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 sixth (60 month, May 7, 2016 through May 5, 2017) Risk Evaluation and Mitigation Strategy (REMS) Consolidated Assessment Report for Extended-Release and Long-Acting (ER/LA) opioid analgesic products

Date: **February 14, 2018**

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Therapeutic Class:	Extended-Release and Long-Acting opioid analgesic (ER/LA) products
Submission Date:	**July 7, 2017**
Drug Master File (DMF) #:	**031551**

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
fentanyl TD	ANDA 77775	Noven	ANDA withdrawn		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		

Drug Name	Application Type/ Number	Applicant/ Sponsor	SDN	eCTD sequence #	Submission Date
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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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
DB7	Division of Biometrics 7
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 database
LTE	Long-Term Evaluation

MG	Medication Guide
MTF	Monitoring the Future
NIDA	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

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1 EXECUTIVE SUMMARY

This integrated review, written by the Division of Risk Management (DRISK) and the Division of Epidemiology II (DEPI), evaluates the sixty (60) month risk evaluation and mitigation strategy (REMS) Assessment Report for the extended-release/long-acting (ER/LA) opioid analgesics REMS and is the sixth report since approval of the REMS on July 9, 2012. It includes information on all 8 elements as delineated in the ER/LA opioid analgesics REMS Assessment Plan contained in the July 9, 2012 approval letter. This assessment report,submitted on July 7, 2017, 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. A total of 208,040 healthcare professionals and 88,316 prescribers have completed REMS Program Companies (RPC)-funded training.

- After review of the 60-month REMS assessment report, we find the report to be complete, however, we are unable to determine whether the REMS is meeting its goal due to the inability for the submitted surveillance data to inform whether the REMS has reduced addiction, unintentional overdose, and death. The RPC submitted a concept paper for a separate study to evaluate the effect of completing REMs-compliant training on prescriber knowledge, prescribing practices, and patient outcomes. FDA provided comments on the concept paper and requested a revised concept paper to be submitted with the 72-month report. This study may allow a meaningful evaluation of changes in the prescribing practices of prescribers who take REMS-compliant training.

The following is a summary of the findings from this assessment report:

- As of February 29, 2017, there have been 430,859 Participants in RPC –funded CE activities, and 208,040 individuals that completed an activity. Of the completers, there were 88,316 ER/LA opioid analgesic prescribers who completed accredited REMS-compliant CE activities ("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*."). This represents 46% of the goal of 192,000.
- Since 2012, the RPC has issued 7 Requests for Applications (RFAs) and awarded funding to support 919 **REMS-compliant CE** programs through 37 grants to accredited CE Providers and the CE Provider's 100+ educational partners. Of these 919 REMS-compliant CE activities, 174 were available during this reporting period. A total of 128 activities were presented as live training, 45 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 Division of Epidemiology II (DEPI-II) reviewed the submitted HealthCore Integrated Database (HIRD) and limited Medicaid **surveillance data**, Medical examiner data for three states, CDC WONDER data (from National Vital Statistics System Multiple Cause-of-Death Public Use Record files), and the Monitoring the Future (MTF) survey. In summary, the data on fatal and non-fatal opioid overdoses showed varying trends in different data sources and populations and did not allow for a robust assessment of national trends in opioid overdose and death. For the 72-month assessment, FDA is not requesting data from HIRD/Medicaid or state medical examiners, but rather is requesting nationally representative data from emergency department and hospital discharges, and the addition of national data from death certificate literal text (using the newly available Drug-Involved Mortality linked database) to better assess national trends in prescription opioid overdose and death. The MTF survey continues to show a downward trend in the use of narcotics other than heroin among adolescents nationally. FDA recommends that the RPC add another national survey to supplement the MTF to capture abuse trends in other age groups. FDA also recommends that the RPC submit limited analyses of poison center data to enhance the surveillance of misuse- and abuse-related adverse outcomes involving opioid analgesics. While epidemiologic surveillance data are valuable for understanding national trends in misuse and abuse and related adverse outcomes of interest, these data do not inform whether this REMS is having the desired impact on these outcomes. Therefore, FDA is not requesting formal comparison of means or trends across pre- and post-REMS periods in the future, but rather simple analyses depicting annual or quarterly trends over time. The main results from the analysis of submitted data are summarized below

- Opioid overdose or poisoning in a commercially-insured population
    - These data suggest that among commercially-insured ER/LA opioid analgesic users, the incidence of prescription opioid overdose or poisoning increased from the pre-REMS period to the active REMS period in the HealthCore Integrated Research Database (HIRD). This result differed from the 48 month assessment where the incidence of prescription opioid overdose or poisoning was slightly lower in the active REMS period than the pre-REMS period for all ER/LA opioid analgesic users.
    - The HIRD data also suggest that prescription opioid overdose death decreased numerically among those prescribed ER/LA opioids from the pre-REMS period to the active REMS period, but this decrease was not statistically significant.
- Opioid overdose or poisoning in a Medicaid population
    - In the Medicaid ER/LA opioid analgesic user population, the incidence of prescription opioid overdose or poisoning was lower in the active

REMS period than the pre-REMS period across all analyses. These results were consistent with what was reported at the 48-month assessment for the Medicaid population.
    - Prescription opioid overdose deaths were not measured in the Medicaid data as the dataset could not be linked to the National Death Index (NDI).
- State medical examiner overdose mortality data
    - The state medical examiner data submitted from three states indicate that the mean population adjusted rate of overdose deaths due to ER/LA opioids decreased across the study period for all three states; although the trend in the active REMS period appears to be increasing. Different ongoing interventions in these states make it difficult to attribute similar trends in mean overdose death rates across the different states to a national-level intervention such as REMS. Therefore, pre-post analysis of prescription opioid overdose deaths from state medical examiner data is difficult to interpret. At this time, FDA is not requesting further analyses of state medical examiner data.
- CDC WONDER national overdose mortality data
    - The CDC WONDER mortality database is a useful resource and shows that age-adjusted prescription opioid-analgesic-related overdose death rate is increasing. However, these data are limited in that they do not allow for surveillance of trends in overdose deaths due to specific opioids. To overcome this limitation, FDA recommends that the RPC explore the new Drug Involved Mortality (DIM) database now available for public use.
- Monitoring the Future (MTF) survey data on nonmedical use of opioids in adolescents
    - Monitoring the future (MTF) data continue to show a downward trend in the use of narcotics other than heroin and the perception of availability of narcotics across all grade levels surveyed from 2010 to 2016. Although MTF is useful for surveillance of non-medical use of opioid analgesics in adolescents, it is not sufficient for understanding the national trends of use, misuse, and abuse of opioid analgesics. FDA recommends that RPC add another national survey that can provide population estimates of use, misuse, and abuse of opioid analgesics to supplement the MTF data.
- FDA also recommends that the RPC submit limited analyses of Poison Center Data to enhance the surveillance of misuse- and abuse-related adverse outcomes involving opioid analgesics.

- Drug Utilization data:
    - The proportion of prescriptions for ER/LA opioid analgesic products for dosage strengths intended for use only in opioid-tolerant patients that were dispensed to opioid non-tolerant patients has decreased from pre-REMS-implementation. The proportion, however, still remains high,

ranging from 27-79% depending on the product. Due to methodological issues described in this review, the evaluation of use in opioid non-tolerant patients may result in an underestimation for patients considered "opioid-tolerant". For this reason the FDA asks the RPC to modify its criteria for determining opioid tolerance.

- The RPC's early fill methodology is inadequate to address whether or not the REMS has impacted inappropriate prescribing, misuse, or abuse of ER/LA products . For more interpretable results, FDA asks the RPC to propose other methods and data sources to provide data regarding the reasons for early fill of ER/LA products.
- Although the RPC has provided the percentage of switches from ER/LA products to IR opioid analgesics based on prescription claims data, the current methods and data sources alone were not informative. For more informative analyses, FDA asks RPC to propose other methods and data sources to provide insight into the reasons for why prescribers switched patients from an ER/LA OA REMS product to a non-REMS opioid product and to expand to other comparator groups that may be used for pain management.

2 INTRODUCTION

This review evaluates the 60-month risk evaluation and mitigation strategy (REMS) assessment report submitted by the REMS Program Companies (RPC) on July 7, 2017 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 7, 2016 through May 5, 2017.

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[1]

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 opioid analgesics formed an industry working group called the **REMS Program Companies (RPC)** to prepare the REMS proposal for FDA approval and to operationalize the REMS program once approved. On July 9, 2012, 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.

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

[1]https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm484714.htm

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 11.1** for the current Assessment Plan.

3.2. FINDINGS FROM PREVIOUS REMS ASSESSMENTS

The review of the 48-month ER/LA REMS assessment report was completed on August 10, 2017. Since the RPC's 60-month assessment report was received prior to the Agency completing a review the 48 REMS assessment report, the RPC received an abbreviated REMS Assessment Acknowledgement Letter (RAAL) which stated that FDA would combine comments on the 48-month and 60-month REMS assessment reports (see **Appendix Section 11.2)**. This communication was sent to the RPC on July 14, 2017. The FDA's proposed (not sent) 48-month comments are in **Appendix Section 11.3**. Given that the RPC did not have the 48-month comments/feedback prior to constructing the 60-month REMS assessment report, many of the analyses provided in the 60-month report are similar to those of the 48-month report. Thus, on October 31, 2017, the RPC was sent preliminary comments regarding the 60-month report and a request for information for some assessments elements to be submitted to the FDA by the RPC on/by 02/01/2018 (see **Appendix Section 11.4).** These comments focused on obtaining more useful information in specific areas including on surveillance data using electronic healthcare data, drug utilization data, additional comments on Concept paper #1 (initial comments sent 2/10/17), as well as comments on stakeholder surveys.

3.3. REMS MODIFICATIONS

REMS Modification #5 (S-071) was approved on **September 30, 2016** and consisted of the relocation of the product-specific information section from the Blueprint for Prescriber Education to the FDA website located at http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM515636.pdf.

REMS Modification #6 (S-074) was approved on **May 26, 2017** to align the REMS document and REMS materials to the Safety Labeling Changes approved on December 16, 2016 to include warnings regarding opioids and: serotonin syndrome with concomitant use of serotonergic drugs; adrenal insufficiency; and androgen insufficiency. Other additional minor modifications were added as well.

A REMS Modification Notification letter was sent on September 28, 2017, which included a modified draft FDA Blueprint for Prescriber Education as well as the the need for a REMS for immediate-release (IR) opioid analgesic products intended for use in outpatients to ensure the benefits of all of these drugs outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse.

4. REVIEW METHODS AND MATERIALS

- July 9, 2012 Supplement/REMS approval for ER/LA opioid analgesics Letter (J. Racoosin)
- September 30, 2016 Supplement and REMS Modification Approval Letter (S. Hertz)
- December 16, 2016 Safety Labeling Change Approval Letter (S. Hertz)
- February 10, 2017 email from FDA (W. Brown) to the RPC regarding Concept Paper #1.
- May 26, 2017 Supplement and REMS Modification Approval Letter (J. Racoosin)
- July 7, 2017 60-Month REMS Assessment Report Submission
- July 14, 2017, REMS Assessment Acknowledgement Letter (J. Racoosin)
- September 28, 2017 REMS Modification Notification Letter (J. Racoosin)
- October 31, 2017, email from FDA (W. Brown) to the RPC: 72-month, Assessment proposal: RPC Communication to FDA for the ER/LA Opioid Analgesics REMS
- January 12, 2018 RPC response to a January 8, 2018 FDA Information Request (IR)
- January 30, 2018 RPC response to an October 31, 2017 IR.

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*."

The Supporting Document (SD) states that at least annually from the date of initial approval of the REMS, the DEA Registration Database will be reviewed and a Dear

DEA-Registered Prescriber #3 letters (DDRP-3) 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.

The DDRP-3 was distributed by e-mail, fax, and via the United States Postal Service (USPS). The REMS Communication Vendor used its proprietary database of healthcare providers who have "opted in" to receive electronic communications on drug safety alerts and REMS Communication Letters. The database of opt-in prescribers was then matched to the list of DEA-registered prescribers to identify those to receive electronic communications. After removal of duplicate registrations, registrations with address errors, and records from deceased registrants, the target registrant audience for receipt of the annual distribution of the DDRP-3 as of 26 June 2016, totaled **110,055 (108,750 unique registered prescribers and 1,305 hospitals/clinics**). The identified 108,750 unique registered prescribers were unique individual practitioners or mid-level practitioners who have prescribing authority. Prescribers on the DEA master registration file (DEA file), but not on the REMS Communication Vendor opt-in list, received the letter through USPS mail. Addresses for mailing the letters were obtained from the DEA list or from matching the DEA list to the American Medical Association (AMA) list of physicians. In cases where the electronic communication was undeliverable, prescribers were sent a letter by direct mail to the address indicated on the DEA or AMA file within 30 days after sending the electronic communication. The RPC states that currently there is no reliable method for tracking accurate volumes of unopened/unread e-mails.

Electronic (e-mail and facsimile) communications for annual distribution of the DDRP -3 were initiated on July 11, 2016. Mailing of hardcopy communications was initiated on July 18, 2016. An initial distribution was completed July 18, 2016 to the full audience. A second distribution was then completed on September 16, 2016 to any returned mail from the initial distribution for which a secondary address was found.

Of the 108,750 individual registered prescribers targeted, a total of 102,960 (94.6%) registrants were reached, of which 4,636 letters were delivered by e-mail, 108 by fax, and 98,216 by USPS. A total of 5,790 letters that were sent by USPS were returned as undeliverable. The Communication Vendor sent hard copy DDRP-3s by USPS to 1,295 hospitals/clinic registrants, of which 1,253 (96.0%) were delivered.

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 and met the education provider's criteria for passing. Components of an educational activity include instruction, assessment of learning, and potentially, evaluation*."

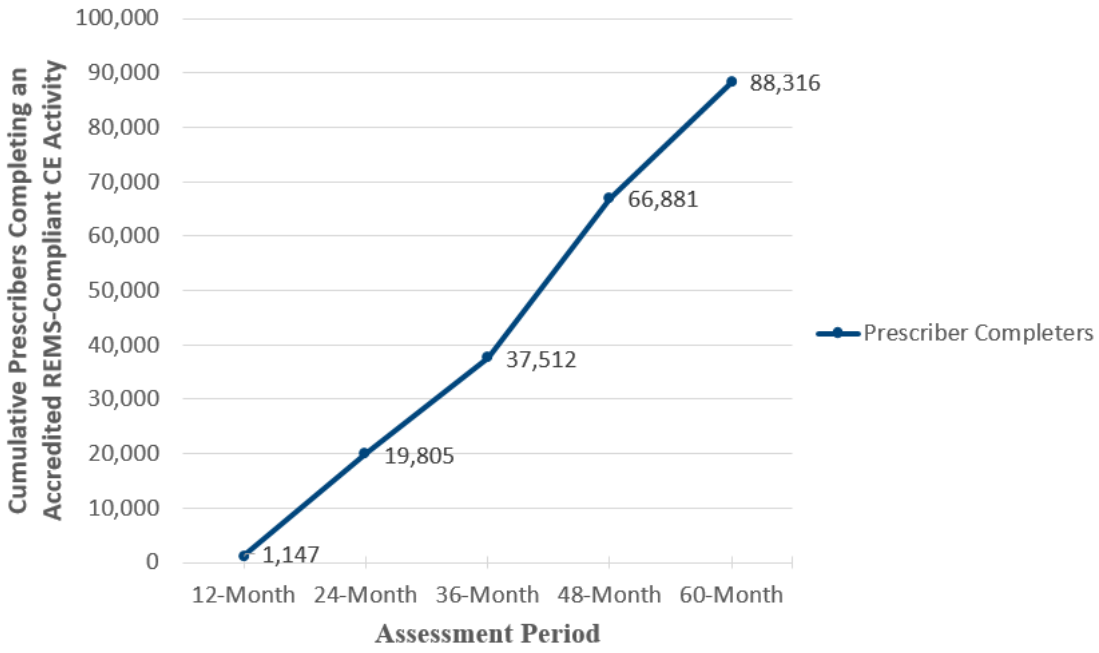
REMS compliant-training is characterized as: 1) training offered by an accredited CE provider to licensed prescribers; 2) includes all elements of the FDA Blueprint; 3) includes a knowledge assessment of all of the sections of the FDA Blueprint, and 4) is subject to independent audit to confirm that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

To fulfill the reporting requirements for this element, each independent accredited CE Provider transmitted required information associated with their RPC-supported, accredited REMS-compliant CE activities to the appropriate National Accrediting Bodies. These Accrediting Bodies then compiled this data in accordance with the MedBiquitous Medical Education Metrics Specifications (MEMS) V2.0.

5.2.2. Numbers Trained

The data cut-off for this current 60-month report was February 28, 2017, which represents the 4-year training milestone of 192,000 prescribers completing REMS-compliant CE training. **As of February 29, 2017**, **88,316** ER/LA prescribers have completed accredited REMS-compliant CE activities, representing 46% of the goal of 192,000; 21,435 of these 88,316 ER/LA prescribers completed accredited REMS-compliant CE activities during this reporting period (March 1, 2016 to February 28, 2017). **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**

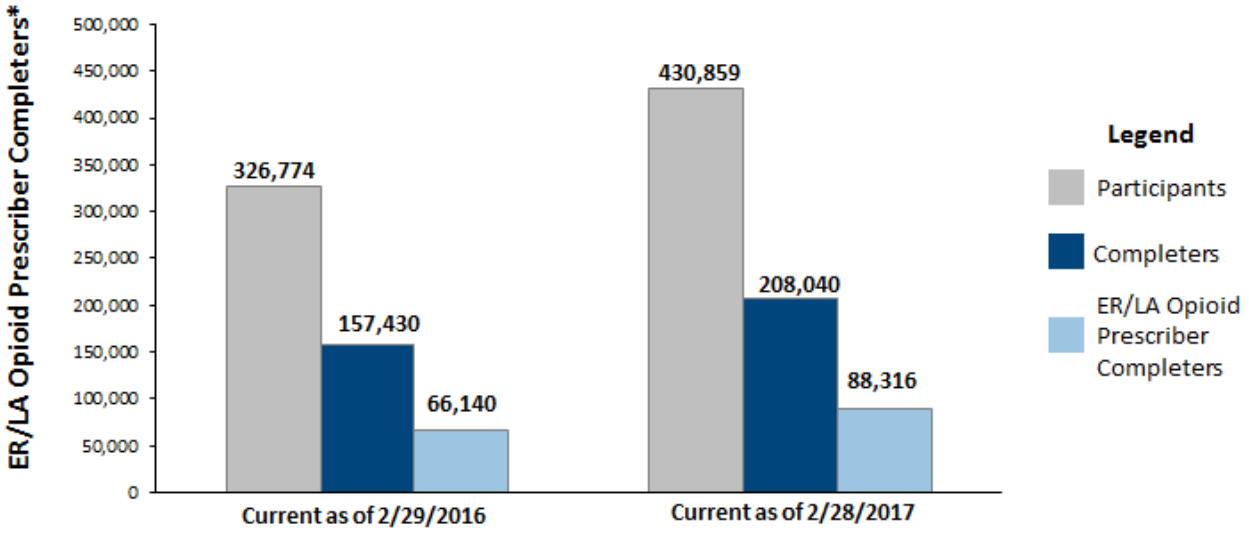


In **Figure 2** (reproduced from the RPC's Figure 5), participants in the REMS-compliant activities are summarized by their status as to whether they were a

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 (February 28, 2013- February 28, 2017)



*Per the MEMS Implementation Guidelines, ER/LA Opioid Prescriber-Completers are individual clinicians registered with the DEA to prescribe Schedule 2 and/or 3 controlled substances and has written at least one ER/LA opioid script in the past year AND completed all components of an educational activity and meeting the education provider's criteria for passing.

Note: Quarterly update data is unaudited and provided by CE Providers directly to the RPC. Collection and reporting of participants and completers are not required by the MEMS Implementation Guidelines.

Of the 430,859 Participants, 88,316 (20.5%) were Prescriber Completers. In addition, of 208,040 individuals that completed a REMS-compliant activity, only 42.5% (88,316/208,040) 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. Of note, while the 48-month reported that there were a total of 66,881 Prescriber Completers, the 60-month report revised that number to 66,140.

The RPC states that the participant/partial completer data, presented above is not comprehensive as not all RPC-supported CE Providers record information that they and CE Accreditors consider optional. MedBiquitous is collaborating with stakeholders to revise MEMS 2.0 specifications to allow for capture of standard learner data.

The RPC states that they had expected that the goal of 192,000 for this reporting period could be met or exceeded based on the 220,529 prescribers projected to be reached by CE Providers that received funding. However, after implementation of accredited REMS-compliant CE activities, revised prescriber completer estimates were provided by select grantees. As in previous assessments, the RPC reiterates that CE Providers have informed them that it is considerably more challenging than initially expected to attract ER/LA prescribers to participate in REMS-compliant activities and to keep them engaged through completion of the full activity and CE program assessment. Three general categories of challenges have been previously identified by the CE providers in regards to getting prescribers to complete the training:

1. **Lack of awareness of the REMS and the importance of completing ER/LA REMS accredited REMS-compliant CE activities**
    a. Prescribers have insufficient awareness/understanding of REMS in general; thus they often can't differentiate REMS-compliant programs from other activities that are available
    b. the length of the CE program (3+ hours) is unappealing
    c. Some prescribers (e.g. pain specialists) may choose a different CE activity since they may think they already know the material.
    d. RPC has launched a campaign to increase awareness of the program with a logo, rolled out February 2017

2. **Education is not tailored to the adult professional learner**
    a. The length of activities and the associated time commitment for completion, coupled with no accommodation for demonstration of prior knowledge or competency is problematic
    b. The activities include a greater-than-usual number of registration questions required of REMS activity participants
    c. The experience is primarily didactic;
    d. Modules 5 and 6 are readily available through off/online free resources and could be made available but not taught during the program.
    e. The Blueprint itself has a significant amount of redundancy, and too-specific information

3. **Available opioid education competes with REMS-compliant CE**
    a. Innumerable non-RPC funded CE activities related to opioids and pain management are available
    b. Clinicians are more likely to complete programs that meet state requirements for licensure regardless if RPC-funded or not
    c. Other programs cover opioid risk management and pain management, rather than having a singular focus on ER/LA products

d. Co-ordination among federal agencies would be extremely helpful.

