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 third (24 month, May 11, 2013 through May 9, 2014) Risk Evaluation and Mitigation Strategy (REMS) Consolidated Assessment Report for Extended-Release and Long-Acting (ER/LA) opioid analgesic products

Date: **February 26, 2015**

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

Submission Date: **July 9, 2014**

Drug Name	Dosage and Route	Application Type/ Number	Applicant/ Sponsor
BUTRANS (buprenorphine)	transdermal system	NDA 021306	Purdue
DURAGESIC (Fentanyl Transdermal System)	transdermal system	NDA 019813	Janssen
fentanyl	transdermal system	ANDA 077449	Aveva
fentanyl	transdermal system	ANDA 077154	Mallinkrodt
fentanyl	transdermal system	ANDA 076258	Mylan Techno
fentanyl	transdermal system	ANDA 077775	Noven
fentanyl	transdermal system	ANDA 077062	Par
fentanyl	transdermal system	ANDA 076709	Watson

Drug Name	Dosage and Route	Application Type/ Number	Applicant/ Sponsor
ZOHYDRO ER (hydrocodone bitartrate)	extended-release capsules	NDA 202880	Zogenix
EXALGO (hydromorphone hydrochloride)	extended-release capsules	NDA 021217	Mallinkrodt
hydromorphone hydrochloride	extended-release tablets	NDA 202144	Actavis
DOLOPHINE (methadone hydrochloride)	tablets	NDA 006134	Roxane
methadone hydrochloride	tablets	ANDA 040517	Mallinkrodt
methadone hydrochloride	oral solution	ANDA 087393	Roxane
methadone hydrochloride	oral concentrate	ANDA 089897	Roxane
methadone hydrochloride	oral solution	ANDA 087997	Roxane
methadone hydrochloride	tablets	ANDA 040241	Sandoz
methadone hydrochloride	tablets	ANDA 090635	ThePharma Network
methadone hydrochloride	oral solution	ANDA 090707	VistaPharm
METHADOSE (methadone hydrochloride)	tablets	ANDA 040050	Mallinkrodt
AVINZA (morphine sulfate)	extended-release capsules	NDA 021260	King
EMBEDA (morphine sulfate and naltrexone hydrochloride	extended-release capsules	NDA 022321	Alpharma
KADIAN (morphine sulfate)	extended-release capsules	NDA 020616	Watson
morphine sulfate	extended-release capsules	ANDA 079040	Actavis
morphine sulfate	extended-release tablets	ANDA 076412	Mallinkrodt
morphine sulfate	extended-release tablets	ANDA 76438	Mallinkrodt
morphine sulfate	extended-release tablets	ANDA 200824	Mylan
morphine sulfate	extended-release tablets	ANDA 200812	Par
morphine sulfate	extended-release tablets	ANDA 078761	Ranbaxy
morphine sulfate	extended-release tablets	ANDA 074769	Rhodes
morphine sulfate	extended-release tablets	ANDA 074862	Rhodes
morphine sulfate	extended-release capsules	ANDA 202104	Upsher-Smith
morphine sulfate	extended-release tablets	ANDA 075295	Vintage
MS CONTIN (morphine sulfate)	controlled-release tablets	NDA 019516	Purdue

Drug Name	Dosage and Route	Application Type/ Number	Applicant/ Sponsor
OXYCONTIN (oxycodone hydrochloride	controlled-release tablets	NDA 022272	Purdue
TARGENIQ ER (oxycodone HCl and naloxone HCl)	extended-release tablets	NDA 205777	Purdue
OPANA ER (oxymorphone hydrochloride)	extended-release tablets	NDA 021610	Endo
OPANA ER (oxymorphone hydrochloride)	extended-release tablets	NDA 201655	Endo
oxymorphone hydrochloride	extended-release tablets	ANDA 079040	Actavis
oxymorphone hydrochloride	extended-release tablets	ANDA 079087	Impax
oxymorphone hydrochloride	extended-release tablets	ANDA 202946	Mallinkrodt
oxymorphone hydrochloride	extended-release tablets	ANDA 200822	Roxane
NUCYNTA ER (tapentadol)	extended-release tablets	NDA 200533	Janssen

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1 EXECUTIVE SUMMARY

This review evaluates the 24-month risk evaluation and mitigation strategy (REMS) assessment report for the extended-release/long-acting (ER/LA) opioid analgesics which 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, 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 pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

One year after the first CE training was made available, 20,345 ER/LA opioid analgesic prescribers have completed the REMS Program Companies (RPC) supported REMS-compliant training towards the goal of 80,000 trained in 2 years by the end of February 2015. An audit of 10% of the 262 RPC-supported, REMS-compliant educational activities available revealed that 82% of these programs met all criteria for REMS-compliant CE. Five programs did not meet expectations relating to obtaining and prominently displaying financial relationships of faculty; the RPC has rectified these deficiencies.

Patient survey respondents had a high understanding of the key risk messages (risk of and consequences of abuse and misuse, what to do in case of overdose, appropriate storage, not sharing with others, and how to use the drug safely), although there was a lower understanding of aspects of safe storage and using the drug safely.

The surveillance data from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS ®) System (RADARS) and the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) provided a number of findings. For the vast majority of RADARS programs analyzed, the event rates of abuse, misuse, and major medical outcomes including hospitalization, death, and Emergency Department (ED) visits *decreased* for the ER/LA opioid analgesics from the pre-REMS-implementation period. RADARS data also indicate that in most cases the event rates for the immediate-release (IR) opioids and prescription stimulants decreased as well.

Drug utilization databases show that from the pre-REMS implementation period to post-period, the average 3-month prescription volume decreased by 3.2% for the ER/LA opioid analgesics and 3.6% for the IR opioids (both decreases statistically significant). Additionally, there was a statistically significant decrease in average 3-month prescriptions volumes for most of the identified prescribing specialties with the exception of nurse practitioners and physician assistants who both demonstrated statistically significant increases in prescribing of ER/LA opioid analgesics. The reason for the increased prescribing in nurse practitioners and physician assistants is unknown at this time.

The drug utilization data regarding the use of ER/LA opioid analgesics in opioid non-tolerant individuals is of questionable validity due to the definition of opioid tolerance that was applied in the analysis. The rate of early prescription fills ("early refills") decreased for all individual ER/LA opioids analgesics, but these data are difficult to interpret in isolation since many diverse factors can lead to early refills.

Data regarding the impact of the ER/LA opioids analgesics REMS on patient access were limited to the aforementioned drug utilization data as well as findings from the patient and the baseline prescriber surveys. Access for legitimate patients may not be overly problematic.

The REMS Assessment Report is complete. We conclude, based on these preliminary data, that the REMS may be making progress towards meeting its goal to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioids analgesics while maintaining patient access to pain medications. We base our conclusions on the following: surveillance data may suggest that the serious adverse outcomes that this REMS was created to address may have decreased, or at least not substantially increased; patients appear to have a good understanding of the risks, and the prescription volume of ER/LA opioid analgesics has decreased, including reductions in volume among prescribers such as dentists for whom there is little reason to be prescribing an ER/LA opioid analgesic. However, it is not clear whether these decreases represent positive changes or reductions in access to medications by legitimate patients. Additional information, that is forthcoming in future assessments, is needed to determine if the REMS goal is actually being met.

1.1 LIST OF ABBREVIATIONS

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

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

2 INTRODUCTION

This review evaluates the 24-month risk evaluation and mitigation strategy (REMS) assessment report submitted by the REMS Program Companies (RPC) on July 9, 2014 for extended-release/long-acting (**ER/LA)** opioid analgesics 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 11, 2013 through May 9, 2014.

3 BACKGROUND

3.1 REGULATORY HISTORY

ER/LA opioid analgesics 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 opioid analgesic 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 (see http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm251830.htm).

In accordance with section 505-1 of the Federal Food Drug and Cosmetic Act, the FDA determined that a REMS was necessary for all ER/LA opioid analgesic drug products to ensure that their benefits outweigh their risks, especially with regard to specific adverse outcomes 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/LA opioid analgesics 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 the ER/LA opioid analgesics.

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

3.2 APPROVED 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 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 the ER/LA opioid analgesics. All elements in FDA's "*Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint")*" must be included in the training to be considered "REMS-compliant training." The NDA/ANDA holders must inform prescribers of the existence of the ER/LA opioid analgesics REMS and the importance of successfully completing the voluntary training.
- **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.

3.3 REMS ASSESSMENT PLAN

The **FULL REMS Assessment Plan** can be found in the **Appendix Section 9.1** of this review. With each assessment period, additional assessment elements are added until the 4th assessment (year 3) as follows:

- 6 month assessment: continuing education (CE) grants status; updates on REMS website as well as prescriber and organizational letters;
- One year assessment: updates on REMS-compliant CE, prescriber and organizational letters, and CE grants;
- Two-year assessment: Updates on: the prescriber letter and number of prescribers trained; results of audits of CE trainings; evaluation of patient understanding; surveillance results; drug utilization patterns; and patient access;
- Three-year (and subsequent) assessment(s): All metrics as discussed in the two-year assessment with the addition of: and evaluation of prescriber knowledge; additional surveillance data involving validated ICD-9 and ICD-10 codes to evaluate opioid overdoses as well as medical examiner data.

The following portion of the Assessment Plan (taken from the July 9, 2012 REMS approval letter) specifically outlines the information needed for the 2 year assessment report:

"The third REMS assessment, due two years from the date of this letter, should include the following information:

1. "Prescriber Letter #3
    a. date when letter was posted on the ER/LA Opioid REMS website
    b. number of prescriber letters electronically sent, received, undeliverable, and opened, and
    c. number of prescriber letters mailed and undeliverable.

2. Prescriber Training: The number of prescribers of ER/LA opioids 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 providers to provide the REMS-compliant training. Audits must be conducted on a random sample of 1) at least 10% of the training funded under the ER/LA Opioid REMS, and 2) 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 "2" 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 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. Surveillance Results: 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.

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

7. Patient Access: An evaluation of changes in patient access to ER/LA Opioids.

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

3.4 FINDINGS FROM FDA REVIEW OF PREVIOUS ASSESSMENT

The Agency notified the RPC on October 24, 2013 that the 12-month assessment report was complete. In addition, the following comments were conveyed to the RPC:

- the RPC should develop plans to increase the number of prescribers completing CE training (1,147 from the one-year assessment)
- FDA agreed with the RPC request to modify their centralized call center to utilize an interactive voice mail/message retrieval system
- the RPC should analyze the prescriber survey participants' percentage of correct responses on the key risk messages, stratified by professional degree; and
- the RPC should provide a frequency distribution of the number and percentage of prescriber and patients survey participants who got 0, 1, 2, etc., correct responses.

3.5 REMS MODIFICATIONS

During this reporting period, there was a major REMS modification approved on April 15, 2014, to align the REMS with the September 10, 2013 safety labeling changes (SLC). The SLC included the following:

- A new indication for ER/LA opioid analgesics (new class language that states "the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate"
- New warning for Neonatal Opioid Withdraw Syndrome[1]

[1] The labeling states: "*For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged maternal use of Tradename during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening and requires management according to*

- Updated language for the following Warnings and Precautions:
    - Addiction, Abuse, and Misuse
    - Life-Threatening Respiratory Depression
    - Accidental Ingestion
    - Cytochrome P450 3A4 Interaction (for applicable products)
- Revisions to the Blueprint to incorporate updated product-specific titration language.

These modifications were submitted by the RPC on June 13, 2014 and approved August 19, 2014.

4 REVIEW METHODS AND MATERIALS

- July 9, 2012 Supplement/REMS approval for ER/LA opioid analgesics Letter from DAAAP (J. Racoosin)
- February 14, 2013 DRISK (J. Ju) review of the 6-month ER/LA opioid analgesics Assessment Report
- August 30, 2013 2013 DRISK (J. Ju) review of the 12-month ER/LA opioid analgesics Assessment Report.
- March 13, 2014 Division of Biometrics VII review of REMS Survey Assessment Protocol (J-Y Lee)
- March 28, 2014 DRISK (J. Ju) review of Review of Proposed Methodology and Survey Instruments
- July 9, 2014 Final Baseline Prescriber Survey Report from the RPC
- July 9, 2014 ER/LA opioid analgesics REMS 24-Month Assessment Report
- August 11, 2014 ER/LA Product list accessed from FDA ER/LA opioid analgesics REMS website
- September 24, 2014 RPC response to FDA July 31, 2014 Information Request (IR)
- September 24, 2014 RPC response to FDA September 4, 2014 IR
- October 1. 2014 Division of Epidemiology II Review of a Final Study Protocol for PMR #2065-4 (ER/LA Opioid Analgesics "Doctor Shopping" Studies) (Drs Secora, McAninch, and Dormitzer)
- October 24, 2014 RPC response to FDA October 6, 2014 IR
- December 16, 2014 RPC response to FDA's request from an October 24, 2014 meeting between the FDA and RPC.
- January 8, 2015 Statistical Review and Evaluation from CDER's Division of Biometrics 7 (R. Izem and C Hsueh) regarding statistical analyses performed by the RPC in the Assessment Report

protocols developed by neonatology experts. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn."

5 REVIEW RESULTS

5.1 ELEMENT 1 – PRESCRIBER LETTER

This REMS Assessment element states that the RPC is to report:

a. "*date when letter was posted on the ER/LA Opioid REMS website;*
b. *number of prescriber letters electronically sent, received, undeliverable, and opened; and*
c. *number of prescriber letters mailed and undeliverable*."

During this reporting period, a third **Dear DEA-Registered Prescriber** Letter (DDRP Letter 3) was used to announce the approval of the ER/LA opioid analgesics REMS and availability of ER/LA opioid analgesics REMS-related CE to newly DEA-registered Schedule II and III prescribers. The letter was distributed electronically by e-mail, via facsimile and via United States Postal Service (USPS). During this reporting period, DDRP Letter 3 was sent to all new DEA registrants and a number of registered hospitals/clinics. Of the 84,009 registrants targeted, a total of 78,888 registrants were reached, of which 1,724 letters were delivered by e-mail, 1,140 by fax, and 76,024 by USPS. In addition, the communication vendor attempted to send hard copy DDRP Letter 3 by USPS to 799 hospitals/clinic registrants, of which 760 (95.1%) were delivered. Of the 84,009 prescribers that were targeted, 93.9% of DDRP Letter 3 was delivered. The RPC states that there is currently no reliable method for tracking accurate volumes of unopened/unread e-mails. Information about the posting of DDRP Letter 3 to the web was not provided in the report.

5.2 ELEMENT 2 - PRESCRIBER TRAINING

This assessment element states: "*The number of prescribers of ER/LA opioids who have completed REMS-compliant training. Performance goals, based on the 2011 estimate that 320,000 prescribers are active prescribers of ER/LA opioids (prescribers who have prescribed an ER/LA opioid within the last 12 months), are as follows:*

- *Within two years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of active prescribers) are to have been trained*"

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

5.2.1 RPC Data for Prescriber Training

The ER/LA opioid analgesics REMS was approved on July 9, 2012, and the first RPC-supported REMS-compliant CE activity was launched on February 28, 2013. Since that time, **20,345 ER/LA opioid prescribers** have completed **RPC-supported REMS-compliant training**. Of these, 19,198 ER/LA opioid analgesic prescribers completed

REMS compliant training during this reporting period (May 11, 2013 – February 28, 2014).

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

Since the RPC did not provide the number of ER/LA opioid analgesics prescribers (if any) who completed **non-RPC-supported** REMS complaint training, on September 4, 2014, an Information Request (IR) was sent to the RPC regarding this issue. On September 24, 2014, the RPC provided the following response:

> "*When aggregating data for the 24-month assessment report, 5 non-RPC-funded CE activities have been reported through the CE Data Aggregation System as being compliant with the FDA Blueprint. However, the 320 completers from these programs were not included in the total reported to FDA in the 24-month assessment because we could not confirm that these programs had been audited or that they met all REMS requirements. RPC is exploring ways to engage non-RPC supported providers who report REMS-compliant activities to ensure that the appropriate audits are performed so we can count the completers toward the REMS goals*."

After the first REMS-compliant CE was launched on February 28, 2013, additional REMS-compliant CE programs have continued to debut throughout 2013 and 2014. During this reporting period (May 11, 2013 and February 28, 2014), 262 RPC-supported, REMS-compliant educational activities began and were active. These activities were accredited by one of the eight National Accrediting Bodies and have been provided in live format (which includes *Congress Symposium or Session; Grand Rounds; Meeting Series; Symposium; Live-Webinar; Teleconference*) (n=236); and internet formats (n=26). The majority of ER/LA opioid analgesic prescribers who completed training participated in live training activities.

During this reporting period, of the 19,198 ER/LA opioid analgesics prescribers who completed REMS-compliant training:

- 70.3% were physicians
- 18.6% were "advanced practice" nurses
- 6.1% were physician assistants
- 5% were "other" (mostly "uncategorized responses")

The type of practice was an optional category captured on only 7,993 ER/LA opioid analgesic prescribers (41.6% of total) in this reporting period that took that CE training. For those prescribers for whom a practice area was reported, **72.4**% were **primary care physicians**, 17.6% were "non-pain specialists" and 10% were pain specialists.

The performance goals for this element are focused on active prescribers of ER/LA opioid analgesics defined as prescribers who have prescribed an ER/LA opioid analgesic within the last 12 months. However, the RPC is aware (for example) that in addition to 10,530 prescribers who completed a REMS-compliant CE training via the Collaborative for REMS Education organization (CO*RE) curriculum, 16,000 individuals who did not meet the "active prescriber" criteria outlined above also completed this REMS-compliant CE training offered by CO*RE. Specifically, the majority of these 16,000 did not meet the qualifying criterion of having written an ER/LA opioid analgesic prescription within the year prior to training. The RPC speculates these individuals may have been nurses, pharmacists, etc. The RPC also states that CE Providers have stated that it is more challenging than expected to attract ER/LA opioid analgesics prescribers to their REMS-compliant activities and to engage them to completion.

A description of all REMS-compliant CE activities available May 11, 2013 to February 28, 2014, by Grantee, is provided in **Table 1** (reproduced directly from the RPC's Table 4):

Table 1: RPC-Supported REMS-Compliant CE Activities Available during the Reporting Period (May 11, 2013 – February 28, 2014)

GRANTEE[1]	PROGRAM START DATE	PROGRAM FORMAT(S)	NUMBER OF ACTIVITIES
Trustees of Boston University	February 28, 2013	Live training and Internet-based	35
CO*RE (Collaborative for REMS Education)	March 13, 2013	Live training and Internet-based	171
Association for Hospital Medical Education	August 29, 2013	Live training and Internet-based	49
American College of Physicians/Pri-Med	June 7, 2013	Live training and Internet-based	5
Utah Medical Association Foundation	January 1, 2014	Internet-based	1
University of Washington School of Medicine	February 2, 2014	Internet-based	1
TOTAL			262

[1] The table is organized by start date of the activities; if there were multiple activities, the start date reflects date of first activity.

Since the approval of the REMS on July 9, 2012, the RPC has partnered with the following CE stakeholder organizations:

- Conjoint Committee on Continuing Education (CCCE)
- Council of Medical Specialty Societies
- MedBiquitous Consortium
- National CE Accrediting Bodies
- National CE Provider Organizations
- National Professional Societies

The RPC reports that following their Year 2 Request for Application (RFA) (issued May 2013), they funded 7 additional CE activities available to train prescribers on the FDA Blueprint. Also 3 extensions were granted to ongoing programs funded in the Year 1 RFA cycle.

5.2.2 Reviewer (I. Cerny) Comments

1. The REMS assessment element for the reach of training specifies that "Within two years from the time the first REMS-compliant training becomes available, 80,000 prescribers are to have been trained." The first REMS-compliant RPC-funded CE activity was launched February 28, 2013, approximately 7 months after the REMS was approved. REMS-compliant RPC-funded CE programs continue to roll-out. The cut-off date for the data provided in this assessment report is February 28, 2014. Thus at this juncture, only one year's worth of data have been gathered to assess this element. The RPC states that "*while 20,345 prescriber completers to date would not suggest attainment of the goal of 80,000 by February 28, 2015 under the assumption of a linear rate, the CE community expects a non-linear and increasing rate of prescribers completing REMS-compliant training.*" The 2-year training numbers are due July 2015. It is hoped that the CE Community's prediction of a non-linear increasing rate of training will indeed be fulfilled.
2. The RPC should describe the specific challenges that they are encountering in getting prescribers to complete the trainings as well as their plans to address these challenges.
3. The SD states that a secondary outcome measure will be the number of prescribers who have completed some but not all portions of a training activity. The RPC report does not provide this information and should provide this information in subsequent reports. In addition, in subsequent reports, the RPC should more fully provide information on the number of non-prescribers who completed REMS-compliant CE training.

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 providers to provide the REMS-compliant training. Audits must be conducted on a random sample of 1) at least 10% of the training funded under the ER/LA Opioid REMS, and 2) 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 "(element 2)" 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 training should also be assessed as to whether or not the content is free from promotional material. Additionally, the SD states that accreditation bodies of CE providers would be considered independent of the RPC and would be eligible to conduct the audits.

5.3.1 RPC Data for CE Audits

In the 12-month Assessment Report, the RPC lays out their logistics for the independent audit process. Following approval of an RPC-supported educational grant, a Letter of Agreement (LOA) is sent to the CME/CE recipient of the grant. This LOA contains language for assuring that the CME/CE activity meets the requirements for independent education of National Accrediting Bodies. The LOA also stipulates the independent audit requirements, confirms the CE provider's agreement to participate in the audit, and obtains permission for the accrediting body to report REMS-compliant activity data, including independent audit results, to the RPC. The RPC states that similar steps were taken with all of the CME/CE providers such as the ACCME and AAFP.

The RPC states that audits are to occur prior to the time that the educational activity/material is encountered by any learners. The accrediting body is to provide written documentation of the independent audit results to the RPC.

Independent audits were conducted on **10% of the RPC-supported, REMS-compliant CE activities** by 5 nationally recognized accrediting bodies during this reporting period. All 5 bodies noted below submitted audit reports and the data from these reports are shown in **Table 2** below (reproduced entirely from Table 5 of the RPC's report):

Table 2: Summary of Successful Independent Audit Reports

ACCREDIT-ING BODY	NUMBER OF AUDIT REPORTS RECEIVED	NUMBER OF AUDIT REPORTS MEETING CRITERIA FOR REMS COMPLIANT CE *(AS DEFINED IN REMS SUPPORTING DOCUMENT)*	RESULTS		
			CONTENT OF THE TRAINING COVERS ALL COMPONENTS OF THE FDA BLUEPRINT APPROVED AS PART OF THE REMS	POST-COURSE KNOWLEDGE ASSESSMENT MEASURES KNOWLEDGE OF ALL SECTIONS OF THE FDA BLUEPRINT	CE TRAINING WAS CONDUCTED IN ACCORDANCE WITH THE STANDARDS FOR CE OF THE ACCME®, OR OF ANOTHER CE ACCREDITING BODY APPROPRIATE TO THE PRESCRIBERS' MEDICAL SPECIALTY OR HEALTHCARE PROFESSION
ACCME	13	8	✓	✓	✓
AAFP	8	8	✓	✓	✓
AANP	2	2	✓	✓	✓
AOA	3	3	✓	✓	✓
ANCC	1	1	✓	✓	✓
TOTAL	27	22			

Of the 262 CE activities, 27 (10.3%) were audited. All of the audited programs: covered all components of the FDA blueprint; had post-course knowledge assessments of all sections of the blueprint; and were conducted in compliance with the standards of the accrediting body.

Of the 27 total audit reports received, one program could not be assessed (see below). Of the remaining 26 assessable programs, 22 (84.6 %) met all criteria for REMS-compliant CE as defined in the REMS documents. All 5 programs that were identified as not meeting all criteria for REMS-compliant CE were accredited by the ACCME and were judged to not meet expectations relating to obtaining and prominently displaying financial relationships of faculty and/or staff involved in the activity. A 6th ACCME program did not meet criteria regarding "scope of evaluation" (not defined). However, the RPC states that the ACCME noted that "*this could not yet be assessed because the activity was still underway at the time of the audit*." The RPC states that some of the activities that underwent or will undergo audits are already in progress or were completed prior to the audit. In response to these 5 non-compliant trainings, the RPC states that they are following up with each provider to ensure appropriate remediation. In addition, the RPC states that in the future, CE providers will be required to submit activities for audit prior to launch so necessary remediation can be implemented prior to the program going live.

Lastly, the submitted assessment report did not include any information regarding audit results of **non-RPC-funded** REMS-compliant training. Auditing of these non-RPC-funded programs is required only if these participants are to contribute to the total numbers trained. On September 4, 2014, the RPC was sent an IR about these non-RPC-funded REMS-compliant programs. On September 24, 2014, the RPC provided the following response:

> "*The RPC has not been informed of any independent audits of non-RPC supported REMS-compliant CE activities. Audit results from non-RPC supported REMS-compliant CE activities will be included in future assessment reports should we be made aware of them. As stated above, RPC has knowledge of 5 non-RPC-funded CE activities that have been reported through the CE Data Aggregation System as Blueprint-compliant activities by a CE Provider or Accreditor… Since these activities were not supported by the RPC, we cannot impose an independent audit unless requested to do so by the Provider of the education. Audit results from non-RPC supported CE activities will only be included in future assessment reports should we receive a request for independent audit. ER/LA opioid prescriber completer totals from such programs will only be applied toward the REMS goals if REMS compliance is assured*."

5.3.2 Reviewer (I. Cerny) Comments

1. Although the RPC states that audits were to occur prior to the time that an educational activity is encountered by any learners, they also admit that "*some activities that underwent or will undergo audits are already in progress or were completed prior to the* audit." Given that programs are debuting all the time, and

the timeframes involved, it is likely that the audit will be catching mostly programs that have already debuted.

2. The RPC reports that they were not able to provide information regarding non-RPC-funded CE activities: since they do not support these activities, they have no jurisdiction to impose an audit upon them. The RPC was able to provide information that 320 prescribers had taken non-RPC-supported training. The RPC should be asked for their process as to how they identify these programs. Also, since the assessment plan states that the RPC is also to audit non-RPC-supported CE programs, the RPC should investigate how to enter into agreements with these non-RPC-supported providers so as to be able to conduct an audit of their programs.

5.4 PRESCRIBER SURVEY

A prescriber survey will be provided with the next assessment report. In addition, the RPC will conduct a long-term evaluation (LTE) designed to assess prescribers' knowledge and practice changes 6 months to one year after completing a REMS-compliant CE course. The RPC created an RFP which was disseminated on April 25, 2014. Proposals were due to RPC on May 14, 2014; four proposals were received and the vendor selection process is underway. The RPC's goal is to have a contract in place by mid-September 2014. The protocol for the LTE will be submitted for FDA's 90-day review. The results of the LTE will be included in the 36- Month FDA Assessment Report.

5.5 ELEMENT 4 – PATIENT SURVEY

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

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

The patient survey was pretested in 21 patients prescribed ER/LA opioid analgesics to identify any limitations with the survey instrument and survey process. Patients were identified from medical and pharmacy claims in the HealthCore Integrated Research Database (HIRD). The database contains claims data from commercially-insured patients in the US, with dates of service for all non-capitulated (no set amount paid to providers to cover health care costs) ambulatory, emergency department, inpatient, and outpatient encounters for members with eligibility at the time of service. Patients were eligible to participate if they were adults age 18 or older who filled at least one prescription for an ER/LA opioid analgesic between December 1, 2012 and November 30, 2013. Patients were excluded if they failed to validate date of birth or name; did not fill a prescription in the 12 months prior to the survey; were employed as a physician, employed or family member employed with survey vendor, RPC, or FDA; or unsure of the opioid or class

prescribed. Approximately 11,801 patients were eligible to complete the survey. A total of 1,923 patients (16%) were contacted via mail or telephone. Out of those, 221 were excluded during screening leaving 1,702 contacted patients. A total of 413 patients completed the survey (70% by phone and 30% online) for a response rate of 24% among the contacted respondents; 266 users of oral, non-methadone opioids:102 patch users, 45 methadone users.

