

# United States Senate

September 19, 2023

The Honorable Robert Califf  
Commissioner  
U.S. Food & Drug Administration  
10903 New Hampshire Ave  
Silver Spring, MD 20993-0002

RE: Opioid Postmarketing Requirement Consortium Study 3033-11

Dear Commissioner Califf:

We write to express concern about the use of enriched enrollment randomized withdrawal (EERW) research methods to evaluate extended-release and long-acting opioids. As part of the U.S. Food and Drug Administration's (FDA's) efforts to respond to the opioid and overdose epidemic, it has undertaken a review of the risks associated with extended-release and long-acting opioids to treat chronic pain, including hyperalgesia.<sup>1</sup> This is an essential component of ensuring that patients with chronic pain are adequately treated without exposing them to unnecessary risks of misuse, dependence, and overdose. Unfortunately, as part of this review — and despite the availability of other study methods — the FDA is considering using EERW studies,<sup>2</sup> which risk biasing findings in favor of opioid use and exposing clinical trial participants to opioid dependence and withdrawal. The FDA must continue its efforts to evaluate the risks opioids present and reconsider the use of EERW studies.

In 2021, 17,000 people in the United States died from prescription opioid overdose, representing a 5-fold increase since 1999.<sup>3</sup> In total, since 1999, more than a quarter of a million Americans have died from overdoses involving prescription opioids.<sup>4</sup> These deaths are attributable to the scourge of pharmaceutical companies and consulting firms knowingly marketing addiction-causing drugs and leading the United States into a decades-long opioid epidemic that has since intensified into an overdose epidemic.<sup>5</sup> Regrettably, the FDA approved

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<sup>1</sup> PMR 3033-11.

<sup>2</sup> Jerome Schofferman & Daniel Mazanec, *Evidence-Based Management of Low Back Pain*, Mosby (Mar. 2, 2011), <https://www.sciencedirect.com/science/article/abs/pii/B978032307293900012X>

<sup>3</sup> Centers for Disease Control and Prevention, *Opioid Overdose* (Aug. 23, 2023), <https://www.cdc.gov/drugoverdose/deaths/opioid-overdose.html>.

<sup>4</sup> *Id.*

<sup>5</sup> Press Release, U.S. Department of Justice, Opioid Manufacturer Purdue Pharma Pleads Guilty to Fraud and Kickback Conspiracies (Nov. 24, 2020), [Office of Public Affairs | Opioid Manufacturer Purdue Pharma Pleads Guilty to Fraud and Kickback Conspiracies | United States Department of Justice](https://www.justice.gov/opa/pr/2020/11/20201124-opioid-manufacturer-purdue-pharma-pleads-guilty-to-fraud-and-kickback-conspiracies); Barry Meier, *Origins of an Epidemic: Purdue Pharma Knew Its Opioids were Widely Abused*, N.Y. Times (May 29, 2018), <https://www.nytimes.com/2018/05/29/health/purdue-opioids-oxycotin.html>; Betsy Reed, *Johnson & Johnson boosted opioid sales via 'cynical brainwashing', court hears*, The Guardian (May 28, 2019), <https://www.theguardian.com/us-news/2019/may/28/johnson-johnson-opioid-trial-oklahoma>; Meryl Kornfield et al.,

these drugs before it adequately understood their profound impact, helping to facilitate this crisis.<sup>6</sup> This history demands ongoing and careful review of opioid safety.

EERW studies are clinical trials that involve two phases. The first phase is the selection period, during which all participants are prescribed opioids with doses at their highest level of tolerance.<sup>7</sup> Next, participants enter a maintenance period used to ensure that they sustain the opioids' pain-relieving effects at optimal doses.<sup>8</sup> If participants do not respond to the opioids or are unable to tolerate their negative effects, they are excluded from the study.<sup>9</sup> In the second phase, participants who were not excluded from the study are split into two groups. One group stops receiving the opioids and instead receives a placebo; the second group continues to receive the opioids.<sup>10</sup>

Concerns regarding EERW studies are well documented. Members of Congress have asked the FDA questions about EERW studies,<sup>11</sup> and in legislation funding the federal government in fiscal year 2023, Congress directed the FDA to “conduct a study to review EERW study designs” with the understanding “that the FDA has approved new drug applications for opioids following completion of clinical trials using enriched enrollment, randomized, withdrawal (EERW) designs.”<sup>12</sup> This study is intended to specifically look at the use of EERWs to approve new opioids.