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 3):

Figure 3: RPC-Supported, REMS-Compliant ER/LA Prescribers Completing Training by Profession during the Reporting Period 01 March 2016-28 February 2017)

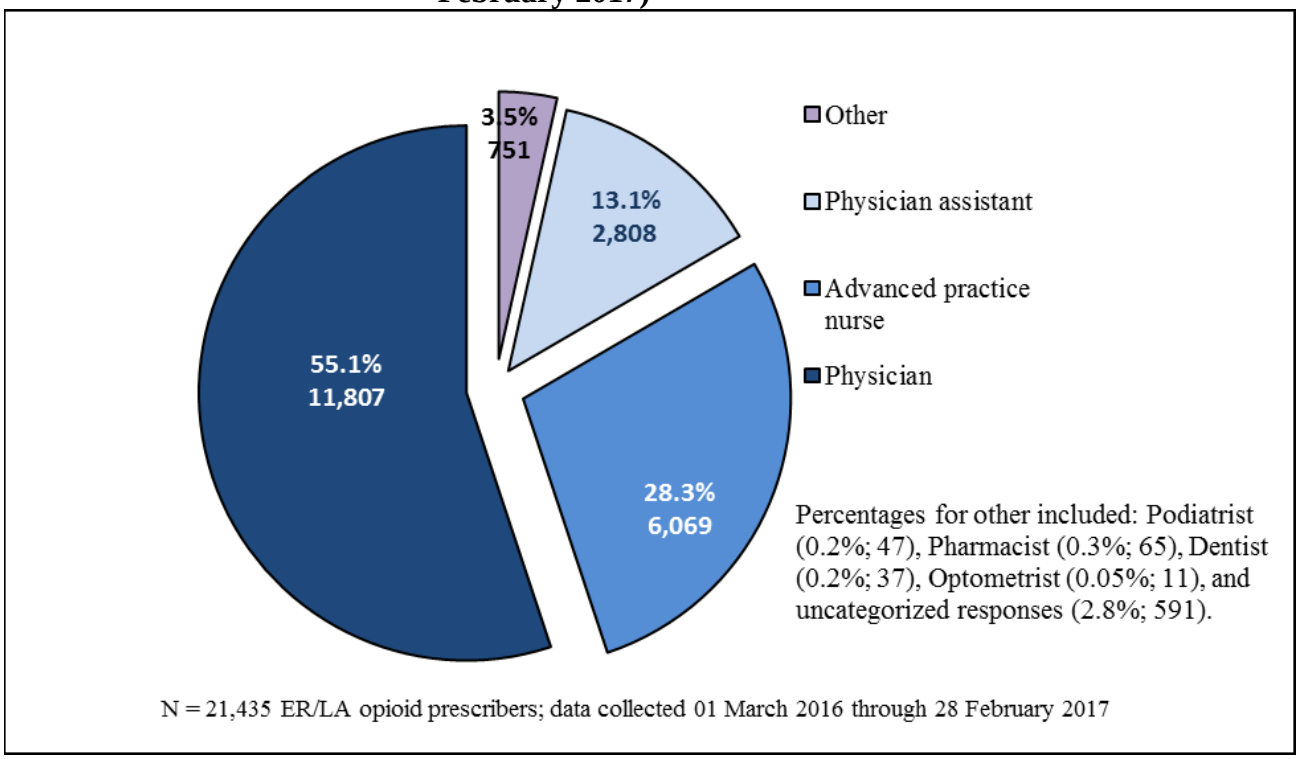


Table 1 (reviewer-generated) compares the professions data in Figure 3 to the data in the 3 previous assessment reports, with the percent completing RPC-funded training per profession per reporting year. Of note is that physicians, while still the profession with the majority of training completers, now comprise only 55% of completers whereas they represented 70% of completers just three years earlier. Both Advanced Practice Nurses and Physicians Assistants have been slowly completing a larger proportion of training over the past three years.

Table 1: Percent of Professions Completing RPC Training per Last Four Reporting periods

Profesions Completing RPC Training	24-month report	36-month report	48-month report	60-month report
Physicians	70%	67%	61%	55%
Advanced Practice Nurses	19%	24%	27%	28%
Physicians Assistants	6%	7%	6%	13%
TOTAL	95%	98%	94%	96%

A small percentage of training has been completed by prescribers such as podiatrists, pharmacists, dentists, and optometrists.

Figure 4 (taken directly from the RPC assessment report's Figure 4) provides data on ER/LA prescriber completers regarding the general practice type (primary care, pain specialist, non-pain specialist). Since practice type was an optional MedBiquitous metric category captured by only some CE Providers, these data are captured for only 11,297 ER/LA prescribers, representing 52.7% (11,297/21,435) of all ER/LA prescribers completing an RPC-supported REMS-compliant CE activity this reporting period.

Figure 4: ER/LA Prescribers Completers by Practice Type during the Reporting Period (01 March 2016-28 February 2017)

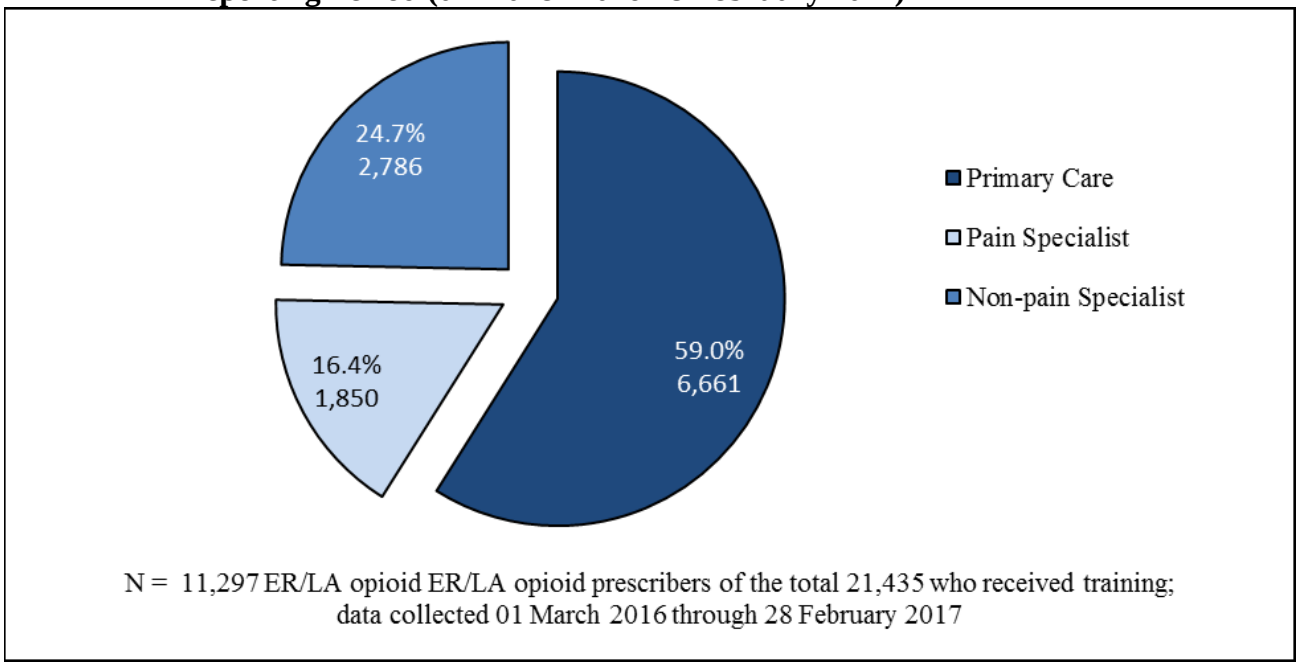


Table 2 (reviewer-generated) compares the practice type data in Figure 4 to the data in the 3 previous assessment reports, with the percent completing RPC-funded

training practice type per reporting year. While the primary care setting remains the practice type with the largest contribution to training completion, the relative contribution of the primary practice setting has been decreasing over the past three years in favor of increasing percentages for pain specialists and non-pain-specialists.

Table 2: Percent of Practice Types Completing RPC Training per Last Four Reporting periods

Practice Types Completing RPC Training	24-month report	36-month report	48-month report	60-month report
Primary Care	72%	66%	62%	59%
Pain Specialists	10%	13%	16%	16%
Non-Pain Specialists	18%	21%	22%	25%
TOTAL	100%	100%	100%	100%

5.2.3. Non-RPC-Funded Training

The RPC states that during the reporting periods for the 24-Month, 36-Month, and 48-Month Assessment Reports, a total of 24 activities were reported by non-RPC supported CE Providers to ACCME as being accredited REMS-compliant as per the Program and Activity Reporting System (PARS) database.

Per the ACCME, a REMS-related activity is one that does not meet all criteria necessary to be considered REMS-compliant. The RPC can confirm that for the 24-Month, 36-Month, and 48-Month FDA Assessment Reports, 22 activities were reported to the ACCME as being non RPC-supported and REMS-related, with 0 additional activities reported to the ACCME as being non RPC-supported and REMS-related during the 60-Month FDA Report period. Therefore, for the reporting period which spans the 24-Month FDA Assessment Report to the 60-Month FDA Assessment report, 38 activities have been reported to the ACCME as non RPC-supported and REMS-compliant, and 22 activities have been reported to the ACCME as non RPC-supported and REMS-related in total
CE Providers that created and implemented these non-RPC REMS-compliant programs indicate that they had approximately **3,098 training completers**. During this current reporting period, the RPC became aware of 14 additional non-RPC funded activities that were reported to ACCME as being REMS-compliant for a total of 38 non RPC-supported, REMS-compliant CE activities (confirmed by the RPC in a 1/12/18 response to a 1/8/18 FDA IR). In addition, the RPC's 1/12/18 IR response noted that or the 24-Month, 36-Month, and 48-Month REMS Assessment Reports, 22 activities were reported to the ACCME as being non RPC-supported and *REMS-related,* with 0 additional *REMS-related* activities reported during the 60-Month FDA Report period. The ACCME has defined a *REMS-related* activity as one that does not meet all criteria necessary to be considered REMS-compliant.

The ACCME has stated that since data reported on these non-RPC activities are incomplete compared with the information reported for RPC-supported activities and since the CE Providers reporting the information have not granted permission to ACCME to disclose their data, data on the 38 activities reported to ACCM+E as REMS-compliant cannot be provided to RPC. The RPC also states (as in previous reports) that since the collection of prescriber completer data are only mandated for RPC-supported activities, the prescriber completer data reported for the non-RPC activities is likely incomplete. Thus, in all assessment reports to date, prescribers reported as completing non-RPC-supported REMS-compliant activities are not included in the total number of prescriber completers reported in Assessment Element 1. The RPC states that they continue to explore ways to identify prescriber completers of non-RPC supported CE that aligns with the FDA Blueprint and conforms fully to the REMS requirements.

5.2.4. RPC Support of REMS-Compliant CE

Each year, the RPC issues a Request for Applications (RFA) to secure, support and make available accredited REMS-compliant CE activities that train prescribers on the ER/LA REMS Blueprint. Since 2012, the RPC has issued seven RFAs and awarded funding to support **919 accredited REMS-compliant CE activities** through 37 grants to accredited CE Providers and the CE Provider's 100+ Educational Partners. A description of all accredited REMS-compliant CE activities available 01 March 2016 to 28 February 2017, organized by Grantee, is provided in **Appendix 11.5**.

On March 7, 2017, the RPC issued one extension RFA (RFA 080317) that was posted on the REMS website. Based on interactions with the FDA, the RPC chose to limit the RFA cycle to only extend support for current RPC-funded CE Providers with ongoing accredited REMS-compliant CE activities since the RPC is anticipating a revised FDA Blueprint.

Of the 919 accredited REMS-compliant CE activities that have been launched, 174 were available during this reporting period:

- 128 activities were live training
- 45 were internet-based enduring or live webinar programs
- 1 program was print-based.

Additional REMS-compliant CE work occurring from March 2, 2015 to February 28, 2017 included:

- Discussions with MedBiquitous on how to include prescribers who prescribe under an institutional DEA number.
- Strengthen the relationship with the CCCE whose members include 25 national organizations representing the professions of medicine, nursing, pharmacy, dentistry, NPs, and PAs.

- Identifying the highest priorities and challenges regarding REMS-compliant CE activities
- An outreach campaign, with a logo and tagline to increase awareness of REMS-compliant CE activities.
- Modification and launch of a new mobile-optimized website for REMS-compliant CE activity

RPC has also:

- Hosted two teleconferences to enable RPC-supported CE Providers to share general experiences and challenges in providing accredited REMS-compliant CE activities as well as best practices
- Developed and implemented a plan for regular milestone-related calls with CE Grantees and CE team members to discuss progress toward goals, challenges, and steps to increase reach and completion rates.
- Provided grant funding for programs with unique and innovative formats more conducive to the adult learner.
- Worked with the CCCE to include demonstration of prior knowledge as part of REMS-compliant CE activities.

5.2.5. Updates to Assessment Element #1

The FDA informed the RPC that FDA was interested in collecting a standard set of demographic characteristics across all accredited CE Providers which included:

- Medical degree
- Specialty
- Years in practice
- Gender
- Geographic region
- Prescribing volume in the past month on average
- ER/LA opioid analgesics prescribed within the past six months

The MedBiquitous Metrics Working Group (which includes CE Providers, the FDA, and MedBiquitous) and the RPC have discussed the FDA's request. Based on the privacy concerns noted by the non-governmental members of the Working Groups, prescribing volume and the ER/LA prescribed have been removed from the requested list of prescriber characteristics. Also, medical degree was removed since it was believed that this item overlaps with already collected profession metric. Lastly, gender was removed because the FDA agreed that this data element was not needed.

The MedBiquitous Metrics Working Group continues to discuss the collection of specialty, years in practice, and geographic region.

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.

A total of 174 CE activities took place during this reporting period and of these, 20 (11.5%) were audited. Details of the independent audit reports submitted by the six nationally recognized Accrediting Bodies are shown in **Table 3** (reproduced from the RPC's Table 5):

Table 3: 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	10	2	0
American Academy of Physician Assistants	7	1	0
American Association of Nurse Practitioners	11	1	0
American Nurses Credentialing Center	16	2	0
American Osteopathic Association	12	2	0
Accreditation Council for Continuing Medical Education	118	12	2
TOTAL	**174**	**20**	**2**

A total of 68% of the conducted activities were accredited by ACCME, while 12 of the 20 (60%) of the randomly selected audited programs were accredited by ACCME. Both of the audit deviations (or "observations" as they are referred to by the RPC) occurred with ACCME programs. Regarding these deviations:

- One deviation occurred because the program had "*No Mechanism to Resolve Conflict of Interest for All Involved in Control of Content*."
- The second deviation occurred because the program had "*No Mechanism to Resolve Conflict of Interest for All Involved in Control of Content*" and because "*Relevant Financial Relationships Were Not Disclosed to Learners"*.

The RPC reports that the deviations for these two reports could not be remediated; therefore, no prescriber completers associated with these activities (N = 339; data on file) are included in the total prescriber completer counts.

5.3.1. Reviewer Comments

1. Over the past 4 reports the number of deviations gone from 5 (24-month); to 9 (36-month); to 4 (48-month); to 2 (60-month). Across these four reports, ALL of these deviations have been related to issues of disclosure of financial interests or inability to resolve financial conflicts of interest. It is encouraging that the numbers of such events per audit appear to be trending downward. Additionally, the RPC has prudently decided to exclude completers of these affected trainings from its total number of training completers. However, additionally:
    a. The RPC should similarly exclude participants in these affected trainings from the total number of participants in RPC-supported trainings; and
    b. The RPC should reach out to the ACCME to ask them to proactively solidify their processes to prevent these financial deviations from continuing to occur.

5.4. KNOWLEDGE SURVEYS – ELEMENTS 4 AND 5

Element 4 states:
"Evaluation of Prescriber Understanding:

a. The results of an evaluation of ER/LA opioid prescribers' awareness and understanding of the serious risks associated with these products and their awareness of appropriate prescribing practices for ER/LA opioids, comparing the awareness and understanding of prescribers who have taken the REMS-compliant training with those who have not taken such training. This evaluation may include, for example, surveys of healthcare providers.

b. The results of any long-term evaluation of prescribers of ER/LA 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."

Element 5 states:
"*Evaluation of Patient Understanding:*
The results of an evaluation of patients' understanding of the serious risks of these products and their understanding of how to use these products safely. This evaluation may include, for example, surveys of patients."

5.4.1. Reviewer Comments:

1. In the October 31, 2017 email to the RPC, comments about the Prescriber and Patient surveys were conveyed. To summarize:
    a. FDA agrees with the RPC's proposal to eliminate the Follow-up Prescriber Survey.
    b. FDA recommends that the RPC conduct uniform data collection on the prescriber characteristics across all CE providers.
    c. Regarding the patient survey, the survey respondents were not representative of the drug use population for race, income, education level, and payer sources. Thus, future surveys should utilize data sources that can allow for recruitment of a representative sample of patients and caregivers. The RPC is to provide a detailed description of the new proposed data source(s) along with limitations of the data source(s) in the 72-month assessment report.

5.5. 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.*"

5.5.1. Background

The purpose of the epidemiologic surveillance data is to monitor the scope and trends in opioid misuse and abuse and the related outcomes of addiction, overdose, and death. Ongoing surveillance of these outcomes is necessary to inform regulatory decisions related to these products and this REMS, but the goal of the surveillance data is not to assess the impact of the REMS itself, due to the many secular trends and concurrent interventions that will inevitably confound this assessment.

5.5.2 Data Provided by the RPC

The RPC submitted five different epidemiologic data sources for surveillance of misuse, abuse, overdose, addiction, and deaths for the 60-Month ER/LA REMS Assessment Report. These data sources are summarized below in **Table 4**.

Table 4: Summary of Data Provided from the RPC
Surveillance of Emergency Department Visits, Hospitalizations and Deaths due to Opioid Overdose and Poisoning Events • HealthCore Integrated Research Database • Medicaid Data from Three States
Mortality Rates Resulting from Opioid Overdose • State Medical Examiner Databases (Florida, Washington, and Oregon) • Centers for Disease Control and Prevention Online Data for Epidemiological Research Publicly-Accessible Data
Surveillance of Opioid Abuse, Misuse, and Addiction • Monitoring the Future (MTF)

5.5.3. Health Core Integrated Research Database (HIRD)/Medicaid Data

An administrative claims-based cohort study was conducted using HIRD and de-identified Medicaid data from three states. Date and cause of death were obtained for commercially insured patients from the National Death Index (NDI) but not for Medicaid patients due to restricted access to personally identifiable information. The study population for the primary analysis included patients dispensed at least one ER/LA opioid analgesic during at least one REMS period with at least six months of continuous coverage prior to dispensing to ascertain baseline patient characteristics. The study also included additional analyses of patients without ER/LA opioid exposure, and those with at least one dispensing of an IR opioid analgesic.

Outcome included ED visits and hospitalization due to prescription opioid overdose or poisoning. Prescription overdose or poisoning was defined using claims from ED or inpatient settings with International Classification of Diseases, Ninth Revision,

Clinical Modification (ICD-9-CM) diagnosis codes indicating poisoning and accidental poisoning by opioids[2] in any position on a claim. All analyses were performed separately for commercially-insured patients and patients enrolled in Medicaid. Analyses compared the outcome in the pre-REMS period and the active REMS period, adjusting for other measurable differences between patients in the compared periods using propensity score matching.

HIRD Data Analysis Results

The HIRD data for the 60-month ER/LA REMS assessment incorporated one additional year of data (July 2013 - September 2016) compared to the 48-month assessment (July 2013 - August 2015). For the 60-month data, among all ER/LA opioid analgesic users, the unadjusted incidence of prescription opioid overdose or poisoning was slightly higher in the active-REMS period than the pre-REMS period. When stratified by use, the incidence was higher in the active REMS period for new users but lower for non-new users. These results were not consistent with results reported for the 48-month assessment, where the unadjusted incidence of prescription opioid overdose or poisoning was slightly lower in the active REMS period than the pre-REMS period for all ER/LA opioid analgesic users. For prescription opioid overdose deaths, there was a numerical decrease from the pre-REMS period to the active-REMS period. This is contrary to the 48-month report, where there was a numerical increase in the prescription opioid overdose deaths from the pre-REMS period to the active REMS period. However, these estimates were imprecise due to small number of events.

Medicaid Claims Data Analysis Results

The Medicaid data for the 60-month ER/LA REMS assessment also incorporated one additional year of data. The incidence of prescription opioid overdose or poisoning was substantially higher for the Medicaid population compared to the commercially insured population. In the Medicaid population, the unadjusted incidence of prescription opioid overdose or poisoning was lower in the active REMS period than the pre-REMS period across all analyses. These results were consistent with what was reported at the 48-month assessment.

[2] (965.00: poisoning by opium (alkaloids), unspecified, 965.02: poisoning by methadone, 965.09: poisoning by other opiates and related narcotics, E850.1: accidental poisoning by methadone and E850.2: accidental poisoning by other opiates and related narcotics)

Reviewer Comments:

1. Assessment of prescription opioid overdose or death from HIRD and Medicaid data across different REMS implementation periods is difficult to interpret due to changes in commercial insurance and Medicaid coverage, including expanded access and changes in covered benefits.[3] For the HIRD population, there was a numerical increase in the incidence of opioid overdose and poisoning and a numerical decrease in the opioid overdose deaths from the pre-REMs to the active-REMS period with one additional year of data though the observed estimates were imprecise. It is unclear if the observed changes are meaningful or due to chance or selection bias due to changes in the commercial insurance market or other factors. In the Medicaid analysis, the direction of change in non-fatal prescription opioid overdose rates was consistent for 48- and 60-month assessment, but Medicaid data could not be linked to NDI to assess change in prescription opioid overdose deaths.
2. Furthermore, the insurance claims codes used to capture prescription opioid overdose or poisoning have not been adequately validated, and it is unknown to what degree they reflect actual overdose cases.
3. HIRD data from commercially insured patients and the Medicaid data from a few states may not be generalizable to the U.S population.
4. Understanding trends in prescription opioid overdose and death continues to be of great interest to FDA. The purpose of the epidemiologic surveillance data is to monitor the scope and trends in prescription opioid misuse, abuse, addiction, overdose, and death and not to assess the impact of the REMS itself, due to the many secular trends and concurrent interventions that will confound the assessment. Therefore, formal comparison of means or trends across specific time periods (Pre-REMS versus active-REMS periods) or comparisons between ER/LA and IR formulations are not necessary for surveillance purposes.

