



# FDA's Risk Evaluation and Mitigation Strategies: Uncertain Effectiveness in Addressing the Opioid Crisis

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### Why OIG Did This Review

While the opioid crisis continued with nearly 47,000 deaths in 2018, the Food and Drug Administration (FDA) used Risk Evaluation and Mitigation Strategies (REMS) as tools to mitigate misuse and abuse of opioids. REMS have the potential to help address the opioid crisis, but previous Office of Inspector General work from 2013 raised concerns about FDA's oversight and the overall effectiveness of REMS programs. This review determines the extent to which FDA has held drug manufacturers accountable for mitigating the risk of opioid misuse and abuse through REMS. It complements OIG's past work tracking opioid use among Medicare and Medicaid beneficiaries and provides insight into the Federal response to the national opioid crisis.

### How OIG Did This Review

We analyzed documents related to the REMS for transmucosal immediate-release fentanyl (TIRF) and extended-release/long-acting opioids (ER/LA) from 2011 through 2017, including all drug manufacturer-submitted assessments, FDA decision memoranda, assessment reviews, inspection reports, and other analyses and correspondence. We also interviewed FDA staff about REMS oversight.

## FDA's Risk Evaluation and Mitigation Strategies: Uncertain Effectiveness in Addressing the Opioid Crisis

### Key Takeaways

Although opioid prescribing has decreased, data quality issues have made it challenging for FDA to determine whether the two REMS for opioids have been effective. Furthermore, REMS may not be well-suited to quickly address the opioid crisis.

The Food and Drug Administration (FDA) can require drug manufacturers to develop and implement a Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of a drug outweigh its risks. A REMS is a drug safety program that is intended to mitigate a specific serious risk associated with the use of a drug. FDA can require a REMS if it determines that placing a drug's risks on the FDA-approved drug label is insufficient to protect patients. FDA specifies the requirements and approves

the REMS. However, the drug manufacturer is responsible for developing and implementing the program. Following approval of the REMS, the manufacturers submit assessments detailing how the REMS is performing and whether it is meeting its goals to FDA.

Transmucosal immediate-release fentanyl (TIRF) drugs and extended-release/long-acting (ER/LA) opioids are two major classes of opioids that pose serious risk of addiction, abuse, and overdose. In 2011 and 2012, FDA approved the REMS for TIRF drugs and the REMS for ER/LA opioids, respectively, just as opioid prescribing reached its peak. The two REMS are intended to mitigate risks of abuse and misuse while maintaining access to these two classes of opioids. These REMS represent important pieces of the Federal efforts to address the opioid public health crisis.

### What OIG Found

While the severity of the opioid crisis became more apparent over time and the Federal Government and States launched initiatives to combat opioid abuse, FDA struggled to measure the effectiveness of the REMS for TIRF drugs and for ER/LA opioids in mitigating the misuse of opioids.

For the REMS for TIRF drugs, FDA found data in the assessments suggesting that the manufacturers were not meeting all their goals and also found the data for some of the REMS goals to be inadequate. From 2014 to 2017, FDA consistently responded to its concerns about the data by requesting better data from the TIRF drug manufacturers or conducting its own analysis. In 2019, FDA announced a proposed modification to the TIRF REMS that places a greater emphasis on ensuring that patients who are prescribed TIRF drugs

are opioid-tolerant, including required documentation and a patient registry to capture needed data. However, the new goals no longer say that TIRF drugs should be prescribed and dispensed “only to appropriate patients” (i.e., patients with breakthrough cancer pain), which may signal to prescribers that prescribing TIRF drugs off-label to treat patients with wide-ranging pain symptoms (i.e., low-level chronic pain, post-operative acute pain, etc.) is appropriate.

Similarly, in assessments from 2014 through 2017, poor data left FDA unable to determine whether the REMS for ER/LA opioids was meeting its overarching goal of reducing serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of the drugs. However, FDA did find that manufacturers repeatedly missed the REMS’ targets for training prescribers. As it did with the TIRF REMS, FDA requested that manufacturers of ER/LA opioids submit more and better data from different sources. However, FDA was often so late in providing its reviews to the manufacturers that manufacturers had no time to respond to FDA’s concerns before their next assessments were due. Finally, in 2018 FDA modified the REMS goals for ER/LA opioids, moving away from an attempt to measure outcomes to measuring voluntary prescriber training meant to educate prescribers about risks.

FDA faced additional challenges to ensuring that these REMS mitigate opioid misuse and abuse. In addition to limitations in the data from the drug manufacturers, FDA faced measurement challenges, such as a lack of baseline data, limited surveillance data, and the inability to distinguish the effects of the REMS separate from the other initiatives addressing opioid misuse and abuse. Some opioid manufacturers engaged in deceptive marketing practices that undermined the REMS’ educational messages regarding risk. Furthermore, the fact that both REMS are what is known as “shared system” REMS—meaning that they aggregate their data across drugs and product categories—can mask problems with individual drugs or product categories. Finally, FDA has limited authority to enforce manufacturers’ compliance with their REMS.

### **What OIG Recommends and How the Agency Responded**

The opioid crisis has cost the United States hundreds of thousands of lives and billions of dollars. Although opioid prescribing has decreased by 34 percent since 2012, opioids are still heavily prescribed, and overdoses have continued to claim thousands of lives annually.

Among its other efforts to combat this public health emergency, FDA has used REMS to help mitigate the risk posed by opioids. On the basis of our review, REMS are not well-suited to quickly address the opioid crisis. The REMS for TIRF drugs and ER/LA opioids both rely largely on educating prescribers about the risks of these drugs. This takes time to have an impact on prescribing habits and can be countered by pharmaceutical marketing campaigns designed to increase prescribing. In addition, FDA’s deliberate approach to decision-making, which relies on scientifically robust data, focused FDA’s attention for years on improving the serious data-quality issues.

While FDA and other agencies in HHS continue to address the opioid crisis using a variety of efforts, OIG has the following recommendations for FDA to improve these two opioid REMS:

- use the new TIRF REMS patient registry to monitor for known areas of risk, such as inappropriate conversions (i.e., switching a patient between different TIRF drugs inappropriately) and off-label prescribing;
- strengthen the REMS for opioid analgesics (the successor to the REMS for ER/LA opioids) by requiring training for prescribers;
- enhance its REMS assessment review process by completing its reviews in a timely fashion and seeking information on inappropriate prescribing trends from FDA's Office of Prescription Drug Promotion; and finally,
- seek additional authority to ensure that manufacturers are held accountable when appropriate.

FDA concurred with our first and third recommendations. It did not concur with our second recommendation. It is considering our fourth recommendation.

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# BACKGROUND

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## Objective

To determine the extent to which FDA held drug manufacturers accountable for mitigating the risk of opioid misuse and abuse through Risk Evaluation and Mitigation Strategies (REMS).

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Opioids are powerful, pain-relieving drugs that must be prescribed and used carefully to ensure that their benefits outweigh their risks. Public health experts believe that opioids have been overprescribed since the drugs first became prominent in the mid-1990s. Recent State court settlements have held opioid drug manufacturers accountable for damages resulting from deceptive opioid marketing that started in the mid-1990s.<sup>1</sup>

The widespread overprescribing of opioids in the United States led to increases in opioid-related deaths and opioid dependence treatment.<sup>2</sup> According to the Centers for Disease Control and Prevention (CDC), more than 232,000 people in the United States died from prescription opioid-related overdoses between 1999 and 2018.<sup>3</sup> In 2018, nearly 47,000 people in the United States—an average of 128 people a day—died of opioid-related overdoses, with a quarter of those overdose deaths involving prescription opioids.<sup>4</sup> In 2017, the Acting Secretary of Health and Human Services declared the opioid epidemic a national public health emergency.<sup>5</sup> Added to the toll in lives is an economic toll—researchers estimate that the economic burden from opioid misuse and abuse in the United States exceeds \$78 billion annually.<sup>6</sup>

Within the U.S. Department of Health and Human Services, the Food and Drug Administration (FDA) can play a significant role in the Federal effort to combat opioid abuse. FDA's efforts to address the opioid public health crisis include, but are not limited to, the following: (1) requiring safety-related labeling changes for the extended-release/long-acting (ER/LA) opioid analgesics; (2) requiring manufacturers of ER/LA opioids to formally study the adverse outcomes of abuse, misuse, addiction, overdose, and death among patients prescribed long-term opioid therapy; (3) expanding access to naloxone (a drug that can reverse opioid overdoses); (4) promoting access to medication-assisted treatment for opioid addiction; (5) encouraging opioid formulations that deter abuse; and, (6) encouraging novel, nonopioid treatments for pain.<sup>7</sup>

Another tool that FDA has to address the opioid public health crisis is REMS, a drug safety program. In 2007, after the drug rofecoxib (Vioxx) was associated with a high number of deaths from heart attack and stroke, Congress gave FDA the authority to require drug manufacturers (or companies that own an FDA-approved application) to develop REMS.<sup>8</sup> Required by FDA for certain medications, a REMS is a structured plan

that is intended to manage specific serious safety concerns. The REMS for opioids are intended to mitigate the risk of misuse, abuse, addiction, accidental overdose, and death, while maintaining patient access to these medications. This study focuses on the REMS for two classes of opioids: ER/LA opioids and transmucosal immediate release fentanyl (TIRF) drugs.

## Opioids and the REMS program

### Prescription Opioids

Opioid analgesics approved for marketing in the U.S. come in a variety of chemical formulations, strengths, and delivery systems. For example, some opioids provide an analgesic effect over 24 hours or longer (extended release products), as opposed to immediate release opioids, which act more quickly and last only several hours.<sup>9</sup> Fentanyl, which is 50 to 100 times more powerful than morphine, is a fast-acting opioid approved for breakthrough cancer pain.<sup>10</sup> Opioids can create a euphoric effect, which makes them vulnerable to abuse and misuse (i.e., taking them in a way other than prescribed).

Although opioid prescribing has decreased 34 percent since its peak in 2012, providers prescribed about 80 percent more opioids in 2018 than they did during the 1990s.<sup>11, 12</sup> Experts believe that the long-term trend of overprescribing is a key factor that led to the current opioid crisis.<sup>13, 14</sup> As awareness about the dangers of opioids increased among prescribers and patients, and prescribing decreased, patients who had become addicted to opioids sought heroin and illegally sourced fentanyl. Drug overdose deaths reached a record high in 2017, driven largely by heroin and fentanyl.<sup>15</sup>

### FDA's REMS Program

FDA may approve a drug for marketing in the United States if it is safe and effective for its intended use, although the drug may still have harmful or undesirable side effects.<sup>16</sup> FDA considers a drug safe if its potential benefits outweigh its known and potential risks. Routine measures, such as FDA-approved prescribing information found on a drug's label, may help to ensure this balance for most drugs. However, when there are serious safety concerns about a drug, FDA can require a REMS to ensure that the benefits of the drug outweigh the risks.<sup>17</sup>

A REMS is a drug safety program that uses strategies beyond FDA-approved labeling and is intended to mitigate a specific, serious risk associated with the use of the drug. REMS can include a variety of elements intended to mitigate risk for a drug that would otherwise be unavailable due to known serious risks.<sup>18, 19</sup> These REMS elements may include drug manufacturers providing FDA-approved training to prescribers, or restrictions on how a drug should be prescribed. When establishing the elements in a REMS, FDA considers the burden to the health care delivery system (for example, prescribers and pharmacies) and patient access to the drug.<sup>20</sup>

After FDA decides a REMS is necessary and specifies the requirements, it approves the REMS designed by a drug manufacturer, who is responsible for implementing the program.<sup>21</sup> The drug manufacturer is required to submit assessment reports (assessments) to FDA detailing the implementation and compliance with the requirements as well as the goals and subgoals (FDA refers to these as objectives).<sup>22</sup> Assessments may include updates from the drug manufacturer on its efforts to inform prescribers and other stakeholders about the risk of the drug. The REMS assessment also includes surveillance or other patient outcome data; results of surveys; results of audits; and other metrics as specified in the REMS assessment plan.

