



October 18, 2022

The Honorable Robert M. Califf, MD
Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Building 32, Room 2346
Silver Spring, MD 20993

Dear Commissioner Califf:

We are writing to express our concern that consumers are generally unaware of the inherent dangers posed by prescription opioids. We believe that the Department of Health and Human Services (HHS) and the Food and Drug Administration (FDA) have an opportunity to ameliorate this problem by:

- Requiring all opioid prescriptions to clearly display the following warning: *Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended.*
- Ensuring that signs be prominently displayed in all emergency rooms, pharmacies and doctors' offices that share the same information; and
- Conducting an extensive review of all federal agency opioid safety educational materials to ensure that they are accurate, consistent, easy-to-read and include information on the breathing dangers of opioids.

Despite many public and private initiatives to address the opioid crisis, the stark reality is that much more needs to be done. Recent statistics underscore the problem: overall opioid-involved overdose deaths have risen sharply since 2012. Data recently released by the Centers for Disease Control (CDC) showed that there were 80,816 opioid-related deaths in 2021 (out of a total of 107,622 drug overdose deaths).¹

We believe that an important way to make progress in reducing overdose deaths is to educate consumers on the inherent dangers of opioids. A key gap in current opioid safety materials is the lack of understanding about the *inherent dangers* of opioid analgesics, including the risks associated with opioid-induced respiratory depression. Respiratory depression occurs when opioids depress the body's natural instinct to breathe, and results in dangerous decreases in blood oxygen levels that can lead to severe brain damage, organ failure and death.

However, current federal agency opioid safety materials, brochures, toolkits and other provider- and consumer-facing information is insufficient, and many publications ignore, minimize or misstate the dangers of respiratory depression posed by opioids' very nature, and focus only on the dangers of the *misuse* of opioids. To be clear, fatal and non-fatal

¹ https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/202205.htm.

opioid overdoses can occur even when an individual does not abuse or misuse an opioid, and even when a patient is taking opioids exactly as prescribed by their doctor. **Moreover, manufacturers include these dangers in their package warnings (“Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended,”) but federal agencies, including the FDA, have failed to pass that life-saving information along to consumers.**

For example, as required by law, the Food and Drug Administration (FDA) requires that opioid analgesic manufacturers explicitly warn consumers about the threats posed by opioids. These warnings are clear and unambiguous: ***Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended.***²

The Centers of Medicare and Medicaid Services (CMS) has long recognized the fatal consequences of opioid-induced respiratory depression and has concluded that ***“Most opioid-related adverse events are preventable ,”***³and that *...the sedating effects of opioids make it difficult at times to properly assess the patient’s level of sedation. It can be erroneously assumed that patients are asleep when they are actually exhibiting progressive symptoms of respiratory compromise - somnolence, decreased respiratory rate, and decrease in oxygen levels. These symptoms, if unrecognized, can progress to respiratory depression and even death.*⁴

In fact, on August 10, 2022, in the Fiscal Year 2023 Medicare Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Policy Changes Final Rule⁵ CMS concluded the following:

*The most serious opioid-related adverse events include those involving respiratory depression, which can lead to brain damage and death.*⁶ *Opioid related adverse events have both a negative impact on patients and financial implications.*

*[I]n a review of cases from a malpractice claims database in which there was opioid-induced respiratory depression among post-operative surgical patients, 97 percent of these adverse events were judged preventable with better monitoring and response.*⁷

² Manufacturer warnings mention the dangers multiple times. **Examples:** “Life-Threatening Respiratory Depression: Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death; Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely . . . ; Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients; Monitor patients closely for respiratory depression, especially within the first 24-72 hours of initiating therapy and following dosage increases with OXYCONTIN and adjust the dosage accordingly; Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death; Serious, life-threatening, or fatal respiratory depression may occur; CONTRAINDICATIONS: Significant respiratory depression; ...serious, life-threatening, or fatal respiratory depression can occur at any time during the use of OXYCONTIN...; Patients with Chronic Pulmonary Disease: OXYCONTIN-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of OXYCONTIN; Labor or Delivery Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate; Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who are not opioid-tolerant or when opioids were co-administered with other agents that depress respiration; Pharmacodynamics Effects on the Central Nervous System: Oxycodone produces respiratory depression by direct action on brain stem respiratory centers.”

³ Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2023 Rates. Department of Health and Human Services, Centers for Medicare & Medicaid Services; CMS–1771–F; RIN 0938–AU84. 48780 Federal Register; Vol. 87, No. 153; August 10, 2022. Pg. 49234. <https://www.govinfo.gov/content/pkg/FR-2022-08-10/pdf/2022-16472.pdf>.

⁴ **Examples:** “CMS recognizes that opioids have a sedating effect and that patients can become overly sedated and suffer respiratory depression or arrest, which can be fatal; ...opioid-induced respiratory compromise has resulted in inpatient deaths that might have been prevented with appropriate assessment and vigilant monitoring of respiration and sedation levels; Factors that place patients receiving opioids at higher risk for over sedation and respiratory depression: Snoring or history of sleep apnea, No recent opioid use or first-time use of IV opioids, Increased opioid dose requirement or opioid habituation, Longer length of time receiving general anesthesia during surgery; Adverse patient reactions, such as anaphylaxis or opioid-induced respiratory depression, require timely and appropriate intervention, per established hospital protocols, and must also be reported immediately to the practitioner responsible for the care of the patient; CMS acknowledges the dangers of adverse drug reactions in stating that hospitals are encouraged to educate the patient and his/her representative and/or family members about notifying nursing staff promptly when there is difficulty breathing or other changes that might be a reaction to medication.”

⁵ Eg., Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2023 Rates. Department of Health and Human Services, Centers for Medicare & Medicaid Services; CMS–1771–F; RIN 0938–AU84. 48780 Federal Register; Vol. 87, No. 153; August 10, 2022. Pgs. 49233-49234. <https://www.govinfo.gov/content/pkg/FR-2022-08-10/pdf/2022-16472.pdf>.

⁶ *Id.*, Jungquist CR, Quinlan-Colwell A, Vallerand A, et al. (2020). American Society for Pain Management Nursing Guidelines on Monitoring for Opioid-Induced Advancing Sedation and Respiratory Depression: Revisions. *Pain Manag Nurs*.21(1):7-25. Epub 2019 Jul 31; Ramchandran SK, Haider N, Saran KA, et al. (2011). Life-threatening critical respiratory events: a retrospective study of postoperative patients found unresponsive during analgesic therapy. *Journal of Clinical Anesthesia*. 23(3):207-213; Dahan A, Aarts L, Smith TW. (2010). Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression. *Anesthesiology*. 112(1):226-238.

⁷ *Id.*, Lee, L.A., Caplan, R.A., Stephens, L.S., et al. (2015). Postoperative opioid-induced respiratory depression: a closed claims analysis. *Anesthesiology*, 122(3): 659-65.

The Joint Commission has issued Sentinel Event Alerts stating that, “. . . ***opioid analgesics may be associated with adverse effects, the most serious effect being respiratory depression . . .***”⁸

However, these warnings are not adequately communicated to individuals taking opioids or those who care for them. Researchers have consistently found that current warnings are not effective, nor do they convey sufficient information for individuals to balance the risks and benefits.