According to patient reports, the majority of patients were ages 50-64 (58%); female (62%); used oral drugs that were not methadone only (65%); Caucasian (93%); married (71%); and used ER/LA opioid analgesics for arthritis, arthropathies, osteoarthritis, and musculoskeletal pain (89%). Over half of patients (59%) had an annual income of at least $50,000 and half were college graduates or completed graduate school (50%). Most patients had used an ER/LA opioid analgesic before the most recent prescription (83%). Almost half reported that they prescribed the ER/LA opioid analgesic by a pain specialist (43%) followed by other type of specialist (31%), and primary care providers (24%). The most common drugs used as reported by survey respondents were: oxycodone (41%), fentanyl (19%), and morphine (14%). Only 17% of respondents were new users, and 54% of respondents reporting 12 months or more since they were first prescribed the ER/LA opioid analgesic.

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

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

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

Key risk message 1: The patient understands the serious risks associated with the use of their ER/LA opioid analgesic. This key risk message included questions about the risks and side effects associated with the use of ER/LA opioid analgesics. (See ***Table 3***)

- Respondents' understanding of this key risk message was high. Eighty-four percent of participants were aware that ER/LA opioid analgesics can cause dizziness, lightheadedness, and sleepiness. Ninety-four percent of participants were aware of the problems that overdoses can cause (i.e. breathing problems, slow breathing that can lead to death).
- Overall, 79% of respondents answered both questions correctly for this risk message; 19% answered 1 of 2 correctly and 2% answered both incorrectly.

Table 3: Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics: Key Risk Message 1

Question	Responses n (%) N=413
Key Risk Message 1: The patient understands the serious risks associated with the use of their ER/LA opioid analgesic	
Overdose may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death.	Correct: 386 (94%) Incorrect: 10 (2%) Don't Know: 16 (4%)
ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy.	Correct: 345 (84%) Incorrect: 46 (11%) Don't Know: 21 (5%)

Key risk message 2: The patient knows what to do if they too much drug (See ***Table 4***).

- Respondent's understanding was high. The majority of respondents (88%) knew to seek emergency medical help for overdose, even if the patient felt fine and knew to seek emergency help if experienced side effects such as trouble breathing, chest pain, or swelling of their face, tongue, or throat (97%).
- Overall, 86% of respondents answered both questions correctly for this risk message.

Table 4: Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics: Key Risk Message 2

Question	Responses n (%) N=413
Key Risk Message 2: The patient knows what to do if they take too much drug.	
Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fine.	Correct: 363 (88%) Incorrect: 22 (5%) Don't Know: 26 (6%)
Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics.	Correct: 400 (97%) Incorrect: 10 (2%) Don't Know: <5 (1%)

Key risk message 3: The patient understands the need to store the drug in a safe place (See ***Table 5***).

- The majority of respondents knew that unused ER/LA opioid analgesics should not be thrown in the trash (91%) and that a child could die if they take or use ER/LA opioids (93%).
- Only 66% of respondents were aware the ER/LA opioid analgesics should not be stored in the medicine cabinet with other medications in the household.

- Overall, 57% of respondents answered all three questions correctly and 36% answered 2 out of the 3 correctly.

Table 5: Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics: Key Risk Message 3

Question	Responses n (%) N=413
Key Risk Message 3: The patient understands the need to store the drug in a safe place.	
Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household.	Correct: 271 (66%) Incorrect: 96 (23%) Don't Know: 46 (11%)
Do not throw away any unused ER/LA opioid analgesics in the trash.	Correct: 375 (91%) Incorrect: 22 (5%) Don't Know: 16 (4%)
A child could die if they take or use the respondent's ER/LA opioid analgesics.	Correct: 384 (93%) Incorrect: 14 (3%) Don't Know: 15 (4%)

Key risk message 4: The patient knows they should not share the drug with anyone (See ***Table 6***).

- There was a very high understanding of this key risk message. The majority of respondents were aware that ER/LA opioid analgesics should not be given to other people with the same condition (98%) and selling or giving away ER/LA opioid analgesics was against the law (97%).
- Overall, 96% of respondents answered both questions correctly.

Table 6: Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics: Key Risk Message 4

Question	Responses n (%) N=413
Key Risk Message 4: The patient knows they should not share the drug with anyone.	
Do not give ER/LA opioid analgesics to other people who have the same condition as you.	Correct: 406 (98%) Incorrect: 6 (1%) Don't Know: <5 (1%)
Selling or giving ER/LA opioid analgesics is against the law.	Correct: 402 (97%) Incorrect: 11 (3%) Don't Know: 0 (0%)

Key risk message 5: The patient understands how to use the drug safely (See ***Table 7***).

- There was a high level of understanding for some questions. Most respondents knew that they should talk to their healthcare provider before stopping ER/LA opioid analgesics (84%), they should talk to their healthcare provider if the current dose doesn't control their pain (94%), they should inform their healthcare provider about all other medications being used (96%), that it is not okay to drink alcohol while using ER/LA opioid analgesics (93%), they should inform their healthcare provider about a history of drug or alcohol abuse or mental health problems (91%), and they should inform their healthcare provider about over the counter medications and vitamins or supplements (89%).
- There was a lower level of understanding in terms of awareness that patients should read the medication guide every time a prescription is filled (56%) and that it is okay to drink caffeine while using ER/LA opioid analgesics (49%).
- Overall, 15% of respondents answered all eight questions correctly; 44% answered 7 out of 8 correctly, and 27% answered 6 out of 8 correctly.
- Seventy percent of non-methadone oral drug users answered both of the cohort specific questions correctly. Responses were split between patch users with 48% of respondents answering all three questions correctly and 42% answering 2 out of 3 correctly.

Table 7: Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics: Key Risk Message 5

Question	Responses n (%) N=413
Key Risk Message 5: The patient understands how to use the drug safely.	
Talk to a healthcare provider prior to stopping ER/LA opioid analgesics	Correct: 346 (84%) Incorrect: 49 (12%) Don't Know: 18 (4%)
Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control your pain.	Correct: 389 (94%) Incorrect: 18 (4%) Don't Know: 6 (1%)
It is not okay to drink alcohol while taking or using ER/LA opioid analgesics.	Correct: 385 (93%) Incorrect: 12 (3%) Don't Know: 16 (4%)
Read the attached MG every time an ER/LA opioid prescription is filled.	Correct: 231 (56%) Incorrect: 145 (35%) Don't Know: 37 (9%)
Inform healthcare providers about all the other medications being used.	Correct: 398 (96%) Incorrect: 13 (3%) Don't Know: <5 (1%)
Inform healthcare providers about any history of abuse of street or prescription drugs, alcohol addiction, or	Correct: 375 (91%)

mental health problems.	Incorrect: 28 (7%) Don't Know: 10 (2%)
Inform healthcare providers about over the counter medicines, vitamins, and dietary supplements.	Correct: 368 (89%) Incorrect: 38 (9%) Don't Know: 7 (2%)
It is okay to drink caffeine while using ER/LA opioid analgesics.	Correct: 202 (49%) Incorrect: 60 (15%) Don't Know: 148 (36%)
ER/LA opioid analgesics should not be split or crushed if the respondent is having trouble swallowing their medication. (only for non-methadone oral drug users)	Correct: 206 (77%) Incorrect: 23 (9%) Don't Know: 37 (14%)
Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed. (only for non-methadone oral drug users)	Correct: 244 (92%) Incorrect: 15 (6%) Don't Know: 5 (2%)
Inform healthcare providers of any fever (only for patch and no methadone users)	Correct: 74 (73%) Incorrect: 14 (14%) Don't Know: 14 (14%)
Do not use a hot tub or sauna while using ER/LA opioid analgesics is pain persists (only for patch and no methadone users)	Correct: 84 (82%) Incorrect: 8 (8%) Don't Know: 10 (10%)
Do not cut ER/LA opioid analgesics patches in half to use less medicine. (only for patch and no methadone users)	Correct: 84 (82%) Incorrect: 7 (7%) Don't Know: 11 (11%)

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

There were 14 questions that accessed patient receipt and comprehension of the Medication Guide and Patient-Counseling Document (PCD)(See ***Table 8***). Most respondents reported receiving the Medication Guide from their pharmacists with their last fill (90%) while 91% of respondents received the Medication Guide from their pharmacist in the last 12 months. Of the respondents that received the Medication Guide, 97% read all with each pharmacy fill (15%) or read all (66%) or some (16%) of the Medication Guide at least once. The majority of respondents that received the Medication Guide (94%) understood all or most of the information. Respondents that received the Medication Guide were less likely to be first-time users (29% vs 16%). The main source of the Medication Guide was the pharmacist (92%). Other sources included their HCP (42%), the internet (38%), another HCP (28%), and somewhere else (21%).

Only 38% of respondents reported receiving the PCD from their healthcare provider when the ER/LA opioid analgesic was first prescribed and only 27% of respondents reported receiving the patient counseling document in the last 12 months. Only 26% reported that their HCP referenced the PCD in the past 12 months. Of the respondents that received the PCD, 77% understood all or most of the information. Compared to non-recipients, respondents that had received the PCD had more often seen a HCP in the past month (58% vs. 45%) or filled an ER/LA opioid analgesic prescription in the past month (60% vs. 49%).

Table 8: Patient-Reported Receipt and Comprehension of the Medication Guide and Patient-Counseling Document

Question	**Responses n (%) N=413**
Medication Guide (MG) Questions	
Received MG from pharmacist with the last ER/LA opioid analgesic prescription fill	Yes: 373 (90%) No: 21 (5%) Not sure: 19 (5%) Refused: 0 (0%)
Received MG from pharmacist in the last 12 months	Yes: 374 (91%) No: 23 (6%) Not sure: 16 (4%) Refused: 0 (0%)
Received MG from non-pharmacist in the last 12 months	Yes: 53 (13%) No: 337 (82%) Not sure: 23 (6%) Refused: 0 (0%)
Read MG	Never read any: 14 (3%) Read some, at least once: 64 (16%) Read all, at least once: 274 (66%) Read all, with each pharmacy fill: 61 (15%) Refused: 0 (0%)
Offer to explain MG	Yes: 267 (65%) No: 128 (31%) Not sure: 18 (4%) Refused: 0 (0%)
Accepted offer to explain MG	Yes: 147 (55%) No: 119 (45%) Not sure: 1 (<1%)

	Refused: 0 (0%)
Usefulness of the information in the MG	Not useful at all: 6 (1%) Not very useful: 15 (4%) Somewhat useful: 164 (40%) Very useful: 224 (55%) Refused: 0 (0%)
Understanding of the information in the MG	Did not understand it at all: <5 (1%) Understood some of the information: 6 (1%) Understood about half of the information: 11 (3%) Understood most of the information: 137 (33%) Understood all of the information: 251 (61%) Refused: <5 (1%)
Patient Counseling Document (PCD) Questions	
Received PCD from healthcare provider when first prescribed the current ER/LA opioid analgesic	Yes: 155 (38%) No: 135 (33%) Not sure: 123 (30%) Refused: 0 (0%)
Received PCD from healthcare provider when prescribed the current ER/LA opioid analgesic in the last 12 months	Yes: 111 (27%) No: 207 (50%) Not sure: 95(23%) Refused: 0 (0%)
Healthcare provider referred to or discussed PCD when prescribing the current ER/LA opioid analgesic in the last 12 months	Yes: 109 (26%) No: 206 (50%) Not sure: 98 (24%) Refused: 0 (0%)
Understanding of the information discussed from the PCD	Did not understand it at all: 23 (8%) Understood some of the information: 5 (2%) Understood about half of the information: 11 (4%) Understood most of the information: 64 (21%) Understood all of the information: 169 (56%)

	Refused: 32 (11%)

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

Five survey items assessed patient's perceived access to treatment and satisfaction with access to pain medications (See ***Table 9***). In terms of perceived access, 73% agreed they were able to get a prescription when needed. Thirty percent of respondents felt they had to go to their HCP too often when ER/LA opioids were needed.

Most respondents reported satisfaction with their access to ER/LA opioid analgesics. The majority were satisfied with their ability to get a prescription (80%), with their access to ER/LA opioid analgesics (81%), and with their ability to get ER/LA opioid analgesics from the pharmacy (79%).

Table 9: Patients' Perceived Access to Treatment and Satisfaction with Access

Question	**Responses n (%) N=413**
Able to get a prescription for ER/LA opioid analgesics through my healthcare provider when needed	Agreed: 302 (73%) Disagreed: 62 (15%) Neither agreed not disagreed: 49 (12%)
Satisfied with ability to get a prescription for ER/LA opioid analgesics	Agreed: 329 (80%) Disagreed: 46 (11%) Neither agreed not disagreed: 37 (9%) No response: 1(<1%)
Satisfied with access to ER/LA opioid analgesics	Agreed: 336 (81%) Disagreed: 38 (9%) Neither agreed not disagreed: 38 (9%) No response: 1 (1%)
Does not have to go to healthcare provider too often when more ER/LA opioid analgesics are needed	Agreed: 223 (54%) Disagreed: 122 (30%) Neither agreed not disagreed: 68 (16%)
Satisfied with ability to get ER/LA opioid analgesics from a pharmacy	Agreed: 326 (79%) Disagreed: 52 (13%) Neither agreed not disagreed: 35 (8%)

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

Survey items assessed patient-reported frequency of appropriate prescriber behaviors (see ***Table 10***). The majority of respondents agreed that their HCP asked about medical history when prescribing (93%), talked about how much medication to take or use when

prescribing (95%), and discussed opioid choice including the benefits and risks associated with opioid therapy and important safety information (78%). Sixty-one percent of respondents reported that their HCP discussed what to do if a dose was missed. A little over half of respondents reported that their HCP talked about what to do with extra medication when prescribing (54%) and discussed how to safely discontinue the current ER/LA opioid analgesic (54%). Patient-reported responses were low for other appropriate prescriber behaviors. Respondents reported that their HCP always or regularly used the PCD for discussion (24%), cautioned about the risks associated with use (52%), discussed how to safely discontinue (38%), counseled on common side effects (50%), instructed about the importance of and how to safely dispose of unused medication (34%), instructed to keep medication away from children (49%), and instructed not to share medication (54%). Only 46% of respondents reported completing a Patient Prescriber Agreement (PPA) or patient contract. Respondents reported that their HCP never used the PCD for discussion (31%), discussed how to safely discontinue (27%), instructed about the importance and how to safely dispose of any unused ER/LA opioid analgesics (35%), instructed to keep medication away from children (24%), and instructed not to share medication (24%).

Table 10: Patient-Reported Frequency of Appropriate Prescriber Behaviors

Question	**Responses n (%) N=413**
Used the patient counseling document (PCD) on ER/LA opioids for discussion	Always: 64 (15%) Regularly: 33 (8%) Sometimes: 68 (16%) Rarely: 44 (11%) Never: 129 (31%) Don't know: 74 (18%) No response: 1 (1%)
Cautioned about important risks associated with ER/LA opioid analgesics, including overdose or taking too much	Always: 131 (32%) Regularly: 83 (20%) Sometimes: 72 (17%) Rarely: 43 (10%) Never: 63 (15%) Don't know: 20 (5%) No response: 1 (1%)
Discussed how to safely discontinue ER/LA opioid analgesics if they are no longer needed	Always: 97 (23%) Regularly: 60 (15%) Sometimes: 72 (17%) Rarely: 43 (10%) Never: 111 (27%) Don't know: 29 (7%)

	No response: 1 (1%)
Counseled on the most common side effects from using ER/LA opioid analgesics	Always: 120 (29%) Regularly: 87 (21%) Sometimes: 96 (23%) Rarely: 46 (11%) Never: 48 (12%) Don't know: 16 (4%)
Instructed about the importance and how to safely dispose of any unused ER/LA opioid analgesics	Always: 87 (21%) Regularly: 52 (13%) Sometimes: 60 (15%) Rarely: 35 (8%) Never: 144 (35%) Don't know: 35 (8%)
Instructed about keeping ER/LA opioid analgesics safe and away from children	Always: 140 (34%) Regularly: 61 (15%) Sometimes: 52 (12%) Rarely: 41 (10%) Never: 98 (24%) Don't know: 20 (5%) No response: 1 (<1%)
Instructed not to share ER/LA opioid analgesics with anyone else	Always: 166 (40%) Regularly: 59 (14%) Sometimes: 39 (9%) Rarely: 32 (8%) Never: 99 (24%) Don't know: 18 (4%)
Healthcare provider asked about medical history when prescribing ER/LA opioid analgesics*	Agreed: 385 (93%) Disagreed: 14 (3%) Neither agreed not disagreed: 14 (3%)
Healthcare provider talked about how much medication to take or use when ER/LA opioid analgesics were prescribed*	Agreed: 393 (95%) Disagreed: 13 (3%) Neither agreed not disagreed: 7 (2%)
Healthcare provider talked about what to do with extra medication when ER/LA opioid analgesics were prescribed*	Agreed: 218 (53%) Disagreed: 143 (35%) Neither agreed not disagreed: 49 (12%) No response: 1 (<1%)

Healthcare provider discussed opioid choice, including the benefits and risks associated with opioid therapy, and important safety information when prescribing the current ER/LA opioid analgesic in the last 12 months*	Yes: 321 (78%) No: 78 (19%) Not sure: 14 (3%) Refused: 0 (0%)
Healthcare provider discussed how to safely discontinue the current ER/LA opioid analgesic when it was prescribed in the last 12 months*	Yes: 221 (54%) No: 176 (43%) Not sure: 16 (4%) Refused: 0 (0%)
Healthcare provider discussed what to do if a dose was missed of the current ER/LA opioid analgesic when it was prescribed in the last 12 months*	Yes: 252 (61%) No: 138 (33%) Not sure: 23 (6%) Refused: 0 (0%)
Healthcare provider completed a Patient Prescriber Agreement (PPA) or patient contract when the current ER/LA opioid analgesic was prescribed in the last 12 months*	Yes: 191 (46%) No: 149 (36%) Not sure: 73 (18%) Refused: 0 (0%)

*Different response options across survey questions

Conclusions

Overall, respondents had a high understanding of the key risk messages, though the survey respondents were not representative of the drug use population. There was a lower understanding of aspects of safe storage and using the drug safely. The majority of respondents received the Medication Guide in the last 12 months (90%) but only 27% of respondents received the PCD in the last 12 months. Most respondents reported satisfaction with access to ER/LA opioid analgesics and agreed that they were able to get a prescription when needed. Patient-reported frequency of appropriate prescriber behaviors was low.

5.5.1 Reviewer's (S. Harris) Comments/Recommendations:

- The list of drugs included in the patient survey included drugs that are no longer prescribed. The drug list should be reviewed by the RPC and the review team prior to the next survey to ensure that drugs that are not currently prescribed are removed and the drug lists in the patient and prescriber surveys are consistent.

- The survey respondents were not representative of the drug use population. All survey respondents were commercially insured while only over half of patients used a third-party payer (54%) according to drug use data provided in the REMS assessment report (See Section 5.6). The remaining patients used Medicare Part D (36%), Medicaid (5%), and cash (5%). Drug utilization data showed that 23% of patients were age 65 or older, while only 4% of survey respondents were age 65 or older. For subsequent surveys, an alternative recruitment source should be used for

the survey or to supplement the HIRD database that includes patients on Medicaid and Medicare.

- Additional questions should be added to the survey to assess knowledge of: constipation as a side effect of use of ER/LA opioid analgesics, proper disposal of ER/LA opioids, and what to do if you miss a dose of the prescribed ER/LA opioid.
- Caregivers should be recruited for inclusion in the next survey.
- Consider oversampling for or a sub-study focusing on new users. Only 17% of respondents were new users and over half (54%) of respondents reporting 12 months or more since they were first prescribed ER/LA opioid analgesics. Results may differ for new users.
- Change the Likert scale utilized in the current survey to True/False/Don't Know.
- Patients are excluded from the survey if they are unsure of the opioid or class prescribed. A listing of drug should be provided to patients, along with pictures for online survey respondents, to ensure that patients that are using ER/LA opioid analgesics are not incorrectly considered ineligible.
- At least 30% of respondents were not sure if they received the PCD. The RPC should provide a blurred version of the document for online participants.
- Future survey results tables should provide results for each question with counts and percentages for each response option.

5.6 ELEMENT 5 – SURVEILLANCE MONITORING

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

The SD further spells out that trends in the following surveillance systems before and after the REMS is implemented (that is, after the roll-out of REMS-compliant CE) will be evaluated:

1. Emergency department (ED) visits for opioid overdose and poisoning events using either a nationally representative database of ED visits, subject to availability, or an analysis of public and/or private insurance claims databases (a commercial insurance plan claims database (e.g., Healthcore or Marketscan) plus a Medicaid claims database linked to a mortality database. A plan for validation of ICD-9 codes using medical record reviews and other supplemental data will be developed. The algorithms developed in PMR study 2065-3 for ER/LA opioid analgesics to evaluate the feasibility of developing diagnostic algorithms to exclude analgesic-related overdose/poisonings and opioid AEs that are not overdoses, as well as to differentiate between unintentional and suicide overdoses will be used.

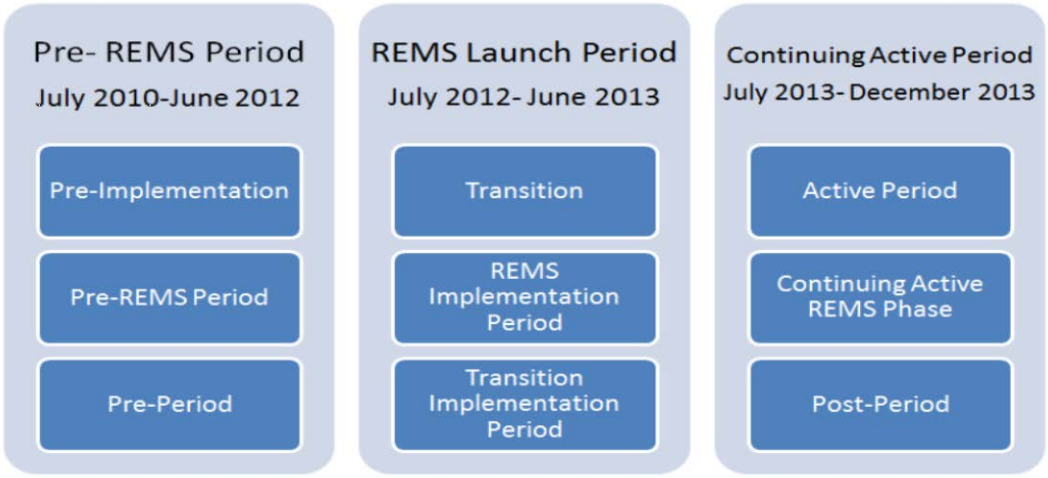
2. Intentional exposures among adolescents and adults, including severity and deaths, using a Poison Center Program (e.g., RADARS® System).
3. Unintentional exposures among infants and children, including severity and deaths, using a Poison Center Program (e.g., RADARS® System).
4. Rates of people in substance abuse treatment programs abusing ER/LA opioid analgesics, as well as source of acquiring the ER/LA opioid analgesics, as compared to comparator IR opioids and benzodiazepines using the national surveillance systems among substance treatment seekers (e.g., Inflexxion's NAVIPPRO® ASI-MV and CHAT systems).
5. Mortality rates resulting from drug poisoning associated with active pharmaceutical ingredients included in the ER/LA opioid analgesic REMS, but not specifically those formulations covered by the class REMS (e.g., oxycodone, but not specifically ER or IR oxycodone) using state medical examiner databases from multiple states, including but not limited to Florida and Washington states.
6. Surveys of abuse in adolescents and adults to assess trends in reported abuse of opioids, not specifically ER/LA opioid analgesics, using the National Survey on Drug Use and Health (NSDUH) and Monitoring the Future (MTF) publicly-accessible annual reports.

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

5.6.1 Time Periods Assessed

The RPC notes that three distinct time periods were evaluated for Assessment Elements related to surveillance monitoring. However, since multiple data sources were used to fulfill these 3 elements, the terminology used varies; however, the RPC states that while the terminology may differ, the data periods described are maintained across all data sources. **Figure 1** below (taken directly from the RPC report's Figure 6) describes the relationships between the terminologies used by each data source:

Figure 1: Surveillance Monitoring Time Periods



In a September 24, 2014 response to an FDA IR, the RPC clarified how the dates of the REMS launch period and the Continuing Active Period were determined: " *While the first REMS-compliant CE program launched on February 28, 2013, it took several months for marketing campaigns to commence and other programs to launch. By the end of June 2013, the first three CE programs were fully launched and a total of ten CE activities had occurred…For this reason, the metrics subteam decided the most descriptive comparisons over time would include the period preceding approval of the REMS, the year during which the REMS components and educational activities were initiated ("REMS Launch Period"), and the subsequent "Continuing Active Period," during which time it is thought the first true impact of the full REMS would be realized."*

5.6.2 RADARS Data

Introduction: The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS ®) System is comprised of multiple programs which gather data from differing populations along the spectrum of drug abuse.

Poison Center Program

The RADARS System Poison Center (PC) Program obtains data from laypersons and healthcare providers who are seeking advice regarding potential toxic exposures, including prescription opioids and prescription stimulants. The PC Program gathers data from 49 regional US PC in 46 states, including urban, suburban, and rural regions (covering over 90% of the US population). Investigators at each participating PC collect data using a nationally standardized electronic health record. PC data collected through RADARS System provide an estimate of change in intentional abuse, misuse, emergency department visits and deaths associated with these drugs. In addition to obtaining exposure and substance data, the PC Program collects demographic, clinical effects, treatment, and medical outcomes information.

The SD cites RADARS as an example of a suitable database to assess these exposures as well as to assess:

- Intentional exposures among adolescents and adults, including severity and deaths; and
- Unintentional exposures among infants and children, including severity and deaths

In addition to the RADARS system collecting data intentional exposure calls that are measures of drug abuse through the PC Program, RADARS also collects data on abuse through the RADARS Treatment Center (TC) Program. In the TC Program, abuse is measured by survey respondent endorsing the use of an ER/LA opioid analgesic "to get high" in the past 30 days (also referred to as "past 30 day mentions).

The TC Program combines data from two distinct RADARS System programs: Opioid Treatment Program (OTP) and Survey of Key Informants' Patients Program (SKIP). The OTP and the SKIP use the same core data collection form and complement each other by providing information from patients entering both private and public opioid addiction

treatment programs. Patients enrolling in the study are voluntarily recruited and complete a self-administered anonymous questionnaire within the first week of admission. The objectives of these programs are to estimate 1-month prevalence and the injection rate of prescription and illicit opioid and non-opioid drugs among patients admitted to opioid treatment programs. In addition, they seek to determine the patient's drug of choice and the source of the primary drug.

The OTP involves 77 methadone maintenance treatment programs in both urban and rural areas across 37 states. The SKIP Program involves 155 substance abuse treatment programs covering 47 states. These primarily private treatment centers are balanced geographically with representation from urban, suburban, and rural centers.

The RADARS system also collects data on abuse through the College Survey (CS) Program. In the CS Program, abuse is defined as the endorsement of the non-medical use of a drug in the past 90 days. The CS is an online questionnaire that collects data from self-identified students attending a 2- or 4-year college, university, or technical school at least part-time during the specified sampling period. The objectives of the CS Program are to estimate the scope misuse/abuse of prescription drugs among US college students, determine the drug source, and determine the route of drug administration among these students. A target of 2000 surveys is completed three times per year with enrollment stratified to ensure nationwide distribution of respondents. Students are sent an invitation to participate in the study and receive credits upon completion of the survey.

Outcome Variables to be assessed by RADARS: **Table 11** (reproduced directly from the RPC's Table 7.3) below summarizes the outcome variables of interest captured by the three aforementioned RADARS program:

Table 11: Outcomes by RADARS® System Program

RADARS SYSTEM Program	Abuse	Misuse	Serious Adverse Events	Death	Unintentional Therapeutic Errors	Pediatric Unintentional General Exposures	Adolescent Abuse
Poison Center Program	X	X	X	X	X	X	X
Treatment Center Programs Combined	X						
College Survey Program	X						

Intentional Abuse is captured by the PC, TC, and CS programs. In the P**C** Program, intentional abuse case was defined as: "*an exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high euphoric effect or some other psychotropic effect*" In the TC Program abuse was measured by a survey respondent endorsing the use of an ER/LA opioid analgesic to get high in the past 30 days. In the CS, abuse was defined as the endorsement of the non-medical use of a drug in the past 90 days.

In the PC data, **intentional misuse** was defined as: "*an exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of psychotropic effect*."

