**Food and Drug Administration**
**Center for Drug Evaluation and Research**
**Final Summary Minutes of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee Meeting**
**May 5, 2025**

**Location:** FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public also had the option to participate via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform.

**Topic:** The Committees discussed the findings of the completed extended-release/long-acting opioid analgesic (ER/LA OA) postmarketing requirements (PMRs) 3033-1 and 3033-2 (link to Release and Reissue letter).

These PMRs are prospective (3033-1) and retrospective (3033-2) epidemiologic studies that examined the serious risks and predictors of misuse, abuse, addiction, and fatal and non-fatal opioid overdose in patients with long-term use of opioid analgesics for management of chronic pain, including patients prescribed ER/LA OAs.

These summary minutes for the 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) of the Food and Drug Administration were approved on June 19, 2025.

I certify that I attended the 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) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Jessica Seo, PharmD, MPH
Acting Designated Federal Officer, DSaRM

/s/
Brian T. Bateman, MD, MSc
Acting Chairperson, DSaRM

**Final Summary Minutes of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee Meeting**
**May 5, 2025**

The Drug Safety and Risk Management Advisory Committee (DSaRM) and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on May 5, 2025, at FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, Maryland. The public also had the option to participate via an online teleconferencing and/or video conferencing platform, and the meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and the Opioid Post Marketing Requirements Consortium (OPC). The meeting was called to order by Brian T. Bateman, MD, MSc, (Acting Chairperson). The conflict of interest statement was read into the record by Jessica Seo, PharmD, MPH (Acting Designated Federal Officer). There were approximately 100 people in attendance in-person and approximately 237 people online. There were 10 Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, approximately ten to twelve weeks following the meeting date.

**Agenda:**

The Committees discussed the findings of the completed extended-release/long-acting opioid analgesic (ER/LA OA) postmarketing requirements (PMRs) 3033-1 and 3033-2 (link to Release and Reissue letter).

These PMRs are prospective (3033-1) and retrospective (3033-2) epidemiologic studies that examined the serious risks and predictors of misuse, abuse, addiction, and fatal and non-fatal opioid overdose in patients with long-term use of opioid analgesics for management of chronic pain, including patients prescribed ER/LA OAs.

**Attendance:**

**Drug Safety and Risk Management Advisory Committee Members Present (Voting)**: Maryann Amirshahi PharmD, MD, MPH, PhD, BCPS, FACMT, FACEP, FASAM, FCP; Michael C. Dejos, PharmD, MBA, BCPS, CHOP, CPPS; James Floyd, MD, MS; Krista F. Huybrechts, MS, PhD; Elizabeth Rebo, PharmD, MBA, CPPS

**Drug Safety and Risk Management Advisory Committee Members Not Present (Voting)**: Sascha Dublin, MD, PhD; John B. Hertig, PharmD, MS, CPPS, FASHP; Vincent Lo Re III, MD, MSCE (*Chairperson*); Mara McAdams DeMarco, MS, PhD;

**Drug Safety and Risk Management Advisory Committee Member Not Present (Non-Voting)**: Ignacio Rodriguez, MD (*Industry Representative*)
**Anesthetic and Analgesic Drug Products Advisory Committee Members Present (Voting)**: Mark C. Bicket, MD, PhD, FASA;

**Anesthetic and Analgesic Drug Products Advisory Committee Members Not Present (Voting):** Maryam Jowza, MD; Maura S. McAuliffe, CRNA, MSN, MSNA, PhD, FAAN; Michael Sprintz, DO, DFASAM

**Anesthetic and Analgesic Drug Products Advisory Committee (Non-Voting)**: Jeffrey B. Reich, MD (*Industry Representative*)

**Temporary Members (Voting)**: Brian T. Bateman, MD, MSc *(Acting Chairperson);* William C. Becker, MD; Carlos Blanco, MD, PhD; David Frank, PhD (*Patient Representative*); Adam J. Gordon, MD, MPH, FACP, DFASAM; Elizabeth Joniak-Grant, PhD *(Patient Representative*)*;* Mary Ellen McCann, MD, MPH (*via video conferencing platform*); Lawrence 'Rick' Phillips, EdD (*Acting Consumer Representative)*; Abigail B. Shoben, PhD

