Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) Document

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The Policy

Synopsis
The Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS) updates pre-existing directives in the 2012 Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics REMS. Although the Food and Drug Administration’s (FDA) previous REMS addressed just ER and LA opioid analgesics, the updated version also includes immediate-release (IR) opioid analgesics, which account for about 90 percent of all opioid pain medications prescribed for outpatient use. Other significant changes include the addition of expanded education on pain treatment alternatives to opioids, training for healthcare providers involved in pain management, and new medication labeling information.

The aim of the Opioid Analgesic REMS is to educate those who prescribe or provide opioid medications with respect to writing prescriptions or helping patients manage pain. Healthcare providers must ensure that any opioid medication dispensed is appropriate for a patient’s condition and that patients take the correct dose for a reasonable duration. Pharmacists, nurses, and other practitioners are encouraged to consider the risks of opioid medications and apply this knowledge through patient counseling and monitoring to prevent opioid addiction and abuse. This training, provided through the REMS program, is based on the Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain (Blueprint).

The Blueprint focuses on educational programs concerning the fundamentals of acute and chronic pain management. It defines the
definitions and mechanisms of pain as well as listing the important elements of assessing patients in pain. There are thorough explanations on how to create specific pain treatment plans for different patients; for instance, nonpharmacologic therapies, adjuvant medications, and opioid analgesics. The Blueprint provides a framework for the safe prescribing of opioid analgesics.

**Context**

In 2007, the *Food and Drug Administration Amendments Act of 2007 (H.R. 3580)* [14] gave the FDA more responsibility and control over drug safety. As a provision, the FDA conditioned the marketing of certain drugs on the submission and approval of *Risk Evaluation and Mitigation Strategies* [15] (REMS). The FDA may require a REMS to ensure that a drug’s benefits outweigh its risks. This drug safety program promotes the safe use of medications and seeks to minimize the risks of addiction and overdose.

The REMS requirement applies when the FDA finds that safety measures beyond labeling are necessary to ensure that a drug’s benefits outweigh its risks. While all medications must have labeling [16] to inform users of risks, only 76 drugs [17] require a REMS. In this case, the FDA has developed a REMS for opioid analgesics.

The original 2012 Opioid Analgesics REMS only covered 63 opioid products. On September 18, 2018, the REMS was updated to encompass 347 opioid products by including IR opioids.


This surge in opioid-related deaths -- commonly referred to as the opioid crisis [18] -- is in part the result of an increased prevalence [20] of prescription opioid abuse, which stems from an increase in opioid administration in healthcare. HHS declared [21] the crisis a nationwide public health emergency. Commentators [22] in the public health field have posited that “[o]verprescribing of [opioid drugs] has led to a sharp increase in the prevalence of opioid addiction, which in turn has been associated with a rise in overdose deaths and heroin use.”

These deaths are in part attributed [23] to hospitals and healthcare providers that are quick to distribute opioid medications for acute pain complications. A 2011 report [23] by the National Academies of Science, Engineering, and Medicine revealed that 60 [10] percent of Americans who enter the emergency department with acute pain conditions leave with a prescription for opioid analgesics. However, the frequency at which opioids are prescribed is not the only factor affecting access. According to the 2016 [24] National Survey on Drug Use and Health, 53 percent of opioid abusers reported that a friend or relative was their drug source, and 35 percent reported that they misused a physician’s prescription.

**Policy History**

The initial REMS, which only applied to extended-release and long-acting (ER/LA) opioid analgesics, was issued in July 2012. The REMS was modified in June 2015 to include the *Butrans transdermal patch* [25] and revised titration information for *Dolophine* [26] or *methadone HCl tablets* [27]. On September 18, 2018, the FDA expanded this REMS to address immediate-release (IR) opioids and to include expanded education on pain treatment alternatives to opioids, training for healthcare providers involved in pain management, and new medication labeling information.

**The Science**

**Science Synopsis**

**Opioid analgesics** [28] are drugs used for the treatment of pain. Some opioids are prescription painkillers, such as OxyContin. Other opioids, such as heroin, are illegal. External or synthetic [29] opioid drugs can disrupt the body’s natural regulation of neurotransmission even when patients take their recommended dosages, resulting in patients who suffer with substance abuse.

**Substance use disorder** [30] is the compulsive urge to use a certain substance, such as a drug, even when the substance has harmful effects and is not medically necessary. Opioid use disorder is particularly dangerous because opioids alter [29] the user’s brain chemistry, resulting in dependence after use for an extended time. Opioids mimic the neurotransmitters [31] by attaching to
receptors in the brain to release dopamine [32], serotonin [33], endorphins [34], and oxytocin [35], which are neurotransmitters and hormones that can relieve pain and produce feelings of pleasure.

The euphoric effects of opioids overstimulate [36] the body, which can lead to an individual developing tolerance [37] to these drugs over time after repeated use. To offset drug tolerance, higher doses are needed to achieve the same euphoric effects.