Unintentional therapeutic errors were defined as: "*an unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person or administration of the wrong substance.*"

In addition, other outcomes included **"Major Medical Outcome, Hospitalization, or Death;" "Death;" "Pediatric Unintentional General Exposures"** (from PC data, defined as cases in children under 6 years with a reason code of unintentional general); **"Adolescent Abuse"** (from PC data, defined as cases 13 to 19 years coded as intentional abuse (and is a subset of all intentional abuse cases note).

ER/LA opioid analgesics studied included methadone tablets and solution, as well as ER formulations of oxycodone, hydrocodone, hydromorphone, morphine (tablets and solution), oxymorphone, tapentadol, and fentanyl and buprenorphine transdermal delivery systems (TDS).

5.6.2.1 Data Analysis

Data were analyzed as follows:

- Data were grouped into the following three time-periods (as previously defined): Pre-Implementation (third quarter 2010 through second quarter 2012), Transition (third quarter 2012 through second quarter 2013), and Active Period (third quarter 2013 forward).
- Measures were evaluated in reference to rates per 100,000 population, rates per 1,000 prescriptions, and rates per 100,000 dosing units. Data on projected number of prescriptions dispensed by drug and formulation as well as projected number of dosing units dispensed by drug and formulation were obtained from IMS Health.
- Poisson regression was used to compare changes in rates of abuse, misuse, and death over time within the ER/LA opioid analgesic REMS group to changes in rates among the comparator groups.
- All analyses and confidence intervals were two-sided, and a p-value <0.05 is interpreted as evidence of statistical significance.

5.6.2.2 RADAR Data Results

Reviewer (I. Cerny) Note: Although the RPC presents per 100,000 overall population data, due to the vast differences in market share amongst the various ER/LA opioid analgesics, this reviewer has chosen to focus mainly on the per 1,000 prescriptions data and somewhat on the per 100,000 dosage units data.

In the tables that follow, for data presented, in the "Active to Pre-Implementation % Change" columns:

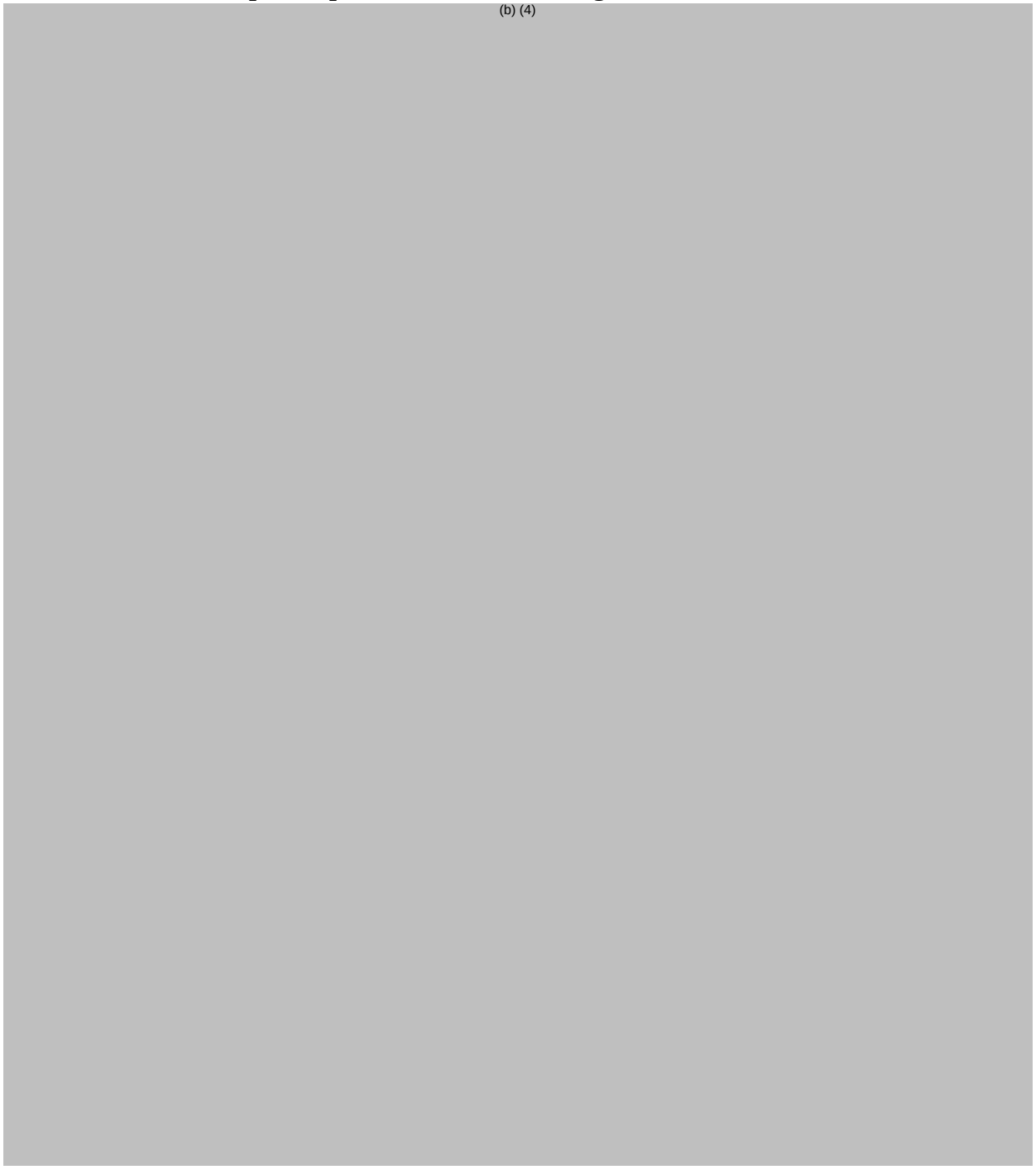
- an item typed in red font indicates a statistically significant decrease;
- an item typed in blue font indicates a statistically significant increase;

- an item typed in green font indicates a non-significant increase; and black font indicates a non-significant decrease.

Table 12 below (composite of several RPC tables) summarizes the percent changes in events for each RADARS program for the ER/LA opioid analgesic class, as a whole, compared to the IR opioid class, using either rates per 1,000 prescriptions or rates per 100,000 dosing units dispensed as denominators:

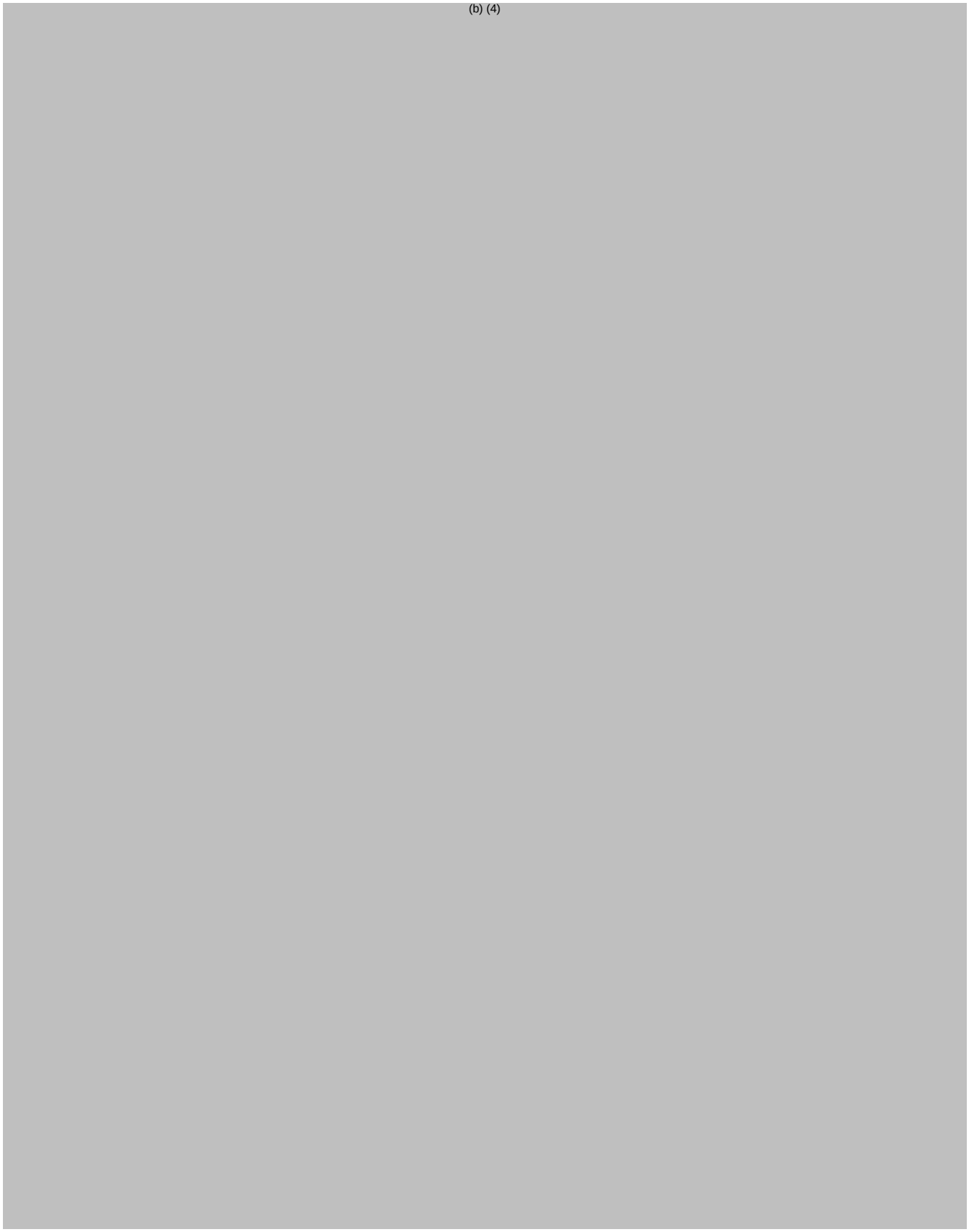
Table 12: Percent Change from Active period to REMS Pre-Implementation Period for the ER/LA Opioid Analgesics and IR Opioids for each RADARS program using 1,000 prescriptions or 100,000 dosing units as denominators

(b) (4)



* **red font** indicates a statistically significant decrease; **blue font** indicates a statistically significant increase; **green font** indicates a non-significant increase; and **black font** indicates a non-significant decrease. PC =Poison Center and ED = Call resulted in Emergency Department Visit as determined by the poison centers

(b) (4)



(b) (4)

See **Appendix Section 9.2**. for the results of individual ER/LA opioid analgesic products from the various RADARS programs (**Tables 27** through **50**)

5.6.2.3 Reviewer (I. Cerny) Comments Regarding RADARS Data

1. Part of the adverse events of interest that the REMS is to mitigate are addiction and unintentional overdose. The RADARS data do not directly measure addiction per se. The RADARS programs capture abuse as an outcome, and the TC program deals with a population that is (likely) addicted to opioids, but the specific outcome of addiction is not captured. Regarding unintentional overdose, this also is not directly addressed. The presented data only address unintentional exposure in the pediatric population. Unintentional exposures in the pediatric population are likely to be treated presumptively as unintentional overdoses. Also, the pediatric population is likely the population of most concern for this outcome. It is likely that events of unintentional overdose are included in the ED Treated and Released data as well as the Major Medical Outcome, Hospitalization, and Death metric, but these overdose events are not presented separately. The RPC should present unintentional exposure data from the PC program grouped by age to better inform this outcome of interest.

2. Decreases were in the outcomes of interest, misuse, abuse, overdose, death were observed for the ER/LA opioid analgesics. At the same time, decreases were also noted for IR opioids and prescription stimulants. As a result, the direct impact of the ER/LA opioid analgesic REMS is difficult to assess because these two other classes of commonly abused drugs that do not have a REMS demonstrated similar decreases in event rates. Whether the data seen here indicate an issue with the surveillance databases, a true overall decrease in national trends for drug misuse/abuse, or some effect of the ER/LA opioid analgesic REMS cannot be determined. However, the decrease in outcomes of interest with ER/LA opioid analgesics has been greater than that seen with IR opioids and prescription stimulants, and this difference may be, in part, due to the REMS program.

3. RADARS treatment center data have a number of limitations: both the OTP and SKIP use convenience sampling and survey only a limited number of centers. These programs are proxy measures of community abuse and may not reflect all abuse in the community nor do they reflect the overall availability of opioids in

communities. Treatment center clients may also differ from other populations with respect to access to and preference for different drug formulations.

In addition, while the RADARS data resource can provide valuable insights into medical outcomes that are the result of prescription drug abuse, they too are not without limitations. These should be kept in mind when interpreting analyses and placing the results in context with other investigations. RADARS data is derived from calls to the National Poison Data System, which is voluntary call center targeted towards potentially poisonous or toxic exposures. It is not an active surveillance system. As such, it shares many of the limitations of other similar systems, such as FDA's FAERS. When examining trends over time, calls to poison control centers may be influenced by many factors such as familiarity with the symptoms of opioid overdose; fewer calls may come to the centers because patients and providers know to go directly to emergency departments, and health care providers there know how to treat opioid overdoses. Given these factors, broad inferences and generalized statements based on these data should be interpreted with caution. Furthermore, this dataset is also not a good data source to collect information on serious outcomes such as hospitalizations or death and results in serious under-count of these events. This is a serious challenge to fully evaluating the REMS program, and other data sources need to be explored by the RPC to capture these more serious outcomes.

4. In subsequent assessment report submissions of the RADARS data, the RPC should:
    a. Include a summary table for the individual ER/LA opioid analgesics, an example of which is provided as **Table A** of review **Section 8 (Recommendations – Comments to Sponsor)**
    b. Present unintentional exposure data from the PC program grouped by age to better inform this outcome of interest
    c. Include RADARS Emergency Department Treated/Evaluated and Released Data, presented separately for adult and pediatric patients and explore other data sources that can better capture emergency department visits, hospitalizations and deaths.
    d. As per Drs. Izem and Hsueh of CDER's Division of Biometrics 7[2], the RPC should make the following adjustment to their statistical analysis section:
        i. Regarding the presentation of results: RPC's assessment RADARS report Tables 8-13 reported p-values testing for significant change between the pre-REMS period and the post REMS period but neither the text in Section 7 nor the footnote

[2] January 8, 2015 Statistical Review and Evaluation from CDER's Division of Biometrics 7 (R. Izem and C Hsueh) regarding statistical analyses performed by the RPC in the Assessment Report

in the tables explained exactly how each rate was derived and which test was used. It is unclear which of the two models (mean model or spline models) listed in Appendix D was used to derive the p-values in Tables 8-13 and we recommend for the RPC to add a description of the method used in a footnote for each table. Similarly, we recommend using footnotes in Table 15 to explain the data source for each projection.

ii. *About methods: In both of the models proposed in the RADARS data analysis section, the unit of analysis is zip code (spatial) and quarter (time). Thus, testing for change between pre and post period for each outcome is investigating whether the average rate of events over time for the average zip code has changed from the pre-REMS period to the post-REMS period. If the unit of analysis is indeed the zip code and quarter, it is unclear whether the Poisson regression in both models includes a term for overdispersion. Considering the between zip code variability, the overdispersion parameter may not be negligible and we recommend including it in the models.*

iii. *In addition to these two models, we recommend using non-parametric tests (such as bootstrap or randomization tests) on national estimates per quarter to test for differences in the rates between the pre and the post period.*

5.6.3 NAVIPPRO Data

Introduction: The National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) is a comprehensive risk management program for prescription opioids, stimulants, and other Schedule II or III therapeutic agents. NAVIPPRO was developed with support from the National Institutes of Health (NIH), the National Institute on Drug Abuse (NIDA), as well as industry sponsorship. NAVIPPRO system provides product-specific surveillance information from both proprietary and public data sources in order to monitor emerging trends in substance abuse from various populations. Two of NAVIPPRO's proprietary data streams—the ASI-MV® for adults and CHAT® for adolescents—were used to monitor trends in abuse and drug source.

The Addiction Severity Index-Multimedia Version (**ASI-MV)** collects data through a computerized interview on substances used and abused by adults in treatment for substance use disorders. Data are collected using a self-administered and structured computerized interview. The ASI-MV collects individual-level data across a series of domain areas, including demographic, medical, employment/support status, alcohol/drug use, legal, family/social status, and psychiatric status and includes product-specific questions on use and abuse of prescription medications. The ASI-MV assessment captures product-specific data related to past 30 day use and abuse for over 60 brand and generic prescription opioid products, including information on routes of administration and sources of procurement for each product.

The Comprehensive Health Assessment for Teens (**CHAT**) is a computerized behavioral health assessment targeted to adolescents age 18 and younger entering treatment for drug or alcohol abuse. Questions included in the assessment are related to adolescent experiences in five domain areas: self and personality factors, family and peer relations, physical and emotional health, psychological issues, and drug use experiences. CHAT was developed with support from the National Institutes of Health (NIH) and the National Institute on Drug Abuse (NIDA). The assessment collects data on abuse of prescription medications at a product-specific level, including photographs of brand and generic medications and their street names, routes of administration, and sources of procurement. Similar to the ASI-MV, CHAT collects data on the use and abuse of opioids, as well as psychosocial factors related to substance abuse that are specific to this younger population.

5.6.3.1 NAVIPPRO Study Design

The overall objective of this study was to evaluate trends in abuse and source of ER/LA opioid analgesics before and after the shared REMS intervention was implemented by examining changes in past 30-day abuse within the ASI-MV and CHAT samples across three time periods:
The NAVIPPRO study can be described as a cross-sectional, observational surveillance study. The following time periods were assessed:

- Pre-REMS period (baseline—July 2010 through June 2012)
- REMS implementation period (time 1—July 2012 through June 2013)
- Continuing active REMS phase (time 2—July 2013 through December 2013).

The denominators used for analyses in this study include all unique individuals assessed for treatment by the ASI-MV during the study time period.

The *primary objective/analyses* for this study compared the prevalence, among all ASI-MV respondents, of past 30-day abuse (by any route of administration) for ER/LA opioid analgesics during each study time period.

Secondary objectives/analyses examined past-30-day abuse rates of the ER/LA opioid analgesic compounds/ subgroups as well as comparisons of the ER/LA opioid analgesic group as a whole with IR opioids as a group and benzodiazepines using the same study time period comparisons as the primary objectives. Note that the ASI-MV and CHAT do not collect data for benzodiazepines as a single category, but rather these products are grouped in a general category of "sedatives, tranquilizers and sleeping pills." However, this caveat noted, the class will continue to be reported as "benzodiazepines" even though it does contain some other products as well. For both the primary and secondary analyses, a logistic regression model was employed to estimate and compare changes in the odds of abuse.

Tertiary objectives/analyses evaluated source of procurement of ER/LA opioid analgesics (own prescription, multiple doctors, family member or friend, and "illicit" source) as a group and at the ingredient level to examine any changes in the proportion of the source

reported by individuals assessed by the ASI-MV indicating past 30-day abuse of ER/LA opioid analgesics overall and by compound. An additional tertiary objective was to examine quarterly trends of abuse of ER/LA opioid analgesics as a group and at the compound/subgroup level.

For this analysis, standard logistic regression models were employed. A GEE-type logistic regression model was employed to estimate and compare changes in the odds of abuse for compound/subgroup-level over time. In this model, the fixed effects include a compound-indicator variable (morphine ER, oxymorphone ER, methadone, and the other ER opioid group), and a phase indicator variable (pre-REMS phase, REMS implementation phase, and continuing active REMS phase), and the interaction of both fixed effects. Both variables are treated as categorical. The binary dependent variable is endorsement/no endorsement of abuse in the past 30 days for any of drugs comprising each level of the compound/subgroup-level groups.

Data for the ER hydrocodone product (Zohydro) were sparse due to the limited amount of time that the product was on the market prior to report cut-offs. Thus these data are not included in this report.

5.6.3.2 ASI-MV Results

Population: 209,756 unique adults from sites within the ASI-MV substance abuse treatment network were included in the ASI-MV analyses across the total study period July 2010 through December 2013. The population characteristics were as follows:

- Ages:
  - 46% were 21 – 34 years
  - 36% were 35 – 54 years
- Gender: 65% were male
- Races:
  - 59% were Caucasian
  - 19% were African American
  - 16% were Hispanic/Latino
  - 6% were other race
- Marital status:
  - 57% were never married
  - 23% were Separated, divorced, widowed
  - 19% were married
- 60% were prompted by the criminal justice system to pursue treatment

A trend analysis across each of the study periods is not provided for hydromorphone ER and tapentadol ER due to the low number of cases observed.

Table 13 below (composite of several RPC tables) summarizes the ASI-MV past 30-day Abuse results for the ER/LA opioid analgesics, IR opioids, and benzodiazepine classes:

Table 13: ASI-MV Past 30-Day Abuse for ER/LA Opioid Analgesics and Comparator groups over Baseline over the Three Study Time Periods with Change over time in Prevalence,

**Abuse = any abuse in the past 30 days prior to assessment
blue font indicates a statistically significant increase; **black font** indicates a non-significant decrease; and green font indicates a non-significant increase.

The source of procurement of the abused product is summarized in **Table 14** (reproduced from an RPC table) below (the NAVIPPRO category of "illicit" is defined as "*bought it online without a doctor's visit, from a dealer [a known seller], wrote or bought a fake prescription, stole them, traded for it, and 'other'*"):

Table 14: ASI-MV Change in Abuse Source of Procurement for the ER/LA Opioid Analgesic Group among Those with 30-day Abuse

SOURCE OF PROCUREMENT		Pre-REMS (2 years)	TIME 1 (1 YEAR)	TIME 2 (6 MONTHS)	PRE VS.v TIME 2: RELATIVE RISK/ODDS RATIO (% CHANGE)	95% CI	p-VALUE
(b) (4)							

* Cases per 100 ASI-MV assessments

**Abuse = any abuse in the past 30 days prior to assessment

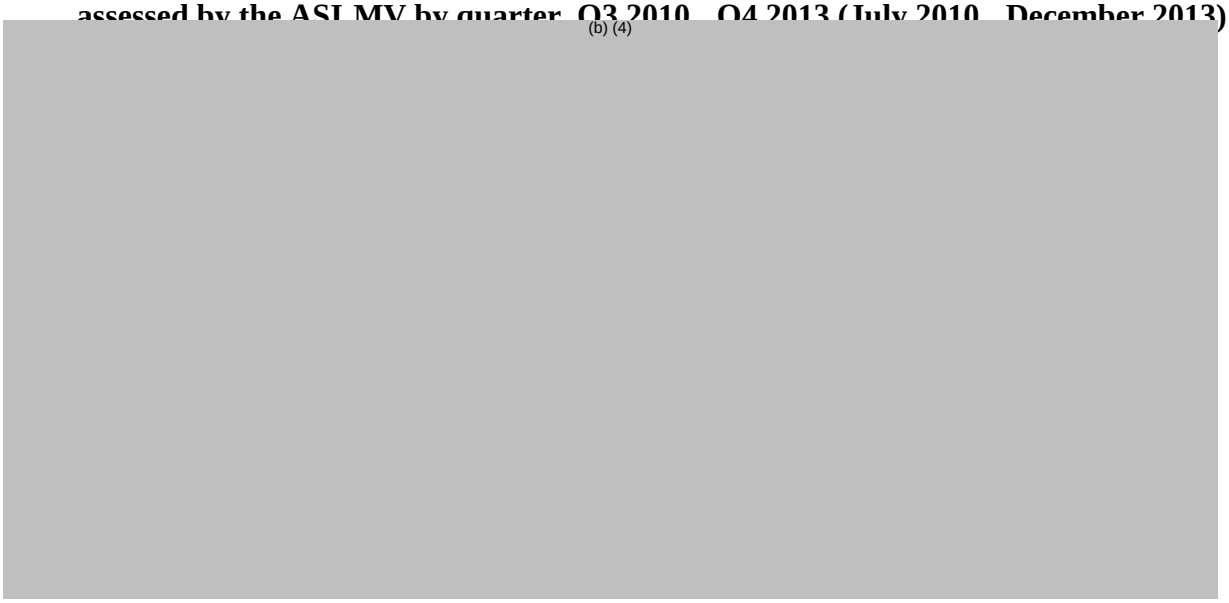
* **red font** indicates a statistically significant decrease; **blue font** indicates a statistically significant increase;

(b) (4)

Figure 2 (reproduced from an RPC Figure) below graphically represents the changes in 30-day abuse for the individual ER/LA opioid analgesic compounds:

Figure 2: Past 30-day abuse for compound-level groups among all individuals assessed by the ASI-MV by quarter, Q3 2010 – Q4 2013 (July 2010 – December 2013)

(b) (4)

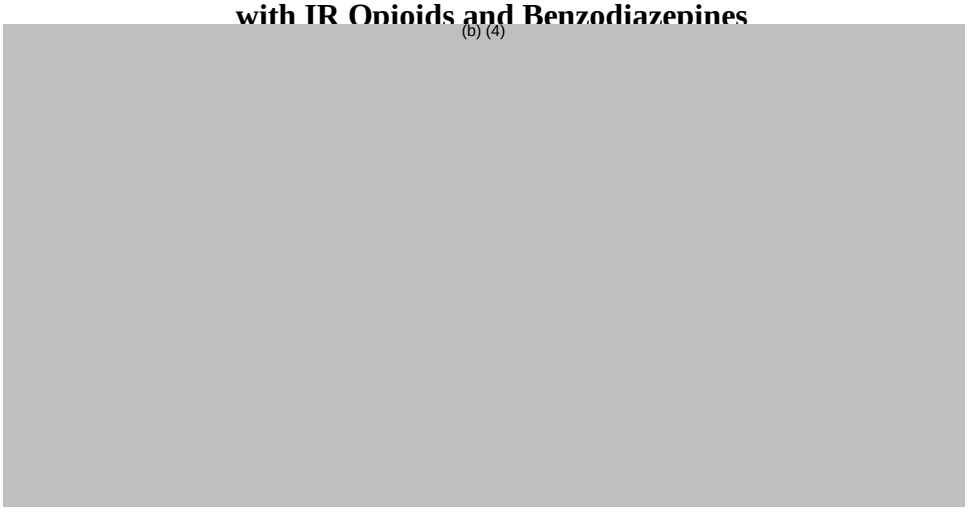


5.6.3.3 CHAT Results

(b) (4)

Table 15: CHAT Data: Past 30-Day Abuse for ER/LA Opioid Analgesics Compared with IR Opioids and Benzodiazepines

(b) (4)



(b) (4)

5.6.3.4 Reviewer (I. Cerny) Comments Regarding NAVIPPRO Data

1. The 22% statistically significant increase in abuse determined by the ASI-MV is at odds with the findings of the RADARS PC Intentional abuse and the TC program as well as perhaps even NAVIPPRO's CHAT program, The RADARS CS program does indicate an (non-statistically significant) increase in abuse. Thus although most of the programs indicate a decrease in abuse, not all measures across all of the programs are in agreement, which is likely to relate to the limitations of each data source in ascertaining the outcomes of most interest: addiction, overdose and death. The RPC hypothesizes that these discrepancies may be a result of the different data sources and the means in which data are obtained. As an example, the RPC notes that the RADARS System data are restricted to individuals who are seeking treatment for opioid abuse, while NAVIPPRO collects data from individuals seeking treatment for any substance abuse. The RPC also states that differences may be due to the ASI-MV's use of the denominator of abuse of any prescription opioids whereas the RADARS

System analysis uses census population, prescription number or dosing unit number. The RPC also notes that there can be substantial variability in the results across geographic regions, as well as by private versus public treatment centers.

2. RPC concludes that the CHAT data indicate that as for source of procurement, ER/LA opioid analgesics were primarily obtained from "illicit" sources (between 67% and 70%) and family and friends (50% to 62%). This reviewer is not able to verify these conclusions or numbers from the data provided.

3. While the NAVIPPRO ASI-MV data resource can provide valuable insights into prescription drug abuse issues, it is not without limitations. These limits should be kept in mind when interpreting the results of analyses. Since the ASI-MV is used to assess individuals for all types of substance abuse, if ER/LA opioid analgesic abuse remains unchanged but abuse of other substances decreases, then the proportion of "cases of ER/LA opioid analgesic abuse per 100 ASI-MV assessments" will increase, even if the prevalence of ER/LA opioid analgesic abuse in this population actually did not change.

