

Citizen Petition

The undersigned submit this petition under Section 355(e) of the Federal Food, Drug, and Cosmetic Act and under Food and Drug Administration (FDA) regulations at 21 C.F.R. § 10.30 to request the Commissioner of Food and Drugs to immediately seek removal of ultra-high dosage unit (UHDU) oral and transmucosal analgesics from the market. We believe the risks of UHDU orally administered opioid analgesics outweigh their benefits.

A. ACTION REQUESTED

FDA should immediately seek removal of oral and transmucosal UHDU opioid analgesics from the market.

B. STATEMENT OF GROUNDS

1. Identifying UHDU Opioid Analgesics

Opioid molecules differ in the amount required to produce an effect of given intensity, also called potency. The morphine milligram equivalent (MME) daily dose for each opioid can be calculated using a conversion factor. UHDU opioids are formulations that when taken as directed exceed 90 MME/day, a dose the Centers for Disease Control and Prevention (CDC) has determined to be dangerously high.¹

An example of an extended release (ER) UHDU opioid is the OxyContin 80 milligram tablet. A patient directed to take one tablet twice a day is consuming 160 milligrams of oxycodone per day, which is equal to 240 MME/day and far greater than the CDC's recommended 90 MME/day upper dose. Because only one pill is taken at a time, the patient and prescriber may not appreciate that this is an extremely high dose. If FDA responds to this request, it will seek removal of the OxyContin 80mg tablet.

An example of an immediate release (IR) UHDU opioid is IR oxycodone 30mg tablets which are typically taken four times a day. When IR oxycodone 30mg is taken as prescribed the total daily dose is 120mg of oxycodone, which is equal to 180 MME. If FDA responds to this request, it will seek removal of the IR oxycodone 30mg tablet.

Oxycodone is not the only opioid molecule available in an oral or transmucosal ultra high dosage formulation. IR and ER hydromorphone, IR and ER morphine, IR and ER oxymorphone, ER hydrocodone, methadone, and IR transmucosal fentanyl are also available in ultra-high dosages that exceed 90 MME when taken as directed.

2. Risks of UHDU opioid analgesics when misused

FDA recently announced that decisions involving opioids will be made within a new benefit-risk framework that evaluates not only the outcomes of prescription opioids when used as

¹ Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA. 2016;315(15):1624-1645.

prescribed, but also the public health effects of inappropriate use.² Utilization of this new benefit-risk framework that takes opioid misuse into account was also a key recommendation in a report by the National Academies of Sciences, Engineering, and Medicine.³ As FDA applies this new framework, UHDU opioids are an important starting point because they are especially dangerous when misused.

In 2015, 11.5 million Americans are estimated to have misused prescription opioids. The most commonly reported motivation for misuse (63%) was to relieve physical pain.⁴ A friend or family member lacking a tolerance to opioids who borrows a single dose of an UHDU opioid for pain relief could experience life-threatening respiratory depression. An overdose could also occur in the opioid-tolerant patient who accidentally takes just one extra dose or who intentionally takes an extra dose for unrelieved pain.

UHDU opioids are especially dangerous when misused for recreational purposes or to experience the effect, a practice that is common among adolescents and young adults. In 2015, there were 969,000 youths aged 12 to 17 who misused prescription pain relievers, and 3.0 million young adults aged 18 to 25.⁵ An opioid naive adolescent who makes the mistake of experimenting with an UHDU opioid could easily suffer a fatal overdose. Experimentation with a low dosage opioid is also dangerous but less likely to lead to death.

UHDU opioids also pose a risk to young children. An analysis of 13,052 pediatric hospitalizations for opioid poisonings found a nearly 2-fold increase from 1997 to 2012.⁶ The largest percentage increase in hospitalizations over time occurred among toddlers and preschoolers. Data on the opioid dosage involved in these poisonings was not available but it is likely that morbidity and mortality was greater in cases involving UHDU opioids. In 2015, opioid poisoning claimed the lives of 51 toddlers under the age of 5, a 265% increase from 14 deaths in 2000.⁷

3. Benefits and risks of UHDU opioid analgesics taken as prescribed for chronic pain

In developing the CDC Guideline for Opioid Prescribing for Chronic Pain, CDC conducted a systematic review of the scientific evidence to identify the effectiveness, benefits, and harms of long-term opioid therapy for chronic pain. CDC found only one study addressing effectiveness of high dose opioids for outcomes related to pain control, function, and quality of life.⁸ This randomized trial found no difference in pain or function between a more liberal

² Gottlieb A, Woodcock J. Marshaling FDA Benefit-Risk Expertise to Address the Current Opioid Abuse Epidemic. *JAMA*. 2017;318(5):421-422.

