Regulatory Background and the Evolving Opioid Landscape

May 5, 2025
Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM)
and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

Discussion of Findings From the Extended-Release/Long-Acting Opioid Analgesic Observational Postmarketing Requirement Studies

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Outline

- Meeting Purpose
- Background and Regulatory History of the Extended-Release/Long-Acting (ER/LA) Opioid Analgesic (OA) Postmarketing Requirements (PMRs)
- Overview of the ER/LA OA PMRs
- The Evolving Opioid Landscape
- Selected Regulatory Actions Since PMRs Were Issued
- Current OA Labeling Relevant to the PMRs
- Discussion Questions

Meeting Purpose

- To have a public, transparent discussion and receive external expert input on the completed PMR studies 3033-1 and 3033-2, epidemiologic investigations examining risks of and potential risk factors for misuse,[1] abuse,[2] addiction,[3] and fatal and non-fatal opioid-involved overdose in patients with long-term use of OAs

1. FDA label defines ***misuse*** as the intentional use, for therapeutic purposes, of a drug in a manner other than as prescribed or by an individual for whom it was not prescribed.
2. FDA label defines ***abuse*** as the intentional, nontherapeutic use of a drug for its desirable psychological or physiological effects.
3. FDA label defines ***addiction*** as a cluster of behavioral, cognitive, and physiological phenomena that may include a strong desire to take the drug, difficulties in controlling drug use …, and possible tolerance or physical dependence.

We recognize that certain language may perpetuate stigma toward individuals who use substances or who have substance use disorders. The terminology used in the PMRs is based on statutory and regulatory usage of these terms. FDA is committed to reducing stigma and ensuring access to evidence-based treatment for individuals with substance use disorders.

BACKGROUND AND REGULATORY HISTORY OF THE ER/LA OA PMRS

Background and Regulatory History

1990s

- Increased prescribing of OAs for acute and chronic non-cancer pain
  - Most prescriptions were for immediate-release/short-acting (IR/SA) OAs
  - Newer ER/LA OA (e.g., MS Contin, OxyContin, Duragesic) use was much lower, but growing
    - Generally available in higher dosage strengths
    - Compared to IR/SA OAs, on average, ER/LA OA prescriptions had
      - higher daily doses[1]
      - higher total morphine milligram equivalents (MMEs) of opioid per prescription[2]

1. Miller N. Prescription Opioid Duration of Action and the Risk of Unintentional Overdose Among Patients Receiving Opioid Therapy. JAMA Intern Med. 2015
2. FDA analysis IQVIA National Prescription Audit™, U.S. Launch edition. Data years 1992-2023. Data extracted July 2024.

Background and Regulatory History

Late 1990s - Early 2000s

- Increasing reports of misuse and abuse of prescription opioids
- Alarming rise in fatal overdoses involving prescription opioids
- FDA responded using its regulatory authorities available at the time, e.g.,
  - Strengthened warnings in labels for certain products to alert prescribers about risks of misuse and abuse[1]
  - Warning letters citing manufacturers' violative promotional materials[2]

1. Timeline of Selected FDA Activities and Significant Events Addressing Substance Use and Overdose Prevention | FDA
2. Food and Drug Administration. Warning Letter. Available at: https://wayback.archive-it.org/7993/20170112065652/http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCcompanies/UCM168946.pdf

Background and Regulatory History

2007

- Food and Drug Administration Amendments Act (FDAAA) provided FDA new authorities
- Among these, FDA could now require of drug application holders:
  - Postmarketing requirements (PMRs): safety studies[1]
    - Assess a known serious risk related to the use of the drug
    - Assess signals of serious risk related to the use of the drug
    - Identify an unexpected serious risk when available data indicate the potential for a serious risk
  - Safety-related labeling changes, based on new safety information
  - Risk evaluation and mitigation strategies (REMS[2]) for medications with serious safety concerns to ensure benefits outweigh risks

1. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarketing-requirements-and-commitments-introduction
2. https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems

Background and Regulatory History

2012

- ER/LA OA REMS approved
  - Goal: reduce the risk of abuse, misuse, addiction, overdose, and deaths due to OAs
  - Required manufacturers make available at no/nominal cost continuing education on safe ER/LA OA prescribing, adhering to an FDA-approved blueprint[1]
- Public scientific workshop, other stakeholder input
  - Discussed knowledge gaps related to treatment of chronic non-cancer pain
  - Raised concerns about safety of longer-duration and higher-dose OA therapy
- FDA literature review
  - Concluded more information needed on the serious risks of misuse, abuse, addiction, overdose, and death with long-term use of OAs for chronic pain
  - Association seen between higher daily doses and risk of overdose

1. Food and Drug Administration. Historical Information on REMS for Opioid Analgesics. Available at: https://www.fda.gov/drugs/information-drug-class/historical-information-rems-opioid-analgesics.

Background and Regulatory History

2013

- FDA issued five PMRs to ER/LA OA application holders to assess the risks associated with long-term[1] use of OAs for chronic pain among patients using ER/LA OAs
  - Provide quantitative estimates and identify potential risk factors for these known serious risks
  - FDA was concerned about heightened risks for ER/LA OAs due to higher dosage strengths and use at higher daily doses
- Companies were encouraged to work together to fulfill the PMRs
  - Formed the Opioid PMR Consortium (OPC)

1. There is no universally accepted definition of long-term use, although many studies have used three months, or 90 days, as a marker of long-term use.

OVERVIEW OF THE ER/LA OA PMRs

Original 2013 ER/LA OA PMRs

PMR #	Description (Excerpted in Relevant Part)
2065-1	Conduct one or more studies to provide quantitative estimates of the serious risks of and evaluate risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of OAs for management of chronic pain among patients prescribed ER/LA OAs.
2065-2	Develop and validate measures of misuse, abuse, addiction, overdose and death, which will be used to inform the design and analysis of PMR 2065-1.
2065-3	Conduct a study to validate coded medical terminologies used to identify opioid-related adverse events (misuse, abuse, addiction, overdose, death) in any existing postmarketing databases to be employed in the studies. These validated codes will be used to inform the design and analysis of PMR 2065-1.
2065-4	Conduct a study to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR 2065-1.
2065-5*	Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain.

Source: https://www.fda.gov/media/86875/download
*PMR 2065-5, the hyperalgesia clinical trial, will not be a topic for discussion at this AC meeting
Abbreviations: ER/LA, extended-release/long-acting; OA, opioid analgesic; PMR, postmarketing requirement

Development and Oversight of ER/LA OA PMR Studies

2014-2016

- FDA Steering Committee formed
- Public scientific meeting convened to discuss design considerations for the studies
  - Scientific expert panel provided input on study concepts and timelines presented by the OPC
  - Determined multiple, separate studies were necessary to fulfill several of the PMRs
- In 2016, the original 5 PMRs were reissued as 11 separate PMRs* to track individually
  - 2 main observational studies (3033-1 and 3033-2)
  - 8 supportive studies (3033-3 through 3033-10)
- Study protocols were refined by OPC and approved by FDA scientific review teams

*PMR 3033-11, the hyperalgesia clinical trial, was discussed at a separate AC meeting in April 2024 and is not a topic for discussion at this meeting

2016: Main Observational ER/LA OA PMRs

PMR#	Description (Excerpted in Relevant Part)
3033-1	A prospective, observational study designed to quantify the serious risks of misuse, abuse, and addiction associated with long-term use of OAs for management of chronic pain among patients prescribed ER/LA OAs.* a. Estimate the incidence of misuse, abuse, and addiction associated with long-term use of OAs for chronic pain. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors … b. Evaluate and quantify other risk factors….
3033-2	An observational study designed to measure the incidence and predictors of opioid overdose and death, as well as opioid abuse/addiction, using patient health records, insurance claims, and death records.* a. Estimate the incidence of abuse/addiction, overdose, and death associated with long-term use of OAs for chronic pain. Stratify overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors … b. Evaluate and quantify other risk factors….

***Although the original focus was on patients receiving ER/LA OAs, both PMR studies were later broadened to include patients with new long-term use of <u>any</u> Schedule II opioid analgesics for chronic pain.**

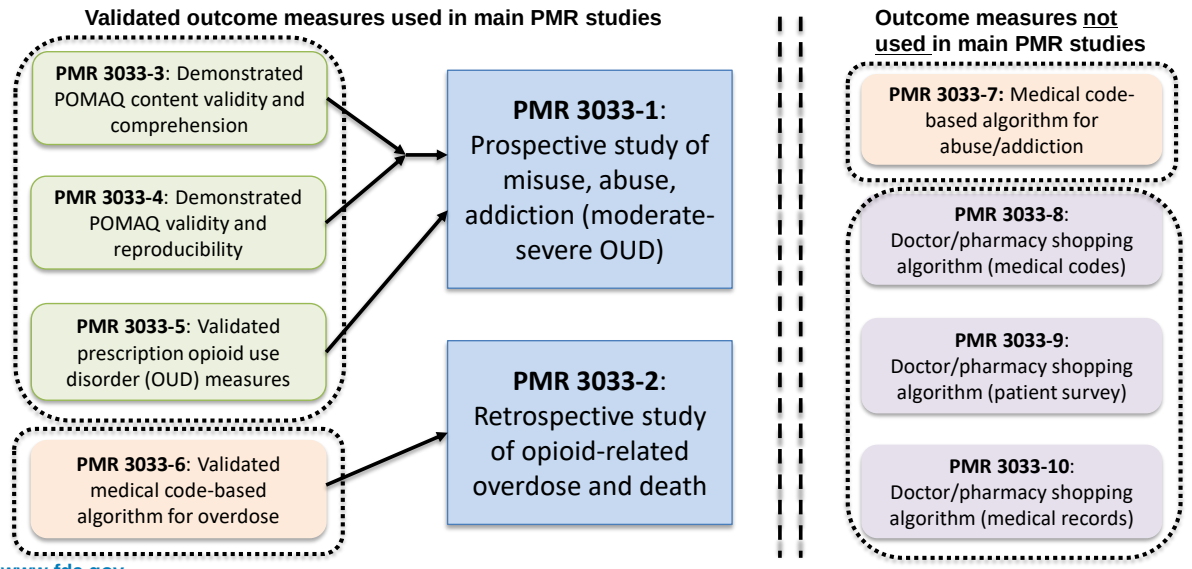
Source: Food and Drug Administration. Release from Postmarketing Requirement and New Postmarketing Requirement letter.
Abbreviations: ER/LA, extended-release/long-acting; OA, opioid analgesic; PMR, postmarketing requirement

2016: Supportive ER/LA OA PMRs

PMR#	Description (Excerpted in Relevant Part)
3033-3	A prospective observational study designed to assess the **POMAQ**. Patient understanding of the concepts of misuse and abuse will also be obtained.
3033-4	An observational study to evaluate the **validity and reproducibility of the POMAQ,** which will be used to identify opioid abuse and misuse behaviors among participants who have chronic pain….
3033-5	An observational study to **validate measures of prescription opioid substance use disorder and addiction** in patients who have received or are receiving OAs for chronic pain
3033-6	An observational study to develop and **validate an algorithm using coded medical terminologies** and other electronic healthcare data **to identify opioid-related overdose and death**
3033-7	An observational study to develop and **validate an algorithm using coded medical terminologies to identify** patients experiencing prescription **opioid abuse or addiction**
3033-8	An observational study **using coded medical terminologies** and other electronic healthcare data **to define and validate doctor/pharmacy shopping outcomes** by examining their association with abuse and/or addiction
3033-9	An observational study **using a validated patient survey to evaluate** the association between **doctor/pharmacy shopping outcomes** and self-reported misuse and abuse
3033-10	An observational study **using medical record review to evaluate** the association between **doctor/pharmacy shopping outcomes** and patient behaviors suggestive of misuse, abuse and/or addiction

Source: Food and Drug Administration. Release from Postmarketing Requirement and New Postmarketing Requirement letter. Available at: https://www.fda.gov/media/95546/download Accessed 12/5/2024
Abbreviations: ER/LA, extended-release/long-acting; OA, opioid analgesic; PMR, postmarketing requirement; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire

Foundational/Supportive Observational PMRs



THE EVOLVING OPIOID LANDSCAPE

Efforts to Address the Growing Opioid Crisis

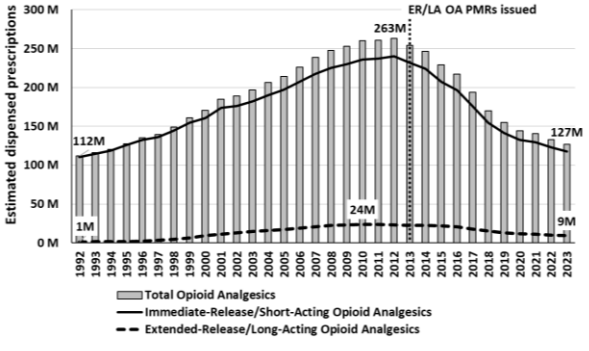
- Myriad federal, state, and local efforts to address the opioid crisis

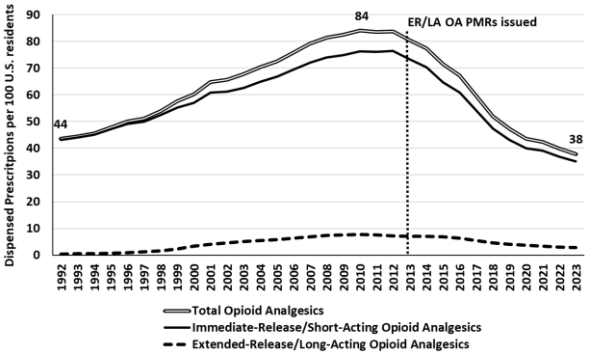
FDA actions, e.g., REMS,[1] labeling,[2] rescheduling recommendations,[2] drug withdrawals,[3] OTC naloxone[4]	**Other federal efforts,** e.g., CDC Guideline on Opioid Prescribing,[5] OUD treatment supports	**State, insurance, institutional policies and regulations,** e.g., PDMPs, prior auth, CE mandates[6]	**Law enforcement initiatives,** e.g., targeting drug diversion, rogue pain clinics and pharmacies

- Many focused on reducing inappropriate or unnecessary prescribing
- Some guidelines were misapplied and enforced as hard limits, resulting in abrupt tapering or discontinuation, and dismissal of patients[7]

1. Risk Evaluation and Mitigation Strategies
2. Overdose Prevention Activities Timeline: https://www.fda.gov/drugs/food-and-drug-administration-overdose-prevention-framework/timeline-selected-fda-activities-and-significant-events-addressing-substance-use-and-overdose
3. https://www.fda.gov/news-events/press-announcements/fda-requests-removal-opana-er-risks-related-abuse
4. OTC, over-the-counter; https://www.fda.gov/news-events/press-announcements/fda-approves-first-over-counter-naloxone-nasal-spray
5. Centers for Disease Control and Prevention Clinical Practice Guideline for Prescribing Opioids for Pain, United States; Dowell et al., 2016, 2022
6. PDMP, Prescription drug monitoring programs; CE, Continuing education
7. Dowell et al. No Shortcuts to Safer Opioid Prescribing, *NEJM*, 2019

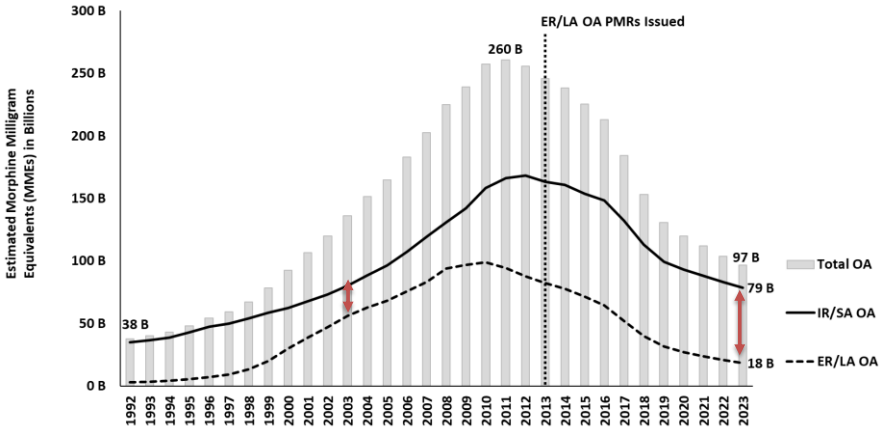
Trends in OA Prescriptions, Total and Population-Adjusted





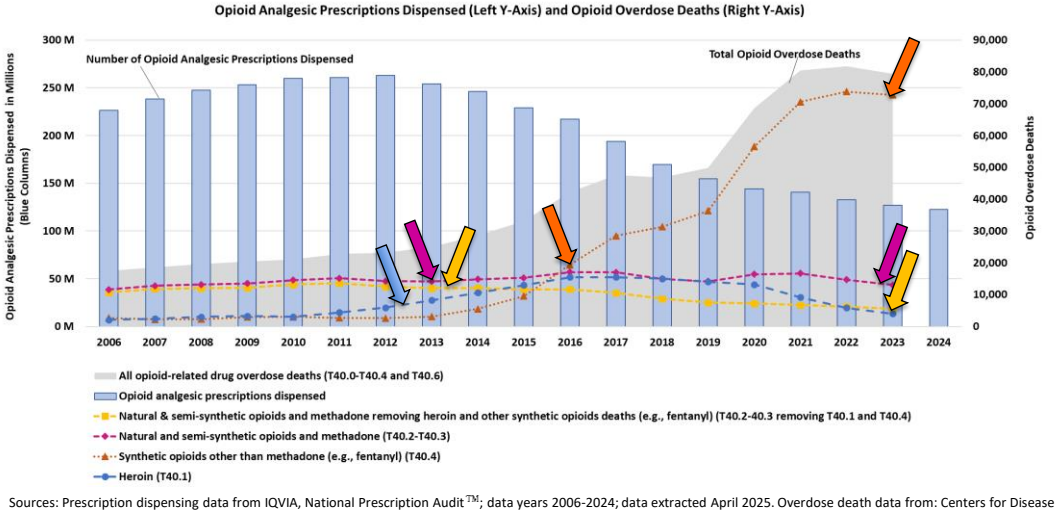
Nationally Estimated Number of Opioid Analgesic Prescriptions Dispensed From U.S. Retail and Mail-Order Pharmacies, by Formulation, Total (left) and Per 100 U.S. Residents (right), 1992 Through 2023 Annually.
Sources: IQVIA National Prescription Audit™, U.S. Launch edition, data years 1992-2023, data extracted July 2024; U.S. Census Bureau, www.census.gov.
Results in these figures may differ from other results due to different data sources used.
Abbreviation: ER/LA, extended-release/long-acting; M, millions; OA, opioid analgesic; PMRs, postmarketing requirements

Trends in Total MMEs



Nationally Estimated Annual Morphine Milligram Equivalents (MMEs) for Opioid Analgesics Dispensed From U.S. Retail and Mail-Order Pharmacies, Stratified by Formulation, 1992 to 2023.
Source: IQVIA National Prescription Audit™, U.S. Launch edition. Data years 1992-2023.
Data extracted July 2024. Sources for MME conversion factors: Centers for Disease Control and Prevention, NDC and Oral MME Conversion File, 2019 version, https://www.cdc.gov/drugoverdose/resources/data.html. McPherson ML, Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing, 2nd Edition, American Society of Health-System Pharmacists, 2018. Medscape, Opioid Equivalents and Conversions, https://emedicine.medscape.com/article/2138678-overview.GlobalRPh, Opioid conversions calc (single agent) equianalgesic, http://globalrph.com/narcoticonv.htm.
Abbreviations: B, billions; ER/LA OA, extended-release/long-acting opioid analgesic; IR/SA OA, immediate-release/short-acting opioid analgesic; U.S., United States

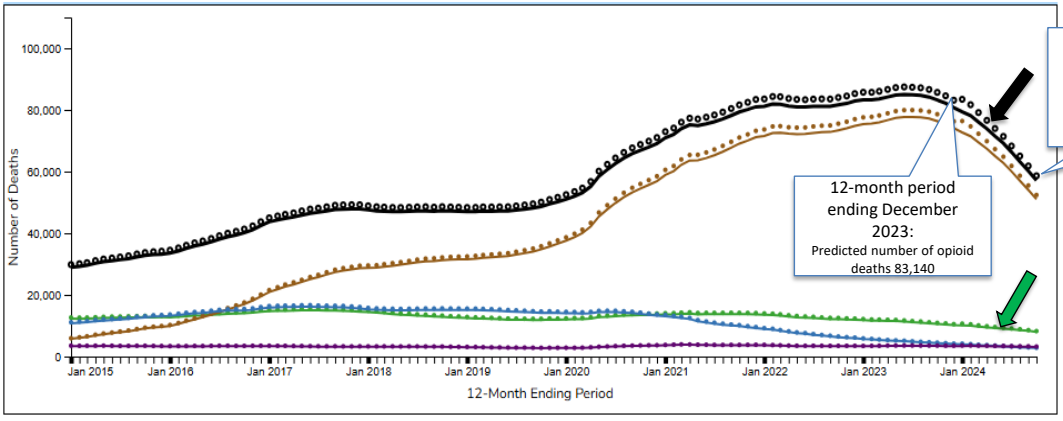
Trends in Opioid-Involved Overdose Deaths



Sources: Prescription dispensing data from IQVIA, National Prescription Audit ™; data years 2006-2024; data extracted April 2025. Overdose death data from: Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System, Provisional Mortality on CDC WONDER Online Database. Data are from the final Multiple Cause of Death Files, 2018-2023, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. 2024 data from CDC WONDER are not included as they are only available as partial year at the time of the analysis. Accessed at http://wonder.cdc.gov/mcd-icd10-provisional.html on 04/07/2025.
Abbreviation: CDC, Centers for Disease Control and Prevention

Trends in Opioid-Involved Overdose Deaths

12 Month-ending Provisional Number of Drug Overdose Deaths by Drug or Drug Class: United States



Source: NCHS, National Vital Statistics System. Estimates for 2024 are based on provisional data. Estimates for 2015-2023 are based on final data (available from: https://www.cdc.gov/nchs/nvss/mortality_public_use_data.htm).
Notes: *Reported* provisional counts for 12-month ending periods are the number of deaths received and processed for the 12-month period ending in the month indicated. Provisional counts may not include all deaths that occurred during a given time period. Therefore, they should not be considered comparable with final data and are subject to change. *Predicted* provisional counts represent estimates of the number of deaths adjusted for incomplete reporting (see **source reference for additional notes**)

Legend for Drug or Drug Class

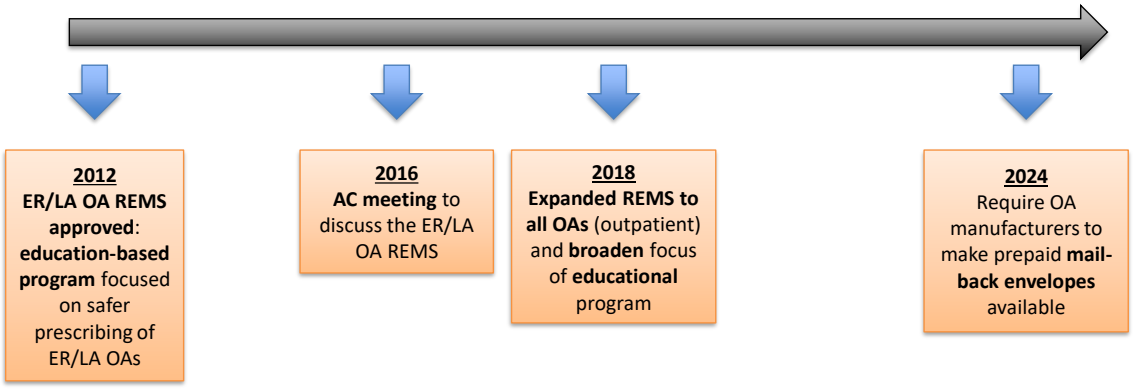
- Heroin (T40.1)
- Methadone (T40.3)
- Natural & semi-synthetic opioids (T40.2)
- Opioids (T40.0-T40.4,T40.6)
- Synthetic opioids, excl. methadone (T40.4)