   Additionally, although treatment centers and other substance abuse assessment sites from multiple states contribute to the data resource, these data are not nationally representative. In addition, sites participating in the ASI-MV program may not contribute data consistently throughout the year. Also, individuals being assessed for substance abuse treatment may be more advanced in their abuse and/or addiction, and may have different preferences, behaviors, and access to opioids from those who are earlier in the drug abuse and/or addiction trajectory.

   There are a number of factors that can influence the number and timing of individuals entering treatment and contributing data to the NAVIPPRO ASI-MV database. These can include, among other things, the availability of spaces in treatment programs, which can be affected by political, social, geographic, and economic factors not necessarily related to the prevalence of prescription opioid abuse in the community. Lastly, all data are self-reported which carries a number of limitations, such as recall bias. For these reasons, ASI-MV data cannot be used to estimate the prevalence or trends in abuse in the general population or on a national level. Despite these limitations, NAVIPPRO ASI-MV data provide valuable information on product-specific abuse behaviors, particularly route of administration, in a high-risk "sentinel" population.

4. In subsequent assessment report submissions of NAVIPPRO data, the RPC should:
   a. Include a more detailed data presentation regarding the CHAT sources of procurement as was provided for the ASI-MV data;
   b. Include a summary table for the individual ER/LA opioid analgesic agents as seen in **Table A** of review **Section 8 (Recommendations – Comments to Sponsor)**

c. As per Drs. Izem and Hsueh of CDER's Division of Biometrics 7, the RPC should make the following adjustment to their statistical analysis section:

   i. *The logistic model used is not consistent with the one used in RADARS. This model has a different unit of analysis than RADARS and does not use any outside counts as reference. More precisely, the unit of analysis is over all zip codes rather than separate for each zip code as in RADARS. Moreover, the fit odds ratio do not use population size, total prescriptions dispensed or total dose units dispensed as a reference as in RADARS. We recommend using models similar to RADARS and adding our recommendations made regarding the RADARS section to the NAVIPPRO methods.*

   ii. *The number of sites used changes from one quarter to another adding to the level of variability of measurement. We recommend Inflexxion restrict their analyses to "stable" reporting centers over time.*

5.6.4 Utility of ICD Codes for OOP Study

This study compared the diagnoses of Opioid Overdose and Poisoning (OOP) events identified by electronic medical record (EMR) to ICD-9 and ICD-10 codes for opioid-related poisoning codes and opioid-specific adverse event (AE) codes. The purpose was to determine the positive predictive value of ICD-9 and ICD-10 codes in identifying OOP events. However, these OOP validation data submitted in this report are also a part of the requirements for PMR # 2065-3. Thus, once data using these validated codes are available, they will be reviewed under the PMR by both OND and OSE's DEPI.

The RPC's summary of the initial phases of code validation is summarized in **Appendix Section 9.6** of this review. This reviewer (I. Cerny) notes that it appears that nothing is reported as to whether or not efforts were made to enhance the positive predictive value of the Opioid-specific ICD-9 AE codes (albeit, with only 13% accuracy at first pass). In addition, the specific data for the AE codes combined with overdose symptoms are not presented in the report - only a summary is provided. It is assumed that these specific data will be available through the PMR.

5.6.5 NSDUH and MTF Data

The RPC utilized "Surveys of abuse in adolescents and adults to assess trends in reported abuse of opioids, not specifically ER/LA opioid analgesics, using the National Survey on Drug Use and Health (NSDUH) and Monitoring the Future (MTF) publicly-accessible annual reports."

NSDUH is an annual survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA). Approximately 67,500 persons 12 years old or older are interviewed by NSDUH each year, providing information on the use of illicit drugs, alcohol, and tobacco in the civilian, non-institutionalized population of the US. A

scientific random sample of households is selected across the US. Since the survey is based on a random sample, each selected person represents more than 4,500 US residents. The most recent publically available NSDUH survey results were released in September 2013, and include data from 2012. The report also describes data trends from 2002 through 2012. NSDUH describes use of illicit drugs, and provides some information on non-medical use of prescription drugs including pain relievers. However, **NSDUH cannot be used to specifically identify exposures to ER/LA opioid analgesics.**

MTF studies are conducted annually by the University of Michigan's Institute for Social Research. MTF provides data on substance use of adolescents, college students, and adults through age 55. Since data from high school students are released separately from college students and adults, the data available for this assessment include a high-level analysis of 2013 data for 8^{th} , 10^{th} , and 12^{th} grade students and an in-depth analysis of 2012 data for 8^{th} , 10^{th} , and 12^{th} grade students, college students, and adults through the age of 55. MTF studies collect data on use of opioids without a prescription and specifically include questions about use of **OxyContin** and **Vicodin**.

Since the ER/LA opioid analgesics REMS was approved on July 9, 2012, the RPC states that NSDUH and MTF data in this analysis will serve as a foundation for future surveillance monitoring. Some measures that extend into 2013 are also reported.

A summary of the most relevant data will be presented here, while a few additional data will be included in **Appendix Section 9.4.**

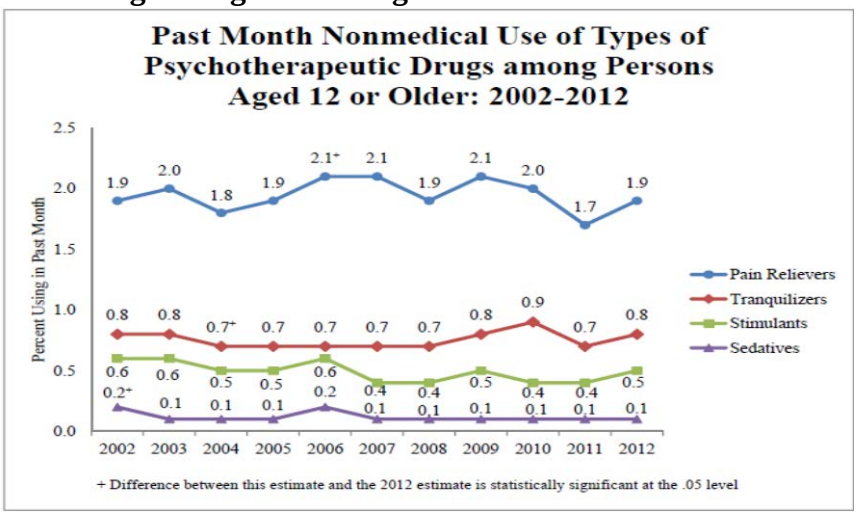
5.6.5.1 Results of NSDUH and MTF Data

Opioid-related highlights from the 2012 NSDUH database are as follows;

- The number and percentage of persons aged 12 or older estimated to be current nonmedical users of pain relievers in 2012 (4.9 million or 1.9 %) were similar to those in 2011 (4.5 million or 1.7 %) and in 2007 to 2010 (ranging from 4.7 million to 5.3 million and from 1.9% to 2.1 %).
    - Of those persons aged 12 or older in 2011-2012 who used pain relievers non-medically in the past year, 54.0% reported obtaining their most recently used drug from a friend or relative for free; 19.7% reported receiving them through a prescription from one doctor and 10.9% purchased them from a friend or relative; 10.9% bought from a friend or relative; 4.0% took pain relievers from a friend or relative without asking ; and 4.3% obtained pain relievers from a drug dealer or other stranger.
- In 2012, an estimated 7.3 million persons age 12 and over had illicit drug dependence or abuse, and 2.1 million of these had pain reliever dependence or abuse. This number was similar to the number in each year from 2007 through 2011 and was higher than the number in each year from 2002 through 2006.

Figure 3 below (taken directly from the RPC report) demonstrates how the overall class of pain relievers has been used non-medically over time as compared to other psychotherapeutic agents:

Figure 3: Past Month Non-medical Use of Types of Psychotherapeutic Drug among Persons Aged 12 or Older: 2002 – 2012



Opioid-related highlights from the 2013 MTF database are as follows;

- Percentages of 12th graders who reported trying a narcotic drug other than heroin in their lifetime, in the last year and in the last 30 days were 11.1%, 7% and 2.8%, respectively.
- There was a *decrease* of 1.1% from 2012 and 1.9% from 2010 in 12th graders who reported that they had tried a narcotic drug other than heroin at some point in their life.
- Since 2010, there has been a *decrease* of 1.6% in 12th graders who use narcotics other than heroin.
- Since 2010, there has been a gradual *decline* in the reported use of narcotics other than heroin within the past 30 days (3.6% in 2010 to 2.8% in 2013).
- **OxyContin** and **Vicodin** use:
  - Use of OxyContin within the past year was reported by 2.0%, 3.4%, and 3.6% of 8th, 10th, and 12th graders respectively. Compared to 2012, these figures represent an increase of 0.4% in both 8th and 10th graders, but a decline of 0.7% in 12th graders.
  - Use of Vicodin was reported by 1.4%, 4.6% and 5.3% of 8th, 10th and 12th graders, respectively. Compared to 2012, these figures represent a stable rate for 8th graders, an increase of 0.2% for 10th graders and a decline of 2.2% for 12th graders.
- When asked how difficult they thought it would be to get narcotic drugs other than heroin, 9.7%, 22.5%, 46.5% of 8th, 10th, and 12th graders said they would be fairly easy or very easy to get.
- A total of 18.5% of those aged 19-30 surveyed had used a narcotic other than heroin in their lifetime, and approximately 7% reported use within the last year.

While about 33%, 31%, 25%, and 27% of 35, 40, 45, and 50 year olds reported trying a narcotic other than heroin for non-medical reasons in their lifetime, only approximately 2% of each of these age groups reporting using a narcotic other than heroin within the past 30 days.

In addition, **Table 16** below (reproduced from the RPC's report) describes the percentage of MTF-surveyed 8th, 10th and 12th graders who believe that a certain activity carries "great risk":

Table 16: MTF: Trends in Harmfulness of Drugs a Perceived by 8th, 10th, AND 12th Graders: Percentage of Those Surveyed Who Respond "Great Risk"

HOW MUCH DO YOU THINK PEOPLE RISK HARMING THEMSELVES (PHYSICALLY OR IN OTHER WAYS), IF THEY…	2010	2011	2012			2013			2012-2013 CHANGE		
	12th	12th	8th	10th	12th	8th	10th	12th	8th	10th	12th
Try OxyContin® once or twice	-	-	21.9	30.9	-	19.9	29.4	-	-2.0	-1.5	-
Take OxyContin® occasionally	-	-	35.3	48.3	-	32.6	44.7	-	-2.8	-3.6	-
Try Vicodin once or twice	-	-	17.5	23.2	-	15.0	21.0	-	-2.5	-2.2	-
Take Vicodin occasionally	-	-	29.4	40.3	-	26.2	36.0	-	-3.2	-4.2	-
Try any narcotic other than heroin (codeine, Vicodin, OxyContin®, Percocet, etc.) once or twice	40.4	39.9	-	-	38.4	-	-	43.1	-	-	+4.8
Take any narcotic other than heroin occasionally	54.3	54.8	-	-	53.8	-	-	57.3	-	-	+3.5
Take any narcotic other than heroin regularly	74.9	75.5	-	-	73.9	-	-	75.8	-	-	+1.9

*significance of at least 0.05
Source: Monitoring the Future Study 2013, Overview

5.6.5.2 Reviewer (I. Cerny) Comments Regarding NSDUH and MTF Data

A great deal of data for both NSDUH and the MTF are presented in the assessment report. However, only the MTF data focus on one particular ER/LA opioid analgesic agent (Oxycontin). Although overall these data are interesting, it is unclear what if any useful information they shed on the effectiveness of the REMS. The FDA ER/LA opioid analgesic REMS Review Team intends to indicate to the RPC that they need not continue to send in these data.

5.7 ELEMENT 6 - DRUG UTILIZATION

The Assessment Element states: "Evaluation of drug utilization patterns."

However, the SD provides additional detail: "A drug utilization study will be conducted to describe trends in the number of prescriptions for class REMS ER/LA opioid

analgesics and comparator products using a national prescription database system (e.g., IMS Xponent or VONA). Specifically the following will be assessed:

- National trends in number of prescriptions dispensed from outpatient retail pharmacy settings for ER/LA opioid analgesics stratified by prescriber specialty.
- National trends in number of prescriptions dispensed from outpatient retail pharmacy settings for comparator products stratified by prescriber specialty, including:
    - Opioid analgesics not covered by the class REMS for ER/LA opioid analgesics, i.e., immediate-release
    - Prescription NSAID analgesics (e.g., celecoxib) that is an "analgesic control" group
    - Selected benzodiazepines that are frequently abused (e.g., alprazolam) that is an "abuse control" group
- Switches from ER/LA opioid analgesics to comparator analgesics with introduction of REMS."

The SD also specifically lays out the objectives of such an analysis:

i. "To estimate trends by month in the number of prescriptions for a one-year period before, and each month after, the implementation of the REMS
ii. To compare average number of prescriptions for each 3-month period for the year before and after the implementation of the class-wide REMS
iii. To compare the trends in prescribing by prescriber specialty"

5.7.1 Drug Utilization Methods/Design

To evaluate the above objectives, a retrospective cross-sectional study using data drawn from the IMS Health, National Prescription Audit™ (NPA™) for outpatient retail pharmacy settings only and IMS Health, LifeLink™ patient-level longitudinal prescription (LRx) database was conducted. Comparators were broken into three categories:

- IR opioid analgesics not covered by the class REMS for ER/LA opioid analgesics
- Prescription Non-steroidal Anti-Inflammatory Drug (NSAID), celecoxib, as an "analgesic control" group. Celecoxib was selected because all strengths require prescriptions.
- Benzodiazepines as an "abuse control" group

Patients meeting *all* of the following criteria were selected for inclusion:

- At least one prescription for one of the above products
- Continuous eligibility in the LRx database
- Activity by patients in the LRx database

Monthly prescription volume was assessed for all ER/LA opioid analgesics and comparator products prescriptions dispensed in the pre-REMS period (July 1, 2011 through June 30, 2012), during the transition implementation period (July 1, 2012 through June 30, 2013) and after the implementation of the REMS (July 1, 2013 through December 31, 2013). Counts of prescription volumes (n) were aggregated for ER/LA opioid analgesics and comparators.

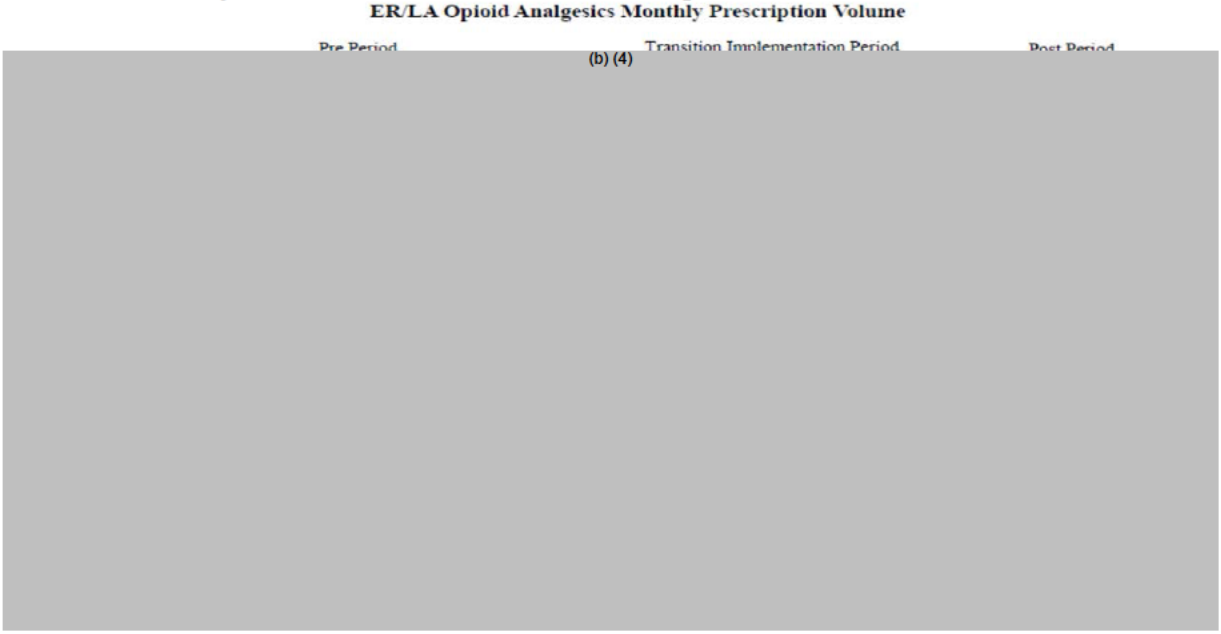
Trends and changes over time were estimated by prescriber specialty for all REMS ER/LA opioid analgesics and all comparator products. The prescriber specialties of interest appear to have been pre-specified.

Switching from an ER/LA opioid analgesic to other products was evaluated among all patients with a prescription for an ER/LA opioid analgesic. Switching was defined as filling a prescription for a new product (IR opioid or celecoxib) that is different from the prescription in the previous 3 months. Patients without a prescription for any ER/LA opioid analgesic in the previous 3 months, but who have a prescription for an ER/LA opioid analgesic in the current month were defined as new patients. Patients with a prescription for the same ER/LA opioid analgesic in the previous 3 months and in the current months were defined as continuing patients.

5.7.2 Results: Drug Utilization

Figure 4 (taken directly from the RPC's 9/24/14 IR response) below compares the monthly trend for outpatient retail prescriptions dispensed for the ER/LA opioid analgesic class as a whole versus individual ER/LA opioid analgesic products:

Figure 4: *Monthly trend* of prescriptions for ER/LA opioid analgesics and comparators 1-year before and each month after implementation of REMS



(RPC Comment: "*As FDA requested, the figure's "Morphine Products" category includes morphine sulfate, morphine sulfate beads and morphine-naltrexone*")

Table 17 below (composite of several RPC tables) presents tabular data that are very similar to those in Figure 5, an *average 3-month dispensed prescription volume* for ER/LA opioid analgesics, comparators, and individual ER/LA opioid analgesics:

Table 17: Comparison of the Average 3-Month Prescription volume between the `Pre-Period and Post-Period for ER/LA Opioid Analgesics, Comparators, and Individual ER/LA Opioid analgesics

(b) (4)

red font indicates a statistically significant decrease; **blue font** indicates a statistically significant increase; and **black font** indicates a non-significant decrease

(b) (4)

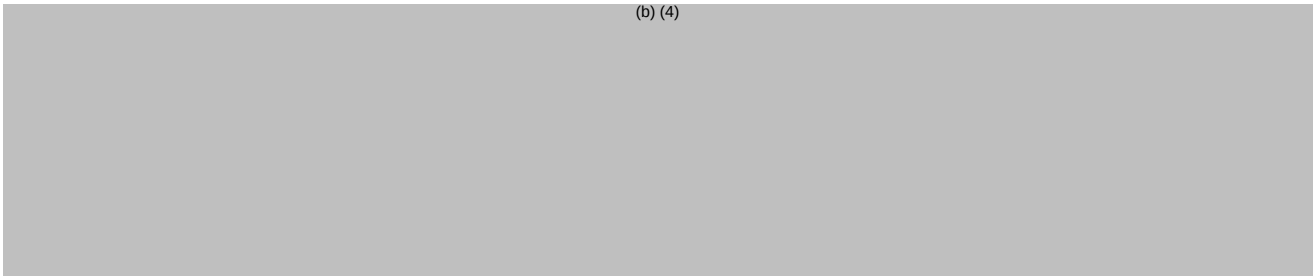


Table 18 (reproduced from the RPC report) describes the changes over time in the number of dosing units per prescription over time:

Table 18: Mean Dosing Units/Prescription for ER/LA Opioid Analgesics by Formulation and Period from the 3rd Quarter 2010 to the 4th Quarter 2014

(b) (4)

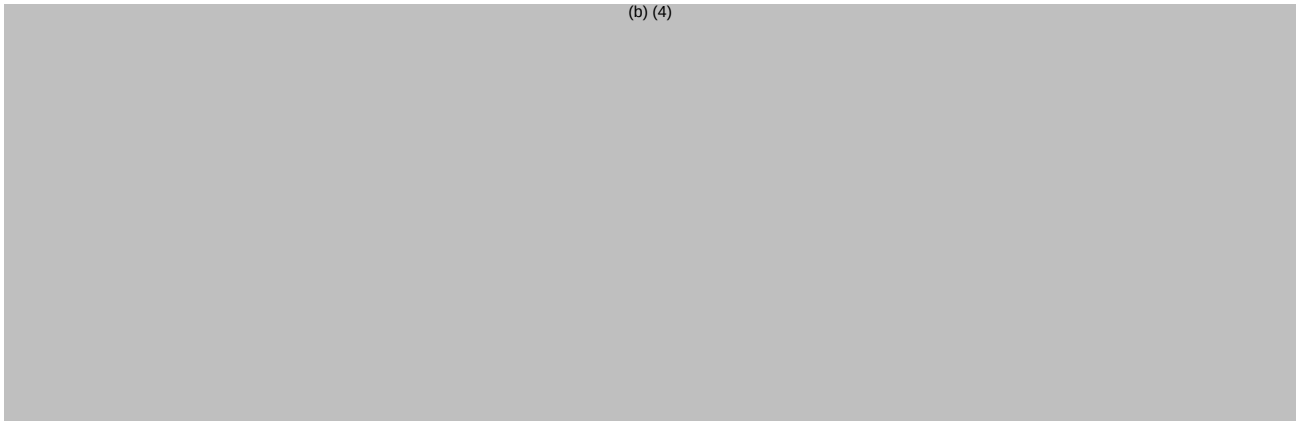
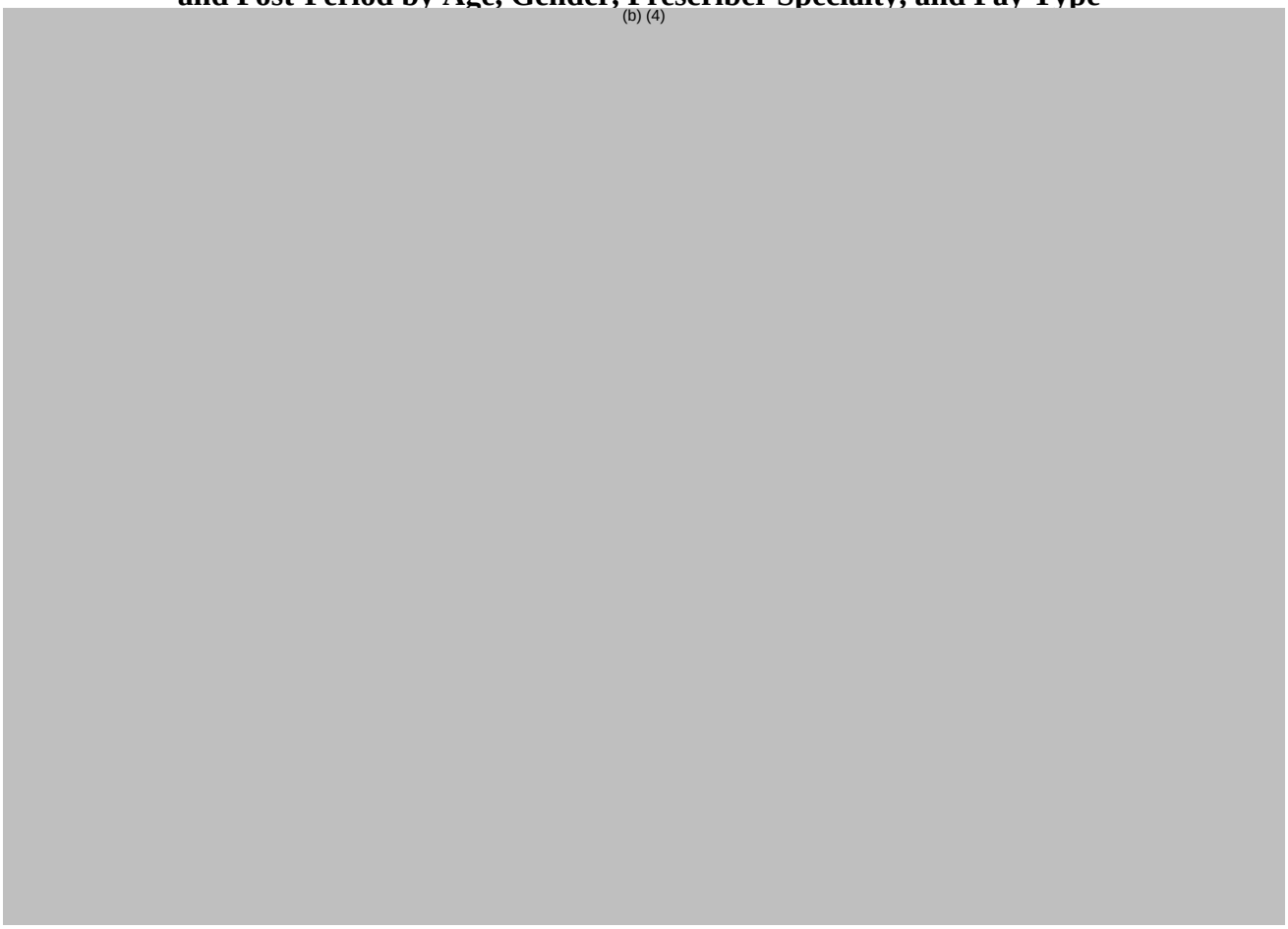


Table 19 below (a modification of an RPC table) presents pre- and post-period changes for various demographics of the populations receiving an ER/LA opioid analgesic prescription:

Table 19: Comparison of the *Average 3-Month* Prescriptions between the Pre-Period and Post-Period by Age, Gender, Prescriber Specialty, and Pay Type

(b) (4)



(b) (4)

Table 19-A: Specialty Breakout of the "All Other" Group: Comparison in the Total Average Quarterly Prescriptions of ER/LA Opioid Analgesics by Prescriber Specialty between the Pre-Period and Post-Period.

(b) (4)

(b) (4)

Table 19-B: Mean Monthly Prescription Volume by Specialty and Drug Category

(b) (4)

(b) (4)

(b) (4)

Figure 5 (taken directly from the RPC's 24-month report's Figure 32) below compares the monthly trend of switching from ER/LA opioid analgesics to IR opioids overall and by specialty:

Figure 5: Monthly trend of switching from ER/LA opioid analgesics to IR opioids overall and by prescriber specialty

Rate of Switch to IR Opioids

Pre Period Transition Implementation Period Post Period

(b) (4)

5.7.3 Reviewer (I. Cerny) Comments Regarding Drug Use Data

1. It is difficult to interpret much of the utilization data presented in the RPC's report without additional data. Fewer overall prescriptions are indeed being dispensed for ER/LA opioid analgesics and IR opioids from outpatient retail pharmacies.

However, without additional data that can more directly inform why prescription rates have declined, it is not clear what these decreases indicate. The data does not inform us of the reasons for dispensing or the appropriateness of that dispensing. It is also unknown how many prescriptions may have been written and not dispensed, a possible metric in the assessment of patient access. The specialty data are also open to differing interpretations. Dentists and surgeons appear to be prescribing ER/LA opioid analgesics less frequently. This may be a positive sign in that these specialties generally treat short-term pain for which ER/LA opioid analgesic therapy is not appropriate. However, it is not clear why fewer ER/LA opioid analgesics were prescribed by oncologists and hospice/palliative medicine specialists. Additional data are needed to interpret this finding as well. In addition, the aggregated prescription data only represents the volume of prescriptions dispensed from outpatient retail pharmacies and may underrepresent prescriber specialties of prescriptions dispensed from other settings of care such as long-term facilities, mail-order/specialty pharmacies, or clinics. Without additional data/perspective, we do not know why these decreases have occurred since multiple variables can impact prescribing such as cost, insurance reimbursements, or overall increased awareness about prescribing of ER/LA opioid analgesics or opioids in general.

2. It may be a cause for concern that Medicare Part D prescriptions for ER/LA opioid analgesics rose 18%. Also, the largest decrease (36%) in prescriptions written for the various pay types/groups was for Medicaid patients. However, a limitation of these observations is these data were generated using IMS Health, LifeLink which underrepresents Medicare, Medicaid and cash prescriptions. Thus it is difficult to interpret these results without additional information.

3. Much of the analyses by prescriber specialty and by payment method were conducted using NPA which is primarily outpatient retail pharmacy data and does not include mail order or long term care facilities. Thus prescribers working in these settings (e.g., hospice and palliative care) are likely underrepresented.