FDA's goal is to review a manufacturer's assessment within 6 months.<sup>23, 24</sup> However, FDA told us that more complex assessments may require more time than that to thoroughly review and analyze the data submitted. Multiple divisions within FDA's Center for Drug Evaluation take part in reviewing the assessments.<sup>25</sup> FDA verifies all information that drug manufacturers submit, including statistical analyses, and decides whether to modify the REMS.

Drug manufacturers of products that are in the same class of drug (e.g., a brand-name drug and its generic equivalents) may combine their efforts in what is known as a shared system REMS. In a shared system REMS, multiple drug manufacturers share in the implementation and structure of a single REMS, which aids efficiency and lessens the burden on individual manufacturers, as well as on prescribers and pharmacies. Within a shared system REMS, drug manufacturers may hire contractors to administer the plan and to aggregate data across all drugs within the class. Such aggregated data may include utilization, adverse events, and survey data. The REMS for ER/LA opioids and for TIRF drugs are both shared system REMS.

## REMS for TIRF drugs and ER/LA opioids

### TIRF Drugs

TIRF drugs are short-acting, high-potency, opioid analgesics approved for breakthrough pain in cancer patients who are opioid-tolerant.<sup>26</sup> TIRF drugs are 50 to 100 times more powerful than morphine. Because TIRF drugs are so potent, non-opioid-tolerant patients who use this class of drugs are at an increased risk of life-threatening respiratory depression. Furthermore, because of the pharmacokinetic differences among TIRF drugs, prescribers should exercise care when converting between TIRF drugs—i.e., when switching a patient from one TIRF drug to another—or the patient may have an increased risk of a fatal overdose. Patients must also take care to prevent accidental exposure of TIRF drugs to anyone other than the patient, particularly children.



## Goals of the REMS for TIRF drugs

The overarching goal of the TIRF REMS is to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

- Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients;
- Preventing inappropriate conversion between TIRF medicines;
- Preventing accidental exposure to children and others for whom [TIRF medicines were] not prescribed; and
- Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

Source: FDA's final review of REMS for TIRF drugs, 2011.

FDA approved the shared system REMS for TIRF drugs in 2011; it initially included five drugs produced by four drug manufacturers.<sup>27</sup> Since 2015, FDA has modified the shared system TIRF REMS to include nine drugs produced by eight drug manufacturers.<sup>28, 29</sup> TIRF medicines include fentanyl sublingual and buccal tablets; lozenges; nasal sprays; and buccal-soluble film.

Because TIRF drugs have such high risk, the TIRF REMS is designed to be restrictive. Some of its requirements are as follows:

- Prescribers and pharmacists must become certified by taking training every 2 years and enrolling with the REMS program.
- Representative samples of prescribers and pharmacists must take a knowledge survey for each assessment.
- Only specially certified pharmacies can dispense TIRF drugs.
- TIRF drugs can be dispensed for outpatient use only with evidence of safe-use conditions.
- Patients must complete a Prescriber-Patient Agreement Form that states they understand the risks of TIRF drugs. Patients must renew these forms every 2 years.

The TIRF drug manufacturers submit REMS assessments to FDA at 6 months and 12 months after the initial approval date of the REMS, and annually thereafter. FDA's goal is to review each assessment within 6 months of receiving it and provide feedback to the drug manufacturers. Each assessment includes updates on the implementation of the various REMS elements or analyses based on data from the period of the assessment. See Appendix A for a detailed list of the TIRF REMS' requirements, by assessment period.

## Extended release/long-acting opioid drugs

ER/LA opioids are powerful analgesic medications approved to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. FDA approved the shared system REMS for ER/LA opioids in 2012. Initially, it applied to 16 drugs produced by 8 drug manufacturers. As of 2017, it covered 67 brand-name and generic drugs produced by 33 drug manufacturers.<sup>30</sup> The most prescribed ER/LA opioids are oxycodone, morphine, fentanyl, and methadone.<sup>31</sup>

### Goal of the REMS for ER/LA opioids

**The goal of the REMS for ER/LA opioids is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of these medications while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.**

Source: FDA's review of manufacturers' 6-month assessment report for the REMS for ER/LA opioids, 2013.

The main component of the ER/LA REMS was a voluntary education program for prescribers. The REMS required drug manufacturers to make education programs available to prescribers of ER/LA opioids. The drug manufacturers met this requirement by providing grants to accredited continuing education organizations. These organizations designed and administered the educational materials based on core educational messages provided by FDA.<sup>32</sup> Each annual assessment had a training target for the number of prescribers who should be trained by certain time intervals after training became available:

- 2 years: 80,000 prescribers
- 3 years: 160,000 prescribers
- 4 years: 192,000 prescribers.<sup>33</sup>

The additional components of the REMS for ER/LA opioids include:

- a medication guide that is dispensed with each prescription;<sup>34</sup>
- a timetable for the drug manufacturers to submit assessments;
- a patient counseling document for prescribers to assist them in properly counseling patients;
- letters to prescribers informing them of the existence of the REMS and educational activities; and
- a website and call center with information that prescribers can use to aid in counseling patients on the risks and benefits of ER/LA opioids.<sup>35</sup>

As with the TIRF REMS, manufacturers of ER/LA opioids submit REMS assessments to FDA at 6 months and 12 months after the initial approval date of the REMS, and annually thereafter. Each assessment includes updates on the implementation of the different REMS elements or analyses based on data from the assessment period. See Appendix A for a detailed list of requirements of the REMS for ER/LA opioids, by assessment period.

## Previous OIG work

This work contributes to the Office of Inspector General's body of work on opioids by shedding light on the role that REMS have played in addressing the opioid epidemic. A 2013 OEI report on FDA's REMS program raised concerns about FDA's process for reviewing REMS and the overall effectiveness of the program.<sup>36</sup> Specifically, the report found that for the REMS we reviewed, (1) half of the assessments that drug manufacturers submitted were incomplete, (2) less than 15 percent of REMS had met their goals, (3) FDA had not identified reliable methods to assess the effectiveness of REMS, and (4) FDA's review teams for manufacturers' assessments exceeded its goal of 60 days for almost all assessments.

The OIG report made seven recommendations based on its findings. The three recommendations that remain unimplemented are those for FDA to (1) identify REMS that are not meeting their goals and take appropriate actions to protect the public health, (2) seek legislative authority to enforce FDA assessment plans, and (3) ensure that assessment reviews are timely.<sup>37</sup>

## Methodology

### Scope

We limited our study to the shared system REMS for ER/LA opioids and TIRF drugs from their approval by FDA (2012 and 2011, respectively) through 2017. We based the study on reviews of drug manufacturer assessments submitted to FDA and related documents from that period, and interviews with relevant FDA officials.

### Document review

We analyzed all documentation for the REMS for ER/LA opioids and TIRF drugs, including the following: the 6-, 12-, 24-, 36-, 48-, and 60-month assessments submitted by drug manufacturers through 2017; FDA reviews of these manufacturers' assessments; inspection reports; and other analyses and correspondence. Both REMS have continued to be in effect during the period of our analysis.

We analyzed the documents for the two REMS to identify several elements, including the extent to which:

- drug manufacturers submitted their assessments on time;

- drug manufacturers' assessments were complete;
- FDA submitted its reviews of those assessments on time;
- FDA identified deficiencies or requested modifications; and
- the REMS for ER/LA opioids and for TIRF drugs were meeting their respective goals.

## Interviews

We conducted structured interviews with FDA staff. We asked them questions about FDA oversight of the REMS for ER/LA opioids and for TIRF drugs and about the challenges they face. We also asked FDA about its policies and procedures related to REMS oversight and updates on implementing recommendations from the 2013 OIG report.

## Standards

We conducted this study in accordance with the *Quality Standards for Inspection and Evaluation* issued by the Council of the Inspectors General on Integrity and Efficiency.

# FINDINGS

## FDA's reviews raised questions about the effectiveness of the REMS for TIRF drugs, but data quality affected timely oversight

After FDA approved the REMS for TIRF drugs in 2011, TIRF manufacturers spent the first 2 years getting their REMS established. FDA found the assessments that drug manufacturers submitted during this time to be timely and complete.

Starting with the 24-month assessment and continuing through the 60-month assessment, FDA found data in the assessments suggesting that the manufacturers were not meeting all their goals. FDA also found the data for some of the REMS goals to be inadequate. Given FDA's deliberate approach to decision-making that relies on scientifically robust data, FDA consistently responded to its concerns about the data by requesting better data from the TIRF drug manufacturers or conducting its own analysis.

In March 2019 FDA announced a modification to the TIRF REMS. This modification included new goals and processes aimed at better ensuring safer, more appropriate prescribing of TIRF drugs.

### FDA reviews raised questions about the TIRF REMS's ability to measure and meet its goal to mitigate the risk of misuse and abuse

Starting with the 36-month assessment, FDA struggled to determine from the data that TIRF manufacturers submitted how well they were meeting the TIRF REMS' overarching goal and subgoals. For example, FDA found in its reviews of the 36-month and 48-month assessments that it could not determine whether manufacturers were meeting the TIRF REMS' overarching goal. (FDA did not directly address the overarching goal in its review of manufacturers' 24-month assessment.) FDA also found that it could not determine from the assessments at the 24-, 36-, 48-, and 60-month points—assessments that manufacturers submitted from 2013 to the end of 2016—whether manufacturers had met many of the TIRF REMS' subgoals. In five instances, FDA determined that two of the subgoals had not been met or had