Recommendations for the RPC:

1. FDA is no longer requesting further analyses of HIRD and limited Medicaid databases to assess changes in the incidence of prescription opioid overdose and death.
2. FDA is not requesting formal comparison of means or trends across pre-REMS and active-REMS periods for surveillance.
3. RPC should utilize new data sources to assess trends in the incidence of prescription opioid overdose and poisoning. These should include data from a diverse population, including all payer sources, from a nationally

[3] http://www.commonwealthfund.org/publications/issue-briefs/2017/may/effect-aca-health-care-access

representative sample or one that includes a large and stable coverage area drawing from multiple geographic regions. These data sources might include but are not limited to 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). For the 72-month assessment:

a. Provide quarterly trends of prescription opioid overdose rates with estimates of precision. Also, provide rates for heroin for context.[4]
b. Analyses should use validated code algorithms for prescription opioid overdose, heroin overdose, etc. (i.e., those being developed in the ER/LA opioid analgesic Post Marketing Requirements)
c. Provide a detailed description of the data source, limitations, and methods used for the above analyses.

Address the potential impact of changes from ICD-9 to ICD-10 codes on prescription opioid overdose rates using sensitivity analyses or statistical adjustment.[5]

5.5.4 Medical Examiner Data

The 60-month assessment report included medical examiner mortality data from three states (Washington state, Oregon, and Florida) from 2010 through the most recent available year of data (2015 or 2016). For the 60-month assessment, Florida replaced Utah from the 48-month report as data from Utah were not available as of the reporting cut-off date. Prescription dispensing data from QuintilesIMS was updated and the starting year for trend analysis was restricted to 2010 for the 60-month report instead of 2006 for previous reports. Dosing unit adjusted rates for prescription opioid overdose death were not provided as part of the 60-month overdose death trend analyses. For each state, data were obtained for all deaths involving poisioning as an underlying cause of death, or poisoning by any substance as a contributing cause. Four outcomes were assessed, 1) underlying cause of death for prescription opioid with an ER/LA formulation excluding hydrocodone, 2) any cause of death for prescription opioids with an ER/LA formulation excluding hydrocodone, 3) underlying cause of death for prescription opioid excluding hydrocodone, 4) any cause of death for prescription opioids excluding hydrocodone. Hydrocodone and benzodiazepines were selected as comparators

[4] TedescoD, Asch SM, Curtin C, Hah J, McDonald KM, Fantini MP, Hernandez-Boussard T. Opioid Abuse And Poisoning: Trends In Inpatient And Emergency Department Discharges. Health Aff (Millwood). 2017 Oct 1;36(10):1748- 1753.

[5] Heslin KC, Owens PL, Karaca Z, Barrett ML, Moore BJ, Elixhauser A. Trends in Opioid-Related Inpatient Stays Shifted after the US Transitioned to ICD-10-CM Diagnoses Coding in 2015. Med Care, 2017 Nov;55(11):918-923.

because the hydrocodone market is comprised predominantly of IR products, and benzodiazepine prescribing would not likely be directly affected by the ER/LA REMS. Results of the analysis of mean population and prescriptions-adjusted death rates with 95% confidence intervals are shown below.

Florida: As shown in **Figure 5** (copied directly from RPC's Figure 15), and Table 5 (copied directly from RPC's Table 12), for population adjusted death rates, there was a statistically significant decrease from the pre-REMS to the active-REMS period for prescription opioids with an ER/LA formulation (excluding hydrocodone) and benzodiazepine, and a non-statistically significant decrease from the pre-REMS to the active-REMS period for hydrocodone. For prescription-adjusted death rates, there was a non-statistically significant decrease from the pre-REMS to the active-REMS period for prescription opioids with an ER/LA formulation (excluding hydrocodone), a statistically significant decrease from the pre-REMS to the active-REMS period for benzodiazepines, and a statistically significant increase from the pre-REMS to the active-REMS period for hydrocodone. However, both population- and prescription-adjusted death rates appears to be increasing in the active-REMS period for prescription opioids with an ER/LA formulation (excluding hydrocodone) and benzodiazepines.

Figure 5: Florida Population- and Prescription-Adjusted Death Rates for Prescription Opioids with an ER/LA Formulation Excluding Hydrocodone, Benzodiazepenes, and Hydrocodone.

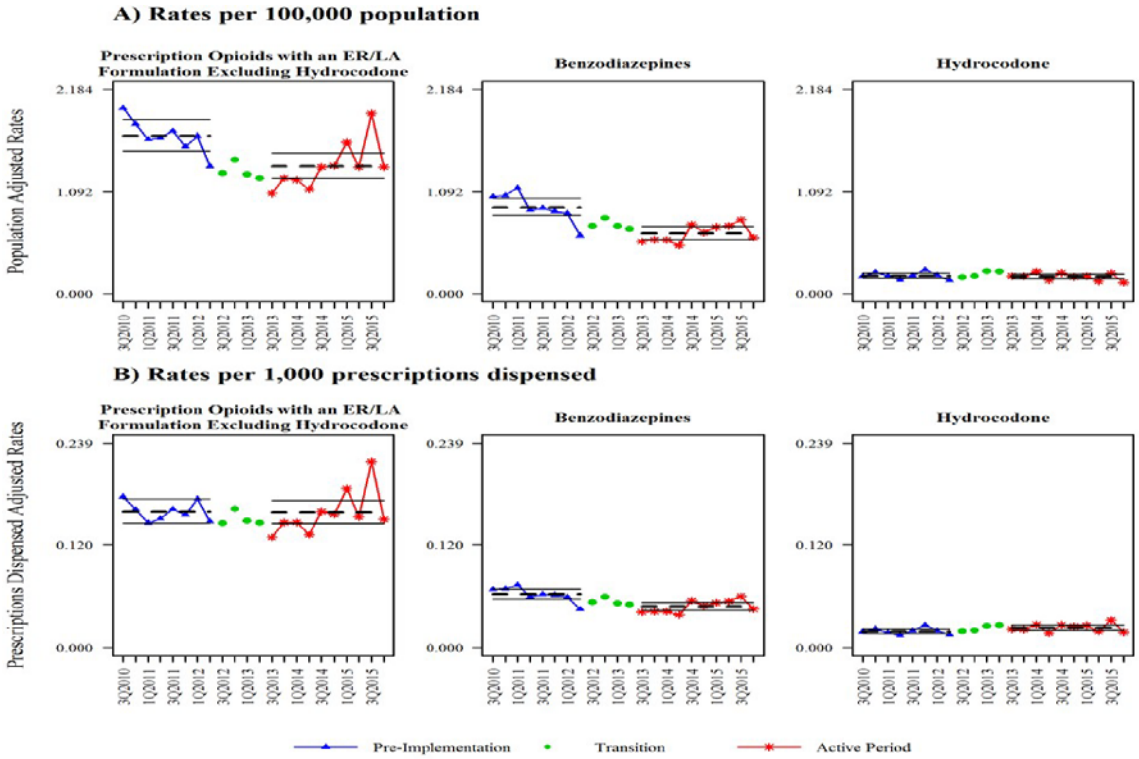


Table 5: Florida Population- and Prescription-Adjusted Death Rates for Prescription Opioids with an ER/LA Formulation Excluding Hydrocodone, Benzodiazepenes, and Hydrocodone.

Drug Group	Pre-Implementation Mean Exposure	Active Period Mean Exposure	Active to Pre-Implementation % change (95% CI)	P-value for % change	P-value for Interaction[1]
Population Adjusted Rates/100,000					
Prescription Opioids with an ER/LA Formulation Excluding Hydrocodone	1.68	1.36	-18.96% (-29.61%; -6.70%)	.003	.
Benzodiazepines	0.92	0.65	-30.07% (-39.47%; -19.21%)	<.001	.152
Hydrocodone	0.19	0.18	-5.31% (-21.70%; 14.52%)	.574	.197
Prescription Adjusted Rates/1,000					
Prescription Opioids with an ER/LA Formulation Excluding Hydrocodone	0.16	0.16	-0.70% (-12.03%; 12.09%)	.910	.
Benzodiazepines	0.06	0.05	-22.96% (-32.47%; -12.11%)	<.001	.005
Hydrocodone	0.02	0.02	22.15% (1.31%; 47.28%)	.036	.069

Oregon: As shown in **Figure 6** (copied directly from RPC's Figure 19), and Table 6 (copied directly from RPC's Table 16), for population-adjusted death rates, there was a statistically significant decrease from the pre-REMS to the active-REMS period for prescription opioids with an ER/LA formulation (excluding hydrocodone) and hydrocodone, and a non-statistically significant decrease from the pre-REMS to the active-REMS period for benzodiazepines. For prescription-adjusted death rates, there was a non-statistically significant decrease from the pre-REMS to the active-REMS period for prescription opioids with an ER/LA formulation (excluding hydrocodone) and hydrocodone, and a non-statistically significant increase from the pre-REMS to the active-REMS period for benzodiazepines. Again, the trend appears to be increasing in the active-REMS period for both population- and prescription-adjusted death rates for prescription opioids with an ER/LA formulation (excluding hydrocodone).

Figure 6: Oregon Population and Prescription-Adjusted Death Rates for Prescription Opioid with an ER/LA Formulation Excluding Hydrocodone, Benzodiazepenes, and Hydrocodone.

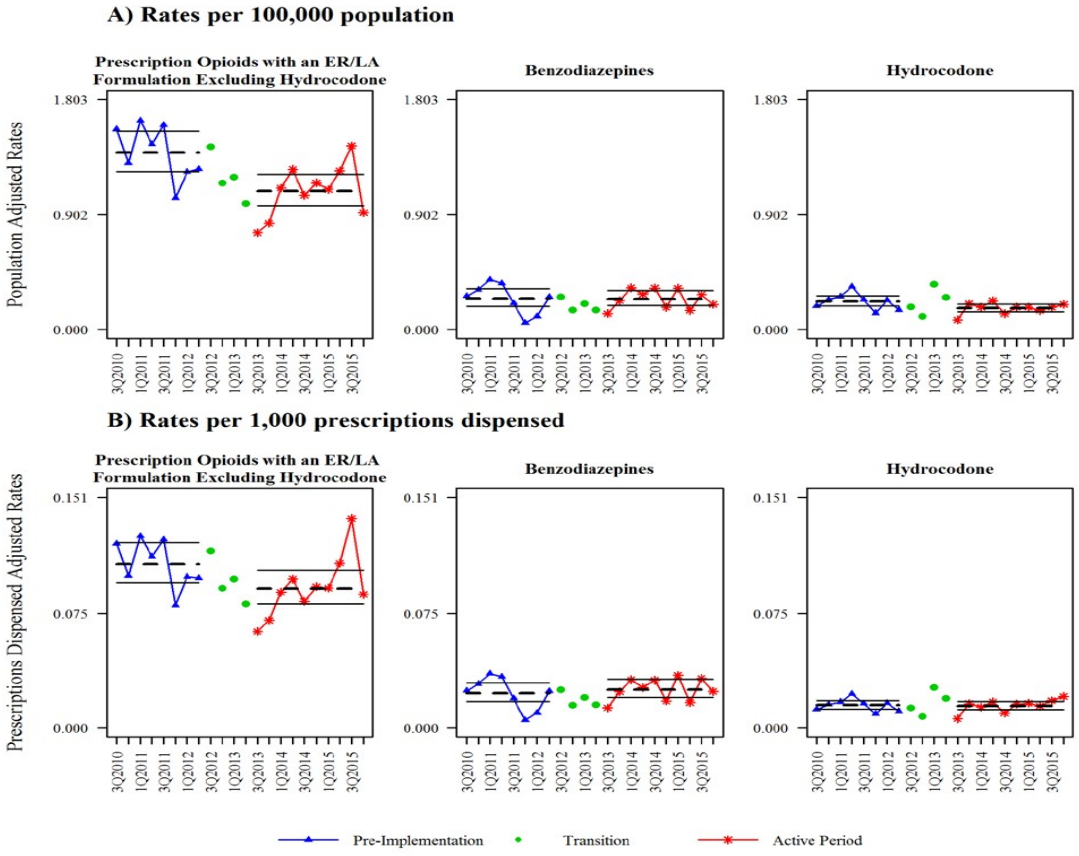


Table 6: Oregon Population and Prescription-Adjusted Death Rates for Prescription Opioid with an ER/LA Formulation Excluding Hydrocodone, Benzodiazepenes, and Hydrocodone.

Drug Group	Pre-Implementation Mean Exposure	Active Period Mean Exposure	Active to Pre-Implementation % change (95% CI)	P-value for % change	P-value for Interaction[1]
Population Adjusted Rates/100,000					
Prescription Opioids with an ER/LA Formulation Excluding Hydrocodone	1.39	1.09	-21.59% (-33.19%; -7.97%)	.003	.
Benzodiazepines	0.24	0.24	-1.02% (-31.81%; 43.68%)	.957	.260
Hydrocodone	0.22	0.17	-23.81% (-40.92%; -1.74%)	.036	.851
Prescription Adjusted Rates/1,000					
Prescription Opioids with an ER/LA Formulation Excluding Hydrocodone	0.11	0.09	-14.83% (-28.25%; 1.09%)	.066	.
Benzodiazepines	0.02	0.03	11.36% (-22.33%; 59.67%)	.558	.188
Hydrocodone	0.01	0.01	-3.44% (-25.97%; 25.95%)	.796	.436

Washington: As shown in **Figure 7** (copied directly from RPC's Figure 23) and Table 7 (copied directly from RPC's Table 20), for population adjusted death rates, there was a statistically significant decrease from the pre-REMS to the active-REMS period for prescription opioids with an ER/LA formulation (excluding hydrocodone) and benzodiazepines, and a non-statitiscally significant decrease from the pre-REMS to the active-REMS period for hydrocodone. For prescription-adjusted death rates, there was a statistically significant decrease from the pre-REMS to the active-REMS period for prescription opioids with an ER/LA formulation (excluding hydrocodone) and benzodiazepines, and a non-statistically significant increase from the pre-REMS to the active-REMS period for hydrocodone. Again, the trend appears to be increasing in the active-REMS period for both population- and prescription-asjusted death rates for prescription opioids with an ER/LA formulation (excluding hydrocodone).

Figure 7: Washington Population and Prescription-Adjusted Death Rates for Prescription Opioid with an ER/LA Formulation Excluding Hydrocodone, Benzodiazepenes, and Hydrocodone.

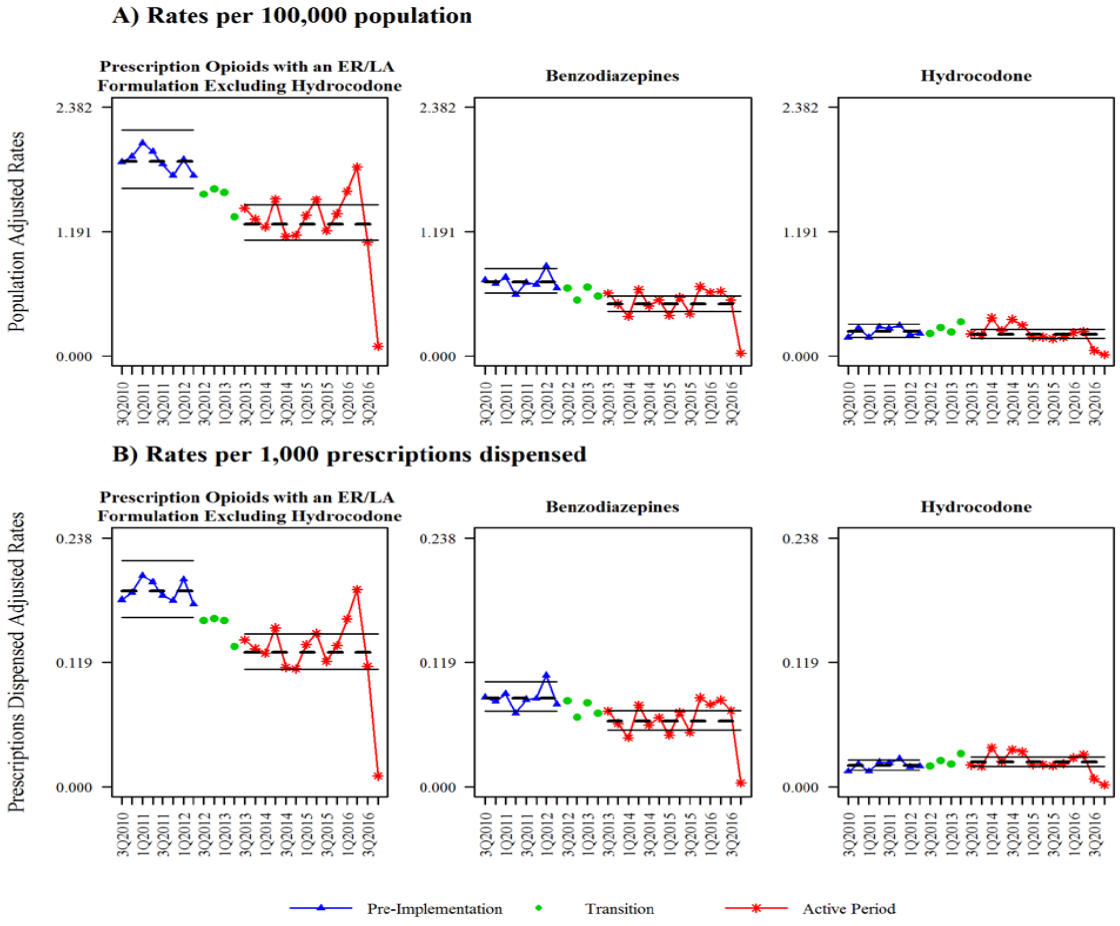


Table 7: Washington Population and Prescription-Adjusted Death Rates for Prescription Opioid with an ER/LA Formulation Excluding Hydrocodone, Benzodiazepenes, and Hydrocodone

Drug Group	Pre-Implementation Mean Exposure	Active Period Mean Exposure	Active to Pre-Implementation % change (95% CI)	P-value for % change	P-value for Interaction[1]
Population Adjusted Rates/100,000					
Prescription Opioids with an ER/LA Formulation (Excluding Hydrocodone)	1.87	1.27	-32.15% (-44.39%; -17.21%)	<.001	.
Benzodiazepines	0.71	0.50	-29.98% (-43.82%; -12.73%)	.002	.835
Hydrocodone	0.24	0.21	-11.87% (-37.01%; 23.30%)	.461	.189
Prescription Adjusted Rates/1,000					
Prescription Opioids with an ER/LA Formulation Excluding Hydrocodone	0.19	0.13	-31.40% (-43.59%; -16.57%)	<.001	.
Benzodiazepines	0.09	0.06	-25.87% (-40.46%; -7.71%)	.007	.605
Hydrocodone	0.02	0.02	16.28% (-13.68%; 56.64%)	.321	.004

DEPI Reviewer Comments:

Mean population-adjusted death rates due to prescription opioids with an ER/LA formulation, benzodiazepines, and hydrocodone decreased across the study period for all three states; however, the trend in the active REMS period appeared to be increasing for prescription opioids with an ER/LA formulation making this pre-post analysis using mean rates difficult to interpret. The sharp drop in opioid overdose deaths in the last quarter reported for Washington may be due to incomplete or missing data. Furthermore, there may be multiple different interventions occurring in each state, making it difficult to attribute similar trends in prescription opioid overdose death rates across each state to a national-level intervention such as the REMS. In addition, the data presented for these three states do not represent national trends and are likely not generalizable to the U.S population.

DEPI Recommendations for the RPC:

FDA is not requesting further analyses of state medical examiner data at this time.

5.5.5 CDC Wonder Mortality Data

In response to the FDA's request for trends in prescription opioid analgesic-related drug overdose deaths, the RPC analyzed data from CDC Wonder national-level drug overdose death data.

Design and Methods

The RPC evaluated trends in prescription opioid overdose death in the U.S. between 2006 and 2015 using data from CDC WONDER. These data are from the National Vital Statistics System Multiple Cause-of-Death Public Use Record files. Data in these records are based on death certificates. Overdose deaths are defined as those with an underlying cause of death codes identified in **Table 8** using ICD-10 external cause of injury codes. This includes injury deaths of any intent (unintentional, suicide, homicide, or undetermined).

Table 8: ICD-10 Underlying Cause of Death Codes	
X40-X44	Unintentional overdose
X60 – X64	Suicide
X85	Homicide
Y10 –Y14	Undetermined intent

Among deaths with drug overdose as the underlying cause of death, the type of opioid is indicated by ICD-10 opioid codes T40.0, T40.1, T40.2, T40.3, T40.4 or T40.6. For this report ICD-10 T40.2 (Natural and semisynthetic opioids), T40.3 (methadone), T40.4 (Synthetic opioids, other than methadone) were selected to represent opioid overdose deaths (**See Table 9**) The ICD-10 codes T40.0 (opium), T40.1 (heroin), and T40.6 (other unspecified narcotics) were not included in this analysis.