For example, the FDA’s Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain states: *[O]pioids carry risks not present with most non-opioid analgesics, specifically the risks of addiction, abuse and misuse, which can lead to respiratory depression, overdose and death.*”

To the contrary, opioid overdoses do *not* occur only when an individual abuses or misuses an opioid, and opioid-induced respiratory depression and death can occur even when someone is taking an opioid ***exactly as prescribed by their doctor.***

One recent analysis of REMS Continuing Medical Education (CME) activities found that severe adverse effects of opioids, ***such as respiratory depression***, were minimized in comparison to minor adverse effects like opioid-induced constipation. Further, less than a third of the educational materials reviewed mention that opioids are dangerous even when used as prescribed. The risk of opioid overdose was not emphasized in any of the reviewed training materials. These findings point to serious knowledge gaps that need to be addressed. Severe adverse effects of opioids, such as respiratory depression, are only presented in opioid safety educational materials as “supporting actors,” with less than a third of the educational activities examined mentioning that opioids are dangerous *even when used as prescribed*” when in fact, “opioids used exactly as prescribed and without concomitant medications can cause respiratory depression, and death.”

Therefore, we ask that you mandate that opioid safety warnings adequately, safely, and appropriately reflect the science: that opioids can cause deadly respiratory depression which can cause permanent brain damage or death, even when taken at the prescribed dosage. All educational materials, including toolkits, care instructions, pamphlets, brochures, and signage at doctors’ offices must amplify the dangers of opioid-induced respiratory depression in an accurate and understandable way.

Medical professionals, experts and patient advocates agree. For example, researchers at Stanford University School of Medicine⁹ recommend that patients be educated and warned of the dangers of opioid-induced respiratory depression: *[Opioids] can kill you by slowing down your breathing and your heart rate until you stop breathing and your heart stops beating... It can also cause breathing problems at night, when you may stop breathing for a few seconds. The result is that you may not get enough oxygen to your lungs, and you will die.*

The Anesthesia Patient Safety Foundation states: *Patients receiving prescription opioids (post-operatively, acute, chronic or other) are at risk of serious, life-threatening or fatal respiratory depression, even when the opioids are used as recommended. Patients, providers, caregivers and the public should be educated on the risks of opioids, including slowed or stopped breathing. Respiratory depression, if not immediately recognized and treated, can lead to the lack of oxygen to vital organs, cardiac arrest, brain damage or death within minutes.*

Without a coordinated effort to develop and implement provider and patient education that accurately depicts current research and data regarding the inherent dangers of opioids, such as respiratory depression, we will continue to stigmatize individuals with acute and chronic pain, limit access to multimodal therapies including opioid analgesics when appropriate and fail to protect individuals taking opioids from overdose and perpetuate the opioid crisis.

⁸ **Examples:** “The hospital monitors the use of opioids to determine if they are being used safely (for example, the tracking of adverse events such as respiratory depression; When opioids are administered, the potential for opioid-induced respiratory depression should always be considered because: The risk may be greater with higher opioid doses, The occurrence may actually be higher than reported, There is a higher incidence observed in clinical trials, Various patients are at higher risk, including patients with sleep apnea, patients who are morbidly obese, who are very young, who are elderly, who are very ill, and who concurrently receive other drugs that are central nervous system and respiratory depressants (e.g., anxiolytics, sedatives); providers should Educate and assess the understanding of staff that care for patients receiving opioids about the potential effect of opioid therapy on sedation and respiratory depression.”

⁹ Lembke A, Humphreys K, Newmark J. Weighing the Risks and Benefits of Chronic Opioid Therapy. Am Fam Physician. 2016 Jun 15;93(12):982-90. PMID: 27304767.

We greatly appreciate your consideration of this request and look forward to working with you to keep individuals taking opioids safe and reduce opioid overdose. We welcome the opportunity to discuss this important issue with you. If you have any questions or would like to engage further, please contact Dr. Joseph Szokol, Chief Health Policy Officer of the American Society of Anesthesiologists at (224) 522-8009.

Sincerely,

American Association for Respiratory Care

American College of Chest Physicians

American Society of Anesthesiologists

Anesthesia Patient Safety Foundation

Louise Batz Patient Safety Foundation

Patient Safety Movement Foundation

Physician-Patient Alliance for Health & Safety