United States Senate
Washington D.C. 20510

October 19, 2022

VIA ELECTRONIC TRANSMISSION

The Honorable Robert M. Califf, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, M.D. 20993

Dear Commissioner Califf:

The U.S. Food and Drug Administration (FDA) serves a key role in accelerating the development and approval of breakthrough medicine to address unmet needs. None is more critically important than addressing the ongoing opioid epidemic. Physicians and other health care providers strive to keep patients out of the hospital and at home, healthy with their loved ones. Having the best tools and resources in their toolkit helps them achieve that mission. Therefore, we request the FDA prioritize new drug and device applications for non-opioid therapies for the treatment of pain and to help patients suffering from substance use disorder (SUD).

The opioid epidemic affects millions of Americans. Since 1999, more than 932,000 people have died from a drug overdose, and the rates have only accelerated in recent years.[1] However, substance use disorder and related deaths as a result of prescription opioids are decreasing. This decrease can be attributed to physicians and other health care providers' leadership in utilizing other treatments for pain and increasing patient awareness. In a recent report released by the American Medical Association, opioid prescribing continues on a downward trend.[2] In fact, physicians reduced opioid prescribing in every state by nearly 50 percent. They also increased the use of state prescription monitoring programs and other resources, some of which were provided by Congress.

Congress has taken swift action to save lives, promote better alternatives for treating pain, and help patients with SUD on their road to recovery. And Congress frequently collaborated with the U.S. Department of Health and Human Services (HHS) to achieve these goals. In 2017, the then-Acting HHS Secretary declared the opioid epidemic a public health emergency and announced a five-point strategy to reduce these rates.[3] Among the strategies, HHS supported advancing the practice of pain management. In

[1] U.S. Centers for Disease Control and Prevention, Death Rate Maps & Graphs, accessed September 20, 2022, https://www.cdc.gov/drugoverdose/deaths/index.html.
[2] American Medical Association, 2022 Overdose Epidemic Report, https://www.ama-assn.org/system/files/ama-overdose-epidemic-report.pdf.
[3] U.S Department of Health and Human Services, Press Release: HHS Acting Secretary Declares Public Health Emergency to Address National Opioid Crisis, October 26, 2017, https://public3.pagefreezer.com/browse/HHS.gov/31-12-

2018, the FDA approved the first non-opioid treatment to help adult patients manage opioid withdrawal symptoms after non-use.[4] Since its approval, health care providers have found it more helpful than previous methods. In a study published this year, nearly two-thirds of patients treated in an outpatient setting managed with this product reached opioid-free status at 30 days post-withdrawal.[5] This result included patients discontinuing heroin and fentanyl and the medication achieved more success than previous treatment models. This treatment option also allowed for a better transition into long-term care including medications to treat SUD (i.e. Naloxone) and non-medication methods. In 2020, the FDA approved a new non-opioid combination therapy for patients suffering from mild-to-moderate pain of acute musculoskeletal disorders.[6] It was approved two months ahead of the PDUFA goal date. We should continue to encourage the use of existing non-opioid based pain therapies and seek new innovations to improve options for patients.

Four years ago, the FDA Commissioner announced the agency would start to work on developing industry guidance to spur innovation on non-opioid therapies while Congress' was collaborating with his team on new initiatives to include in the SUPPORT for Patients and Communities Act. Congress' most comprehensive response to the opioid epidemic.[7] Among the provisions, Congress directed the FDA to issue guidance to help address challenges in developing non-addictive pain therapies and foster the development of novel analgesic drugs by assisting sponsors with the development of non-opioid alternatives for acute and chronic pain management.[8] They maintained active communication with prospective sponsors in mitigating potential uncertainty and risk for developing these products. While FDA has made efforts to confront the opioid crisis over the past several years, opioid addiction, abuse, and misuse remain major public health issues across the country.[9] And in the midst of the COVID-19 pandemic, FDA assured Americans that it would continue prioritizing the opioid crisis and use all facets in their regulatory authority to combat this growing threat.[10]

In February, FDA issued the guidance providing recommendations to pharmaceutical manufacturers developing non-opioid analgesics for acute pain lasting up to 30 days.[11] While the guidance specifically states that FDA "encourages early discussion of products that could eliminate or reduce opioid analgesic use and may be suitable for expedited reviews," the current availability of non-opioid therapies for pain management remains alarmingly insufficient. This is especially true for the treatment of chronic pain (including low back pain), which may present the greatest opportunity to avoid long-term opioid use and risk of addiction.

2020T08:51/https://www.hhs.gov/about/news/2017/10/26/hhs-acting-secretary-declares-public-health-emergency-address-national-opioid-crisis.html.