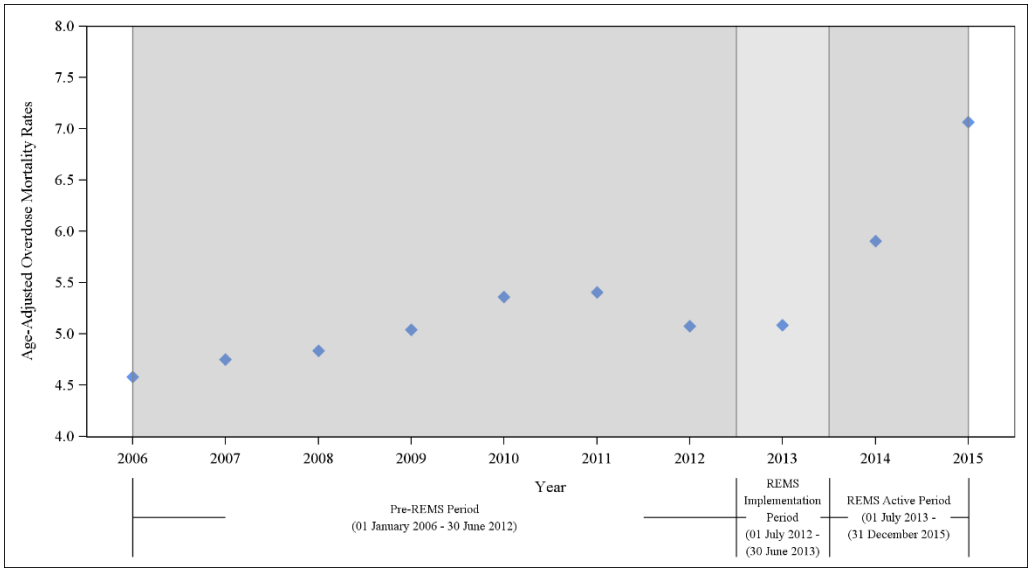
Table 9: ICD-10 Codes to Identify Opioid Overdose Deaths	
Natural and semisynthetic opioids	T40.2
Methadone	T40.3
Synthetic opioids, other than methadone	T40.4

Mortality rates were calculated, using U.S. residents as the denominator. Population data were obtained from the U.S. Bureau of the Census and represented the population enumerated as of April 1st for census years and estimated as of July 1st for all other years. Both crude and age-adjusted rates were calculated by age group each year and for the three time periods (Pre-REMS period, REMS implementation period, active REMS period). Age-adjusted mortality rates were calculated using the direct method, and adjusted to the 2000 U.S standard population.

Results

The age-adjusted prescription opioid analgesic-related drug overdose mortality rates showed an increase from 2006 to 2015 (4.58 to 7.06 deaths per 100,000 population, respectively). (**Figure 8**, copied directly from the RPC's Figure 27)

Figure 8: Age-Adjusted Death Rates for Prescription Opioid Analgesic-Related Drug Overdose Deaths (Expressed per 100,000 population) for the Period January 1, 2006 through December 31, 2015.



When stratified by age group, the largest relative percent change in prescription opioid overdose death rate across the study period was observed in ages 65 to 75. In this age group, age-adjusted prescription opioid overdose death rates increased 172% from 1.06 to 2.89 prescription opioid overdose deaths per 100,000 U.S population from 2006 to 2015. The next largest relative increase was in those aged 55 to 64 years (144% increase), 25 to 34 years (72% increase) and 75 to 84 (60% increase) (**Table 10**) (copied directly from RPC's Table 28).

Table 10: Total Number of Prescription Opioid Analgesic-Related Drug Overdose Deaths and Age-Specific Death Rates Over the Study Period (January 1, 2006 through December 31, 2015) in the U.S.

Year/ Age Group	2006 N Rate	2007 N Rate	2008 N Rate	2009 N Rate	2010 N Rate	2011 N Rate	2012 N Rate	2013 N Rate	2014 N Rate	2015 N Rate
Under 1 year	9 0.22	8 0.19	7 0.17	9 0.22	10 0.25	11 0.28	16 0.41	9 0.23	8 0.20	12 0.30
1 - 4	21 0.13	30 0.19	35 0.22	27 0.17	25 0.15	32 0.20	23 0.14	27 0.17	34 0.21	38 0.24
5 - 14	29 0.07	37 0.09	37 0.09	20 0.05	39 0.10	25 0.06	20 0.05	21 0.05	22 0.05	25 0.06
15 - 24	1,614 3.77	1,670 3.87	1,584 3.65	1,551 3.56	1,694 3.88	1,585 3.62	1,250 2.84	1,163 2.64	1,364 3.10	1,714 3.92
25 - 34	2,709 6.88	2,895 7.29	2,894 7.20	3,109 7.63	3,499 8.52	3,549 8.49	3,254 7.69	3,221 7.52	3,908 8.99	5,225 11.87
35 - 44	3,599 8.32	3,563 8.33	3,534 8.38	3,577 8.62	3,750 9.13	3,793 9.33	3,570 8.81	3,482 8.60	4,183 10.34	5,128 12.67
45 - 54	4,177 9.65	4,304 9.80	4,614 10.38	4,776 10.64	4,889 10.86	4,988 11.15	4,675 10.55	4,643 10.60	5,077 11.70	5,569 12.92
55 - 64	1,246 3.90	1,548 4.67	1,686 4.94	2,036 5.75	2,275 6.24	2,392 6.28	2,562 6.64	2,933 7.46	3,404 8.50	3,895 9.55
65 - 74	203 1.06	231 1.17	294 1.43	358 1.69	320 1.47	402 1.79	476 1.98	575 2.28	714 2.71	795 2.89
75 - 84	83 0.63	78 0.60	81 0.62	98 0.75	89 0.68	90 0.68	113 0.85	105 0.78	124 0.91	140 1.01
85+	34 0.70	44 0.87	33 0.64	36 0.67	63 1.15	48 0.84	49 0.83	56 0.93	57 0.93	55 0.87
Age not stated	2	1	1	2	1	3	0	2	1	2

Reviewer Comments:

1. Prescription opioid drug overdose death data obtained from the National Vital Statistics System are grouped by broad ICD-10 codes. In addition, a substantial number of current death certificates for drug overdoses lack information on involvement of specific drugs.[6] Furthermore, illicitly manufactured fentanyl is not distinguishable from prescription fentanyl on death certificates. Although informative for monitoring prescription opioid overdose trends broadly, these data do not allow for surveillance of trends in overdose deaths due to specific prescription opioid analgesics.

[6] Ruhm CJ. Geographic Variation in Opioid and Heroin Involved Drug Poisoning Mortality Rates. Am J Prev Med 2017 Dec;53(6):745-753.

2. CDC WONDER mortality data from the Multiple Cause of Death files is a valuable resource for surveillance of prescription opioid analgesic- and heroin-related drug overdose deaths in U.S residents. These data, though representative of the U.S population, lack the specificity to trend drug overdose deaths due to specific prescription opioids. To overcome this limitation, we suggest that the RPC explore the new Drug Involved Mortality (DIM) data now available for public use through the Research Data Center at https://www.cdc.gov/rdc/b1datatype/dt1229.html. DIM contains National Vital Statistics System mortality files linked to electronic files containing literal text containing drug-specific information from death certificates. For the 72-month assessment, RPC should continue to update CDC Wonder mortality data, trend the age-adjusted prescription opioid overdose mortality by quarter and stratify by the opioid codes listed above, as well as heroin. The RPC should also analyze the DIM data as specified below.

Recommendations for the RPC:

1. In the 72-month assessment report, provide;
    a. Quarterly trends (2006 through 2016) of counts and population age-adjusted overdose mortality rates stratified by opioid classification ICD-10 groupings (natural and semi-synthetic opioids, methadone, synthetic opioids other than methadone, and heroin).
    b. Visual depiction of trend data, as above, stratified by sex and age group.
    c. Quarterly trends of the proportion of prescription opioid overdose deaths, stratified as above, that also involve; 1) benzodiazepines, and 2) heroin

2. Provide a detailed description of the data source, limitations, and methods used for the above analyses.

3. For more drug specific information on opioid analgesic-related drug overdose deaths, we recommend using the Drug Involved Mortality (DIM) data, now available for public use through the Research Data Center. https://www.cdc.gov/rdc/b1datatype/dt1229.html. For the 72-month assessment:
    a. For all available data years, provide quarterly trends of all drug overdose and prescription opioid overdose death counts and populations rates.
    b. Among all drug overdose deaths for each quarter, provide the count and proportion for which no specific drugs were identified.
    c. Among all opioid overdose deaths for each quarter, provide the count and proportion for which no specific opioids were identified.

d. For all available data years, provide quarterly trends of prescription opioid overdose deaths counts and population rate by each prescription opioid molecule (i.e., hydrocodone, oxycodone, methadone, fentanyl, morphine, oxymorphone, hydromorphone, meperidine, codeine, buprenorphine, tramadol, tapentadol), and heroin.
e. For each prescription opioid molecule, provide overdose death rates relative to total prescription volume, measured both as the number of prescriptions and as the number of tablets dispensed in the U.S.
f. For each opioid molecule, indicate the proportion of death cases mentioning this opioid molecule that were single drug versus multi-drug overdoses.
g. For each year, provide the proportion of fatal prescription opioid overdose deaths that involved; 1) benzodiazepines, 2) heroin.

4. Provide a detailed description of the data source, limitations, and methods used for the above analyses.

5.5.6. Monitoring the Future (MTF)

MTF surveys have been conducted annually since 1975 and include both cross-sectional surveys and longitudinal follow-up of age cohorts. MTF surveys provide data on the substance use of American adolescents, college students, and high school graduate adults through age 55.

Design and Methods

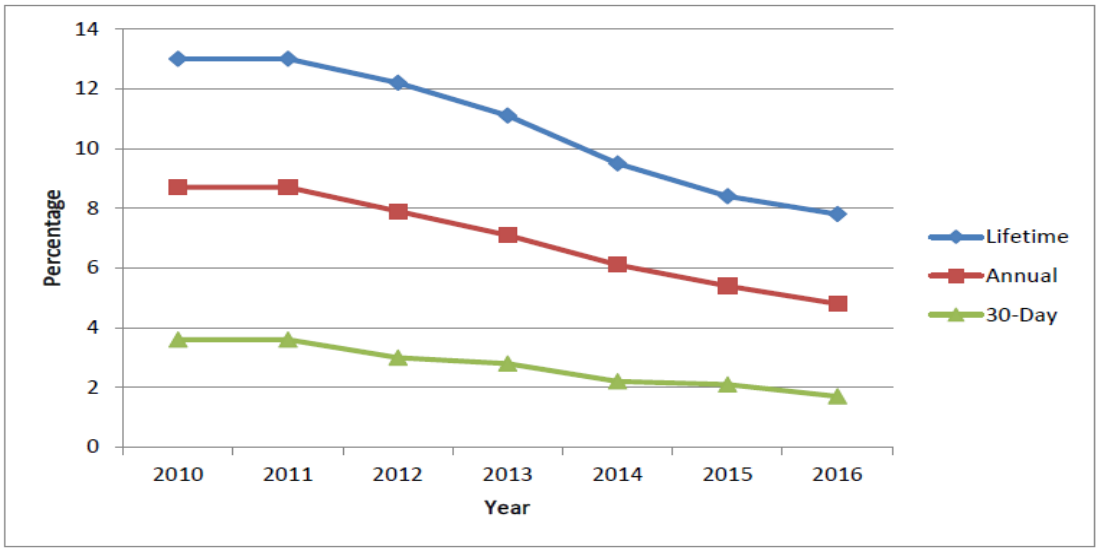
MTF survey is a repeated series of surveys in which nationally representative samples of 8th, 10th, and 12th graders are randomly chosen to complete the same survey to see how drug use patterns change over time. During the spring of each year, approximately 50,000 students in about 420 public and private middle and high schools nationwide are surveyed. A multi-stage random sampling procedure is used to provide a nationally representative sample of students at each grade level.[7] In addition, a randomly selected sample from each senior class are followed up with a mailed questionnaire for several years after high school. Participation is voluntary, and surveys are self-administered and completed during normal classroom time. Parents are notified and given the option to opt their child out. In the survey, usage levels are measured at three levels: lifetime use, use in the last 12 months, and use in the last 30 days. For narcotics, respondents are asked to only include use without a doctor's direction.

[7] Design of Monitoring the Future. Assessed at http://monitoringthefuture.org/purpose.html on 11/20/2017

Results

In 2016, the MTF survey collected data from 45,500 students in 372 secondary schools, including approximately 17,600 8th graders, 15,200 10th graders, and 12,600 12th graders. Among 12th graders, non-medical use of prescription opioids, defined as "use of narcotics other than heroin (without doctor's orders)" declined from 2010 to 2016 (**Figure 9**) (copied directly from the RPC's Figure 28).

Figure 9: Use of Narcotics Other than Heroin Among 12 Graders (2010 – 2016)



The annual prevalence of Oxycontin and Vicodin use declined from 2010 to 2016 for 8th, 10th, and 12th graders (**Figures 10 & 11**) (copied directly from the RPC's Figures 29 & 30).

Figure 10: Annual Prevalence of OxyContin Use Among 8th, 10th, and 12th Grade Students

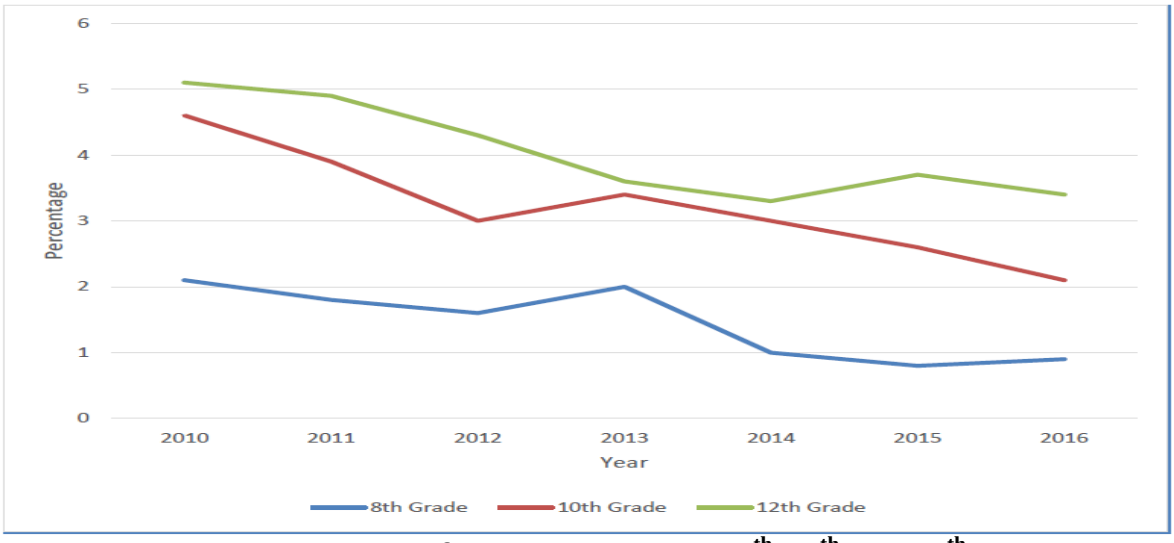
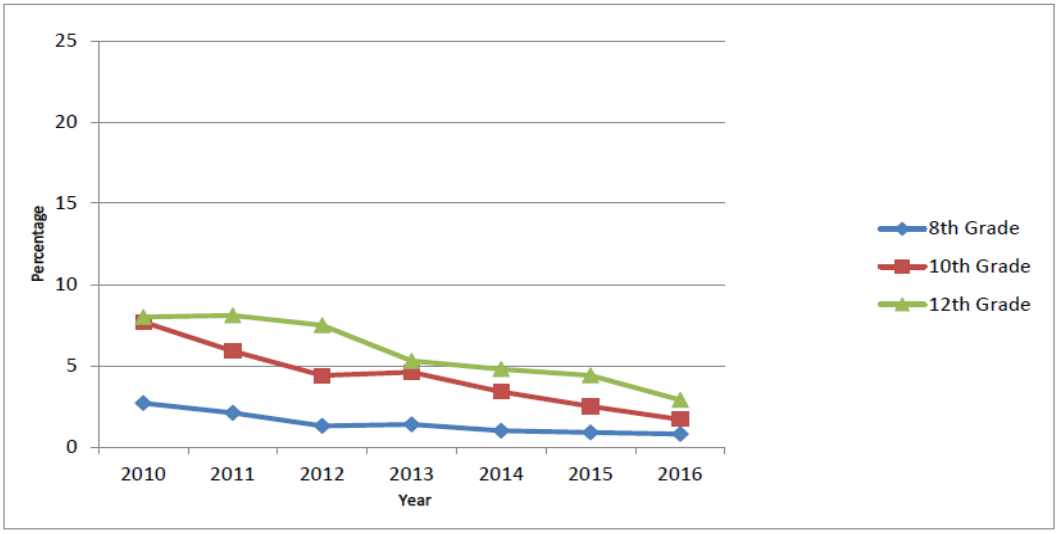
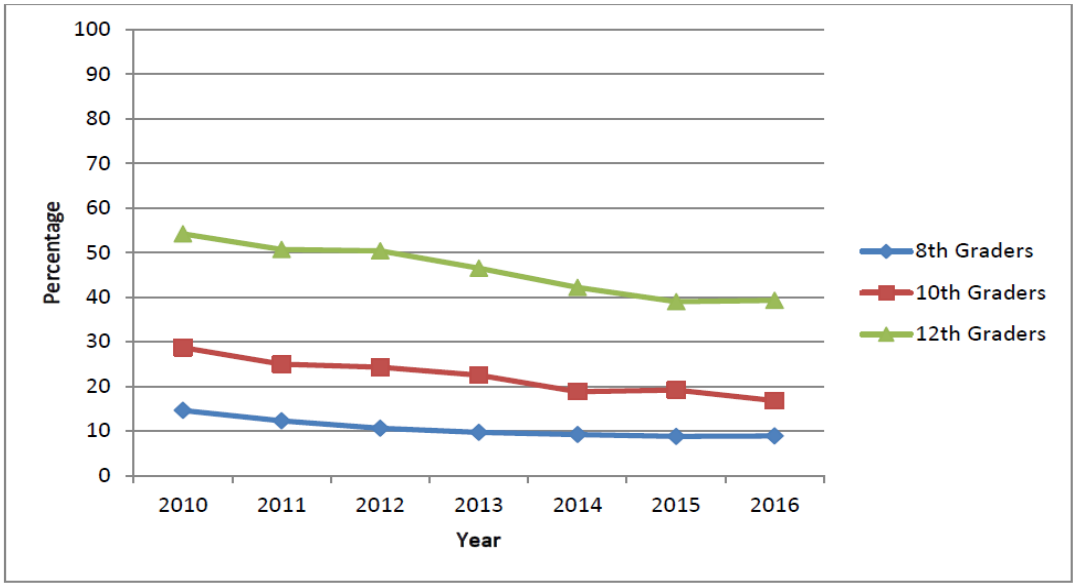


Figure 11: Annual Prevalence of Vicodin Use Among 8th. 10th, and 12th Grade Students



Similarly, perceived availability of these drugs declined among high school students (**Figure 12**) (copied directly from the RPC's Figure 31).

Figure 12: Perceived Availability of Narcotics Other than Heroin Among 8th, 10th, and 12th Graders: Easy or Easy to Get (2012- 2016).



In 2016, among 12th graders, perception of harmfulness of trying prescription opioids (Oxycontin and Vicodin, and other narcotics other than heroin) once or twice was 44%, occasionally was 56%, and regularly was 72%. Perception of harmfulness of taking prescription opioids was higher among 12th graders than 8th and 10th graders.

Reviewer's Comments:

1. Despite the limitation that the MTF surveys are serial cross-sectional surveys administered to different students every year, FDA continues to find MTF to be a valuable source of surveillance of non-medical use of opioid analgesics in adolescents. Generally, MTF data continue to show a downward trend in the use of narcotics other than heroin among all grade levels surveyed from 2010 to 2016. The data also show a decreasing perception of availability of narcotics over time across all grade levels surveyed. Furthermore, in 2016, more 12th graders than 8th and 10th graders perceived taking narcotics a great risk. Compared to 2015, there was a slight increase in the annual prevalence of OxyContin use and perceived harmfulness of taking narcotics among 8th graders. MTF data are not sufficient for understanding the national trend of use, misuse, and abuse of opioid analgesics among all ages, as MTF only surveys adolescents and young adults. Therefore, we recommend adding another national survey that can provide population estimates of use, misuse, and abuse of opioid analgesics in older age groups.

Recommendations for the RPC:

For the 72-month assessment report:

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

2. Provide results of analyses from one or more additional national survey data sources that can provide population estimates for the prevalence of use, misuse, and abuse of specific opioid analgesics (e.g., hydrocodone, oxycodone, fentanyl) as well as the prevalence of opioid use disorders in those using, misusing, and abusing these opioids. FDA would be interested in further descriptive characterization of these populations and behaviors (e.g., frequency of use, motivation for use, polysubstance abuse, pain and psychiatric conditions), as well as trends over time, as the data allow. Provide data on the prevalence of use, misuse, and abuse of heroin for context.

3. Provide a detailed description of the data source(s), limitations, and methods used for the above analyses.

5.5.7 Poison Centers: Additional Source of Epidemiologic Surveillance Data

FDA believes that despite their limitations, national poison center call data may contribute timely information to a multi-faceted surveillance program intended to understand trends in adverse outcomes and healthcare utilization related to use, misuse, and abuse of opioid analgesics. Therefore, FDA is asking that the RPC submit poison control data as part of the 72-month report, with key modifications to previously submitted reports.

Recommendations for the RPC:

For the 72-month assessment report:

1. Provide analyses of national (or near-national) poison center call data as follows, for the study period January 1, 2009 through the most recent quarter of data available:
    a. For the opioid categories listed below, provide tabular display of counts and 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.
        i. All opioid analgesics combined
        ii. ER/LA opioid analgesics

iii. IR opioid analgesics
iv. Individual opioid product groups (e.g., IR hydrocodone combination analgesics, IR oxycodone single-entity products, IR codeine combination analgesics, ER oxycodone products, ER morphine products, fentanyl transdermal products, etc.) as well as heroin.

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.

2. Provide tabular display of counts and 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 for:
    - All opioid analgesics combined
    - ER/LA opioid analgesics
    - IR opioid analgesics

3. For each year of the study period, provide tabular display of counts and tabular and graphic display of the proportion of intentional exposures calls and intentional abuse calls that also involved a benzodiazepine, among
    - All opioid analgesics combined
    - ER/LA opioid analgesics
    - IR opioid analgesics

4. For each year of the study period, provide the counts and proportion of all intentional and unintentional exposure calls that came from health care facilities, for
    - All opioid analgesics combined
    - ER/LA opioid analgesics
    - IR opioid analgesics

5. For each year of the study period, provide
    - Total population covered by the poison center program, and clarify how the coverage area is determined
    - Total number of intentional and unintentional (together and separately) human drug exposure calls within this coverage area, by age group.

6. Provide a detailed description of the data source, limitations, and methods used for the above analyses.

7. Provide a documented dataset of outcome counts in ZIP code catchment areas by quarter so that FDA can reproduce the 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), and dosage units' dispensed count (used in the adjustment). The data should be provided in a SAS export format.