³ Bonnie RJ, Kesselheim AS, Clark DJ. Both Urgency and Balance Needed in Addressing Opioid Epidemic: A Report From the National Academies of Sciences, Engineering, and Medicine. *JAMA*. 2017;318(5):423-424.

⁴ Han B, Compton WM, Blanco C, et al. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Ann Intern Med*. 2017;167(5)

⁵ Hughes, A., Williams, M. R., Lipari, R. N., Bose, J., Copello, E. A. P., & Kroutil, L. A. *Prescription drug use and misuse in the United States: Results from the 2015 National Survey on Drug Use and Health*. NSDUH

⁶ Gaither JR, Leventhal JM, Ryan SA, et al. National Trends in Hospitalizations for Opioid Poisonings Among Children and Adolescents, 1997 to 2012. *JAMA Pediatrics*. 2016;170(12):1195-1201.

⁷ CDC Vital Statistics WONDER database.

⁸ Naliboff BD, Wu SM, Schieffer B, et al. A randomized trial of 2 prescription strategies for opioid treatment of chronic nonmalignant pain. *J Pain* 2011;12:288–96.

opioid dose escalation strategy and maintenance of current dosage. At the same time, CDC noted serious harms related to high dose opioid therapy.

Higher opioid dosages are associated with increased overdose risk. CDC's review included four well designed studies that evaluated similar MME/day dose ranges for association with overdose risk.⁹ Compared with opioids prescribed at <20 MME/day the odds of overdose among patients prescribed opioids for chronic nonmalignant pain were:

- 1.3 to 1.9 for dosages of 20 to <50 MME/day
- 1.9 to 4.6 for dosages of 50 to <100 MME/day
- 2.0 to 8.9 for dosages of \geq 100 MME/day

Compared with dosages of 1-<20 MME/day, the absolute risk difference approximation was:

- 0.15% for fatal overdose and 1.40% for any overdose at dosages of 50 to <100 MME/day
- 0.25% for fatal overdose and 4.04% for any overdose at dosages of \geq 100 MME/day

CDC found that keeping dosages under 50 MME/day reduces overdose risk among a large proportion of patients and that dosages under 50 MME/day are safer than dosages of 50–100 MME/day, and that dosages under 20 MME/day are safer than dosages of 20–50 MME/day. CDC's expert consensus was that increasing dosages to 50 or more MME/day increases overdose risk without necessarily adding benefits for pain control or function.

Dose-related serious harms are not limited to risk of overdose. High dose opioids are associated with increased risk for motor vehicle accidents, fractures from falls, immune suppression, and opioid associated androgen deficiency which can cause reduced libido, erectile dysfunction, fatigue, depression, decreased muscle mass, weight gain, osteoporosis and infertility.

One of the most serious adverse events associated with high dosages is development of an opioid use disorder. A person taking a relatively low dose of prescribed opioids is 15 times as likely to develop an opioid use disorder (OUD) as a person who has not been prescribed opioids. The risk continues to rise as doses increase; at high doses (\geq 120 mg MED) of

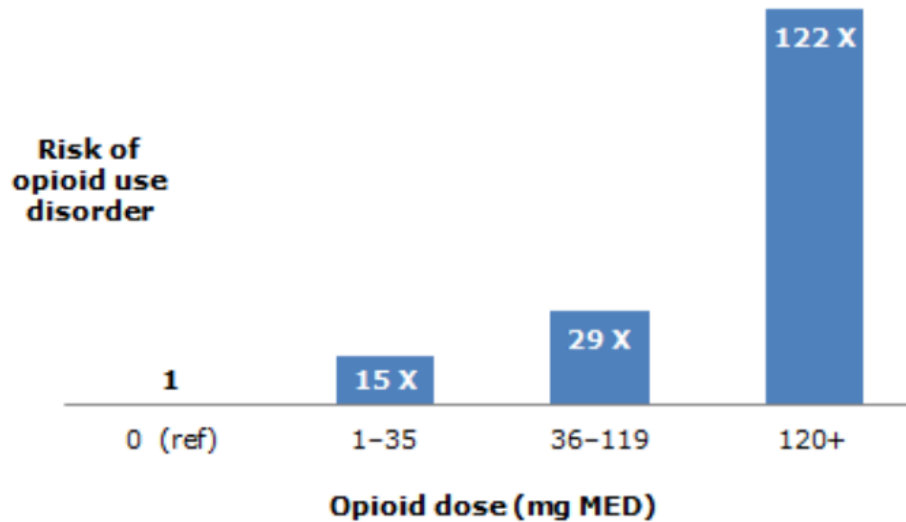
⁹ Zedler B, Xie L, Wang L, et al. Risk factors for serious prescription opioid-related toxicity or overdose among Veterans Health Administration patients. *Pain Med* 2014;15:1911–29.