#### Goal—REMS for TIRF Drugs

Mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

#### Subgoals

Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

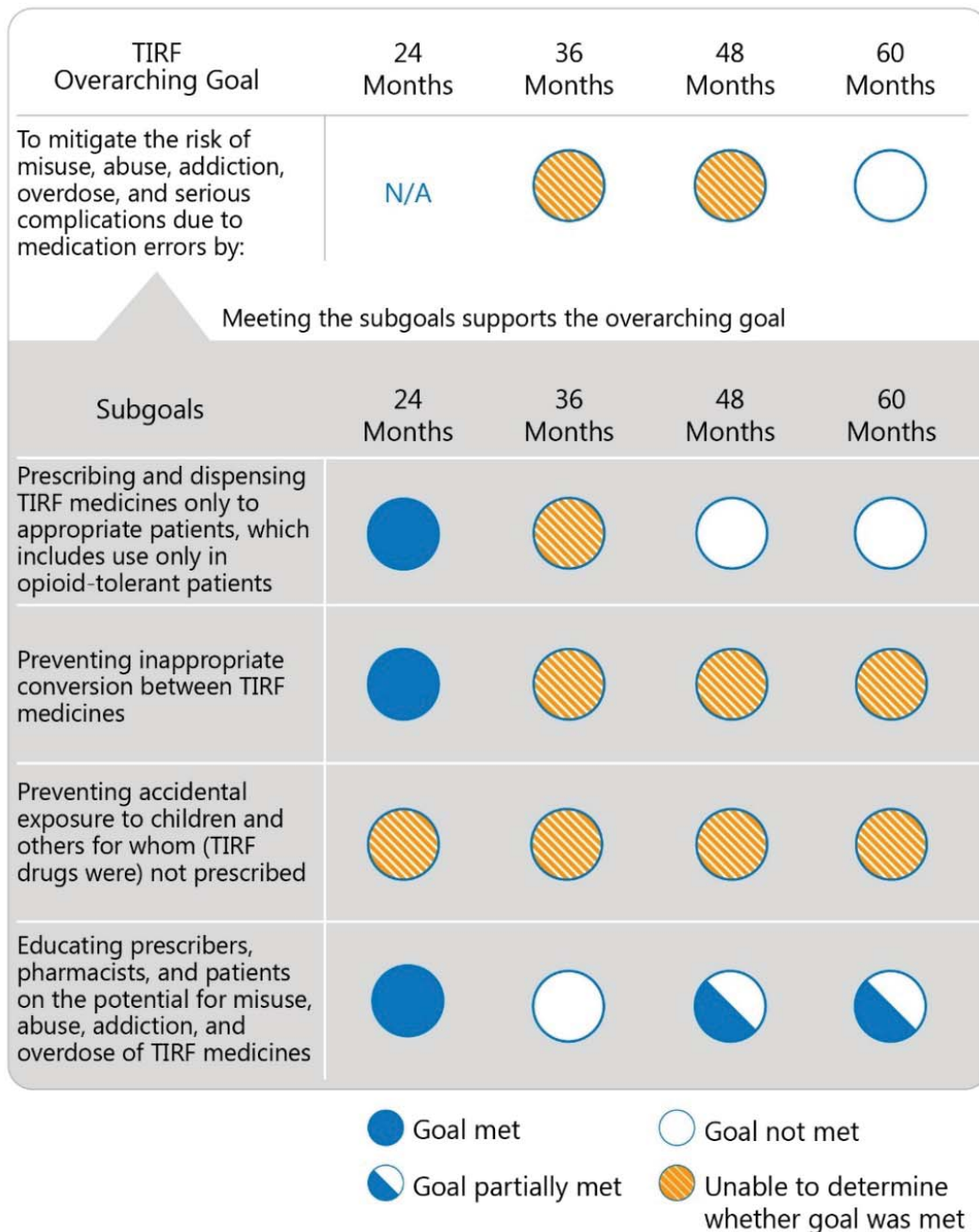
Preventing inappropriate conversion between TIRF medicines.

Preventing accidental exposure to children and others for whom TIRF medicines were not prescribed.

Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

been only partially met. In its review of the 60-month assessment, FDA determined that manufacturers had not met the REMS' overarching goal. See Exhibit 1.

**Exhibit 1: After its 24-month assessment review, FDA was increasingly unable to determine whether manufacturers met the overarching goal and subgoals of the TIRF REMS**



Source: OIG analysis of FDA documents.  
 Note: FDA did not directly address the overarching goal in its review of the assessment that manufacturers submitted at the 24-month point of the REMS.

## FDA worked with manufacturers to get better data and analysis from 2014 through 2017

FDA's reviews of the 24-, 36-, 48-, and 60-month assessments consistently raised concerns about some of the data that manufacturers had submitted, which sometimes made it difficult for FDA to determine whether manufacturers were meeting the REMS' overarching goal and subgoals. In an effort to obtain high-quality data to support its decision making, FDA requested additional data and analysis from drug manufacturers after each review, starting with its review of the 24-month assessment, which it completed in 2014.

### 24-month assessment

- Disorganized data
- Data that did not directly address the goals

Submitted:

December 2013

Review Completed:

June 2014

FDA noted that drug manufacturers' data in the 24-month assessment were disorganized and did not directly measure the goals of the TIRF REMS. In particular, FDA noted that the data were inadequate to address the goals related to inappropriate conversions and opioid tolerance. FDA found adverse-event data to be problematic, as those data lacked clinical details including information about inappropriate conversions, opioid tolerance, and patient outcomes. Additionally, FDA found the dispensing data that drug manufacturers submitted to address the subgoal of preventing inappropriate conversions between TIRF drugs—conversions that could lead to an increased risk of fatal overdoses—did not directly measure outcomes for this subgoal (e.g., by using claims data to show that physicians who converted their patients from one TIRF drug to another did so correctly). Rather, the TIRF manufacturers submitted survey data that measured prescribers' awareness of the dangers of inappropriate conversions between TIRF drugs.

Furthermore, FDA's review found that survey data included within the assessment raised questions about whether the REMS was meeting the fourth subgoal, related to educating prescribers and pharmacists. The data that manufacturers submitted showed that only 59 percent of prescribers and 47 percent of pharmacists surveyed knew the correct medical indication for TIRF drugs (breakthrough cancer pain).<sup>38</sup> In both instances, the FDA reviewer was uncertain as to whether prescribers were unaware of the approved indication for TIRF drugs, or prescribers knew the approved indication and disregarded it.

- In response to these concerns, FDA asked for more and better data in its review of the 24-month assessment. For example, FDA asked for additional adverse-event data (including details of how the data were collected) and for questions to be added to the surveys.

### 36-month assessment

- Data that did not directly address the goals

Submitted:

December 2014

Review Completed:

July 2014

For the 36-month assessment, which FDA received in late 2014, FDA once again determined the data to be inadequate with regard to the same three subgoals (i.e., those related to opioid tolerance, inappropriate conversions, and adverse events).

FDA noted that the manufacturers submitted adverse events reports as evidence related to the subgoals regarding prescribing only to opioid-tolerant patients and avoiding inappropriate conversions between TIRF drugs. However, these reports do not capture information about patients' opioid tolerance or inappropriate conversions between TIRF drugs. These reports, as well as FDA's own analysis, left FDA unable to

determine whether the TIRF REMS was meeting its overall goal of mitigating the risk of misuse and abuse that can lead to addiction, overdose, and serious complications due to medication errors.<sup>39</sup>

- In response, FDA requested better data from drug manufacturers when it completed its review. For example, FDA provided drug manufacturers with explicit instructions on how to conduct analyses to determine whether only opioid-tolerant patients were being prescribed TIRF drugs and to identify inappropriate conversions between TIRF drugs.

#### 48-month assessment

- Lack of prescriber knowledge of appropriate prescribing

Submitted:

December 2015

Review Completed:

June 2016

In December 2015, the 48-month assessment that manufacturers submitted continued to raise FDA's concerns that the subgoals related to opioid tolerance, inappropriate conversion, and preventing adverse events were not being met.

FDA remained concerned about the quality of data on prescribing only to opioid-tolerant patients. In response, it asked manufacturers for better data, and they submitted patient summary data that were aggregated. Those data suggested that 42 percent of patients were not opioid-tolerant when they were first prescribed a TIRF drug, potentially exposing these patients to an increased risk of life-threatening respiratory depression. An FDA reviewer shared these concerns with the manufacturers and wrote: "[T]his finding is concerning and the [drug manufacturers] should investigate and implement a process to ensure that TIRF prescribers are aware of the need for their patients to be opioid-tolerant."<sup>39</sup>

Similarly, FDA again raised concerns about the subgoal related to inappropriate conversion between TIRF drugs. Incomplete data in the assessment showed that about 17 percent of patients had been switched by their prescribers from one regimen of TIRF drugs to another. Among those 17 percent of patients, about one-fifth were switched to yet another regimen of TIRF drugs. However, these data submitted by the drug manufacturers did not measure whether these conversions between TIRF drugs were inappropriate. FDA called for further study by the manufacturers.

Finally, FDA found that the manufacturer data on adverse events raised concerns about off-label prescribing of TIRF drugs. Those data showed that among the 291 deaths associated with TIRF drugs, as many as 57 percent may have involved off-label use.<sup>40</sup> The prescriber survey data demonstrated that some prescribers believed that chronic *noncancer* pain was an appropriate indication for prescribing TIRF drugs. These prescribers stated that they were prescribing TIRF drugs for back pain, neuropathic pain, and post-operative pain. Their motivation for prescribing TIRF drugs off-label included the failure of other drugs, as well as TIRF drugs' efficacy and fast-acting nature.

- In response to these findings, FDA requested that the drug manufacturers conduct additional analysis on opioid tolerance—to include (for comparison purposes) analysis on opioid tolerance before and after the 2011 establishment of the REMS—as well as analysis on inappropriate conversions.



FDA also requested a meeting to discuss prescribers' low awareness of the appropriate medical indications for prescribing TIRF drugs.

#### 60-month assessment

- Concerning data on opioid tolerance
- FDA's analysis suggests an increase in adverse events over time

Submitted:

December 2016

Review Completed:

December 2017

The 60-month assessment again caused FDA concern regarding opioid tolerance, adverse events, off-label prescribing, and provider education. For example, FDA found that the assessment contained concerning data regarding opioid tolerance. The drug manufacturers' data showed that 35 to 55 percent of patients who were prescribed a TIRF drug were not opioid-tolerant.<sup>41</sup> Non-opioid-tolerant patients who use TIRF drugs are at an increased risk of life-threatening respiratory depression.

FDA also found that the 60-month assessment included inadequate data, specifically on adverse events. In response, FDA conducted its own analysis of adverse events and off-label use covering the previous 20 years, which raised further questions about the REMS' effectiveness and data quality.<sup>42</sup> FDA found that the number of adverse event cases suggesting off-label use increased after 2011. FDA also noted that rates of abuse adjusted for prescribing level increased after the REMS was established. FDA wrote: "[T]he current presentation of the data suggests that, despite the presence of a REMS, we observed an increasing trend in prescription-adjusted rates of abuse and other significant outcomes for TIRFs over the time period."<sup>43, 44</sup>

In addition, the data in the assessment raised questions about the effectiveness of the educational efforts. FDA determined that manufacturers had only partially met the TIRF REMS' subgoal of educating prescribers, pharmacists, and patients on TIRF risks. TIRF prescribers and pharmacists who were enrolled in REMS—and thus had received training on the appropriate prescribing of TIRF drugs and their risks—failed to correctly answer questions in a survey about key risk messages. For example, 23 percent of prescribers incorrectly responded that patients could continue to take TIRF medicines even after discontinuing around-the-clock use of opioids. The TIRF REMS training states that patients who do this are at an increased risk of death. Like prescribers, the surveyed patients and pharmacists also consistently failed to answer questions correctly. See Appendix B for the results of the knowledge survey goals required by the REMS for TIRF drugs that failed to meet performance goals.

- In response to these findings, FDA requested that the drug manufacturers conduct additional analysis on opioid tolerance. It also requested that the drug manufacturers submit adverse-event data broken out by each TIRF drug. FDA held a public advisory committee meeting about the TIRF REMS in 2018.

## FDA modified the goals of the TIRF REMS in 2019 to improve processes for appropriate prescribing

FDA required modification, March 2019

In August 2018, FDA held a public advisory committee meeting to discuss results from the manufacturers' assessments of the TIRF REMS and possible modifications to the structure of the TIRF REMS. A group of researchers submitted comments to the advisory committee that also questioned the efficacy of the TIRF REMS and contended that FDA had years of evidence pointing to inappropriate prescribing and limited oversight.<sup>45</sup>

The advisory committee meeting included recommendations that would lead to a modification to the TIRF REMS. The advisory committee recommended that no further study of inappropriate conversions was needed as the data suggested that dosing conversions between TIRF medicines occurred infrequently, and that conversion guidance for prescribers is available in labeling and other online sources.<sup>46</sup> In the same meeting, FDA clarified that the TIRF REMS was not necessarily intended to restrict off-label prescribing, but rather to ensure patients who were prescribed the drug were opioid-tolerant.<sup>47</sup>

In March 2019 FDA announced a modification to the TIRF REMS. This modification included new goals and processes. The new goals place a greater emphasis on ensuring that patients who are prescribed TIRF drugs are opioid-tolerant. New processes include requiring documentation that patients are opioid-tolerant and creating a patient registry to better monitor adverse events, including accidental exposure, misuse, abuse, addiction, and overdose. In a letter to manufacturers of TIRF drugs, FDA cited the inadequacy of available data submitted by manufacturers in assessment reports as the reason for creating the patient registry.