5.6. ELEMENT 7 - DRUG UTILIZATION

This 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 purpose of the drug utilization data is to provide descriptive analyses to help understand utilization trends of opioid analgesic products. Ongoing monitoring of these trends are necessary to inform regulatory decisions related to these products and this REMS. There are many secular trends and concurrent interventions in the local, state, and federal level that will most likely confound this assessment. Thus, the goal of the drug utilization data is not to assess the impact of the REMS itself; rather, it is to understand and provide national utilization trends of opioid analgesic use. The following are objectives of this element:

- To obtain national trends in number of prescriptions for ER/LA opioids alone and stratify by patient characteristics and prescriber specialties
- To obtain national trends in number of prescriptions for comparator products (IR opioids, celecoxib, benzodiazepines, and tramadol) and prescriber specialty
  To obtain the absolute number and proportion of patients who switched from ER/LA opioids to comparator products (IR opioids, celecoxib, and tramadol) with the introduction of the REMS

5.6.1. Data source utilized by the RPC

The RPC utilized two QuintilesIMS databases to provide the presented utilization data for the 60-months assessment:

QuintilesIMS, National Prescription Audit (NPA):
The NPA measures the outflow of prescriptions from retail pharmacies, mail service houses, or Long Term Care (LTC) facilities into the hands of consumers. NPA data will be used to project analyses to national estimates that are

representative of the U.S population with a prescription from a retail pharmacy or long-term care facility.

QuintilesIMS, Lifelink (LRx):
The LRx database contains electronic dispensed prescription records at the anonymized patient-level collected from retail, LTC, and specialty and mail order pharmacies. Through agreements with a variety of data contributors, the warehouse represents dispensed prescriptions for 88% of the retail pharmacy channel, 65% for traditional and mail order, and 42% of LTC. Data are available from 2004 and approximately 98% of claims are available for analyses within 12 days of being dispensed. National Council for Prescription Drug Programs claims include those reimbursed by cash, Medicare, Medicaid, and other third party transactions. The database includes deidentified patient longitudinal prescription claims data, such as age, sex, 3-digit ZIP codes, dispensed drug (through National Drug Code (NDC)), molecule, form, strength, quantity, and days' supply. Other relevant data include method of payment and patient out-of-pocket costs. Currently the database contains data for over 220 million unique de-identified patients and one million physicians. It provides the breadth necessary to measure prescribing behavior at the territory and provider level, while the patient tracker provides the depth to understand treatment trends, such as new therapy starts and product switching. All data are Health Insurance Portability Accountability Act (HIPAA) compliant to protect patient privacy.

The study dates for each assessment study are July 1, 2010 through December 31, 2016. All analyses were stratified by channels, retail and long-term care (LTC), and the following time periods:

- Pre-Implementation: July 2010– June 2012
- Implementation: July 2012– June 2013
- Active: July 2013– December 2016

5.6.2. Results from RPC

In a given reporting month, patients who had at least one prescription claim for any of the ER/LA opioid analgesics included in the class REMS or for any of the comparator products (which included IR opioids, celecoxib, benzodiazepines, and tramadol) were included.

Table 11 below (copied directly from the RPC's Table 31) compares the changes in average quarterly prescriptions (from IMS's retail channel) pre- and post-REMS for the ER/LAs as a class, individual opioids available in ER/LA formulations, IR opioids, celecoxib, benzodiazepines, and tramadol. The table indicates that:

- Average quarterly prescription volume **decreased** (statistically) significantly pre- to post-REMS for the ERLAs by 6.9% and the IR opioids by 15.6%;

- Morphine, fentanyl transdermal, and oxycodone remained the market leaders amongst the ER/LAs;
- Pre- to post-REMS fentanyl transdermal average quarterly prescription volume **decreased** statistically significantly by 4.7% while average quarterly prescription volume decreased statistically significantly by 26% for oxycodone;
- Methadone had the fourth highest average quarterly prescription volume amongst the ER/LAs; however, methadone prescription average quarterly prescription volume **decreased** by 23.8%;
- On the other hand, morphine average quarterly prescription volume **increased** statistically significantly by 8.5%;
- It appears that the decrease in the overall average quarterly prescription volume for ER/LAs as a class was driven by the decreases in oxycodone and methadone.

Table 11: **Comparison of the Average Quarterly Prescription Volume across the Pre-Implementation Period and the Active Period (For Retail Channel)**

	Prescription Volume				Pre-Implementation Versus Active Period		
	Pre-Implementation		Active Period		Statistical Comparison	Percent Change Within Product Type	
Products[1]	Mean	95% CI	Mean	95% CI	% Change	95% CI	P-value (T-test)
Total ER/LA opioids	5,568,183	(5,458,138; 5,694,829)	5,181,985	(5,059,453; 5,370,890)	-6.9	(-9.63; -4.24)	<.001
Comparators							
IR opioids	46,382,812	(45,677,450; 47,137,287)	39,152,639	(36,336,237; 43,966,922)	-15.6	(-21.70; -9.48)	<.001
Celecoxib	2,004,875	(1,910,702; 2,112,569)	1,797,013	(1,742,056; 1,863,303)	-10.4	(-13.61; -7.13)	<.001
Benzodiazepines	20,914,395	(20,710,417; 21,232,442)	20,840,908	(20,530,557; 21,342,579)	-0.4	(-2.05; 1.35)	.671
Tramadol	8,209,288	(7,437,901; 9,371,852)	10,157,896	(9,935,595; 10,395,992)	23.7	(17.67; 29.80)	<.001

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	% Change	95% CI	P-value (T-test)
ER/LA opioids							
Buprenorphine film	—		12,647	(1,295; 20,889)	—	—	—
Buprenorphine TD	78,365	(26,521; 106,272)	154,521	(149,024; 163,181)	97.2	(72.14; 122.22)	<.001
Fentanyl TD	1,243,506	(1,231,412; 1,257,772)	1,185,090	(1,155,272; 1,235,798)	-4.7	(-8.14; -1.26)	.010
Hydrocodone bitartrate	—		35,486	(11,449; 57,167)	—	—	—
Hydromorphone HCl	24,634	(14,380; 41,447)	43,012	(36,574; 50,312)	74.6	(39.74; 109.46)	<.001
Methadone HCl	975,038	(945,413; 993,508)	743,366	(671,561; 828,038)	-23.8	(-30.27; -17.25)	<.001
Morphine sulfate	1,464,964	(1,391,404; 1,550,032)	1,590,192	(1,568,678; 1,630,170)	8.5	(5.42; 11.68)	<.001
Morphine-naltrexone	14,933	(4; 44,812)	14,829	(1,560; 29,078)	-0.7	(-115.70; 114.30)	.990
Oxycodone HCl	1,500,556	(1,291,861; 1,871,114)	1,110,145	(1,047,656; 1,185,408)	-26.0	(-34.71; -17.33)	<.001
Oxymorphone HCl	268,289	(228,277; 333,779)	238,226	(231,030; 246,201)	-11.2	(-20.72; -1.69)	.023
Tapentadol HCl	34,977	(3,270; 57,260)	73,311	(65,315; 85,269)	109.6	(64.03; 155.17)	<.001

Table 12 (copied directly from RPC's Table 2 in Appendix 13) compares the changes in average quarterly prescription volume in the parameters noted in **Table 8** above pre- and post-REMS in the IMS retail and LTC channels.

Observations from Table 12 include:

- The retail channel average quarterly prescription volume for ER/LAs in the post-REMS active period was 5.18 million prescriptions versus 0.88 million prescriptions in the LTC channel;
- In both channels IR opioid use was far more prevalent than ER/LA usage although the ratio of average quarterly prescription volume of IRs to ER/LAs was approximately 7.5 to 1 in the retail channel and 3.5 to 1 in the LTC channel;
- While ER/LA average quarterly prescription volume decreased statistically significantly in the post-REMS period in the retail channel, no such decrease was noted in the LTC channel. However, while IR opioid use also decreased significantly in the retail channel, use of IR opioids in the LTC *increased* significantly;
- Fentanyl transdermal, morphine, and oxycodone were the most commonly used ER/LA products in both channels;

- Average quarterly prescription volume of oxycodone decreased statistically significantly in both channels, while average quarterly prescription volume of tramadol increased statistically significantly in both channels.

Table 12: Summary of Retail and LTC Channel Results for Changes in ER/LA Opioids and Comparator Products Prescription Volumes

Metric	Retail Channel	LTC Channel
Total ER/LA opioid average quarterly prescription volume: change from Pre-Implementation to Active Period	6.9% decrease (P<.001)	0.1% decrease (P = .983)
Total ER/LA opioid average quarterly prescription volume: Pre-Implementation Period	5.57 million prescriptions	0.88 million prescriptions
Total ER/LA opioid average quarterly prescription volume: Active Period	5.18 million prescriptions	0.88 million prescriptions
Largest ER/LA opioid prescription volume share throughout study periods	Fentanyl TD Morphine sulfate Oxycodone HCl	Fentanyl TD Morphine sulfate Oxycodone HCl
Largest **decreases** in average quarterly prescription volume from the Pre-Implementation Period to the Active Period	Oxycodone HCl: 26.0% decrease (P<.001) Methadone HCl: 23.8% decrease (P<.001)	Oxycodone HCl: 11.5% decrease (P = .020)
Largest **increases** in average quarterly prescription volume from the Pre-Implementation Period to the Active Period	Tapentadol HCl: 109.6% increase (P<.001) Buprenorphine TD: 97.2% increase (P<.001) Hydromorphone HCl: 74.6% increase (P<.001)	Tapentadol HCl: 289.4% increase (P<.001)* Buprenorphine TD: 249.1% increase (P<.001)* Hydromorphone HCl: 133.3% increase (P<.001)*
Comparator products: **changes** in average quarterly prescription volume between the Pre-Implementation and the Active Periods	IR opioids: 15.6% decrease (P<.001) Celecoxib: 10.4% decrease (P<.001) Benzodiazepines: No statistically significant change Tramadol: 23.7% increase (P<.001)	IR opioids: 4.1% increase (P = .030) Celecoxib: No statistically significant change Benzodiazepines: 12.4% increase (P<.001) Tramadol: 34.4% increase (P<.001)
Comparator products average quarterly prescription volume: Pre-Implementation Period	IR opioids: 46.38 million Celecoxib: 2.00 million Benzodiazepines: 20.91 million Tramadol: 8.21 million	IR opioids: 2.99 million Celecoxib: 0.13 million Benzodiazepines: 1.82 million Tramadol: 0.66 million
Comparator products average quarterly prescription volume: Active Period	IR opioids: 39.15 million Celecoxib: 1.80 million Benzodiazepines: 20.84 million Tramadol: 10.16 million	IR opioids: 3.11 million Celecoxib: 0.13 million Benzodiazepines: 2.05 million Tramadol: 0.89 million

Table 13 (copied from the RPC report's Utilization Section 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:

- While average quarterly prescription volume decreased statistically significantly pre- to post-REMS period for all age groups 0-64 years, adults ≥ 65 years experienced a statistically significant increase in the same metric over the same period.
- While both females and males experienced statistically significant decreases in ER/LA average quarterly prescription volume, females continue to account for a higher percentage of ER/LA use than males (26% greater post-REMS average quarterly prescription volume);
- 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 those associated with the primary care provider (PCP) specialty decreased statistically significantly pre- to post-REMS by 19.9%. This specialty was far and away the largest prescriber group for the ER/LAs. The only other specialties noting statistically significant increases in ER/LA average quarterly prescription volume were 'Hospice and Palliative Care' and "Pain."

- 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 40.1% and 36.7% 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 13: Comparison of the Average Quarterly Prescription Volume Across the Pre-Implementation and Active Periods by Age, Sex, Prescriber Specialty, and Pay Type (Retail Channel)

Product* by Patient Age, Sex, Prescribing 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	25,064	(23,311; 27,641)	21,997	(18,058; 25,851)	-12.2	(-23.06; -1.41)	.029	-12.6	(-24.17; -1.77)	.041
19-40	843,653	(777,742; 922,549)	615,483	(548,454; 672,630)	-27.0	(-33.61; -20.49)	<.001	-27.3	(-34.56; -19.95)	<.001
41-64	3,477,646	(3,404,175; 3,551,357)	3,206,674	(3,084,325; 3,349,245)	-7.8	(-10.89; -4.70)	<.001	-7.5	(-11.13; -4.67)	<.001
≥65	1,221,820	(1,194,527; 1,258,215)	1,337,831	(1,323,163; 1,364,803)	9.5	(7.05; 11.94)	<.001	8.9	(6.80; 11.85)	<.001
Patient sex										
Male	2,488,324	(2,427,761; 2,572,765)	2,287,686	(2,230,726; 2,371,357)	-8.1	(-10.96; -5.16)	<.001	-7.5	(-10.94; -4.97)	<.001
Female	3,079,859	(3,030,377; 3,123,985)	2,894,298	(2,828,727; 2,999,532)	-6.0	(-8.58; -3.47)	<.001	-6.0	(-8.48; -3.55)	<.001

Table 13: Comparison of the Average Quarterly Prescription Volume Across the Pre-Implementation and Active Periods by Age, Sex, Prescriber Specialty, and Pay Type (Retail Channel), continued

Product* by Patient Age, Sex, Prescribing 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
Pay type										
Cash	283,001	(261,512; 333,292)	205,727	(193,991; 228,383)	-27.3	(-34.81; -19.80)	<.001	-27.0	(-35.87; -20.14)	<.001
Medicaid	388,567	(317,419; 443,309)	209,948	(188,691; 238,508)	-46.0	(-55.74; -36.19)	<.001	-51.1	(-54.95; -29.58)	<.001
Medicare Part D	1,698,134	(1,646,094; 1,799,870)	2,050,085	(2,024,440; 2,084,337)	20.7	(18.42; 23.03)	<.001	20.9	(18.14; 23.52)	<.001
Third Party	3,198,480	(3,126,739; 3,305,272)	2,716,225	(2,600,601; 2,843,583)	-15.1	(-18.41; -11.74)	<.001	-14.4	(-18.20; -11.84)	<.001

Table 13: Comparison of the Average Quarterly Prescription Volume Across the Pre-Implementation and Active Periods by Age, Sex, Prescriber Specialty, and Pay Type (Retail Channel), continued

Product* by Patient Age, Sex, Prescribing 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
Prescribing specialty										
Anesthesiologist	426,290	(424,270; 434,556)	423,251	(414,243; 434,606)	-0.7	(-2.79; 1.36)	.482	0.1	(-2.79; 1.51)	.785
Dentist	3,770	(3,278; 4,269)	1,882	(1,531; 2,202)	-50.1	(-60.38; -39.78)	<.001	-49.9	(-60.53; -40.07)	<.001
Emergency Medicine	41,829	(39,326; 45,958)	27,293	(25,515; 29,031)	-34.8	(-40.91; -28.59)	<.001	-35.9	(-40.69; -28.22)	<.001
Hospice and Palliative Medicine	13,357	(13,110; 14,220)	14,924	(14,500; 15,848)	11.7	(7.39; 16.08)	<.001	12.1	(7.98; 15.50)	<.001
Neurologist	137,893	(130,853; 147,932)	104,302	(94,142; 116,151)	-24.4	(-30.89; -17.83)	<.001	-26.3	(-31.92; -17.18)	<.001
Nurse Practitioner	423,711	(394,267; 461,359)	593,442	(560,774; 632,469)	40.1	(31.86; 48.25)	<.001	40.6	(31.81; 48.18)	<.001

Table 13: Comparison of the Average Quarterly Prescription Volume Across the Pre-Implementation and Active Periods by Age, Sex, Prescriber Specialty, and Pay Type (Retail Channel), continued

Product* by Patient Age, Sex, Prescribing 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
Prescribing specialty										
Anesthesiologist	426,290	(424,270; 434,556)	423,251	(414,243; 434,606)	-0.7	(-2.79; 1.36)	.482	0.1	(-2.79; 1.51)	.785
Dentist	3,770	(3,278; 4,269)	1,882	(1,531; 2,202)	-50.1	(-60.38; -39.78)	<.001	-49.9	(-60.53; -40.07)	<.001
Emergency Medicine	41,829	(39,326; 45,958)	27,293	(25,515; 29,031)	-34.8	(-40.91; -28.59)	<.001	-35.9	(-40.69; -28.22)	<.001
Hospice and Palliative Medicine	13,357	(13,110; 14,220)	14,924	(14,500; 15,848)	11.7	(7.39; 16.08)	<.001	12.1	(7.98; 15.50)	<.001
Neurologist	137,893	(130,853; 147,932)	104,302	(94,142; 116,151)	-24.4	(-30.89; -17.83)	<.001	-26.3	(-31.92; -17.18)	<.001
Nurse Practitioner	423,711	(394,267; 461,359)	593,442	(560,774; 632,469)	40.1	(31.86; 48.25)	<.001	40.6	(31.81; 48.18)	<.001

Table 13: Comparison of the Average Quarterly Prescription Volume Across the Pre-Implementation and Active Periods by Age, Sex, Prescriber Specialty, and Pay Type (Retail Channel), continued

Product* by Patient Age, Sex, Prescribing 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
Oncologist	204,775	(197,667; 213,529)	175,626	(168,747; 183,455)	-14.2	(-17.94; -10.52)	<.001	-14.1	(-18.01; -10.52)	<.001
Pain	678,785	(661,338; 701,052)	722,998	(712,963; 737,372)	6.5	(4.21; 8.82)	<.001	6.2	(4.11; 8.96)	<.001
PCP	2,249,302	(2,126,706; 2,398,992)	1,801,617	(1,693,005; 1,906,944)	-19.9	(-25.06; -14.75)	<.001	-20.5	(-25.67; -15.09)	<.001
Pediatrician	39,680	(37,541; 41,832)	29,910	(27,880; 31,547)	-24.6	(-29.15; -20.09)	<.001	-25.1	(-29.90; -19.96)	<.001
Physical Medicine and Rehabilitation	481,760	(476,457; 490,527)	453,388	(442,550; 466,576)	-5.9	(-8.29; -3.49)	<.001	-5.9	(-8.44; -3.29)	<.001
Physician Assistant	335,020	(310,718; 366,006)	457,835	(437,554; 483,510)	36.7	(29.52; 43.80)	<.001	37.7	(29.12; 43.41)	<.001
Rheumatologist	84,606	(79,689; 89,397)	65,728	(58,651; 71,877)	-22.3	(-28.97; -15.65)	<.001	-21.5	(-30.39; -15.45)	<.001
Surgeon	165,280	(151,950; 182,736)	113,134	(109,506; 121,201)	-31.6	(-37.66; -25.44)	<.001	-30.6	(-39.25; -24.98)	<.001
Other	282,125	(262,402; 328,220)	196,654	(176,900; 221,613)	-30.3	(-38.74; -21.85)	<.001	-32.6	(-40.33; -22.11)	<.001

Table 14 and **Table 15** (from Table 3 and Table 9 in the RPC's Appendix 13) summarizes the average quarterly prescription volume across retail and LTC channels for the data as captured in Table 11 directly above.

Observations from Table 12 and Table 13 below include:

- As would be expected, the highest average quarterly prescription volume is for patients ≥65 years of age in the LTC setting versus patients 41-64 years in the retail channel; however, whereas average quarterly prescription volume for those patients ≥65 years of age statistically significantly increased in the retail setting, it remained the same in the LTC setting.
- While ER/LA average quarterly prescription volume decreased statistically significantly for males and females in the retail setting, in the LTC setting average quarterly prescription volume remained the same for females but *increased* statistically significantly for males.
- As compared to the retail setting, in the LTC setting average quarterly prescription volume:
    - statistically significantly increased for prescriptions written by emergency medicine and pediatricians;
    - statistically significantly decreased for Pain medicine.

Table 14: Summary of Retail and LTC Channel Results for Changes in Total ER/LA Opioid Prescription Volumes by Patient Characteristics

Metric	Retail Channel	LTC Channel
Total ER/LA opioid average quarterly prescription volume: changes from the Pre-Implementation Period to the Active Period by age group	0 to 18 years: 12.2% decrease (P = .029) 19 to 40 year: 27.0% decrease (P<.001) 41-64 years: 7.8% decrease (P<.001) ≥65 years: 9.5% increase (P<.001)	0 to 18 years: 106.6% increase (P<.001) 19 to 40 years: 8.9% decrease (P = .002) 41-64 years: No statistically significant change ≥65 years: No statistically significant change
Age group with highest quarterly total ER/LA opioid prescription volume across study periods	41-64 years	≥65 years
Total ER/LA opioid average quarterly prescription volume: changes from the Pre-Implementation Period to the Active Period for females and males	Females: 6.0% decrease (P<.001) Males: 8.1% decrease (P<.001)	Females: No statistically significant change Males: 6.9% increase (P – .001)
Total ER/LA opioid average quarterly prescription volume for females and males in the Pre-Implementation Period	Females: 3.08 million Males: 2.49 million	Females: 0.61 million Males: 0.27 million
Total ER/LA opioid average quarterly prescription volume for females and males in the Active Period	Females: 2.89 million Males: 2.29 million	Females: 0.59 million Males: 0.29 million
Total ER/LA average quarterly prescription volume: changes from the Pre-Implementation Period to the Active Period by pay type	Cash: 27.3% decrease (P<.001) Medicaid: 46.0% decrease (P<.001) Medicare Part D: 20.7% increase (P<.001) Third Party: 15.1% decrease (P<.001)	Cash: No statistically significant change Medicaid: 18.7% decrease (P<.001) Medicare Part D: 11.5% increase (P = .003) Third Party: 18.3% decrease (P<.001)

Table 15: Summary of Retail and LTC Channel Results for Changes in ER/LA Opioid and Comparator Product Prescription Volumes by Provider Specialty

Metric	Retail Channel	LTC Channel
Largest average quarterly ER/LA opioid prescription volume: Pre-Implementation Period	PCP: 2.25 million	PCP: 0.62 million
Total ER/LA opioid average monthly prescription volume among specialties for which the REMS was hypothesized to have **greater impact** on prescribing: change between the Pre-Implementation and Active Periods		
Decreases	Dentist: 50.1% decrease (P<.001) Emergency Medicine: 34.8% decrease (P<.001) Neurologist: 24.4% decrease (P<.001) PCP: 19.9% decrease (P<.001) Pediatrician 24.6% decrease (P<.001) Rheumatologist: 22.3% decrease (P<.001) Surgeon: 31.6% decrease (P<.001)	Neurologist: 46.3% decrease (P<.001) PCP: 8.8% decrease (P<.001)
Increases	Nurse Practitioner: 40.1% increase (P<.001) Physician Assistant: 36.7% increase (P<.001)	Emergency Medicine: 34.9% increase (P<.001) Pediatrician: 14.4% increase (P<.001) Nurse Practitioner: 38.3% increase (P<.001) Physician Assistant: 49.5% increase (P<.001)
No statistically significant change	N/A	Dentist Rheumatologist Surgeon

Metric	Retail Channel	LTC Channel
Total ER/LA opioid average monthly prescription volume among specialties hypothesized to be **less affected** by the REMS: change between the Pre-Implementation and Active Periods		
Decreases	Oncologist: 14.2% decrease (P<.001) Other: 30.3% decrease (P<.001) Physical Medicine and Rehabilitation: 5.9% decrease (P<.001)	Physical Medicine and Rehabilitation: 35.9% decrease (P<.001) Anesthesiologist: 20.9% decrease (P<.001) Pain: 52.2% decrease (P<.001)
Increases	Hospice and Palliative Medicine: 11.7% increase (P<.001) Pain: 6.5% increase (P<.001)	Other: 35.6% increase (P<.001)
No statistically significant change	Anesthesiologist	Oncologist Hospice and Palliative Medicine

5.6.3. Reviewer Comments

1. The retail and long term care utilization data provided by the RPC are helpful. However, FDA suggests exploring other data sources that will encompass utilization of ER/LA opioid analgesic products across ALL outpatient settings of

care (i.e., specialty clinics, ambulatory clinics, and non-emergency room outpatient hospital settings, etc.) to provide a more comprehensive utilization analyses of ER/LA opioid analgesic products in the U.S. market. Moreover, because the goal of the drug utilization data is not to assess the impact of the REMS itself, but rather to understand and provide national trends of opioid analgesic use, we request the RPC to present all the data from the results section in a more meaningful and interpretable format. FDA wishes to evaluate changes over time, which is not possible with the RPC's current method of aggregating data into two time periods, pre- and post- REMS. The aggregated means do not provide the granularity needed for appropriate evaluation of prescription patterns for changes over time.