---- Reported Value

O Predicted Value

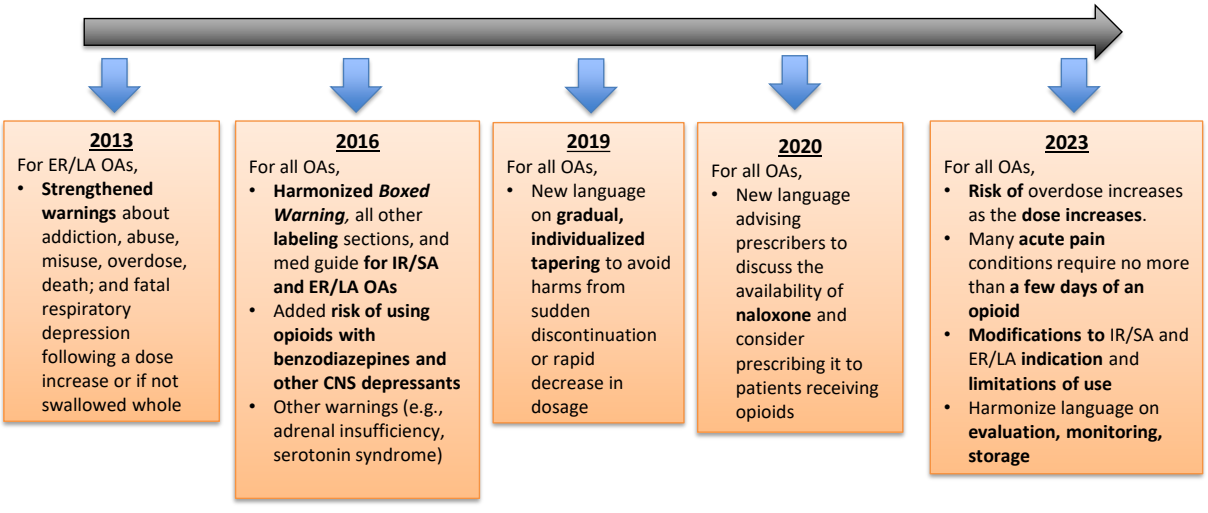
SELECTED FDA REGULATORY ACTIONS SINCE PMRs WERE ISSUED

Major OA REMS Actions



Source: Overdose Prevention Activities Timeline: https://www.fda.gov/drugs/food-and-drug-administration-overdose-prevention-framework/timeline-selected-fda-activities-and-significant-events-addressing-substance-use-and-overdose
Abbreviations: AC, Advisory Committee; ER/LA, extended-release/long-acting; OA, opioid analgesic; REMS, risk evaluation and mitigation strategies

Selected Required Major OA Safety Labeling Changes



Source: Overdose Prevention Activities Timeline: https://www.fda.gov/drugs/food-and-drug-administration-overdose-prevention-framework/timeline-selected-fda-activities-and-significant-events-addressing-substance-use-and-overdose
Abbreviations: ER/LA, extended release/long-acting; CNS, central nervous system; IR/SA, immediate-release/short-acting; OA, opioid analgesic

CURRENT OPIOID ANALGESIC LABELING RELEVANT TO THE PMRs

Example of Current OA Labeling: Boxed Warning

WARNING: SERIOUS AND LIFE-THREATENING RISKS FROM USE OF [DRUG]

•[DRUG] exposes users to risks of **addiction, abuse, and misuse**, which can lead to overdose and death. **Assess patient's risk before prescribing** and reassess regularly for these behaviors and conditions.

•**Serious, life-threatening, or fatal respiratory depression** may occur, especially during initiation or following a dosage increase. To reduce the risk of respiratory depression, proper dosing and titration of [DRUG] are essential.

•**Accidental ingestion** of [DRUG] , especially by children, can result in a fatal overdose of [DRUG].

•**Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants**, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation.

•If opioid use is required for an extended period of time in a pregnant woman, advise the patient of the risk of Neonatal Opioid Withdrawal Syndrome, which may be life-threatening if not recognized and treated. Ensure that management by neonatology experts will be available at delivery.

•Healthcare providers are strongly encouraged to complete a REMS-compliant education program and to counsel patients and caregivers on serious risks, safe use, and the importance of reading the Medication Guide with each prescription.

•Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose ….

Source: Drugs@FDA, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Example of Current OA Labeling: Indications and Limitations of Use

IR/SA OAs

[DRUG] is an opioid agonist indicated for the **management of pain severe enough to require an opioid analgesic** and for which **alternative treatments are inadequate**.

Because of the risks of addiction, abuse, and misuse with opioids, which can occur at any dosage or duration, reserve [DRUG] for use in patients for whom alternative treatment options …

- Have not been tolerated or are not expected to be tolerated.
- Have not provided adequate analgesia or are not expected to provide adequate analgesia.

ER/LA OAs

[DRUG] is an opioid agonist indicated for the management of **severe and persistent pain that requires an extended treatment period** with a daily opioid analgesic and for which **alternative treatment options are inadequate**.

Because of greater risks of overdose and death with extended-release/long-acting opioid formulations, reserve [DRUG] for use in patients for whom alternative treatment options (e.g., non-OAs or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

Source: Drugs@FDA, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Example of Current OA Labeling: Dosage and Administration

- Use the **lowest effective dosage** for the **shortest duration** of time consistent with individual patient treatment goals. Because the **risk of overdose increases as opioid doses increase**, reserve titration to higher doses of [DRUG] for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose opioid clearly outweigh the substantial risks.
- **Many acute pain conditions … require no more than a few days** of an opioid analgesic…
- **Respiratory depression** can occur at any time during opioid therapy, **especially when initiating and following dosage increases** with [DRUG] ….

Source: Drugs@FDA, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Example of Current OA Labeling: Warnings and Precautions

Addiction, Abuse, and Misuse

- Although the risk of **addiction** in any individual is unknown, it can occur in patients appropriately prescribed [DRUG]. Addiction can occur **at recommended dosages and if the drug is misused or abused**.
- **Assess each patient's risk** for opioid addiction, abuse, or misuse prior to prescribing [DRUG], **and reassess** all patients receiving [DRUG] for the development of these behaviors and conditions.
- Risks are increased in patients with a **personal or family history of substance abuse** (including drug or alcohol abuse or addiction) **or mental illness** (e.g., major depression).
- The potential for these risks should not, however, prevent the proper management of pain in any given patient.

Source: Drugs@FDA, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

Example of Current OA Labeling: Tapering

- **Do not abruptly discontinue [DRUG] in patients who may be physically dependent** on opioids**.** Rapid discontinuation…has resulted in **serious withdrawal symptoms, uncontrolled pain, and suicide**…
- There are **no standard opioid tapering schedules** that are suitable for all patients. Good clinical practice dictates a patient-specific plan to **taper the dose of the opioid gradually**….
- It is important to **ensure ongoing care** of the patient and to **agree on an appropriate tapering schedule** and follow-up plan….
- Ensure that a **multimodal approach** to pain management, including **mental health support** (if needed), is in place….

Source: Drugs@FDA, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

DISCUSSION QUESTIONS FOR THE COMMITTEES

Discussion Questions

1. **Discuss your interpretation of the estimates of the incidence and prevalence of misuse, abuse, and opioid use disorder (OUD) in patients using OAs long-term (PMR 3033-1). Please also comment on factors influencing your interpretation, e.g.,**
   - Study strengths and limitations
   - Definitions and measurements of these outcomes, including the two different definitions of OUD (i.e., DSM-5-OUD, pain-adjusted DSM-5-OUD)
   - Generalizability of findings and relevance to patients currently using OAs given the evolving opioid landscape
   - Consistency of findings with other available evidence or clinical experience
2. **Discuss your interpretation of the estimates of the incidence of opioid-involved overdose or opioid-related overdose death (OOD) in patients using OAs long-term (PMR 3033-2). Please also comment on factors influencing your interpretation, e.g.,**
   - Study strengths and limitations
   - Ascertainment of opioid overdose and any potential for bias
   - Heterogeneity of results across study populations, particularly those with Medicaid versus commercial insurance
   - Generalizability of findings and relevance to patients currently using OAs given the evolving opioid landscape
   - Consistency of findings with other available evidence or clinical experience
3. **Discuss your interpretation of the risk factor analyses in PMRs 3033-1 and 3033-2 and what you see as the most important findings. Please consider:**
   - The study designs and analytic approaches
   - Consistency of findings with other available evidence or clinical experience

   In particular, please comment on the study results related to dose and formulation (ER/LA versus IR/SA).
4. **Given your interpretation of the findings from these studies and what is currently in FDA-approved OA labeling, are there any novel findings that you believe FDA should communicate to healthcare providers, patients, and other members of the public?**

U.S. FOOD & DRUG ADMINISTRATION

Key Methodological and Statistical Considerations for Extended-Release/Long-Acting Opioid Analgesic Postmarketing Requirement Studies 3033-1 and 3033-2

May 5, 2025

Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

Hana Lee, PhD
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Office of Biostatistics
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Outline

Postmarketing Requirements (PMR) Study 3033-1

- Design overview
- Key considerations
  - Cohort retention
  - Risk factor analysis

PMR Study 3033-2

- Design overview
- Key considerations
  - The ICD code-based algorithm for identification of OOD
  - Cohort retention
  - Additional consideration on risk factor analysis: Switch/add analysis
  - Site heterogeneity and generalizability

Concluding Remarks

Abbreviations: ICD, International classification of diseases; OOD, opioid-involved overdose or opioid overdose-related death

PMR Study 3033-1

PMR 3033-1: Study Design Overview

PMR Study	3033-1	
	Prospective	**Cross-Sectional**
Goal	Estimate the incidence and prevalence of, and identify risk factors for misuse, abuse, and OUD	
Population	• ER/LA cohort (new ER/LA OA use) • LtOT cohort (new long-term ER/LA or Schedule II OA use)	Patients regularly using OAs for ≥1 year, at least 1 ER/LA OA prescription
Data sources	• Electronic health records (EHR), claims, patient questionnaire & interview • 10 sites in the United States*	
Study period	August 2017 to October 2021	September 2017 to February 2019
Primary outcomes	Survey- and interview-based a. Past-3-month misuse, abuse (questionnaire: POMAQ) b. Past-12-month OUD (interview: PRISM-5-Op)	
Follow-up	a. Misuse and Abuse: Every 3 months till 12-months b. OUD: At 12 months	a. None

* Only 9 sites were included in the cross-sectional study

 Abbreviations: ER/LA, extended-release, long-acting; LtOT, long-term Schedule II opioid therapy; OA, opioid analgesic; OUD, opioid use disorders; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Health Disorders

Prospective Study: Key Eligibility Criteria

Prospective study	Key Inclusion Criteria	Key Exclusion Criteria
ER/LA cohort	• ≥ 28 days' supply of an ER/LA OA + a subsequent ER/LA OA prescription, within a 90-day period before the baseline interview • No ER/LA OA use in the six months prior to the 28 days' supply	Record of OUD, or, receiving treatment for OUD (EHR/claims)
LtOT cohort	• ≥ 70 days' supply of an ER/LA OA or a Schedule II OA, within a 90-day period before the baseline interview • No ER/LA OA or Schedule II OA use in the six months prior to the 70 days' supply	

Prospective and Cross-Sectional Studies: Key Inclusion/Exclusion Criteria

- At least 12 months of health plan enrollment or with evidence of receiving care (EHR/claims)
- No record of being in hospice or a terminal diagnosis (chart review or self-report)

Abbreviations: ER/LA, extended-release, long-acting; ERH, Electronic health records; LtOT, long-term Schedule II opioid therapy; OA, opioid analgesic; OUD, opioid use disorders

Eligibility: Key Change From Initial Plan and Impact

Background

- Initial recruitment plan: The prospective study to recruit only the **ER/LA cohort** (patients with new long-term ER/LA OA use)
- Decline in ER/LA OA prescribing
  - ➔ Wouldn't meet recruitment goals
  - ➔ Eligibility criteria revised to include the **long-term Schedule II opioid therapy (LtOT cohort)** (new long-term Schedule II OA use)
- Plan: Combine the **ER/LA** and **LtOT** cohorts if sufficiently similar with respect to various patient characteristics
  - ➔ Two cohorts were substantially different
  - ➔ Two cohorts were analyzed separately

Statistical Analysis

PMR Study	3033-1	
	Prospective	**Cross-Sectional**
Primary outcome measure	Incidence	Prevalence
Risk Factor analysis		
Goal	**Exploratory:** To identify factors associated with increased or decreased risk of outcomes	
Potential risk factors	1. Sociodemographic 2. OA-related (e.g., dose, formulation, opioid moiety, duration) 3. SUD history 4. Health- and pain-related 5. Mental health and social 6. Genetic factors Collected from: - EHR - claims - questionnaires - interview	
	Measured at baseline	Measured at the same time of the outcome assessment
Model	Logistic regression; Odds Ratio (OR)	
Analyses	• Unadjusted • Demographically adjusted (age, sex, race, and ethnicity) • Fully adjusted – Included significant factors (p-value < 0.10) in unadjusted analyses – Age, sex, race, and ethnicity were forced in	

Abbreviations: EHR, electronic health records; OA, opioid analgesic; SUD, substance use disorder