#### **Goals of the REMS for TIRF drugs (submitted by drug manufacturers in 2019; currently under FDA review)**

- 1. Mitigate the risk of overdose by:**
  - a) Requiring documentation of opioid tolerance with every TIRF prescription for outpatient use.**
  - b) Requiring inpatient pharmacies to verify opioid tolerance in inpatients who require TIRF medicines while hospitalized.**
  - c) Educating prescribers, pharmacists, and patients that the safe use of TIRF medicines requires patients to be opioid-tolerant throughout treatment.**
- 2. Mitigate the risk of accidental exposure by educating health care providers (HCPs) and patients about proper storage and disposal of TIRF medicines.**
- 3. Assess safe use and trends in accidental exposure, misuse, abuse, addiction, and overdose by enrolling all patients who receive a TIRF medicine for outpatient use in a registry.**

Source: FDA's REMS modification letter to manufacturers of TIRF drugs, 2019.

The modifications hold some promise for enhancing the TIRF REMS, but they may not fully address all the shortcomings that FDA identified. For example, the addition of a registry will likely lead to better data on adverse events. However, the proposed goals no longer say that TIRF drugs should be prescribed and dispensed "only to appropriate patients" (i.e., patients with breakthrough cancer pain), which may signal to prescribers that prescribing TIRF drugs off-label to treat patients with wide-ranging pain symptoms (i.e., low-level chronic pain, post-operative acute pain, etc.) is appropriate. Off-label prescribing is legal, but can be abused, as it has been with TIRF

drugs in the past. Lastly, the new goals do not directly address inappropriate conversions.

*"The prescribing of these medicines for non-FDA approved uses to non-opioid-tolerant patients tells us that there may be a disconnect between prescriber knowledge and prescriber behavior.... While all opioids pose serious risks, these are not your typical opioids and should be prescribed by providers with extra care and attention."*

**Former FDA Commissioner Scott Gottlieb, M.D.**

Source: Statement by then-Commissioner Scott Gottlieb, March 27, 2019.

## After being unable to determine whether the REMS for ER/LA opioids reduced adverse outcomes, FDA modified the REMS' goal to focus instead on education

In 2012, the year after FDA approved the TIRF REMS, FDA approved the REMS for ER/LA opioids. ER/LA opioids are powerful analgesic medications approved to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment. ER/LA opioids are addictive and are more commonly prescribed than TIRF drugs.

The manufacturers of ER/LA opioids spent the first 2 years getting their REMS established. FDA found the assessments that drug manufacturers submitted during this time (at 6 and 12 months) to be timely and complete. The goal of the REMS for ER/LA opioids was to reduce serious adverse outcomes. While baseline data on adverse outcomes caused by ER/LA opioids was available, FDA found that it was not possible to attribute any changes in adverse outcomes directly to the REMS efforts. A peer-reviewed research article published in December 2019 cited similar findings.<sup>48</sup> Furthermore, FDA questioned manufacturer-submitted data on ER/LA opioids, but its late reviews limited the effectiveness of its oversight and delayed its eventual modification of the REMS.

### FDA could not determine whether the REMS for ER/LA opioids was meeting its overarching goal of reducing serious adverse outcomes, but the agency found that manufacturers did not meet targets for training prescribers

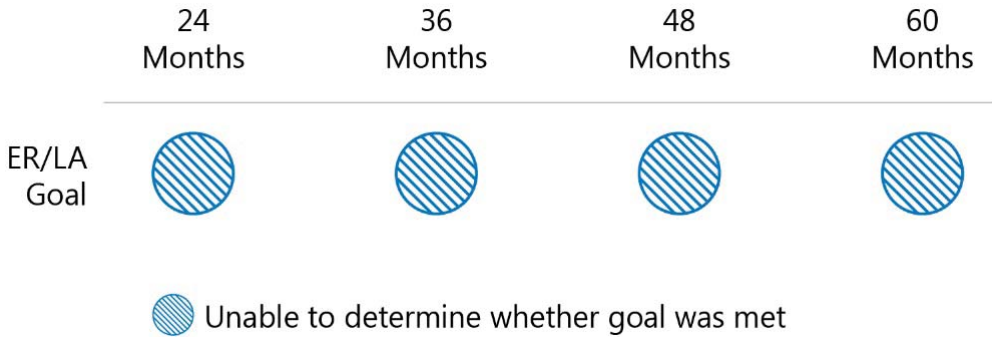
Starting with the 24-month assessment in 2014, FDA reviewers were skeptical of ER/LA opioid manufacturers' claims about reducing adverse outcomes. In an effort to obtain high-quality data to

Reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics, while maintaining patient access to pain medications

support its decision making, FDA stated that it would need more data to confirm manufacturers' claims about progress.

Despite having received additional data from manufacturers, FDA remained skeptical upon reviewing the 36-month assessment (submitted in 2015). That was the first assessment that included all necessary data to address progress in reducing adverse outcomes, and the drug manufacturers reported decreases both in adverse outcomes and in prescribing. However, upon further analysis, FDA found that both had been decreasing since before the REMS began, making it impossible for FDA to attribute the decreases to the REMS with the data provided by drug manufacturers. As a result, FDA was unable to determine whether the manufacturers met the REMS' goal in the 36-month review and all subsequent reviews.<sup>49</sup> See Exhibit 2.

**Exhibit 2: FDA was unable to determine whether manufacturers met the overarching goal of the REMS for ER/LA opioids**



Source: OIG analysis of FDA documents

In addition, FDA found that manufacturers of ER/LA opioids failed to meet training targets. For the three assessment periods in which the manufacturers were required to report the number of prescribers trained on safe prescribing habits for opioids, manufacturers failed to achieve even half their annual training targets. They noted that it was considerably more challenging than expected to get prescribers to take the training, because many other sources for training related to opioids became available. Prescribers could not distinguish between training associated with REMS. See Exhibit 3.

### Exhibit 3: Manufacturers of ER/LA opioids failed to achieve even half of the REMS' targets for training prescribers

Assessment	Target number	Actual number	Percentage of target
36-month	80,000	37,512	47%
48-month	160,000	66,881	42%
60-month	192,000	88,316	46%

Source: OIG analysis of FDA documents

### FDA's late reviews of the assessments from manufacturers of ER/LA opioids limited the effectiveness of its oversight

From 2015 through 2018, FDA was late in completing its reviews of assessments from manufacturers of ER/LA opioids (see Appendix C). In 2015, FDA took just 1 month beyond its goal of 6 months to complete the review, but by 2016, FDA was late by 6 months. That means that after receiving the 36-month assessment from manufacturers of ER/LA opioids, FDA took more than a year to request, in July 2016, that the manufacturers find other data sources and conduct new analyses to properly assess whether the REMS had contributed to the decreases in adverse outcomes and prescribing. Five weeks later, in September 2016, manufacturers submitted their 48-month assessment. This assessment contained data and analysis methods that mirrored what manufacturers had submitted in the 36-month assessment. FDA had determined those methods to be inadequate, but 5 weeks was not enough time for manufacturers of ER/LA opioids to revise their approach.

FDA continued to be late in its reviews of manufacturers' assessments, further disrupting the intended cycle. In June 2017, when FDA received the 60-month assessment from manufacturers, it had not yet completed its review of the 48-month assessment. FDA informed the drug manufacturers that it would withhold comments on the 48-month assessment and submit them along with its comments on the 60-month assessment. FDA was 2 months late in submitting its review of manufacturers' 60-month assessment (together with its comments on the 48-month assessment). As a result, manufacturers of ER/LA opioids were unable to address the deficiencies that FDA identified in the 48-month assessment until they submitted the 72-month assessment.

### In 2018, FDA modified the REMS to make the overarching goal more measurable by focusing on education rather than outcomes

FDA required modification:  
September 2018

Shortly after the 72-month assessment period, and after 4 years of questioning drug manufacturers' ability to measure the REMS's success in reducing prescribing rates and serious adverse outcomes, FDA modified the REMS for ER/LA opioids. In 2018,

FDA completely changed the goal and also modified the REMS to include not just ER/LA opioids, but also immediate-release opioids. Accordingly, FDA changed the name of the REMS, making it the REMS for Opioid Analgesics.

The REMS' new goal no longer focuses on outcomes; instead, it changes the focus to education for prescribers and healthcare providers. Although education is measurable, it does not necessarily follow that prescriber and healthcare provider education mitigates the risk of opioid misuse and abuse. Rather, the goal now focuses on prescribers and other healthcare providers being trained on the fundamental concepts of pain management and how to counsel

patients about the safe use of opioids. During a 2016 advisory committee meeting, FDA sought feedback from committee members on the issue of mandatory training for prescribers. Most advisory committee members recommended that training be required.<sup>50</sup> FDA decided—citing potential impact on appropriate patient access and burden to the health care delivery system—that the modified REMS would not require prescribers to take the training; training remains voluntary.

To educate prescribers and other healthcare providers (including pharmacists and nurses) on the treatment and monitoring of patients with pain by:

1. Ensuring that training is effective in educating prescribers and other health care providers, and
2. Informing patients about their roles and responsibilities regarding their pain treatment plan

## FDA faces challenges to ensuring that REMS mitigate opioid misuse and abuse

While the severity of the opioid crisis became more apparent over time and the Federal Government and States launched initiatives to combat opioid abuse, FDA was struggling to measure the effectiveness of the REMS for TIRF drugs and the REMS for ER/LA opioids in mitigating the misuse of opioids. According to FDA, the following factors have contributed to the agency's struggles to ensure that the two REMS meet their goals: difficulty in measuring progress, the mandate to minimize the extent to which REMS creates a burden to the health care system, and limited enforcement authority.

### Because of measurement challenges, FDA struggled to determine the extent to which REMS were effective

FDA faces measurement challenges in addition to the limitations in the data from the drug manufacturers. For example, the lack of baseline data, such as that on preventing inappropriate conversions between TIRF medications, hampers meaningful comparisons. FDA also stated that surveillance data are limited because no single, reliable national databases exist that capture all adverse events. Additionally, no good linkages exist across the existing surveillance databases.

Further complicating FDA's ability to determine whether REMS are effective are the various other efforts underway to address the opioid epidemic. These efforts include (among others) new standards for prescribing opioids and increased use of prescription drug monitoring programs. These additional efforts have made it difficult to determine whether REMS are having a positive impact or other interventions are responsible for the outcomes. The array of initiatives addressing opioid misuse and abuse make it difficult to distinguish the individual effects of the REMS.

Finally, although FDA told us that opioid manufacturers had made a good-faith effort to meet the requirements of the REMS, some manufacturers engaged in deceptive marketing tactics. For example, recent State court settlements have held opioid drug manufacturers accountable for damages resulting from deceptive opioid marketing that started in the mid-1990s.<sup>51</sup> Such deceptive marketing practices may undermine the educational messages of the REMS training and the overall effectiveness of the two REMS.

### **Shared system REMS help reduce burden but may mask problems with individual drugs or product categories**

Shared system REMS aid efficiency and lessen the burden on individual manufacturers, prescribers, and pharmacies. Indeed, the Food and Drug Administration Amendments Act, which provided FDA with the authority to require REMS, calls on FDA to minimize the burden of REMS on the health care system and patients.