4. Without more detailed information it is difficult to determine what switching from an ER/LA opioid analgesic to an IR opioid represents with regards to prescribing patterns.

5. In Subsequent assessment report submissions of drug utilization data, the RPC should:
    a. Include a summary table for the individual ER/LA opioid analgesic agents as seen in **Table B** of **Appendix Section 9.7**.
    b. Include a more detailed description of the ER/LA opioid analgesic prescribing activities of their largest group, the "**all other**" in a manner similar to what was provided in their October 22, 2014 response to an FDA IR.
    c. Since many of the figures presented have data bunched so as to render the presentation uninterpretable, provide a more informative presentation of

the switch data and other utilization data in a manner similar to the presentation of data in Table 25 of the 24-month assessment report.

d. Add prescription data from long-term care and mail order/specialty pharmacies so as to be able to fully capture all spectrums of prescriber types and patient settings.
e. As per Drs. Izem and Hsueh of CDER's Division of Biometrics 7, the RPC should make the following adjustment to their statistical analysis section:
    i. *Student t-test was used to compare prescription volumes between two periods (such as pre and post period or pre and transition period). Although the t-test can work with small samples, the normality assumption may not hold. In addition, if there is seasonality in the data then having different seasons in the compared periods could be problematic as significant changes between periods could be due to seasonal effects. Thus we recommend that for any pairwise comparison of periods (a) use nonparametric tests such as permutation test or Wilcoxon rank-sum test because these tests work for small samples (b) use periods covering the same seasons to control for the seasonal effects in the pairwise comparison.*
    ii. *When more data points become available in the post-period (at least 12 data points), the RPC should consider performing time series analysis (e.g. segmented regression analysis of interrupted time series[1]) to evaluate the REMS effect.*
    iii. *Many of the Assessment report's Utilization Figures present drugs that are clumped near the bottom of the figures making it hard to see the pattern of change in use over time for each drug. In future report submissions, the figures could be split into as many as 4 different figures, each showing the monthly trend for a quartile of the drug use market. In this manner, a curve for a drug would be shown with comparable drugs in terms of drug use in the same figure (or for the overall ER/LA group if the team decides to go by drug group instead of individual drug).*

5.8 ELEMENT 6: CHANGES IN PRESCRIBER BEHAVIOR

Assessment Element: "Evaluation of changes in prescribing behavior of prescribers, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills. Provide the methodology for this analysis."

This section focuses on a study to evaluate changes in prescribing behavior of prescribers using one or more databases.

Three such prescribing outcome measures are:

1. whether products that are indicated for use only in opioid-tolerant patients (i.e., fentanyl transdermal patches and extended-release hydromorphone pills) are prescribed to opioid-non-tolerant/opioid-naïve patients,

2. whether products whose labels indicate that higher dosage strengths should only be used in opioid-tolerant patients are prescribed with a high starting dose in opioid non-tolerant/opioid-naïve patients, and
3. whether the proportion of patients prescribed ER/LA opioid analgesics who receive an early refill for an opioid prescription changes.

The RPC added an objective to compare the concomitant use of benzodiazepines with ER/LA opioid analgesics before and after REMS implementation.

All of these objectives were evaluated through the same retrospective cross-sectional study (drug utilization patterns), described in Assessment Element 6. The measures were aggregated monthly and/or quarterly in the pre-period (July 1, 2010 through June 30, 2012), transition implementation period (July 1, 2012 through June 30, 2013), and post-period (July 1, 2013 through December 31, 2013).

5.8.1 Prescriber Behavior Results

Prescribing Patterns in Opioid Tolerant versus Non-Tolerant Patients:
The RPC (and the SD) define an opioid non-tolerant patient as an individual who has not received an opioid for 6 months. For the purposes of this study this term is used synonymously with opioid naïve.

In the RPC's September 24. 2014 response to a September 4, 2014 IR, the RPC clarified that: "*opioid tolerance was defined as a dichotomous variable. That is, all persons who received an opioid within the previous 6 months, regardless of dose or duration, were considered opioid tolerant. Conversely, non-opioid tolerant persons were defined as individuals who had not received an opioid within the previous 6 months. Medication dose and the duration of observed therapy were not considered in the identification of non-opioid tolerant patients*. "

Fentanyl transdermal patches and ER hydromorphone pills are indicated for use **only** in opioid tolerant patients. **Table 20** below (modification of an RPC table) compares the relative number of prescriptions for these two products for opioid-tolerant/non-tolerant individuals and the change in prescriptions from the pre- to post-periods.

Table 20: Comparison of the Average Monthly Volume of Products for Opioid Tolerant Patients Prescribed to Opioid Tolerant/Non-Tolerant Patients from the Rep- to Post-Periods.

(b) (4)

red font indicates a statistically significant decrease; **blue font** indicates a statistically significant increase;

(b) (4)

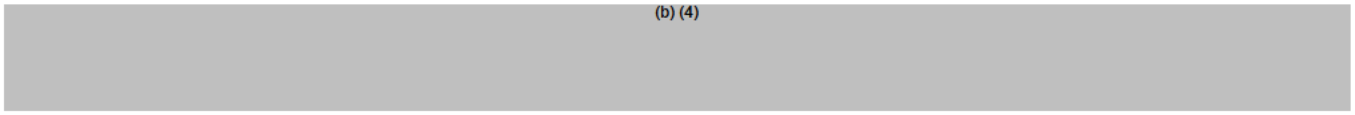


Table 21 below (reproduced directly from Table 30 of the RPC's report) is a list of the products whose labels indicate that higher dosage strengths should only be used in opioid tolerant patients:

Table 21: Product Strengths Exceeding Recommended Starting Dose for Non-Opioid Dependent Patients

PRODUCT	DOSE STRENGTH EXCEEDING RECOMMENDED STARTING DOSE FOR NON-OPIOID DEPENDENT PATIENTS
Buprenorphine	10 mcg/ hr, 15 mcg/ hr, & 20 mcg/ hr
Morphine Sulfate	100 mg, 100 mg/12 hr, 100 mg/24 hr, 130 mg/24 hr, 150 mg/24 hr, 200 mg, & 200 mg/24 hr
Morphine Sulfate Capsules	90 mg/24 hr & 120 mg/24 hr
Oxycodone	15 mg, 20 mg, 20 mg/12 hr, 30 mg, 40 mg, 40 mg/12 hr, 60 mg, 80 mg, 80 mg, & 160 mg/12 hr
Oxymorphone	7.5 mg, 7.5 mg/12 hr, 10 mg, 10 mg/12 hr, 15 mg, 15 mg/12 hr, 20 mg, 20 mg/12 hr, 30 mg, 30 mg/12 hr, 40 mg, & 40 mg/12 hr
Tapentadol	100 mg/12 hr, 150 mg/12 hr, 200 mg/12 hr, & 250 mg/12 hr

Regarding use of the “high-starting dose” for opioid-tolerance drugs, the RPC does not provide detailed data as is shown in Table 49, but instead provides the following narratives:

(b) (4)

Figure 6: Monthly trend in the early refill rate of ER/LA opioid analgesics among patients with early refills before and throughout the transition implementation period

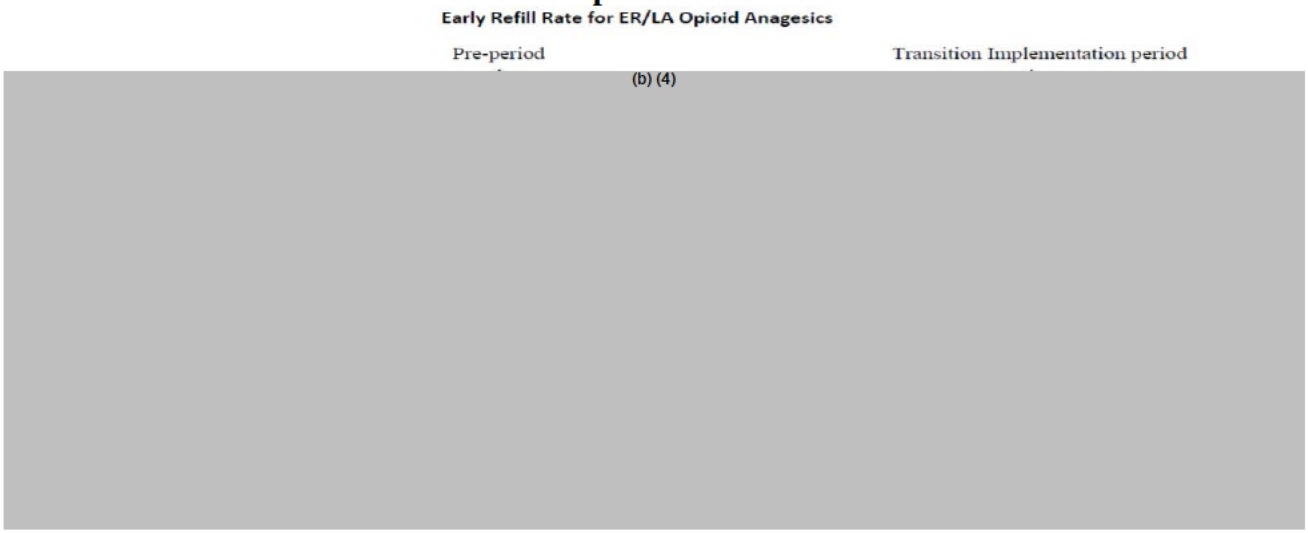
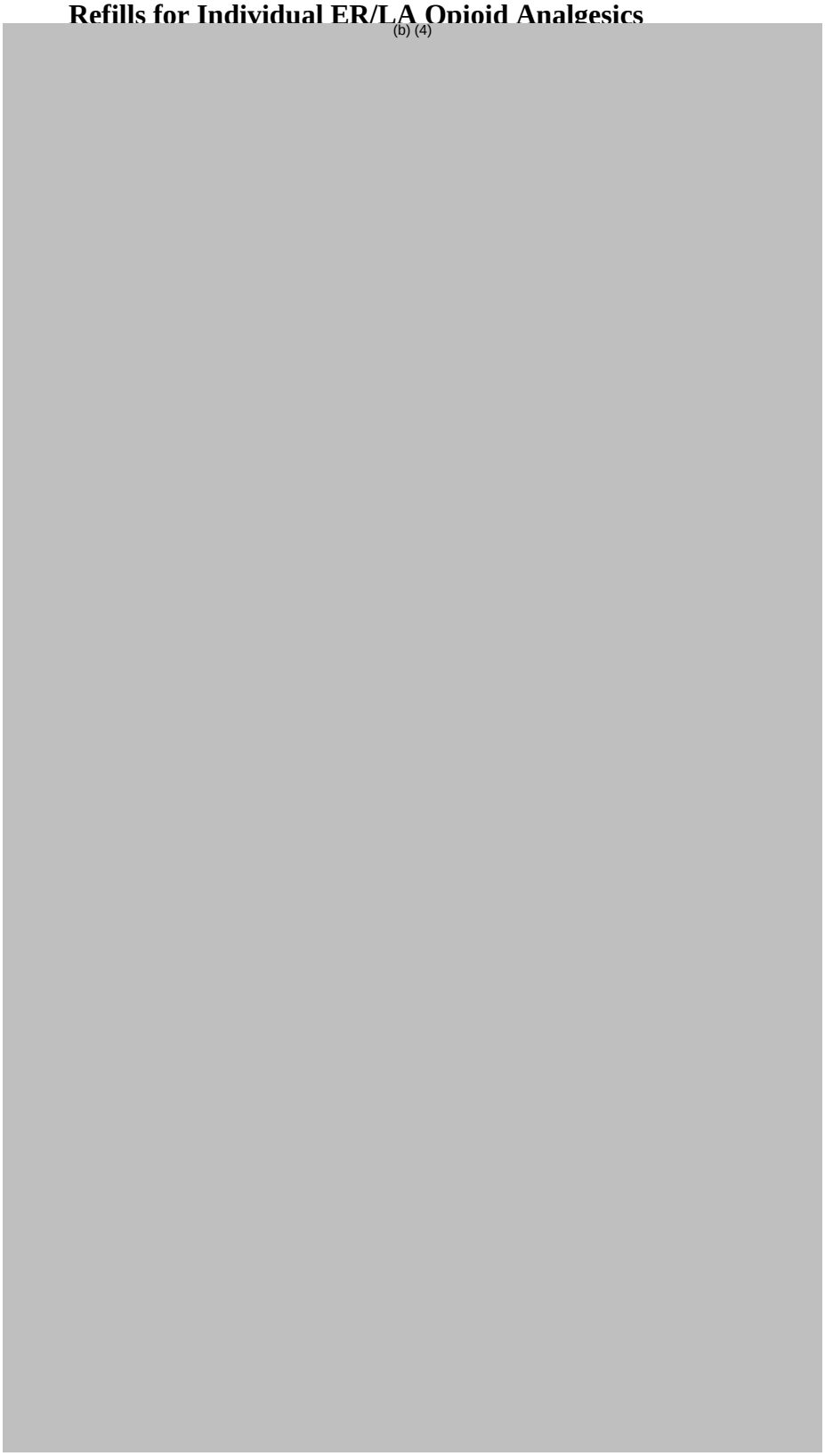
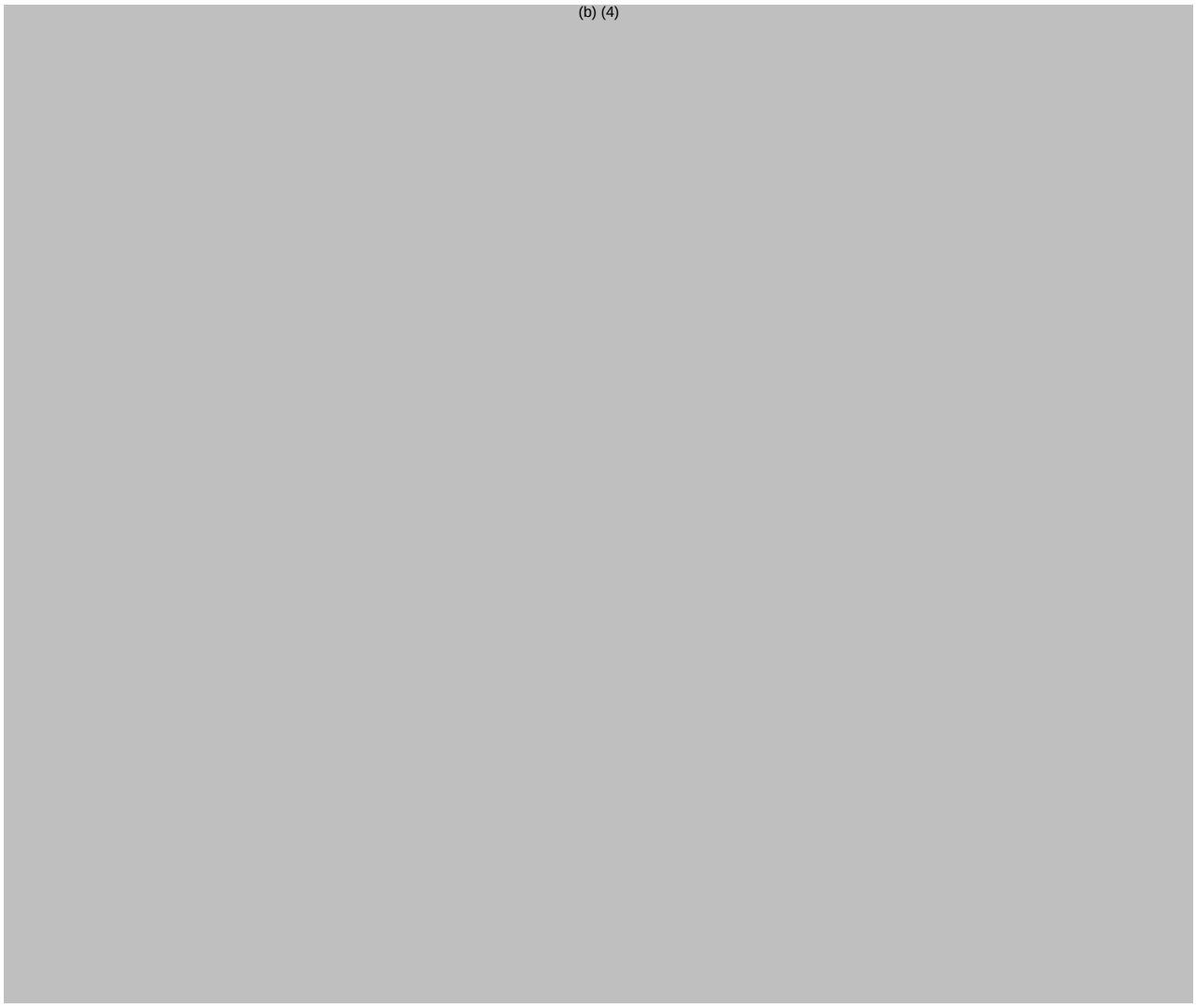


Table 22 (modification of an RPC table) summarizes the results of Figure 7 regarding changes in the monthly patient volumes of individual ER/LA opioid analgesics regarding early refills. The RPC states that specific outcome measures calculated were the proportion of patients receiving early refills as well as the early refill rate by monthly patient cohort:

Table 22: Pre- versus Post-period Rate of Early Refills and Proportion of Early Refills for Individual ER/LA Opioid Analgesics

(b) (4)





5.8.2 Reviewer (I. Cerny) Comments:

1. The RPC and SD definition of opioid tolerance used in the original REMS Assessment Report is very different from the definition of opioid tolerance that FDA has used in the labeling of opioids products, namely a patient taking 60 mg of morphine (or a morphine equivalent) for at least a week. In fact, the definition applied by the RPC to these data (as little as one dose of an ER/LA opioid analgesic in the previous 6 months) is so loose that it likely renders any conclusions meaningless regarding any differences between the opioid tolerant and opioid non-tolerant populations in the RPC data.

   In FDA's October 24, 2014 meeting with the RPC, FDA requested that the RPC submit an alternative algorithm of opioid tolerance for these data. In addition, FDA explained to the RPC that it is not necessary to present these data for all of the individual ER/LA opioid analgesic products, but focus on hydromorphone, fentanyl and one additional product (a product for which the label provides differing doses

for opioid non-tolerant and opioid tolerant patients). RPC agreed to submit these data by mid-December.

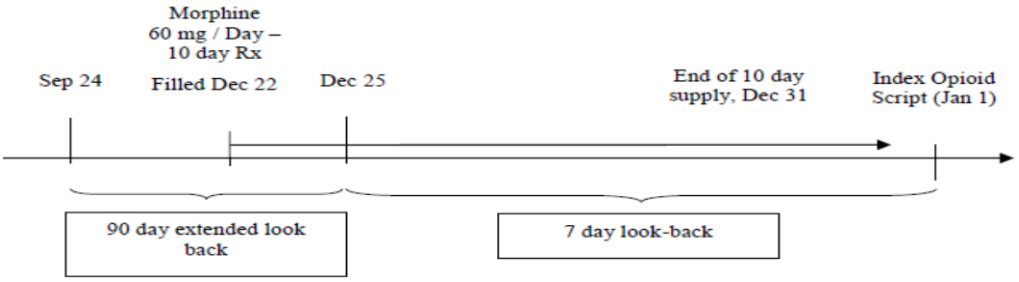
On December 16, 2014, the RPC submitted a proposed protocol for the evaluation of ER/LA opioid analgesic use in opioid tolerant/non-tolerant patients. The protocol states that to define a patient as opioid tolerant, a patient must have at least one opioid episode with 60 mg oral morphine or an equivalent product daily dose that spans 7 consecutive days prior to the index ER/LA opioid analgesic prescription. For purposes of this analysis, an index prescription must be filled for one the following drugs of interest:

- Fentanyl transdermal patches
- Hydromorphone extended-release
- Morphine extended-release (90 mg unit strength or greater, tablets or capsules)

Both fentanyl patches and hydromorphone ER are indicated for only for use in opioid tolerant patients (regardless of dose). Morphine ER 90 mg dosage units or greater are also indicated for use only in opioid tolerant patients. In addition to these products, the RPC will use morphine extended release <90 mg, indicated for use with opioid non-tolerant and tolerant patients, as a control group.

Figure A below indicates how the RPC plans to operationalize this analysis using IMS's LifeLink™ patient-level longitudinal prescription (LRx) database:

Figure A: Timeframe for calculation of opioid tolerance prior to the index opioid prescription



The ER/LA Review Team will evaluate this proposal and inform the RPC of its comments.

2. Regarding the early refill data, the RPC does not clearly distinguish and define the "rate of early refill" versus "proportion of patients with early refill." In addition, as has been discussed with aspects of the utilization data, the metric of early refills is also difficult to interpret in isolation. While patients who abuse drugs are prone to requesting early refills, so are patients with increasing pain such as the more advanced stages of cancer. In discussions with OSE's DEPI (A. Secora and J. McAninch), early refills can be a useful indicator of abuse, but only when combined with other outcome measures (such as, for example, number of prescribers, number

of pharmacies visited, type of payment, etc.). At a minimum, the early fills tracked could be focused on those written by the same prescriber (see: *Willy ME, Graham DJ, Racoosin JA, Gill R, Kropp GF, Young J, Yang J, Choi J, MaCurdy TE, Worrall C, Kelman JA. Pain Med. 2014 Sep;15(9):1558-68*). The FDA ER/LA REMS Review Team is continuing discussions on the most appropriate metrics to track.

3. As discussed with other utilization data, the early fill data presented in this section were presented as narrative summaries versus complete data presentations. Do to the poor readability of the presented figures, in subsequent assessment report submissions, the RPC should include a presentation of these early refill data in a manner similar to the data presentation in Table 25 of the current assessment report. In addition, this data presentation should include an analysis of early refills per the medical specialties addressed in other portions of the presented drug utilization data.

5.9 ELEMENT 7: ACCESS TO ER/LA OPIOID ANALGESICS

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

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

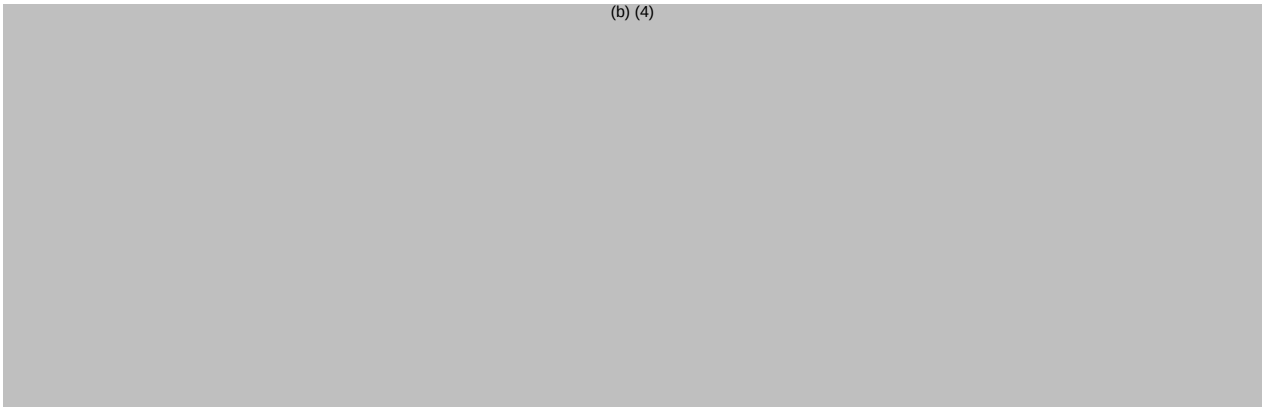
- Changes in prescribing will be compared in prescribers from specialties whose prescribing is hypothesized to be relatively unaffected by the REMS (such as oncologists and hospice providers) versus those for whom the REMS could have greater impact on prescribing (e.g., dentists). This will be conducted using the methodology described for Utilization patterns above.
- A set of questions will be added to the REMS prescriber survey and to the REMS patient survey to assess whether prescribers and patients perceive an impact of the ER/LA opioid analgesic REMS on access to treatment. For prescribers, survey items will assess whether the implementation has led to a switch in medications that they prescribe and their perception of a change in access to ER/LA opioid analgesics for patients who the prescriber judges to have a medical need. For patients, survey items will assess whether patients perceive a change following implementation of the REMS in: 1) physicians' prescribing of pain medication; 2) access to medications to treat pain; and 3) satisfaction with pain treatment. These additional questions will be added to the REMS prescriber survey described in Assessment #3 and the REMS patient survey described in Assessment #4.

5.9.1 Access Results

The RPC presents total average monthly prescription data of specialists' prescribing of ER/LA opioid analgesics and IR Opioids over time (see **Table 23** below, a composite of several RPC tables) to inform one aspect of patient access:

Table 23: A Comparison in Total Average Monthly Prescriptions of ER/LA Opioid

(b) (4)



red font indicates a statistically significant decrease; **blue font** indicates a statistically significant increase; and **black font** indicates a non-significant decrease

(b) (4)

Prescriber Survey:

The RPC conducted a prescriber survey in 2013 (included in the 12-month assessment report reviewed by DRISK's J. Ju). Eligible participants included doctors of medicine, (MD), doctors of osteopathy (DO), nurse practitioners (NP), and physician assistants (PA) who had prescribed an ER/LA opioid analgesic (transdermal patch, methadone, and oral products) at least once in the year prior to the survey administration, as identified by the IMS XPonent. Prescribers who completed REMS-compliant training prior to the survey were ineligible to participate.

From that survey, the following questions were relevant to access:

1. "*In your opinion, what impact does the FDA-required REMS for ER/LA Opioid Analgesics have on the ability of patients who need opioids to get them? (makes it more difficult/easier/no impact for patients to get opioids)*"
2. "*On a scale of 0 to 10, how easy has it been in the past month for patients who are indicated to receive ER/LA opioids to access such an extended-release opioid (zero meaning no access and 10 meaning extremely easy to access)?*"
3. "*Ease of access can impact both risk of opioid abuse and patients who require opioids. Do you think the current level of access to ER/LA opioid analgesics for patients who are indicated to take them is (too easy, too difficult, about right)?"*
4. *"In your opinion, what have the obstacles been to patient access of prescription opioids for pain control medical needs in the past month?"*

Table 24 (taken from the RPC report) addresses Question 1 directly above:

/

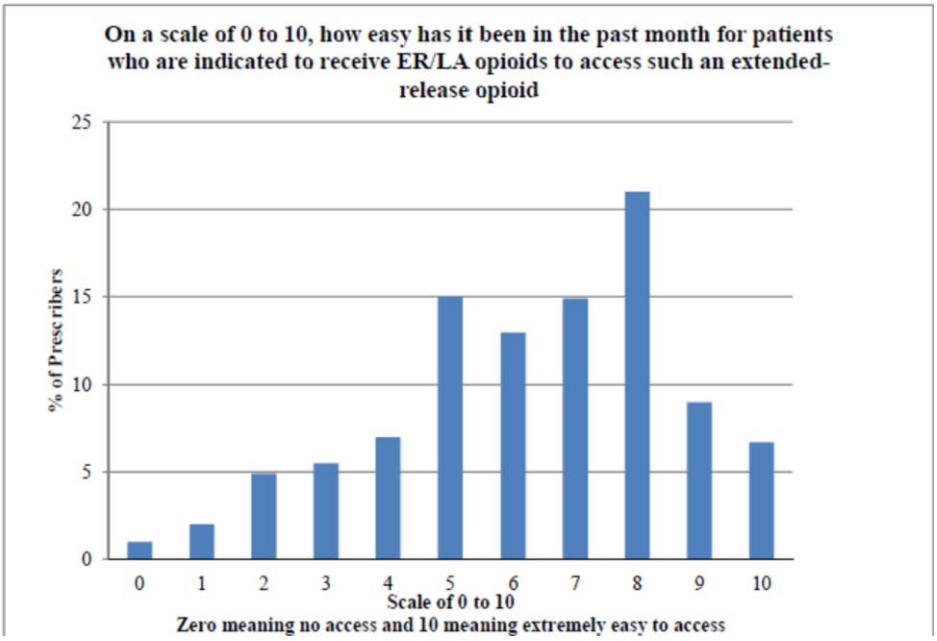
Table 24: Prescribers' Assessment of the Impact of the REMS on ER/LA Opioid Analgesic Access for Patients

PRESCRIBERS' ASSESSMENTS OF THE IMPACT OF THE FDA-REQUIRED RISK EVALUATION AND MITIGATION STRATEGY (REMS)	N = 605	%
It makes it more difficult for patients to get opioids	225	37.2
It makes it easier for patients to get opioids	10	1.7
It doesn't have any impact on patient access to opioids	180	29.8
I don't know	190	31.4
Total	605	100

Regarding the impact of the REMS upon ER/LA opioid analgesic availability, 61% either stated that the REMS has had no impact or did not know. Approximately 2% thought the REMS made it easier to get access to ER/LA analgesic opioids. However, 37% thought that the REMS indeed made it more difficult to get access to opioids.