[4] U.S. Food and Drug Administration (FDA), Press Release: FDA approves the first non-opioid treatment for management of opioid withdrawal symptoms in adults, May 16, 2018, https://www.fda.gov/news-events/press-announcements/fda-approves-first-non-opioid-treatment-management-opioid-withdrawal-symptoms-adults.

[5] Gripshover, Jeanne, and Thomas Kosten, "Managing Opioid Withdrawal in an Outpatient Setting With Lofexidine or Clonidine," *Cureus* 14, no. 8 (2022), 10.7759/cureus.27639.

[6] Business Wire, Opioid-free Pain Med Orphengesic Forte by Galt Pharmaceuticals Approved by FDA, July 16, 2020, https://www.businesswire.com/news/home/20200716005252/en/Opioid-free-Pain-Med-Orphengesic-Forte-by-Galt-Pharmaceuticals-Approved-by-FDA.

[7] Pub. L. No. 115-271 (2018).

[8] *Id*.

[9] FDA, *Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse*, accessed September 25, 2022, https://www.fda.gov/drugs/information-drug-class/timeline-selected-fda-activities-and-significant-events-addressing-opioid-misuse-and-abuse.

[10] FDA, Statement: FDA Takes Further Steps to Confront Opioid Crisis Through Risk Evaluation and Mitigation Strategy Programs, December 23, 2020, https://www.fda.gov/news-events/press-announcements/fda-takes-further-steps-confront-opioid-crisis-through-risk-evaluation-and-mitigation-strategy.

[11] FDA, Development of Non-Opioid Analgesics for Acute Pain; Draft Guidance for Industry (FDA-2021-N-0556), February 16, 2022, https://www.fda.gov/media/156063/download.

No new analgesic medications were approved in 2021. The few pain management drugs that were approved by the FDA in the immediately preceding years were primarily in migraine or postoperative pain indications.[12] In our discussions with pharmaceutical manufacturers regarding the status of innovation of bringing non-opioid therapies to market, we learned that FDA has been unwilling to work collaboratively with sponsors to rapidly develop new product candidates. This is also reflected in submitted comments.

The need for better engagement is underscored by an industry report highlighting that clinical success in drug development has been extremely difficult for this therapy class.[13] There is only a 2 percent probability of FDA approval from phase 1, compared to an overall 10 percent success rate across all diseases. The report also highlighted how private company investment, as measured by venture capital into U.S. companies with lead stage programs in pain, is 3.6 percent of total drug development venture funding. For venture funding of novel R&D, pain has received 17 times less venture capital than oncology over the last decade.

It is our understanding that this issue has not been resolved and has caused delays in development timelines and potential new options for patients. To help facilitate our goal to fully execute the provisions of SUPPORT for Patients and Communities Act, we ask that you provide a response to this letter with answers to the following questions:

1. Has the FDA acknowledged issues outlined by industry stakeholders on FDA-sponsor engagement?
2. How will FDA reconsider the issue of potentially disincentivizing pharmaceutical manufacturers from developing non-opioid therapies for the indication of general or chronic pain?
3. As stated in the PDUFA letter, the FDA agreed to enhance and expand communication with drug sponsors. How is FDA working to ensure agency staff are currently communicating with sponsors in a timely manner?
4. Has FDA received new drug applications eligible for Fast Track, Priority Review, or Breakthrough Therapy designation for non-opioid products for pain management within the last four years?
    a. If so, how many have received designation for either Fast Track, Priority Review, or Breakthrough Therapy?
    b. How many applications have received final agency action? If not, how is FDA working with developers to provide a clear and predictable regulatory path to incentivize and encourage development of non-opioid pain treatments?
    c. How is the agency considering the risks and benefits for patients of non-opioid pain treatments given the potential public health benefit?
5. What has the FDA done to achieve its stated goal of prioritizing the review and approval of non-opioid therapies for acute and chronic pain?

[12] FDA, Advancing Health Through Innovation: New Drug Therapy Approvals 2021, January 2022, https://www.fda.gov/media/155227/download.
[13] Biotechnology Innovation Organization, The State of Innovation in Highly Prevalent Chronic Diseases, Volume II: Pain and Addiction Therapeutics, February 2018, https://go.bio.org/rs/490-EHZ-999/images/BIO_HPCP_Series-Pain_Addiction_2018-02-08.pdf.

Now is the time to provide patients with safe and effective non-opioid alternatives to prescription opioids for pain management. We would appreciate a reply no later than Wednesday, November 9, 2022. Thank you for your attention to this matter. We look forward to your reply.

Sincerely,

Roger Marshall, M.D.
U.S. Senator

James Lankford
U.S. Senator

Shelley Moore Capito
U.S. Senator

Marsha Blackburn
U.S. Senator