However, a shared system REMS can also lead to less precise analysis. In the aim of reducing burden, shared system REMS aggregate data across drugs and product categories. When needed to further explore a potential problem or safety concern, FDA has requested product-specific data from manufacturers to support its analysis. For example, when FDA conducted its review of TIRF drug manufacturers' 48-month assessment, it began to get a clearer picture of how TIRF drugs were prescribed off-label. When FDA reviewed the 60-month assessment, it more clearly established that this was the case but was still unable to determine whether the problem was caused by one specific TIRF product. After this review, FDA had to request that the drug manufacturers submit product-specific reports in their 72-month assessment.

### **FDA has limited enforcement authority associated with REMS; it did not exercise that authority for the opioid REMS**

For a manufacturer that violates an approved REMS, FDA can exercise its authority and regulatory discretion to, among other things, deem a drug misbranded or impose civil monetary penalties.<sup>52, 53</sup> As of September 2019, FDA had not determined that there were violations of either of the two shared system REMS. FDA told us that sometimes a REMS may not be meeting its goals because of unforeseen

circumstances and through no fault of a manufacturer. Under those circumstances, FDA would generally modify a REMS.



# CONCLUSION / RECOMMENDATIONS

With nearly 47,000 overdose deaths in 2018, the opioid crisis continues to be a serious public health emergency and has an associated economic burden that is estimated at \$78 billion annually. Most overdose deaths have been caused by illegally sourced fentanyl, but people who abuse opioids are often introduced to opioids via prescriptions for legal opioids. Although opioid prescribing has been decreasing since 2012, opioids are still heavily prescribed.

FDA has taken many steps to address the opioid crisis, such as expanding access to naloxone and promoting access to medication-assisted treatment for opioid addiction. Among those steps, FDA has also used REMS.

Based on our review, it appears that REMS are not well-suited to quickly address the opioid crisis. The REMS for TIRF and ER/LA opioids both rely largely on prescriber education to change prescribing habits. This takes time to have an impact and can be countered by pharmaceutical marketing campaigns designed to increase prescribing. In addition, FDA's deliberate approach to decision-making—which is central to its mission to protect the public's health—relies on scientifically robust, accurate data, which focused FDA's attention, for years, on improving the serious data-quality issues in the manufacturer-submitted assessments.

By 2019, FDA modified both REMS. The updated goals for the REMS for TIRF drugs hold some promise. The more prescriptive goals focus on areas of high concern such as prescribing only to opioid-tolerant patients and establish requirements to gather better data to better monitor adverse events, including accidental exposure, misuse, abuse, addiction, and overdose. However, the new goals omit references to appropriate prescribing and inappropriate conversions, which are also of concern. In addition, although the changes to the REMS for ER/LA opioids (which has been broadened and is now the REMS for opioid analgesics) include a new goal that focuses on education and training, FDA made that training voluntary rather than requiring that providers take the REMS training, in part because of its concerns about burden on drug manufacturers, prescribers, and pharmacies.

## **We recommend that FDA:**

### **Use the new TIRF REMS patient registry to monitor for known areas of risk, such as inappropriate conversions and off-label prescribing**

The previous goals for the TIRF REMS specifically addressed inappropriate conversions. FDA's review of multiple TIRF assessments demonstrated that this was

an area of risk and concern. However, FDA's modification of the TIRF REMS eliminated this goal. According to FDA, the data suggested that dosing conversions between TIRF medicines occurred infrequently, and that conversion guidance for prescribers is available in labeling and other online sources. However, prescribers do not always seek out labeling and other sources for dosing information. Because of the differences among TIRF drugs, prescribers should exercise care when converting between TIRF drugs—i.e., when switching a patient from one TIRF drug to another—or the patient may have an increased risk of a fatal overdose. Given that the new patient registry will make data more readily available, FDA should monitor the data for inappropriate conversions.

The new proposed goals for the TIRF REMS also no longer state that TIRF drugs should be prescribed and dispensed “only to appropriate patients.” Supporting this decision, FDA stated that the REMS for TIRF drugs was not intended to prevent off-label prescribing, but rather to ensure that patients who were prescribed the drug were opioid-tolerant.

We appreciate that FDA does not want to interfere with the prescribing habits of physicians and that off-label prescribing is generally legal; however, using TIRF drugs for a purpose other than for which they were clinically tested and approved could have serious health consequences. Furthermore, off-label prescribing has been a known area of risk for TIRF drugs. In May 2019, a Federal jury found executives from the pharmaceutical company that makes Subsys (a TIRF medicine included in the REMS) guilty of bribing medical practitioners to prescribe Subsys off-label.<sup>54</sup> FDA approved TIRF drugs for the management of breakthrough pain in adult cancer patients who are already tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain. TIRF drugs are 50 to 100 times more powerful than morphine and can cause life-threatening respiratory depression in patients who are not opioid-tolerant.

Given the risk, monitoring off-label prescribing could flag safety issues. Concerning patterns of off-label prescribing could be flagged for further review regarding clinical safety or referred to enforcement agencies for possible violations of off-label marketing by manufacturers.

## **Strengthen the REMS for opioid analgesics (the successor to ER/LA opioids) by requiring prescriber training**

FDA should take advantage of its existing authorities and require prescriber training for the REMS for opioid analgesics rather than leaving it voluntary. Although changing prescriber behavior through education certainly has its limits, as this report acknowledges, taking strong steps to ensuring that prescribers have the expertise to appropriately prescribe opioids is critical. Prescribers are the clinical gatekeepers for drugs that have harmed patients and communities across the country. Furthermore, during a 2016 advisory committee meeting, most of the advisory committee members recommended that training be required. There are a number of ways that FDA could

do this while working to minimize burden on providers. For example, according to FDA, most, but not all, States currently require some opioid-related education for physicians' State licensure. FDA could allow this training, if the content meets FDA approval, to meet some or all of the mandated prescriber training needed for the REMS.

## **Enhance its REMS assessment review process**

FDA should take additional steps to enhance its review of the REMS assessments submitted by manufacturers for the REMS for TIRF and opioid analgesics. First, FDA should strive to meet its REMS review goal of 6 months. We recognize the challenges inherent in balancing FDA's reliance on careful analysis with the importance of providing timely feedback to manufacturers. However, fighting the opioid epidemic is a top HHS priority and, in response to the urgent need to continue to combat the opioid crisis, FDA should strive to do more to ensure its reviews are completed in time for manufacturers to be able to respond to the feedback in the next assessment. Second, FDA should seek to include a wide range of information to fully understand prescribing patterns and their association with opioid abuse, misuse, and overdoses. For example, FDA could include information from FDA's Office of Prescription Drug Promotion in its REMS assessment review process. This office has the potential to provide useful information regarding how manufacturers are promoting opioids and inappropriate opioid prescribing trends.

## **Seek additional authority to ensure that manufacturers are held accountable when appropriate**

FDA can exercise its authority and regulatory discretion to, among other things, deem a drug misbranded or impose civil monetary penalties on manufacturers that violate approved REMS. However, these measures are not necessarily practical for simple violations of REMS requirements and could reduce access to appropriately prescribed drugs. FDA should seek additional, more streamlined authority to levy fines against companies when they violate their REMS. One example of a violation might be a manufacturer failing to make a good-faith effort to provide data to FDA that are readily available.

# AGENCY COMMENTS AND OIG RESPONSE

FDA concurred with our first recommendation and noted that its 2019 proposed modification of the REMS for TIRF drugs would add a patient registry. This registry would enable FDA to better monitor usage in outpatients taking a TIRF medicine with respect to opioid tolerance and related serious adverse events including overdose and death. This registry will capture specific drug and dosing information for each patient, allowing for the monitoring of inappropriate dosing conversions between TIRF medicines. Furthermore, it will also capture information on the type of pain the patient is experiencing (e.g., cancer or noncancer pain), which will enable monitoring of off-label use. We look forward to FDA providing an update on its monitoring efforts in its Final Management Decision.

FDA did not concur with our second recommendation and noted that it supports education for all opioid prescribers but does not believe that mandating education through the REMS for opioid analgesics (the successor to ER/LA opioids) is a practical solution. FDA stated that such a mandate would require setting up a restrictive program, similar to the REMS for TIRF drugs, but on a much larger scale. FDA noted that by raising barriers to health care providers, such a system could restrict patient access to the medications. We acknowledge that establishing a restrictive system for the REMS for opioid analgesics could be burdensome and potentially impact patient access to these drugs. However, given that providers are the frontline gatekeepers for drugs that contribute to the opioid crisis, it is critical that their clinical decisions be informed by the most up-to-date, unbiased science regarding the benefits and risks of prescribing opioids. In the 2016 meeting of the advisory committee for the REMS on ER/LA opioids, committee members echoed this critical need by providing broad support for required education. To reduce the burden and potential for affecting patient access to opioids, FDA could try other approaches to requiring training, such as by modifying the REMS for opioid analgesics to require that manufacturers conduct more aggressive outreach to prescribers regarding training. FDA could also consider working with the States that currently do not require training as a condition of physicians' State licensure.

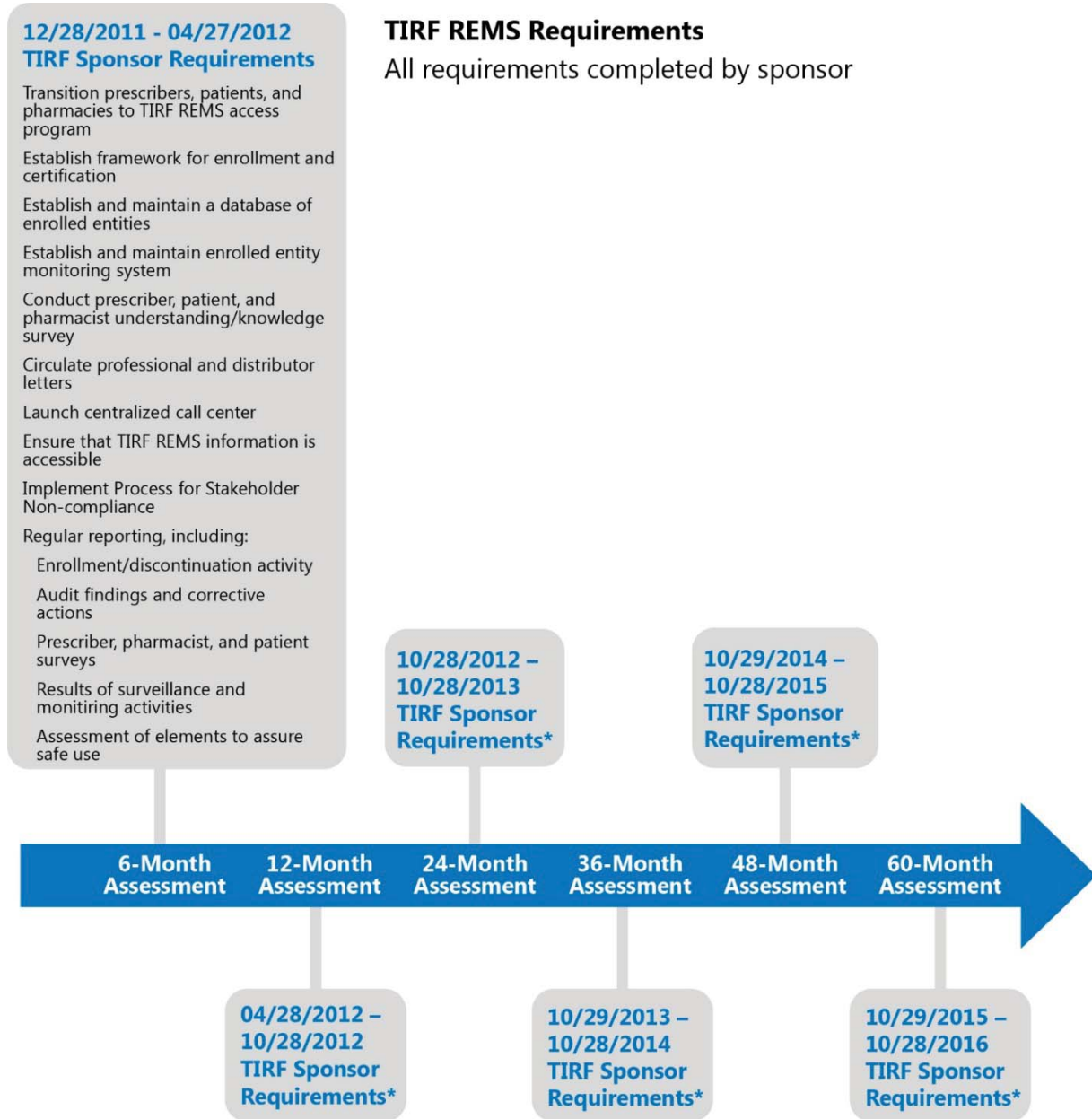
FDA concurred with the third recommendation and highlighted an April 2020 workgroup established to oversee the REMS Assessment Modernization and Improvement Project as a means to improve the efficiency of its REMS assessment reviews. This workgroup will also consider whether other offices within FDA, such as FDA's Office of Prescription Drug Promotion, should be regularly consulted as part of the REMS assessment review process. We appreciate FDA's efforts to establish a workgroup charged with improving the REMS assessment review process. We look forward to FDA detailing in its Final Management Decision the steps it has taken or plans to take to enhance that process, including any role for consulting other offices within FDA, as well as any outcomes achieved.