**FDA Participants (Non-Voting):** Gerald Dal Pan, MD, MHS; Jana McAninch, MD, MPH, MS; Tamra Meyer, PhD, MPH; Cynthia Kornegay, PhD; Hana Lee, PhD; Leah Crisafi, MD, FASA; Mark A. Liberatore, PharmD, RAC;

**Acting Designated Federal Officer (Non-Voting)**: Jessica Seo, PharmD, MPH

**Open Public Hearing Speakers Present:** Michael T. Abrams, MPH, PhD (Public Citizen*)*; Andrew Kolodny, MD (Physicians for Responsible Opioid Prescribing); Diana Zuckerman, PhD (National Center for Health Research); Caleb Alexander, MD, MS; Nancy Connolly, MD, MPH; Ravi Gupta, MD, MSHP; Danesh Mazloomdoost, MD (Wellward Medical); Jane C. Ballantyne, MD, FRCA; Gary M. Franklin, MD, MPH (Washington State Dept. of Labor Statistics and Washington Agency Medical Director's Group); Paul Hennessy

***The agenda was as follows:***

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| 8:00 a.m. | Call to Order and Introduction of Committee | **Brian T. Bateman, MD, MSc**<br>Acting Chairperson, AADPAC |
| 8:05 a.m. | Conflict of Interest Statement | **Jessica Seo, PharmD**<br>Designated Federal Officer, DSaRM |
| 8:10 a.m. | FDA Opening Remarks | **Leah Crisafi, MD, FASA**<br>Commander, US Public Health Service<br>Director<br>Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP), Office of Neuroscience<br>Office of New Drugs, CDER, FDA |

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| 8:15 a.m. | Regulatory Background and the Evolving Opioid Landscape | **Jana McAninch, MD, MPH, MS**<br>Associate Director for Public Health Initiatives<br>Office of Surveillance and Epidemiology (OSE)<br>CDER, FDA |
| 8:45 a.m. | **Industry Presentations** | **Opioid PMR Consortium (OPC)** |
| | Opioid PMR Consortium Introduction and PMR Overview | **Alexander M. Walker, MD, DrPH**<br>Adjunct Professor, Epidemiology,<br>Harvard T.H. Chan School of Public Health |
| | Study 3033-1 - Incidence or Prevalence of and Risk Factors for Developing Prescription Opioid Misuse, Abuse or Addiction Among Patients Prescribed Long-term Opioid Therapy | **Bobbi Jo Yarborough, PysD**<br>Senior Investigator,<br>Kaiser Permanente Center for Health Research |
| | Study 3033-2 - Incidence and Prognostic Factors for Opioid-involved Overdose or Opioid Overdose-Related Death (OOD) | **John D. Seeger, PharmD, PsyD**<br>Vice President for Epidemiology,<br>RTI-HS<br>Adjunct Assistant Professor, Epidemiology, Harvard T.H. Chan School of Public Health |
| | Conclusions | **Alexander M. Walker, MD, DrPH** |
| 10:15 a.m. | Clarifying Questions | |
| 10:30 a.m. | **Break** | |
| 10:45 a.m. | **FDA Presentations** | |
| | Key Methodological and Statistical Considerations for ER/LA OA PMR Studies 3033-1 and 3033-2 | **Hana Lee, PhD**<br>Staff Fellow<br>Division of Biometrics VII (DB-VII)<br>Office of Biostatistics (OB)<br>Office of Translational Sciences (OTS), CDER, FDA |
| | Key Study Findings and Interpretation of ER/LA OA PMR Studies 3033-1 and 3033-2 | **Cynthia Kornegay, PhD**<br>Epidemiologist<br>Division of Epidemiology II (DEPI-II)<br>Office of Pharmacovigilance and Epidemiology (OPE)<br>OSE, CDER, FDA |
| 11:55 a.m. | Clarifying Questions | |

