPC-supported activities, the completer data reported for these activities may be incomplete. Also, due to the confidentiality of data for non-RPC supported activities, the RPC cannot directly verify with certainty that these CE activities are indeed REMS-compliant or REMS-related. The RPC continues to actively explore ways to identify prescriber completers of non-RPC supported CE that is indeed REMS-compliant.

5.2.4. RPC Support of REMS-Compliant CE

REMS-compliant CE-related undertakings during the current reporting period included:

- Executing the Prescriber Follow-up and Long-term Evaluation Surveys
- Discussions with Medbiquitous on how to handle prescribers who prescribe under an institutional DEA number;

- The Conjoint Committee for Continuing Education (CCCE), FDA, accredited CE Providers, CE Accreditors and the RPC, discussed what are believed to be the highest priorities in meeting challenges in accredited REMS-compliant CE activities including awareness of REMS-compliant CE and the creation of an outreach campaign which includes a logo and tagline to increase awareness of REMS-compliant CE.

Prior to the Joint FDA Advisory Committee Meeting in May 2016, the RPC limited their 2016 RFA cycle only to supporting current RPC-funded CE Providers with ongoing REMS-compliant CE, since outcomes from the Advisory Committee could potentially prompt changes to REMS-compliant CE.

Since 2012, the RPC has issued 6 Request for Applications (RFAs) and awarded funding to support 783 REMS-compliant CE through 28 grants to accredited CE Providers and the CE Provider's 100+ educational partners. Of these 783 REMS-compliant CE activities, 278 were available during this reporting period. A total of 212 activities were presented as live training, 65 were internet-based enduring programs, and one program was performance improvement (e.g., an activity that evaluated improvements in prescriber behaviors using patient data). A summary of CE activities All activities were accredited by at least one of six National Accrediting Bodies. A description of all accredited REMS-compliant CE activities available this reporting period, organized by Grantee, is provided in **Appendix 10.3**. Approximately 59% of the CE activities for this reporting period were made available by CO*RE, followed by Boston University which made available 16.5% of the activities.

5.2.5. FDA Request: Additional Demographic Data

On February 29, 2016, FDA requested that the RPC collect particular demographic characteristics of prescriber completers from all accredited CE Providers to be reported in the annual assessments. These data would be used in part to compare prescribers who complete the Prescriber Follow-up Survey and the Long-term Evaluation Survey. These demographics included:

1. Medical degree
2. Specialty
3. Years in practice
4. Gender
5. Geographic region
6. Prescribing volume in the past month on average
7. ER/LAs prescribed within the past 6 months

The RPC reports that none of these demographic data are currently collected by all CE Providers. The CE Providers have provided the feedback regarding this FDA request, mainly stating that the addition of questions to collect these data will add substantial burden to the process for the learner, provider, and grantee. In addition, the CE providers believe that recall bias may affect data quality, while some prescribers may be concerned that their responses may be seen as a collection of prescriber identifying information.

5.2.6. Reviewer Comments

1. As of February 29, 2016, 66,881 ER/LA prescribers completed accredited REMS-compliant CE activities, representing 42% of the goal total (160,000). While the goal of 160,000 prescriber completers as not been met, it is encouraging that over 326,000 healthcare professionals began the training and nearly 160,000 completed the training, unfortunately 57.5% did not meet the specific criteria for a prescriber completer.

2. The RPC points out and the FDA acknowledges that there are a number of factors that likely interfere with the attainment of higher numbers of prescriber completers including:
    a. The number of criteria that need to be fulfilled to be considered a "prescriber completer;
    b. The number of competing opioid educational programs (both private and governmental);
    c. The length of the program in part due to the FDA Blueprint;
    d. The lack of awareness of the REMS and the accompanying REMS-compliant CE.

3. To date, the RPC has issued 6 RFAs and awarded funding to support 783 REMS-compliant CE through 28 grants. Thus the RPC has made significant strides in making REMS-compliant training available.

4. The RPC's presentation of prescribing professions includes pharmacists and optometrists. It is unclear under what circumstances these two professions would prescribe ER/LAs.

5. Ideally, FDA and other significant providers of opioid/pain management training would harmonize the key messages in their trainings. This would allow for an expansion of the reach of the key risk messages.

5.3. ELEMENT 3 – 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 SD states that the *objectives of the audit are to ensure:*

1. *The content of the educational activity is factually correct*
2. *The content of the educational activity is complete in touching all points of the blueprint available on the FDA website and includes a knowledge assessment of all sections of the blueprint*
3. *The process of creating and distributing the CE activity(s) meet ACCME's and other accrediting bodies' standards and are independent of the pharmaceutical industry's influence, and that the content is free from promotional material.*

The audits should occur at least once for each activity, preferably prior to finalization of the CME/CE content, and be repeated if substantial changes to content are made.

The RPC reiterates that the CE activity audits are based on a random sample of at least 10% of the RPC-supported, accredited REMS-compliant CE activities as well as REMS-compliant training not funded by the RPC but is to be counted towards meeting the REMS performance goals. The RPC also reiterates that the audits occur at least once for each activity selected for an audit, preferably prior to finalization of the CME/CE content, and are repeated if substantial changes to content are made.

As noted previously, a total of 278 CE activities took place during this reporting period and of these, 29 (10.4%) were audited during this reporting period. Details of the independent audit reports submitted by the six of seven nationally recognized Accrediting Bodies, are shown in **Table 1** (reproduced in its entirety from the RPC report's Table 5):

Table 1: 48-Month FDA Assessment Report Audit Summary

Accrediting Body	Number of Activities Conducted	Number of Audit Reports Received	Audit Reports with Observations
American Academy of Family Physicians	19	2	0
American Academy of Physician Assistants	8	1	0
American Association of Nurse Practitioners	10	1	0
American Nurses Credentialing Center	12	1	0
American Osteopathic Association	18	2	0
Accreditation Council for Continuing Medical Education	210	22	4
Utah Medical Association Foundation	1	0	0
TOTAL	**278**	**29**	**4**

Twenty-two of the 29 audited programs (76%) came from the Accreditation Council for Continuing Medical Education (ACCME).

5.3.1. Audit Results

Four of the 29 audit reports (14%) included at least one deficiency related to **collecting, disclosing, or resolving financial relationships.** Details on the deficiencies noted are as follows:

- Audit Report 1 did not collect/obtain all relevant financial relationships and did not have results or conclusions from an independent review of the activity.
- Audit Report 2 did not collect/obtain all relevant financial relationships and did not disclose relevant financial relationships to learners prior to the start of the activity
- Audits Report 3 and 4 had no mechanism to resolve conflicts of interest for all involved in control of the content

Only the deficiency reported with Audit Report 4 was not resolved prior to finalization of this Assessment Report. Thus, all prescriber completers associated with this activity (N = 7; data on file) did not count toward the total prescriber completer counts. However, the prescriber completers associated with the other three activities for which deficiencies were noted did count towards the total prescriber completer counts since all findings had been remediated prior to finalization of this Assessment Report.

The RPC notes that the number of audit deficiencies decreased from nine (all dealing with financial disclosures) in the 36-month assessment report to four in the current assessment report.

5.4. ELEMENT 4: PRESCRIBER SURVEYS

"*Evaluation of Prescriber Understanding:*

- *The results of an evaluation of ER/LA opioid analgesic 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.*
- *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 six months to one year after they completed the REMS compliant training*".

5.4.1. Element 4A – Follow-Up Prescriber Survey

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

Methods

The 48-month prescriber follow-up survey was conducted between March 7, 2016 and May 30, 2016. Respondents were recruited from two sources: through CE Providers who invited prescribers who had completed an ER/LA opioid analgesic accredited REMS-compliant CE activity and through IMS prescription data. 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 9,400 email invitations were sent to prescribers identified through CE providers (representing 10 of 11 CE providers that received grants from the RPC). Of those 482 prescribers accessed the survey. Of those 300 prescribers (48%) completed the survey (all by internet). A total of 15,103 invitations were sent by mail to prescribers identified through IMS prescription data. Of those 433 prescribers accessed the survey. Of those 331 prescribers (52%) completed the survey (99% by internet). In total there were 631 respondents.

While those invited from IMS were supposed to serve as the population who had not completed a REMS-compliant CE activity, approximately 33% of respondents recruited through IMS reported that they *had* completed a REMS-compliant continuing education (CE) and 17% did not remember. Of the prescribers surveyed, more than half reported prescribing ER/LA opioid analgesics between one and 20 times in the month prior to the survey (63%). The most frequently reported ER/LA opioid analgesics prescribed included: Oxycontin ER (68%), MS Contin (66%) and fentanyl transdermal system (61%). Over half of respondents were male (53%). Over half of respondents were Doctors of Medicine (MD) or Doctors of Osteopathy (DO) (61%), followed by nurse practitioners (19%) and physician assistants (17%). Approximately 53% of MDs and Doctors of Osteopathy (DO) had been practicing medicine for over 15 years (see Table 2 below).

Table 2: Description of Survey Participants			
	Baseline (n=605)	**36-Month Survey (n=612)**	**48-Month Survey (n=631)**
Gender	Male: 407 (67%) Female: 197 (33%)	Male: 333 (54%) Female: 274 (45%) Prefer not to answer: 5 (1%)	Male: 333 (53%) Female: 284 (45%) Prefer not to answer: 14 (2%)
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%)	MD: 335 (53%) DO: 47 (7%) Nurse Practitioner: 118 (19%) Advanced Practice Nurse: 26 (4%) Physician Assistant: 105 (17%)
Specialty	General Practice: 307 (51%) Pain Medicine: 55 (9%) Internal Medicine: 51 (8%) Orthopedics: 44 (7%) Oncology: 42 (7%) Rheumatology: 23 (4%) Neurology: 18 (3%) Anesthesiology: 9 (2%) Hospice/Palliative Care: 9 (2%) Other: 47 (8%)	General Practice: 307 (51%) Pain Medicine: 55 (9%) Internal Medicine: 51 (8%) Orthopedics: 44 (7%) Oncology: 42 (7%) Rheumatology: 23 (4%) Neurology: 18 (3%) Anesthesiology: 9 (2%) Hospice/Palliative Care: 9 (2%) Other: 47 (8%)	General Practice: 285 (45%) Pain Management: 100 (16%) Internal Medicine: 42 (7%) Orthopedics: 31 (5%) Oncology: 39 (6%) Rheumatology: 3 (1%) Neurology: 12 (2%) Anesthesiology: 21 (3%) Hospice/Palliative Care: 21 (3%) Other: 77 (12%)

The RPC conducted a comparison of the IMS survey respondents with all prescribers who have prescribed an ER/LA medicine in the past 12 months. Results showed that for the survey respondents, MDs or DOs were underrepresented (53% compared to 76%) and that the prescribing specialty of pain management was over-represented (11% compared to 1%).

Table 3: Comparison of IMS Survey Responders with All ER/LA Prescribers

	48-Month Follow-up Prescriber Survey Respondents for IMS: self-reported (n=331)	All Prescribers Who Have Prescribed an ER/LA Medicine (n=356,742)*
Medical Profession	MD or DO (53%) NP or APN (26%) PA (21%)	MD or DO (76%) NP or APN (12%) PA (8%)
Prescribing specialties	General Practice/Internal medicine (48%) Pain Management (11%) Other (14%) Oncology (10%) Orthopedics (2%)	General Practice/Internal medicine (54%) Pain Management (1%) Other (39%) Oncology (4%) Orthopedics (5%)
Geographic Distribution	West (25%) Central (30%) South (20%) East (19%) Northeast (7%)	West (23%) Central (29%) South (22%) East (15%) Northeast (10%)

*IMS database (extracted March 2016; all prescribers who have prescribed ER/LA medicines in the last 12 months.

FDA asked the RPC to propose methods to standardize the results of the survey sample to the general population of ER/LA opioid analgesic prescribers. The RPC proposed the identification of prescribers from the total IMS database based on the HCP having written one or more prescriptions for an ER/LA opioid analgesic in the prior 12 months. Stratified random sampling was used. For the IMS sample, the Sponsor standardized the survey responses by adjusting each responder using weights based on: 1) selection probability and 2) response probability. The Sponsor conducted a stratified random sampling constructed by three prescriber characteristics (medical specialty, prescribing frequency, and product prescribed) to select the final sample of invitees from the IMS database.

The sample selection probability was calculated as the number of invited prescribers divided by the total number of prescribers in each stratum. The Sponsor compared the prescriber characteristic between all invited IMS prescribers and the IMS prescribers who completed the survey and identified 2 characteristics (prescribing frequency and specialty) which had a relevant impact on the correct response rates. The response probability was then calculated as the number of respondents in each category (prescribing frequency by specialty) divided by the total number of invited prescribers in the respective category. The overall weight of each responder was the inverse of the product of the selection probability and the probability of responding. The standardization was applied to the percentages of correct responses to each key risk message and to the composite score. For the CE completer sample, the Sponsor did not standardize the key risk messages because data on prescriber characteristics across all CE providers was incomplete. Unknown proportion of prescribers who completed an ER/LA REMS-complaint CE training is another limitation for the standardization.

5.4.1.1. Reviewers' Comments (S. Harris and Y. Hsueh):

- Respondents were recruited from IMS data in order to recruit prescribers who had not taken a REMS compliant CE activity. Thirty-three percent (33%) of respondents recruited from IMS data reported completing a REMS-complaint CE activity. In addition, since the information is self-reported, there is no way to confirm that the CE activities that were completed by the providers were REMS compliant. There are numerous opioid or pain trainings available that providers may have taken that are not considered REMS compliant.
- The specialties provided in the survey were self-reported. There was no comparison provided with respondents recruited from CE providers because data was not collected consistently across all providers.
- While information is provided on the number of CE Providers that participated in recruitment, there is no information provided about how many respondents came from which CE providers. Were they all represented? Did more participants come from a particular grantee? In addition, of the participants what type of activity did they participate in (i.e. web-based, live, etc). This information should be provided for the current and future assessments.
- The standardization of survey results from the IMS sample to the target population is acceptable but it only addressed the generalizability not comparability. For the CE completer sample, no standardization of survey result to the target population was performed due to the incomplete data collection of prescriber characteristic across all CE providers. We recommend the Sponsor conducts uniform data collection on the prescriber characteristic across all CE providers.
- We have concerns about the comparability in the two samples. We observed notable differences between the IMS sample and the CE Completer sample in almost all of the prescriber characteristics the Sponsor reported (and they are very limited). We recommend the sponsor corrects for confounding in pairwise comparisons for any observed differences in characteristics. However, note that given the study design of these surveys, any control for confounding is only possible for observed characteristics. We recommend the Sponsor considers alternative designs (e.g., randomized experiment or self-control) that we presented in the May 2016 AC to adjust for both observed and unobserved characteristics.

The survey contained questions addressing six key risk messages that coincided with the six areas of the FDA Blueprint: 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.

- 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.
- Most respondents were aware of the correct indication for ER/LA opioid analgesics with 82% correctly identifying chronic non-cancer pain. Thirty-one percent (31%) of respondents incorrectly chose breakthrough pain from cancer. Respondents recruited from CE providers were more likely to select the correct response (88%) versus those from IMS that reported completing a CE activity (80%) and those recruited from IMS that did not complete a CE activity (76%).
- Overall, 82% of respondents met or exceed the 80% threshold (6 out of 7 questions correct).

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.

- 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

(99.7%), and general medical status of the patient (99%). Only 29% 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, 87% correctly answered titrate doses based on efficacy and tolerability while only 74% correctly answered consider a rescue medication for breakthrough pain.
- Most respondents were aware that fatal respiratory depression may occur, with the highest risk at initiation and when the dose is increased (93%).
- Only 45% 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.
- Overall, 43% of respondents met or exceed the 80% threshold (7 out of 8 questions correct).

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.

- The majority of respondents were aware of the PPA, what it includes, its purpose, and when it should be signed. Twenty-four percent (25%) of respondents incorrectly thought that the PPA was a legal requirement.
- Most respondents understood the need 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%), 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 with 55% incorrectly selecting true, or that drug screening should not be systematically performed for all patients with 78% incorrectly selecting true.
- Most respondents were aware of the appropriate ways to monitor patient adherence in regards to misuse and abuse:
    - Document drug seeking behaviors (97%)
    - Utilize state Prescription Drug Monitoring Programs (96%)
    - Use drug testing for both screening and confirmatory tests (95%)
    - Periodically re-evaluate therapy (98%)
    - Perform medication reconciliation by counting leftover drug supplies (90%).

- Overall, 90% of respondents met or exceed the 80% threshold (12 out of 15 questions correct).

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.

- The majority of respondents were aware of the signs and symptoms of respiratory depression such as reduced urge to breathe (88%), decreased rate of respiration (98%), and profound sedation (94%). Respondents were less aware that sighing patterns of breathing (79%) is a sign/symptom of respiratory depression.
- 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%), anxiolytics (95%), alcohol (99%), and illegal drugs (99.8%). Respondents were less aware that caffeine did not potentiate the risk of serious overdose and death (72%).
- 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%). Most respondents were aware that transdermal patches with a matrix formulation should not be cut prior to use (91%).
- The majority of respondents knew that patients should be counseled about the importance of adhering to a dosage regimen as prescribed (98%), that it is illegal to sell or give away ER/LA opioid analgesics (97%), and that ER/LA opioid analgesics can cause serious side effects that can lead to death, even when used as recommended (96%).
- Overall, 95% of respondents met or exceed the 80% threshold (12 out of 15 questions correct).

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.

- Ninety percent (90%) of respondents were aware that some opioids can increase QTc interval.
    - Respondents were also aware that the most common long-term side effect of ER/LA opioid analgesics was constipation (90%).
- Respondents had a high awareness of the serious risk that the REMS was put in place to mitigate: addiction (89%), unintentional overdose (95%), and death (95%).