Finally, FDA did not explicitly concur with our fourth recommendation. It noted that it will form a working group to explore the feasibility of legislative language to provide more streamlined authority than FDA currently has to levy fines against manufacturers when they violate their REMS. We ask that FDA, in its Final Management Decision, specify the status of this working group.

Appendix D provides the full text of FDA's comments.

# APPENDIX A

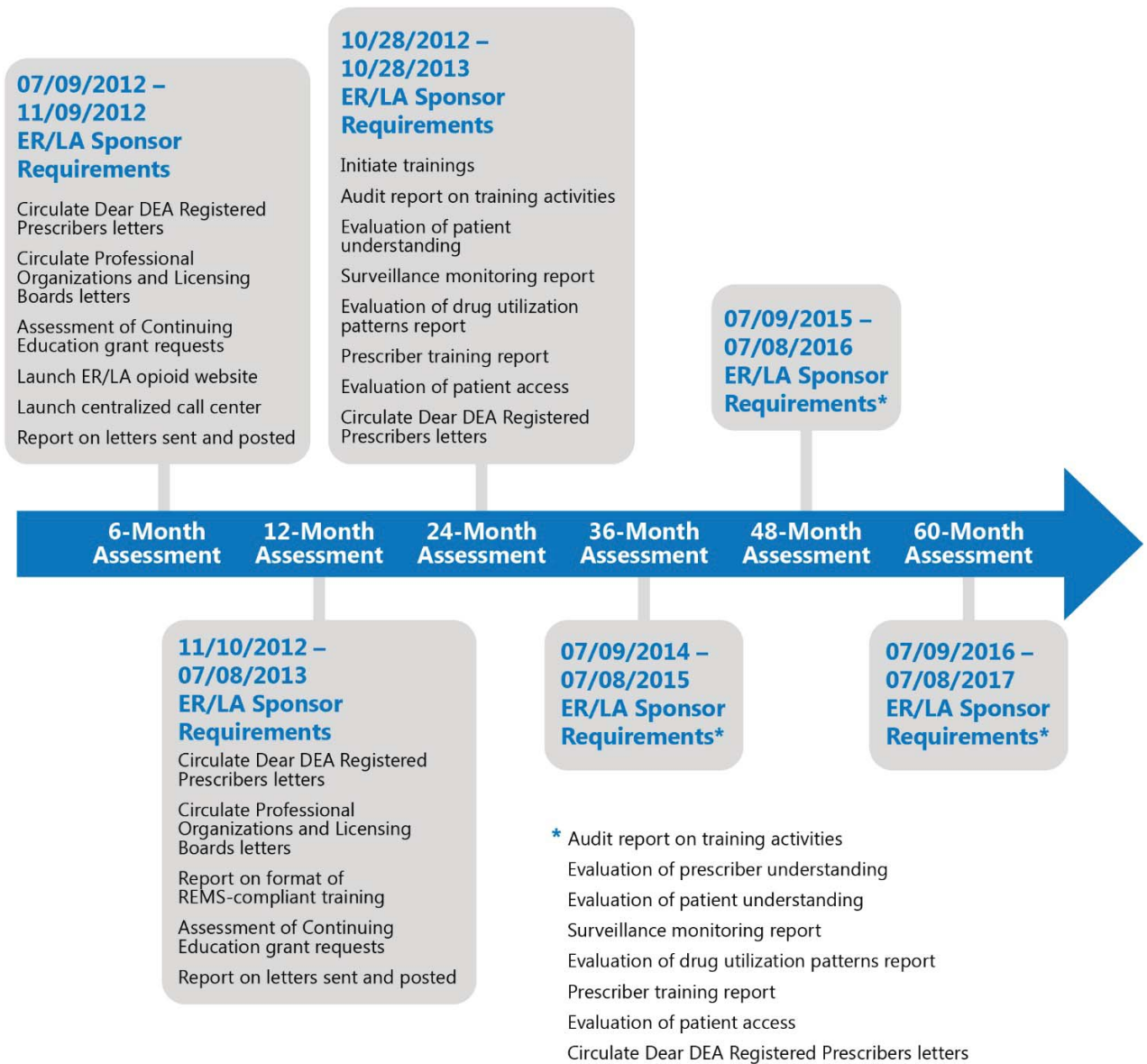
## Requirements of the REMS for TIRF drugs and for ER/LA opioids, by assessment period



\* Maintain enrolled entities database  
 Maintain REMS compliance monitoring system  
 Conduct prescriber, pharmacist, and patient understanding/knowledge surveys  
 Regular reporting

## Requirements of the REMS for ER/LA Opioids

All requirements completed by sponsor



# APPENDIX B

## Results of knowledge surveys required by the REMS for TIRF drugs failed to meet performance goals

Key risk message	Goal	12-mo result	24-mo result	36-mo result	48-mo result	60-mo result
<b>Patients</b>						
TIRF medicines are not approved for chronic noncancer pain	80%	24%	21%	25%	44%	39%
A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine	80%	43%	34%	37%	39%	40%
<b>Prescribers</b>						
Per the approved labelling for TIRF medicines, TIRFs cannot be prescribed to opioid-tolerant patients with chronic non-cancer pain	80%	54%	59%	62%	65%	78%
If patients stop taking their around-the-clock opioid medicine, they cannot continue to take their TIRF medicine	80%	69%	58%	61%	73%	77%
Prescribers must not convert to another TIRF on a microgram-to-microgram basis because it could result in a fentanyl overdose	80%	76%	75%	74%	77%	79%
<b>Pharmacists</b>						
A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine	80%	N/A	N/A	N/A	42%	41%
According to the product labeling, a cancer patient may not start a TIRF medicine and an around-the-clock opioid at the same time	80%	N/A	65%	63%	69%	62%
Per the approved labelling for TIRF medicines, TIRFs cannot be prescribed to opioid-tolerant patients with chronic non-cancer pain	80%	30%	47%	44%	51%	51%

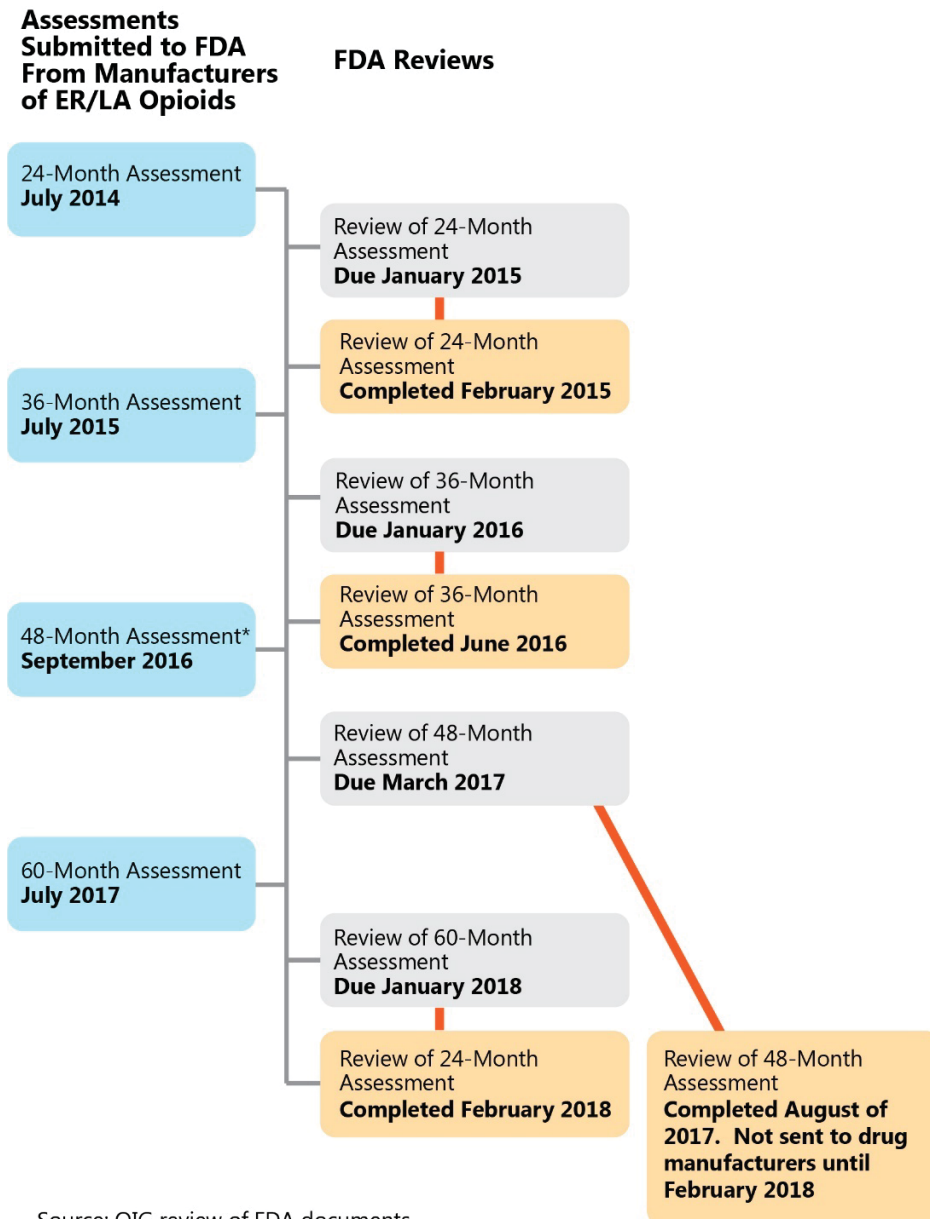
Source: FDA reviews of data submitted by the TIRF REMS administrator



# APPENDIX C

## Timeline for manufacturer submissions and FDA reviews, July 2014-February 2018

Manufacturers submitted timely assessments, but FDA was often late with its reviews.\*



Source: OIG review of FDA documents.

\* The manufacturers of ER/LA opioids requested and received from FDA an extension for the 48-month assessment.