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| 12:10 p.m. | **Lunch** | |
| 1:00 p.m. | **Open Public Hearing** | |
| 2:00 p.m. | Charge to the Committee | **Jana McAninch, MD, MPH, MS** |
| 2:05 p.m. | Questions to the Committee/Committee Discussion | |
| 3:30 p.m. | **Break** | |
| 3:45 p.m. | Questions to the Committee/Committee Discussion (cont.) | |
| 5:00 p.m. | **Adjournment** | |

***Questions to the Committee:***

1. **DISCUSSION:** Discuss your interpretation of the estimates of the incidence and prevalence of misuse, abuse, and Opioid Use Disorder (OUD) in patients using Opioid Analgesics (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

   ***Committee Discussion****: In their interpretation of the estimates of the incidence and prevalence of misuse, abuse, and OUD in PMR 3033-1, Committee members were in general agreement that while the study was well-conducted, there were concerns about generalizability and how to interpret/apply the quantitative estimates given the evolving landscape. Most felt the findings reinforced known risks but did not necessarily provide compelling new evidence to change clinical practice or labeling.*

   *In terms of specific study strengths and limitations influencing their interpretation, several panel members commended the rigorous study design with careful patient selection and high retention rate, noting the large sample size and use of patient interviews/self-reported measures. Panelists cited the predominantly White, older, English-speaking sample, as well as exclusion of certain geographic regions as limitations to generalizability of the population studied. One panel member also pointed to the risk assessment occurring at one time point rather than capturing changes over time as a limitation, another panel member noted the selection of patients naive to Schedule II opioids starting long-term therapy narrowed the applicability of the results, and a third noted that conditioning enrollment on long-term use*

*could underestimate potential harms because the patients had to survive without an overdose to be included in the long-term use cohort. One member noted that those who volunteer for studies are fundamentally different from those who don't.*

*With respect to the definitions and measurements of the outcomes in PMR 3033-1, views on the pain-adjusted OUD measure varied, with some panel members expressing concern it may underestimate true OUD rates by excluding problems arising from pain-related opioid use. Several panel members considered standard DSM-5 OUD to be a more clinically relevant definition. Panel members also expressed concern that the definition of misuse in the study may be an overestimation of problematic use of OAs.*

*In commenting on the generalizability and relevance of the findings given the evolving opioid landscape, it was noted the data were collected 5-6 years ago. Several panel members acknowledged the opioid prescribing landscape has changed significantly and the study results may not reflect current prescribing patterns or patient populations. It was also suggested the long-term Schedule II opioid therapy (LtOT) cohort may be more relevant to current practice than the new ER/LA cohort.*

*Regarding consistency of the study findings with other available evidence, many panel members noted that estimates from PMR 3033-1 are generally consistent with ranges reported in published literature and felt the results reinforce known risks of higher doses and longer duration of use. A couple of panel members highlighted that the lack of evidence on long-term effectiveness of OAs remains a key issue.*

*Please see the transcript for details of the Committee's discussion.*

2. **DISCUSSION**: Discuss your interpretation of the estimates of the incidence of fatal and nonfatal overdose 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

***Committee Discussion**: In discussing their interpretation of the estimates of the incidence of fatal and nonfatal overdose in patients using OAs long-term, the Committee members agreed that overall PMR 3033-2 was well-done and provided important insights. Particularly, the inclusion of a large Medicaid population was seen as a strength of the study, while limitations included factors such as loss to follow-up that potentially biased estimates lower, lack of detail on overdose specifics, and a focus only on the first overdose event. In addition,*

*it was noted that the impact of switching to ER/LA opioids was difficult to interpret due to potential confounding by dose changes.*

*In terms of ascertainment of opioid overdose and any potential for bias, one panel member remarked that loss to follow-up likely led to an underestimation of risk, as patients developing OUD may disproportionately lose insurance coverage. There was also a comment that information on intentional vs. unintentional overdoses and involvement of illicit opioids could help better inform providers on future overdose mitigation strategies.*