- Most respondents were aware that central nervous system depressants can have a potentiating effect on sedation and respiratory depression caused by opioids (98%) 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 (91%).
- Fewer respondents were aware that for some ER products, patients must be opioid tolerant before using certain strengths or certain daily doses (78%), that MAOIs are not the preferred antidepressant for use with ER/LA opioid analgesics (78%),
- Most respondents (92%) 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 (92%).
- Only 75% of respondents were aware that some ER opioid formulations may rapidly release opioids when exposed to alcohol.
- Respondents were aware that ER/LA opioid analgesics are included in the Controlled Substance Act because of their potential risk for abuse (89%). The majority of respondents were aware of federal regulations for writing a prescription for an ER/LA opioid analgesic: 86% were aware that refills are not allowed, 95% aware that refills cannot be phoned in, and 90% aware that prescriptions cannot be faxed.
    - Only 26% were aware that there are no specific federal limits on quantities of ER/LA opioid analgesics dispensed via prescription.
- Only 78% of respondents knew that 'patients that are not opioid tolerant can initiate opioid therapy with any type of ER/LA opioid analgesic' was an incorrect statement.
- Overall, 72% of respondents met or exceeded the 80% threshold (answered 17 out of 21 questions correctly).

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.

- Eighty-five percent (85%) of respondents correctly answered that with methadone, the peak of respiratory depression can occur later and can persist longer than the analgesic effects.
- Fewer respondents correctly answered questions related to dosing and conversion:

  - 73% of respondents reported that conversion of patients to or from methadone using equianalgesic tables can result in overdose and death.
  - High prescribers of oral ER/LA opioid analgesics had higher knowledge scores than low prescribers (80% vs. 68%).[3]
  - High prescribers of methadone had higher knowledge scores than low prescribers (84% vs. 77%).
- Only a little over half (55%) 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 (67% vs. 58%).
- Respondents were less aware of what patient was considered opioid tolerant with only 39% correctly selecting patients who are taking 25 mcg/hour transdermal fentanyl for at least 7 days as tolerant and 70% selecting patients who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer.
- Only 68% 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.
- Only 58% of respondents knew what to do if a patient treated with a transdermal opioid developed a high fever (because of the risk of overdose with fever, monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary.
- Overall, only 21% of respondents met or exceeded the 80% threshold (answered 7 out of 8 questions correctly).

Educational Materials Questions:

Out of the 631 prescribers:

- 60% were aware of the ER/LA Opioid Analgesics REMS Program. (72% CE provider respondents ; 79% IMS respondents-reported completing a CE activity; 35% IMS respondents-reported not completing a CE activity)
- 62% were aware of the Medication Guide (65% CE provider respondents; 82% IMS respondents-reported completing a CE activity; 48% IMS respondents-reported not completing a CE activity). The main source of awareness for CE

[3] 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.

provider respondents was conferences (48%) followed by online download (29%) and sales representative (27%). The main source of awareness for IMS respondents -reported completing a CE activity was conferences (50%) followed by sales representative (46%) and mailing (39%). The main source of awareness for IMS respondents -reported not completing a CE activity was conferences (31%), followed by mailings (30%) and sales representatives (28%).

- 27% were aware of the Dear DEA Registered Prescriber Letter (30% CE provider respondents; 37% IMS respondents-reported completing a CE activity; 17% IMS respondents-reported not completing a CE activity); the main source of awareness for all respondents was mailing.
- 40% were aware of the Patient Counseling Document (47% CE provider respondents; 52% IMS respondents-reported completing a CE activity; 25% IMS respondents-reported not completing a CE activity). The main source of awareness for CE provider respondents was conferences (48%) followed by online download (28%) and email (23%). The main source of awareness for IMS respondents -reported completing a CE activity was conferences (45%) followed by sales representative (46%) and mailing (39%). The main source of awareness for IMS respondents -reported not completing a CE activity was conferences (31%), followed by mailings (30%) and sales representatives (29%).
- 39% were aware of the ER/LA REMS website (46% CE provider respondents; 60% IMS respondents-reported completing a CE activity; 18% IMS respondents-reported not completing a CE activity). The main source of awareness for CE provider respondents was conferences (38%) followed by email (34%). The main source of awareness for IMS respondents -reported completing a CE activity was conferences (37%) followed by sales representative (34%) and email (32%). The main source of awareness for IMS respondents -reported not completing a CE activity was conferences (30%), followed by email (33%) and mailing (28%).
- 41% were aware of the availability of REMS-compliant activities(58% CE provider respondents; 60% IMS respondents-reported completing a CE activity; 9% IMS respondents-reported not completing a CE activity)

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.

- 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 (66%), insurance authorizations and approvals (65%), patient's ability to pay (52%), and physician’s willingness to prescribe (49%).

- Respondents were asked about the current level of access to ER/LA opioid analgesics for patients that are indicated to take them. Half of respondents (50%) thought the ease of access was about right. Twenty-three percent (23%) of respondents thought access was too difficult and 18% reported access as too easy.
- 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 29% of respondents reported that there was no impact.
- Respondents were asked how the types of medications they prescribe have changed since the implementation of the REMS in July 2012. Overall, while a little under half reported no change (42% overall; 42% CE provider respondents; 40% IMS respondents-reported completing a CE activity; 44% IMS respondents-reported not completing a CE activity), 21% of respondents reported they have limited which ER/LA opioid analgesic they prescribe, 26% reported prescribing more non-opioid medications, and 24% reported prescribing fewer ER/LA opioid analgesics.
- Most respondents (61%) reported that in the past three months, they had considered prescribing ER/LA opioid analgesics but decided not to. Main reasons included: the prescriber is selecting patients differently based on assessment (43%) and the prescriber changed to prescribing more non-opioid medications (43%).
- Respondents reported their activities when prescribing an ER/LA opioid analgesic. While most respondents reported warning patients not to break, chew, or crush their oral ER/LA opioid (91%), explaining what to do if a dose is missed (80%), and advising patient how to safely taper their dose when discontinuing (83%). A smaller percentage of respondents (61%) reported that they use the patient counseling document (PCD) for discussions with patients. CE provider respondents were more likely to report using the PCD, using structured interview tools to assess patient risks, completing a patient-prescriber agreement (PPA), performing urine drug tests than IMS respondents.
- 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 (96%) and common side effects (99%), discuss how to safely taper the ER/LA opioid analgesic if it is no longer needed (83%), 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 (89%). Fewer respondents reported always or regularly using the PCD with patients (49%; CE provider respondents 51% vs. IMS respondent (reported not completing a REMS compliant CE activity; 41%) vs IMS respondent (reported completing a REMS compliant CE activity; 59%),

instructing patients on how to dispose of unused ER/LA opioid analgesics (76%), and discussed with patients what to do if a dose is missed (75%).

- 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 (98%). Fewer respondents reported that they always or regularly: use structured interview tools or screening tools to assess patients risk of abuse or misuse (69%), perform urine drug tests (74%), or complete a PPA or patient contract when the ER/LA opioid analgesic is first prescribed (76%).

Overall Prescriber Scores by Key Risk Message

Table 4 shows the weighted and un-weighted mean prescribers scores for each of the six key risk messages. The un-weighted mean prescriber score was greater than or equal to 80% for key risk messages 1, 3, 4, and 5. The mean score was less than 80% for domains 2 and 6. When weighed, the mean score for KRM5 dropped below the 80% threshold.

Table 4: Overall Prescriber Scores by Key Risk Messages (Un-weighted and Weighted)

Key Risk Messages	Un-weighted Prescriber Score Mean	Weighted Prescriber Score Mean
KRM 1: Patients should be assessed for treatment with ER/LA opioid analgesic therapy.	87.3	85.5
KRM 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.	77.0	75.7
KRM 3: Management of ongoing therapy with ER/LA opioid analgesics is important.	84.0	82.2
KRM 4: It is important to counsel patients and caregivers about the safe use of ER/LA opioid analgesics.	91.3	89.6
KRM 5: Prescribers must be familiar with general drug information concerning ER/LA opioid analgesics.	80.9	78.7
KRM 6: Prescribers must be familiar with product-specific drug information concerning ER/LA opioid analgesics.	57.8	54.6

5.4.1.2. Summary of Prescriber Follow-up Survey

Among the surveyed respondents, 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 terms of access, respondents reported that the main barriers to patient access to prescription opioids analgesics are insurance coverage and insurance authorizations and approvals. Almost half of respondents (49%) reported that physician's willingness to prescribe was a barrier to patient access. While half of respondents thought patients' access to ER/LA opioid analgesics were about right, at least 23% 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 (29%). While 42% of respondents reported no changes in the types of medications prescribed since implementation of the REMS, 26% reported prescribing more non-opioid medications and 24% reported prescribing fewer ER/LA opioid analgesics.

3.1.1.15.5.1.3. Overall Reviewers' Comments on the Follow-Up Survey

Overall, the comparison of prescribers that are recruited from IMS data versus prescribers that are recruited from CE providers does not accomplish the original goal of the survey; to compare prescribers that completed training to prescribers that did not complete training since IMS respondents also self-reported completion of REMS compliant training. In addition, since the information is self-reported there is no way to know for certain if the completed CE activity was REMS compliant.

This survey has a number of limitations including the use of a convenience sample, incomplete data collection of prescriber characteristics, and notable differences between samples which may affect the comparability and generalizability of the survey results to the overall populations of healthcare providers who prescribe ER/LA opioid analgesics.

The RPC proposed the elimination of this survey stating that the activities will be addressed in the proposed concept papers. We agree with the proposal and we recommend the elimination of this survey for future assessments.

5.4.2. *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 in 2014 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 March 7, 2016 and June 13, 2016. 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 (6 to 12 months prior to survey completion). Data on the number of CE providers who assisted in recruitment was not reported. A total of 6,955 prescribers were invited through email (representing all 11 CE providers that received grants from the RPC). A total of 930 (14%) prescribers responded to the invitation, 843 (91%) agreed to participate, 643 (69%) were eligible, and 588 (63%) completed the survey. Most participants completed the survey by internet (99%).

A little over half of respondents were male (53%), MD/DOs (66%), and had been in clinical practice for more than 15 years (59%). The main specialty reported was pain management (32%) followed by other (21%), general practice/family medicine/internal medicine (13%), and hospice/palliative care (10%). Almost half of prescribers reported prescribing ER/LA opioid analgesics on average between one to 10 times per month (47%), with 14% reporting prescribing 51 times of more in the past month. The most commonly prescribed ER/LA were MS Contin (68%), Oxycontin ER (65%), Duragesic (52%), and fentanyl (generic) (59%). The top geographic region reported was the West (28%) followed by Central (23%), and the South (18%).

Table 5 shows a comparison of LTE survey respondents with all REMS-compliant CE completer prescribers. Results showed while respondents were similar in terms of medical profession, respondents from the specialties of general practice and internal medicine was underrepresented in the survey while pain management respondents were over-represented.

Medical Profession	MD or DO (66%) NP or APN (25%) PA (9%)	MD or DO (65%) NP or APN (25%) PA (5%)
Prescribing specialties	General Practice/Internal medicine (8%) Pain Management (21%) Other (1%) Oncology (4%)	General Practice/Internal medicine (55%) Pain Management (7%) Other (7%) Oncology (3%)

FDA asked the RPC to propose methods to standardize the results of the survey sample to the general population of ER/LA opioid analgesic prescribers that took a REMS-compliant CE training. The RPC standardized the survey responses by adjusting each responder using the weights based on the response probability. Based on the limited and incomplete data collection of prescriber characteristics across all CE providers, the characteristics used to adjust for the response probability is depend on the availability. In the 48-Month opioid analgesics LTE survey, two prescriber characteristics (type of physician and degree) were used to adjust for the response probability.

5.4.2.1. Reviewers' comments (S. Harris and Y. Hsueh):

- While information is provided on the number of CE Providers that participated in recruitment, there is no information provided about how many respondents came from which CE providers. Were they all

represented? Did more respondents come from a particular grantee? In addition, of the respondents, what type of activity did they participate in (i.e. web-based, live, etc). This information should be provided for the current and future assessments.

- The data of the prescriber characteristics for the target population is very limited and incomplete. We have concerns about the use of incomplete data for the standardization. We recommend the Sponsor conducts uniform data collection on the prescriber characteristic across all CE providers.

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 correct indication for ER/LA opioid analgesics, risks of overdose and abuse, knowing when to appropriately refer high-risk patients to pain management specialists, and understanding opioid tolerance criteria (*see Table 6*).

- Respondents were aware of risk factors for opioid abuse such as history of psychiatric disorders, past or current alcohol or drug abuse, and a family history of illicit drug use or alcohol abuse, and were aware that prescribers should refer patients at high risk for drug abuse to a pain management specialist.
- Eighty-percent (80%) of respondents were aware of the correct indication for ER/LA opioid analgesics (chronic non-cancer pain) while some respondents selected incorrect indications such as breakthrough pain from cancer (25%) and acute or postoperative pain (15%).
- When presented with a case, respondents were less aware of risk factors for opioid abuse (such as age, gender, and cigarette smoking). Overall, most respondents were aware of steps to take to further assess possible abuse.
- There were 7 questions in this risk message with 18 correct responses. Sixty-six percent (66%) of respondents met or exceeded the 80% threshold (15 out of 18 correct responses).

Table 6: Prescriber Understanding of Blueprint Message 1: Patients Should Be Assessed for Treatment with ER/LA Opioid Analgesics Therapy
[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) n (%)
A patient with a history of substance abuse must not be prescribed an ER/LA opioid	True: 29 (9%) **False: 293 (89%)** I don't know: 6 (2%)	True: 67 (11%) **False: 506 (86%)** I don't know: 15 (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: 319 (97%)** False: 7 (2%) I don't know: 2 (1%)	**True: 572 (97%)** False: 14 (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%)	**A personal history of psychiatric disorders: 508 (86%)** **A personal history of past or current alcohol or drug abuse: 587 (99.8%)** A family history of hypercholesterolemia: 38 (7%) **A family history of illicit drug use or alcohol abuse: 534 (91%)** None of the above: 1 (<1%) I don't know: 0 (0%)
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%)	Acute or postoperative pain: 87 (15%) As needed for headache or migraine pain: 21 (4%) Dental abscess pain: 36 (6%) Breakthrough pain from cancer: 149 (25%) **Chronic non-cancer pain: 473 (80%)** None of the above: 72 (12%) I don't know: 4 (1%)
Case Elliott: Elliot is a thin, anxious 27-year-old man who is new to the area and comes to see you at 3:50 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		

Table 6: Prescriber Understanding of Blueprint Message 1: Patients Should Be Assessed for Treatment with ER/LA Opioid Analgesics Therapy
[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) n (%)
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%)	**27 years old: 331 (56%)** **Male gender: 260 (44%)** Chronic left knee pain from skiing accident: 128 (22%) **Request for specific drugs: 555 (94%)** **Cigarette smoking: 309 (53%)** I don't know: 7 (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%)** **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%)	**Ask for contact information for his primary physician: 513 (87%)** **Ask Elliott to provide a urine sample for drug screen: 545 (93%)** **Ask Elliott about his family's use of drugs and alcohol: 500 (85%)** **Check the state prescription monitoring program database for Elliott's prescription history (where available): 571 (97%)** **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: 557 (95%)** I don't know: 4 (1%)

Table 6: Prescriber Understanding of Blueprint Message 1: Patients Should Be Assessed for Treatment with ER/LA Opioid Analgesics Therapy
[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) n (%)
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%)**	**Obtain a comprehensive urine drug screen: 463 (79%)** Get a full psychiatric evaluation: 75 (13%) **Complete a comprehensive pain history and physical examination: 576 (98%)** **Obtain a signed Patient Prescriber agreement for opioids: 508 (86%)** Check for police records: 45 (8%) **I don't know: 4 (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 7 below*).

- Respondents were aware that fatal respiratory depression may occur with the highest risk upon initiation (93%) and that doses should be titrated based on efficacy and tolerability when initiating ER/LA opioid analgesics (80%).
- Respondents were less aware when initiating a patient on an ER/LA opioid analgesic that a rescue medication should be considered for break-through pain (75%)
- When presented with a case, respondents were not able to identify which ER/LA opioid analgesic should be used based on the patient's current medication and symptoms (31%). They were also unable to identify how doses should be modified once on treatment (62%).

- There were 4 questions in this risk message with 5 correct responses. Fifty-one percent (51%) of respondents met or exceeded the 80% threshold (4 out of 5 correct responses).

Table 7: Prescribers Understanding of Blueprint Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioids
[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) n (%)
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%)	Start with the highest recommended dose of the ER/LA opioid analgesic and decrease the dose depending on tolerability: 3 (1%) **Consider a rescue medication for breakthrough pain: 443 (75%)** If switching from an immediate-release opioid, convert to an equianalgesic dose: 338 (58%) **Titrate doses based on efficacy and tolerability as indicated in the product label: 473 (80%)** None of the above: 17 (3%) I don't know: 3 (<1%)
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%)	**True: 546 (93%)** False: 26 (4%) I don't know: 16 (3%)
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	**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	**Embeda® ER (morphine sulfate and naltrexone hydrochloride),** **20 mg/0.8 mg once daily: 182 (31%)** Duragesic® (fentanyl transdermal system), one (1) 12 mg patch every 3 days: 207 (35%) Oxycontin® ER (oxycodone

Table 7: Prescribers Understanding of Blueprint Message 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioids
[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) n (%)
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):	(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%)	hydrochloride), 60 mg once a day: 83 (14%) MS Contin® (morphine sulfate), 30 mg twice per day: 150 (26%) I don't know: 65 (11%)
In managing Nancy's treatment, you decide to rotate her medication to oxymorphone ER. The 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):	Start her on a 24-hour dose of 12.5 mg oxymorphone ER (new opioid) based on the 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%)	Start her on a 24-hour dose of 12.5 mg oxymorphone ER (new opioid) based on the table: 153 (26%) **Reduce the starting dose of oxymorphone ER (new opioid) by 25% to 50%: 364 (62%)** Taper her from the oxycodone before starting oxymorphone ER: 22 (4%) Keep increasing the dose of oxycodone to establish pain control before rotating her to oxymorphone ER: 23 (4%) I don't know: 26 (4%)

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 8*).