# APPENDIX D

## Agency Comments

**DATE:** September 1, 2020

**TO:** Deputy Inspector General Suzanne Murrin

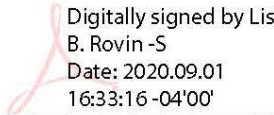
**FROM:** Director, Public Health Strategy and Analysis Staff

**SUBJECT:** FDA's Comments to OIG Draft Report: *FDA's Risk Evaluation and Mitigation Strategies: Uncertain Effectiveness To Address the Opioid Crisis*, OEI-01-17-00510

FDA is providing the attached general and technical comments to the OIG Draft Report, *FDA's Risk Evaluation and Mitigation Strategies: Uncertain Effectiveness To Address the Opioid Crisis*, OEI-01-17-00510.

We appreciate the opportunity to review and comment on this draft report before it is published.

Lisa B.  
Rovin -S



Digitally signed by Lisa  
B. Rovin -S  
Date: 2020.09.01  
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Lisa Rovin  
Director, Public Health Strategy and Analysis Staff

Attachment

**FDA’s General Comments to OIG’s Draft Report: *FDA’s Risk Evaluation and Mitigation Strategies: Uncertain Effectiveness To Address the Opioid Crisis*, OEI-01-17-00510**

FDA appreciates the opportunity to review and comment on OIG’s draft report. The Agency’s responses to each of OIG’s recommendations are below.

**1. Recommendation: Use the new TIRF REMS patient registry to monitor for known areas of risk, such as inappropriate conversions and off-label prescribing**

The previous goals for the TIRF REMS specifically addressed inappropriate conversions. FDA’s review of multiple TIRF assessments demonstrated that this was an area of risk and concern. However, FDA’s modification of the TIRF REMS eliminated this goal. According to FDA, the data suggested that dosing conversions between TIRF medicines occurred infrequently, and that conversion guidance for prescribers is available in labeling and other online sources. However, prescribers do not always seek out labeling and other sources for dosing information. Because of the differences among TIRF drugs, prescribers should exercise care when converting between TIRF drugs—i.e., when switching a patient from one TIRF drug to another— or the patient may have an increased risk of a fatal overdose. Given that the new patient registry will make data more readily available, FDA should monitor the data for inappropriate conversions.

The new goals for the TIRF REMS also no longer state that TIRF drugs should be prescribed and dispensed “only to appropriate patients” (i.e., opioid-tolerant patients with breakthrough cancer pain). Supporting this decision, FDA stated that the REMS for TIRF drugs was not intended to prevent off-label prescribing, but rather to ensure patients who were prescribed the drug were opioid-tolerant.

We appreciate that FDA does not want to interfere with the prescribing habits of physicians and that off-label prescribing is legal; however, using TIRF drugs for a purpose other than for which they were clinically tested and approved could have serious health consequences. Furthermore, off-label prescribing has been a known area of risk for TIRF drugs. In May 2019, a Federal jury found executives from the pharmaceutical company that makes Subsys (a TIRF medicine included in the REMS) guilty of bribing medical practitioners to prescribe Subsys off-label.<sup>54</sup> FDA approved TIRF drugs for the management of breakthrough pain in adult cancer patients who are already tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain. TIRF drugs are 50 to 100 times more powerful than morphine and can cause life-threatening respiratory depression in patients who are not opioid-tolerant.

Given the risk, monitoring off-label prescribing could flag safety issues. Concerning

patterns of off-label prescribing could be flagged for further review regarding clinical safety or referred to enforcement agencies for possible violations of off-label marketing by manufacturers.

***FDA Response: FDA concurs with this recommendation***

*In March 2019, FDA notified application holders of the TIRF medicines that the TIRF REMS would require a modification to address the concerning use of TIRF medicines in patients not tolerant to opioid analgesics and to better capture adverse events of interest and patient outcomes.*

*The REMS modification will include a requirement that opioid tolerance is verified prior to dispensing of each TIRF prescription. The “opioid tolerance form” will collect information on the moiety, formulation, strength, route of administration, dose and frequency of the concomitant opioid analgesic(s). Prescriptions will not be authorized for dispensing until the form is completed. The form will also capture information on the specific TIRF medicine that is being prescribed, including the strength, dose and frequency. This information will be captured for each patient and will allow for monitoring of inappropriate dosing conversions between TIRF medicines. Additionally, the form will capture information on the type of pain the patient is experiencing (e.g., cancer pain or non-cancer pain).*

*The REMS modification will also include the addition of a patient registry which will enable the Agency to better monitor safe use in outpatients taking a TIRF medicine with respect to opioid tolerance and related serious adverse events including overdose and death.*

*The proposed TIRF REMS modification was submitted to FDA in July 2019 and is currently undergoing FDA review. While the proposal was under review, the TIRF sponsors changed their REMS vendor to better meet the needs of the required modifications which required additional time for amendments to the supplement and FDA review. We anticipate taking action on this supplement by the end of the calendar year.*

**2. Recommendation: Strengthen the REMS for opioid analgesics (the successor to ER/LA opioids) by requiring prescriber training**

FDA should take advantage of its existing authorities and require prescriber training for the ER/LA REMS rather than leaving it voluntary. Although changing prescriber behavior through education certainly has its limits, as has been acknowledged in this report, taking strong steps to ensuring that prescribers have the expertise to appropriately prescribe opioids is critical. They are the clinical gatekeepers for drugs that have harmed patients and communities across the country. Furthermore, during a 2016 advisory committee meeting, almost all the advisory council members recommended that training be required. There are a number of ways that FDA could do this while working to minimize burden on providers. For example, according to FDA, most, but not all, States currently require some opioid-related education for physicians’ State licensure. FDA could allow

this training, if the content meets FDA approval, to meet some or all of the mandated prescriber training needed for the REMS.

***FDA Response: FDA does not concur with this recommendation.***

*FDA has supported education of all prescribers of opioid analgesics but believes that mandating it through a REMS is not the best, or even a practical, method to implement mandatory training. It has been suggested that other approaches could also be considered that would be more appropriate, such as a linkage between prescriber education and DEA registration for purposes of controlled substance prescribing.*

*At the May 3-4, 2016 joint Drug Safety and Risk Management (DSaRM) Advisory Committee and Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) meeting, FDA summarized for the committees the impact that a restrictive REMS for ER/LA/IR opioid analgesics would have on the healthcare delivery system. Mandatory training through a REMS would require restricted distribution of the drugs even if FDA allowed for state licensure-required opioid-education to meet some or all of the mandated prescriber training needs. Other REMS with mandatory education for prescribers require application holders to develop registries and a closed distribution program that is capable of verifying with each prescription that the prescriber has undergone training before the drug is dispensed to a patient. Such REMS programs typically also require registration of prescribers to confirm or document the successful completion of mandatory training. We anticipate that in order to implement a mandatory training program for the OA REMS, a similar registration process would be required for prescribers to verify the REMS-compliant or acceptable state opioid-related training that they completed.*

*Restrictive REMS programs also require that only participating pharmacies that have been certified can order and dispense these products. Certified pharmacies are required to verify that the prescriber has met the training requirements prior to dispensing each prescription. FDA has concerns about the feasibility of such an approach and the considerable burden it would impose on an already burdened health care system. Based on estimates presented at the 2016 joint AC meeting, the approximately 67,000 retail pharmacies in the United States that dispense opioid analgesics could be required to verify training of the approximately 1.5 million opioid analgesic prescribers. Approximately 154 million opioid analgesic prescriptions were dispensed in 2019 in the United States<sup>1</sup>. The number of stakeholders impacted by a restrictive OA REMS far exceeds any other approved REMS. FDA presented data at the 2016 AC meeting regarding the number of patients, prescribers and pharmacies that participate in approved REMS programs. The table below includes data presented at the AC and includes the active prescribers, pharmacies and patients impacted in 2015 under the TIRF REMS and Isotretinoin Shared REMS, as well as the potential active prescribers and pharmacies that would be impacted by the ER/LA and OA REMS if restrictions were in*

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<sup>1</sup> Source: IQVIA, National Prescription Audit (NPA). Data Extracted Feb 2020

place.

<i>Stakeholders Impacted in 2015</i>			
<i>REMS Program</i>	<i>Active prescribers</i>	<i>Active outpatient/ specialty pharmacies</i>	<i>Patients</i>
<i>TIRF Shared REMS<sup>2</sup></i>	<i>9096</i>	<i>42,316</i>	<i>8740*</i>
<i>Isotretinoin Shared REMS<sup>3</sup></i>	<i>18,461</i>	<i>46,726</i>	<i>234,622</i>
<i>ER/LA Opioid Analgesics</i>	<i>320,000<sup>4</sup></i>	<i>67,000<sup>5</sup></i>	<i>3.8 million<sup>6</sup></i>
<i>ER/LA and IR Opioid Analgesics</i>	<i>1.5 million<sup>7</sup></i>	<i>67,000</i>	<i>67 million<sup>8</sup></i>
<i>*New patients only</i>			

*Additional separate implementation systems would be required to allow closed health care systems (e.g., Department of Defense, the Veterans Health Administration, and Kaiser Permanente) to comply. The opioid manufacturers would be the governing body that certifies prescribers, pharmacies, and healthcare system and governs the implementation of the restrictive REMS program.*

*A training requirement mandated through a REMS could negatively impact access to opioids among patients who need them for pain control. Patients could simply be turned away at the pharmacy if their prescriber has not undergone the training or failed to appropriately document the training. The DSaRM and AADPAC committees agreed that mandatory prescriber education should be required in order to prescribe an ER/LA or ER/LA and IR opioid analgesic, but emphasized that this mandate should be linked with a mechanism that does not require a secondary check [by pharmacists or others], such as a mechanism through state licensure or DEA registration, not through a REMS.*

*On May 9-10, 2017 (about a year after the joint AC meeting), FDA held a public workshop to seek input on how to best support prescriber and other HCP education on appropriate pain management and opioid analgesic prescribing. Panelists generally agreed that prescribers of opioids, as well as other healthcare providers that are part of the team treating patients with pain, would benefit from a basic level of education on*

<sup>2</sup> Source of data is from the 48<sup>th</sup> Month TIRF REMS Assessment Report submitted by the TIRF REMS Industry Group to DMF 027320.

<sup>3</sup> Source of data is from the 3 Year iPLEDGE REMS Assessment Report submitted for Absorica (NDA 21951).

<sup>4</sup> Estimated number of ER/LA opioid analgesic prescribers at the time the ER/LA Opioid Analgesics REMS was approved in July 2012.

<sup>5</sup> Approximate number of retail pharmacies in the U.S.

<sup>6</sup> Approximate number of patients that received an ER or LA opioid analgesic prescription from U.S. outpatient retail pharmacies. (Source: IQVIA Total Patient Tracker™, data accessed December 2019, www.iqvia.com).

<sup>7</sup> Approximate number of prescribers registered with the DEA.

<sup>8</sup> Approximate number of patients that received an opioid analgesic prescription from U.S. outpatient retail pharmacies. (Source: IQVIA Total Patient Tracker™, data accessed December 2019, www.iqvia.com).

*pain management, including safe opioid prescribing as well as other elements. Although there was not consensus on the issue of whether prescriber education should be mandatory, many participants supported mandatory education. Those opposed to a mandatory approach felt that an educational requirement would place additional burdens on HCPs and that an unintended consequence would be that HCPs would choose not to prescribe opioid analgesics, potentially reducing access for patients who need them for pain control. Most indicated that if education were to be mandated, it should be done at the State or local level (e.g., health care systems) rather than at the Federal level. We would like to point out that to-date, at least 40 states mandate some type of opioid continuing education for physician state licensure.*

*FDA continues to support education for all opioid analgesic prescribers to make certain that prescribers (a) are properly informed about appropriate prescribing recommendations, (b) understand how to identify the risk of abuse in individual patients, and (c) know how to get patients with addiction into treatment. However, the Agency agrees with advisory committee experts that use of a REMS to require training could have serious, detrimental unintended consequences.*

### **3. Recommendation Enhance its REMS assessment review process**

FDA should take additional steps to enhance its review of the REMS assessments submitted by manufacturers for the REMS for TIRF and opioid analgesics. First, FDA should strive to meet its REMS review goal of 6 months. We recognize the challenges inherent in balancing FDA's reliance on careful analysis with the importance of providing timely feedback to manufacturers. However, fighting the opioid epidemic is a top HHS priority and, in response to the urgent need to continue to combat the opioid crisis, FDA should strive to do more to ensure its reviews are completed in time for manufacturers to be able to respond to the feedback in the next assessment.