Figure 7 below (taken from the RPC report) addresses Question 2 directly above:

Figure 7: Distribution of Responses Regarding Ease of Patient Access to ER/LA Opioid Analgesics, Based on a Scale of 0 To 10



The data in Figure 8 are tilted more towards easiness of access (>75% of prescribers rate access >5 on the scale) for patients in whom opioid therapy is indicated. If indeed the REMS has made access more difficult, overall access still seems to be fairly easy.

Table 25 (taken from the RPC report) addresses Question 3 above:

Table 25: Ease of Appropriate Access to ER/LA Opioid Analgesics for Patients

EASE OF ACCESS CAN IMPACT BOTH RISK OF OPIOID ABUSE AND PATIENTS WHO REQUIRE OPIOIDS. DO YOU THINK THE CURRENT LEVEL OF ACCESS TO ER/LA OPIOID ANALGESICS FOR PATIENTS WHO ARE INDICATED TO TAKE THEM IS:		
	N	%
Too easy	106	17.5
Too difficult	87	14.4
About right	350	57.9
I don't know	62	10.2
Total	605	100

Approximately 58% of prescribers thought that ease of access to ER/LA opioid analgesics is about right. Approximately 18% thought it was too easy; however, 14% thought it was too difficult.

Table 26 (taken from the RPC report) addresses Question 4 above:

Table 26: Prescribers' Assessment of Patient Obstacles to ER/LA Opioid Analgesic Access

IN YOUR OPINION, WHAT HAVE THE OBSTACLES BEEN TO PATIENT ACCESS TO PRESCRIPTION OPIOIDS FOR PAIN-CONTROL MEDICAL NEEDS IN THE PAST MONTH? PLEASE SELECT ALL THAT APPLY.	N = 605	%
Insurance coverage	423	69.9
Insurance authorizations and approvals	413	68.3
Patients' ability to pay	373	61.7
Stigma regarding opioids	197	32.6
Pharmacy authorization	143	23.6
Pharmacy stocking issues	165	27.3
Physicians do not want to prescribe ER/LA opioids because they do not wish to complete REMS training	161	26.6
Patients are afraid to take ER/LA opioids because of risk warnings	125	20.7
Legal liability or malpractice concerns	247	40.8
Other	30	5.0

Regarding obstacles to ER/LA opioid analgesic access, 27% state that they do not wish to prescribe ER/LA opioid analgesics because they do not want to complete the REMS training (recall that the physicians taking part in this survey were not to have completed the REMS training). However, this factor ranks 6th out of 9 choices and is substantially less that the first three reasons which involve financial issues (selected by 82%+ of prescribers) as well as legal concerns (41%).

Patient Survey: A detailed discussion of the patient survey is presented in Section 6.4 of this review. The RPC cites the following data from the patient survey to inform access issues:

- 73% of patients were able to obtain a prescription when needed for pain.
- Access did not vary by ER/LA opioid analgesic type;
- Respondents who did not understand the Medication Guide or had only one recorded ER/LA opioid analgesic dispensing less often confirmed their access to obtain a prescription
- Overall satisfaction with access was reported by a lower percentage of single dispensing users (74%) and respondents with a knowledge score <70% (59%)
- 82% reported general satisfaction with access to ER/LA opioid analgesics
- 46% felt that they needed to see prescriber too often
- The 10% that were dissatisfied had total annual household income of at least $100,000, were more often non-Caucasian and more likely to have ER/LA opioid analgesic prescribed by a pain specialist

The RPC states that "*there is no indication that the REMS is having a negative impact on access to ER/LA opioid analgesics as reported by patients and prescribers*."

5.9.2 Reviewer (I. Cerny) Comments

1. As with the utilization data, the RPC presents the average monthly prescriptions written by specialists. And as seen in the utilization data, with the exception of pain and "all other" (most prominently in this category, nurse practitioners and physician's assistants), the average monthly prescriptions written by specialists decreased from the pre- to post-periods for both ER/LA opioid analgesic and IR opioids. These data are presented to inform the issue of patient access. However, it is not clear how these data inform the issue of access, since it is difficult to determine how an increase or decrease in prescriptions of a product correlates with access.

2. The prescriber survey does appear to inform the access question somewhat and it does appear that access for legitimate patients is not considered a problem by the majority of prescribers. However, it is not clear the prescribers would always be informed of patient access problems. Regarding the impact of the REMS upon ER/LA opioid analgesic availability, approximately 2% thought the REMS made it easier to get access to opioids whereas 37% thought that the REMS indeed made it more difficult. It would be valuable to provide a follow-up question to those who choose either of these answers to try to ascertain which particular aspects of this REMS either ease or interfere with access.

3. The patient survey provides some information about access; however, since (understandably) there are no questions about the REMS, and no pre-REMS data

are presented, these data are difficult to interpret as far as informing access questions.

4. Following the October 24, 2014 meeting with the RPC, they requested that the FDA consider the utility of the access-related questions (50-53) of the Prescriber Survey and provide any additional comments or suggested questions for incorporation into the protocol. The internal FDA review team has been working with CDER's Economics Staff's Marta Wosinska to develop a more specifically targeted protocol.

6. CONCLUSIONS

6.1. APPLICANT'S CONCLUSIONS

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

"*RPC has met all REMS requirements to date...Overall the REMS assessments indicate substantial improvements in various indicators, including patient knowledge; misuse, abuse, and major medical outcomes including death; as well as prescribing behaviors, all while preserving access to valuable pain therapies…Surveillance monitoring results indicate that for the most part the REMS has had a positive effect…Assessment of drug utilization showed changes that are consistent with the desired outcomes of the REMS…. There is no indication that the REMS is having a negative impact on access from results of patients and prescribers surveys…Since many interventions targeting opioid analgesics occurred during the time period of the REMS, the aforementioned effects cannot be attributed specifically to the REMS… The RPC will continue to implement the REMS to build upon the positive impact seen to date….*"

6.2. REVIEWERS' CONCLUSIONS

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 pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

A primary intervention of this REMS is a voluntary training program for prescribers. It is hoped that prescribers who take this training will be sufficiently informed so that serious adverse outcomes (such as addiction, unintentional overdose, death) will be reduced by reducing inappropriate prescribing, misuse and abuse. One year after the first CE program went live, a total of 20,345 ER/LA opioid analgesics prescribers have completed RPC-supported REMS-compliant training. The RPC states with the continuing addition of CE programs, the CE community expects a surge in trainings towards meeting the goal of 80,000 prescribers trained within 2 years. This prediction/ scenario may be overly optimistic. It would be helpful for the RPC to enter into a data-sharing agreements with

as many of the non-RPC-funded ER/LA opioid analgesics training programs as possible, not only in terms of being able to count course participants, but also to assure the quality of the training.

The data regarding the prescription volume of ER/LA opioid analgesics dispensed by various prescribing specialties, for most specialties, indicate decreases over time (with the exception of nurse practitioners and physician's assistants). Without additional data it is difficult to interpret these findings. Increases and decreases could be due to patient variables, insurance coverage or other financial decisions, or overall increased awareness of risks. For example, while a decrease in dispensed prescriptions written by dentists writing for an ER/LA opioid analgesic is probably appropriate, there may be a need for further explanation as to why there were fewer dispensed prescriptions written by hospice and palliative care prescribers for ER/LA opioid analgesics. In addition, prescriptions dispensed from the other settings of care such as long-term facilities and mail-order/specialty pharmacies are not included in the analyses; the data on some prescriber specialties and patient subgroups (e.g. those over 65 years of age) may be underrepresented. The volume of prescriptions written and not dispensed was not measured in the drug utilization analyses, this could be an additional metric in the assessment of patient access. However, overall there has been a statistically significant reduction in the number of prescriptions for ER/LA opioid analgesic and IR opioid classes as well as a reduction (non-significant) in prescriptions for celecoxib. It is not clear that these findings are the result of the ER/LA opioid analgesic REMS.

For the vast majority of RADARS programs utilized, the event rates for the majority of outcomes assessed (abuse in both adults and adolescents; misuse; major medical outcomes/ hospitalizations/ deaths; deaths; ED visits; unintentional therapeutic errors; pediatric unintentional general exposures; pediatric ED visits) for ER/LA opioid analgesics have ***decreased*** from the pre-REMS-implementation period to the active period. However, poison center data do not capture individuals who do not contact poison centers prior to going to the ED, hospital, or morgue, and similarly do not capture health professionals in those settings who do not call the poison center. Thus, how and if these RADARS findings relate to what is transpiring in the general population is unclear.

The assessment of decreases in most of the outcomes for ER/LA opioid analgesics may not be attributable to the REMS program because two other classes of commonly abused drugs, IR opioids and prescription stimulants (neither of which have a REMS), also demonstrated decreases in event rates. However, it is possible that efforts (including the ER/LA opioid analgesic REMS) to raise awareness about the abuse potential of opioid analgesics have increased awareness of drug abuse of other drug classes as well.

There are important limitations of the data sources analyzed in detecting the events of interest – particularly the most serious events of hospitalization and death. Whether these findings indicate an issue with the surveillance databases, a true overall decrease in national trends for drug misuse and abuse, or some effect of the ER/LA opioid analgesic REMS is unclear. Since the decrease in outcomes of interest with ER/LA opioid opioids has been slightly greater than that seen with IR opioids and prescription stimulants, this

slight difference may reflect an effect of the ER/LA opioid analgesic REMS as well as perhaps the many other ER/LA opioid analgesic-specific initiatives that have been enacted at both the federal and state level in recent years. Furthermore, although decreases were noted in the RADARS Poison Center data for major medical outcomes/ hospitalizations/ deaths, these data are very limited. That is because these major outcomes are not adequately captured in calls to Poison Centers and will result in serious undercounts of these outcomes.

Additional data forthcoming in the next assessment include whether the first training milestone will be met, an updated evaluation of prescriber understanding, and data on ED visits for opioid overdose/poisoning using a database of ED visits, claims data and validated ICD-9 codes.

Based on these preliminary data, the REMS may be making progress towards meeting its goals.

6.3. REVIEW TEAM CONCLUSION

On October 14, 2014, DRISK, DPV, DEPI, OB, DAAAP, and the Office of Compliance met to discuss the assessment for the ER/LA opioid analgesics REMS. In addition, during standing meetings of the ER/LA opioid analgesics REMS Implementation team, discussion of various assessment report issues occurred. Overall, the team believes the assessment is complete and the REMS may be making progress towards meeting its goals. However, in the review and discussions of the information provided in this assessment report, a number of questions have arisen regarding the value of certain metrics presented in the report (that are mostly presented of metrics of interest in the SD). The review team has formed a small working group that will be reviewing these metrics and discussing their utility.

7. RECOMMENDATIONS

This assessment report is complete in addressing the issues outlined in the approved REMS assessment plan. Thus we recommend sending the applicant a REMS "complete with comments" letter.

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

1. Describe the specific challenges that you are encountering in getting prescribers to complete the trainings as well as your plans to address these challenges.

2. Regarding REMS-Compliant trainings that are not RPC-funded, detail the processes that you have used to identify them.

3. One of the secondary outcome measures stated in the Supporting Document that you have not included in this report is the number of prescribers who have completed some but not all portions of a training activity. Include this metric in your subsequent

assessment reports. In addition, in subsequent reports, provide full data regarding non-prescribers that completed CE training but are not counted towards REMS goals.

4. In subsequent assessment report analyses of RADARS data:
    a. Include a summary table for the individual ER/LA opioid analgesic agents as seen in the attached sample table, **Table A** below,
    b. Present unintentional exposure data from the PC program grouped by age to better inform this outcome of interest.
    c. Include RADARS Emergency Department Treated/Evaluated and Released Data for adult and pediatric patients presented separately.
    d. Make the following adjustments to your statistical analysis section:
        i. Regarding the presentation of results: your assessment report RADARS Tables 8-13 reported p-values testing for significant change between the pre-REMS period and the post REMS period but neither the text in Section 7 nor the footnote in the tables explained exactly how each rate was derived and which test was used. It is unclear which of the two models (mean model or spline models) listed in Appendix D was used to derive the p-values in Tables *8-13.* Thus you should add a description of the method used in a footnote for each table. Similarly, use footnotes in Table 15 to explain the data source for each projection.
        ii. About methods: In both of the models proposed in the RADARS data analysis section, the unit of analysis is zip code (spatial) and quarter (time). Thus, testing for change between pre and post period for each outcome is investigating whether the average rate of events over time for the average zip code has changed from the pre-REMS period to the post-REMS period. If the unit of analysis is indeed the zip code and quarter, it is unclear whether the Poisson regression in both models includes a term for overdispersion. Considering the between zip code variability, the overdispersion parameter may not be negligible and should be included it in the models.
        iii. In addition to these two models, you should use non-parametric tests (such as bootstrap or randomization tests) on national estimates per quarter to test for differences in the rates between the pre and the post period.

5. In subsequent assessment report submissions of NAVIPPRO data:
    a. Include a more detailed data presentation regarding the CHAT sources of procurement as was provided for the ASI-MV data;
    b. Provide more detailed information as to how you calculate “Prevalence” and “Odd of Abuse.”
    c. Include a summary table for the individual ER/LA opioid analgesic agents as seen in the attached sample table, **Table A** (below)
    d. Make the following adjustments to your statistical analysis section:

i. The logistic model used is not consistent with the ones used in RADARS. This model has a different unit of analysis than RADARS and does not use any outside counts as reference. More precisely, the unit of analysis is over all zip codes rather than separate for each zip code as in RADARS. Moreover, the fit odds ratio do not use population size, total prescriptions dispensed or total dose units dispensed as a reference as in RADARS. You should use models similar to RADARS and apply our recommendations made regarding RADARS data to your NAVIPPRO methods.
ii. The number of sites used changes from one quarter to another adding to the level of variability of measurement. Inflexxion should restrict their analyses to "stable" reporting centers over time.

6. In subsequent assessment report submissions of drug utilization data:
    a. Include a summary table for the individual ER/LA opioid analgesic agents as seen in **Table B** (below).
    b. Include a more detailed description of the ER/LA opioid analgesic prescribing activities of their largest group, the "all other" in a manner similar to what was provided in your October 22, 2014 response to an FDA IR.
    c. Provide an explanation of how you calculate "switch rates" and the specific data and database(s) used for this calculation.
    d. Add prescription data from long-term care and mail order/specialty pharmacies so as to be able to fully capture all spectrums of prescriber types and patient settings.
    e. Make the following adjustment to your statistical analysis section:
        i. Student t-test was used to compare prescription volumes between two periods (such as pre and post period or pre and transition period). Although the t-test can work with small samples, the normality assumption may not hold. In addition, if there is seasonality in the data then having different seasons in the compared periods could be problematic as significant changes between periods could be due to seasonal effects. Thus we recommend that for any pairwise comparison of periods (a) use nonparametric tests such as permutation test or Wilcoxon rank-sum test because these tests work for small samples (b) use periods covering the same seasons to control for the seasonal effects in the pairwise comparison.
        ii. When more data points become available in the post-period (at least 12 data points), consider performing time series analysis (e.g. segmented regression analysis of interrupted time series1) to evaluate the REMS effect.
        iii. In many of the Assessment report's Utilization Figures there are multiple drugs that are clumped near the bottom of the figures making it hard to see the pattern of change in use over time for each drug. In future report submissions, the figures could be split

into as many as 4 different figures with different scales on the y-axis, each showing the monthly trend for a quartile of the drug use market. In this manner, a curve for a drug would be shown with comparable drugs in terms of drug use in the same figure. In addition, provide data presentations of your endpoints of interest (switches, early refills, etc.) in a manner similar to the presentation of data in Table 25 of the 24-month assessment report.

7. Provide a critical integrated summary to better explain the differences between the results seen from the different analyses of the RADARS and NAVIPPRO data with regard to changes in abuse, addiction, overdose and death over time. Explain, from your perspective, which analyses should be considered most reliable. In addition, explain why these streams of evidence should be viewed as consequences of the REMS, as opposed to the results of other interventions.

8. The NSDUH and MTF data that you provided were interesting but not directly informative of what is occurring with the ER/LA opioid analgesics. These data need not be submitted with your next assessment report. However, other data sources need to be explored to capture the more serious outcomes encountered with ER/LA opioid analgesics, particularly death.

9. In subsequent assessments, utilize the definition of opioid tolerance as indicated in your December 16, 2014 submission. In addition, regarding the data presentation of data in this section in your report (prescriber behavior), there were portions that were presented as narrative summaries versus complete data presentations. In subsequent submissions, include the complete data in a manner of presentation similar to Table 31 of your assessment report.

10. (emailed to the TRIG on February 13, 2015) In subsequent submissions of patient surveys:
    a. Since the HIRD database is not representative of the total patient population that is using ER/LA opioid analgesics (it includes only commercially insured patients and does not include patients on Medicaid or Medicare), an alternative recruitment source should be used for subsequent surveys that also includes patients on Medicaid and Medicare. This alternative source can be used as the main recruitment source or as a supplement to the current database used. Please notify the FDA once you have identified the alternative source for the patient survey.
    b. Review the list of ER/LA opioid analgesics in the patient and prescriber surveys to make sure they are consistent and remove drugs that are not currently prescribed.
    c. Change the Likert scale utilized in the current survey to True/False/Don't Know.
    d. Caregivers should be recruited for inclusion in the next survey.
    e. Consider oversampling for or a sub-study focusing on new users. Over half (54%) of respondents reported 12 months or more since they were

first prescribed ER/LA opioid analgesics, and the results may differ for new users.

f. Patients are excluded from the survey if they are unsure of the opioid or class prescribed. A listing of ER/LA opioid analgesics should be provided to patients, along with pictures for online survey respondents, to ensure that patients who are using ER/LA opioid analgesics are not incorrectly considered ineligible.
g. Blurred versions of the Medication Guide and Patient Counseling Document should be provided before the questions related to the documents for online participants.
h. Future survey results tables should provide results for each question with counts and percentages for each response option.
i. For Section KA1, add a question to assess knowledge of constipation as a side effect of use of ER/LA opioid analgesics. Example question: "Constipation is a possible side effect when using [OPIOID]". (True/False/Don't Know)
j. For Section KA1, add a question about proper disposal of ER/LA opioid analgesics. Example question: It is okay to flush unused ER/LA opioid analgesics down the toilet". (True/False/Don't Know)
k. For Section KA1, add a question about what to do if you miss a dose of the ER/LA opioid analgesic. Example question: "If you miss a dose of the ER/LA opioid analgesic, you should take the missed dose as soon as possible". (True/False/Don't Know)
l. In the ER/LA opioid analgesic access section of the patient survey, there are three survey items in question AT1 (AT1c, AT1d, and AT1e) that are not related to access. These questions should be moved to question AT2 and the response options should be changed to: always, regularly, rarely, never, and I don't know.
m. For questions AT2 a-g, the response option "Sometimes" should be removed to coincide with the prescriber survey.

Table A: Sample Summary Table for Individual ER/LA Opioid Analgesic Product Data

	RADARS Program/Metric (per 1,000 URDD) - Pre-REMS to Post Period % change																										NAVIPPRO - Pre-REMS to Post Period % change				Drug Utilization			
	PC Intentional Abuse	P value, 95% CI	PC Misuse	P value, 95% CI	PC Major Medical Outcome, Hospitalization, Death	P value, 95% CI	PC Death	P value, 95% CI	PC Unintentional Therapeutic Error	P value, 95% CI	ED: Treated/Evaluated and Released	P value, 95% CI	PC Pediatric Unintentional General Exposures	P value, 95% CI	PC Pediatric Unintentional Major Medical Outcome, Hospitalization, and Death	P value, 95% CI	Pediatric Unintentional Exposures ED Data: Treated/Evaluated and Released	P value, 95% CI	PC Adolescent Intentional Abuse	P value, 95% CI	Treatment Center Programs	P value, 95% CI	College Survey Program	P value, 95% CI	ASI-MV: Prevalence (Cases per 100 ASI-MV)*	P value, 95% CI	CHAT: Prevalence (Cases per 100 ASI-MV)*	P value, 95% CI	RX #: Pre-REMS (July 2010-June	RX #: Active (July 2013 – December	% Change	P value, 95% CI
ER/LA REMS Opioids																																		
IR Prescription Opioids																																		
ER Morphine																																		
ER Oxymorphone																																		
Methadone																																		
Buprenorphine TDS																																		
Fentanyl TDS																																		
ER Oxycodone																																		
ER Hydromorphone																																		
ER Tapentadol																																		
ER Hydrocodone																																		

Table B: Sample Summary Table for Individual ER/LA Opioid Analgesic Product Drug Utilization Data

Classes/Products	Mean Rx Volume (monthly or quarterly) Pre-REMS (Dates covered)	Mean Rx Volume (monthly or quarterly) Active Period (Dates covered)	Pre V. Active	
			P-Value	% Change
TOTAL ER/LAs				
IR Opioids				
Celecoxib				
Benzodiazepines				
Buprenorphine TDS				
Fentanyl TDS				
Hydromorphone ER				
Methadone				
Morphine Sulfate ER				
Oxycodone ER				
Oxymorphone ER				
Tapentadol ER				
Hydrocodone ER				

8. APPENDIX

8.1. CURRENT ASSESSMENT PLAN

(Language taken from the July 9, 2012 REMS Approval letter)

1. **The first REMS assessment**, due not later than six months from the date of REMS approval, should provide a report on the actions you have taken to implement the REMS since it was approved. The report should include the following information:

a. Grant Proposals: The status of the requests for proposals for grants for CE training including: 1) how many have issued and when will the next requests for proposals issue; 2) the number of proposals submitted in response to each request; 3) the number of grants awarded; 4) a list of the grantees; 5) the date when each of the grantees will make their CE training available; 6) a high-level description of each program (e.g., web based, live); and 7) an estimate of how many prescribers are expected to be trained under each program.

b. Evaluation Grants: The status of the requests for proposals for special grants to CE providers or other CE organizations with expertise in assessing CE outcomes who agree to conduct long-term evaluation of prescribers of ER/LA opioids who have taken training funded under this REMS to determine these prescribers' knowledge retention and practice changes 6 months to 1 year after they completed the REMS- compliant training including: 1) the number of proposals submitted in response to each request, 2) the number of grants awarded, 3) a list of the grantees, 4) the date when each of the grantees will conduct their REMS-compliant training, and 5) the dates of their follow-up evaluation.

c. Functional Components:

i. Date when the ER/LA Opioid REMS website was live and functional.

ii. Prescriber Letter 1: 1) Date when letter was posted on the ER/LA Opioid REMS website 2) number of prescriber letters electronically sent, received, undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.

iii. Professional Organization/Licensing Board Letter 1: 1) Date when the letter was posted on the ER/LA Opioid REMS website, 2) number of letters electronically sent, received, undeliverable, and opened, and 3) number of letters mailed and undeliverable.

iv. Date when the single number toll free call center was operational.

2. **The second REMS assessment**, due one year from the date of this letter, should include the following information:

a. Functional Components:

i. Training: 1) Date the first REMS-compliant training was available; 2) a high- level description of the training (e.g., web based, live); 3) the number of prescribers that have undergone the training, and 4) an estimate of how many prescribers will be trained under the program(s).

ii. Prescriber Letter 2: 1) Date when letter was posted on the ER/LA Opioid REMS website, 2) number of prescriber letters electronically sent, received, undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.

iii. Professional Organization/Licensing Board Letter 2: 1) Date when the letter was posted on the ER/LA Opioid REMS website, 2) number of letters electronically sent, received, undeliverable, and opened, and 3) number of letters mailed and undeliverable.

b. Grant Proposals: An update on the status of the requests for proposals for grants for REMS-compliant training, including: 1) new grant requests for proposals published; 2) the number of proposals submitted in response to each request; 3) the number of grants awarded; 4) a list of the grantees; 5) the date when each grantee will make or has made their REMS-compliant training available; 6) a high-level description of each program (e.g., web based, live), and 7) an estimate of how many prescribers will be trained under each program.

c. Evaluation Grants: The status of the requests for proposals for special grants to CE providers who also agree to conduct long-term evaluation of prescribers of ER/LA opioids who have taken their 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 including: 1) the number of proposals submitted in response to each request, 2) the number of grants awarded, 3) a list of the grantees, 4) the date when each of the grantees will conduct their REMS- compliant training, and 5) the dates of their follow-up evaluation.

3. **The third REMS assessment**, due two years from the date of this letter, should include the following information:

a. Prescriber Letter 3: 1) Date when letter was posted on the ER/LA Opioid REMS website, 2) number of prescriber letters electronically sent, received, undeliverable, and opened, and 3) number of prescriber letters mailed and undeliverable.

b. Prescriber Training: 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:

i. 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;
ii. 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;
iii. 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.

c. Independent Audit: The results of an independent audit of the quality of the content of the educational materials used by providers to provide the REMS-compliant training. Audits must be conducted on a random sample of 1) at least 10% of the training funded under the ER/LA Opioid REMS, and 2) 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 3a., and must evaluate:

i. whether the content of the training covers all elements of the FDA "blueprint" approved as part of the REMS;
ii. whether the post-course knowledge assessment measures knowledge of all sections of the FDA "blueprint"; and
iii. 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.

d. 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.

e. Surveillance Results: 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.

f. Drug Utilization Patterns: An evaluation of drug utilization patterns, including: an evaluation of prescribing behaviors of the prescribers of

ER/LA opioids, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills;

g. Patient Access: An evaluation of changes in patients access to ER/LA Opioids.

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

i. Goals: An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

4. **The fourth and subsequent REMS assessments** should include the following information:

a. Prescriber Letter 3: 1) number of prescriber letters electronically sent, received, undeliverable, and opened, and 2) number of prescriber letters mailed and undeliverable.

b. Prescriber Training: The number of prescribers of ER/LA opioids who have completed REMS-compliant training (see 3.a above).

c. 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 (see 3.b above).

d. Evaluation of Prescriber Understanding:

i. 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.

ii. 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.

e. 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. (See 3.c above).

f. Surveillance Results: Results of surveillance and monitoring for misuse, abuse, overdose, addiction, and death (see 3.e above).

g. Drug Utilization Patterns: An evaluation of drug utilization patterns (see 3.f above).

h. Patient Access: An evaluation of changes in patient access to ER/LA opioids.

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

j. Goals: An assessment of the extent to which the elements to assure safe use are meeting the goal or goals to mitigate a specific serious risk listed in the labeling of the drug, or whether the goal or goals or such elements should be modified.

Definitions: For purposes of these REMS assessments, the following definitions apply:

1. *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.

2. *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.

8.2. RADARS INDIVIDUAL COMPOUND DATA:

The following section reviews the data for each individual RADARS program. All "mention" counts tables are reproduced directly from the RPC's September 24, 2014 response to an FDA IR. All data tables are a summation of data found in various tables in both the originally submitted REMS report and the September 24, 2014 response.

PC Intentional Abuse Data:

Table 27 below (reproduced directly from the RPC's September 24, 2014 IR response) indicates the number of mentions for each ER/LA opioid analgesics in the RADARS PC Intentional Abuse data:

Table 27: RADARS® PC Intentional Abuse Exposure Mentions for the Pre-Implementation, Transition, and Active Periods.

Drug Group	Pre-Implementation Mentions	Transition Mentions	Active Period Mentions
	(b) (4)		

Table 28 (modification of an RPC table) displays the mean Intentional Abuse exposure rates separated by rates for prescriptions per 1,000 or per 100,000 dosing units, with percent changes and statistical analyses for the three study time periods for ER/LA opioid analgesics and comparators.

Table 28: Adult/Adolescent Intentional Abuse Exposure Rates Adjusted for Prescriptions Dispensed or Dosing Units Dispensed for the Pre-Implementation, Transition, and Active Period time periods, the percent change from Pre-Implementation to Active Period, the p-values for the percent change, and the p-values for the difference in percent change between ER/LA opioid analgesics and comparators.