Key Considerations for PMR 3033-1

1. Cohort retention and impact of loss-to-follow-up
2. Overarching considerations for risk factor analysis

*Additional considerations for outcome definitions and measurement will be covered in Dr. Kornegay's presentation

Cohort Retention in PMR 3033-1

PMR 3033-1 Prospective Study

Primary Outcome	Assessment Tool	Assessment Time	Final Sample Restriction	Final Sample Size at 12 months (Retention, %)
Misuse (Past-3-month)	POMAQ	• Baseline • 3 months • 6 months • 9 months • 12 months	• No outcome at baseline assessment • Completed minimum one follow-up (3-, 6-, 9-, or 12-month) assessment	N=1,807 (81%)
Abuse (Past-3-month)				N=2,062 (93%)
OUD (Past-12-month)	PRISM-5-Op	• Baseline • 12 months	• No outcome at baseline assessment • Completed 12-month assessment	N=1,952 (88%)

- Retention rates at 12 months were high: Ranged from 81% to 93%
- Loss-to-follow-up is unlikely to have a substantial impact on outcome estimates and risk factor analyses

Abbreviations: OUD, opioid use disorders; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Health Disorders

Considerations for Risk Factor Analysis (1)

Strengths

- Examined comprehensive sets of potential risk factors
- Various modeling approaches (unadjusted, demographically adjusted, and fully adjusted) were conducted

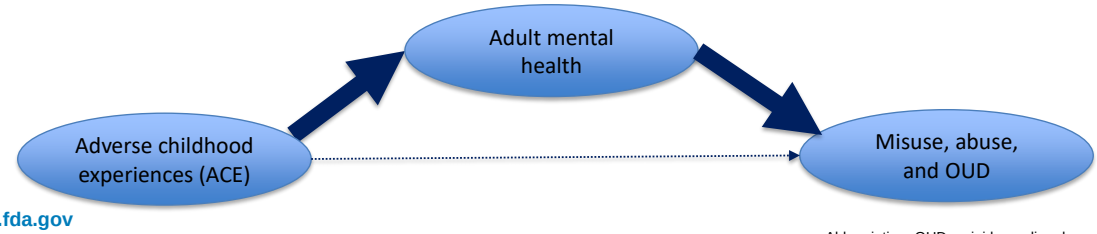
Limitations and Considerations

- Statistical power analysis: Power to detect true risk factors could be insufficient for
  - Outcomes with low prevalence/incidence (e.g., OUD [opioid use disorder])
  - Risk factors with small sample sizes (e.g., morphine for misuse)
- No multiplicity adjustment was considered due to the exploratory nature of the risk factor analysis

Considerations for Risk Factor Analysis (2)

Additional Considerations

- FDA focused on fully adjusted results for the purpose of risk factor identification; some cautions are warranted
  - Fully adjusted analyses included many variables ➔ reduced power and precision
  - Final risk factors selected by statistical cutpoints (not literature- nor causal diagram-based) ➔ exclusion of important risk factors and/or inclusion of mediators



Abbreviation: OUD, opioid use disorders

Considerations for Risk Factor Analysis (3)

Summary and Strategy

- Some true relationships may have been missed (low power, data-driven approach)
- Some observed significant results could be due to chance (multiplicity)
- FDA's interpretation of the findings considered:
  - Direction, strength, and consistency of observed associations
  - Regulatory interest (e.g., OA-related factors)
  - Findings from other studies

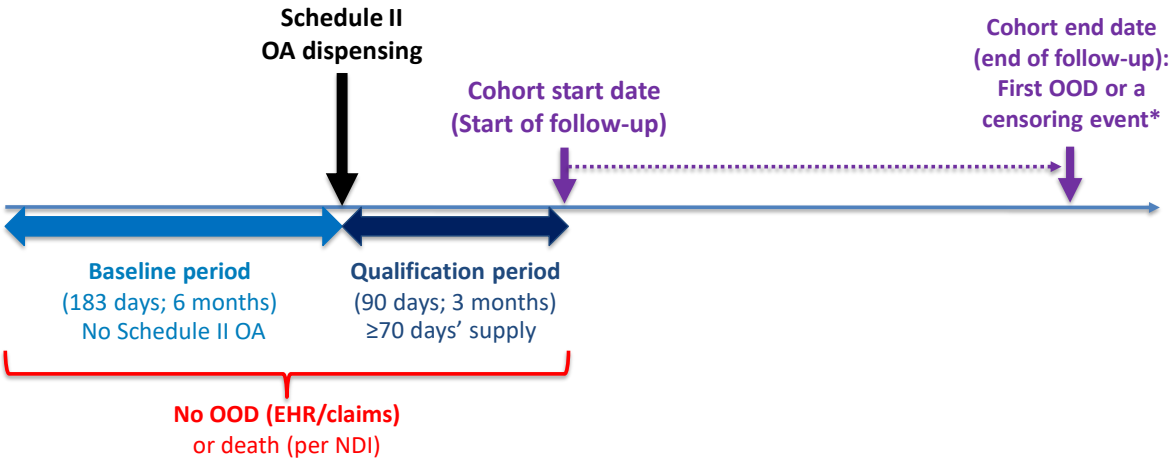
PMR Study 3033-2

PMR Study 3033-2 Design Overview

PMR Study	3033-2 Retrospective Cohort
Goal	Estimate incidence of and identify risk factors for opioid-involved overdose or opioid overdose-related death (OOD)
Population	Patients with new long-term Schedule II OA use
Data sources	• EHR, claims, National Death Index (NDI) • 4 sites: Medicaid from State of Tennessee (VUMC) Non-profit managed care system (KPNW) Commercial insurance databases (HealthCore and Optum)
Outcomes	Algorithm-identified OOD with linkage to NDI
Study period	January 2006 to December 2016
Follow-up	5-years for primary analysis

Abbreviations: KPNW, Kaiser Permanente Northwest; VUMC, Vanderbilt University Medical Center

Key Eligibility: OOD Exclusion



*Censoring events included: administrative end date, start date of a nonhospital institutional stay, the day preceding the 80th birthday, date of death
Abbreviations: NDI, national death index; OA, opioid analgesic; OOD, opioid-involved overdose or opioid overdose-related death; S2, Schedule II

PMR 3033-2: Statistical Analysis

PMR Study	3033-2 Retrospective Cohort
Primary outcome measure	• Cumulative incidence estimated by Kaplan-Meier curve • Incidence rate } By site, and overall
	Risk Factor Analysis
Model	Cox regression; Hazard Ratio (HR)
Potential risk factors	1. Sociodemographic 2. OA-related (dose, formulation, opioid-moiety) 3. SUD history 4. Health- and pain-related 5. Mental-health and social factors } Coded data from EHR & claims

Risk factor analyses	• Unadjusted
	• Demographically adjusted (age, sex, calendar era, and U.S. Census region)
	• Fully adjusted
	  • Included all factors then conducted stepwise selection
	  • Age, sex, and OA formulation (ER/LA vs. IR/SA) were forced in
	• **Meta-analysis** (of four study sites)

Abbreviations: EHR, electronic health records; ER/LA, extended-related long-acting; IR/SA, immediate-release short-acting; OA, opioid analgesic; U.S., United States

Statistical Analysis: Exploratory Switch/Add Analysis

PMR Study	3033-2 Retrospective Cohort
Population (subgroup)	Patients dispensed an IR/SA OA during the qualification period and then either switched to or added ER/LA or a new IR/SA OA medication (**ER/LA switch/add patients** vs. **IR/SA switch/add patients**)
Goal	To examine risk of OOD associated with switching to or adding an ER/LA OA (**ER/LA switch/add patients)** compared to switching to or adding a new IR/SA OA (**IR/SA switch/add patients)**
Covariate imbalances	• Two groups differed with respect to potential risk factors around the time of switch/add event ➔ Propensity score weighting was conducted • All risk factors were balanced after weighting (standardized mean difference <0.2)
Final analysis model	Cox model with a single, binary indicator for **ER/LA switch/add patients** vs. **IR/SA switch/add patients** (reference)

Abbreviations: ER/LA, extended-related long-acting; IR/SA, immediate-release short-acting; OA, opioid analgesic

Key Considerations for PMR 3033-2

1. The ICD code-based algorithm for identification of OOD
2. Cohort retention
3. Risk factor analysis
4. Site heterogeneity and generalizability

PMR 3033-2: The ICD Code-Based Algorithm (1)

Initial Development of the OOD Algorithm

- In PMR 3033-6, using patients with an elevated risk of overdose at KPNW site

Strengths

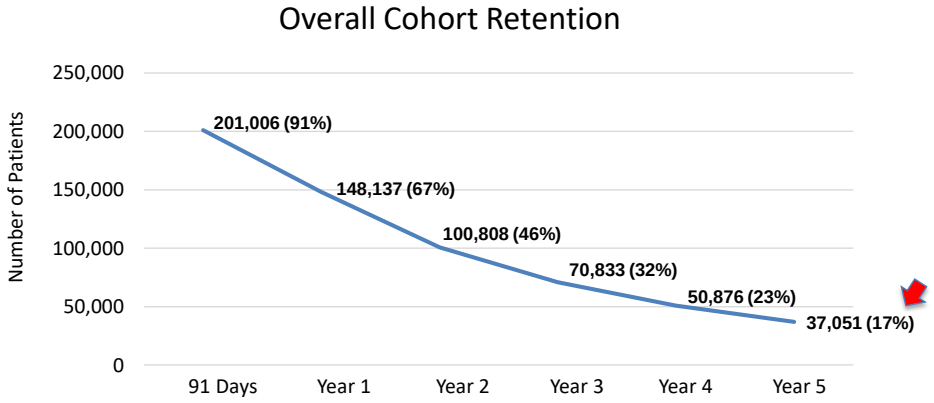
- Validation in PMR 3033-6: high performance (i.e., high sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV])
- Validated across different settings (in both PMR 3033-6 and PMR 3033-2)
- Linkage to the National Death Index (NDI)

PMR 3033-2: The ICD Code-Based Algorithm (2)

Limitations and Considerations

- Relying on medical documentation:
  - OOD events must come to the attention of a healthcare professional
  - Some fatal OOD events may have not been recorded as such by death certifier
- Focusing on **incident OOD** among **patients with new long-term OA use who had no OOD for at least 9 months** (baseline + qualification periods) ➔ Limits generalizability of findings
  - Study population likely at lower risk of OOD than general population initiating new OA
  - Follow-up censored at the first OOD event ➔ subsequent OOD including a fatal overdose following a non-fatal overdose not captured
- We focused on overall OOD estimates because of poor performance of the intentionality algorithm (e.g., sensitivity as low as 45% in PMR 3033-6 and 51% in PMR 3033-2)

PMR 3033-2: Cohort Retention (1)



Source: Adapted from Table 18 in the FDA briefing document. Original sources include Site Final Reports Tables 5 and 7 and the Whiscon Report Tables 7-16 and 7-17

PMR 3033-2: Cohort Retention (2)

Observation: About 17% remained at the end of the 5 years

Considerations:

- Loss-to-follow-up (LTFU) was expected given the longitudinal nature of study and health insurance turnover
- Primary outcome measures accounted for LTFU:
  - Cumulative incidence: The Kaplan-Meier estimate considers only patients at risk, over time
  - Incidence rate: person-time denominator reflects actual time patients are at risk
- Bias (in the incidence OOD estimates and risk factor analysis results) may arise if patients who were LTFU had systematically different risk of OOD than those who remained in the cohort

PMR 3033-2: Additional Considerations for Risk Factor Analysis

Recap: Goal - Exploratory

- To identify factors associated with increased or decreased risk of opioid-related outcomes
- Not designed to:
  - Test specific hypotheses (e.g., a factor increases/decreases the risk)
  - Evaluate pre-specified causal relationships

Additional Consideration in PMR 3033-2

- Switch/add analysis
  - Exploratory in nature: Added after recruitment challenges necessitating the addition of the LtOT cohort in PMR 3033-1 and a similar expansion to PMR 3033-2
  - Did not adjust for changes in dose that occurred with the switch/add event

PMR 3033-2: Site Heterogeneity and Generalizability (1)

- Inclusion of multiple sites in various care settings was intentional to improve generalizability. Some level of heterogeneity was expected.
- However, substantial heterogeneity was observed; mainly due to a small number of sites (n=4) with Medicaid site being notably different than the others:
  - Limited interpretability of the overall incidence estimates
  - FDA focused on site-specific OOD estimates