- Overall, most respondents were aware of how prescribers should monitor patient adherence and periodically evaluate pain control.
- Only 58% of respondents correctly answered a case question about next steps if their patient admits to diverting their prescribed opioid.
- There were 6 questions in this risk message with 14 correct responses. Eighty-seven percent (87%) of respondents met or exceeded the 80% threshold (12 out of 14 correct responses).

Table 8: Prescribers' Understanding of Blueprint Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics is Important
[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) 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 RPClycerides: 66 (20%) **Periodically re-evaluate therapy: 322 (98%)** **Perform medication reconciliation by counting leftover drug supplies: 305 (93%)** None of the above: 0 (0%) I don't know: 2 (1%)	**Document any "drug seeking" behavior: 573 (97%)** **Utilize state Prescription Drug Monitoring Programs: 574 (98%)** **Use urine drug testing for both screening and confirmatory tests: 563 (96%)** Perform laboratory testing for serum RPClycerides: 89 (15%) **Periodically re-evaluate therapy: 576 (98%)** **Perform medication reconciliation by counting leftover drug supplies: 542 (92%)** None of the above: 0 (0%) I don't know: 1 (<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	Write for a 4-day supply of ER and IR oxycodone, to last until you contact his previous	Write for a 4-day supply of ER and IR oxycodone, to last until you contact his previous

Table 8: Prescribers' Understanding of Blueprint Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics is Important
[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) n (%)
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):	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%)	prescriber on Monday: 35 (6%) **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: 538 (92%)** 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: 4 (1%) Report him to the police as he is obviously diverting drug to pay for marijuana: 5 (1%) I don't know: 6 (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. 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%)	Ask her to bring her son in at her next clinic visit to counsel them both: 167 (28%) **Tell her you will not prescribe ER/LA opioid analgesics for her: 340 (58%)** Call the other physician to complain: 7 (1%) Report this as a felony for dispensing opioids without a license: 32 (5%) I don't know: 42 (7%)
Case Danielle:		

Table 8: Prescribers' Understanding of Blueprint Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics is Important
[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) n (%)
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%)	**Assessment of the continued need for ER/LA opioid analgesics: 525 (89%)** Comprehensive physical examination and full laboratory work-up at each visit: 141 (24%) **Pain control and functional improvement evaluation: 563 (96%)** **Asking about changes in medications or the patient's medical condition: 559 (95%)** Not doing a urine drug screen: 85 (15%) **Checking the state Prescription Monitoring Program database for prescription history (where available): 527 (90%)** I don't know: 5 (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?	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%)	Lab error: 1 (<1%) Infrequent "recreational use" of cocaine: 25 (4%) **Diversion of prescribed opioid: 500 (85%)** Need for in-depth psychodynamic in-office counseling sessions: 51 (9%) I don't know: 11 (2%)

Table 8: Prescribers' Understanding of Blueprint Message 3: Management of Ongoing Therapy with ER/LA Opioid Analgesics is Important [Correct answer bolded]		
Question	**36 Month (n=328) n (%)**	**48 Month (n=588) n (%)**
Select the one best response.		
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%)	**Collect a sample for urine drug screen: 480 (82%)** Refuse to give her a refill until the date when her prescription would have been used up: 154 (26%) **Ask where she keeps her medications and how she secures them: 552 (94%)** Consider rotating her to another opioid: 174 (30%) I don't know: 3 (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 of the need to counsel about safe use of the ER/LA opioids and of use of the Patient Counseling Document (PCD) (See *Table 9*).

- Overall, most respondents were aware of the appropriate safe use counseling topics for patients. Respondents were also aware of instructions to give patients when starting ER/LA opioid analgesics including not to drink alcohol.
- There were 7 questions in this risk message with 16 correct responses. Ninety-six percent (96%) of respondents met or exceeded the 80% threshold (13 out of 16 correct responses).

Table 9: Prescribers' Understanding of Blueprint Message 4: The Importance of Counseling Patients and Caregivers about Safe Use of ER/LA opioid analgesics.

[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) 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%)	True: 32 (5%) **False: 540 (92%)** I don't know: 16 (3%)
A patient should be told not to cut an extended release tablet in half to reduce the dose.	**True: 299 (91%)** False: 27 (8%) I don't know: 2 (1%)	**True: 545 (93%)** False: 36 (6%) I don't know: 7 (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%)	**Yes: 583 (99%)** No: 2 (<1%) I don't know: 3 (1%)
Anxiolytics	**Yes: 317 (97%)** No: 4 (1%) I don't know: 7 (2%)	**Yes: 562 (96%)** No: 11 (2%) I don't know: 15 (3%)
Alcohol	**Yes: 327 (99.7%)** No: 1 (<1%) I don't know: 0 (0%)	**Yes: 582 (99%)** No: 1 (<1%) I don't know: 5 (1%)
Illegal drugs	**Yes: 328 (100%)** No: 0 (0%) I don't know: 0 (0%)	**Yes: 585 (99.5%)** No: 0 (0%) I don't know: 3 (1%)
Caffeine	Yes: 30 (9%) **No: 238 (73%)** I don't know: 60 (18%)	Yes: 59 (10%) **No: 426 (72%)** I don't know: 103 (18%)
When counseling patients about the safe use of ER/LA opioid analgesics, prescribers should inform patients of the following. Select all that apply.	N/A	**The importance of adhering to a dosage regimen as prescribed: 573 (97%)** Store ER/LA opioid analgesics in a medicine cabinet with other medications in the household: 102 (17%) **It is illegal to sell or give away ER/LA opioid analgesics: 579 (99%)**

Table 9: Prescribers' Understanding of Blueprint Message 4: The Importance of Counseling Patients and Caregivers about Safe Use of ER/LA opioid analgesics.

[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) n (%)
		Dispose of unused prescription opioids by throwing them in the trash: 78 (13%) **ER/LA opioid analgesics can cause serious side effects that can lead to death, even when used as recommended: 569 (97%)** None of the above: 1 (<1%) I don't know: 2 (<1%)
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%)	Take oxymorphone ER tablets whole with enough water to swallow them: 519 (88%) For a smaller dose, cut the tablet in half: 14 (2%) Throw away the leftover oxycodone in the trash: 44 (8%) Don't drink alcohol while taking the oxymorphone ER: 564 (96%) Store the tablets in the bathroom medicine cabinet: 44 (8%) I don't know: 5 (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 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.		

Table 9: Prescribers' Understanding of Blueprint Message 4: The Importance of Counseling Patients and Caregivers about Safe Use of ER/LA opioid analgesics.

[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) n (%)
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%)	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: 320 (54%) **Stress the safety concerns when ER/LA opioid analgesics are taken by someone for whom they are not prescribed: 554 (94%)** **Recommend storing medication in a safe and secure place away from children, family members, and visitors: 580 (99%)** Tell her that if she cannot safeguard her medications, you will consider an alternative treatment plan and therapy: 462 (79%) I don't know: 3 (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 including constipation and Fred or his caregivers should let you know if he has any bowel issues: 311 (95%)**	What to do for a missed dose: Double up with the missed tablet to keep pain under control: 61 (10%) **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: 562 (96%)** **Discuss the risks of long-term opioid use including constipation and Fred or his caregivers should let you know if he has any bowel issues: 552 (94%)**

Table 9: Prescribers' Understanding of Blueprint Message 4: The Importance of Counseling Patients and Caregivers about Safe Use of ER/LA opioid analgesics.

[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) n (%)
	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%)	Avoid discussing addiction potential, respiratory depression, and death with such an elderly patient or his caregivers: 30 (5%) Discontinuing treatment: Just stopping ER/LA opioid analgesics is OK if you are not addicted: 10 (2%) I don't know: 4 (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 10 below*).

- There were 7 questions in this risk message. Overall, 48% of respondents answered all 7 questions correctly, 34% answered 6 correctly, and 13% answered 5 correctly.
- Eighty-two percent (82%) of respondents met or exceeded the 80% threshold (6 out of 7 correct responses).

Table 10: Prescribers' Understanding of Blueprint Message Key Risk Message 5: Prescribers must be familiar with general drug information concerning ER/LA opioid analgesics.

[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) 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%)	**True: 584 (99%)** False: 2 (<1%) 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%)	**True: 474 (81%)** False: 25 (4%) I don't know: 89 (15%)
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%)	True: 20 (3%) **False: 488 (83%)** I don't know: 80 (14%)

Table 10: Prescribers' Understanding of Blueprint Message Key Risk Message 5: Prescribers must be familiar with general drug information concerning ER/LA opioid analgesics.

[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) n (%)
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%)	**True: 5511 (94%)** False: 14 (2%) I don't know: 23 (4%)
The most common long-term side effect of ER/LA opioid analgesics is constipation.	N/A	**True: 560 (95%)** False: 17 (3%) I don't know: 11 (2%)
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%)	**True: 565 (96%)** False: 11 (2%) I don't know: 12 (2%)
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%)	True: 104 (18%) **False: 448 (76%)** I don't know: 36 (6%)

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 11 below*).

- Respondents were less aware of product-specific drug information. For example, respondents were less aware of which patients were considered opioid-tolerant, how to properly dispose of transdermal patches, what to do if a patient with a patch developed a high fever, and which specific opioid to avoid when presented with a case scenario.
- There were six questions in this risk message with 8 correct responses. Twenty-two percent (22%) of respondents met or exceeded the 80% threshold of 7 out of 8 correct responses.

Table 11: Prescribers' Understanding of Blueprint Message Key Risk Message 6: Prescribers must be familiar with product specific drug information concerning ER/LA opioid analgesics.

[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) n (%)
For methadone, the peak of respiratory depression can occur later and can persist longer than the analgesic effects.	**True: 286 (87%)** False: 10 (3%) I don't know: 32 (10%)	**True: 521 (89%)** False: 19 (3%) I don't know: 48 (8%)
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%)	**True: 453 (77%)** False: 80 (14%) I don't know: 55 (9%)
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%) I don't know: 11 (3%)	**Who are using 25 mcg/hour transdermal fentanyl for at least 7 days: 250 (43%)** Who are not currently taking opioid therapy, but have no known intolerance or hypersensitivity to the drug fentanyl: 69 (12%) **Who are taking at least 60 mg oral morphine/day or an equianalgesic dose of another opioid for one week or longer: 433 (74%)** None of the above: 107 (18%) I don't know: 28 (5%)
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%)	True: 96 (16%) **False: 432 (74%)** I don't know: 60 (10%)
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 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%)	Remove the patch until the fever is below 102F: 95 (16%) Switch the patient to another ER/LA opioid analgesic: 59 (10%) **Monitor the patient closely for opioid side effects and reduce the dose of the patch if necessary: 330 (56%)** Move the patch to another location on the body: 2 (<1%) I don't know: 102 (17%)
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.		

Table 11: Prescribers' Understanding of Blueprint Message Key Risk Message 6: Prescribers must be familiar with product specific drug information concerning ER/LA opioid analgesics.

[Correct answer bolded]

Question	36 Month (n=328) n (%)	48 Month (n=588) n (%)
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%)	**Butrans® (buprenorphine transdermal system): 198 (34%)** Embeda® ER (morphine sulfate and naltrexone hydrochloride): 115 (20%) EXALGO® (hydromorphone hydrochloride): 124 (21%) **Dolophine® (methadone hydrochloride): 399 (68%)** None of the above: 54 (9%) I don't know: 62 (11%)

Overall Prescriber Scores by Blueprint Domain

Table 12 shows the mean prescribers scores for each of the six blueprint domains. The mean prescriber score was greater than or equal to 80% for domains 1, 3, 4, and 6. The mean score was less than 80% for domains 2 and 6.

Table 12: Overall Prescriber Scores by Blueprint Domain

FDA Blueprint Domain	Prescriber Score Mean (95% CI)
FDA Blueprint 1: Patients should be assessed for treatment with ER/LA opioid analgesic therapy.	83.8 (82.7, 84.8)
FDA Blueprint 2: Prescribers must be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics.	68.3 (66.7, 69.9)
FDA Blueprint 3: Management of ongoing therapy with ER/LA opioid analgesics is important.	90.0 (89.1, 90.9)
FDA Blueprint 4: It is important to counsel patients and caregivers about the safe use of ER/LA opioid analgesics.	94.3 (93.7, 95.0)
FDA Blueprint 5: Prescribers must be familiar with general drug information concerning ER/LA opioid analgesics.	89.2 (88.1, 90.2)
FDA Blueprint 6: Prescribers must be familiar with product-specific drug information concerning ER/LA opioid analgesics.	64.1 (62.5, 65.7)
Overall Score	84.7 (84.0, 85.3)

Prescriber Behavior Questions:

These questions assessed changes in prescribing practices, behaviors, and opinions after participating in a REMS-compliant CE activity:

- 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 (61%), counsel patients on the importance of keeping ER/LA opioid analgesics safe and away from children (55%), instruct patients that it is illegal to sell, share, or give away ER/LA opioid analgesics (50%), counsel patients on the most common side effects from opioid use (52%), instruct patients about the importance of and how to safely dispose of their unused opioids (46%), discuss with patients how to safely taper their ER/LA opioid analgesics if it is no longer needed (43%), discuss with patients what to do if a dose is missed (32%), and use the PCD for discussions with patients (30%). Respondents also reported that they more often reassess the need for opioids (63%), check the state Prescription Monitoring Program database for prescription history (57%), use structured interview tools or screening tools to assess patient's risk of abuse or misuse (41%), perform urine drug tests (42%), or complete a patient-prescriber agreement (PPA) or patient contract when the ER/LA opioid analgesics is first prescribed (43%).
- 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 (65%), patient non-compliance with dose reconciliation efforts (57%), patients continue to identify new ways of drug-seeking behavior not currently addressed in the REMS-compliant CE for ER/LA opioid analgesics (54%), and insurance issues (51%).
- 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 (56%) 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 changed to prescribing more non-opioid medications” (49%) and “I am selecting my patients differently based on assessment” (48%).
- Respondents were asked how the types of medications they prescribe have changed since participation in a REMS–compliant CE activity. Overall, while 34% reported no change; 39% reported prescribing more non-opioid medications, 21% of respondents reported prescribing ER/LA opioid analgesics less often, 21% reported limiting the ER/LA opioid analgesics prescribed, and 18% reported prescribing ER/LA opioid analgesics more often.

5.4.2.2. Summary of Long-Term Evaluation Prescriber Survey

Overall, surveyed 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 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, patient non-compliance, and patients continuing to identify new drug-seeking behaviors that were not addressed in the training activity.
Overall, this survey has a number of limitations including the use of a convenience sample and incomplete data collection of prescriber characteristics which may affect the generalizability of the survey results to the overall populations of prescribers who have taken REMS-compliant CE training.

5.4.2.3. Reviewers' comments on Long-term Evaluation Prescriber Survey (S. Harris and Y. Hsueh):

- The data of the prescriber characteristics for the target population is very limited and incomplete. From RPC response to FDA on March 11 2016, sponsors reported that only 6% of eligible prescribers completed the survey. Furthermore, there was no consistency in the (few) variables collected by different CE providers. Some CE providers did not provide any data to sponsors. Sponsors only used two variables (type of physician and degree) to standardize the data. Thus, we have concerns about the use of incomplete data for the standardization. We recommend the Sponsor conducts uniform data collection on the prescriber characteristic across all CE providers.
- In future assessments, the RPC should provide information including: how many respondents came from which CE providers? Were they all represented? Did more respondents come from a particular grantee? In addition, of the respondents, what type of activity did they participate in (i.e. web-based, live, etc).
- This survey was not completed in the 60-month REMS assessment. We would like the RPC to conduct this survey with the 72-month assessment.

5.5. ELEMENT 5: PATIENT SURVEY

"*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. This evaluation may include, for example, surveys of patients*."

The purpose of the 48-month patient survey 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 RPC communicated that the comments were sent too late to be incorporated into the 36-month assessment report but would be considered for the 48-month 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 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. Commercially- insured and Medicare insured 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). Caregivers of commercially insured ER/LA opioid users were identified through claims data. Medicaid insured patients were recruited through a patient panel. Patients were eligible to participate if they were adults age 18 or older who filled at least one prescription for an ER/LA opioid analgesic between October 1, 2014 and September 30, 2015. Patients were excluded if they were not contacted in year one or two, did not give verbal informed consent, failed to validate date of birth or name; did not fill a prescription for an ER/LA opioid analgesic in the past 12 months; were non-English speaking; were employed as a physician, or were employed or family member employed with survey vendor, RPC, or FDA. Approximately 18,031 commercially insured patients and 6,106 Medicare insured patients were eligible to complete the survey. A total of 14,000 patients were contacted via mail. Out of those, 136 were excluded during screening and 16 refused to participate. A total of 444 patients completed the survey (391 commercially-insured, 40 Medicare insured, and 13 caregiver respondents). An additional 41 Medicaid insured patients were recruited through a patient panel.

Most respondents were between the ages of 45 to 64 (62%); male (61%); privately insured (83%); White or Caucasian (91%). Over half of patients (55%) were

college or community college/technical school graduates or completed graduate school (55%).

The RPC provided a comparison of survey respondents to all ER/LA opioid users in the general US population. See Table 13.

Table 13: Patient Survey Respondents Compared to All ER/LA opioid users in the General Population

	Patient Survey	**Medical Expenditure Panel Survey (MEPS)***
Insurance Status	Any private (83%) Public only (17%) Uninsured (0%)	Any private (63%) Public only (28%) Uninsured (9%)
Age	65 or older (17%)	65 or older (22%)
Race	Caucasian (91%) African American (3%) Other (6%)	Caucasian (82%) African American (13%) Other (5%)
Education	Less than high school (2%) High School/GED (14%) College graduate or graduate school (41%)	Less than high school (20%) High School/GED (26%) College graduate or graduate school (21%)

*Medical Expenditure Panel Survey, 2012(weighted estimates of ER/LA opioid users)

FDA asked the RPC to propose methods to standardize the results of the survey sample to the general population of patients prescribed ER/LA opioid analgesics. The RPC standardized the survey results to the distribution of all ER/LA opioid analgesic users in the HealthCore Integrated Research Database (HIRD). For all commercial and Medicare insured patients in the HIRD, a weighted sample was created based on age, sex, region, and opioid prescriber type. For Medicaid, a weighted sample based on age and sex was created using available data used as a standard.