In addition to developing tolerance, the body can become dependent [38] on opioid analgesics. In response to the changes in neurotransmitter levels that opioid medications provide, the body decreases production of these chemicals. Therefore, if drug use stops, the body will not function properly because it has become reliant on opioids and, consequently, accustomed to producing decreased levels of these neurotransmitters. This deficiency can cause both physical and psychological pain, a condition known as withdrawal [29]. Effects of withdrawal involve the change of receptor levels on the cell surface, signaling molecules, and more.

However, the body can only withstand a certain dosage of opioids: once this threshold is surpassed, an overdose [39] occurs. During an overdose, the user experiences depression of the central nervous system, which causes loss of consciousness and inability to breathe. Without emergency treatment, overdose will result in death.

Another concern is that prescription opioids can function as gateway drug [40], inducing the use of riskier, illegal opioids such as heroin. Approximately four to six percent [18] of those who misuse prescription opioids later transition to using heroin. About 80 percent [18] of heroin users first misused prescription opioids.

### Scientific Assumptions

- It is critical that healthcare practitioners are knowledgeable about the risks associated with opioid analgesics as they pertain to their patients as well as from a public health perspective (Background): Researchers believe that educating healthcare practitioners will cause them to prescribe or provide less [41], which in turn will decrease addiction rates.

- There is tension between the need to adequately treat a large number of Americans with acute or chronic pain and a nationwide epidemic of prescription opioid abuse (Background): Many healthcare professionals consider opioids the standard and most effective treatment for acute and chronic pain, but some researchers suggest that there are other options [42] that may pose fewer health risks and be more effective for certain individuals.

### Scientific Controversies / Uncertainties

Healthcare providers disagree on whether opioids are the most effective pain relief treatment.

Some researchers [28] state that opioids are "the most reliable analgesic agents" and that "the efficacy of opiates is ... broadly accepted ... Beyond potent analgesia, opiates reduce anxiety and produce mild sedation and a palpable sense of well-being ... These are an unmitigated benefit for patients who would otherwise have to endure the pain and suffering of acute or terminal medical conditions ... there is no debate over the short-term use of opiates."

Contrastingly, the National Safety Council [43] (NSC) Medical Advisor has characterized [44] opioids' benefits as minimal and undermined by adverse side effects. This 2014 NSC report notes that although "opioid medications are often referred to as 'powerful painkillers' ... the evidence shows that they are mild to moderate painkillers and less effective than over-the-counter ibuprofen." This report further emphasizes that opioids have side effects that harm many individuals in the U.S. every year. Furthermore, the report asserts that, by imposing restrictions on the prescription of opioids, policymakers can entice prescribers to select other medications that are more effective.

Similarly, physicians and health policy scholars [45] have claimed that "an increased awareness of the right to pain relief, the support of various organizations supporting the use of opioids in large doses, and finally, aggressive marketing by the pharmaceutical industry ... are based on unsound science and blatant misinformation and accompanied by the dangerous assumptions that opioids are highly effective and safe, and devoid of adverse events when prescribed by physicians."

Other medical experts [20] have noted an absence of evidence that increased medical use of opioids results in reduced chronic pain. They conclude that clinical trials have failed to provide adequate evidence of the long-term effectiveness of opioids.
Endorsements & Opposition

- Purdue Pharma L.P., manufacturer of OxyContin and other opioids, press release [46], July 9, 2012: “Purdue supports the goals of enhanced prescriber and patient education as part of a comprehensive approach necessary to address the misuse, abuse, and diversion of prescription medicines, while ensuring these medications remain accessible for people with chronic, moderate to severe pain, when appropriate.”

- FDA Commissioner Scott Gottlieb M.D., press release [47], August 1, 2018: “We are committed to striking a careful balance between access and safety, based on reliable evidence. Our REMS are an important tool for helping to ensure safe use and reduce the risk of abuse and misuse. Making sure they’re achieving their purpose is critical.”

- American Association of Family Physicians, press release [48], July 12, 2017: “Requiring all physicians or prescribers to complete the same education regardless of whether a relevant performance gap in this area exists would be a disservice to that physician and their patients since it will result in unnecessary time spent away from patient care. The FDA should focus less on an individualized clinician approach that ignores team-based care, and more on promoting patients as stakeholders in their own care via shared-decision making and collaborative physician-patient management plans.”

Related Policies

H.R. 6133 - Informing Opioid Prescribing Through Evidence-Based Guidelines Act of 2018 [49]
This policy authorizes the Commissioner of Food and Drugs to impose evidence-based opioid prescription guidelines intended to prevent addiction and abuse.

H.R. 5809 - Postoperative Opioid Prevention Act of 2018 [50]
This policy aims to decrease the risk of opioid misuse by encouraging non-opioid prescriptions for the management of post-surgical pain. Like the Opioid Analgesic REMS, this legislation seeks to deter opioid prescriptions and incentivize alternative treatments for patients in need of pain-relief.

Recommended Citation

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