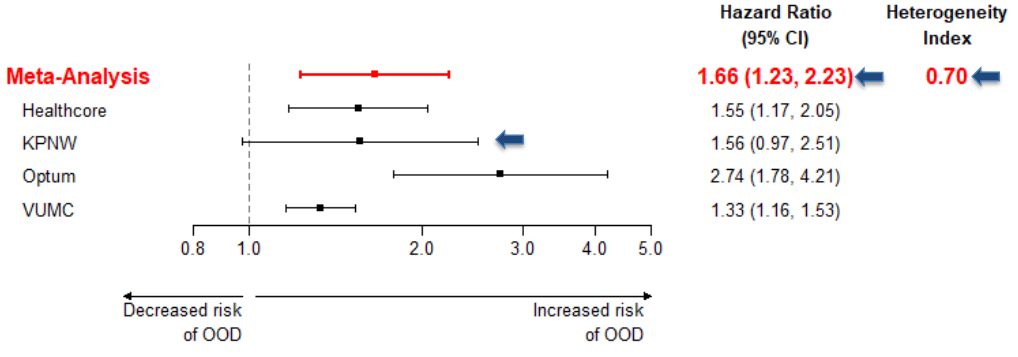
PMR 3033-2: Site Heterogeneity and Generalizability (2)

Impact on Meta-Analysis

- Substantial site heterogeneity also complicated interpretation of meta-analysis results
  - Interpretation of results with substantial heterogeneity warrants caution
  - Still, some results with substantial heterogeneity remain meaningful, particularly when the direction of associations is consistent across sites

PMR 3033-2: Site Heterogeneity and Generalizability (3)

Diagnosis of Alcohol Use Disorder



Other similar examples: lower OA dose category, antidepressants, benzodiazepines, and diagnosis of psychosis

Abbreviations: CI, confidence interval; KPNW, Kaiser Permanente Northwest; OOD, opioid-involved overdose or opioid overdose-related death; VUMC, Vanderbilt University Medical Center

Concluding Remarks

Concluding Remarks

- During the development and refinement of the PMR studies, competing priorities influenced the designs and methods of choice
- The findings from these PMR studies must be interpreted in light of the key methodological and statistical considerations discussed

U.S. FOOD & DRUG ADMINISTRATION

Key Study Findings and Interpretation of Extended-Release/Long-Acting Opioid Analgesic Postmarketing Requirement Studies 3033-1 and 3033-2

May 5, 2025
Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM)
and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

Cynthia Kornegay, PhD
Epidemiologist
Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Outline

- **Postmarketing Requirement (PMR) 3033-1**
  - Primary Outcome Definitions
  - Findings, Considerations, Interpretation:
    - Characteristics of Study Populations
    - Incident and Prevalent Misuse, Abuse, and Opioid Use Disorder (OUD)
    - Associations Between Selected Potential Risk Factors and Misuse, Abuse, and OUD
- **PMR 3033-2**
  - Findings, Considerations, Interpretation:
    - Characteristics of Study Populations
    - Incident Opioid-Involved Overdose or Opioid Overdose-Related Death (OOD)
    - Associations Between Selected Potential Risk Factors and Incident OOD
- **Overall Summary, Interpretation, and Concluding Remarks**

PMR 3033-1

PMR 3033-1 Studies: Primary Outcome Definitions

Outcome (Measurement Tool)	Definition
Misuse (POMAQ)	Intentional use of a drug for a **therapeutic purpose** inappropriately **outside label directions** or **in a way other than prescribed or directed by a health care practitioner**.
Abuse (POMAQ)	Intentional use of a drug for a **non-therapeutic purpose**, repeatedly or sporadically, for the purpose of **achieving a positive psychological or physical effect**.
Moderate-to-Severe Pain-Adjusted DSM-5-OUD (PRISM-5-Op)	Patients **with ≥4 pain-adjusted DSM-5 criteria for OUD related to prescription OA use, *or* ≥2 DSM-5 criteria for OUD related to heroin**. Withdrawal and tolerance criteria considered positive only when OAs were taken other than as prescribed.

Abbreviations: DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; OA, opioid analgesic; OUD, opioid use disorder; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Health Disorders, DSM-5, Opioid Version

Definitions: Pain-Adjusted and Standard DSM-5-OUD

- PRISM-5-Op developed to add information needed to assess OUD in patients on long-term OA therapy

Substance Use Disorder Criteria	Pain-Adjusted DSM-5-OUD (Primary Outcome)	DSM-5-OUD
Tolerance[1]	Positive only if this occurs when opioids are taken **other than as prescribed**	Positive only if this occurs when opioids are taken **other than as prescribed**
Withdrawal, or use to avoid withdrawal[1]		
Persistent desire or repeated attempts to quit/cut down	Positive only if repeated unsuccessful ***attempts*** were made to quit or cut down	Positive if there is a persistent desire even without attempts to quit or cut down
Use in physically hazardous situations	Positive only if this occurs for a ***nonpain[2] reason***	Positive **regardless of reason**
Social/interpersonal problems due to use		
Neglected major roles to use		
Used larger amounts/longer		
Much time spent using		
Continued use despite physical or psychological problems		
Activities given up to use		
Craving		

[1] The DSM-5 recommends not diagnosing prescription OUD in individuals using opioids as prescribed when the only criteria met are tolerance and/or withdrawal.
[2] Nonpain reasons include: to feel high, to feel less depressed/nervous/angry, to help sleep (other than pain relief), to prevent or treat withdrawal, to feel relaxed or mellow, because you saw something that reminded you of the medication
Abbreviations: DSM, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; OA, opioid analgesic; OUD, opioid use disorder; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Health Disorders, DSM-5, Opioid Version

Outcome Validation: POMAQ and PRISM-5-Op

- **POMAQ validated in PMR 3033-3 and 3033-4**
  - PMRs 3033-3 and 3033-4: acceptable face validity, content validity and reproducibility
- **PRISM-5-Op validated in PMR 3033-5**
  - Evidence that changes made to PRISM-5 for patients on long-term OA therapy did not compromise validity
  - Several different metrics: test-retest reliability, factor analysis, expert review, associations between the OUD measures and selected external validators
- **FDA concurred the POMAQ and PRISM-5-Op were appropriate measurement tools for use in PMR 3033-1**
  - Requested estimates using both pain-adjusted and non-pain-adjusted DSM-5-OUD measures

Selected Demographic, Mental Health, and SUD Characteristics of Study Populations in PMR 3033-1

	Prospective ER/LA Cohort[1] (N=978)	Prospective LtOT Cohort[1] (N=1,244)	Cross-Sectional (N=1,212)
Age group			
18-49 years	24.1%	27.8%	20.3%
50+ years	75.9%	72.2%	79.7%
Sex = female	56.9%	59.4%	57.3%
MDD (past year)	15.1%	12.8%	13.9%
MDD (prior to past year)	25.6%	20.7%	23.1%
GAD (past year)	21.9%	23.6%	26.0%
PTSD (past year)	14.7%	12.5%	15.4%
Borderline personality disorder (past year)	8.7%	8.6%	7.3%
4+ ACEs	37.0%	36.5%	37.8%
Antidepressant use (past year)	60.9%	49.5%	62.0%
Elixhauser Comorbidity Index ≥2	80.4%	75.8%	78.2%
Nonopioid/non-nicotine SUD (past year)	6.5%	8.3%	4.7%
OUD (past year)	3.1%	1.6%	Not assessed

Source: Tables 12 and 29 of the FDA Briefing Document.
[1]Measured at baseline.
Abbreviations: ACE, adverse childhood experience; ER/LA, extended-release/long-acting; GAD, generalized anxiety disorder; MDD, major depressive disorder; PTSD, posttraumatic stress disorder; SUD, substance use disorder

Selected OA-Related Characteristics of Study Populations in PMR 3033-1

	Prospective ER/LA Cohort[1] (N=978)	Prospective LtOT Cohort[1] (N=1,244)	Cross-Sectional (N=1,212)[2]
Predominant Formulation[3]			
ER/LA	39.6%	2.2%	66.2%
IR/SA	60.4%	97.8%	33.8%
Predominant Opioid Moiety[3]			
Oxycodone	27.5%	34.6%	27.6%
Morphine	26.5%	2.0%	36.7%
Hydrocodone	19.4%	57.8%	10.2%
Average Daily OA Dose at Baseline			
<50 MMEs	46.2%	86.1%	20.5%
50-89 MMEs	32.2%	10.3%	27.1%
90-119 MMEs	10.1%	1.9%	16.2%
120+ MMEs	11.2%	1.4%	36.3%

Source: Tables 12 and 29 of the FDA Briefing Document.
[1] Represents use during a 90-day period within six months of the patient's baseline interview.
[2] Represents use during the 12-month period prior to the patient's study interview.
[3] List of opioid moieties is not comprehensive. Predominance based on opioid with greatest total day's supply or most prescriptions if there was a tie.
Abbreviations: ER/LA, extended-release/long-acting; IR/SA, immediate-release/short-acting; MME, morphine milligram equivalent; OA, opioid analgesic

PMR 3033-1 Findings: Incident and Prevalent Misuse, Abuse, and OUD

PMR 3033-1 Studies: Incidence and Prevalence of Misuse, Abuse, and OUD

	Opioid Misuse[1] % (95% CI)	Opioid Abuse[1] % (95% CI)	Moderate-to-Severe OUD[2,3] % (95% CI)	
			Pain-adjusted DSM-5-OUD[4]	DSM-5-OUD
Prospective ER/LA Cohort: 12-month Incidence	22.8 (21.6, 24.0)	9.4 (7.7, 11.6)	1.4 (0.9, 2.3)	5.8 (4.5, 7.3)
Prospective LtOT Cohort: 12-month Incidence	21.6 (18.3, 25.5)	8.6 (7.4, 10.0)	1.6 (0.9, 2.9)	3.4 (2.3, 5.1)
Cross-Sectional Study: Prevalence	14.6 (12.6, 17.0)	6.0 (4.8, 7.6)	2.7 (1.8, 4.0)	6.3 (4.3, 9.1)

Source: Tables 8 and 13 in the FDA Briefing Document.
[1]12-month misuse and abuse incidence was calculated using the past-3-month measure, as assessed at 3, 6, 9, and 12 months from baseline (prospective study). Misuse and abuse prevalence was measured using the past-3-month measure at the single interview (cross-sectional study).
[2]OUD is past-12-months for both studies (measured at 12 months from baseline in the prospective study and the single interview in the cross-sectional study).
[3]There were 0 patients in the prospective ER/LA cohort, 3 patients in the prospective LtOT cohort, and 2 patients in the cross-sectional study with heroin use disorder.
[4]Primary OUD definition in PMR 3033-1.
Abbreviations: CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders; LtOT, long-term opioid therapy; OUD, opioid use disorder; PMR, postmarketing requirement

Summary and Interpretation of Misuse, Abuse, and OUD Estimates

- Misuse, abuse, and OUD estimates from these studies fall within range of values reported in literature:
  - E.g., Vowles (2015)[1] meta-analysis
    - Misuse prevalence 2% to 56% (mean 24%)
    - Abuse prevalence 8% (from a single study)
    - Addiction prevalence 0.7% to 23% (mean 9%)
- Wide range of published estimates may be due to varied study populations, outcome definitions and ascertainment, and time periods
- Estimates relevant for population of patients starting or continuing *long-term* OA therapy; does not inform risks in patients with shorter periods of use

[1] Vowles, KE, ML McEntee, PS Julnes, T Frohe, JP Ney, and DN van der Goes, 2015, Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis, Pain, 156(4):569-576.

Additional Considerations for OUD Measurement

- Estimates using the **pain-adjusted DSM-5-OUD** definition[1] were substantially **lower** than those using the standard **DSM-5-OUD** definition
  - Pain-adjusted criteria are narrower (less sensitive, more specific)
- Both could still misclassify OUD, e.g.,
  - Pain-adjusted DSM-5-OUD criteria could potentially under-diagnose OUD if patients used OAs to manage pain associated with withdrawal in the setting of a use disorder
  - Standard DSM-5-OUD criteria could over-diagnose OUD if the patient had continued use of OAs for pain despite physical problems or if attempts to taper/discontinue OAs were unsuccessful due to uncontrolled pain
- Findings highlight the complexity of identifying OUD in patients using OAs long-term for pain
- Will be asking the committee members to discuss the OUD definitions and how they affect the interpretation of the OUD estimates

[1] The pain-adjusted DSM-5-OUD definition was the primary OUD definition in PMR 3033-1.