5.5.1. Reviewers' comments (Y. Hsueh):

- We have concerns about the HIRD sample not being representative of the target population for race, income, education level, and payer type. Therefore, the standardization which was based on all ER/LA opioid analgesic users in HIRD is not appropriate. Although the Sponsor included Medicare, Medicaid, and caregiver patients into the Year 3 survey, the numbers of participant from these sources are very limited. We recommend the Sponsor utilizes another data source which is representative of target population for the patient survey.

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 14 below*)

- Overall, respondents' understanding of this key risk message was high. Ninety-four percent (94%) of respondents were aware that ER/LA opioid analgesics can cause dizziness, lightheadedness, and sleepiness. Ninety-eight percent (98%) of respondents were aware of the problems that overdoses can cause (i.e. breathing problems, slow breathing that can lead to death). Respondents were aware that constipation was a possible side effect of opioid use (95%). Most respondents knew that addiction (94%), death (81%), and unintentional overdose (85%) were risks associated with the use of opioids. Fewer respondents were aware that opioids can cause serious side effects that can lead to death even when used as recommended (75%).

Table 14: 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 (%)**	**48-Month (n=485) N (%)**
Overdose may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death.	Correct: 386 (94%)	Correct: 394 (93%)	Correct: 473 (98%)
ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy.	Correct: 345 (84%)	Correct: 342 (81%)	Correct: 455 (94%)
Constipation is a possible side effect of opioids.	N/A	N/A	Correct: 463 (95%)
Opioids cans cause serious side	N/A	N/A	Correct: 365

effects that can lead to death, even when used as recommended.			(75%)
Addiction is a risk associated with the use of opioids.	N/A	N/A	Correct: 457 (94%)
Death is a risk associated with the use of opioids.	N/A	N/A	Correct: 394 (81%)
Unintentional overdose is a risk associated with the use of opioids.	N/A	N/A	Correct: 410 (85%)

Key risk message 2: The patient knows what to do if they too much drug (See *Table 15 below*).

- Respondent's understanding was high. The majority of respondents (90%) 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 (98%).

Table 15: 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 (%)**	**48-Month (n=485) N (%)**
Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fine.	Correct: 363 (88%)	Correct: 374 (88%)	Correct: 436 (90%)
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%)	Correct: 412 (97%)	Correct: 477 (98%)

Key risk message 3: The patient understands the need to store the drug in a safe place (See *Table 16 below*).

- The majority of respondents knew that unused ER/LA opioid analgesics should not be thrown in the trash (90%) and that a child could die if they take or use ER/LA opioid analgesics (92%).

- Only 70% of respondents were aware the ER/LA opioid analgesics should not be stored in the medicine cabinet with other medications in the household.

Table 16: 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 (%)**	**48-Month (n=485) N (%)**
Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household.	Correct: 271 (66%)	Correct: 300 (71%)	Correct: 341 (70%)
Do not throw away any unused ER/LA opioid analgesics in the trash.	Correct: 375 (91%)	Correct: 393 (93%)	Correct: 436 (90%)
A child could die if they take or use the respondent's ER/LA opioid analgesics.	Correct: 384 (93%)	Correct: 393 (93%)	Correct: 448 (92%)

Key risk message 4: The patient knows they should not share the drug with anyone (See *Table 17 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 (99%) and selling or giving away ER/LA opioid analgesics was against the law (99%).

Table 17: 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 (%)**	**48-Month (n=485) N (%)**
Do not give ER/LA opioid analgesics to other people who have the same condition as you.	Correct: 406 (98%)	Correct: 415 (98%)	Correct: 478 (99%)
Selling or giving ER/LA opioid analgesics is against the law.	Correct: 402 (97%)	Correct: 413 (98%)	Correct: 478 (99%)

Key risk message 5: The patient understands how to use the drug safely (See *Table 18 below*).

- There was a high level of understanding for most questions. Most respondents knew that they should talk to their healthcare provider before stopping ER/LA opioid analgesics (96%), they should talk to their healthcare provider if the current dose doesn't control their pain (85%), they should inform their healthcare provider about all other medications being used (95%), that it is not okay to drink alcohol while using ER/LA opioid analgesics (95%), they should inform their healthcare provider about a history of drug or alcohol abuse or mental health problems (94%), and they should inform their healthcare provider about over the counter medications and vitamins or supplements (93%).
- There was a lower level of understanding in terms of awareness that patients should read the Medication Guide every time a prescription is filled (75%) and that it is okay to drink caffeine while using ER/LA opioid analgesics (57%).

Table 18: 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 (%)**	**48-Month (n=485) N (%)**
Talk to a healthcare provider prior to stopping ER/LA opioid analgesics	Correct: 346 (84%)	Correct: 357 (84%)	Correct: 467 (96%)
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%)	Correct: 405 (96%)	Correct: 413 (85%)
It is not okay to drink alcohol while taking or using ER/LA opioid analgesics.	Correct: 385 (93%)	Correct: 394 (93%)	Correct: 461 (95%)
Read the attached MG every time an ER/LA opioid analgesic prescription is filled.	Correct: 231 (56%)	Correct: 232 (55%)	Correct: 365 (75%)
Inform healthcare providers about all the other medications being used.	Correct: 398 (96%)	Correct: 394 (93%)	Correct: 462 (95%)
Inform healthcare providers about any history of abuse of street or prescription drugs, alcohol addiction, or mental	Correct: 375 (91%)	Correct: 382 (90%)	Correct: 456 (94%)

Table 18: 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 (%)**	**48-Month (n=485)** **N (%)**
health problems.			
Inform healthcare providers about over the counter medicines, vitamins, and dietary supplements.	Correct: 368 (89%)	Correct: 369 (87%)	Correct: 452 (93%)
It is okay to drink caffeine while using ER/LA opioid analgesics.	Correct: 202 (49%)	Correct: 207 (49%)	Correct: 277 (57%)

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. Most respondents reported receiving the Medication Guide from their pharmacist with their last fill (92%) while 92% of respondents received the Medication Guide from their pharmacist in the last 12 months. Of the respondents that received the Medication Guide, 80% either read all with each pharmacy fill (18%) or read all (62%) of the Medication Guide at least once. The majority of respondents that read the Medication Guide (93%) understood all or most of the information. 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 33% 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 27% reported that their HCP referenced the PCD in the past 12 months. Of the respondents that received the PCD, 58% understood all or most of the information.

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 19*). In terms of perceived access, 70% agreed they were able to get a prescription when needed and 64% of respondents felt they did not have 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 (83%). The majority were satisfied with their ability to get a prescription (82%) and with their ability to get ER/LA opioid analgesics from the pharmacy (84%).

Table 19: Patients' Perceived Access to Treatment and Satisfaction with Access			
Question	**24-Month (n=413) N (%)**	**36-Month (n=423) N (%)**	**48-Month (n=485) N (%)**
Able to get a prescription for ER/LA opioid analgesics through my healthcare provider when needed for pain	Agreed: 302 (73%)	Agreed: 300 (71%)	Agreed: 341 (70%)
Satisfied with ability to get a prescription for ER/LA opioid analgesics	Agreed: 329 (80%)	Agreed: 349 (83%)	Agreed: 399 (82%)
Satisfied with access to ER/LA opioid analgesics	Agreed: 336 (81%)	Agreed: 329 (78%)	Agreed: 402 (83%)
Does not have to go to healthcare provider too often when more ER/LA opioid analgesics are needed	Agreed: 223 (54%)	Agreed: 227 (54%)	Agreed: 309 (64%)
Satisfied with ability to get ER/LA opioid analgesics from a pharmacy	Agreed: 326 (79%)	Agreed: 337 (80%)	Agreed: 407 (84%)

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. Respondents reported that their HCP discussed opioid choice including the benefits and risks associated with opioid therapy and important safety information (78%). Patient-reported responses were lower for other appropriate prescriber behaviors. Sixty-one percent (61%) 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 discussed how to safely discontinue the current ER/LA opioid analgesics (54%). Only 49% of respondents reported that their HCP completed a PPA or patient contract when their current ER/LA opioid analgesic was prescribed.

5.5.2. Summary of Patient Survey

Although the survey respondents were not representative of the population prescribed ER/LA opioid analgesics, those surveyed had a high understanding of the key risk messages.. 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 (92%) but only 33% 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.

5.5.3. Reviewers' comments (S. Harris and Y. Hsueh on Patient Survey:

Survey results were similar to the survey results from the 36-month assessment. As in the previous survey, the survey respondents were not representative of the drug use population for race, income, education level, and payer type since the HIRD sample is not representative. Therefore, the standardization which was based on all ER/LA opioid analgesic users in HIRD is not appropriate. The RPC utilized different databases to recruit Medicare patients and Medicaid patients but the sample size was small. In addition, caregivers were allowed to participate but only 13 completed the survey. Future surveys should use another data source in order to recruit a representative sample of patients who are prescribed ER/LAs.

5.6. ELEMENT 6 – SURVEILLANCE MONITORING

This assessment element states: "***Results of surveillance for misuse, abuse, overdose, addiction, and death.*** *Surveillance needs to include information on changes in abuse, misuse, overdose, addiction, and death for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency departments, addiction treatment centers, poison control call centers). The information should be drug-specific whenever possible*."

The SD further spells out *that the overall surveillance objective is to evaluate for trends before and after the shared REMS is implemented to collectively assess for changes in misuse, abuse, overdose, addiction, and death for different risk groups and settings….*

The SD lays out the following metrics to be evaluated:

- *Emergency department (ED) visits and other events for opioid overdose and poisoning events using either a national representative database of ED visits subject to the availability, or an analysis of public and/or private insurance claims databases (a commercial insurance plan claims database, e.g., Healthcore or Marketscan, plus a Medicaid claims database) with an assessment of deaths among those prescribed ER/LA opioids linked to the database. A validation study of International Classification of Disease codes used to detect opioid overdose and poisoning (OOP) events audited against a medical chart review will be conducted prior to this study, as described at the end of the description of Assessment #5.*
- *Intentional exposures stratified by age group (children, adolescents and adults), including severity and deaths, using nationally-based poison control surveillance data.*

- *Unintentional exposures stratified by age group (children, adolescents and adults), using nationally-based poison control surveillance data.*
- *Rates of individuals in substance abuse treatment programs abusing ER/LA opioids, as well as source of acquiring the ER/LA opioids, as compared to comparator IR opioids and benzodiazepines using the national surveillance systems among substance treatment seekers.*
- *Mortality rates resulting from drug poisoning associated with active pharmaceutical ingredients included in the ER/LA opioid REMS, but not specifically those formulations covered by the class REMS (e.g., oxycodone, but not specifically ER or IR oxycodone) using state medical examiner databases from selected states (e.g., Florida and Washington).*

The SD reiterates that as much as possible, the surveillance plan should be based on drug-specific information.

5.6.1. Background

The FDA review of the 36-month ER/LA opioid analgesic REMS concluded that the submitted epidemiologic surveillance data were not capable of evaluating the impact of the REMS CE activities on prescriber behavior or adverse patient outcomes.[4]

DRISK has consulted our colleagues in Division of Epidemiology II (DEPI) for their expertise in assessing the epidemiology and drug utilization surveillance data that has been included by the RPC in their 48-month assessment report. In response, on April 3, 2017, the DEPI Staff (J. McAninch and J. Wong) composed a Memo of their Review of the 48-month epidemiology and drug utilization surveillance data submitted by the RPC[5]. The data presented below are mostly from that memo. For additional detail tables, and figures, the reader is referred to the DEPI memo.

In addition, at the May 2016 Advisory Committee (AC), committee members concurred with FDA's assessment that the submitted epidemiologic surveillance data were not capable of evaluating the impact of the REMS CE. The AC members also agreed that a more rigorous study should be explored to directly evaluate the effect of the REMS CE on prescribing behavior and patient outcomes. Thus, following the AC, FDA requested that the RPC submit a concept paper proposing an epidemiologic study that examines changes in prescribing behavior and patient

[4] McAninch J and Secora A. "DEPI review of 36 month ERLA opioid REMS surveillance studies FINAL. Uploaded to DARRTS May 17, 2016.

[5] April 3, 2017 DEPI Memo (J. McAninch and J. Wong) Review of 48-month epidemiology and drug utilization surveillance data

outcomes, comparing providers who have participated in a REMS CE activity to those who have not. As part of the 48-month REMS assessment, the RPC has submitted such a concept paper, which has also been reviewed separately by the Division of Epidemiology II (DEPI) and the Division of Biometrics VII[6].
In addition, FDA has determined that continuing limited surveillance of specific adverse outcomes is informative since knowledge of these trends could help inform future directions of this REMS. Thus, in FDA's July 7, 2016 REMS Assessment Acknowledgement Letter, the RPC was sent the following recommendations regarding their surveillance data with regards to the 48-month REMS Assessment:

- "*Do not submit RADARS or NAVIPPRO data*
- *Submit an update on the status of outcome validation studies and National Death Index linkage in the HealthCore Integrated Research Database (HIRD) and Medicaid studies as well as the potential for linkages between these databases and data on prescriber training completion.*
- *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*."

5.6.2. Data Provided by the RPC

The RPC submitted the following epidemiologic studies/data:

1. Data from the HealthCore Integrated Research Database (HIRD) as well as a subset of Medicaid programs (3 states, not further identified) to assess changes in emergency department (ED) visits, hospitalizations, and death due to Opioid Overdose and Poisoning (OOP) among individuals prescribed ER/LAs. As compared to the 36-moth assessment, the current assessment includes one additional year of data, propensity score matching, and linkage of the HIRD cohort to the National Death Index (NDI). Although these data reference previous validation work at Kaiser Northern California that found a positive predictive value of 83% for analgesic-related overdoses/poisonings, DEPI points out that no further detail on this validation study was provided in the report.
2. An analysis of state medical examiner data from Oregon, Utah (both new for this assessment report) and Washington State.
3. Publically-available data from Monitoring the Future (MTF) for 2010-2015. MTF captures the prevalence of non-medical use of prescription opioids among high school and college students and high school graduates through age 55 years.
4. Protocol for Concept Paper #1comparing prescribing behavior and patient outcomes, comparing providers who have participated in a REMS CE activity to those who have not.

[6] February 7, 2017 Review (J. McAninch, YH Hsueh) of Submitted Concept Paper #1

5. Time periods assessed were as follows;
    a. Pre-REMS – July 2010 – June 2012
    b. REMS Launch: July 2012 – June 2013
    c. Post-REMS/Active: July 2013 – December 2015

5.6.3. HIRD and Medicaid Data

DEPI notes that in the **HIRD** data, the **unadjusted** incidence of ED visits and hospitalizations for OOP did **not** change significantly across study periods using a composite endpoint of either fatal or non-fatal opioid overdose. The prevalence of various overdose risk factors such as psychiatric comorbidities (e.g., anxiety disorder, sleep disorder, depression) increased across study periods, both in ER/LA opioid recipients and in the commercially-insured cohort overall. However, when propensity-score adjustment was performed to control for the noted differences, **OOP rates decreased 19%** comparing the pre- to post-REMS implementation periods (a significant difference). DEPI notes that this decline was driven by non-new (prevalent) users and thus was not significant among new ER/LA users.

ER/LA opioids were dispensed, with or without IR opioids, to 1% of HIRD patients in the pre-period and 0.8% in the active REMS period. However, IR opioids were dispensed to 18.4% of patients in the pre-period and 16.2% of patients in the active REMS period. Across all HIRD patients (with or without an opioid dispensing), the incidence of OOP did not change significantly across study periods, but the incidence of OOP increased significantly by 19% among IR opioid recipients. Looking at those HIRD patients with an OOP event, 32-35% had at least one ER/LA dispensing prior to the event while 47-48% had at least one IR opioid dispensing prior.

Among ER/LA users in the HIRD, the incidence of overdose death increased slightly (non-significantly) across time periods (exposed person time), even after propensity score adjustment; however, DEPI points out that the precision of these estimates was low. All-cause mortality did not change in the unadjusted comparison (exposed person-time) but did increase 4% (statistically significant) after propensity score adjustment. A slight increase in all-cause mortality among ER/LA users during unexposed person-time was removed after propensity score adjustment.

In the 3-state **Medicaid** cohort, the **unadjusted** incidence of OOP among ER/LA users decreased non-significantly across study periods. However, after propensity score adjustment, the **incidence of OOP decreased by 25**%, which was described by DEPI as nearly statistically significant (using exposed person time.) The unadjusted incidence of OOP among **all patients** in the Medicaid cohort (regardless of opioid dispensing history) increased significantly across study periods, while the incidence among IR opioid users was unchanged. DEPI states that the Medicaid claims data were not linked to the NDI.