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*Inside the Sales Machine of the ‘Kingpin’ of Opioid Makers*, Wash. Post (May 10, 2022),

<https://www.washingtonpost.com/investigations/interactive/2022/mallinckrodt-documents-doctors-sales/>; Michael Forsythe & Walt Bogdanich, *McKinsey Settles for Nearly \$600 Million Over Role in Opioid Crisis*, N.Y. Times (Nov. 5, 2021), <https://www.nytimes.com/2021/02/03/business/mckinsey-opioids-settlement.html>.

<sup>6</sup> Karen Feldsler, *What Led to the Opioid Crisis—and How to Fix It*, Harvard T.H. Chan School of Public Health (Feb. 9, 2022), <https://www.hsph.harvard.edu/news/features/what-led-to-the-opioid-crisis-and-how-to-fix-it/>; Korin Miller, *Study Reveals FDA History of Approving Opioids with Limited Science Data*, Very Well Health News (Sept. 30, 2020), [Study Reveals FDA History of Approving Opioids with Limited Scientific Data \(verywellhealth.com\)](https://www.verywellhealth.com/study-reveals-fda-history-of-approving-opioids-with-limited-scientific-data/); Press Release, Food and Drug Administration, Statement from FDA Commissioner Scott Gottlieb, M.D. on the Agency’s 2019 Policy and Regulatory Agenda for Continued Action to Forcefully Address the Tragic Epidemic of Opioid Abuse (Feb. 26, 2019), <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-2019-policy-and-regulatory-agenda-continued>.

<sup>7</sup> Andrew R. Moore et al., *Systemic Review of Enriched Enrollment, Randomized Withdrawal Trial Designs in Chronic Pain*, 156(8) PAIN 1382-1395 (2015), [https://journals.lww.com/pain/abstract/2015/08000/systematic\\_review\\_of\\_enriched\\_enrolment,.6.aspx](https://journals.lww.com/pain/abstract/2015/08000/systematic_review_of_enriched_enrolment,.6.aspx).

<sup>8</sup> *Id.*

<sup>9</sup> Andrea D Furlan et al., *A Comparison Between Enriched and Nonenriched Enrollment Randomized Withdrawal Trial of Opioids for Chronic Noncancer Pain*. *Pain Res Manage* 16(5), 337-351 (2011), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3206784/>.

<sup>10</sup> *Id.*

<sup>11</sup> Letter from U.S. Senators Margaret Hassan & Edward J. Markey, to FDA Commissioner Scott Gottlieb (Mar. 27, 2019), <https://www.hassan.senate.gov/imo/media/doc/Hassan%20Letter%20to%20FDA.pdf>.

<sup>12</sup> Joint Explanatory Statement Accompanying Division A – Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, 2023 Congressional Directives, at 52-53, <https://www.appropriations.senate.gov/imo/media/doc/Division%20A%20-%20Agriculture%20Statement%20FY23.pdf>.

Additionally, an FDA-commissioned report noted fundamental flaws in EERW design.<sup>13</sup> By exposing all participants to opioids in the first phase of the study, its structure may identify which participants are on placebo or remain on opioids in the second phase of the study; placebo-taking participants may demonstrate symptoms of withdrawal when they are no longer taking opioids. This structure may undermine the study's unbiased nature and ultimately impact its accuracy. Even more concerning, according to this report, EERW studies are known to underestimate opioids' adverse effects, which may militate in favor of FDA opioid approvals that needlessly expose people to risks associated with opioids. Notably, participants who do not tolerate the negative side effects of the opioids do not proceed to the double-blind phase of the trial and, therefore, do not affect the study's results.<sup>14</sup>