*With respect to the observed heterogeneity of results across study populations, it was acknowledged significantly higher rates of opioid-related overdose deaths were observed in the Medicaid vs. commercially insured study populations. One panel member noted that regular medical visits appeared to have a protective effect, which may partly explain higher rates of overdose in Medicaid populations who potentially have less access to routine care. Another panel member remarked the difference observed was expected due to a higher prevalence of risk factors in Medicaid populations.*

*Regarding generalizability of findings and relevance to patients currently using OAs, panel members pointed to lack of geographic representativeness. Another panelist cautioned on the generalizability of incidence rates from the Tennessee Medicaid cohort in PMR 3033-2 to other Medicaid populations, as states can vary in their Medicaid policies.*

*The Committee members were in agreement the findings from PMR 3303-2 were generally consistent with other observational studies on overdose incidence rates, although one panel member commented the five-year cumulative incidence of overdose of 4% in the Medicaid population was considered notably high.*

*Please see the transcript for details of the Committee's discussion.*

3. **DISCUSSION:** 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).

    ***Committee Discussion:*** *In discussing the important findings from PMRs 3033-1 and 3033-2, the panel members viewed the risk factor analyses as generating hypotheses rather than providing definitive conclusions. A need for more rigorous statistical approaches was emphasized, as well as further research to clarify the relationships between various factors and opioid-related risks.*

    *In considering the study designs and analytic approaches, panel members commented that the approaches used were outdated and additional analyses using other techniques would be*

*useful. Suggestions for more sophisticated methods like prediction models, machine learning approaches such as super learners, or a priori selection of key risk factors of interest with correction for multiple testing were proposed. Several panel members were in agreement that the exploratory nature of the analysis and lack of a causal framework made interpretation difficult. Gabapentinoid use was discussed for its observed association with increased risk of pain-adjusted OUD, but panelists cautioned against over-interpreting this finding due to potential confounding factors and statistical limitations.*

*In discussing available evidence or clinical experience, it was acknowledged that study results from PMRs 3033-1 and 3033-2 were consistent with previous studies in showing higher opioid dose was associated with higher risk of overdose. The finding that hydromorphone use was associated with an increase in abuse risk compared to oxycodone was seen as notable and worthy of further study.*

*Regarding the study results in relation to dose, it was discussed that the study did not account for dose changes over time or the impact of external factors influencing dosing during the study period, making it difficult to draw conclusions about dose from the data presented. Panel members commented that the relationship between formulation (ER/LA vs IR/SA) and risk of misuse was not clear-cut. Some findings suggested lower misuse with ER/LA OAs compared to IR/SA OAs, but it was proposed that daily dose might be more important than formulation type.*

*There was also a call for more research on the impact of specific opioids, regardless of formulation, due to pharmacological differences.*

*Please see the transcript for details of the Committee's discussion.*

4. **DISCUSSION**: 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?

***Committee Discussion**: The Committee members were in general agreement that while there weren't many truly novel findings from their review of PMRs 3033-1 and 3033-2, there were several important points that the FDA should consider communicating or emphasizing to healthcare providers, patients, and other members of the public. Suggestions included reiterating the lack of data regarding efficacy of long-term use of opioids and further emphasizing that higher doses of opioids are associated with increased risk of adverse effects, with several panel members cautioning against specifying a particular threshold at which risk increases. There was support from several panel members for the current labeling language of "using the lowest effective dose for the shortest possible duration." One panel member voiced support for providing more specific quantitative information about the risks of misuse, abuse, and OUD to help providers with risk communication and informed decision-making.*

*Several Committee members cautioned against specifying maximum MME (morphine milligram equivalent) doses or thresholds, as this could be misused or misinterpreted. The importance of being careful and precise with any label changes was also emphasized to avoid unintended consequences. One panel member also proposed including top-line summary measures for opioid use disorder from PMRs 3033-1 and 3033-2 in the postmarketing study information or educational materials, while another suggested more qualitative information, describing the range of risk estimates. One panel member commented the evidence on significantly elevated risk of adverse outcomes associated with recent substance abuse history was possibly more than what is currently stated in the labeling. A suggestion was made to consider communication about the importance of using opioids as part of a multimodal pain management approach, rather than in isolation.*

*Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 4:25pm ET.