5.6.3.1. Conclusions

DEPI's analysis of the data suggests that OOP appears to have decreased especially in ER/LA users; however, the reasons for such potential decreases are likely not attributable only to the REMS. Quoting DEPI:

> *"…after adjusting for changes in the risk profile of the commercially-insured and Medicaid cohorts in the study, the incidence of OOP has declined in these populations across the study period. This apparent decline may be related to the REMS, to other factors such as dosing restrictions or increased use of prescription drug monitoring programs (PDMPs), or to some combination of these. The study also suggests that the decreases may be more pronounced among ER/LA recipients than among immediate-release opioid (IR) recipients. The declines also appear to be limited to non-new, or prevalent, ER/LA users, a finding that remains somewhat difficult to interpret. All the findings from these analyses remain exploratory, as the validation studies for a claims-based opioid overdose algorithm have not yet been completed.*
>
> *While not statistically significant, the change in overdose death rates in the HIRD was in the opposite direction from the change in OOP incidence based on ED visit and hospitalization claims. This is an important exploratory finding, suggesting that ED visits/hospitalizations may not be a good indicator of trends in overdose deaths associated with receipt of specific drugs or drug classes. The increase in opioid overdose deaths among ER/LA opioid recipients, although again not statistically significant, is consistent with trends in national mortality data on fatal opioid overdose and poisoning.*[7]
>
> *The generalizability of this study is limited. Patterns seen in the commercially-insured population may not reflect patterns in other populations. Also, the Medicaid cohort includes only three states and therefore may not reflect trends and patterns in the Medicaid population nationally. Although the investigators attempted to control for changes in the risk profile of the cohort over time using propensity score adjustment, it is unclear whether the cohorts were truly comparable across time periods, as many factors—for example BMI, socioeconomic status, and tobacco and alcohol use—are poorly captured in claims.*

[7] Rudd RA et al. Increases in Drug and Opioid-Involved Overdose Deaths — United States, 2010–2015. *MMWR* Early Release December 16, 2016/65. Accessed online on December 20, 2016 at https://www.cdc.gov/mmwr/volumes/65/wr/mm655051e1.htm?s_cid=mm655051e1_w

The evolving nature of commercial insurance and Medicaid coverage, and the geographic variation in these changes, limit the ability to evaluate trends in opioid overdose using these data alone…Future assessments might focus efforts on describing national trends in prescription opioid overdoses using electronic healthcare data that is not dependent on payer type. Some examples might include Healthcare Cost and Utilization Project (HCUP) databases such as the Nationwide Emergency Department Sample (NEDS), State Emergency Department Databases (SEDD), National (Nationwide) Inpatient Sample (NIS), and State Inpatient Databases (SID)."

5.6.4. Medical Examiner Data

For both **Oregon** and **Washington, overdose deaths** attributed to opioids with an ER/LA formulation **declined** across the study periods, using both population and utilization denominators.

- For Oregon, the most recent quarters of data suggest a plateau or possible increase. In addition, for Oregon, prescription-adjusted deaths declined during the pre-period while population-adjusted declined somewhat less.
- The Washington State data in this assessment report continue the trends seen in the 36-month report; however, DEPI notes a sharp drop during the most recent quarter raises a question of incomplete data for this quarter

Both population- and utilization-adjusted rates of **overdose deaths** involving opioids with an ER/LA formulation **increased** in the **Utah** data across the study periods although the increase in mean death rate was only significant using the population denominator.

5.6.4.1. Conclusions

DEPI concludes that:

"*The cross-state differences emphasize the regional variability, not just in cross-sectional estimates of overdose rates, but in trends, within the broader national epidemic of opioid overdose. The data also validate our concerns regarding using a single state (WA) to monitor overdose death trends, as was done in the 36-month assessment. The cause of the differences across states is not entirely clear, but may involve variation in the duration of the epidemic in each state and in state-level interventions such as opioid dosing legislation, prescribing guidelines, CE requirements, and integration and utilization of PDMPs. The differential availability of heroin, illicit fentanyl, and other drugs, as well as differences in medical examiner death investigations and documentation practices may also play a role*."

Thus, DEPI points out the differences in the data observed from the three states and the importance of not relying on only one state when attempting to make overall national conclusions.

5.6.5. Monitoring the Future (MTF)

The MTF asks high school students, college students and high school graduates about the non-medical use of prescription opioids by asking about their "use of narcotics other than heroin (without doctor's orders)." The data appears to indicate a decline in the non-medical use of opioids from 2010 to 2015 in this population whether measured as lifetime, annual, or past-30 day non-medical use. Among high school students, the magnitude of this decline appears to be greater for Vicodin than for OxyContin and the perceived availability of these drugs also declined during this time period among high school students.

5.6.5.1. Conclusions

DEPI points out that although they had requested data going back to 2006, the RPC provided data as far back as only 2010. DEPI also states that the sampling methodology of MTF allows for reliable trending over time; however this survey may miss many high-risk adolescents and young adults, including those who have dropped out of high school or entered the juvenile justice system. Additionally, DEPI points out that the terminology used in this survey, "narcotics other than heroin (not under doctor's orders)," is not ideal,

Data from the National Survey on Drug Use and Health (**NSDUH**) is not included in this current assessment report. DEPI points out that since major changes in the survey questions on prescription opioid occurred in 2015, at present, this survey is less useful for tracking trends. However, DEPI states that the utility of NSDUH could be reconsidered for surveillance in future assessments following the REMS expansion.

5.6.6. Concept Paper #1

As discussed in this review's Section 5.6.1, the May 2016 AC members concurred with FDA's assessment that the submitted epidemiologic surveillance data were not capable of evaluating the impact of the REMS CE. The AC members also agreed that a more rigorous study should be explored to directly evaluate the effect of the REMS CE on prescribing behavior and patient outcomes. Thus, following the AC, FDA requested that the RPC submit a concept paper proposing an epidemiologic study that examines changes in prescribing behavior and patient outcomes, comparing providers who have participated in a REMS CE activity to those who have not. Thus as part of the 48-month REMS assessment, the RPC has submitted such a concept paper ("*Evaluation of the Impact of the REMS on Prescribing Practices and Patient Outcomes and Prescriber and Patient Knowledge"***)**, which at the request of DRISK has been reviewed by the Division of Epidemiology II (DEPI) and the Division of Biometrics VII (DB VII) (see February 7, 2017 Review [J. McAninch and YH Hsueh] of Submitted Concept Paper).

DEPI and DB VII summarize that in Concept Paper #1, RPC is proposing a retrospective cohort study utilizing the Amazing Charts Electronic Health Record (EHR) database, linked to prescriber participation in a Pri-Med REMS-compliant

CE training. The study is to assess prescribing characteristics and outcomes before and after completion of REMS-compliant CE training using an interrupted time series approach and a propensity score matched control group of providers who have not participated in a Pri-Med REMS-compliant CE training. The study is to also have a survey component, recruiting from the REMS-compliant CE trained and control provider groups and their patients, comparing results for the two groups and then linking provider knowledge scores with EHR data on prescribing behavior.

Comments regarding this concept paper were conveyed to the RPC on February 10. 2017. DEPI and DBVII provide comments to the RPC that are in **Section 9** ("Comments for the Sponsor") of this review.

5.7. ELEMENT 7 - DRUG UTILIZATION

The Assessment Element states: "*An evaluation of drug utilization patterns, including: an evaluation of prescribing behaviors of the prescribers of ER/LA opioid analgesics, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills."*

The SD provides additional detail: "*A drug utilization study will be conducted to describe trends in the number of prescriptions for class REMS ER/LA opioid analgesics and comparator products using a national prescription database system (e.g., IMS Xponent or VONA). Specifically the following will be assessed:*

- *National trends in number of prescriptions for ER/LA opioids and by type of prescriber.*
- *National trends in number of prescriptions for comparator products and by type of prescriber, including:*
    - *Opioid analgesics not covered by the class REMS for ER/LA opioids, i.e.,immediate-release*
    - *Prescription NSAID analgesics (e.g., celecoxib) that is an "analgesic control" group*
    - *Selected benzodiazepines that are frequently abused (e.g., alprazolam) that is an"abuse control" group*
- *Switches from ER/LA opioids to comparator analgesics with introduction of REMS.*
- *A study to evaluate changes in prescribing behavior of prescribers using one or more databases will be conducted. Specifically the following will be assessed:*
    - *For products that are indicated for use in opioid-tolerant patients only, trends in prescriptions to non-opioid tolerant patients and starting at high dosage strengths in opioid non-tolerant patients*
    - *For products that are indicated for use in opioid-tolerant and non-opioid-tolerant patients, trends in patients starting at high dosage using an appropriate database*

- *For all products included in the class, excessive prescriptions for early refills"*

5.7.1. Background

As discussed in this review's Section 5.6.1, in FDA's July 7, 2016 REMS Assessment Acknowledgement Letter, the following recommendations were made to the RPC regarding the utilization data of interest to be included in the 48-month REMS Assessment:

- *"Submit an analysis of national trends in drug utilization as previously outlined....(T)he analysis should include additional IR comparator products (i.e., combination oxycodone/acetaminophen, oxycodone/aspirin, oxycodone/ibuprofen, IR and ER tramadol and tramadol/acetaminophen).*
- *In your analysis of prescription 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."*

DEPI's Drug Utilization (DU) team has reviewed and provided comments on these data and these comments are contained in the previously noted April 3, 2017 DEPI Staff (J. McAninch and J. Wong) review memo.

5.7.2. Drug Utilization

As directed in FDA's July 7, 2016 REMS Assessment Acknowledgement Letter, the RPC's submitted IMS Health data included oxycodone-containing combination products (i.e. oxycodone/acetaminophen, oxycodone/ibuprofen, oxycodone/aspirin) in the immediate-release (IR) opioid comparator group. In addition, the RPC added long-term care pharmacies to outpatient retail pharmacies to assess national drug utilization data. **Table 20** below (copied directly from the RPC's Table 30) compares the changes in average quarterly prescriptions (from retail and long-term care pharmacies) pre- and post-REMS for the ER/LAs as a class, individual opioids available in ER/LA formulations, IR opioids, celecoxib, and benzodiazepines. The table indicates that the average quarterly prescription volume decreased (statistically) significantly pre- to post-REMS for the ERLAs by 5.3% and the IR opioids by 12.3%. Oxycodone, Morphine, and Fentanyl transdermal remained the market leaders amongst the ER/LAs. While the decrease in the average quarterly prescription volume was slight (but statistically significant) at 2.3% for the fentanyl transdermal products, the decrease was pronounced, 23% for oxycodone (statistically significant). On the other hand, morphine average quarterly prescription volume increased statistically significantly by 8.9%. It appears that the overall driver in the decrease for average quarterly prescription volume for ER/LAs as a class was drive by the decrease in oxycodone.

Table 20: Retail Channel - Comparison of the Average Quarterly Prescription Volume across the Pre-Implementation and Active Periods

Products[1]	Prescription Volume				Pre-Implementation Versus Active Period		
	Pre-Implementation		Active Period		Statistical Comparison	Percent Change Within Product Type	
	Mean	95% CI	Mean	95% CI	P-value (T-test)	% Change	95% CI
ER/LA opioids							
Buprenorphine TD	78,365	(26,521-106,272)	151,769	(134,169-163,181)	<.001	93.7	(63.70-123.64)
Fentanyl TD	1,244,204	(1,232,398-1,258,016)	1,215,108	(1,190,081-1,235,847)	0.004	-2.3	(-3.79--0.89)
Hydrocodone bitartrate	—	—	23,131	(7,903-46,897)	—	—	—
Hydromorphone HCl	24,634	(14,380-41,447)	46,403	(40,254-58,518)	<.001	88.4	(51.39-125.34)
Methadone HCl	975,183	(945,501-993,674)	781,611	(708,956-857,867)	<.001	-19.8	(-25.12--14.57)
Morphine sulfate[2]	1,469,363	(1,399,689-1,550,133)	1,599,916	(1,568,644-1,630,665)	<.001	8.9	(5.54-12.23)
Morphine-naltrexone	15,061	(4-45,235)	5,748	(1-14,103)	0.358	-61.8	(-203.59-79.91)
Oxycodone HCl	1,502,153	(1,291,884-1,878,898)	1,156,164	(1,102,436-1,214,943)	<.001	-23.0	(-32.59--13.47)
Oxymorphone HCl	268,439	(228,305-333,896)	238,787	(229,396-246,203)	0.059	-11.0	(-22.56-0.47)
Tapentadol HCl	34,977	(3,270-57,260)	68,264	(64,495-74,255)	0.001	95.2	(49.22-141.12)
Total ER/LA opioids	5,575,301	(5,458,378-5,718,070)	5,279,401	(5,200,299-5,392,833)	<.001	-5.3	(-7.12--3.49)
Comparators							
IR opioids	46,426,331	(45,728,857-47,180,141)	40,731,749	(37,575,791-44,263,899)	<.001	-12.3	(-17.70--6.83)
Celecoxib	2,004,907	(1,910,706-2,112,623)	1,820,219	(1,760,768-1,894,204)	<.001	-9.2	(-12.55--5.87)
Benzodiazepines	20,915,094	(20,712,077-21,232,509)	21,059,013	(20,813,618-21,408,001)	0.255	0.7	(-0.55-1.92)

[1] No data shown for oxycodone HCl-naloxone HCl because the drug was not released in the US
[2] Includes morphine sulfate beads

Table 21 below (copied from the RPC report's Table 12) compares pre- and post-REMS prescription volumes (from retail and long-term care pharmacies) across age, sex, prescriber specialty, and pay types. The table indicates that while adults aged 19 to 64 experienced statistically significant decreases in the average quarterly prescription volume from the pre- to post-REMS period, adults ≥ 65 years experienced a statistically significant increase in the same metric over the same period. Similarly with pay type, only Medicare Part D prescriptions for ER/LAs statistically significantly increased in average quarterly prescription volume while all other pay types (especially Medicaid) indicated statistically significant decreases. The average quarterly prescription volume stemming from prescription written by primary care providers (PCP) decreased statistically significantly by 17.6%. This specialty was far and away the largest prescriber group for the ER/LAs. As noted in previous assessment reports, the average quarterly prescription volume from prescriptions written by nurse practitioners and physician's assistants increased statistically significantly by 38.3% and 34.0% respectively. When the RPC was questioned about this in the 12-month report, they presented data that indicated that nurse practitioners and physician's assistants also wrote for statistically significantly higher volumes of many other classes of chronically administered medications

Table 21: Retail Channel—Comparison of the Average Quarterly Prescription Volume Across the Pre-Implementation and Active Periods by Age, Sex, Prescriber Specialty, and Pay Type

Product* by Patient Age, Sex, Prescriber Specialty, and Pay Type	Average Quarterly Prescription Volume				Comparison Across Periods					
	Pre-Implementation Period		Active Period		Pre-Implementation vs Active					
					Means comparison (Student's t-test)			Medians comparison (Wilcoxon Rank-Sum test)		
	Mean	95% CI	Mean	95% CI	% change	95% CI	P-value	% change	95% CI	P-value
ER/LA opioids										
Patient age										
0-18	27,886	(26,325-30,790)	26,349	(24,229-28,027)	-5.5	(-12.25-1.22)	0.102	-5.6	(-12.99-1.39)	0.110
19-40	867,140	(798,078-950,493)	667,089	(621,350-732,499)	-23.1	(-29.10--17.04)	<0.001	-23.0	(-30.08--16.50)	<0.001
41-64	3,490,676	(3,413,851-3,573,564)	3,287,481	(3,221,067-3,374,316)	-5.8	(-7.92--3.72)	<0.001	-6.2	(-8.57--3.78)	<0.001
≥65	1,189,599	(1,164,541-1,225,556)	1,298,481	(1,259,807-1,329,244)	9.2	(6.75-11.56)	<0.001	9.1	(6.65-11.54)	<0.001
Patient sex										
Male	2,480,886	(2,416,767-2,572,891)	2,319,211	(2,276,820-2,376,215)	-6.5	(-8.59--4.44)	<0.001	-6.4	(-8.87--4.27)	<0.001
Female	3,094,415	(3,041,612-3,145,179)	2,960,190	(2,911,082-3,016,618)	-4.3	(-6.00--2.68)	<0.001	-4.9	(-6.37--2.72)	<0.001
Prescriber specialty										
Anesthesiologist	446,874	(443,813-456,368)	448,350	(435,855-456,939)	0.3	(-1.27-1.93)	0.668	1.1	(-1.39-2.05)	0.286

Table 21: Retail Channel—Comparison of the Average Quarterly Prescription Volume Across the Pre-Implementation and Active Periods by Age, Sex, Prescriber Specialty, and Pay Type

Product* by Patient Age, Sex, Prescriber Specialty, and Pay Type	Average Quarterly Prescription Volume				Comparison Across Periods					
	Pre-Implementation Period		Active Period		Pre-Implementation vs Active					
					Means comparison (Student's t-test)			Medians comparison (Wilcoxon Rank-Sum test)		
	Mean	95% CI	Mean	95% CI	% change	95% CI	P-value	% change	95% CI	P-value
Dentist	3,665	(3,124-4,165)	1,974	(1,567-2,358)	-46.2	(-56.34--35.96)	<0.001	-48.2	(-55.77--34.28)	<0.001
Emergency Medicine	43,637	(41,135-48,340)	30,859	(29,801-32,407)	-29.3	(-35.29--23.27)	<0.001	-31.6	(-35.17--24.06)	<0.001
Hospice and Palliative Medicine	12,268	(12,007-12,949)	13,306	(12,935-14,199)	8.5	(4.02-12.91)	0.001	7.7	(3.53-14.07)	0.001
Neurologist	139,421	(131,971-150,030)	110,051	(99,576-119,895)	-21.1	(-26.79--15.34)	<0.001	-19.1	(-27.80--14.09)	<0.001
Nurse Practitioner	421,001	(391,981-458,095)	582,160	(535,401-627,694)	38.3	(29.77-46.79)	<0.001	38.3	(27.80-46.38)	<0.001
Oncologist	197,473	(190,190-206,344)	174,466	(168,990-181,175)	-11.7	(-14.49--8.81)	<0.001	-12.2	(-14.83--9.07)	<0.001
Pain	666,973	(650,048-688,144)	716,613	(701,771-729,463)	7.4	(5.33-9.55)	<0.001	7.9	(4.95-10.02)	<0.001
PCP	2,248,860	(2,123,848-2,404,434)	1,853,607	(1,765,595-1,964,659)	-17.6	(-21.65--13.50)	<0.001	-16.6	(-21.79--12.58)	<0.001
Pediatrician	40,075	(38,091-42,219)	31,183	(29,701-33,165)	-22.2	(-26.19--18.18)	<0.001	-22.7	(-27.19--17.86)	<0.001
Physical Medicine and Rehabilitation	488,418	(483,331-496,373)	467,951	(459,831-479,616)	-4.2	(-5.94--2.44)	<0.001	-4.2	(-6.44--2.30)	0.001
Physician Assistant	334,751	(311,125-365,035)	448,576	(421,409-481,467)	34.0	(26.69-41.31)	<0.001	32.7	(24.87-41.53)	<0.001
Rheumatologist	84,054	(78,972-89,092)	68,957	(64,732-73,564)	-18.0	(-22.63--13.29)	<0.001	-16.1	(-22.80--12.90)	<0.001
Surgeon	164,294	(150,978-181,565)	119,175	(113,825-126,381)	-27.5	(-33.22--21.70)	<0.001	-27.6	(-35.03--20.36)	<0.001
Other	283,538	(263,687-331,045)	212,173	(190,902-240,374)	-25.2	(-33.14--17.19)	<0.001	-24.9	(-33.06--16.70)	<0.001
Pay type										
Cash	282,755	(259,862-335,711)	216,502	(196,489-249,376)	-23.4	(-32.16--14.71)	<0.001	-23.3	(-33.97--14.49)	0.001
Medicaid	391,015	(318,837-447,939)	221,293	(198,165-240,738)	-43.4	(-54.12--32.69)	<0.001	-45.9	(-52.59--25.22)	P<0.001
Medicare Part D	1,700,192	(1,650,311-1,799,493)	2,040,992	(1,993,335-2,082,986)	20.0	(17.37-22.72)	<0.001	20.7	(16.56-23.39)	P<0.001
Third Party	3,201,339	(3,127,329-3,304,783)	2,800,615	(2,737,887-2,899,472)	-12.5	(-14.83--10.20)	<0.001	-12.4	(-15.13--9.60)	<0.001

* Data for oxycodone HCL-naloxone HCL were not included in analyses because the drug was not released in the US

† Includes morphine sulfate beads

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5.7.3. Conclusions

The DEPI DU team states that the RPC's inclusion of the long-term care setting helps the included utilization data to be more generalizable to the U.S. population. The team indicates that additional data such as from inpatient hospital settings, rehabilitation facilities, or pain clinics will also make the data even more generalizable.