2. Regarding the switch analyses, we recommend longitudinal patient-level analysis to demonstrate switching. We also note two major limitations. Although the data are important, the current switch analysis is inconclusive because the patterns in switching based on prescription claims alone do not provide the intent or reason for the switch. Additionally, based on claims data only, it is inconclusive that the patient was switched from an ER/LA to the comparator drug for the same indication or if the comparator product was started due to a new indication. In the absence of data capturing the intent or reason for switching, these data are difficult to interpret because we do not know how the REMS has impacted the prescriber's decision to switch. For example, did the prescriber switch products because the REMS was too burdensome or was it for a legitimate clinical reason (i.e., inadequate pain control, or for a new indication). Secondly, FDA needs clarification as to why tramadol was separated out from the IR opioid analgesic product group as its own comparator group; additionally, please clarify if tramadol IR products were also included in the IR opioid analgesics group. Finally, although prescribers may be switching patients from ER/LA opioid analgesics to some of the currently selected comparator groups (*IR opioid analgesics, celecoxib, and tramadol),* there are other comparator products that should be considered that are not included in the current switching analyses (i.e., gabapentinoids, serotonin-norepiephrine reuptake inhibitors). FDA recommends the RPC expand to other potential comparator groups that may be used for pain management.

5.6.4 Recommendations to RPC

1. The retail and long term care utilization data provided by the RPC are helpful. However, FDA suggests exploring other data sources that will encompass utilization of ER/LA opioid analgesic products across all <u>outpatient</u> settings of care (i.e., specialty clinics, ambulatory clinics, and non-emergency room outpatient hospital settings, etc.) to provide a more comprehensive utilization analyses of ER/LA opioid analgesic products in the U.S. market
2. For the data reported in the results section, we request the RPC to present the data in a more meaningful and interpretable format by 1) removing the pre- and post-

REMS periods, 2) provide the **actual quarterly prescription counts** for each product and for each group (total ER/LA, IR opioid analgesics, celecoxib, benzodiazepines, tramadol), rather than the aggregated means reported in the 60-months assessment in both channels, retail and LTC.

3. The switch analyses data obtained using the current methods and data sources alone were not informative. Data solely based on dispensed prescription claims are insufficient to determine the validity and appropriateness of the prescribing patterns. For more informative analyses, propose other methods and data sources to provide insight into the reasons for why prescribers are switching from a ER/LA opioid REMS product to a non-REMS opioid product .
4. For the current selected comparator groups, expand to other comparator groups that may be used for pain management. In addition, IR tramadol needs to be included as part of the IR opioid analgesic product group and not stand alone as its own comparator group.

5.6.5. ER/LA Prescriber IR Response

In the FDA's October 31, 2018 email conveying preliminary comments to the RPC regarding their 60-month assessment report, an IR for the RPC was included that asked: "*During the development of the ER/LA Opioid Analgesic REMS, the Industry Working Group (IWG) provided data on the number of prescribers of these products in order to better understand how many prescribers ideally should take the continuing education trainings. The FDA requests the RPC provide the following information* ***on or before February 1, 2018***."

The RPC's January 30, 2018 response to this Information Request is entitled "**Assessment of the Number of Opioid Providers in the United States"** and used the IQVIA Xponent database, which provides detailed retail prescriber and plan level (Rx) prescription data across all retail and mail classes for the US and Puerto Rico. Xponent coverage includes retail, mail service, long-term care, and managed care channels. The study period was January 1, 2011 through December 31, 2016 (the calendar years with complete data after the REMS program initiated). Prescribers were included if they were associated with ≥1 prescription claim for an opioid.

The following definitions were used:

All prescribers—All prescribers of all specialties (including mid-level prescribers, defined as Nurse Practitioners and Physician Assistants) and prescribers with unknown specialty (none were identified)

Prescribers—All prescribers, *except* for Nurse Practitioners, Physician Assistants, and prescribers with unknown specialty

- **ER/LA opioid analgesics**—The number of prescribers who prescribed at least 1 ER/LA opioid analgesic

ER/LA opioid analgesics subject to REMS—All prescribers, defined as the number of prescribers who prescribed at least 1 ER/LA opioid analgesic subject to the REMS (excludes intravenous methadone)

- **IR opioid analgesics**—The number of prescribers who prescribed at least 1 IR opioid analgesic
- **IR opioid analgesics subject to REMS**—The number of prescribers who prescribed at least 1 IR opioid analgesic subject to the REMS (excludes intravenous IR opioids such as fentanyl, morphine, meperdine, nalbuphine, and pentazocine, combination products the contain aspirin/butalbital/codeine, and oral agents such as propoxyphene).

Table 16 (taken entirely from the RPC's Table 4 of their January 30, 2018 IR response) presents the findings of their analysis:

Table 16: Number of prescribers who prescribed ≥1 opioid (immediate-release or Extended-release) by all opioids (ER/LA and IR opioids) and opioids subject to the Modified Opioid Analgesics REMS Program in the IQVIA Xponent database from 01 January 2011 to 31 December 2016

	2011		2012		2013		2014		2015		2016	
	N	%	N	%	N	%	N	%	N	%	N	%
ER/LA opioids subject to REMS												
All prescribers	361,074	100.0	371,737	100.0	375,248	100.0	379,360	100.0	374,570	100.0	363,722	100.0
Prescribers	310,039	85.9	314,255	84.5	310,350	82.7	307,562	81.1	299,316	79.9	285,154	78.4
Nurse Practitioners and Physician Assistants	51,035	14.1	57,482	15.5	64,898	17.3	71,798	18.9	75,254	20.1	78,568	21.6
IR opioids subject to REMS												
All prescribers	971,983	100.0	1,040,009	100.0	1,061,306	100.0	1,074,498	100.0	1,058,658	100.0	1,067,820	100.0
Prescribers	842,035	86.6	887,460	85.3	895,881	84.4	891,509	83.0	875,667	82.7	870,110	81.5
Nurse Practitioners and Physician Assistants	129,948	13.4	152,549	14.7	165,425	15.6	182,989	17.0	182,991	17.3	197,710	18.5
All ER/LA opioids												
All prescribers	361,075	100.0	371,739	100.0	375,251	100.0	379,362	100.0	374,577	100.0	363,726	100.0
Prescribers	310,040	85.9	314,257	84.5	310,353	82.7	307,564	81.1	299,323	79.9	285,157	78.4
Nurse Practitioners and Physician Assistants	51,035	14.1	57,482	15.5	64,898	17.3	71,798	18.9	75,254	20.1	78,569	21.6
All IR opioids												
All prescribers	974,422	100.0	1,042,665	100.0	1,064,103	100.0	1,077,680	100.0	1,062,548	100.0	1,072,638	100.0
Prescribers	844,253	86.6	889,862	85.3	898,446	84.4	894,415	83.0	879,220	82.7	874,532	81.5
Nurse Practitioners and Physician Assistants	130,169	13.4	152,803	14.7	165,657	15.6	183,265	17.0	183,328	17.3	198,106	18.5

5.6.5.1. Reviewer Comments

1. While Xponent coverage is excellent for retail/mail service channels, it does not provide total coverage of long-term care, and managed care channels. In addition, neither inpatient/hospital setting nor cash prescriptions are included.
2. From 2011 through 2016, the number of prescribers of ER/LA products subject to the REMS remained essentially the same (around 361,000 to 363,000) whereas the number of prescribers of IR opioids that are to be covered by the new REMS rose very slightly (from around 972,000 to 1,068,000).
3. While prescriptions for ER/LAs covered by the REMS are still primarily written by physicians (78.4% of prescriptions for 2016), this percentage has decreased since 2011 when 85.9% were written by physicians. Meanwhile, the percent of prescriptions written by nurse practitioners and physician assistants has increased from 14.1% in 2011 to 21.6% in 2016, an increase of 53%.
4. Similarly, while prescriptions for IR opioid analgesics that are to be covered by the REMS are still primarily written by physicians (81.5% of prescriptions for 2016), this percentage has decreased since 2011 when 86.6% were written by physicians. Meanwhile, the percent of these prescriptions written by nurse practitioners and physician assistants has increased from 13.4% in 2011 to 18.5% in 2016, an increase of 38%.
5. These increases in prescriptions written by mid-level practitioners from 2011 through 2016 parallels the increases seen over time in mid-level practitioners comprising an increasing percentage of the professions completing the RPC training over the most recent 4 years (see Table 1 of this review). In addition, in the February 26, 2015 review of the 24-month ER/LA Assessment Report submission, Table 19-B of that review (data provided by the RPC) highlighted that an increasing percentage of prescriptions for other pharmacologic classes of drugs were being written by mid-level practitioners.

5.7. ELEMENT 7, CONTINUED – CHANGES IN PRESCRIBING BEHAVIORS

The purpose of this evaluation is to provide descriptive analyses to help understand prescribing trends of practitioners who prescribe ER/LA opioid analgesic products. Ongoing monitoring of these trends are necessary to inform regulatory decisions related to these products and this REMS. Specifically, the following objectives will be assessed in this section:

- For products indicated for use in opioid-tolerant patients only (i.e., fentanyl transdermal, hydromorphone ER, morphine ER >90mg unit strength), to describe trends in the proportion of prescriptions prescribed for products that are indicated for use in opioid-tolerant patients only to non-opioid-tolerant patients
- For products whose labels indicate that higher dosage strengths should only be used in opioid-tolerant patients, to describe trends in the

proportion of prescriptions prescribed to opioid non-tolerant patients with a high starting dosage strength opioid
- To describe trends in the proportion of prescriptions for ER/LA opioids to patients that have excessive or early refills of prescriptions
- To compare the proportion of patients with concomitant use of benzodiazepines and ER/LA opioids

The above objectives were evaluated using the same retrospective cross-sectional study as the drug utilization data.

5.7.1. Datasource utilized by the RPC

The RPC utilized the same QuintilesIMS databases to provide the presented data on opioid tolerance, early refills, and concomitant use of opioids and benzodiazepines.

The study dates for each assessment study are July 1, 2010 through December 31, 2016. All analyses were stratified by channels, retail and long-term care (LTC), and the following time periods:

- Pre-Implementation: July 2010– June 2012
- Implementation: July 2012– June 2013
- Active: July 2013– December 2016

5.7.2. Results from the RPC

In a given reporting month, patients who had at least 1 prescription claim for any of the ER/LA opioid analgesics included in the class REMS or for any of the comparator products (which included IR opioids, celecoxib, benzodiazepines, and tramadol) were included.

5.7.2.1. Opioid tolerance

Table 17 below (copied directly from the RPC's Table 33) compares the changes in average monthly proportion of opioid non-tolerant patients prescribed products indicated for opioid-tolerant patients only, pre- and post-REMS (from IMS's retail channel). The table indicates that:

- Overall patient volume increased for hydromorphone ER, decreased for morphine ER ≥ 90 mg and fentanyl transdermal from the pre- to post-REMS periods;
- Pre- to post-REMS, the average monthly proportion of opioid non-tolerant patients prescribed ER/LA opioids indicated for use in opioid-tolerant patients only, decreased (statistically) significantly for fentanyl transdermal (-5.2%), hydromorphone ER (-10.2%), and morphine sulfate ER ≥ 90mg (-8.3%).

- Although the percent of opioid non-tolerant patients taking these three classes of products that are indicated only for opioid-tolerant patients has decreased, 27.2 to 46.0% of patients receiving these products were opioid non-tolerant in the post-REMS period. As is discussed in Comment #1 under this review's section 5.7.3, the methods and asumptions to assess opioid tolerance may potentially lead to an *underestimation* of opioid tolerance.

Table 17: Comparison of the Average Monthly Proportion of Opioid Non-Tolerant Patients Prescribed Products Indicated for Opioid-tolerant Patients Only, Across the Pre-Implementation Period and the Active Period

	Average Monthly Patient Volume				Pre-Implementation Versus Active Period		
	Pre-Implementation		Active Period		Statistical Comparison	Percent Change Within Product Types	
ER/LA Opioid[1]	Mean	95% CI	Mean	95% CI	% Change	95% CI	P-value (T-test)
Fentanyl TD							
Tolerant patient volume	177,368	(172,773; 185,171)	180,954	(174,937; 186,300)	2.0	(-1.01; 5.06)	.188
Non-tolerant patient volume	166,845	(161,732; 172,443)	153,980	(149,860; 160,502)	-7.7	(-11.00; -4.42)	<.001
% non-tolerant	48.5%	(46.66%; 49.86%)	46.0%	(45.20%; 47.27%)	-5.2%	(-7.89%; -2.57%)	<.001
Hydromorphone HCl							
Tolerant patient volume	4,078	(2,798; 4,836)	7,576	(6,969; 7,863)	85.8	(67.01; 104.53)	<.001
Non-tolerant patient volume	3,100	(2,168; 3,836)	4,884	(4,217; 4,928)	57.5	(38.07; 76.99)	<.001
% non-tolerant	43.4%	(42.35%; 44.65%)	39.0%	(38.25%; 39.78%)	-10.2%	(-12.74%; -7.60%)	<.001
Morphine sulfate ≥90mg							
Tolerant patient volume	36,975	(35,771; 38,638)	28,271	(27,076; 30,129)	-23.5	(-28.22; -18.86)	<.001
Non-tolerant patient volume	15,557	(14,167; 16,850)	10,623	(9,269; 11,243)	-31.7	(-38.43; -25.01)	<.001
% non-tolerant	29.6%	(26.96%; 31.92%)	27.2%	(25.49%; 28.82%)	-8.3%	(-13.79%; -2.72%)	.004

Table 18 (copied directly from the RPC's Table 5 in Appendix 13) below compares results for changes in ER/LA opioids indicated for use in opioid-tolerant patients prescribed to opioid non-tolerant patients in the IMS retail and LTC channels from pre- and post-REMS. The table indicates that:

- Overall, the change in the average monthly proportion of opioid non-tolerant patients prescribed ER/LA opioid products between the pre- and post- study

periods was the same in the LTC channel as it was in the retail channel with the exception that there was no statistically significant change for hydromorphone in the LTC channel;

Table 18: Summary of Retail and LTC Channel Results for Changes in ER/LA Opioids Indicated for Use in Opioid-Tolerant Patients Prescribed to Opioid-Nontolerant Patients

Metric	Retail Channel	LTC Channel
Average monthly proportion of opioid-nontolerant patients prescribed ER/LA opioids indicated for use in opioid-tolerant patients: change from Pre-Implementation to Active Period	Fentanyl TD: 5.2% decrease (P<.001) Hydromorphone HCl: 10.2% decrease (P<.001) Morphine sulfate ≥90 mg: 8.3% decrease (P = .004)	Fentanyl TD: 2.2% decrease (P<.001) Hydromorphone HCl: No statistically significant change Morphine sulfate ≥90 mg: 9.3% decrease (P<.001)

Table 19 (copied directly from the RPC's Table 34) compares the changes in average monthly proportion of opioid non-tolerant patients with high starting strength ER/LA opioids prescriptions, pre- and post-REMS (from IMS's retail channel). The table indicates that:

- Pre- to post-REMS, the average monthly proportion of opioid non-tolerant patients prescribed a high starting strength of fentanyl transdermal (-5.2%), hydromorphone (-10.2%), morphine sulfate (-7.3%), oxycodone (-9.2%), oxymorphone (-11.2%), and tapentadol (-16.7%), had a statistically significant **decrease**;
- Buprenorphine transdermal was the only product that had a statistically significant **increase** for the average monthly proportion of opioid non-tolerant patients prescribed a high starting strength from pre- to post-REMS;
- Buprenorphine film and hydrocodone bitartrate were not available during the pre-implementation period. Thus, the average monthly proportion of opioid non-tolerant patients prescribed a high-starting strength of buprenorphine film and hydrocodone could not be calculated.
- Although he percentage of opioid non-tolerant patients taking these ER/LA products at doses intended only for opioid-tolerant patients has decreased, depending the the product, the percentage of opioid non-tolerant patients on these drugs was still 27.2% to 78.7%. As discussed in Comment #1 under this review's section 5.7.3, the methods and asumptions to assess opioid tolerance may potentially lead to an *underestimation* of opioid tolerance.

Table 19: Comparison of the Average Monthly Proportion of Opioid Non-Tolerant Patients with High Starting Strength Prescriptions, Across the Pre-Implementation Period and the Active Period

	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	% Change	95% CI	P-value (T-test)
Buprenorphine film (total patients)	—		2,844	(1,233; 4,696)	—	—	—
% of non-tolerant patients	—		1	(70.96%; 78.85%)	—	—	—
Buprenorphine TD (total patients)	15,260	(11,782; 19,896)	36,078	(36,200; 37,765)	136.4	(119.57; 153.27)	<.001
% of non-tolerant patients	74.5%	(74.65%; 76.05%)	78.7%	(77.84%; 79.46%)	5.7%	(4.12%; 7.29%)	<.001
Fentanyl TD (total patients)	344,213	(340,984; 348,690)	334,934	(332,146; 343,339)	-2.7	(-4.61; -0.79)	.006
% of non-tolerant patients	48.5%	(46.66%; 49.86%)	46.0%	(45.20%; 47.27%)	-5.2%	(-7.89%; -2.57%)	<.001
Hydrocodone bitartrate (total patients)	—		8,229	(3,714; 10,985)	—	—	—
% of non-tolerant patients	—		1	(53.89%; 55.67%)	—	—	—
Hydromorphone HCl (total patients)	7,179	(4,966; 9,049)	12,460	(11,427; 12,620)	73.6	(54.83; 92.32)	<.001
% of non-tolerant patients	43.4%	(42.35%; 44.65%)	39.0%	(38.25%; 39.78%)	-10.2%	(-12.74%; -7.60%)	<.001
Morphine sulfate[2] (total patients)	266,661	(253,828; 279,062)	292,787	(290,677; 299,026)	9.8	(7.21; 12.38)	<.001
% of non-tolerant patients	37.9%	(35.10%; 40.33%)	35.2%	(33.50%; 36.80%)	-7.3%	(-11.74%; -2.81%)	.002
Morphine-naltrexone (total patients)	620	(440; 849)	197	(108; 291)	-68.2	(-92.62; -43.86)	<.001
% of non-tolerant patients	34.3%	(24.94%; 40.00%)	27.2%	(24.62%; 29.55%)	-20.6%	(-49.05%; 7.83%)	.150
Oxycodone HCl (total patients)	337,628	(312,497; 358,701)	252,543	(248,790; 265,967)	-25.2	(-29.81; -20.59)	<.001
% of non-tolerant patients	36.0%	(33.55%; 37.95%)	32.7%	(31.59%; 34.24%)	-9.2%	(-13.45%; -4.89%)	<.001
Oxymorphone HCl (total patients)	72,120	(65,192; 80,406)	65,150	(64,328; 66,031)	-9.7	(-15.32; -4.01)	.001
% of non-tolerant patients	33.4%	(32.00%; 35.26%)	29.7%	(28.42%; 31.09%)	-11.2%	(-15.69%; -6.68%)	<.001
Tapentadol HCl (total patients)	9,593	(6,287; 13,802)	18,302	(16,836; 18,860)	90.8	(73.35; 108.20)	<.001
% of non-tolerant patients	53.7%	(51.05%; 56.07%)	44.7%	(43.68%; 46.02%)	-16.7%	(-20.17%; -13.23%)	<.001

Table 20 copied directly from the RPC's Table 6 in Appendix 13) compares results for changes in ER/LA opioids indicated for use in opioid-tolerant patients prescribed to opioid non-tolerant patients in the IMS retail and LTC channels from pre- and post-REMS. The table indicates that:

- Average monthly proportion of opioid non-tolerant patients prescribed a high starting strength ER/LA opioid product was more stable across study periods than in the retail channel;
- No statistically significant changes were observed for hydromorphone, morphine-naltrexone, oxymorphone, and tapendatol in the LTC channel;
- Pre- and post-REMS, the proportion **decreased** in the average monthly proportion of opioid non-tolerant patients prescribed a high starting strength ER/LA opioid products for fentanyl transdermal, morphine sulfate, and oxycodone;
- Pre- and post-REMS, the proportion **increased** in the average monthly proportion of opioid non-tolerant patients prescribed a high starting strength ER/LA opioid products for buprenorphine transdermal.