DRUG or DRUG	PRE-IMPLEMENTATION MEAN (July 2010 -June	TRANSITION MEAN (July 2012 -	ACTIVE PERIOD MEAN (July 2013 -	ACTIVE TO PRE-IMPLEMENTATION % CHANGE (95% CI)	p-VALUE FOR % CHANGE OVER	p-VALUE FOR DIFFERENCE IN
			(b) (4)			

PC Misuse Data:

Table 29 below (reproduced directly from the RPC's September 24, 2014 IR response) presents the mentions for the PC Misuse data:

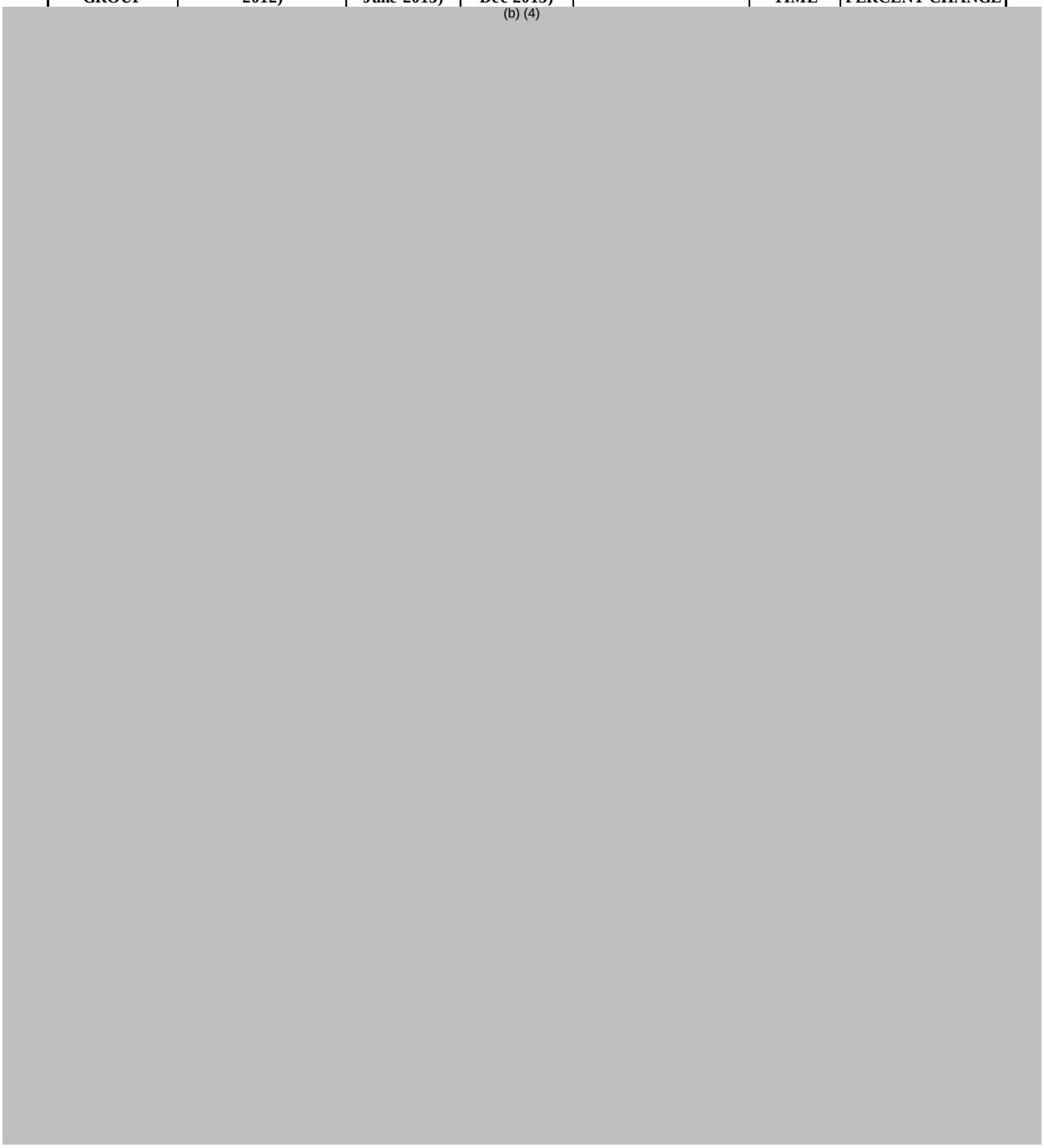
Table 29: RADARS® PC Program Misuse Exposure Mentions for the Pre-Implementation, Transition, and Active Periods.

Drug Group	Pre-Implementation Mentions	Transition Mentions	Active Period Mentions
	(b) (4)		

Table 30 (modification of an RPC table) displays the mean Misuse rates separated by rates for prescriptions per 1,000 or per 100,000 dosing units, with percent changes and statistical analyses for the three study time periods for ER/LA opioid analgesics and comparators.

Table 30: Adult/Adolescent Misuse Rates Adjusted for Prescriptions Dispensed or Dosing Units Dispensed for the Pre-Implementation, Transition, and Active Period time periods, the percent change from Pre-Implementation to Active Period, the p-values for the percent change, and the p-values for the difference in percent change between ER/LA opioid analgesics and comparators.

DRUG or DRUG GROUP	PRE-IMPLEMENTATION MEAN (July 2010 -June 2012)	TRANSITION MEAN (July 2012 - June 2013)	ACTIVE PERIOD MEAN (July 2013 - Dec 2013)	ACTIVE TO PRE-IMPLEMENTATION % CHANGE (95% CI)	p-VALUE FOR % CHANGE OVER TIME	p-VALUE FOR DIFFERENCE IN PERCENT CHANGE
(b) (4)						



PC Program Major Medical Outcome, Hospitalization, or Death Data

Table 31 below (reproduced directly from the RPC's September 24, 2014 IR response) presents the mentions for the PC Major Medical Outcome, Hospitalization, or Death data:

Table 31: RADARS® PC Program Major Medical Outcome, Hospitalization, or Death Exposure Mentions for the Pre-Implementation, Transition, and Active Periods

Drug Group	Pre-Implementation Mentions	Transition Mentions	Active Period Mentions
	(b) (4)		

Table 32 (modification of an RPC table**)** displays the mean Major Medical Outcome, Hospitalization, or Death rates separated by rates for prescriptions per 1,000 or per 100,000 dosing units, with percent changes and statistical analyses for the three study time periods for ER/LA opioid analgesics and comparators

Table 32: Adult/Adolescent Major Medical Outcome, Hospitalization, or Death Rates Adjusted for Prescriptions Dispensed or Dosing Units Dispensed for the Pre-Implementation, Transition, and Active Period time periods, the percent change from Pre-Implementation to Active Period, the p-values for the percent change, and the p-values for the difference in percent change between ER/LA opioid analgesics and comparators

DRUG or DRUG GROUP	PRE-IMPLEMENTATION MEAN (July 2010 -June 2012)	TRANSITION MEAN (July 2012 - June 2013)	ACTIVE PERIOD MEAN (July 2013 - Dec 2013)	ACTIVE TO PRE-IMPLEMENTATION % CHANGE (95% CI)	p-VALUE FOR % CHANGE OVER TIME	p-VALUE FOR DIFFERENCE IN PERCENT CHANGE
(b) (4)						

Since Major Medical Outcomes, Hospitalization, or Death rates for buprenorphine TDS were so low, the statistical model failed to converge and thus no tabular summary is reported.

PC Death Data:

Table 33 (reproduced directly from the RPC's September 24, 2014 IR response) below presents the mentions for the PC Major Medical Outcome, Hospitalization, or Death data:

Table 33: RADARS® PC Program Death Mentions for the Pre-Implementation, Transition, and Active Periods

Drug Group	Pre-Implementation Mentions	Transition Mentions	Active Period Mentions
	(b) (4)		

Table 34 (modification of an RPC table) displays the mean Death rates separated by rates for prescriptions per 1,000 or per 100,000 dosing units, with percent changes and statistical analyses for the three study time periods for ER/LA opioid analgesics and comparators

Table 34: Adult/Adolescent Death Rates Adjusted for Prescriptions Dispensed or Dosing Units Dispensed for the Pre-Implementation, Transition, and Active Period time periods, the percent change from Pre-Implementation to Active Period, the p-values for the percent change, and the p-values for the difference in percent change between ER/LA opioid analgesics and comparators

DRUG or DRUG GROUP	PRE-IMPLEMENTATION MEAN (July 2010 -June 2012)	TRANSITION MEAN (July 2012 - June 2013)	ACTIVE PERIOD MEAN (July 2013 - Dec 2013)	ACTIVE TO PRE-IMPLEMENTATION % CHANGE (95% CI)	p-VALUE FOR % CHANGE OVER TIME	p-VALUE FOR DIFFERENCE IN PERCENT CHANGE
(b) (4)						

Since death rates for oxymorphone, hydromorphone, buprenorphine TDS, and tapentadol were so low, the statistical model failed to converge and thus no tabular summaries are reported for these products.

PC Unintentional Therapeutic Error Data

Table 35(reproduced directly from the RPC's September 24, 2014 IR response) below presents the mentions for the PC Unintentional Therapeutic Error data:

Table 35: RADARS® Unintentional Therapeutic Error Mentions for the Pre-Implementation, Transition, and Active Periods

Drug Group	Pre-Implementation Mentions	Transition Mentions	Active Period Mentions
	(b) (4)		

Table 36 (modification of an RPC table) displays the mean Unintentional Therapeutic Error rates separated by rates for prescriptions per 1,000 or per 100,000 dosing units, with percent changes and statistical analyses for the three study time periods for ER/LA opioid analgesics and comparators

Table 36: Adult/Adolescent Unintentional Therapeutic Error Rates Adjusted for Prescriptions Dispensed or Dosing Units Dispensed for the Pre-Implementation, Transition, and Active Period time periods, the percent change from Pre-Implementation to Active Period, the p-values for the percent change, and the p-values for the difference in percent change between ER/LA opioid analgesics and comparators

DRUG or DRUG	PRE-IMPLEMENTATION MEAN (July 2010 -June	TRANSITION MEAN (July 2012 -	ACTIVE PERIOD MEAN (July 2013 -	ACTIVE TO PRE-IMPLEMENTATION % CHANGE (95% CI)	p-VALUE FOR % CHANGE OVER	p-VALUE FOR DIFFERENCE IN
			(b) (4)			

Emergency Department (ED) Treated/Evaluated and Released Data

The RPC notes that ED visits will be captured by a managed health care facility outcome of "treated/evaluated and released" and may be both urgent care and emergency department visits.

Table 37 (reproduced directly from the RPC's September 24, 2014 IR response) below presents the mentions for the ED Treated/Evaluated and Released data:

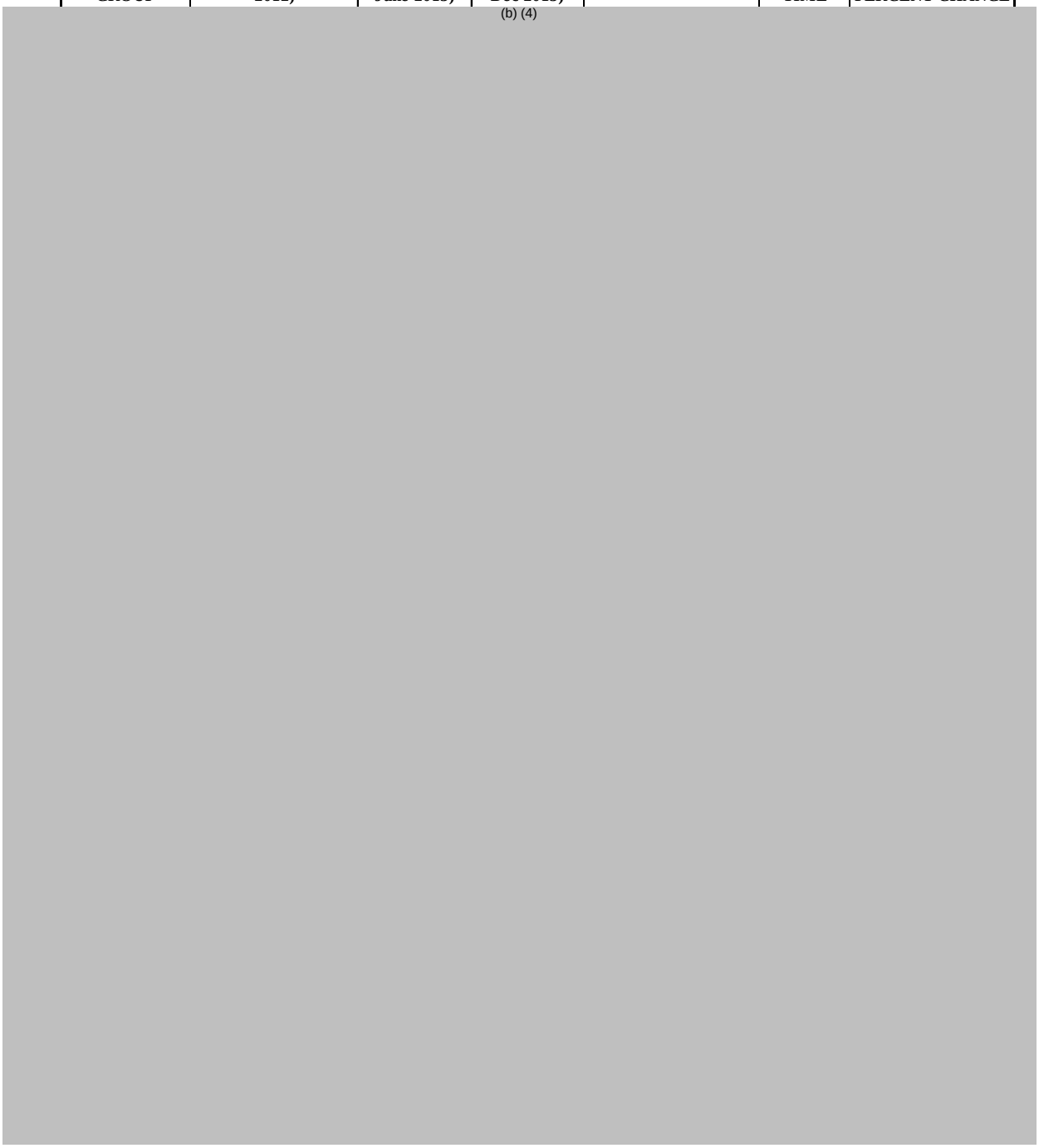
Table 37: RADARS® ED Treated/Evaluated and Released Mentions for the Pre-Implementation, Transition, and Active Periods

Drug Group	Pre-Implementation Mentions	Transition Mentions	Active Period Mentions
	(b) (4)		

Table 38 (modification of an RPC table) displays the mean Unintentional Therapeutic Error rates separated by rates for prescriptions per 1,000 or per 100,000 dosing units, with percent changes and statistical analyses for the three study time periods for ER/LA opioid analgesics and comparators

Table 38: ED Treated/Evaluated and Released Rates Adjusted for Prescriptions Dispensed or Dosing Units Dispensed for the Pre-Implementation, Transition, and Active Period time periods, the percent change from Pre-Implementation to Active Period, the p-values for the percent change, and the p-values for the difference in percent change between ER/LA opioid analgesics and comparators

DRUG or DRUG GROUP	PRE-IMPLEMENTATION MEAN (July 2010 -June 2012)	TRANSITION MEAN (July 2012 - June 2013)	ACTIVE PERIOD MEAN (July 2013 - Dec 2013)	ACTIVE TO PRE-IMPLEMENTATION % CHANGE (95% CI)	p-VALUE FOR % CHANGE OVER TIME	p-VALUE FOR DIFFERENCE IN PERCENT CHANGE
(b) (4)						



PC Pediatric Unintentional General Exposure Data

Table 39 (reproduced directly from the RPC's September 24, 2014 IR response) below presents the mentions for the PC Pediatric Unintentional General Exposure data:

Table 39: RADARS® Pediatric Unintentional General Exposure Mentions for the Pre-Implementation, Transition, and Active Periods

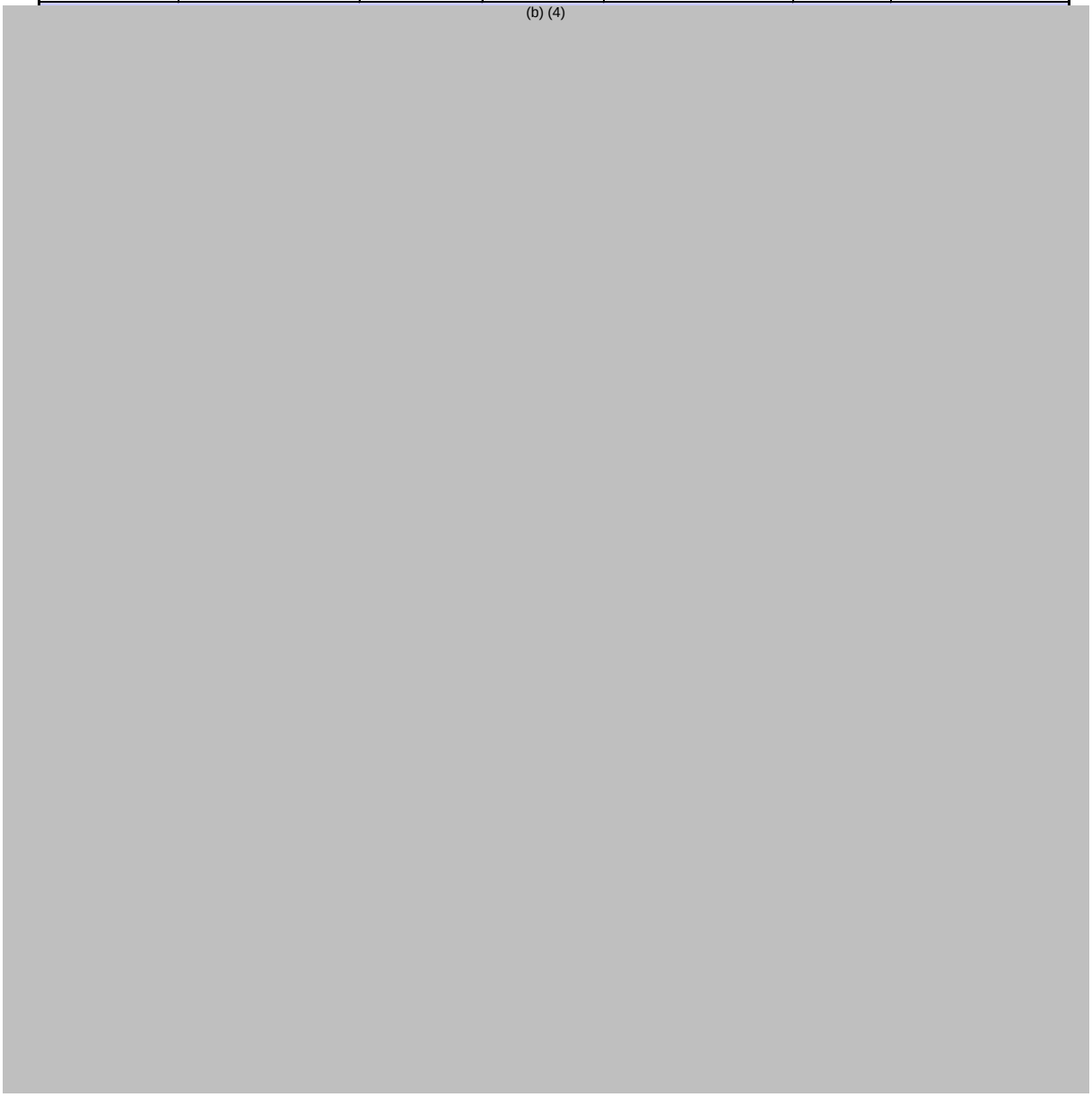
Drug Group	Pre-Implementation Mentions	Transition Mentions	Active Period Mentions
	(b) (4)		

Table 40 (modification of an RPC table) displays the mean Pediatric Unintentional General Exposure rates separated by rates for prescriptions per 1,000 or per 100,000 dosing units, with percent changes and statistical analyses for the three study time periods for ER/LA opioid analgesics and comparators

Table 40: Pediatric Unintentional General Exposure Rates Adjusted for Prescriptions Dispensed or Dosing Units Dispensed for the Pre-Implementation, Transition, and Active Period time periods, the percent change from Pre-Implementation to Active Period, the p-values for the percent change, and the p-values for the difference in percent change between ER/LA opioid analgesics and comparators

DRUG or DRUG GROUP	PRE-IMPLEMENTATION MEAN (July 2010 -June 2012)	TRANSITION MEAN (July 2012 - June 2013)	ACTIVE PERIOD MEAN (July 2013 - Dec 2013)	ACTIVE TO PRE-IMPLEMENTATION % CHANGE (95% CI)	p-VALUE FOR % CHANGE OVER TIME	p-VALUE FOR DIFFERENCE IN PERCENT CHANGE

(b) (4)



As pediatric unintentional general exposure rates for buprenorphine TDS were so low, the statistical model failed to converge and thus no tabular summary is reported.

PC Pediatric Unintentional Exposure Major medical Outcome, Hospitalization, Death Data

Table 41 (reproduced directly from the RPC's September 24, 2014 IR response) below presents the mentions for the PC Pediatric Unintentional General Exposure data:

Table 41: RADARS® Pediatric Unintentional Exposure Major medical Outcome, Hospitalization, Death Mentions for the Pre-Implementation, Transition, and Active Periods

Drug Group	Pre-Implementation Mentions	Transition Mentions	Active Period Mentions
	(b) (4)		

Table 42 (modification of an RPC table) displays the mean Pediatric Unintentional Exposure Major medical Outcome, Hospitalization, Death rates separated by rates for prescriptions per 1,000 or per 100,000 dosing units, with percent changes and statistical analyses for the three study time periods for ER/LA opioid analgesics and comparators

Table 42: Pediatric Unintentional Exposure Major medical Outcome, Hospitalization, Death Rates Adjusted for Prescriptions Dispensed or Dosing Units Dispensed for the Pre-Implementation, Transition, and Active Period time periods, the percent change from Pre-Implementation to Active Period, the p-values for the percent change, and the p-values for the difference in percent change between ER/LA opioid analgesics and comparators

DRUG or DRUG GROUP	PRE-IMPLEMENTATION MEAN (July 2010 -June 2012)	TRANSITION MEAN (July 2012 - June 2013)	ACTIVE PERIOD MEAN (July 2013 - Dec 2013)	ACTIVE TO PRE-IMPLEMENTATION % CHANGE (95% CI)	p-VALUE FOR % CHANGE OVER TIME	p-VALUE FOR DIFFERENCE IN PERCENT CHANGE
Major Medical Outcome, Hospitalization, and Death (Poison Center Program data) (**Pediatric Unintentional Exposures**)						
(b) (4)						

As pediatric unintentional general major medical outcome, hospitalization, or death rates for buprenorphine TDS were so low, the statistical model failed to converge and thus no tabular summary is reported.

Pediatric Unintentional General Exposure ED Treated and Released Data

Table 43 (reproduced directly from the RPC's September 24, 2014 IR response) below presents the mentions for the PC Pediatric Unintentional General Exposure ED Treated and Released data:

Table 43: RADARS® Pediatric Unintentional General Exposure ED Treated and Released Mentions for the Pre-Implementation, Transition, and Active Periods

Drug Group	Pre-Implementation Mentions	Transition Mentions	Active Period Mentions
(b) (4)			

Table 44 (modification of an RPC table) displays the mean Pediatric Unintentional General Exposure ED Treated and Released rates separated by rates for prescriptions per 1,000 or per 100,000 dosing units, with percent changes and statistical analyses for the three study time periods for ER/LA opioid analgesics and comparators

Table 44: Pediatric Unintentional General Exposure ED Treated and Released Rates Adjusted for Prescriptions Dispensed or Dosing Units Dispensed for the Pre-Implementation, Transition, and Active Period time periods, the percent change from Pre-Implementation to Active Period, the p-values for the percent change, and the p-values for the difference in percent change between ER/LA opioid analgesics and comparators

DRUG or DRUG GROUP	PRE-IMPLEMENTATION MEAN (July 2010 -June 2012)	TRANSITION MEAN (July 2012 - June 2013)	ACTIVE PERIOD MEAN (July 2013 - Dec 2013)	ACTIVE TO PRE-IMPLEMENTATION % CHANGE (95% CI)	p-VALUE FOR % CHANGE OVER TIME	p-VALUE FOR DIFFERENCE IN PERCENT CHANGE
ED Data: Treated/Evaluated and Released (Managed Care data) (**Pediatric Unintentional Exposures**)						
Prescription Adjusted Rates/1,000						
			(b) (4)			

As pediatric unintentional general emergency room rates for buprenorphine TDS were so low, the statistical model failed to converge and thus no tabular summary is reported

Adolescent Intentional Abuse Data

The RPC states that the denominator of prescription and units dispensed, reflect the overall drug availability of the community and reflect that drugs are often abused and misused by adolescents even though they are not necessarily prescribed for the adolescent.

Table 45 below (reproduced directly from the RPC's September 24, 2014 IR response) presents the mentions for the PC Adolescent Intentional Abuse data:

Table 45: RADARS® Adolescent Intentional Abuse Exposure Mentions for the Pre-Implementation, Transition, and Active Periods

Drug Group	Pre-Implementation Mentions	Transition Mentions	Active Period Mentions
	(b) (4)		

Table 46 (modification of an RPC table) displays the mean Adolescent Intentional Abuse rates separated by rates for prescriptions per 1,000 or per 100,000 dosing units, with percent changes and statistical analyses for the three study time periods for ER/LA opioid analgesics and comparators

Table 46: **Adolescent Intentional Abuse Rates Adjusted for Prescriptions Dispensed or Dosing Units Dispensed for the Pre-Implementation, Transition, and Active Period time periods, the percent change from Pre-Implementation to Active Period, the p-values for the percent change, and the p-values for the difference in percent change between ER/LA opioid analgesics and comparators**

DRUG or DRUG GROUP	PRE-IMPLEMENTATION MEAN (July 2010 -June 2012)	TRANSITION MEAN (July 2012 - June 2013)	ACTIVE PERIOD MEAN (July 2013 - Dec 2013)	ACTIVE TO PRE-IMPLEMENTATION % CHANGE (95% CI)	p-VALUE FOR % CHANGE OVER TIME	p-VALUE FOR DIFFERENCE IN PERCENT CHANGE
			(b) (4)			

As adolescent intentional abuse for buprenorphine TDS and hydromorphone were so low, the statistical models failed to converge and thus no tabular summaries are reported.