The DU team also states that *"…as mentioned in the 36-months assessment report, we had noted that cross-sectional, aggregated drug utilization data alone are insufficient to assess the impact of the ER/LA REMS program. We recommended the RPC to design longitudinal patient-level studies to track changes in utilization patterns based on prescribing behavior before and after REMS-compliant training by prescribers who have undergone ER/LA REMS training versus prescribers who have not, as well as an assessment of the impact on utilization trends in the respective patient population. In response to our recommendation, the RPC submitted a concept paper* [the previously referred to "Concept paper #1] *proposing an epidemiologic study that examines changes in prescribing behavior and patient outcomes, which is currently being reviewed by DEPI II and DB7.*

Overall, information on the appropriateness of use of drug products and the impact of the REMS on opioid prescribing cannot be ascertained by the data sources and methods used in the current report alone. The RPC would need to address this by designing studies that utilize more appropriate data resources and innovative methods."

Thus the DU Team offers the following comments to the RPC: "The retail and long term care utilization data provided by the RPC are helpful. However, the Agency suggests exploring other data sources that will encompass utilization of ERLA opioid analgesic products not only in the retail and long term care settings but also in other settings of care such as pain clinics, specialty pharmacies, inpatient hospital, etc. to provide a more comprehensive utilization analyses of ERLA opioid analgesic products in the U.S. market."

5.7.4. Opioid Tolerance, Early Refill, Switches

As mentioned previously, in FDA's July 7, 2016 REMS Assessment Acknowledgement Letter, the RPC was told:

- *In your analysis of prescription 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."*

In this report, the RPC has revised the definition for opioid tolerance to opioid usage of at least 60 mg oral morphine (or morphine-equivalents) per day for 7 days consecutively, in the 7 days look-back period prior to the index prescription claim. However, the RPC did not change the additional 90 day look back period to a 30 day look back period as was suggested and instead used a "97-day treatment identification period." **Figures 4a** and **Figure 4b** below (copied in their entirety from the RPC reports Figures 3a and 3b) give examples of scenarios where the RPC would consider a patient to be opioid tolerant (5a) or opioid non-tolerant (5b).

Figure 4a: Example Timeframe for Opioid Tolerance Calculation

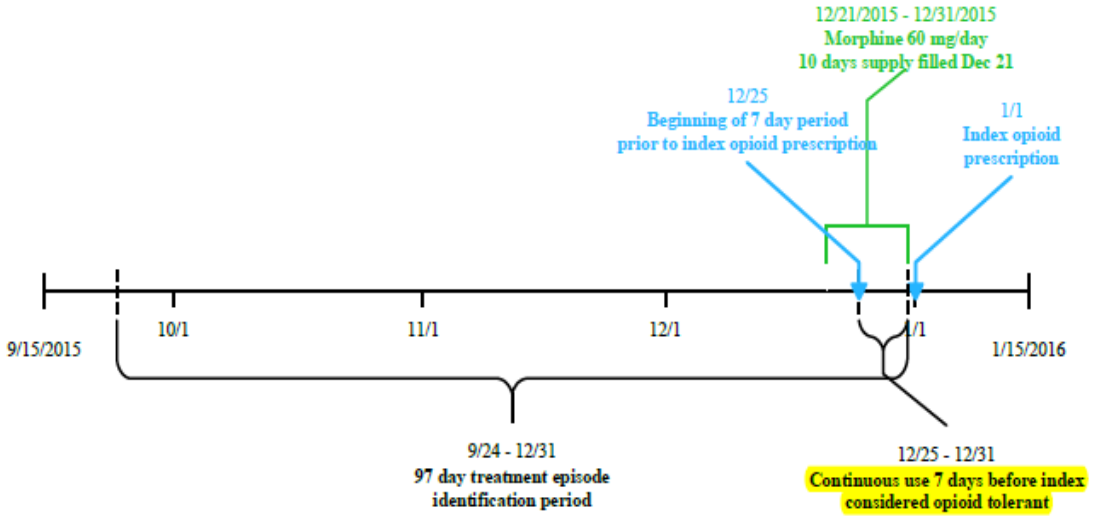

Figure 4b: Example Opioid Prescription during the 97 Day Treatment Episode Identification Period, but Patient is Classified as Non-Opioid Tolerant

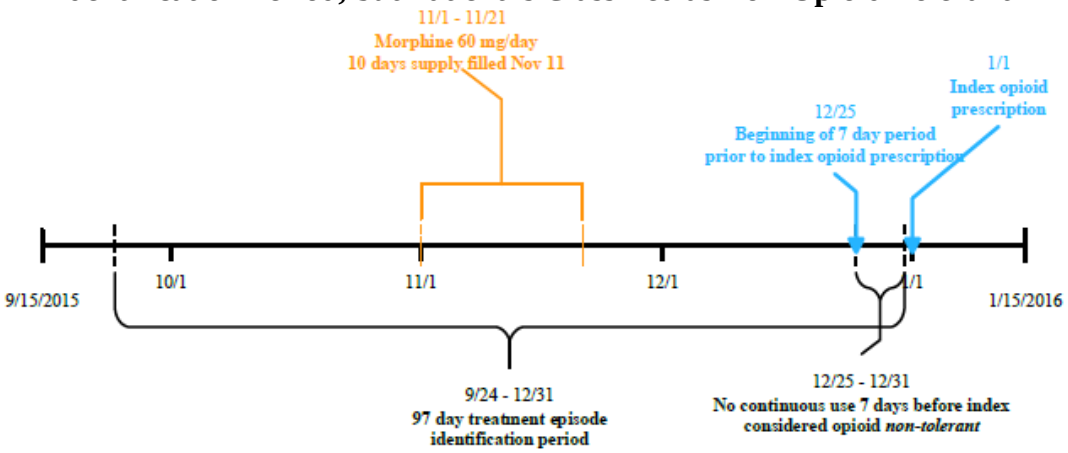

Table 22 below (copied in its entirety from the RPC report's Tables 33) compares the average monthly proportion of opioid non-tolerant patients for ER/LAs across the Pre- and Post-REMS Periods. In every case except for buprenorphine

transdermal the percentage of non-tolerant patients dropped from the pre- to post-REMS period. All of the decreases were statistically significant except for oxycodone. The percentage of opioid non-tolerant patients in the post-REMS period ranged from a low of 26.0% for morphine-naltrexone to 79.6% for buprenorphine transdermal.

Table 22: Comparison of the Average Monthly Proportion of Opioid Non-Tolerant Patients Across the Pre- and Post-REMS Periods

	Average Monthly Patient Volume				Pre-Implementation Versus Active Period		
	Pre-Implementation		Active Period		Statistical Comparison	Percent Change Within Patients	
ER/LA Opioid[1]	Mean	95% CI	Mean	95% CI	P-value (t-Test)	% Change	95% CI
Buprenorphine TD (total patients)	15,396	(11,850.39-20,039.31)	35,334	(33,653.85-38,043.43)	<.001	129.5	(109.84-149.18)
% of non-tolerant patients	75.6%	(75.49%-77.31%)	79.6%	(78.86%-80.43%)	<.001	5.3%	(3.58%-6.95%)
Fentanyl TD (total patients)	344,275	(341,455.95-348,595.77)	342,089	(340,231.85-343,904.96)	0.280	-0.6	(-1.80-0.53)
% of non-tolerant patients	48.3%	(46.40%-49.67%)	46.4%	(45.22%-47.61%)	0.007	-3.9%	(-6.59%--1.12%)
Hydrocodone bitartrate (total patients)	—	—	5,283	(2,518.76-8,716.56)	—	—	—
% of non-tolerant patients	—	—	54.6%	(53.62%-56.33%)	—	—	—
Hydromorphone HCl (total patients)	7,180	(4,971.49-9,052.71)	13,352	(11,826.14-13,992.98)	<.001	85.9	(66.08-105.82)
% of non-tolerant patients	43.6%	(42.57%-44.50%)	39.6%	(38.41%-40.54%)	<.001	-9.2%	(-11.98%--6.52%)
Morphine sulfate[2] (total patients)	70,642	(69,987.29-74,617.17)	43,582	(40,131.08-46,153.07)	<.001	-38.3	(-42.59--34.02)
% of non-tolerant patients	32.4%	(30.14%-34.96%)	28.1%	(26.01%-29.62%)	<.001	-13.3%	(-18.81%--7.84%)
Morphine-naltrexone (total patients)	610	(426.55-830.81)	91	(36.53-140.68)	<.001	-85.0	(-118.67--51.37)
% of non-tolerant patients	34.7%	(26.05%-40.00%)	26.0%	(22.00%-30.23%)	0.228	-25.2%	(-67.41%-17.04%)
Oxycodone HCl (total patients)	339,191	(313,769.12-360,412.61)	263,162	(253,355.58-270,821.77)	<.001	-22.4	(-27.36--17.47)
% of non-tolerant patients	35.7%	(33.23%-37.71%)	33.3%	(31.73%-34.76%)	0.004	-6.8%	(-11.34%--2.31%)
Oxymorphone HCl (total patients)	72,169	(65,103.59-80,457.15)	65,036	(63,979.70-66,417.49)	0.005	-9.9	(-16.57--3.19)
% of non-tolerant patients	33.3%	(31.93%-35.17%)	30.3%	(28.60%-31.56%)	<.001	-9.1%	(-13.87%--4.36%)
Tapentadol HCl (total patients)	9,588	(6,275.33-13,800.73)	17,188	(16,573.21-17,185.77)	<.001	79.3	(63.69-94.87)
% of non-tolerant patients	53.9%	(51.38%-56.46%)	45.2%	(43.84%-46.61%)	<.001	-16.0%	(-19.58%--12.46%)

For the metrics of "early refill" and "switches", the RPC applied the same methodology as used for the 36-month assessment report.

5.7.5. Conclusions

In their previously noted April 3, 2017 review[8], the DEPI/DU team (J. McAninch and J. Wong) provides the following conclusions:

"Opioid Tolerance
However, utilizing only the primary definition for opioid tolerance as described in the study by Willy will result in underestimation for patients considered as "opioid tolerant." For example, if patient receives an opioid prescription in the beginning of December for a 20 day supply it will not overlap the 7 consecutive days prior to the index opioid prescription. The patient would be categorized as a "non-opioid tolerant" patient in this scenario. However, if the RPC also utilized the 30 day look-back period as noted in the Willy et al. paper, then the patient mentioned in the above example will be considered as "opioid tolerant".

Under estimation may also occur for patients considered as "opioid tolerant" for patients who receive prescriptions outside the IMS LRx database pharmacy sample or if patients received prescriptions in settings of care not captured in the database (i.e., inpatient hospital settings, rehabilitation facilities, etc.) The RPC states that eligibility criteria were applied to maximize the available patient history in the LRx database, but the nature of the LRx database means it is unknown whether or not the patient's complete medication history is captured. These restrictions will help maximize that, but without access to the patient's complete medical chart history, one cannot assume that all medications are captured. A more appropriate database would be one which has the ability to look across multiple settings at the unique patient level so that opioid tolerance can be properly identified.

Furthermore, relying solely on electronic healthcare claims data or prescription data may over-estimate the number of patients classified as "opioid-tolerant". For example, after a dental procedure a patient is often prescribed an opioid to be taken as needed for pain. Even though the patient has received the full quantity of the prescription, it does not mean the patient consumed/ingested the total amount of the opioid prescribed. However, according to the electronic prescription data, the patient may be incorrectly categorized as opioid-tolerant. As mentioned in the 36-month assessment report, the Agency agrees with the study objectives; but the

[8] April 3, 2017 DEPI Memo (J. McAninch and J. Wong) Review of 48-month epidemiology and drug utilization surveillance data

methodology and the data source selected are not designed to adequately address these objectives."

"Early refill
As mentioned in the 36-month assessment report, FDA agrees that early refill or early refill attempts by patients for consecutive ER/LA opioid prescriptions prescribed by the same prescriber may be a surrogate metric for abuse behavior, however, this measure has not been validated to our knowledge. But the proposed study methodology is inadequate to address the question posed by the ER/LA opioid REMS. Longitudinal studies that track changes in prescribing behavior at the unique prescriber level before and after REMS-compliant training should be considered for future submissions.

Do not submit early refill data reported through current methodology for future assessments."

"Switch analyses
As mentioned in the 36-month assessment report, although benzodiazepines may be reasonable comparators, the changes in utilization levels alone make it difficult to interpret and understand the results of concomitancy analyses with respect to the REMS. It is also not clear how this specific metric relates to the REMS goals. In the absence of data capturing the intent or reason for switching, these data are difficult to interpret. Further insight into the reasons for switching linked to prescribing is needed for more meaningful results (i.e., REMS too burdensome, prescribers not REMS trained, clinical reason, etc.). The selection of products (e.g. celecoxib, benzodiazepines, and selected IR opioids) used in the assessment for the switch analyses are not comprehensive. There was not enough evidence submitted that these products are the most appropriate and relevant products to include in these switch analyses."

Do not submit switch analyses data reported through current methodology for future assessments. We recommend obtaining other data sources to provide insight into the reason for switching linked to prescribing for more meaningful results (i.e., REMS too burdensome, prescribers not REMS trained, clinical reason (i.e., ER/LA not needed), etc.)."

5.8. 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 SD, this element consists of two components:

- *Changes in prescribing will be compared in 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). This will be conducted using the methodology described for Utilization patterns above.

- *A set of questions will be added to the REMS prescriber survey and to the REMS patient survey to assess whether prescribers and patients perceive an impact of the ER/LA opioid analgesic REMS on access to treatment. For prescribers, survey items will assess whether the 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 will 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. These additional questions will be added to the REMS prescriber survey described in Assessment #3 and the REMS patient survey described in Assessment #4.*

  As directed in the FDA's July 7, 2016 REMS Assessment Acknowledgement Letter, the RPC did not submit the evaluation of patient access (i.e., based solely on utilization data and survey questions) that has been conducted in previous assessments. The RPC did submit a concept paper entitled "*Evaluation of the Impact of the REMS on Patient Access*" which consists of two proposed studies to assess the impact of the REMS on patient access.

Study #1 Objectives:
The objectives of this study are to assess the reasons healthcare providers' prescribing practices changed and the impact of the ER/LA Opioid Analgesics REMS on prescribing behavior.

Methods:
This study would involve 2 phases:

- Phase I: Healthcare Provider Focus Groups: this would be a qualitative research study utilizing focus groups of prescribers of ER/LAs to learn about their prescribing experiences before and after REMS implementation, especially to identify the factors that led them to change their prescribing behavior. The focus group results would help inform the development of the healthcare provider survey to be used in Phase II.

- Phase II: Healthcare Provider Survey: A larger sample of healthcare providers would be invited to complete a survey to determine how often various factors affecting healthcare provider behaviors can affect patient access as reported among new healthcare providers and healthcare providers for whom prescribing practices changed after REMS implementation.

Pharmacy dispensing claims from the HIRD would be used to identify the healthcare provider populations for both study phases The RPC states that they will

also explore the feasibility of identifying prescribers via Medicaid claims). The eligible sample population of healthcare providers would consist of:

i. Healthcare providers who wrote prescriptions for ER/LA prior to implementation of the REMS (July 1, 2012) and whose prescribing patterns changed after implementation of the REMS, **or**
ii. New prescribers of any medication (not limited to ER/LAs) who prescribed this medication in the past 6 months (to ensure that healthcare providers are currently active prescribers for whom recent contact information is available).

For each provider the RPC will identify the number of patients to whom the provider prescribed opioids and for whom pharmacy claims were submitted, as well as identify those prescribers for whom a large change in patient density is observed in more recent data, indicating a change in prescriber behavior.

Each focus group will consist of a 90 minute discussion led by a moderator and be designed to identify factors such as what sources of information the healthcare provider uses to learn about ER/LAs, their perceptions about the regulatory environment, and reasons why prescribing behaviors have changed. Healthcare providers in the Phase 1 focus group study will also discuss how the REMS impacted their prescribing behavior. The RPC anticipates that approximately 6-8 focus groups will be conducted, be held in in 2-3 locations, and each will include 4 healthcare providers. Healthcare providers will be compensated for their time. The main themes and concepts emerging from a review of the interview transcripts will be used to develop the Phase 2 survey questionnaire.

A larger group of healthcare providers will then be invited to participate in Phase 2, a cross-sectional physician survey administered by mail or internet. This survey will be used to determine how often various factors driving changes in healthcare provider behaviors are reported among new healthcare providers and healthcare providers for whom changes in ER/LA prescribing behavior were observed. The survey will include demographic and practice information, specialty, CE training history and past experience with opioids, as well as questions to determine how their prescribing behaviors have changed and the reasons for this change. The RPC estimates that the survey will take approximately 15 minutes to complete, and survey respondents will be compensated for their time.