Table 20: Summary of Retail and LTC Channel Results for Changes in High Starting Strength ER/LA Opioids Prescribed to Opioid-Nontolerant Patients

Metric	Retail Channel	LTC Channel
ER/LA products with a **decrease** in an average monthly proportion of opioid-nontolerant patients prescribed a high starting strength ER/LA opioid product between the Pre-Implementation and Active Periods	Fentanyl TD: 5.2% decrease (P<.001) Hydromorphone HCl: 10.2% decrease (P<.001) Morphine sulfate: 7.3% decrease (P = .002) Oxycodone HCl: 9.2% decrease (P<.001) Oxymorphone HCl: 11.2% decrease (P<.001) Tapentadol HCl: 16.7% decrease (P<.001)	Fentanyl TD: 2.2% decrease (P<.001) Morphine sulfate: 5.1% decrease (P<.001) Oxycodone HCl: 1.6% decrease (P = .031)
ER/LA products with an **increase** in average monthly proportion of opioid-nontolerant patients prescribed a high starting strength ER/LA opioid product between the Pre-Implementation and Active Periods	Buprenorphine TD: 5.7% increase (P<.001)	Buprenorphine TD: 10.9% increase (P<.001)
ER/LA products with **no change** (or no statistically significant change increase or decrease) in an average monthly proportion of opioid-nontolerant patients prescribed a high starting strength ER/LA opioid product between the Pre-Implementation and Active Periods	Morphine-naltrexone	Hydromorphone HCl Morphine-naltrexone Oxymorphone HCl Tapentadol HCl

5.7.2.2. Early fills

The results for the early fill data will not be discussed because it was not informative for the purpose of this REMS. Please refer to section 5.7.3, for more clarification on this issue.

5.7.2.3. Concomitant Use of Benzodiazepines w/ ER/LA Opioids

Table 21 (copied directly from the RPC's Table 36) compares the changes in average monthly proportion of patients with concomitant use of benzodiazepines with ER/LA opioids, pre- and post-REMS (from IMS's retail channel). The table indicates that:

- Pre- to post-REMS, the average monthly proportion of patients who concomitantly used benzodiazepines with buprenorphine TD (-7%), hydromorphone (-4.4%), methadone (-6%), morphine sulfate (-4.2%), oxycodone (-1.8%), oxymorphone (-3.2%), and tapentadol (-5.5%), had a statistically significant **decrease**;
- No statistically significant **change** in the average monthly proportion of patients who used fentanyl transdermal concomitantly with benzodiazepines, from pre- to post-REMS;
- Buprenorphine film and hydrocodone bitartrate was not available during the pre-implementation period, therefore no change between study periods can be calculated.
- Although concomitant benzodiazepine use decreased significantly for most of the ER/LA products, 23.4 – 29.5% of prescriptions for ER/LAs were accompanied by concomitant benzodiazepine therapy.

Table 21: Comparison of the Average Monthly Proportion of Patients with Concomitant Use of Benzodiazepines and ER/LA Opioids, Across the Pre-Implementation Period and the Active Period

	Average Monthly Proportion of Patients				Pre-Implementation Versus Active Period		
	Pre-Implementation		Active Period		Statistical Comparison	Percent Change Within Products	
ER/LA Opioid	Mean	95% CI	Mean	95% CI	% Change	95% CI	P-value (T-test)
Buprenorphine film							
Total patient volume	—	—	3,956	(2,082; 6,056)	—	—	—
% concomitant with benzodiazepines	—	—	0	(23.65%; 26.54%)	—	—	—
Buprenorphine TD							
Total patient volume	22,836	(19,540; 28,280)	45,937	(45,929; 48,606)	101.2	(86.92; 115.40)	<.001
% concomitant with benzodiazepines	25.2%	(24.40%; 25.54%)	23.4%	(23.29%; 23.64%)	-7.0%	(-8.60%; -5.32%)	<.001
Fentanyl TD							
Total patient volume	344,213	(340,984; 348,690)	334,934	(332,146; 343,339)	-2.7	(-4.61; -0.79)	.006
% concomitant with benzodiazepines	29.4%	(29.31%; 29.57%)	29.5%	(29.49%; 29.75%)	0.2%	(-0.36%; 0.82%)	.438
Hydrocodone bitartrate							
Total patient volume	—	—	11,001	(4,729; 14,564)	—	—	—
% concomitant with benzodiazepines	—	—	24.6%	(24.50%; 25.24%)	—	—	—
Hydromorphone HCl							
Total patient volume	7,179	(4,966; 9,049)	12,460	(11,427; 12,620)	73.6	(54.83; 92.32)	<.001
% concomitant with benzodiazepines	29.8%	(29.45%; 30.25%)	28.5%	(28.36%; 29.01%)	-4.4%	(-5.88%; -2.97%)	<.001
Methadone HCl							
Total patient volume	282,039	(282,470; 284,766)	217,404	(204,190; 234,326)	-22.9	(-26.42; -19.41)	<.001
% concomitant with benzodiazepines	28.3%	(28.20%; 28.48%)	26.6%	(26.38%; 27.16%)	-6.0%	(-7.10%; -4.86%)	<.001
Morphine sulfate							
Total patient volume	414,545	(398,681; 430,191)	459,158	(456,290; 463,453)	10.8	(8.82; 12.70)	<.001
% concomitant with benzodiazepines	28.8%	(28.70%; 28.92%)	27.6%	(27.44%; 27.99%)	-4.2%	(-5.15%; -3.18%)	<.001
Morphine-naltrexone							
Total patient volume	5,263	(3; 12,164)	4,838	(2,048; 7,854)	-8.1	(-63.02; 46.90)	.769
% concomitant with benzodiazepines	32.6%	(24.75%; 25.07%)	28.0%	(24.59%; 25.51%)	-14.2%	(-50.78%; 22.28%)	.435

Table 21, *continued*: Comparison of the Average Monthly Proportion of Patients with Concomitant Use of Benzodiazepines and ER/LA Opioids, Across the Pre-Implementation Period and the Active Period

	Average Monthly Proportion of Patients				Pre-Implementation Versus Active Period		
	Pre-Implementation		Active Period		Statistical Comparison	Percent Change Within Products	
ER/LA Opioid	Mean	95% CI	Mean	95% CI	% Change	95% CI	P-value (T-test)
Oxycodone HCl							
Total patient volume	419,408	(393,572; 445,313)	321,849	(316,764; 336,662)	-23.3	(-27.54; -18.98)	<.001
% concomitant with benzodiazepines	29.7%	(29.65%; 29.85%)	29.2%	(29.18%; 29.56%)	-1.8%	(-2.39%; -1.12%)	<.001
Oxymorphone HCl							
Total patient volume	76,885	(69,088; 85,156)	70,184	(69,604; 71,076)	-8.7	(-14.06; -3.36)	.002
% concomitant with benzodiazepines	30.2%	(29.82%; 30.85%)	29.2%	(29.06%; 29.82%)	-3.2%	(-4.76%; -1.70%)	<.001
Tapentadol HCl							
Total patient volume	12,336	(8,559; 17,514)	22,602	(20,334; 23,769)	83.2	(64.40; 102.03)	<.001
% concomitant with benzodiazepines	22.8%	(21.92%; 23.83%)	21.6%	(21.37%; 21.77%)	-5.5%	(-7.35%; -3.69%)	<.001

5.7.3. Reviewer comments

1. We acknowledge RPC's revision on the 90-day look back period (to 90-day treatment identification period) described in the 48-month assessment report; however, utilizing only the primary definition for opioid tolerance which is opioid usage of at least 60mg oral morphine per day (or an equianalgesic dose of another opioid) for 7 days consecutively in the 7 days look-back period prior to the index prescription claim as described in the study by Willy et al. will result in underestimation for patients considered as "opioid-tolerant". Underestimation of patients considered as "opioid-tolerant" may also occur among patients who receive prescriptions outside of the IMS LRx database pharmacy sample or among patients receiving prescriptions in settings of care not captured in the database (such as inpatient setting or rehabilitation facilities). 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 propertly identified. However, relying solely on electronic prescription claims data may overestimate the number of patients classified as "opioid-tolerant" because it relies on assumptions that patients take each dispensed prescription as indicated and all the pills dispensed are used by the patient. Due to the limitations mentioned above with prescription

claims data, the reviewer agrees with the study objectives, but the methodology and data source selected are not designed to adequately address these objectives.

2. Regarding the early fill data, the data obtained using the current methods and data sources alone were not informative as the reasons for early fill are not known. Early fills may be due to legitimate reasons such as inadequate pain management rather than abuse behavior. It is more informative to provide data regarding the reasons for the early fill for more interpretable results.
3. For the concomitancy analyses of benzodiazepines with ER/LA opioids, the current RPC definition of concomitancy between the two groups is too broad, because it does not account for patterns of acute versus chronic use of benzodiazepines. In addition to the benzodiazepines, we request the RPC to also explore concomitant use of opioids with other central nervous system (CNS) depressants (table by class/molecule). It will also be more meaningful if the RPC presents the concomitancy data in a more interpretable format.

5.7.4. Recommendations to RPC

1. 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.
2. For the data reported in the results section, FDA requests that the RPC present the data in a more meaningful and interpretable format by 1) removing the pre- and post- REMS periods; 2) provide the **actual quarterly patient counts for non-tolerant patients** and **total number of patients** on prescribed products (fentanyl TD, hydromorphone ER, morphine ER ≥ 90mg) indicated for opioid-tolerant patients only, rather than the aggregated means reported; 3) provide the **actual quarterly patient counts for non-tolerant patients** and **total number of patients** with high starting strength prescriptions indicated for opioid-tolerant patients, rather than the aggregated means reported in the 60-months assessment.
3. The early fill data obtained using the current methods and data sources alone were not informative. For more informative analyses, please propose other methods and data sources to provide data regarding the reasons for early fills for more interpretable results.

For the concomitancy analyses:

1. Revise the concomitancy definition. This definition needs to be revised to account for patterns of benzodiazepine use such as acute versus chronic use, perhaps by performing a sensitivity analysis for only patients with an actual overlap of therapy of at least one day. Chronic users of benzodiazepines are at a higher risk of experiencing adverse events when taken concomitantly with an ER/LA opioid analgesic.
2. Provide the **actual quarterly patient counts** for concomitant use and **total number of patients** on an ER/LA opioid product, rather than the aggregated

means reported in the 60-months assessment. For more interpretable results, also present the data by quarterly proportion of patients with concomitant use of benzodiazepines divided by all patients with ER/LA opioids.

3. For future analyses, also explore concomitant use of opioids with other central nervous system (CNS) depressants (table by class/molecule).

5.8. ELEMENT 8 – CHANGE IN ACCESS

This Element states:
"An evaluation of changes in patient access to ER/LA opioid analgesics."

The purpose of this element is to monitor patterns of prescribing to identify changes in access to ER/LA opioid analgesic products after implementation of the REMS program. Specific outcomes measured in this section were:

- Monthly volume of prescriptions from specialities (such as oncologists and hospice providers) assumed to be relatively unaffected by the REMS
- Monthly volume of prescriptions from specialties (such as dentists) assumed to be more affected by the REMS

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.

5.8.1. Datasource utilized by RPC

The RPC utilized the same QuintilesIMS databases to provide the presented data on changes in access.

The study dates for each assessment study are July 1, 2010 through December 31, 2016. All analyses were stratified by channels (retail and long-term care (LTC)) and the following time periods:

- Pre-Implementation: July 2010– June 2012
- Implementation: July 2012– June 2013
- Active: July 2013– December 2016

5.8.2. Results from RPC

The results for the changes in prescribing by physician specialty will not be discussed as it the FDA has previously found this evaluation not informative. Please refer to the reviewer comments below (section, 5.8.3) for more clarification on this item.

5.8.3. Reviewer comments

1. As the DEPI DU team mentioned in the 36-month assessment report, in terms of the impact of the REMS on patient access, it is challenging to characterize the impact on patient access using the dispensed prescription data alone. The databases capture the prescription activity for patients who were ultimately able to access opioid medications. It is not known how these data are informative about patients who were unable to access opioid medication, and therefore would not have prescriptions dispensed. In addition, these data do not show if patients encountered challenges or barriers to access. As mentioned in previous assessment recommendations, FDA has requested the RPC not to submit the evaluation of patient access based solely on utilization data and survey questions.

5.8.4. Recommendations to RPC

1. No futher recommendations to RPC at this time. In response to our previous recommendation, the RPC submitted a concept paper [previously referred to "Concept paper #2] for an alternate approach to evaluating the impact of the REMS on patient access, which is currently being reviewed.

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

The RPC concludes that: *" Overall, the REMS assessments indicated high levels of prescriber knowledge and patient knowledge of ER/LA opioid analgesic risks while 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. As discussed with the FDA in multiple forums, the RPC looks forward to a revised Blueprint to expand the existing education that encompasses broader pain management topics and that will be applicable to a more diverse population of HCPs. In addition, the RPC is working diligently on the Concept Papers with a plan to provide an update on these efforts in the next assessment report. Based on these activities, the RPC will communicate proposed substantive changes to the elements required in the REMS Assessment to the FDA."*

6. OTHER OSE DIVISIONS OR OFFICE INPUT/SUMMARY OF ASSESSMENT

DRISK recognizes and appreciates the contributions of the Division of Epidemiology (DEPI II) in reviewing the submitted assessment data and writing the surveillance and utilization sections of this review.

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.

We are unable to determine whether or not the REMS is meeting its goal because 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

On September 28, 2017, the ER/LA Sponsors were sent a REMS Modification Notification letter and sponsors of IR opioid analgesics intended for outpatient use were sent a REMS notification letter. The letters included a modified FDA Blueprint for Prescriber Education for ER/LA Opioid Analgesics as well as the need for a REMS for IR opioid analgesic products to ensure the benefits of all of these drugs outweigh the risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse and misuse.

7.4. REVIEW TEAM CONCLUSION

From September 2017 through November 2017, DRISK, DEPI, DEPI Drug Use, DAAAP, and the Office of Compliance met to discuss the conclusions based on the data in the assessment report.

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).

The review team believes the Assessment to be complete but that it is not possible to determine whether or not the REMS is meeting its goal.

8. RECOMMENDATIONS

We recommend the sponsor be sent a REMS Assessment Acknowledgment letter that includes General Comments.

9. COMMENTS FOR THE SPONSOR

Please send the sponsor a **REMS Assessment Acknowledgement letter** (see CST template (COR-SEC901REMS-10) ((COR-BLASEC901REMS-10) stating the following:

We find the REMS assessment to be complete but we are unable to determine whether or not the REMS is meeting its goal because the surveillance data do not inform the question of whether this REMS is having the desired impact on prescribing or abuse-related outcomes.

Any necessary modifications to the REMS will be provided to the RPC in a separate communication.

General Comments: Please send the following **General Comments** to the sponsor.

The following comments are the same comments emailed to you on October 31, 2017. Additions to these comments are indicated in **bolded font** while the one deletion is indicated by ~~strikeout~~ text:

1. **Surveillance Data**
    a. Purpose of the epidemiologic surveillance data
        i. The purpose of the epidemiologic surveillance data is to monitor the scope and trends in opioid misuse and abuse and the related outcomes of addiction, overdose, and death. Ongoing surveillance of these outcomes is necessary to inform regulatory decisions related to these products and this REMS, but the goal of the surveillance data is not to assess the impact of the REMS itself, due to the many secular trends and concurrent interventions that will inevitably confound this assessment. Therefore, formal comparison of means or trends across specific time periods (Pre-REMS versus active-REMS) is not necessary for surveillance purposes. Nor are we requesting formal comparisons between extended-release/long-acting and immediate release formulations.
        ii. FDA has previously provided comments on the concept paper the RPC submitted as part of the 48-month assessment report for a study of the impact of REMS-compliant training on prescriber behavior and patient outcomes. We concur with the RPC's proposal to provide, as part of the 72-month assessment report, the results of data linkage feasibility assessments that will inform the design of this study. In addition, we request that, as part of the 72-month report, the RPC submit a revised concept paper that incorporates the results of these feasibility assessments as well as changes underway for this REMS, including the IR opioid formulations, the revised blueprint, and the

targeting of training to both prescribers and non-prescriber members of the healthcare team.

b. Surveillance of prescription opioid overdose using electronic healthcare data

i. Understanding trends in prescription opioid overdose continues to be of great interest to FDA; however, the changing commercial insurance and Medicaid coverage landscape presents challenges in evaluation of trends in opioid overdose using insurance claims data. Therefore, FDA is no longer requesting further analyses of HIRD and limited Medicaid databases to assess changes in the incidence of Opioid Overdose and Poisoning (OOP).

ii. Instead, the RPC should utilize new data sources to assess 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 coverage area drawing from multiple geographic regions. These data sources might include but are not limited to 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). For the 72-month assessment:

1. Provide quarterly trends of prescription opioid overdose rates with estimates of precision. Also provide rates for heroin for context.[4]
2. Analyses should use validated code algorithms for prescription opioid overdose, heroin overdose, etc. (i.e., those being developed in the ER/LA opioid analgesic PMRs)
3. Provide a detailed description of the data source, limitations, and methods used for the above analyses. In particular, address the potential impact of changes from ICD-9 to ICD-10 codes on opioid overdose rates using sensitivity analyses or statistical adjustment.[5]

c. Surveillance of overdose deaths involving opioids

i. FDA is not requesting further analyses of state medical examiner data at this time.

ii. FDA finds CDC WONDER mortality data from the Multiple Cause of Death files to be a valuable resource for surveillance of prescription opioid analgesic- and heroin-related drug overdose deaths in U.S. residents. In the 72-month assessment report, provide;

1. Quarterly trends (2006 through 2016) of counts and population age-adjusted overdose mortality rates stratified by opioid classification ICD-10 groupings (natural and semi-synthetic opioids, methadone, synthetic opioids other than methadone, and heroin).
2. Trend data, as above, stratified by sex and age group.
3. Quarterly trends of the proportion of prescription opioid overdose deaths, stratified as above, that also involve 1) benzodiazepines, and **2) heroin**
4. uarterly trends of the proportion of opioid overdose deaths, stratified as above, that also involve benzodiazepines.

iii. Provide a detailed description of the data source, limitations, and methods used for the above analyses.

iv. For more drug specific information on opioid analgesic-related drug overdose deaths, the RPC should use the Drug Involved Mortality (DIM) data, now available for public use through the Research Data Center. https://www.cdc.gov/rdc/b1datatype/dt1229.html. DIM contains National Vital Statistics System mortality files linked to electronic files containing literal text containing drug-specific information from death certificates. For the 72-month assessment:

1. For all available data years, provide quarterly trends of all drug overdose and opioid overdose death counts and populations rates.
2. Among all drug overdose deaths for each quarter, provide the count and proportion for which no specific drugs were identified.
3. Among all opioid overdose deaths for each quarter, provide the count and proportion for which no specific opioids were identified.
4. For all available data years, provide quarterly trends of opioid overdose deaths counts and population rate by each prescription opioid molecule (i.e., hydrocodone, oxycodone, methadone, fentanyl, morphine, oxymorphone, hydromorphone, meperidine, codeine, buprenorphine, tramadol), and heroin.
5. For each prescription opioid molecule, provide overdose death rates relative to total prescription volume, measured both as the number of prescriptions and as the number of tablets dispensed in the U.S.
6. For each opioid molecule, indicate the proportion of death cases mentioning this opioid molecule that were single drug versus poly-drug overdoses.
7. For each year, provide the proportion of fatal prescription opioid overdoses that involved a benzodiazepine.

v. Provide a detailed description of the data source, limitations, and methods used for the above analyses

d. Surveillance of abuse, misuse, and addiction related to opioids using nationally representative surveys

i. FDA finds Monitoring the Future (MTF) to be a valuable source of surveillance of non-medical use of opioid analgesics in adolescents. In the 72-month assessment report, provide updated MTF analyses with the most recent available data and trends going back to 2006. If this is not feasible or scientifically appropriate, provide rationale.

ii. In the 72-month report, provide results of analyses from one or more additional national survey data sources that can provide population estimates for the prevalence of use, misuse, and abuse of specific opioid analgesics (e.g., hydrocodone, oxycodone, fentanyl) as well as the prevalence of opioid use disorders in those using, misusing, and abusing these opioids. FDA would be interested in further descriptive characterization of these populations and behaviors (e.g., frequency of use, motivation for use, polysubstance abuse, pain and psychiatric conditions), as well as trends over time, as the data allow. Provide data on heroin for context.

iii. Provide a detailed description of the data source(s), limitations, and methods used for the above analyses.

e. Additional sources of epidemiologic surveillance data: Poison Center data

i. FDA believes that despite their limitations, national poison center call data may contribute timely information to a multi-faceted surveillance program intended to understand trends in adverse outcomes and healthcare utilization related to use, misuse, and abuse of opioid analgesics. Therefore, FDA is asking that the RPC submit poison control data as part of the 72-month report, with key modifications to previously submitted reports. For the 72-month assessment report, provide analyses of national (or near-national) poison center call data as follows, for the study period January 1, 2009 through the most recent quarter of data available:

1. For the opioid categories listed below, provide tabular display of counts and 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 product groups (e.g., IR hydrocodone combination analgesics, IR oxycodone single-entity products, IR codeine combination analgesics, ER oxycodone products, ER morphine products, fentanyl transdermal products, etc.) as well as heroin.

2. 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.

ii. Provide tabular display of counts and 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 for:

1. All opioid analgesics combined
2. ER/LA opioid analgesics
3. IR opioid analgesics

iii. For each year of the study period, provide tabular display of counts and tabular and graphic display of the proportion of intentional exposures calls and intentional abuse calls that also involved a benzodiazepine, among

1. All opioid analgesics combined
2. ER/LA opioid analgesics
3. IR opioid analgesics

iv. For each year of the study period, provide the counts and proportion of all intentional and unintentional exposure calls that came from health care facilities, for

1. All opioid analgesics combined
2. ER/LA opioid analgesics
3. IR opioid analgesics

v. For each year of the study period, provide

1. Total population covered by the poison center program, and clarify how the coverage area is determined
2. Total number of intentional and unintentional (together and separately) human drug exposure calls within this coverage area, by age group.

vi. Provide a detailed description of the data source, limitations, and methods used for the above analyses.

vii. Provide a documented dataset of outcome counts in ZIP code encatchment areas and at the quarterly level so that FDA can reproduce the 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), and dosage units' dispensed count (used in the adjustment). The data should be provided in a SAS xport format.