Bohnert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA* 2011;305:1315–21.

Dunn KM, Saunders KW, Rutter CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med* 2010;152:85–92.

Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med* 2011;171:686–91.

opioids, the person's risk of developing OUD is 122 times that of a person who has not been prescribed opioids.¹⁰



4. *Impact of removing UHDU opioids*

Removal of UHDU opioids is expected to reduce opioid-related morbidity and mortality in the following groups:

- Opioid tolerant patients prescribed UHDU opioids
- Individuals who misuse opioids for relief of pain, relief of dysphoria or to experience the effect
- Toddlers and preschoolers who experience an accidental opioid poisoning

Removal of UHDU opioids may also help reverse risky prescribing practices that were previously encouraged. The notion that opioids should be prescribed without an upper limit was explicitly endorsed by the American Academy of Pain Medicine (AAPM) and the American Pain Society (APS) in a consensus statement published in 1997.¹¹ Many UHDU opioids entered the market as high dose opioid prescribing became more common. AAPM and APS have since rescinded their previous recommendations but some clinicians continue to prescribe extremely high doses. In 2015, the annual high-dose opioid prescribing rate was

¹⁰ Edlund MJ, Martin BC, Russo JE, DeVries A, Braden JB, Sullivan MD. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. *Clin J Pain*. 2014 Jul;30(7):557-64.

¹¹ The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. *Clin J Pain*. 1997 Mar;13(1):6-8.

6.7 per 100 persons.¹² The availability of UHDU opioids implies that ultra-high dosages are within a safe range. Removing UHDU may help reduce the practice of high dose prescribing that became normative over the past twenty years.

Prescribing opioids at doses greater than 90 MME/day can be appropriate. For example, the benefits of prescribing high doses may outweigh risks when treating severe pain from a life-limiting illness. Removing UHDU orally-administered opioids from the market will result in patients having to swallow more tablets or capsules. But this is unlikely to result in a significant inconvenience or hardship for patients. For example, if IR oxycodone 30mg tablets are removed from the market, a patient who currently takes one tablet every 6 hours would instead take two IR oxycodone 15mg tablets every 6 hours. For patients that may have difficulty swallowing it is important to note that opioid analgesics are available in liquid preparations, sublingual preparations, patches, and suppositories.

5. Conclusion

The harms of UHDU orally administered opioid analgesics outweigh the modest benefit of allowing patients to swallow fewer tablets or capsules. When utilizing the new benefit-risk framework that takes into account inappropriate use, the need for removal of UHDU becomes even more clear. UHDU opioids should be immediately removed from the market to prevent further harm to thousands of adults, adolescents, children and toddlers.

Therefore, for the reasons stated above, we hereby petition the FDA, pursuant to the Federal Food, Drug, and Cosmetic Act; 21 U.S.C. § 355(e); and 21 C.F.R. § 10.30, to seek removal of all orally-administered UHDU opioid analgesics.

C. ENVIRONMENTAL IMPACT STATEMENT

We claim categorical exclusion under 21 C.F.R. § 25.31(a) from the environmental assessment requirement.

D. CERTIFICATION

We certify that, to the best of the knowledge and belief of the undersigned, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

E. CORRESPONDENCE

Please address correspondence to Dr. Andrew Kolodny, Physicians for Responsible Opioid Prescribing, 12800 Whitewater Drive, Suite 100, Minnetonka, MN 55343

¹² Guy GP Jr., Zhang K, Bohm MK, et al. Vital Signs: Changes in Opioid Prescribing in the United States, 2006–2015. *MMWR Morb Mortal Wkly Rep* 2017;66:697–704.

Sincerely,



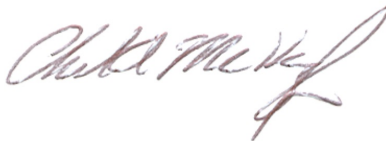
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