The RPC estimates that with a sample of 600 completed surveys, the survey will have a margin of error of ±4% at a 95% level of confidence[2]. This means that if 50% of respondents say they use a Patient-Provider Agreement, the 95% confidence interval for that response rate will range from 46% to 54%.

An analysis will be conducted in which healthcare providers who respond to the survey will be compared to non-responders and to healthcare providers overall regardless of study eligibility in terms of characteristics such as time since first prescription in the database and US region. The RPC will also assess whether

physicians who changed prescribing habits had changes in the proportion of their patient population diagnosed with pain conditions. The RPC states that they will sample healthcare providers from a list that represents all US regions, but they will also explore whether post-hoc weighting or standardization approaches are needed.

Study #2 Objectives:
The objectives of this study are to assess patient access, satisfaction with access, and whether patients perceive that their access to pain medication has changed.

Methods:
Pain patients will be identified through collaboration with patient advocacy groups with both ER/LA users and non-users across the United States recruited. The RPC anticipates that approximately 6-8 focus groups of patients will be conducted, will include 6 patients per group, will be held in 2-3 locations, and will consist of a 90 minute discussion led by a moderator. The moderator will use a discussion guide that will be designed to identify access to pain treatment (ER/LAs, other pain medications, alternative therapies), satisfaction with access to treatment, and factors that have affected patient access to pain management. Participating patients will be compensated for their time. The focus group data will be qualitatively analyzed to determine the main themes and concepts emerging. The RPC will also review the concepts that emerge from these focus groups in the context of the REMS and whether there is a plausible relation between them.

Strengths and Limitations:
The RPC states that their approach allows for assessment that is neither limited to those patients who successfully obtained ER/LAs nor reliant on patients identifying whether they were appropriate candidates for ER/LAs. The RPC also states that, by incorporating a patient perspective that is not limited to individuals who received ER/LAs, understanding of medication access that extends beyond the influence of the REMS will be attained. Another strength pointed out by the RPC includes a qualitative assessment of access from the perspective of pain patients who do and do not use ER/LA opioid analgesics. The RPC states that this will allow for capture of REMS and other non-REMS road blocks to patient access, such as legal changes limiting the number of pills that can be made available, pharmacy refusal to fill prescriptions, prior authorization from health insurance providers, and other access barriers that patients may face.

The RPC states that limitations of their approach include reliance on both healthcare providers and patients speaking truthfully as well as remembering accurately. In addition, patients' experiences may be variable and factors such as changes in insurance formularies or a healthcare provider having received additional training may be unknown to the patient.

Lastly, healthcare providers who continue to have the same prescribing practices before and after the REMS are not included by the RPC

5.8.1. Reviewer Comments

1. The Agency has numerous concerns with and questions about the RPC's proposal. However, the Agency is continuing internal deliberations as to how to best assess patient access, and once internal agreement is reached, comments will be conveyed to the RPC.

5.9. APPLICANT'S OVERALL CONCLUSION OF WHETHER THE REMS IS MEETING THE GOALS

The RPC included the following conclusion regarding whether the ER/LA opioid analgesic REMS is meeting its goal:

"…Based on data from CE Providers, the RPC is aware that 90,549 HCPs have completed an accredited REMS-compliant activity but are not counted in this total number based on the inclusion criteria defined in the REMS (i.e., registered with DEA to prescribe Schedule II and/or III controlled substances and having prescribed at least one ER/LA opioid analgesic in the last year or being unwilling to specify they had done so). While not included in the metric, these 90,549 HCPs play a critical role in the safe use of ER/LA opioid analgesics (assessment and care of patients including important patient education) and can benefit from an accredited REMS-compliant CE activity. In addition, there are multiple instances when HCPs might actually prescribe an ER/LA opioid analgesic without themselves having an individual DEA registration (e.g., residents who utilize an institutional DEA number, PAs/NPs who may prescribe under the DEA number of a collaborating physician).

...The RPC is aware of many other CE activities that are educating ER/LA opioid analgesic prescribers—as well as other HCPs involved in the care of patients who are taking ER/LA opioid analgesics—about the safe use of opioids. The RPC is actively engaged in working to increase REMS awareness among CE Providers who develop these non-RPC-supported activities to encourage them to be REMS-compliant.

…The RPC continues to explore ways to increase prescriber awareness and participation unaccredited REMS-compliant CE activities, including improvements to the REMS website and the REMS awareness campaign.

…Results from the Prescriber Follow-up Survey showed that prescribers understood the assessment, management, and counseling requirements for patients who are being considered for treatment or being treated with ER/LA opioid analgesics, as indicated by at least 80% of prescribers correctly answering 80% or more questions regarding these topics…Prescribers were less knowledgeable about

initiation, modification, and discontinuation of ER/LA opioid analgesic therapy, and about product-specific information about ER/LA opioid analgesics.

... Results from the LTE Survey showed that prescribers that completed a CE course within the past 6 to 12 months demonstrated strong understanding of the monitoring and counseling requirements for patients who are being treated with ER/LA opioid analgesics…Prescribers were less knowledgeable about assessment of patients and initiation of treatment and general information about risks associated with ER/LA opioid analgesic products…

… Patient Survey results indicate that the REMS requirement to make available a Medication Guide continues to be achieved… A small proportion of respondents reported that they received the PCD. This may be due to the fact that prescribers did not specifically refer to the document as the "Patient Counseling Document."

… Surveillance findings cannot be causally attributed to the REMS due to other interventions aimed at decreasing opioid abuse and misuse and their consequences during the same time period, such as implementation of PDMPs, increased law enforcement, institution of guidelines by states or insurance companies, and introduction of abuse deterrent formulations.

… Overall, the REMS assessments indicated high levels of prescriber knowledge and patient knowledge of ER/LA opioid analgesic risks. Reductions in OOP events, as well as improvements in self- reported and objectively measured prescribing behaviors were also observed. Since many interventions targeting opioid analgesics occurred during the time period of the REMS, many of the aforementioned desired effects cannot be attributed solely to the efforts and impacts of the ER/LA Opioid Analgesics REMS Program. However, based on the observed level of understanding among prescribers and patients as well as the proposals for how to assess the REMS included in the requested concept papers, the RPC recommends removal of the existing surveys (Prescriber Follow-up Survey, Prescriber LTE Survey and Patient Survey) from the REMS assessment plan, as these activities will be addressed in the proposed concept papers. The RPC looks forward to a dialogue with FDA over the next months to discuss changes to the REMS, REMS assessment plan and timeline for implementation of a new methodology for REMS assessments."

6 DISCUSSION

6.1. SUMMARY OF ASSESSMENT FINDINGS

The Division of Epidemiology II's (DEPI) review of the submitted surveillance data suggests that the incidence of Opioid Overdose and Poisoning (OOP) ED visits and hospitalizations may have decreased, especially in prevalent ER/LA opioid analgesic users; however, these observed decreases are likely not attributable only to the REMS. The state medical examiner data submitted by the REMS Program

Companies (RPC) indicate that opioid overdose death trends vary considerably across states, and indicate that a larger number of states' data need to be examined so as to be able to monitor overdose death trends. While surveillance data can be valuable for understanding national trends in prescribing patterns and adverse outcomes of interest, these data do not inform the question of whether this REMS is having the desired impact on prescribing or abuse-related outcomes. Concept Paper #1 ("*Evaluation of the Impact of the REMS on Prescribing Practices and Patient Outcomes and Prescriber and Patient Knowledge*"**)** that was submitted in the 48-month Assessment Report has promise for providing valuable information about the impact of the REMS CE training on prescriber behavior and patient outcomes. RPC is now asked to submit a full protocol and Statistical Analysis Plan (SAP) for this study. In addition, the RPC is also asked to explore new data sources for assessing trends in the incidence of prescription opioid overdose-related ED visits and hospitalizations. Additional suggestions for enhancement of the RPC's surveillance data submissions are also provided, including limited analyses of Poison Center Data, Medical Examiner data from additional states, as well as additional years of Monitoring the Future data.

The percentage of opioid non-tolerant patients prescribed ER/LAs in the post-REMS period ranged from 26.0% to 79.6%. However, utilizing only the primary definition for opioid tolerance (as described in the study by Willy[9]) likely results in underestimation for patients considered "opioid tolerant" and thus the RPC is asked to modify its criteria for determining opioid tolerance.

The RPC's early refill methodology is inadequate to address the question posed by the ER/LA opioid REMS. Also, further insight into the reasons for switching linked to prescribing is needed for more meaningful results regarding the switch data.

As of February 29, 2016, there were 66,881 ER/LA prescribers that have completed accredited REMS-compliant CE activities, representing 42% of the goal total (160,000). Thus while the goal of 160,000 prescriber completers as not been met, over 326,000 healthcare professionals began the training and nearly 160,000 completed the training but 57.5% did not meet the specific criteria for a prescriber completer.

The RPC points out many factors that likely interfere with the attainment of higher numbers of prescriber completers such as: the criteria for a "prescriber completer; the number of competing opioid educational programs; the length of the educational programs; and the lack of awareness of the REMS and accompanying REMS-compliant CE.

[9] Willy et al. *Pain Medicine* 2014; 15:1558-1568

Results from the Follow-up Prescriber Survey show that overall, the comparison of prescribers that are recruited from IMS data versus prescribers that are recruited from CE providers does not accomplish the original goal of the survey; to compare prescribers that completed training to prescribers that did not complete training since IMS respondents also self-reported completion of REMS compliant training. In addition, since the information is self-reported there is no way to know for certain if the completed CE activity was REMS compliant.
This survey has a number of limitations including the use of a convenience sample, incomplete data collection of prescriber characteristics, and notable differences between samples which may affect the comparability and generalizability of the survey results to the overall populations of healthcare providers who prescribe ER/LA opioid analgesics.

The RPC proposed the elimination of this survey stating that the activities will be addressed in the proposed concept papers. We agree with the proposal and we recommend the elimination of this survey for future assessments.

Results from the Long-Term Evaluation Prescriber survey showed that surveyed 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, patient non-compliance, and patients continuing to identify new drug-seeking behaviors that were not addressed in the training activity. Overall, this survey has a number of limitations including the use of a convenience sample and incomplete data collection of prescriber characteristics which may affect the generalizability of the survey results to the overall populations of prescribers who have taken REMS-compliant CE training.

Although the survey respondents were not representative of the population prescribed ER/LA opioid analgesics, those surveyed had a high understanding of the key risk messages.. 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 (92%) but only 33% 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 previous assessments. As in the previous surveys, the survey respondents were not representative of the drug use population for race, income, education level, and payer type since the HIRD sample is not representative. Therefore, the standardization which was based on all ER/LA opioid analgesic users in HIRD is not appropriate. The RPC utilized different databases to recruit Medicare patients and Medicaid patients but the sample size was small. In addition, caregivers were allowed to participate but only 13 completed the survey. Future surveys should use another data source in order to recruit a representative sample of patients who are prescribed ER/LA opioid analgesics.

7 CONCLUSIONS

7.1. COMPLETENESS OF REPORT

This assessment report is technically complete and addresses all issues outlined in the approved REMS assessment plan.

7.2. ACHIEVEMENT OF THE GOALS OF THE REMS

The goal of this REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to these pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

As communicated following the review of the 36 month REMS assessment, it is again not possible to determine whether or not the REMS is meeting its goal since the surveillance data do not inform the question of whether this REMS is having the desired impact on prescribing or abuse-related outcomes.

7.3. NEED FOR REMS MODIFICATION NOTIFICATION

The FDA held a meeting with the RPC on January 25, 2017 to inform them of the Agency's intent to add the Immediate-release opioid analgesics to the ER/LA opioid analgesic REMS.

7.4. REVIEW TEAM CONCLUSION

DRISK, DPV, DEPI, OB, DAAAP, and the Office of Compliance have met numerous times to discuss the assessment for the ER/LA REMS. In addition, during standing meetings of the ER/LA opioid analgesics REMS Implementation team, discussion of various assessment report issues occurred.

The aim of a DRISK REMS assessment review is to determine (1) whether the report is complete, and (2) whether the REMS is meeting the goal(s).

Overall, we have concluded that it is not possible to determine whether the REMS is meeting its goal.

8. RECOMMENDATIONS

The RPC was sent a REMS Assessment Acknowledgment letter on July 14, 2017 that indicated that the assessment report was complete. The letter also stated that that stated that "*Given that your 60-month REMS assessment has already been submitted, the Agency will hold its comments on the 48-month REMS assessment for now and convey them along with our comments on the 60-month REMS Assessment*"

Prior to the 60-month assessment report's arrival, FDA had planned to send the RPC the following comments:

1. Because of the many secular trends and other mitigation efforts around prescription opioid abuse and overdose, the epidemiologic surveillance data do not inform the question of whether this REMS is having the desired impact on prescribing or abuse-related outcomes. For this reason, we recommended a new set of studies more appropriately designed to evaluate the impact of REMS training on prescriber knowledge and behavior and patient outcomes, as well as a novel approach to assessing patient access (see our REMS Assessment Acknowledgement Letter of July 7, 2016). Two concept papers were submitted by you in response to this recommendation.

   Despite their limitations, epidemiologic surveillance data can be valuable for understanding national trends in prescribing patterns and adverse outcomes of interest related to prescription opioids, and such information helps inform regulatory decision-making related to this REMS. Because of the inter-related nature of ER/LA and IR opioid use and the anticipated expansion of the REMS to include IR opioids, we are increasingly interested in monitoring national trends in prescribing and adverse outcomes related to *all* prescription opioid analgesics, not just ER/LA opioid analgesics.

   a. <u>Surveillance of prescription opioid overdose rates using electronic healthcare data:</u>

      i. Understanding trends in prescription opioid overdose continues to be of interest to the Agency; however, the evolving commercial insurance and Medicaid coverage landscape presents challenges in evaluation of trends in opioid overdose using insurance claims data. We are not requesting further analyses to assess changes in OOP incidence using the HIRD and limited Medicaid databases. Instead, explore new data sources for

assessing trends in the incidence of prescription opioid overdose-related ED visits and hospitalizations. These should include data from a diverse population, including all payer sources, from a nationally-representative sample or one that includes a large and stable geographic coverage area. Some examples might include the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (HCUP) databases, such as the Nationwide Emergency Department Sample (NEDS), State Emergency Department Databases (SEDD), National (Nationwide) Inpatient Sample (NIS), and State Inpatient Databases (SID).

ii. Analyses should use validated code algorithms for unintentional/intentional prescription opioid overdose, heroin overdose, etc. (i.e., those being developed in the ER/LA opioid analgesic PMRs).

iii. Provide estimates of precision and visual depiction of trends over time, but formal pre-post comparisons are not necessary for surveillance purposes.

iv. Provide a description of the data source and methods used for the above analyses.

b. <u>Surveillance of prescription opioid overdose deaths using of medical examiner data:</u>

i. Provide updated analyses of medical examiner data from these three and as many additional states as possible (we request at least 3 additional states, ideally from different geographic regions).

ii. Since formulation (IR vs. ER) cannot be reliably determined from medical examiner data, rather than grouping cases by "opioids with available ER/LA formulations," provide quarterly trends for in population overdose death rates involving prescription opioids overall, each prescription opioid molecule (i.e., hydrocodone, oxycodone, methadone, fentanyl, morphine, oxymorphone, hydromorphone, meperidine, codeine, buprenorphine, tramadol), and heroin.

iii. Utilization-adjusted analyses should use "dosing units dispensed" as the denominator.

iv. For each opioid molecule, indicate the proportion of death cases mentioning this opioid molecule that were single drug versus poly-drug overdoses.

v. Formal comparison of means analyses (across time periods or comparing opioid molecules) are not necessary.

vi. Inclusion of a separate benzodiazepine comparator group is not necessary. We would, however, be interested in trends in the proportion of fatal prescription opioid overdoses that involve a benzodiazepine.

vii. Provide a description of the data source and methods used for the above analyses.

c. Surveillance of non-medical use of prescription opioids using nationally representative surveys:
   i. We find Monitoring the Future (MTF) to be a valuable source of surveillance of non-medical use of prescription opioid analgesics in adolescents.

   ii. Continue to update the MTF analyses with the most recent available data and provide trends going back to 2006. If this is not feasible or scientifically appropriate, provide rationale.

d. Additional sources of epidemiologic surveillance data: Poison Center data
   i. Despite their limitations, we believe that national poison center call data may contribute timely information to a surveillance program intended to understand trends in adverse outcomes related to use of prescription opioid analgesics. We therefore ask that you provide analyses of national (or near-national) poison center call data as follows, for the study period January 1, 2009 – December 31, 2016:
      A. For the opioid categories listed below, provide tabular and graphic display of population-adjusted and dosing-unit-adjusted quarterly rates, with modeled trend lines and 95% confidence intervals for the following call types: intentional exposures (all), intentional abuse, intentional misuse, unintentional general exposures in children aged 0-5 years, major medical outcome/hospitalization, and death.
         a) All opioid analgesics combined
         b) ER/LA opioid analgesics
         c) IR opioid analgesics
         d) Individual opioid categories:
            1) IR hydrocodone combination analgesics
            2) IR oxycodone single-entity
            3) IR oxycodone combination analgesics
            4) Codeine combination analgesics

5) ER oxycodone
6) ER hydrocodone
7) IR oxymorphone
8) ER oxymorphone
9) IR hydromorphone
10) ER hydromorphone
11) IR morphine
12) ER morphine
13) Fentanyl transdermal (TDS)
14) Fentanyl transmucosal (TIRFs)
15) Tramadol
16) Meperidine
17) Buprenorphine transdermal analgesic products
18) Methadone tablets
19) Heroin

B. Note: it is not necessary to conduct formal comparisons of mean rates or trends across time periods or product groups, or to include a non-opioid comparator group.