2. **Drug Utilization Data**
   a. For the opioid tolerance data:
      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. For the data reported in the results section, we request that the RPC present the data in a more meaningful and interpretable format by 1) removing the pre- and post- REMS periods; 2) provide the actual quarterly patient counts for opioid non-tolerant patients and total number of patients on prescribed products (fentanyl TD, hydromorphone ER, morphine ER ≥ 90mg) indicated for opioid-tolerant patients only, rather than the aggregated means reported; 3) provide the actual quarterly patient counts for opioid non-tolerant patients and total number of patients with high starting strength prescriptions indicated for opioid-tolerant patients, rather than the aggregated means reported in the 60-month assessment.
      iii. Given that the data reported from the current data source based solely on prescriptions claims can either overestimate or underestimate opioid tolerance, we suggest the RPC continue to explore alternative methods and data sources to provide data on prior opioid tolerance among patients prescribed opioid formulations and/or dosage levels that require prior opioid tolerance. Please explore a more appropriate database, possibily one which has the ability to look across multiple settings at the unique patient level so that prior opioid tolerance can be properly identified.
   b. For the overall utilization data reported in the results section, we request that the RPC present the data in a more meaningful and interpretable format by 1) removing the pre- and post- REMS periods; 2) provide the actual quarterly prescription counts for each product and for each group (total ER/LA, IR opioids, celecoxib, benzodiazepines, tramadol), rather than the aggregated means reported in the 60-month assessment in both channels, retail and LTC.
   c. The switch analyses data obtained using the current methods and data sources alone were not informative. Data solely based on dispensed prescription claims are insufficient to determine the appropriateness of the prescribing patterns. For more informative analyses, please propose other methods and data sources to provide insight into the reasons for why

prescribers are switching from a ER/LA opioid REMS product to a non-REMS opioid product . In addition to the current selected comparator groups, please expand to other comparator groups that may be used for pain management.

d. The early refill analyses data obtained using the current methods and data sources alone were not informative. For more informative analyses, please propose other methods and data sources to provide data regarding the reasons for early fill for more interpretable results.
e. 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. This is being addressed through the concept paper provided by the RPC.
f. The retail and long term care utilization data provided by the RPC are helpful. However, FDA suggests exploring other data sources that will encompass utilization of ER/LA opioid analgesic products across all outpatient settings of care (i.e., specialty clinics, ambulatory clinics, and non-emergency room clinics, etc.) to provide a more comprehensive utilization analyses of ERLA opioid analgesic products in the U.S. market.
g. Concomitancy Analyses:
    i. Definition - Concomitant use is defined by the RPCs as a prescription claim for a benzodiazepine within the 3 months prior to REMS opioid products. This definition needs to be revised to account for patterns of benzodiazepine use such as acute versus chronic use, perhaps by performing a sensitivity analysis for only patients with an actual overlap of therapy of at least 1 day. Chronic users of benzodiazepines are at a higher risk of experiencing adverse events when taken concomitantly with a REMS product.
    ii. Results – Provide the actual quarterly patient counts for concomitant use and total number of patients on ER/LA opioid product, rather than the aggregated means reported in Table 36 in the 60-months assessment. For more interpretable results, also present the data by quarterly proportion of patients with concomitant use of benzodiazepines divided by all patients with ER/LA opioids.
    iii. For future analyses, please also explore concomitant use of opioids with other classes of drugs (table by class) with central nervous system (CNS) depressive properties.

3. **KAB Surveys**
    a. For the Follow-up Prescriber Survey, 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. IMS respondents 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 in its current form for the 72-month assessment.

b. Prescriber characteristic data from respondents recruited from CE providers is very limited and incomplete. There was no consistency in the (few) variables collected by different CE providers. Some CE providers did not provide any data. We recommend the RPC conducts uniform data collection on the prescriber characteristics across all CE providers. This will be discussed at an upcoming RPC FDA teleconference regarding the REMS assessment for the modified program.

c. 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 sources 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 utilize other data sources in order to recruit a representative sample of patients who are prescribed and caregivers of patients who are prescribed ER/LA opioid analgesics. Provide a detailed description of the new proposed data source(s) along with limitations of the data source(s) in the 72-month assessment report.~~ **Due to the limitations of the data source for the current patient survey, FDA is requesting that you utilize other data sources to recruit a representative sample of patients and caregivers. In the 72-month assessment, we request that you provide a detailed description of the new proposed data source(s) along with the limitations. Your description should include the following information at minimum:**

   i. **Describe the sampling design and strategy (from selection of invited participants to selection of survey participants) and provide a detailed flow chart showing response and non-response.**
   ii. **Assess whether your survey design is likely to produce generalizable results to the target population (e.g., patients who filled ER/LA opioid prescription).**
   iii. **Propose methods to standardize the results of the survey samples to the target population if generalizability is violated (if applicable).**

4. **CE Activity Audit Comments:**
    a. **Over the past 4 audit reports the number of deviations gone from 5 (24-month); to 9 (36-month); to 4 (48-month); to 2 (60-month). Across these four reports, ALL of these deviations have been related to issues of disclosure of financial interests or inability to resolve financial conflicts of interest. It is encouraging that the numbers of such events per audit appear to be trending downward. Additionally, the RPC has prudently decided to exclude completers of these affected trainings from its total number of training completers. However, additionally:**
        i. **The RPC should similarly exclude participants in these affected trainings from the total number of participants in RPC-supported trainings; and**
        ii. **The RPC should reach out to the ACCME to ask them to proactively solidify their processes to prevent these financial deviations from continuing to occur.**

5. August 24, 2017 and September 28, 2017 submissions regarding the assessment review plan and changes to the Supporting Document to be utilized in the RPC's 72-month assessment report

We have no objections to your review plan for your 72-month submission; however, we strongly suggest that you review the comments above since these may influence the content of your proposed documents and your proposed assessment review plan. We look forward to review of these documents to be placed with the Supporting Document.

10. APPENDIX

10.1. CURRENT 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. 48-MONTH RAAL (JULY 14, 2017)

After consultation between the Office of Surveillance and Epidemiology and the Office of New Drugs, we found the REMS assessment to be complete. Given that your 60-month REMS assessment has already been submitted, FDA 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.

10.3. 48-MONTH REVIEW COMMENTS NOT SENT TO RPC

FDA had planned to send the RPC the following comments regarding their 48-month assessment report However, by the time these comments were cleared, the 60-month assessment report had already been submitted. Thus the RPC was instead sent the comments indicated in Appendix Section 10.2 of this review. The comments that were intended to be sent to the RPC are included below to memorialize the thought process at that regarding the 48-month assessment report data:

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 FDA ; 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. Surveillance of prescription opioid overdose deaths using of medical examiner data:

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, FDA 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."[8]

   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

[8] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm243537.pdf

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
    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, FDA has a number of concerns and questions. However, FDA 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).

10.4. October 31, 2017 Comments Sent to the RPC

As mentioned in Appendix Section 10.2 and 10.3, full comments were not sent to the RPC regarding their 48-month REMS assessment report, since by the time that these comments were cleared, their 60-month assessment report had been submitted. However, since the RPC was not provided feedback from FDA following submission of the 48-month report, much of their 60-month assessment report submission was similar in nature to the 48-month report. Thus, early in the review process for the 60-month report, once FDA confirmed the areas of similarity between the 48- and 60-month assessment reports,

the following comments were sent to the RPC (comments based to a large extent on the comments noted in Appendix Section 10.3):

- In the process of reviewing your 60-month REMS assessment report (submitted July 7, 2017), we note a number of similarities to the 48-month assessment, particularly in the data presentations and analyses. After we complete our full review of your 60-month report, we may have additional comments to convey to you. However, for the aspects of your 60-month report that are similar to your 48-month report, we have provided a list of comments regarding the 72-month assessment report as well as a response to your August 24, 2017 and September 28, 2017 submissions regarding the assessment review plan and changes to the Supporting Document for the RPC's 72-month assessment report. We are also requesting information on prescribers of *all* opioid analgesic products that are subject to the modified opioid analgesic REMS.

6. <u>Surveillance Data</u>

a. The purpose of the epidemiologic surveillance data is to monitor the scope and trends in opioid misuse and abuse and the related outcomes of addiction, overdose, and death. Ongoing surveillance of these outcomes is necessary to inform regulatory decisions related to these products and this REMS, but the goal of the surveillance data is not to assess the impact of the REMS itself, due to the many secular trends and concurrent interventions that will inevitably confound this assessment. Therefore, formal comparison of means or trends across specific time periods (Pre-REMS versus Post-REMS) is not necessary for surveillance purposes. Nor are we requesting formal comparisons between extended-release/long-acting and immediate release formulations.

FDA has previously provided comments on the concept paper the RPC submitted as part of the 48-month assessment report for a study of the impact of REMS-compliant training on prescriber behavior and patient outcomes. We concur with the RPC's proposal to provide, as part of the 72-month assessment report, the results of data linkage feasibility assessments that will inform the design of this study. In addition, we request that, as part of the 72-month report, the RPC submit a revised concept paper that incorporates the results of these feasibility assessments as well as changes underway for this REMS, including the IR opioid formulations, the revised blueprint, and the targeting of training to both prescribers and non-prescriber members of the healthcare team.

b. <u>Surveillance of prescription opioid overdose using electronic healthcare data</u>

i. Understanding trends in prescription opioid overdose continues to be of great interest to FDA; however, the evolving commercial insurance and Medicaid coverage landscape presents challenges in

evaluation of trends in opioid overdose using insurance claims data. Therefore, FDA is no longer requesting further analyses of HIRD and limited Medicaid databases to assess changes in the incidence of Opioid Overdose and Poisoning (OOP).

ii. Instead, the RPC should utilize new data sources to assess 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 coverage area drawing from multiple geographic regions. These data sources might include but are not limited to 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). For the 72-month assessment:

1. Provide quarterly trends of prescription opioid overdose rates with estimates of precision. Also provide rates for heroin for context.
2. Analyses should use validated code algorithms for prescription opioid overdose, heroin overdose, etc. (i.e., those being developed in the ER/LA opioid analgesic PMRs)
3. Provide a detailed description of the data source, limitations, and methods used for the above analyses. In particular, address the potential impact of changes from ICD-9 to ICD-10 codes on opioid overdose rates using sensitivity analyses or statistical adjustment (See attached publication on this topic).

c. <u>Surveillance of overdose deaths involving opioids</u>

i. FDA is not requesting further analyses of state medical examiner data at this time.

ii. FDA finds CDC WONDER mortality data from the Multiple Cause of Death files to be a valuable resource for surveillance of prescription opioid analgesic- and heroin-related drug overdose deaths in U.S. residents. In the 72-month assessment report, provide;

1. Quarterly trends (2006 through 2016) of counts and population age-adjusted overdose mortality rates stratified by opioid classification ICD-10 groupings (natural and semi-synthetic opioids, methadone, synthetic opioids other than methadone, and heroin).
2. Trend data, as above, stratified by sex and age group.

3. Quarterly trends of the proportion of opioid overdose deaths, stratified as above, that also involve benzodiazepines.

iii. Provide a detailed description of the data source, limitations, and methods used for the above analyses.

iv. For more drug specific information on opioid analgesic-related drug overdose deaths, the RPC should use the Drug Induced Mortality (DIM) data, now available for public use through the Research Data Center. https://www.cdc.gov/rdc/b1datatype/dt1229.html. DIM contains National Vital Statistics System mortality files linked to electronic files containing literal text containing drug-specific information from death certificates. For the 72-month assessment:

1. For all available data years, provide quarterly trends of all drug overdose and opioid overdose death counts and populations rates.
2. Among all drug overdose deaths for each quarter, provide the count and proportion for which no specific drugs were identified.
3. Among all opioid overdose deaths for each quarter, provide the count and proportion for which no specific opioids were identified.
4. For all available data years, provide quarterly trends of opioid overdose deaths counts and population rate by each prescription opioid molecule (i.e., hydrocodone, oxycodone, methadone, fentanyl, morphine, oxymorphone, hydromorphone, meperidine, codeine, buprenorphine, tramadol), and heroin.
5. For each prescription opioid molecule, provide overdose death rates relative to total prescription volume, measured both as the number of prescriptions and as the number of tablets dispensed in the U.S.
6. For each opioid molecule, indicate the proportion of death cases mentioning this opioid molecule that were single drug versus poly-drug overdoses.
7. For each year, provide the proportion of fatal prescription opioid overdoses that involved a benzodiazepine.

v. Provide a detailed description of the data source, limitations, and methods used for the above analyses

d. Surveillance of abuse, misuse, and addiction related to opioids using nationally representative surveys

i. FDA finds Monitoring the Future (MTF) to be a valuable source of surveillance of non-medical use of opioid analgesics in adolescents. In the 72-month assessment report, provide updated

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

ii. In the 72-month report, provide results of analyses from one or more additional national survey data sources that can provide population estimates for the prevalence of use, misuse, and abuse of specific opioid analgesics (e.g., hydrocodone, oxycodone, fentanyl) as well as the prevalence of opioid use disorders in those using, misusing, and abusing these opioids. FDA would be interested in further descriptive characterization of these populations and behaviors (e.g., frequency of use, motivation for use, polysubstance abuse, pain and psychiatric conditions), as well as trends over time, as the data allow. Provide data on heroin for context.

iii. Provide a detailed description of the data source(s), limitations, and methods used for the above analyses.

e. Additional sources of epidemiologic surveillance data: Poison Center data

i. FDA believes that despite their limitations, national poison center call data may contribute timely information to a multi-faceted surveillance program intended to understand trends in adverse outcomes and healthcare utilization related to use, misuse, and abuse of opioid analgesics. Therefore, FDA is asking that the RPC submit poison control data as part of the 72-month report, with key modifications to previously submitted reports. For the 72-month assessment report, provide analyses of national (or near-national) poison center call data as follows, for the study period January 1, 2009 through the most recent quarter of data available:

1. For the opioid categories listed below, provide tabular display of counts and 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 product groups (e.g., IR hydrocodone combination analgesics, IR oxycodone single-entity products, IR codeine combination analgesics, ER oxycodone products, ER morphine products, fentanyl transdermal products, etc.) as well as heroin.

2. **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.**

ii. Provide tabular display of counts and 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 for:

1. All opioid analgesics combined
2. ER/LA opioid analgesics
3. IR opioid analgesics

iii. For each year of the study period, provide tabular display of counts and tabular and graphic display of the proportion of intentional exposures calls and intentional abuse calls that also involved a benzodiazepine, among

1. All opioid analgesics combined
2. ER/LA opioid analgesics
3. IR opioid analgesics

iv. For each year of the study period, provide the counts and proportion of all intentional and unintentional exposure calls that came from health care facilities, for

1. All opioid analgesics combined
2. ER/LA opioid analgesics
3. IR opioid analgesics

v. For each year of the study period, provide

1. Total population covered by the poison center program, and clarify how the coverage area is determined
2. Total number of intentional and unintentional (together and separately) human drug exposure calls within this coverage area, by age group.

vi. Provide a detailed description of the data source, limitations, and methods used for the above analyses.

vii. Provide a documented dataset of outcome counts in ZIP code encatchment areas and at the quarterly level so that FDA can reproduce the 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), and dosage units' dispensed count (used in the adjustment). The data should be provided in a SAS xport format.

7. **Drug Utilization Data**

a. 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.
b. The switch analyses data obtained using the current methods and data sources alone were not informative. Data solely based on dispensed prescription claims are insufficient to determine the appropriateness of the prescribing patterns. For more informative analyses, please propose other methods and data sources to provide insight into the reason for switching linked to prescribing for more meaningful results. In addition to the current selected comparator groups, please expand to other comparator groups that may be used for pain therapy.
c. The early refill analyses data obtained using the current methods and data sources alone were not informative. For more informative analyses, please propose other methods and data sources to provide data regarding the reasons for early fill for more interpretable results.
d. 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. This is being addressed through the concept paper provided by the RPC.
e. The retail and long term care utilization data provided by the RPC are helpful. However, FDA suggests exploring other data sources that will encompass utilization of ER/LA opioid analgesic products across all outpatient settings of care (i.e., specialty clinics, ambulatory clinics, and non-emergency room clinics, etc.) to provide a more comprehensive utilization analyses of ERLA opioid analgesic products in the U.S. market.
f. Concomitancy Analyses:
    i. Definition - Concomitant use is defined by the RPCs as a prescription claim for a benzodiazepine within the 3 months prior to REMS opioid products. This definition needs to be revised to account for patterns of benzodiazepine use such as acute versus chronic use, perhaps by performing a sensitivity analysis for only patients with an actual overlap of therapy of at least 1 day. Chronic users of benzodiazepines are at a higher risk of experiencing adverse events when taken concomitantly with a REMS product.
    ii. Results – Provide the actual quarterly patient counts for concomitant use and total number of patients on ER/LA opioid product, rather than the aggregated means reported in Table 36 in the 60-months assessment. For more interpretable results, also present the data by quarterly proportion of patients with concomitant use of benzodiazepines divided by all patients with ER/LA opioids.
    iii. For future analyses, please also explore concomitant use of opioids with other classes of drugs (table by class) with central nervous system (CNS) depressive properties.

8. **KAB Surveys**

   a. For the Follow-up Prescriber Survey, 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. IMS respondents 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 in its current form for the 72-month assessment.

   b. Prescriber characteristic data from respondents recruited from CE providers is very limited and incomplete. There was no consistency in the (few) variables collected by different CE providers. Some CE providers did not provide any data. We recommend the RPC conducts uniform data collection on the prescriber characteristics across all CE providers. This will be discussed at an upcoming RPC FDA teleconference regarding the REMS assessment for the modified program.

   c. 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 sources 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 utilize other data sources in order to recruit a representative sample of patients who are prescribed and caregivers of patients who are prescribed ER/LA opioid analgesics. Provide a detailed description of the new proposed data source(s) along with limitations of the data source(s) in the 72-month assessment report.

9. August 24, 2017 and September 28, 2017 submissions regarding the assessment review plan and changes to the Supporting Document to be utilized in the RPC's 72-month assessment report

We have no objections to your review plan for your 72-month submission; however, we strongly suggest that you review the comments above since these may influence the content of your proposed documents and your proposed assessment review

plan. We look forward to review of these documents to be placed with the Supporting Document.

10. **Information request:**
    a. During the development of the ER/LA Opioid Analgesic REMS, the Industry Working Group (IWG) provided data on the number of prescribers of these products in order to better understand how many prescribers ideally should take the continuing education trainings. The FDA requests the RPC provide the following information **on or before February 1, 2018**:

Number of prescribers of one or more prescriptions for all opioid analgesics subject to the modified Opioid analgesic REMS (i.e., both immediate release and extended-release and long-acting opioid analgesics) for the years 2011-2016. Mid-level practitioners should be separated from other prescribers

10.5. RPC-SUPPORTED REMS-COMPLIANT CE ACTIVITIES

A description of all accredited REMS-compliant CE activities available 01 March 2016 to 28 February 2017, organized by Grantee, is provided in **Table 10.5.1**.:

Table 10.5.1.: RPC Supported REMS-Compliant Continuing Education Activities Available During the Reporting Period (01 March 2016-28 February 2017)

Grantee[1]	Program Start Date[2]	Program Formats	Number of Activities
Aurora Health Care	12/31/2013	Internet-based	1
Texas Medical Association	3/13/2014	Live training	1
Temple University School of Medicine	5/29/2014	Internet-based	1
Nurse Practitioner Healthcare Foundation	8/10/2014	Internet-based	3
		Live training	14
American Society of Addiction Medicine	9/17/2014	Internet-based	4
		Live training	6
California Academy of Family Physicians	9/17/2014	Internet-based	3
		Live training	2
Interstate Postgraduate Medical Association	1/16/2015	Live training	10
Elsevier Office of Continuing Medical Education	2/26/2015	Internet-based	8
University of Nebraska Medical Center, Center for Continuing Education	4/1/2015	Internet-based	1
pmiCME	6/15/2015	Internet-based	1
		Live training	24

American Association of Nurse Practitioners	8/21/2015	Internet-based	4
		Live training	6
Collaborative for REMS Education	8/31/2015	Internet-based	1
		Live training	8
Medscape, LLC	10/20/2015	Internet-based	1
Johns Hopkins University, School of Medicine	11/30/2015	Internet-based	2
Postgraduate Institute for Medicine	12/4/2015	Internet-based	5
Florida Medical Association	1/1/2016	Internet-based	2
		Live training	1
American Osteopathic Association	3/1/2016	Internet-based	1
Boston University School of Medicine	3/1/2016	Internet-based	2
		Live training	15

Grantee[1]	Program Start Date[2]	Program Formats	Number of Activities
American College of Emergency Physicians	3/3/2016	Live training	1
Regional Osteopathic Medical Education	3/5/2016	Live training	3
Global Education Group, Ltd.	3/6/2016	Internet-based	2
		Live training	8
Medical Foundation of Alabama	3/6/2016	Live training	4
American Academy of Physical Medicine And Rehabilitation	4/1/2016	Internet-based	1
		Live training	1
American Osteopathic Academy of Orthopedics	4/7/2016	Live training	1
Arizona Osteopathic Medical Association	4/14/2016	Live training	1
American Academy of Family Physicians	4/15/2016	Internet-based	1
American Academy of Physician Assistants	4/27/2016	Live training	7
American College of Physicians	5/4/2016	Internet-based	1
		Live training	1
Southern Regional Area Health Education Center	7/16/2016	Live training	2
Firelands Regional Medical Center	7/27/2016	Live training	1
American Pain Society	7/29/2016	Internet-based	1
		Live training	1
Pennsylvania Osteopathic Family Physicians Society	8/5/2016	Live training	1

Mississippi State Medical Association Foundation	8/12/2016	Live training	1
American College of Osteopathic Family Physicians	9/18/2016	Live training	1
LAMMICO	9/21/2016	Live training	2
Florida Osteopathic Medical Association	10/7/2016	Live training	1
American Osteopathic Academy of Addiction Medicine	10/22/2016	Live training	1
Michigan State Medical Society	11/4/2016	Live training	1
Northwest Ohio Osteopathic Association	11/12/2016	Live training	1
Dannemiller	NA	print	1
TOTAL			**174**

[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 prescriber completer information for the activity was provided during this reporting period.

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/s/

IGOR CERNY
02/14/2018
60-month ERLA opioid REMS Assessment Review

CYNTHIA L LACIVITA
02/15/2018
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