PMR 3033-1 Findings: Associations Between Selected Potential Risk Factors and Misuse, Abuse, and OUD

Strongest and Most Consistent Risk Factors

Prospective PMR 3033-1	Incident Opioid Misuse		Incident Opioid Abuse		Incident Moderate-to-Severe Pain-Adjusted DSM-5-OUD	
Potential risk factors (yes vs. no, baseline)	ER/LA Cohort	LtOT Cohort	ER/LA Cohort	LtOT Cohort	ER/LA Cohort	LtOT Cohort
	Fully Adjusted ORs (95% CI)		Fully Adjusted ORs (95% CI)		Fully Adjusted ORs (95% CI)	
Non-opioid/non-nicotine SUD (past year)	**2.7 (1.1, 6.7)**	**3.4 (2.3, 5.0)**	**5.5 (2.0, 15.6)**	**2.3 (1.5, 3.5)**	N/I	2.4 (0.5, 11.2)
Non-opioid/non-nicotine SUD (prior to past year)	1.6 (1.0, 2.7)	N/I	1.0 (0.5, 1.9)	1.2 (0.7, 2.0)	N/I	**9.8 (3.1, 30.8)**
POMAQ-classified opioid misuse	Not applicable	Not applicable	**3.0 (1.8, 5.1)**	**2.2 (1.2, 3.8)**	3.4 (0.7, 16.8)	1.9 (0.6, 5.8)
POMAQ-classified opioid abuse	1.3 (0.7, 2.4)	**3.6 (2.3, 5.6)**	Not applicable	Not applicable	N/I	**5.4 (2.3, 12.9)**
OUD-P[1] (past year)	N/I	1.1 (0.3, 3.9)	0.6 (0.1, 4.9)	**5.2 (1.9, 14.8)**	Not applicable	Not applicable

Source: Table 32 in the FDA Briefing Document.
Notes: Fully adjusted models include demographic factors plus other risk factors significantly associated with the outcome in unadjusted analyses. N/I indicates not included in model because these criteria were not met. Statistically significant values ($p<0.05$) are in bold.
[1] Pain-adjusted OUD involving prescription opioids.
Abbreviations: CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ER/LA, extended-release/long-acting; LtOT, long-term opioid therapy; N/I, not included in model; OR, odds ratio; OUD, opioid use disorder; OUD-P, opioid use disorder due to prescription drug use; PMR, postmarketing requirement; SUD, substance use disorder

OA-Related Risk Factors: Prospective Study

Prospective PMR 3033-1	Incident Opioid Misuse		Incident Opioid Abuse		Incident Moderate-to-Severe Pain-Adjusted DSM-5-OUD	
Potential risk factors (measured at baseline)	**ER/LA Cohort**	**LtOT Cohort**	**ER/LA Cohort**	**LtOT Cohort**	**ER/LA Cohort**	**LtOT Cohort**
	Fully Adjusted ORs (95% CI)		**Fully Adjusted ORs (95% CI)**		**Fully Adjusted ORs (95% CI)**	
Predominant OA formulation (ER/LA vs. IR/SA)	1.3 (0.7, 2.2)	N/I	1.3 (0.7, 2.4)	N/I	N/I	N/I
Use of an ADF OA (any vs. none)	N/I	N/I	N/I	N/I	N/I	N/I
Average daily dose at baseline (MME)						
<50	Ref	Ref	Ref	Ref	Ref	Ref
50-89	1.2 (0.8, 1.7)	N/I	N/I	1.2 (0.6, 2.6)	N/I	N/I
90-119	**1.8 (1.0, 3.2)**	N/I	N/I	**2.7 (1.3, 5.6)**	N/I	N/I
≥120	**2.4 (1.2, 4.5)**	N/I	N/I	1.9 (0.2, 15.5)	N/I	N/I
Predominant opioid moiety						
Oxycodone	Ref	Ref	Ref	Ref	Ref	Ref
Hydromorphone	1.4 (0.7, 2.5)	*	**6.8 (3.3, 14.0)**	**6.9 (2.7, 17.6)**	*	*
Hydrocodone	1.1 (0.7, 1.9)	1.2 (0.9, 1.5)	1.8 (0.9, 3.5)	1.5 (1.0, 2.4)	*	2.4 (0.9, 6.4)

Source: Table 32 in the FDA Briefing Document.
* Contained two or fewer events for the given outcome.
Notes: Fully adjusted models include demographic factors plus other risk factors significantly associated with the outcome in unadjusted analyses. N/I indicates not included in model because these criteria were not met. Statistically significant values (p<0.05) are in bold.
Abbreviations: ADF, abuse-deterrent opioid formulation; CI, confidence interval; DSM-5; Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ER/LA, extended-release/long-acting; LtOT, long-term opioid therapy; MME, morphine milligram equivalent; N/I, not included in model; OR, odds ratio; OUD, opioid use disorder; PMR, postmarketing requirement; Ref, reference

OA-Related Risk Factors: Cross-Sectional Study

Cross-sectional PMR 3033-1	Prevalent Opioid Misuse	Prevalent Opioid Abuse	Prevalent Moderate-to-Severe Pain-Adjusted DSM-5 OUD
	Fully Adjusted ORs (95% CI)	**Fully Adjusted ORs (95% CI)**	**Fully Adjusted ORs (95% CI)**
Predominant OA formulation (ER/LA vs. IR/SA)	**0.5 (0.4, 0.7)**	N/I	N/I
Use of an ADF OA (any vs. none)	**0.5 (0.3, 0.8)**	**0.4 (0.3, 0.6)**	N/I
Average daily dose of OAs (MME)			
<50 MME	Ref	Ref	Ref
50-89 MME	N/I	N/I	0.6 (0.2, 1.5)
90-119 MME	N/I	N/I	0.5 (0.2, 1.6)
≥120 MME	N/I	N/I	1.2 (0.4, 3.6)
Predominant opioid moiety			
Oxycodone	Ref	Ref	Ref
Morphine	0.8 (0.4, 1.5)	0.7 (0.3, 1.9)	0.3 (0.1, 1.0)
Hydrocodone	0.6 (0.3, 1.2)	1.5 (0.7, 3.4)	*

Source: Tables 34 (misuse), 35 (abuse), and 36 (OUD) in the FDA Briefing Document.
* Contained two or fewer events for the given outcome.
Notes: Fully adjusted models include demographic factors plus other risk factors significantly associated with the outcome in unadjusted analyses. N/I indicates not included in model because these criteria were not met. Statistically significant values (p<0.05) are in bold.
Abbreviations: ADF, abuse-deterrent opioid formulation; CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ER/LA, extended-release/long-acting; IR/SA, immediate-release/short-acting; N/I, not included in model; OA, opioid analgesic; OR, odds ratio; OUD, opioid use disorder; PMR, postmarketing requirement; Ref, reference

Examples of Differences in Results: Demographically vs. Fully Adjusted Models

Prospective PMR 3033-1	Incident Opioid Misuse		Incident Opioid Abuse		Incident Moderate-to-Severe Pain-Adjusted DSM-5-OUD	
Baseline Risk Factors (yes vs. no)	**ER/LA Cohort**	**LtOT Cohort**	**ER/LA Cohort**	**LtOT Cohort**	**ER/LA Cohort**	**LtOT Cohort**
	Demographically Adjusted ORs (95% CI)		**Demographically Adjusted ORs (95% CI)**		**Demographically Adjusted ORs (95% CI)**	
MDD in past year	1.4 (1.0, 2.0)	1.0 (0.6, 1.9)	1.7 (0.9, 3.2)	**2.0 (1.3, 2.9)**	2.8 (0.9, 8.8)	0.9 (0.3, 3.4)
GAD	**1.9 (1.2, 3.1)**	1.4 (1.0, 2.0)	2.3 (0.9, 8.8)	1.6 (0.9, 2.7)	Not estimable	**3.0 (1.2, 8.0)**
PTSD	**1.5 (1.0, 2.2)**	**2.4 (1.6, 3.4)**	**2.9 (2.4, 3.5)**	**1.8 (1.0, 3.3)**	1.8 (0.9, 3.7)	**4.5 (2.1, 9.5)**
ACE (4+ vs. 0)	**1.9 (1.4, 2.8)**	1.5 (0.9, 2.3)	**3.1 (1.8, 5.1)**	**2.2 (1.4, 3.4)**	1.9 (0.2, 15.9)	Not estimable
	Fully Adjusted ORs (95% CI)		**Fully Adjusted ORs (95% CI)**		**Fully Adjusted ORs (95% CI)**	
MDD in past year	N/I	N/I	N/I	0.8 (0.5, 1.3)	2.6 (1.0, 6.8)	N/I
GAD	1.1 (0.5, 2.2)	0.8 (0.5, 1.1)	1.3 (0.4, 3.8)	N/I	Not estimable	1.2 (0.3, 5.0)
PTSD	**0.6 (0.4, 0.9)**	**1.6 (1.0, 2.6)**	1.7 (0.7, 4.1)	0.8 (0.4, 2.0)	**1.4 (1.0, 2.0)**	1.4 (0.3, 7.0)
ACE (4+ vs. 0)	1.4 (0.7, 2.5)	1.0 (0.5, 1.9)	**2.3 (1.3, 4.0)**	1.1 (0.7, 2.0)	1.3 (0.1, 21.2)	Not estimable

Source: Tables 31 and 32 in the FDA Briefing Document.
Notes: Demographically adjusted models include age, sex, race, ethnicity, and risk factor under study. Fully adjusted models include demographic factors plus other risk factors significantly associated with the outcome in unadjusted analyses. N/I indicates not included in model because these criteria were not met. Statistically significant values (p<0.05) are in bold.
Abbreviations: CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ER/LA, extended-release/long-acting; LtOT, long-term opioid therapy; N/I, not included in model; OR, odds ratio; OUD, opioid use disorder; PMR, postmarketing requirement; PTSD, posttraumatic stress disorder

Examples of Differences in Results Across Study Designs: Prospective vs. Cross-Sectional

Prospective PMR 3033-1	Incident Opioid Misuse		Incident Opioid Abuse		Incident Moderate-to-Severe Pain-adjusted DSM-5-OUD	
	ER/LA Cohort	**LtOT Cohort**	**ER/LA Cohort**	**LtOT Cohort**	**ER/LA Cohort**	**LtOT Cohort**
	Fully Adjusted OR (95% CI)		**Fully Adjusted OR (95% CI)**		**Fully Adjusted OR (95% CI)**	
Male (ref: Female)	1.4 (0.9, 2.1)	1.0 (0.6, 1.7)	1.6 (1.0, 2.7)	1.2 (0.8, 1.8)	1.2 (0.4, 3.5)	1.0 (0.3, 3.2)

Cross-sectional PMR 3033-1	Prevalent Opioid Misuse	Prevalent Opioid Abuse	Prevalent Moderate-to-Severe Pain-adjusted DSM-5-OUD
	Fully Adjusted OR (95% CI)	**Fully Adjusted OR (95% CI)**	**Fully Adjusted OR (95% CI)**
Male (ref: Female)	**1.5 (1.0, 2.3)**	**2.2 (1.1, 4.5)**	**4.1 (1.6, 10.9)**

Source: Tables 32 (prospective study), 34 (cross-sectional study, misuse), 35 (cross-sectional study, abuse), and 36 (cross-sectional study, OUD) in the FDA Briefing Document.
Notes: Fully adjusted models include demographic factors plus other risk factors significantly associated with the outcome in unadjusted analyses. N/I indicates not included in model because these criteria were not met. Statistically significant values (p<0.05) are in bold.
Abbreviations: CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ER/LA, extended-release/long-acting; LtOT, long-term opioid therapy; OR, odds ratio; OUD, opioid use disorder; PMR, postmarketing requirement

Risk Factor Analyses in PMR 3033-1: Overarching Considerations

- Observed associations for individual risk factors varied widely across analyses:
  - Designs (prospective, cross-sectional)
  - Cohorts (ER/LA, LtOT)
  - Models (unadjusted, demographically adjusted, fully adjusted)
  - Outcomes and outcome definitions
- Risk factors included in final model based on statistical cutpoints rather than based on known or suspected causal relationships
  - Over- or under-adjustment possible (e.g., controlling for highly correlated factors or mediators in causal pathway, not including important variables in models)
  - Risk factors included in the fully adjusted models differed by study designs, cohorts, and outcomes
- Many potential risk factors studied
  - Insufficient statistical power for some associations
  - Opportunity for associations due to chance

Risk Factor Analyses in PMR 3033-1: Main Findings

- **History of a nonopioid/non-nicotine substance use disorder (SUD)** was strongest and most consistent risk factor associated with misuse, abuse, and OUD
  - Substantial proportion of patients starting long-term OA therapy had a history of an SUD either in the past year (~5% to 8%) or prior to the past year (~30%)
- **Higher baseline average daily OA dose** was associated with higher risk of misuse in prospective ER/LA cohort analyses, though not associated with abuse or OUD
  - Not included in all fully adjusted models (e.g., cross-sectional study misuse and abuse models)
  - Small number of OUD outcomes per dose category may have contributed to low power to detect an association
- **Baseline hydromorphone (vs. oxycodone) use** was associated with higher risk of abuse in the prospective study (both cohorts)
  - Opioid moiety generally not associated with outcomes in cross-sectional study

Risk Factor Analyses in PMR 3033-1: Main Findings (Cont.)