C. For the opioid categories listed below, provide tabular and graphic display of population-adjusted and dosing-unit-adjusted quarterly intentional abuse call rates, with modeled trend lines and 95% confidence intervals, stratified by the four U.S. Census regions:
   a) All opioid analgesics combined
   b) ER/LA opioid analgesics
   c) IR opioid analgesics

D. For each of the opioid categories listed below, for each year of the study period, provide the counts and proportion of intentional exposures calls and intentional abuse calls that also involved a benzodiazepine:
   a) All opioid analgesics combined
   b) ER/LA opioid analgesics
   c) IR opioid analgesics

E. For each of the opioid categories listed below, for each year of the study period, provide the counts and proportion of all intentional abuse calls and unintentional exposure calls that came from health care facilities.
   a) All opioid analgesics combined
   b) ER/LA opioid analgesics
   c) IR opioid analgesics

F. For each year of the study period, provide
   a) the total population covered by the RADARS poison center program, and clarify how the coverage area is determined

b) the total number of intentional and unintentional (together and separately) human drug exposure calls within this coverage area, by age group.
c) the total number of intentional and unintentional (together and separately) human opioid analgesic exposure calls within this coverage area, by age group.

G. Provide a description of the data source and methods used for the above analyses.

H. Provide a documented dataset of outcome counts in ZIP code encatchment areas and at the quarterly level so that we can reproduce your main adjusted analyses. Thus, this dataset would include the following information: ZIP code identifier, quarter, year, US census region, outcome type (intentional abuse, intentional misuse, unintentional general exposure, major medical outcome/hospitalization, and death), drug type (drug name and formulation), age group, number of cases, ZIP code population count (used in the adjustment), dosage units dispensed count (used in the adjustment). The data is requested to be provided in a SAS xport format.

e. <u>Regarding drug utilization data for prescription opioids using electronic healthcare claims data or prescription data:</u>
   i. In addition to the 7-day look back period, we recommend utilizing a 30-day look-back period as noted in the paper by Willy et al. *Pain Medicine* 2014; 15:1558-1568 to determine opioid tolerance.
   ii. Do not submit switch analyses data reported through current methodology for future assessments. We recommend obtaining other data sources to provide insight into the reason for switching linked to prescribing for more meaningful results (i.e., REMS too burdensome, prescribers not REMS trained, clinical reason (i.e., ER/LA not needed), etc.)
   iii. Do not submit early refill data reported through current methodology for future assessments.
   iv. As mentioned in the previous assessment recommendation, 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.
   v. The retail and long term care utilization data provided by the RPC are helpful. However, the Agency suggests exploring other data sources that will encompass utilization of ERLA opioid analgesic products not only in the retail and long term care settings but also in other settings of care such as pain clinics, specialty pharmacies, inpatient hospital, etc. to provide a more

comprehensive utilization analyses of ERLA opioid analgesic products in the U.S. market.

2. Regarding Concept Paper #1 ("*Evaluation of the Impact of the REMS on Prescribing Practices and Patient Outcomes and Prescriber and Patient Knowledge"***)** that you submitted with your 48-month Assessment Report, we find the proposed study concept to have promise for providing valuable information about the impact of the REMS CE training on prescriber behavior and patient outcomes. We request that the RPC submit a full protocol and Statistical Analysis Plan (SAP) for a study based on Concept Paper #1 to assess the impact of the ER/LA opioid REMS CE on prescriber and patient knowledge, healthcare provider prescribing behavior, and patient outcomes. Below we offer some comments for your consideration. For additional guidance, we refer you to FDA's "Guidance for Industry: Best practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data."[10]

   As you are aware, we intend to add the immediate-release (IR) opioid analgesic products to the ER/LA opioid analgesic REMS, and expand the FDA Blueprint for Prescriber Education for ER/LA Opioid Analgesics. Regardless of these actions, we continue to see value in this study for the current program, and believe that valuable information may be gained that would inform our assessments of future REMS programs. We encourage you to begin to consider how the inclusion of IR products and Blueprint modifications could be incorporated into the current study design and how the design might need to change as a result of these modifications. In preparing the protocol and SAP, address the following questions and recommendations:

   a. The endpoints in this study should align, as closely as possible, with the goals of the REMS and with specific components of the REMS CE training. One of the goals of the REMS is to reduce adverse outcomes associated with inappropriate prescribing. Explain how the metrics you propose will measure appropriateness of prescribing, and consider other relevant practices addressed in REMS CE that could be operationalized to assess the impact of the REMS CE training on prescriber behavior, for example:
      i. Utilization of Prescription Drug Monitoring Programs
      ii. Use of urine drug screens

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10 http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm243537.pdf

iii. Use of opioid risk screening tools
iv. Documented assessment of patient functional status and periodic reassessment of treatment
v. Use of provider-patient agreements
vi. Patient selection for ER/LA opioid analgesic therapy
    A. Use of ER/LA opioid analgesics for inappropriate diagnoses (e.g., migraines, acute post-operative or dental pain)
    B. Referral of high-risk patients to pain management specialist
vii. Referral for behavioral health or substance abuse treatment evaluation when aberrant or "drug seeking" behavior is documented
viii. Lowering of both opioid analgesic and benzodiazepine dose when a drug in one class is initiated in a patient already on a drug in the other class
ix. Avoidance of initiation of a benzodiazepine in a patient already on an opioid analgesic
x. Use of appropriate initial dose when converting IR/short acting (SA) to ER/LA opioid analgesic
xi. Ensuring opioid tolerance criteria are met for patients prescribed specific ER/LA opioid analgesic products at doses that require opioid tolerance
xii. Others?

Consider whether it would be feasible to develop a composite measure, or index, for appropriate prescribing from a combination of metrics such as the examples above and the ones you propose in your concept paper.

Also consider whether there are other patient outcomes that could be operationalized to further evaluate the impact of the REMS training, for example:

i. Functional status/disability
ii. ED visits (if linkages are possible)
    A. Overdose
    B. Pain medication seeking
iii. Overdose death (if linkages are possible)
iv. Others?

b. Explain whether the Amazing Charts EHR is structured to allow direct linkage of a prescription to a diagnosis or diagnoses for which it is prescribed (i.e., the indication for treatment).

c. Clarify whether you will indeed have the capability to link the EMR data to administrative claims data, national death index, or other data

sources (e.g., state medical examiner data, ED/hospital system EMR data) that would allow more complete measurement of overdose and death outcomes, or to prescription dispensing data (e.g., IMS) that would allow more complete assessment of patients' prescription history (e.g., for determining opioid tolerance, or concomitant benzodiazepine use) and providers' prescribing history.

d. Clearly state the primary and secondary hypotheses.

e. Define the study time periods and provide a study timeline.

f. Clarify how you will construct the analytic cohort of prescribers. Can a prescriber serve as both a non-participant healthcare provider earlier in the study period and then a trained healthcare provider later in the study period? Also specify:
   i. Inclusion and exclusion criteria.
   ii. Look back period to determine baseline characteristics/potential confounding variables.

g. Provide the following information:
   i. The percentage of providers/practices subscribing to the Amazing Charts EHR system who opt to contribute patient-level data to the data warehouse.
   ii. Provide the geographic distribution by state and specialty mix of prescribers contributing to the data warehouse.
   iii. The total number of providers who contributed to the data warehouse throughout the study period, as well as the number in the following subgroups if possible:
      A. Completed Pri-Med REMS training (by a certain date?) AND
         a) prescribed at least one ER/LA opioid within the study period
         b) prescribed at least one IR opioid within the study period
      B. Have not completed a Pri-Med REMS training (by a certain date?) AND
         a) prescribed at least one ER/LA opioid within the study period
         b) prescribed at least one IR opioid within the study period
      C. Provide the distribution of insurance coverage (e.g., commercial insurance, Medicaid, Medicare, uninsured/self-pay, other) for patients included in the database.
   iv. Explain how a provider's patient panel will be defined.

A. Patients will have more than one provider or may change providers during the study period. How will this be handled?
B. Explain how patients' continuation in the database will be assessed, i.e. whether they are "active" patients throughout the study period.
C. Will terminal cancer/palliative care patients be excluded or analyzed as a separate group?

h. Provide the total number of patients in the following groups
   i. Received at least one opioid prescription from a Pri-Med trained provider during the study period
   ii. Prescribed more than 30 days of opioids (separately for ER/LA, IR/SA, both) from a Pri-Med trained provider during the study period

i. Provide power/sample size calculations for primary analyses. Propose methods for estimating and accounting for the anticipated misclassification of prescribers in the non-participant group who have actually completed a non-Pri-Med REMS-compliant CE training.

j. Regarding the proposed propensity score matching:
   i. The index date of the non-participant prescribers will be assigned (to be the same as the matched CE-trained participant) after propensity score (PS) matching. This procedure would work if your design only considers time-invariant confounding variables to fit the PS model. However, it may be more appropriate to assign the index date first before fitting a PS model if you have many time-varying confounders. Please clarify when the confounders are captured and whether you believe they are time-invariant.
   ii. Provide full list of confounding variables that will be included in the PS model.
   iii. Provide details on PS model, PS matching algorithm, and software used to do the matching.
   iv. Provide comparisons of providers in terms of demographic and clinical characteristics in Pri-Med and all REMS-compliant CE provider and accreditors. PS matching may not fully control for confounding if there are large imbalances in baseline characteristics at index date.
   v. Diagnostics for PS methods (distribution of PS scores).

k. In a Statistical Analysis Plan, expand on the proposed Interrupted Time Series (ITS) methods.

i. Our understanding is that this model would not only evaluate whether outcome rates have changed before and after training in each group, it may also investigate whether the rates changed over time in the pre-training and post-training periods.
ii. Provide the statistical model you are considering.
iii. Assess which comparisons you can and are powered to make. As described in your concept paper, an index date for the trained healthcare provider will be the date that healthcare provider completed Pri-Med's REMS-compliant CE training. Thus, each matched pair might have different number of data points before and after the CE training. Address if there will be a sufficient number of data points before and after the CE training and how differential follow up and look back will be addressed in these analyses.
iv. Consider conducting difference-in-differences type means analysis as well as ITS analyses when comparing changes across time periods in prescribing behavior and patient outcomes for trained versus untrained prescribers.

l. Assess potential changes in the risk profile of the patient population across the study period, due to implementation of the Affordable Care Act or other factors.

m. Regarding the survey component of this study:
    i. Provide the following information, at a minimum:
        A. Describe the sampling strategy
        B. Address the comparability of surveyed groups to each other.
        C. Address the generalizability of the sample to the target population (e.g., prescribers of ER/LA opioids, patients who filled ER/LA opioid prescription).
        D. Propose methods to standardize the results of the survey samples to the target population if the generalizability is violated (if applicable)
        E. Provide more detail on how you will link the survey responses with the EHR data to assess the extent to which high knowledge scores by survey correlate with observed changes in prescribing (page 4/7 on the concept paper)
    ii. Consider alternate study designs (e.g., self-controlled design, with pre-post surveys)

3. Regarding the Prescriber and Patient Surveys:
    i. For the Follow-up Prescriber Survey:

a. Overall, the comparison of prescriber that are recruited from IMS data versus prescribers that are recruited from CE providers does not accomplish the original goal of the survey; to compare prescribers that completed training to prescribers that did not complete training since IMS respondents also self-reported completion of REMS compliant training. In addition, since the information is self-reported there is no way to know for certain if the completed CE activity was REMS compliant.

   The RPC proposed the elimination of this survey stating that the activities will be addressed in the proposed concept papers. We agree with the proposal and we recommend the elimination of this survey for future assessments.

ii. For the Long-Term Evaluation Survey:

a. The data of the prescriber characteristics for the target population is very limited and incomplete. From RPC response to FDA on March 11 2016, sponsors reported that only 6% of eligible prescribers completed the survey. Furthermore, there was no consistency in the (few) variables collected by different CE providers. Some CE providers did not provide any data to sponsors. Sponsors only used two variables (type of physician and degree) to standardize the data. Thus, we have concerns about the use of incomplete data for the standardization. We recommend the Sponsor conducts uniform data collection on the prescriber characteristic across all CE providers.

b. In future assessments, the RPC should provide information including: how many respondents came from which CE providers? Were they all represented? Did more respondents come from a particular grantee? In addition, of the respondents, what type of activity did they participate in (i.e. web-based, live, etc).

c. This survey was not completed in the 60-month REMS assessment. We would like the RPC to conduct this survey with the 72-month assessment.

iii. For the Patient Survey:

a. For the patient survey, survey results were similar to the survey results from previous assessments. As in the previous surveys, the survey respondents were not representative of the drug use population for race,

income, education level, and payer type since the HIRD sample is not representative. Therefore, the standardization which was based on all ER/LA opioid analgesic users in HIRD is not appropriate. The RPC utilized different databases to recruit Medicare patients and Medicaid patients but the sample size was small. In addition, caregivers were allowed to participate but only 13 completed the survey. Future surveys should use another data source in order to recruit a representative sample of patients who are prescribed ER/LA opioid analgesics.

4. In subsequent assessment reports, explain the difference between the "unique registered prescribers" (73,847 in this report) , and "individual registered prescribers" (73,172 in this report) in your calculations for the distribution of DDRP Letter 3. In addition, in subsequent reports, explain why the number of hospitals targeted (877 in this report) differs from the number of hospitals for which distribution of DDRP Letter 3 was attempted (856 in this report).

5. Regarding your Access Concept Paper, the Agency has a number of concerns and questions. However, the Agency is continuing internal deliberations as to how to best assess patient access, and once internal agreement is reached, comments will be conveyed to the RPC.

6. Your presentation of prescribing professions includes pharmacists and optometrists. Clarify under what circumstances these two professions would prescribe ER/LAs.

7. In your subsequent assessment reports, also provide the numbers of prescribers who completed REMS-compliant CE by the type of format (internet-based, live training, or performance improvement).

9. COMMENTS FOR THE RPC

The RPC was sent a REMS Assessment Acknowledgment letter on July 14, 2017 that indicated that the assessment report was complete. The letter also stated that thatstated that "*Given that your 60-month REMS assessment has already been submitted, the Agency will hold its comments on the 48-month REMS assessment for now and convey them along with our comments on the 60-month REMS Assessment*"

10. APPENDIX

10.1. ASSESSMENT PLAN

1. Documentation of the dissemination of Prescriber Letter 3:
    a. number of prescriber letters electronically sent, received, undeliverable, and opened, and
    b. number of prescriber letters mailed and undeliverable.

2. Prescriber Training: Documentation of the number of prescribers of ER/LA opioid analgesics 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:
    a. 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;
    b. Within three years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of active prescribers) are to have been trained;
    c. Within four years from the time the first REMS-compliant training becomes available, 192,000 prescribers (based on 60% of active prescribers) are to have been trained.

3. Independent Audit: 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.

4. 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 opioids 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.

5. 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. This evaluation may include, for example, surveys of patients.

6. Surveillance Results: Results of surveillance and monitoring for misuse, abuse, overdose, addiction, and death. Surveillance needs to include information on changes in abuse, misuse, overdose, addiction, and death for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency departments, addiction treatment centers, poison control call centers). The information should be drug-specific whenever possible.

7. Drug Utilization Patterns: An evaluation of drug utilization patterns, including: an evaluation of prescribing behaviors of the prescribers of ER/LA opioid analgesics, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills.

8. Patient Access: An evaluation of changes in patient access to ER/LA opioid analgesics.

9. Methodologies: A description of the data sources and the methodologies used to conduct all of the above described analyses.

10. Goals: The requirements for assessments of an approved REMS under section 505-1(g)(3) of the FDCA include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

Definitions:
For purposes of these REMS assessments, the following definitions apply:
REMS-compliant training: Training will be considered "REMS-compliant training" if 1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the FDA "blueprint", 3) it includes a post-course knowledge assessment of all of the sections of the "FDA blueprint", and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met.
FDA Blueprint: A document entitled, "Blueprint for Prescriber Continuing Education Programs Extended-Release and Long-Acting Opioids," approved as part

of this REMS, that contains core messages to be conveyed to prescribers in the training about the risks and appropriate prescribing practices for the safe use of ER/LA opioids.

10.2. 36-MONTH REMS ASSESSMENT ACKNOWLEDGEMENT LETTER (JULY 7, 2016)

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, 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-opioidtolerant 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

10.3. RPC-SUPPORTED REMS-COMPLIANT CE ACTIVITIES DURING THE REPORTING PERIOD

Grantee[1]	Program Start Date[2]	Program Formats	Number of Activities
Utah Medical Association Foundation	3/1/13	Internet-based	1
pmiCME	6/7/13	Internet-based	4
		Live training	12
CO*RE (Collaborative for REMS Education)	6/22/13	Internet-based	23
		Live training	141
Association for Hospital Medical Education	12/31/13	Internet-based	2
University of Washington School of Medicine	1/1/14	Internet-based	3
		Live training	1
Boston University School of Medicine	2/4/14	Internet-based	3
		Live training	43
University of North Texas Health Science Center	5/11/14	Internet-based	9
		Live training	1
Albert Einstein College of Medicine	5/12/14	Internet-based	1
Temple University School of Medicine	7/1/14	Internet-based	1
		Performance improvement	1
Florida Medical Association	10/25/14	Internet-based	1
		Live training	3
Dannemiller, Inc.	1/19/15	Live training	2
		Internet-based	5
Postgraduate Institute for Medicine	3/7/15	Internet-based	10[3]
		Live training	6
University of Nebraska Medical Center	4/1/15	Internet-based	1
		Live training	2
Johns Hopkins University, School of Medicine	11/30/15	Internet-based	1[3]
Global Education Group, Ltd.	2/21/16	Live training	1
TOTAL			278

[1]The table is organized by start date of the activities; if there were multiple activities, the start date reflects date of first activity.
[2]Program start date may be prior to this current reporting period because: (1) activities were not previously provided to the Data Aggregation Vendor, (2) activities were previously provided with zero prescriber completers, or (3) additional completer information for the activity was provided during this reporting period.
[3]Activity included availability of a mobile application.

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/s/

IGOR CERNY
08/10/2017

CYNTHIA L LACIVITA
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