On April 19, 2023, members of the FDA's Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) echoed these concerns. There was widespread agreement among committee members and experts that the EERW methodology was "designed to give a positive result before the study[] even beg[a]n"; that findings from the study would not be generalizable to clinical practice; and that the study could harm patients participating in it.<sup>15</sup> Advisory Committee members were worried about the use of EERW and also critiqued the study's focus on hyperalgesia, as opposed to more common potential harms that occur from opioid exposure, such as addiction.<sup>16</sup>

The potential harm of EERW studies is avoidable. According to the FDA's report, EERW study designs are limited in their ability to inform results more generalizable to a broader population and, particularly with drugs such as opioid analgesics that are widely used and have a wide range of public health impacts, are less informative than other trial designs.<sup>17</sup> Other studies have already evaluated prolonged opioid use without biasing the outcome or exposing patients to risk. A recent randomized placebo-controlled study found that prolonged opioid use was ineffective for acute back and neck pain.<sup>18</sup> The study found that after six weeks, there was no significant difference in pain scores for the patients taking opioids compared to those who took a

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<sup>13</sup> Brilliant Corporation, *External Review of FDA Regulation of Opioid Analgesics: Final Report*, pp. 30-31 (Jan. 25, 2023), <https://www.fda.gov/media/165238/download>.

<sup>14</sup> David J. Kopsky et al., *Study Design Characteristics and Endpoints for Enriched Enrollment Randomized Withdrawal Trials for Chronic Pain Patients: A Systematic Review*, *Pain Res Manage* 15, 479-496 (2022), <https://www.dovepress.com/study-design-characteristics-and-endpoints-for-enriched-enrollment-ran-peer-reviewed-fulltext-article-JPR>.

<sup>15</sup> Paul M. Coplan et al., *Postmarketing Studies Program to Assess the Risks and Benefits of Long-term Use of Extended-Release/Long-Acting Opioid Among Chronic Pain Patients*, *Post Graduate Med.* 132, 44-51 (2020). [Postmarketing studies program to assess the risks and benefits of long-term use of extended-release/ \(tandfonline.com\)](https://www.tandfonline.com/doi/full/10.1080/00140139.2020.1811111).

<sup>16</sup> Lev Facher, *FDA's New Plan to Study Opioids' Effectiveness Faces Resistance*, *Stat News* (Apr. 19, 2023), <https://www.statnews.com/2023/04/19/pain-opioid-study-design-fda-pushback/>.

<sup>17</sup> Brilliant Corporation, *External Review of FDA Regulation of Opioid Analgesics: Final Report*, pp. 30-31 (Jan. 25, 2023), <https://www.fda.gov/media/165238/download>.

<sup>18</sup> Caitlin M.P. Jones et al., *Opioid Analgesia for Acute Low Back Pain and Neck Pain (the OPAL trial): a Randomized Placebo-Controlled Trial*, *The Lancet*, 402, P304-312 (2023), [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(23\)00404-X/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(23)00404-X/fulltext).

The Honorable Robert Califf

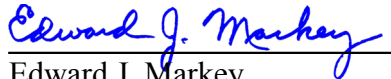
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placebo.<sup>19</sup> After one year, the patients who had been given a placebo had slightly lower pain scores, and the patients who were given opioids were at greater risk of opioid misuse.<sup>20</sup>

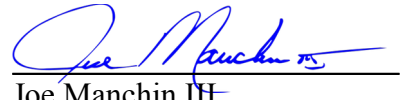
Based on the risk associated with EERW studies and the availability of other study models, we ask the FDA not to permit the use of EERW to determine the long-term efficacy and tolerability of opioids in chronic pain patients. We also urge you to reject EERW study designs for any future new drug applications for opioids and reconsider past opioid approval decisions using EERW. For too long, drug manufacturers have been given the benefit of the doubt in developing and marketing a drug that unleashed a widespread, decades-long epidemic. Using a study model that risks continued bias in favor of approval is unacceptable.

Sincerely,



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Edward J. Markey  
United States Senator



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Joe Manchin III  
United States Senator

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<sup>19</sup> *Id.*

<sup>20</sup> *Id.*