- Multiple **mental health and social factors** associated with misuse, abuse, and OUD
  - Primarily in the demographically adjusted models, less in the fully adjusted models
  - Baseline or past mental health conditions and social risk factors (4+ adverse childhood experiences [ACEs]) were common
- **Predominant use of ER/LA (vs. IR/SA) OA** and **use of an ADF (yes vs. no)** were associated with lower risk of misuse in the cross-sectional study but not prospective study
  - Inferences about formulation limited, as *predominant* ER/LA OA use (not *exclusive* ER/LA OA use) was measured, and all patients in cross-sectional study had ≥1 ER/LA OA prescription
  - Unable to establish temporal relationships due to cross-sectional design

Abbreviations: ADF, abuse-deterrent formulation; ER/LA, extended-release,/long-acting; IR/SA, immediate-release/short-acting; MDD, major depressive disorder; PTSD, post-traumatic stress disorder

PMR 3033-2

PMR 3033-2: Selected Demographic, Mental Health, SUD, and Pain Baseline Characteristics

	HealthCore (N=81,782)	KPNW (N=12,202)	Optum (N=54,515)	VUMC (Medicaid) (N=71,932)
Age, years				
18-44	26.6%	23.7%	36.7%	44.1%
45-54	25.3%	22.0%	31.8%	26.3%
55-79	48.1%	54.3%	31.6%	29.7%
Sex (female)	47.0%	51.6%	45.2%	60.4%
Substance use disorder				
OUD	2.3%	3.0%	2.2%	6.1%
Alcohol use disorder	3.8%	9.0%	2.3%	7.7%
Other SUD	3.2%	6.1%	2.1%	12.0%
Mental health disorder[1]				
Depression	21.5%	34.7%	17.5%	37.7%
Anxiety	30.8%	22.1%	15.1%	27.6%
Psychosis	3.7%	4.2%	2.8%	17.9%
Pain diagnosis cluster[1]				
Limb/extremity/joint	59.7%	69.9%	48.9%	58.8%
Back	54.8%	56.1%	50.9%	63.8%

Source: Table 16 in the FDA Briefing Document.
[1] List of mental health disorders and pain diagnosis clusters are not comprehensive.
Abbreviations: KPNW, Kaiser Permanente Northwest; OUD, opioid use disorder; SUD, substance use disorder; PMR, postmarketing requirement; VUMC, Vanderbilt University Medical Center

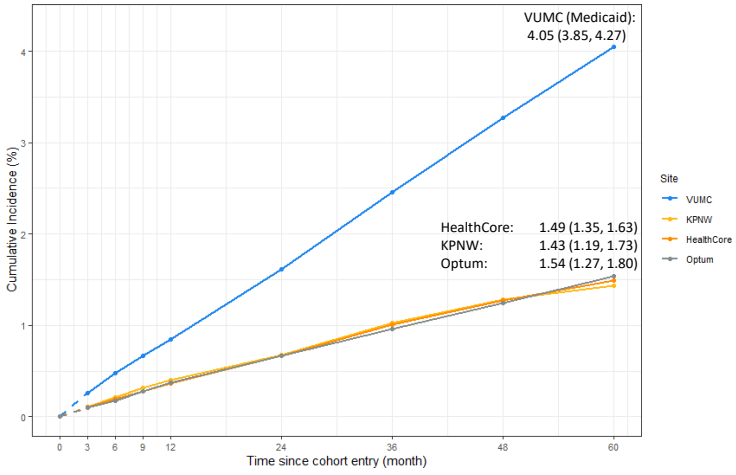
PMR 3033-2: Selected Medication-Related Baseline Characteristics

	HealthCore (N=81,782)	KPNW (N=12,202)	Optum (N=54,515)	VUMC (N=71,932)
Predominant opioid moiety and formulation at cohort start date[1]				
Hydrocodone IR/SA	55.5%	39.8%	55.9%	68.1%
Oxycodone IR/SA	22.4%	32.9%	24.4%	19.0%
QMME (in MMEs)				
<1,500 (≈ 17 MME's per day)	19.5%	33.3%	16.6%	26.3%
1,500 to <2,500	21.1%	18.0%	21.5%	26.5%
2,500 to <3,500	16.0%	14.1%	16.7%	15.1%
3,500 to <6,000	22.0%	18.1%	22.9%	17.8%
≥6,000	21.4%	16.4%	22.3%	14.3%
Median QMME (in MMEs)	3,000	2,400	3,150	2,400
Nonopioid medications[1]				
Antipsychotics	3.6%	4.2%	3.4%	10.7%
Antidepressants	32.4%	39.4%	26.9%	40.6%
Benzodiazepines	39.2%	27.5%	33.0%	22.4%
Gabapentinoids	18.5%	12.9%	19.2%	25.4%

Source: Table 16 in the FDA Briefing Document.
[1] List of predominant opioid moieties and formulations and nonopioid medications are not comprehensive.
Abbreviations: IR/SA, immediate-release/short-acting; KPNW, Kaiser Permanente Northwest; MME, morphine milligram equivalent; PMR, postmarketing requirement; QMME, quarterly/qualifying cumulative MME; VUMC, Vanderbilt University Medical Center

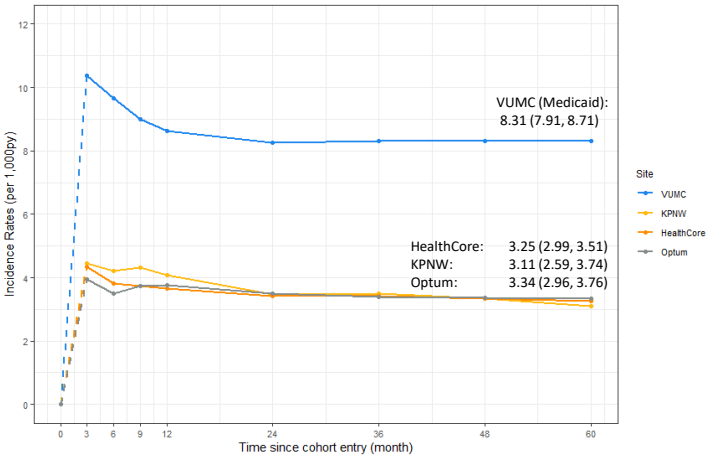
PMR 3033-2 Findings: Incident OOD

PMR 3033-2: Five-Year Cumulative Incidence[1] of OOD by Study Site (%, 95% CI)



Source: FDA-generated figure adapted from Table 43 in the FDA Briefing Document.
[1]The cumulative incidence at month X (%) is the complement of the Kaplan-Meier OOD-free survival preceding month X or on month X measured in the percent (%) scale.
Abbreviations: CI, confidence interval; KPNW, Kaiser Permanente Northwest; OOD, opioid-involved overdose or opioid overdose-related death; PMR, postmarketing requirement; VUMC, Vanderbilt University Medical Center

PMR 3033-2: Five-Year Incidence Rate[1] of OOD by Study Site (Count per 1,000 Person Years, 95% CI)



Source: FDA-generated figure adapted from Table 43 in the FDA Briefing Document.
[1]The incidence rate at month X is the number of total OOD events through month X divided by total person-years through month X multiplied by 1,000.
Abbreviations: CI, confidence interval; KPNW, Kaiser Permanente Northwest; OOD, opioid-involved overdose or opioid overdose-related death; PMR, postmarketing requirement; py, person-years; VUMC, Vanderbilt University Medical Center

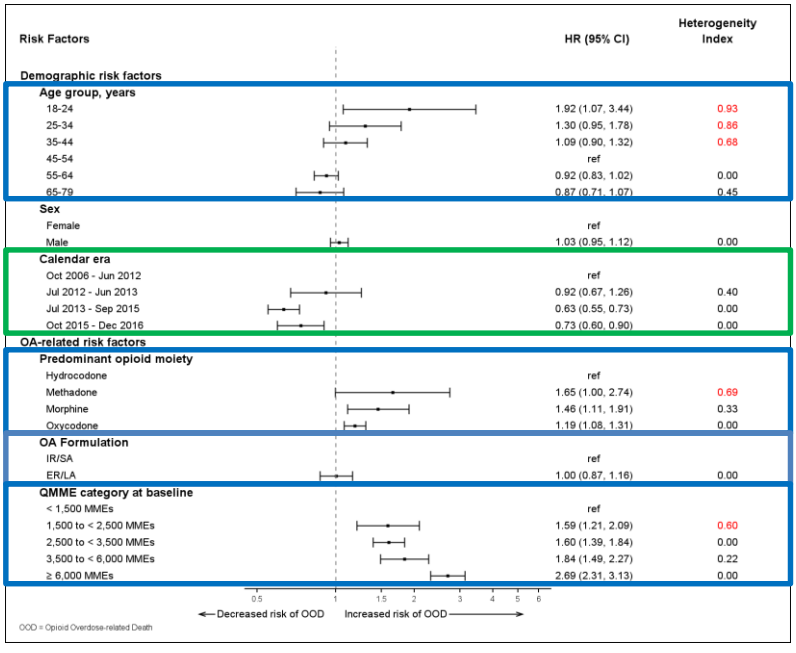
Considerations for Interpreting OOD Estimates

- OOD estimates apply to the specific population of patients starting *long-term* OA therapy; do not inform risks related to shorter-term use
  - Patients with recent opioid overdose were also excluded, thereby selecting for lower risk cohort
- OOD incidence rate highest in the first 90 days of follow-up
  - Possibly due to higher risk during earlier periods of OA therapy, or because patients at highest risk had events earlier and were censored
- Potential attrition bias
- Notable difference between Vanderbilt University Medical Center (VUMC) (Medicaid) estimates and other study sites supports a range of estimates rather than a single "best" estimate
  - VUMC: younger, 2 to 3 times higher baseline OUD prevalence, higher prevalence of alcohol and other SUDs, psychosis compared to other sites; however, total OA dose was not higher
- Estimates were generally within range of published studies in similar populations[1]
  - Direct comparisons difficult due to differences in patient eligibility, study period, follow-up duration, outcome definition, and other parameters

[1] Greene, C, C Kornegay, T Meyer, and G Dal Pan, 2023, Epidemiology: Review of Postmarketing Epidemiologic Studies Assessing Risk Related to OA Duration and Abuse, Addiction, Opioid Use Disorder, Overdose, and Death. TTT # 2023-4352, 2023-4355. Review completed April 10, 2023. Reference ID: 5155228.
Abbreviations: OOD, opioid-involved overdose or opioid overdose-related death

PMR 3033-2 Findings: Associations Between Selected Potential Risk Factors and Incident OOD

PMR 3033-2: Demographic and OA-Related Factors (Meta-Analysis of Fully Adjusted Results)



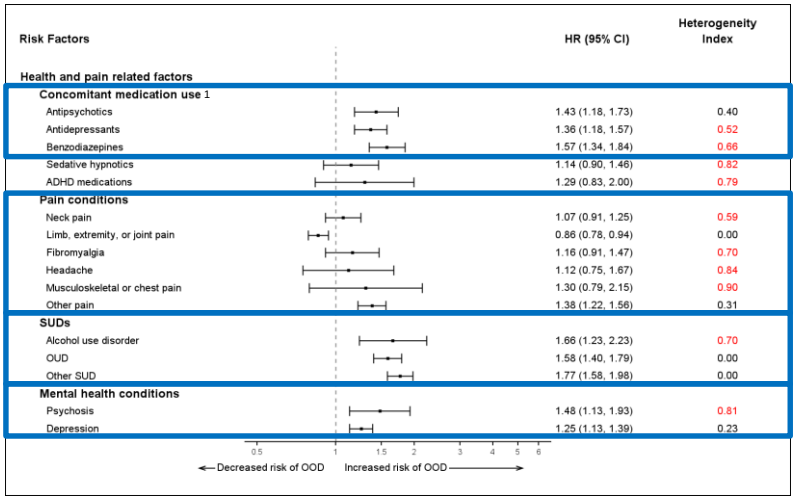
Source: Adapted from Table 19 in the FDA Briefing Document.