TC Data

Table 47 below (reproduced directly from the RPC's September 24, 2014 IR response) presents the mentions for the TC Past 30-day data:

Table 47: RADARS® Treatment Center Past 30 day Mentions for the Pre-Implementation, Transition, and Active Periods

Drug Group	Pre-Implementation Mentions	Transition Mentions	Active Period Mentions
	(b) (4)		

Table 48 (modification of an RPC table) displays the mean **Treatment Center Past 30 day** rates separated by rates for prescriptions per 1,000 or per 100,000 dosing units, with percent changes and statistical analyses for the three study time periods for ER/LA opioid analgesics and comparators

Table 48: Treatment Center Past 30 day Rates Adjusted for Prescriptions Dispensed or Dosing Units Dispensed for the Pre-Implementation, Transition, and Active Period time periods, the percent change from Pre-Implementation to Active Period, the p-values for the percent change, and the p-values for the difference in percent change between ER/LA opioid analgesics and comparators

DRUG or DRUG GROUP	PRE-IMPLEMENTATION MEAN (July 2010 -June 2012)	TRANSITION MEAN (July 2012 - June 2013)	ACTIVE PERIOD MEAN (July 2013 - Dec 2013)	ACTIVE TO PRE-IMPLEMENTATION % CHANGE (95% CI)	p-VALUE FOR % CHANGE OVER TIME	p-VALUE FOR DIFFERENCE IN PERCENT CHANGE
RADARS Treatment Center Programs mean past 30 day mention rates						
(b) (4)						

Note: Stimulant data are not collected in the Treatment Center Programs

CS Data

Table 49 below (reproduced directly from the RPC's September 24, 2014 IR response) presents the mentions for the CS Past 90-day data:

Table 49: RADARS® College Survey Past 90 day Program Mentions for the Pre-Implementation, Transition, and Active Periods

Drug Group	Pre-Implementation Mentions	Transition Mentions	Active Period Mentions
	(b) (4)		

Table 50 (modification of an RPC table) displays the mean College Survey Past 90 day rates separated by rates for prescriptions per 1,000 or per 100,000 dosing units, with percent changes and statistical analyses for the three study time periods for ER/LA opioid analgesics and comparators

Table 50: College Survey Past 90 day Rates Adjusted for Prescriptions Dispensed or Dosing Units Dispensed for the Pre-Implementation, Transition, and Active Period time periods, the percent change from Pre-Implementation to Active Period, the p-values for the percent change, and the p-values for the difference in percent change between ER/LA opioid analgesics and comparators

DRUG or DRUG GROUP	PRE-IMPLEMENTATION MEAN (July 2010 -June 2012)	TRANSITION MEAN (July 2012 - June 2013)	ACTIVE PERIOD MEAN (July 2013 - Dec 2013)	ACTIVE TO PRE-IMPLEMENTATION % CHANGE (95% CI)	p-VALUE FOR % CHANGE OVER TIME	p-VALUE FOR DIFFERENCE IN PERCENT CHANGE
RADARS College Survey Program mean past 90 day mention rates						
(b) (4)						

8.3. NAVIPPRO INDIVIDUAL COMPOUND DATA

Table 51 (modification of an RPC table) below displays Past 30-day Abuse for includes individual ER/LA opioid analgesics:

Table 51: ASI-MV Past 30-Day Abuse for Grouped and Individuals ER/LA opioid analgesics **and Comparator groups over Study Time Periods with Change over time in Prevalence, Odds of Abuse, and Statistical Significance**

		PRE- REMS July 2010 – June 2012 *(total abuse*	Time 1: Implementation Period: July 2012 – June 2013 *(total*	Time 2: Active Period: July 2013 – December	PRE VS.v TIME 2: RELATIVE RISK/ODDS RATIO		p-

(b) (4)

The following **Tables 52 through 60** are reproduced directly from RPC tables supplied in their October 22, 2014 response to an FDA IR:

Table 52: ASI-MV Change in Abuse of "One's Own Prescription" at the Compound Level among those Indicating Past 30-day Abuse of ERLA opioid analgesics

SOURCE OF PROCUREMENT: ONE'S OWN PRESCRIPTION	PRE-REMS 2 YEARS	TIME 1 1 YEAR	TIME 2 6 MONTHS	PRE VS. TIME 1: RELATIVE RISK/ODDS RATIO (% CHANGE)	95% CI	P-VALUE	PRE VS. TIME 2: RELATIVE RISK/ODDS RATIO (% CHANGE)	95% CI	P-VALUE
Cases per 100				1.00			0.80		

(b) (4)

Table 53: ASI-MV Change in Abuse of "One's Own Prescription from Multiple Doctors" at the Compound Level among those Indicating Past 30-day Abuse of ERLA opioid analgesics

SOURCE OF PROCUREMENT: ONE'S OWN PRESCRIPTION, MULTIPLE DOCTORS	PRE-REMS 2 YEARS	TIME 1 1 YEAR	TIME 2 6 MONTHS	PRE VS. TIME 1: RELATIVE RISK/ODDS RATIO (% CHANGE)	95% CI	P-VALUE	PRE VS. TIME 2: RELATIVE RISK/ODDS RATIO (% CHANGE)	95% CI	P-VALUE
(b) (4)									

Table 54: ASI-MV Change in Abuse from Source "Family Member or Friend" at the Compound Level among those Indicating Past 30-day Abuse of ERLA opioid analgesics

SOURCE OF PROCUREMENT: FAMILY MEMBER OR FRIEND	PRE-REMS 2 YEARS	TIME 1 1 YEAR	TIME 2 6 MONTHS	PRE VS. TIME 1: RELATIVE RISK/ODDS RATIO (% CHANGE)	95% CI	P-VALUE	PRE VS. TIME 2: RELATIVE RISK/ODDS RATIO (% CHANGE)	95% CI	P-VALUE
(b) (4)									

Table 55: ASI-MV Change in Abuse from Source "Illicit" at the Compound Level among those Indicating Past 30-day Abuse of ERLA opioid analgesics

SOURCE OF PROCUREMENT: ILLICIT	PRE-REMS 2 YEARS	TIME 1 1 YEAR	TIME 2 6 MONTHS	PRE VS. TIME 1: RELATIVE RISK/ODDS RATIO (% CHANGE)	95% CI	P-VALUE	PRE VS. TIME 2: RELATIVE RISK/ODDS RATIO (% CHANGE)	95% CI	P-VALUE
(b) (4)									

Table 56: CHAT: Past 30-Day Abuse at the ER/LA opioid analgesic Compound level

	BASELINE: PRE-REMS* TOTAL ABUSE CASES (N = 3,337)	BASELINE: PRE-REMS* CASES/ 100 CHAT ASSESSMENTS 2 YEARS	TIME 2: ACTIVE PERIOD* TOTAL ABUSE CASES (N = 1,730)	TIME 2: ACTIVE PERIOD* CASES/ 100 CHAT ASSESSMENTS 6 MONTHS
(b) (4)				

Table 57: CHAT: Source of Procurement "One's Own Prescription" for Individual ER/LA opioid analgesics

	BASELINE: PRE-REMS* OWN PRESCRIPTION (n/n of abuse cases)	BASELINE: PRE-REMS* OWN PRESCRIPTION (%)	TIME 2: ACTIVE PERIOD^ OWN PRESCRIPTION (n/n of abuse cases)	TIME 2: ACTIVE PERIOD^ OWN PRESCRIPTION (%)
		(b) (4)		

Table 58: CHAT: Source of Procurement "One's Own Prescription from Multiple Doctors" for Individual ER/LA opioid analgesics

	BASELINE: PRE-REMS* MULTIPLE DOCTORS (n)	BASELINE: PRE-REMS* MULTIPLE DOCTORS (%)	TIME 2: ACTIVE PERIOD^ MULTIPLE DOCTORS (n)	TIME 2: ACTIVE PERIOD^ MULTIPLE DOCTORS (%)
		(b) (4)		

Table 59: CHAT Source of Procurement "From Family or a Friends" for Individual ER/LA opioid analgesics

	BASELINE: PRE-REMS* FAMILY OR FRIEND (n)	BASELINE: PRE-REMS* FAMILY OR FRIEND (%)	TIME 2: ACTIVE PERIOD+ FAMILY OR FRIEND (n)	TIME 2: ACTIVE PERIOD+ FAMILY OR FRIEND (%)
(b) (4)				

Table 60: CHAT Source of Procurement "Illicit "for Individual ER/LA opioid analgesics

	BASELINE: PRE-REMS* ILLICIT SOURCE (n)	BASELINE: PRE-REMS* ILLICIT SOURCE (%)	TIME 2: ACTIVE PERIOD+ ILLICIT SOURCE (n)	TIME 2: ACTIVE PERIOD+ ILLICIT SOURCE (%)
(b) (4)				

8.4. ADDITIONAL NSDUH FINDINGS

Potentially Opioid-related highlights from the 2012 NSDUH database are as follows;

- 23.9 million Americans aged 12 or older (9.2% of the US population age 12 and above) had used an illicit drug (marijuana/hashish, cocaine [including crack], heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics such as pain relievers, tranquilizers, stimulants and sedatives) during the month prior to the survey interview.
- Approximately 2.4 million persons are estimated to have used psychotherapeutics (including pain relievers) nonmedically for the first time within the past year, which is an average of approximately 6,700 initiates per day.
- Rates of use of psychotherapeutic drugs was highest in the age group 18 – 25 (5.3%) and lowest in adults aged 26 and older (2.1%)
- Among youth aged 12 – 17, non-medical users of pain relievers was highest among 16 and 17 year olds (3.1%). Overall among youth aged 12 - 17, current non-medical use of pain relievers decreased between 2002 (3.2%) and 2012 (2.2%).
- The rate of current non-medical use of pain relievers among young adults aged 18-25 in 2012 (3.8 %) was similar to the 2011 rate (3.6 %), but it was lower than the rates between 2003 (4.7 %) and 2010 (4.4 %).

8.5. SPECIALTY GROUP DEFINITIONS

Table 61: (RPC table) Provider Specialty Group Definitions (IMS Data Analyses)

Pain

APM	PAIN MEDICINE (ANESTHESIOLOGY)
PMD	PAIN MEDICINE
PME	PAIN MANAGEMENT
PMN	PAIN MEDICINE (NEUROLOGY)
PMR	PAIN MEDICINE (PHYSICAL MEDICINE & REHABILITATION)
PPN	PAIN MEDICINE (PSYCHIATRY)

PCP

GP	GENERAL PRACTICE
GPM	GENERAL PREVENTIVE MEDICINE
FM	FAMILY MEDICINE
FP	FAMILY PRACTICE
FPG	GERIATRIC MEDICINE (FAMILY MEDICINE)
IM	INTERNAL MEDICINE
IMA	INTERNAL MEDICINE/ANESTHESIOLOGY
IMG	GERIATRIC MEDICINE (INTERNAL MEDICINE)
IPM	INTERNAL MEDICINE/PREVENTIVE MEDICINE

Dentist

DGP	DENTIST
DNAN	DENTISTRY/ANESTHESIOLOGY
DNED	DENTISTRY/ENDODONTICS
DNOR	DENTISTRY/ORTHODONTICS
DNPD	DENTISTRY/PEDODONTICS
DNPO	DENTISTRY/PROSTHODONTICS
DNPR	DENTISTRY/PERIODONTICS
OMF	ORAL & MAXILLOFACIAL SURGERY

Surgery

CCS	SURGICAL CRITICAL CARE (SURGERY)
CDS	CARDIOVASCULAR SURGERY
CFS	CRANIOFACIAL SURGERY
CHS	CONGENITAL CARDIAC SURGERY (THORACIC SURGERY)
CRS	COLON & RECTAL SURGERY
CTS	CARDIOTHORACIC SURGERY
DS	DERMATOLOGIC SURGERY
ENR	ENDOVASCULAR SURGICAL NEURORADIOLOGY (NEUROLOGY)
ES	ENDOVASCULAR SURGICAL NEURORADIOLOGY (NEUROLOGICAL SURGERY)
ESN	ENDOVASCULAR SURGICAL NEURORADIOLOGY (RADIOLOGY)
FPR	FEMALE PELVIC MEDICINE & RECONSTRUCTIVE SURGERY
FPS	FACIAL PLASTIC SURGERY
GS	GENERAL SURGERY
HNS	HEAD & NECK SURGERY
HPS	HOSPICE & PALLIATIVE MEDICINE (SURGERY)
HS	HAND SURGERY
HSO	HAND SURGERY (ORTHOPEDICS)
HSP	HAND SURGERY (PLASTIC SURGERY)
HSS	HAND SURGERY (SURGERY)
NCC	CRITICAL CARE MEDICINE (NEUROLOGICAL SURGERY)
NS	NEUROLOGICAL SURGERY
NSP	PEDIATRIC SURGERY (NEUROLOGY)
OMF	ORAL & MAXILLOFACIAL SURGERY
ORS	ORTHOPEDIC SURGERY
OSM	SPORTS MEDICINE (ORTHOPEDIC SURGERY)
OSS	ORTHOPEDIC SURGERY OF THE SPINE
PCS	PEDIATRIC CARDIOTHORACIC SURGERY
PDS	PEDIATRIC SURGERY
PS	PLASTIC SURGERY
PSH	PLASTIC SURGERY WITHIN THE HEAD & NECK
PSO	PLASTIC SURGERY WITHIN THE HEAD & NECK (OTOLARYNGOLOGY)
PSP	PLASTIC SURGERY WITHIN THE HEAD & NECK
SO	SURGICAL ONCOLOGY
SPS	SURGERY/PLASTIC SURGERY
TRS	TRAUMA SURGERY
TS	THORACIC SURGERY
TTS	TRANSPLANT SURGERY
UPR	FEMALE PELVIC MEDICINE & RECONSTRUCTIVE SURGERY (UROLOGY)
VS	VASCULAR SURGERY

Table 61: Provider Specialty Group Definitions (IMS Data Analyses), continued

Emergency Medicine

CCE	CRITICAL CARE MEDICINE (EMERGENCY MEDICINE)
EFM	EMERGENCY MEDICINE/FAMILY MEDICINE
EM	EMERGENCY MEDICINE
EMP	PEDIATRICS/EMERGENCY MEDICINE
EMS	EMERGENCY MEDICAL SERVICES
EMSP	EMERGENCY MEDICAL SERVICES (OTHER)
ESM	SPORTS MEDICINE (EMERGENCY MEDICINE)
ETX	MEDICAL TOXICOLOGY (EMERGENCY MEDICINE)
HPE	HOSPICE & PALLIATIVE MEDICINE (EMERGENCY MEDICINE)
MEM	INTERNAL MEDICINE/EMERGENCY MEDICINE
PE	PEDIATRIC EMERGENCY MEDICINE
PEM	PEDIATRIC EMERGENCY MEDICINE (PEDIATRICS)

Oncology

GO	GYNECOLOGICAL ONCOLOGY
HO	HEMATOLOGY/ONCOLOGY
OMO	MUSCULOSKELETAL ONCOLOGY
ON	MEDICAL ONCOLOGY
PHO	PEDIATRIC HEMATOLOGY/ONCOLOGY
RO	RADIATION ONCOLOGY

Hospice and Palliative Medicine

HPA	HOSPICE & PALLIATIVE MEDICINE (ANESTHESIOLOGY)
HPD	HOSPICE & PALLIATIVE MEDICINE (RADIOLOGY)
HPF	HOSPICE & PALLIATIVE MEDICINE (FAMILY MEDICINE)
HPI	HOSPICE & PALLIATIVE MEDICINE (INTERNAL MEDICINE)
HPM	HOSPICE & PALLIATIVE MEDICINE
HPN	HOSPICE & PALLIATIVE MEDICINE (PSYCHIATRY & NEUROLOGY)
HPO	HOSPICE & PALLIATIVE MEDICINE (OBSTETRICS & GYNECOLOGY)
HPP	HOSPICE & PALLIATIVE MEDICINE (PEDIATRICS)
HPR	HOSPICE & PALLIATIVE MEDICINE (PHYSICAL MEDICINE & REHABILITATION)
PLM	PALLIATIVE MEDICINE

All Other

NRP	NURSE PRACTITIONER
PHA	PHYSICIAN ASSISTANT
P	PSYCHIATRY
PM	PHYSICAL MEDICINE & REHABILITATION
AN	ANESTHESIOLOGY
OBG	OBSTETRICS & GYNECOLOGY
N	NEUROLOGY
US	UNSPECIFIED
RHU	RHEUMATOLOGY
XXX	UNKNOWN
CD	CARDIOVASCULAR DISEASE
U	UROLOGY
OTO	OTOLARYNGOLOGY
POD	PODIATRIST
CHP	CHILD & ADOLESCENT PSYCHIATRY
MPD	INTERNAL MEDICINE/PEDIATRICS
PD	PEDIATRICS
PUD	PULMONARY DISEASE
GE	GASTROENTEROLOGY
NEP	NEPHROLOGY
ID	INFECTIOUS DISEASE
OPH	OPHTHALMOLOGY
END	ENDOCRINOLOGY, DIABETES & METABOLISM
VET	VETERINARIAN
OM	OCCUPATIONAL MEDICINE
HOS	HOSPITALIST
D	DERMATOLOGY
HEM	HEMATOLOGY (INTERNAL MEDICINE)
FSM	SPORTS MEDICINE (FAMILY MEDICINE)
GYN	GYNECOLOGY
DR	DIAGNOSTIC RADIOLOGY
PYG	GERIATRIC PSYCHIATRY
PCC	PULMONARY CRITICAL CARE MEDICINE
PTH	ANATOMIC/CLINICAL PATHOLOGY
CHN	CHILD NEUROLOGY
AI	ALLERGY & IMMUNOLOGY
OAR	ADULT RECONSTRUCTIVE ORTHOPEDICS
REN	REPRODUCTIVE ENDOCRINOLOGY & INFERTILITY
TY	TRANSITIONAL YEAR
CN	CLINICAL NEUROPHYSIOLOGY
CCM	CRITICAL CARE MEDICINE (INTERNAL MEDICINE)
IFP	INTERNAL MEDICINE/FAMILY MEDICINE
OPT	OPTOMETRIST

Table 61: Provider Specialty Group Definitions (IMS Data Analyses), continued

All Other

R	RADIOLOGY
OP	PEDIATRIC ORTHOPEDICS
ADM	ADDICTION MEDICINE
CCA	CRITICAL CARE MEDICINE (ANESTHESIOLOGY)
OFA	FOOT & ANKLE ORTHOPEDICS
NM	NUCLEAR MEDICINE
PSY	PSYCHOLOGY
OTR	ORTHOPEDIC TRAUMA
AM	AEROSPACE MEDICINE
ICE	CLINICAL CARDIAC ELECTROPHYSIOLOGY
FPP	PSYCHIATRY/FAMILY MEDICINE
MP	INTERNAL MEDICINE/PSYCHIATRY
PFP	FORENSIC PSYCHIATRY
ADP	ADDICTION PSYCHIATRY
PDO	PEDIATRIC OTOLARYNGOLOGY
PYA	PSYCHOANALYSIS
A	ALLERGY
DIA	DIABETES
NO	NEUROTOLOGY (OTOLARYNGOLOGY)
UP	PEDIATRIC UROLOGY
PHP	PUBLIC HEALTH & GENERAL PREVENTIVE MEDICINE
IC	INTERVENTIONAL CARDIOLOGY
ISM	SPORTS MEDICINE (INTERNAL MEDICINE)
OS	OTHER SPECIALTY
PYN	PSYCHIATRY/NEUROLOGY
SCI	SPINAL CORD INJURY MEDICINE
VIR	VASCULAR & INTERVENTIONAL RADIOLOGY
NPM	NEONATAL-PERINATAL MEDICINE
OMM	OSTEOPATHIC MANIPULATIVE MEDICINE
PRM	PEDIATRIC REHABILITATION MEDICINE
OBS	OBSTETRICS
LM	LEGAL MEDICINE
SME	SLEEP MEDICINE
RNR	NEURORADIOLOGY
MFM	MATERNAL & FETAL MEDICINE
CCP	PEDIATRIC CRITICAL CARE MEDICINE
CPP	PEDIATRICS/PSYCHIATRY/CHILD & ADOLESCENT PSYCHIATRY
PDC	PEDIATRIC CARDIOLOGY
AS	ABDOMINAL SURGERY
ADL	ADOLESCENT MEDICINE (PEDIATRICS)
PG	PEDIATRIC GASTROENTEROLOGY
OT	OTOLOGY
ATP	ANATOMIC PATHOLOGY
HEP	HEPATOLOGY
IG	IMMUNOLOGY
PHL	PHLEBOLOGY
PN	PEDIATRIC NEPHROLOGY
PPR	PEDIATRIC RHEUMATOLOGY
PDE	PEDIATRIC ENDOCRINOLOGY
PA	CLINICAL PHARMACOLOGY
PDP	PEDIATRIC PULMONOLOGY
PSM	SPORTS MEDICINE (PEDIATRICS)
CLP	CLINICAL PATHOLOGY
NMP	NEUROMUSCULAR MEDICINE (PHYSICAL MEDICINE & REHABILITATION)
HMP	HEMATOLOGY (PATHOLOGY)
UM	UNDERSEAS MEDICINE (PREVENTIVE MEDICINE)
PRS	SPORTS MEDICINE (PHYSICAL MEDICINE & REHABILITATION)
PO	PEDIATRIC OPHTHALMOLOGY
DMP	DERMATOPATHOLOGY
AMI	ADOLESCENT MEDICINE (INTERNAL MEDICINE)
PDA	PEDIATRIC ALLERGY
NTR	NUTRITION
NMN	NEUROMUSCULAR MEDICINE (NEUROLOGY)
FOP	FORENSIC PATHOLOGY
PAN	PEDIATRIC ANESTHESIOLOGY
NP	NEUROPATHOLOGY
MG	MEDICAL GENETICS
PDR	PEDIATRIC RADIOLOGY
VM	VASCULAR MEDICINE
PDI	PEDIATRIC INFECTIOUS DISEASE
DBP	DEVELOPMENTAL/BEHAVIORAL PEDIATRICS
BBK	BLOOD BANKING/TRANSFUSION MEDICINE
MDM	MEDICAL MANAGEMENT
PCH	CHEMICAL PATHOLOGY
PTX	MEDICAL TOXICOLOGY (PREVENTIVE MEDICINE)
PRD	PROCEDURAL DERMATOLOGY
PHM	PHARMACEUTICAL MEDICINE
VN	VASCULAR NEUROLOGY
NR	NUCLEAR RADIOLOGY
PRO	PROCTOLOGY
UME	UNDERSEAS MEDICINE (EMERGENCY MEDICINE)
CG	CLINICAL GENETICS
PCP	CYTOPATHOLOGY
NDN	NEURODEVELOPMENTAL DISABILITIES (PSYCHIATRY & NEUROLOGY)
EPL	EPILEPSY
ALI	CLINICAL LABORATORY IMMUNOLOGY (ALLERGY & IMMUNOLOGY)
OCC	CRITICAL CARE MEDICINE (OBSTETRICS & GYNECOLOGY)
CCG	CLINICAL CYTOGENETICS
PDD	PEDIATRIC DERMATOLOGY
SP	SELECTIVE PATHOLOGY
PLI	CLINICAL & LABORATORY IMMUNOLOGY (PEDIATRICS)
THP	TRANSPLANT HEPATOLOGY (INTERNAL MEDICINE)
NDP	NEURODEVELOPMENTAL DISABILITIES (PEDIATRICS)
MM	MEDICAL MICROBIOLOGY
ACA	ADULT CARDIOTHORACIC ANESTHESIOLOGY
AR	ABDOMINAL RADIOLOGY
TR	THERAPEUTIC RADIOLOGY
MSR	MUSCULOSKELETAL RADIOLOGY
PP	PEDIATRIC PATHOLOGY
EP	EPIDEMIOLOGY
CBG	CLINICAL BIOCHEMICAL GENETICS
CMG	CLINICAL MOLECULAR GENETICS
AHF	ADVANCED HEART FAILURE & TRANSPLANT CARDIOLOGY
DDL	CLINICAL & LABORATORY DERMATOLOGICAL IMMUNOLOGY
PDT	MEDICAL TOXICOLOGY (PEDIATRICS)
MGP	MOLECULAR GENETIC PATHOLOGY (PATHOLOGY)
CTR	CARDIOTHORACIC RADIOLOGY

8.6. UTILITY OF ICD CODES FOR OOP STUDY

This study compared diagnoses of OOP events identified by electronic medical record (EMR) ICD-9 and ICD-10 codes (opioid-related poisoning codes and Opioid-specific adverse event (AE) codes) against diagnoses in medical chart review identified as OOP events. The purpose was to determine the positive predictive value of ICD-9 and ICD-10 codes in identifying OOP events. This study was conducted by at the Center for Health Research, Kaiser Permanente Northwest (KPNW).

Study Conduct

The sample included OOP events identified among KPNW's 475,000 members and Kaiser Permanente Northern California's (KPNC) 3 million members between August 2008 and October 2012. KPNW and KPNC databases were searched for ICD-9 codes for non-fatal events and ICD-10 codes for death (selected based on a previously published study as specified in the SD by Dunn et al). OOP events identified from ICD codes were audited through medical chart reviews to determine if the potential OOP event identified by ICD code was a true OOP event. Chart reviews were divided into 5 categories based on their prescription for an opioid as follows:

a) prescriptions for OxyContin or generic ER oxycodone equivalents;
b) prescriptions for immediate-release oxycodone
c) prescriptions for other ER/LAs
d) prescriptions for other opioids (i.e., other immediate-release opioids or extended-release less potent opioids); and
e) no prescription for an opioid within the prior 12 months of the event

All potential OOP events in category (a), and a random proportional sample of those in categories (b), (c), (d) and (e), were audited against a chart review. Chart reviews compared the specificity of the ICD codes of the EMR-identified OOP events (see **Table 42** below for a list of the codes studied) to results of the chart audit summary stratified by covariates such as ICD code, diagnosis, opioids prescribed, and length of opioid prescriptions used.

Results

Opioid-specific ICD-9 AE codes (E935.x and Y45) combined with ICD-9 codes for overdose symptoms (e.g., altered consciousness, respiratory distress, etc.) were only *weakly* predictive of OOP events: only 13% were confirmed as OOP events by chart review.

On the other hand, Opioid-specific ICD-9 poisoning codes (965.xx, E850.x, and X42) were more predictive. Of the 2100 OOP events identified by ICD-9 codes:

52.1% were unintentional opioid overdoses,
18.9% were suicide-related opioid overdoses
13.6% were opioid-related AEs but not overdoses
11.5% were opioid overdoses that occurred in the setting of analgesia rather than anesthesia (e.g., surgery-related)
3.5% were miscoded or undetermined and

0.5% had no chart information in the healthcare system.

Including both unintentional and suicide-related opioid overdoses, the positive predictive value of opioid poisoning/overdose codes was approximately 71% (1,491/2,100). The RPC states that the positive predictive value could be increased:

- to 80.2% (1,491/1,859) if algorithm to exclude cases that had a surgery code or anesthetic procedure code preceding the overdose event could be developed.
- to 94.7% (1,491/1,574) if an algorithm can be developed to exclude opioid AEs that are not overdoses.

The RPC states that PMR study 2065-3 will evaluate the feasibility of developing diagnostic algorithms to exclude analgesic-related overdose/poisonings and opioid AEs that are not overdoses, as well as to differentiate between unintentional and suicide overdoses. In addition, PMR 2065-3 will evaluate the feasibility of using medical record text search, natural language processing, and/or machine learning to search for opioid overdose codes not identified by ICD codes, thereby improving the sensitivity of detecting opioid overdoses. The RPC has developed a RFP to solicit proposals concerning surveillance monitoring studies of ED visits for opioid overdose and poisoning events and will be evaluating proposals to conduct a monitoring study for inclusion in the 36-month FDA Assessment Report.

Table 62: (RPC table) ICD Codes Evaluated in the Study Described in Review Section 6.4.5

Case 1 Definitions: Opioid-related poisoning codes	
ICD code	***Description***
ICD-9	
965.0*	Poisoning by opioids and related narcotics
E850.1	Accidental poisoning by methadone
E950.0	Suicide and self-inflicted poisoning by analgesics, antipyretics, and anti-rheumatics
E980.0	Undetermined poisoning by analgesics, antipyretics, and anti-rheumatics
ICD-10	
T40.0	Poisoning by opium
T40.1	Poisoning by heroin (not included in Dunn et al.)
T40.2	Poisoning by other opioids
T40.3	Poisoning by methadone
T40.4	Poisoning by other synthetic narcotics
X42	Accidental poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified
X62	Intentional self-poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified
Y12	Undetermined poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified
Case 2A definition: Opioid-specific adverse event (AE) codes†	
ICD-9	
E935.0	Adverse effects of heroin
E935.1	Adverse effects of methadone
E935.2	Adverse effects of other opioids and related narcotics
ICD-10	
Y45.0	Adverse effects of opioids and related analgesics
Case 2B definition: Overdose diagnostic codes †	
ICD-9	
276.4	Mixed acid–base balance disorder
292.1	Drug-induced psychotic disorders (including 292.11 and 292.12)
292.81	Drug-induced delirium
292.8*	Drug-induced mental disorder (excluding 292.81)
486	Pneumonia, organism unspecified
496	Chronic airway obstruction, not elsewhere classified
518.81	Acute respiratory failure
518.82	Other pulmonary insufficiency, not elsewhere classified
780.0*	Alteration of consciousness
780.97	Altered mental state
786.03	Apnea
786.05	Shortness of breath
786.09	Dyspnea and respiratory abnormalities — other
786.52	Painful respiration
799.0*	Asphyxia and hypoxemia
E950–E959	Suicide and self-inflicted injury
HCPCS Code	
J2310	Injection, naloxone hydrochloride (not included in Dunn et al.)

* Includes all sub-codes beginning with this code.

† Case definition 2 is met when participants have a code for an opioid-specific AE code (Case 2A definition) plus Case 2B definition: Overdose diagnostic codes

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/s/

IGOR CERNY
02/26/2015
REMS Assessment Review

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