Note: OA-related risk factors measured during the 90 days prior to the patient's cohort entry (qualification period). Demographic risk factors assessed at the patient's start date.

Heterogeneity indices $I^2 > 0.50$ (red) indicate substantial differences between sites

Abbreviations: CI, confidence interval; ER/LA, extended-release/long-acting; HR, hazard ratio; IR/SA, immediate-release/short-acting; MME, morphine milligram equivalent; OOD, opioid-involved overdose or opioid overdose-related death; PMR, postmarketing requirement QMME, quarterly or qualifying MME; ref, reference

PMR 3033-2: Concomitant Medication Use, Pain Conditions, SUD History, and Mental Health Conditions (Meta-Analysis of Fully Adjusted Results)



Source: Adapted from Table 19 in the FDA Briefing Document.

Note: Concomitant medications measured during the 90 days prior to the patient's cohort entry (qualification period). Pain conditions, SUDs, and mental health conditions were assessed using the patient's entire available medical history.

Heterogeneity indices $I^2 > 0.50$ (red) indicates substantial differences between sites.

[1]Only VUMC had sufficient gabapentinoid use to include in the final model: HR = 1.30 (1.18, 1.44)

Abbreviations: ADHD, attention deficit hyperactivity disorder; CI, confidence interval; HR, hazard ratio; OUD, opioid use disorder; ref, reference; PMR, postmarketing requirement; SUD, substance use disorder

PMR 3033-2: Switch/Add Analysis Cohort

- Exploratory analysis in patients exclusively on Schedule II IR/SA OA therapy
- Dose measured with DMME (daily MME); median daily MMEs in 90 days immediately preceding or following switch/add event

Included in model

Not included in model

	IR/SA to IR/SA OA	IR/SA to ER/LA OA
Total = 53,257 (100%)	41,685 (78.3%)	11,572 (21.7%)
Pre-switch median dose (DMME)	13.2	24.1
Post-switch median dose (DMME)	7.8	36.9
Median dose change (DMME)	-5.4	+12.8

Source: Table 20 in the FDA Briefing Document.
*Switched to/added a different predominant opioid moiety
Abbreviations: DMME, daily MME; ER/LA, extended-release/long-acting; IR/SA, immediate-release/short-acting; MME, morphine milligram equivalent; OA, opioid analgesic; PMR, postmarketing requirement

PMR 3033-2: Switch/Add Analysis Findings

- Propensity-score adjusted OOD HR (95% CI) in patients who switched to or added an ER/LA OA vs. an IR/SA OA

Site	End of Switch/Add Episode HR (95% CI)	End of Study HR (95% CI)
HealthCore	2.03 (1.09, 3.78)	1.74 (1.26, 2.41)
KPNW	1.35 (0.38, 4.82)	0.91 (0.47, 1.76)
Optum	1.21 (0.52, 2.84)	1.60 (0.99, 2.59)
VUMC	1.50 (0.82, 2.74)	1.17 (0.99, 1.39)
Meta-analysis, I^{2*}	1.59 (1.10, 2.30), I^2 = 0.00	1.35 (1.02, 1.77), I^2 =0.53
NOTE: Model did not adjust for change in dose (DMME)		

Source: Table 21 in the FDA Briefing Document.
*I^2 is a measure of heterogeneity in the meta-analysis. A value > 0.50 indicates high heterogeneity.
Abbreviations: CI, confidence interval; DMME, daily morphine milligram equivalent; ER/LE, extended-release/long-acting; HR, propensity score weighted hazard ratio; IR/SA, immediate-release/short-acting; KPNW, Kaiser Permanente Northwest; VUMC, Vanderbilt University Medical Center

Risk Factor Findings in PMR 3033-2: Overarching Considerations

- Synthesis of 3033-2 risk factor results faces challenges similar to 3033-1
  - Many potential risk factors studied
    - Potential for chance associations
    - Insufficient statistical power
    - Final risk factors were selected based on statistical cutpoints leading to different sets of variables across sites
      - E.g., sedative hypnotic and gabapentinoid use associated with higher OOD risk at VUMC, but not included in final models for other sites
  - Observed associations for individual risk factors often varied widely across:
    - Models (unadjusted, demographically, fully adjusted)
    - Sites (HealthCore, KPNW, Optum, VUMC)

 Abbreviations: OOD, opioid-involved overdose or opioid overdose-related death; PMR, postmarketing requirement; VUMC, Vanderbilt University Medical Center

Risk Factor Analyses in PMR 3033-2: Main Findings

- Factors associated with increased risk of OOD:
  - **A diagnosis of any SUD** (opioid, alcohol, other)
  - **Higher baseline OA dose** (reference: <1,500 QMMEs)
  - Baseline diagnosis of **depression** or **psychosis**
    - An average of 26% of patients had depression and 8% had psychosis at baseline
- Baseline **benzodiazepine, antipsychotic**, and **antidepressant use**
  - Approximately 32% were on benzodiazepines and 34% on antidepressants at baseline
  - Antidepressant category heterogeneous—including some CNS depressants

Abbreviations: CNS, central nervous system; MME, morphine milligram equivalent; OOD, opioid-involved overdose or opioid overdose-related death; OUD, opioid use disorder; PMR, postmarketing required study; PMR, postmarketing requirement; QMME, qualifying or quarterly morphine milligram equivalent; SUD, substance use disorder

Risk Factor Analyses in PMR 3033-2: Switch/Add Analysis

- **Baseline OA formulation (ER/LA vs IR/SA)** not associated with OOD in main analysis in fully adjusted model
- Exploratory switch/add analysis: increased OOD risk in patients who switched to/added an ER/LA OA vs. those who switched to/added an IR/SA OA
  - Dose changes within same IR opioid moiety not considered in the analysis
  - Change in switch/add dose was not included in model
  - Suggests increase in dose may have been a primary driver of increased OOD risk in patients switching to/adding an ER/LA OA
  - Still, cannot rule out contribution of ER/LA formulation itself

Abbreviations: ER/LA, extended-release/long-acting; FDA, IR/SA, immediate-release/short-acting; OA, opioid analgesic; OOD, opioid-involved overdose or opioid overdose-related death; PMR, postmarketing requirement

Overall Summary and Interpretation of Findings From PMR 3033-1 and PMR 3033-2

Key Overarching Considerations

Strengths

- Large, multi-site studies
- Broad geographic and sociodemographic coverage (e.g., some Medicaid, safety-net clinics)
- External expert input guided design
- Prespecified protocols and analysis plans
- Validated outcome measures
- Prospective, longitudinal, patient-reported data on misuse, abuse, OUD collected at pre-specified timepoints
- Linkages allowed capture of fatal overdoses

Limitations

- Not designed to examine risks associated with shorter term, non-prescribed, or changes in OA use over time, including tapering or discontinuation
- Unclear how estimated incidence and prevalence compare to groups without long-term OA use
- Not designed to evaluate outcome interdependency
- Limited generalizability, e.g., 3033-1 recruited heavily from integrated/managed care, captured specific time period within an evolving opioid landscape

PMR 3033-1 Overall Misuse, Abuse, and OUD Incidence Summary and Interpretation

- **Misuse**[1]: 12-month incidence = 21.6% to 22.8%; prevalence = 14.6%
- **Abuse**[1]: 12-month incidence = 8.6% to 9.4%; prevalence = 6.0%
- **Moderate-to-Severe DSM-5-OUD**[2]:
  - **Pain-adjusted**: 12-month incidence = 1.4% to 1.6%; prevalence = 2.7%
  - **Non-pain-adjusted**: 12-month incidence = 3.4% to 5.8%; prevalence = 6.3%
- Estimates are within ranges of results from similar studies reported in literature
- These risks are described qualitatively in *Boxed Warning* and other sections of OA labeling

[1] 12-month misuse and abuse incidence was calculated using the past-3-month measure, as assessed at 3, 6, 9, and 12 months from baseline (prospective study). Prevalence was measured using the past-3-month measure at the single interview (cross-sectional study).
[2] OUD is past-12-months for both studies (measured at 12 months from baseline in the prospective study and the single interview in the cross-sectional study).

PMR 3033-2 Overall OOD Incidence Summary and Interpretation

- Five-year **cumulative incidence: 1.4% to 4.1%**
  - Steady increase over follow-up
- Five-year **incidence rate: 3.1 to 8.3 per 1000 person-years**
  - Started higher, then decreased and stabilized
- Study may underestimate overall OOD risk in patients starting long-term schedule II OA therapy due to cohort exclusions, potential attrition bias, limiting analysis to first OOD event only, and potential for incomplete capture of OOD events
- Poor performance of intentionality codes limited ability to distinguish suicide attempts from other types of overdoses
- OOD estimates are within ranges reported in literature, but direct comparisons are challenging
- These risks are described qualitatively in *Boxed Warning* and other sections of OA labeling

Overall Risk Factor Summary and Interpretation

- Risk factor analyses were exploratory, not designed to examine individual causal relationships
- Large number of variables, models, cohorts, and outcomes
- Strongest and most consistent risk factors align with OA labeling:
  - Personal history of a substance use disorder
  - Higher OA dose and risk of overdose
  - Mental health disorders
  - Use of CNS depressants, e.g., benzodiazepines and antipsychotics[1]
- Other associations were observed, but inconsistently across cohorts and models,[2] e.g., sex, age, opioid moiety, ADF use, comorbidity score, ACEs, gabapentinoid use

1. Antidepressants are not specified in labeling—heterogeneous group of drugs with both CNS depressants and others
2. Some factors, e.g., gabapentinoid use, were not consistently included in fully-adjusted models, but when included showed consistent associations

Concluding Remarks

- These studies provide a range of quantitative estimates for misuse, abuse, OUD, and overdose in specific patient populations with long-term OA use
  - These risks are qualitatively communicated in current OA labeling
- The main risk factor findings generally align with current OA labeling, namely:
  - Individual patient characteristics (e.g., substance use history, mental health conditions) are important considerations when assessing risk
  - If OAs are indicated, it is important to prescribe the lowest dose and for the shortest time needed, with extra caution at dose increases and in patients using other CNS depressants
- These concepts are also included in OA risk evaluation and mitigation strategy (REMS)-compliant continuing education and other educational programs and guidelines
- Despite some important limitations, the ER/LA OA PMR studies add to the body of evidence on risks associated with long-term use of OAs, in particular by incorporating prospectively collected data, validated outcome measures, and database linkages

BACK-UP SLIDES DISPLAYED

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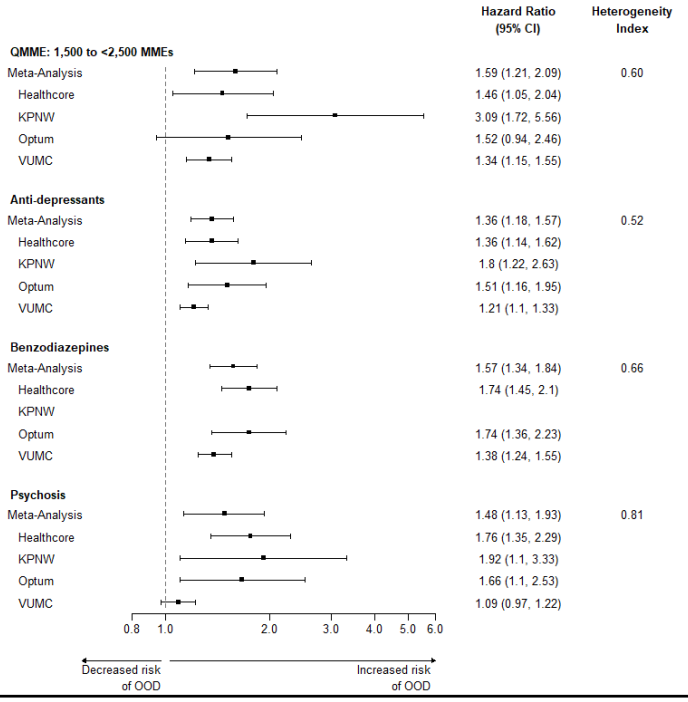
PMR 3033-2: Site Heterogeneity and Meta-Analysis



Abbreviations: CI, confidence interval; KPNW, Kaiser Permanente Northwest; MME, morphine milligram equivalent; OOD, opioid-involved overdose or opioid overdose-related death; QMME, quarterly/qualifying cumulative MMEs; VUMC, Vanderbilt University Medical Center