Second, FDA should seek to include a wide range of information to fully understand prescribing patterns and their association with opioid abuse, misuse, and overdoses. For example, FDA could include information from FDA's Office of Prescription Drug Promotion in its REMS assessment review process. This office has the potential to provide useful information regarding how manufacturers are promoting opioids and inappropriate opioid prescribing trends.

#### ***FDA Response: FDA concurs with this recommendation.***

*FDA agrees with the need to review REMS assessments in a more timely manner. To address this issue, the FDA has initiated a REMS Assessment Modernization and Improvement Project in April 2020 including the formation of several working groups with specific aims to improve the efficiency of our reviews of the REMS Assessment Reports. However, the length of time it has taken for FDA to review REMS assessments reports, particularly assessment reports of complex shared-system REMS such as the Opioid Analgesics REMS and the TIRF REMS, has in large part been a workload and staffing issue. At the current time, there is only a single team of six risk mitigation*

*experts that has lead responsibility for conducting and coordinating the review of each of these REMS assessment reports. FDA receives approximately 50 REMS Assessment Reports per year and has developed internal goal dates for reviewing those assessments and providing feedback to sponsors within 6 months of receipt of the report. Many of these REMS Assessment Reports are complex and lengthy, particularly those involving ETASU REMS and shared-system ETASU REMS and require multidisciplinary review by FDA's risk mitigation experts, social scientists, epidemiologists, clinicians, drug utilization analysts, and other scientists in FDA. Our epidemiologists are also stretched addressing other opioid and other drug safety issues. Our future ability to meet the review goal timelines of 6 months will depend on an increase in staffing. Without additional staffing, we will never attain the goal of timely review of REMS assessment reports.*

*As part of this REMS Modernization and Improvement initiative, the working group will consider when additional disciplines should be consulted to both review the REMS Assessment Reports as well as when to involve other groups where we may request an analysis of other data sources (e.g., FDA's Office of Prescription Drug Promotion review of promotional material).*

*Because we have limited number of staff to work on these issues, we have no specific timelines for completing the work on this project.*

**4. Recommendation: Seek additional authority to ensure manufacturers are held accountable when appropriate**

FDA can exercise its authority and regulatory discretion to, among other things, deem a drug misbranded or impose civil monetary penalties on manufacturers that violate approved REMS. However, these measures are not necessarily practical for simple violations of REMS requirements and could reduce access to appropriately prescribed drugs. FDA should seek additional, more streamlined authority to levy fines against companies when they violate their REMS. One example of a violation might be a manufacturer failing to make a good-faith effort to provide data to FDA that are readily available.

***FDA Response: FDA is considering this recommendation.***

*The Agency will form a working group to explore the feasibility of legislative language that would provide more streamlined authority than FDA currently has to levy fines against companies when they violate their REMS. If the working group formulates an approach that it believes to be feasible, it will draft a proposal and seek an opportunity to propose it to Congress.*



# ACKNOWLEDGMENTS AND CONTACT

## Acknowledgments

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This report was prepared under the direction of Joyce Greenleaf, Regional Inspector General for Evaluation and Inspections in the Boston regional office, and Danielle Fletcher, Deputy Regional Inspector General.

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# ENDNOTES

- <sup>1</sup> *State of Oklahoma vs Purdue Pharma*, No. CJ-2017-816 (filed August 26, 2019). Accessed at <https://nondoc.com/2019/08/26/read-the-full-johnson-johnson-opioid-ruling-from-judge-thad-balkman/> on December 20, 2019.
- <sup>2</sup> National Academies of Sciences, Engineering, and Medicine, *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*, 2017, pp. 1-7 through 1-9.
- <sup>3</sup> CDC, *Opioid Overdose*. Accessed at <https://www.cdc.gov/drugoverdose/data/prescribing/overview.html> on September 8, 2020.
- <sup>4</sup> CDC, *Drug Overdose Deaths*. Accessed at [https://www.cdc.gov/nchs/data/databriefs/db356\\_tables-508.pdf#3](https://www.cdc.gov/nchs/data/databriefs/db356_tables-508.pdf#3) on February 5, 2020.
- <sup>5</sup> The Secretary has renewed the declaration of national public health emergency multiple times since 2017.
- <sup>6</sup> Florence CS, Zhou C, Luo F, Xu L, "The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013," *Med Care* 2016;54(10):901-906.
- <sup>7</sup> FDA, *FDA Opioids Action Plan*. Accessed at <https://www.fda.gov/drugs/information-drug-class/fda-opioids-action-plan> on February 12, 2020.
- <sup>8</sup> The Food and Drug Administration Amendments Act, P.L. No. 110-85 (Sept. 27, 2007) added § 505-1 to the FD&C Act, which allows FDA to require a REMS at the time of a new drug's approval—if FDA, among other things, becomes aware of new safety information—or after a drug has been on the market.
- <sup>9</sup> This review will focus on FDA-approved, outpatient, pain-management opioids: ER/LA opioids and TIRF drugs.
- <sup>10</sup> Fentanyl is 50 to 100 times stronger than morphine, and an illegal version is often mixed with heroin for sale on the street. The number of deaths due to overdoses on fentanyl or other synthetic opioids nearly doubled annually between 2013 and 2016. See CDC, *Data Brief 294—Drug Overdose Deaths in the United States, 1999-2016*. Accessed at: [https://www.cdc.gov/nchs/data/databriefs/db294\\_table.pdf#4](https://www.cdc.gov/nchs/data/databriefs/db294_table.pdf#4) on February 2, 2020.
- <sup>11</sup> Pharmacies dispensed an average of 93 million opioid prescriptions per year from 1991 to 1999. In 2018, pharmacies dispensed 168 million opioid prescriptions. See: CDC, *Prescription Drug Abuse and Overdose in the United States, 2010*. Accessed at [https://secure.in.gov/attorneygeneral/files/Jones\\_Indiana\\_RX\\_Meeting\\_-\\_CJONES\(5\).pdf](https://secure.in.gov/attorneygeneral/files/Jones_Indiana_RX_Meeting_-_CJONES(5).pdf) on January 3, 2018; and CDC, *Annual Surveillance Report of Drug-Related Risks and Outcomes, 2018*. Accessed at <https://www.cdc.gov/drugoverdose/pdf/pubs/2018-cdc-drug-surveillance-report.pdf> January 11, 2019.
- <sup>12</sup> CDC, *U.S. Opioid Prescribing Rate Maps*. Accessed at <https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html> on February 12, 2019.
- <sup>13</sup> National Academies of Sciences, Engineering, and Medicine, *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*, 2017, pp. ix, 1-11, and 1-19.
- <sup>14</sup> Additional factors may have contributed to the opioid crisis, including pain management trends and socioeconomic factors.
- <sup>15</sup> CDC, *Drug Overdose Deaths in the United States, 1999-2017, 2018*. Accessed at <https://www.cdc.gov/nchs/data/databriefs/db329-h.pdf> on February 8, 2019.
- <sup>16</sup> FDA, *Development & Approval Process (Drugs)*. Accessed at <https://www.fda.gov/drugs/developmentapprovalprocess/default.htm> on April 18, 2019.

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<sup>17</sup> FD&C Act § 505-1(a).

<sup>18</sup> FD&C Act § 505-1(e). In instances where FDA determines elements to assure safe use are required, FD&C Act § 505-1(f)(3).

<sup>19</sup> FD&C Act § 505-1(f). REMS may also include, where appropriate, packaging and disposal elements. See FD&C Act § 505-1(e)(4).

<sup>20</sup> FD&C Act § 505-1(f)(5).

<sup>21</sup> FD&C Act § 505-1(a) and (h).

<sup>22</sup> FD&C Act § 505-1(h).

<sup>23</sup> FDA's draft policy and procedures manual was first completed in mid-2018. FDA stated that the document largely codified the procedures that it had been following since it implemented REMS. FDA stated its goal is to review assessments in 6 months, but reviews may take longer depending on their complexity.

<sup>24</sup> FD&C Act § 505-1(h)(1)-(2).

<sup>25</sup> FD&C Act § 505-1(h)(2). The Division of Risk Management leads FDA's review of REMS. Additional divisions potentially involved in a REMS Assessment review include the Office of Compliance; Office of Surveillance and Epidemiology; and Office of New Drugs. See Procedures section from FDA's DRAFT REMS Assessment MAPP, August 18, 2019, available at: <https://www.fda.gov/media/133675/download>.

<sup>26</sup> Patients considered opioid-tolerant are those who are regularly taking at least: 60 mg oral morphine/day; 25 mg transdermal fentanyl/hour; 30 mg oral oxycodone/day; 8 mg oral hydromorphone/day; 25 mg oral oxymorphone/day; or an equianalgesic dose of another opioid for 1 week or longer.

<sup>27</sup> See FDA, *Approved Risk Evaluation and Mitigation Strategies (REMS)—Transmucosal Immediate-Release Fentanyl (TIRF) Products*, <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=60>. The TIRF drugs Fentora and Actiq were in FDA's RiskMAP program, which was the predecessor program to REMS.

<sup>28</sup> FDA, *Approved Risk Evaluation and Mitigation Strategies (REMS)—Transmucosal Immediate-Release Fentanyl (TIRF) Products*, <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=60>.

<sup>29</sup> The TIRF REMS structure that this report presents reflects that which was in place for our review and, therefore, our findings. See p. 14 for a further discussion of the changes to the TIRF REMS.

<sup>30</sup> The structure of the REMS for ER/LA opioids that this report presents reflects that which was in place for our review and, therefore, our findings. See p. 18 for a further discussion of the changes to the REMS for ER/LA opioids.

<sup>31</sup> Utilization data taken from the 60-month assessment report for the REMS for ER/LA opioids.

<sup>32</sup> A draft version of the "FDA Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain" (FDA Blueprint) contained the core messages found in the REMS for ER/LA opioids training.

<sup>33</sup> The ER/LA opioids REMS' training goal of 320,000 prescribers was based on a 2011 estimate of the number of prescribers who had prescribed an ER/LA opioid in the previous year.

<sup>34</sup>In accordance with 21 CFR § 208.24.

<sup>35</sup> This list of requirements is specifically called Elements to Assure Safe Use (ETASU). ETASU is one of the four possible components of every REMS, with the others being a medication guide, a communication plan, and considerations for safe packaging and disposal. Neither the REMS for ER/LA opioids nor the REMS for TIRF drugs includes a communication plan, but

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both include all three remaining components. The Substance Use-Disorder Prevention That Promotes Opioid Recovery and Treatment for Patients and Communities Act (2018) codified changes to FD&C Act § 505-1(e)(4) to include components related to packaging and disposal.

<sup>36</sup> OIG, *FDA Lacks Comprehensive Data To Determine Whether Risk Evaluation and Mitigation Strategies Improve Drug Safety*, OEI-04-11-00510, February 2013.

<sup>37</sup> FDA has implemented four OIG recommendations—those for it to (1) evaluate the Elements to Assure Safe Use of one REMS each year as required by law; (2) to identify incomplete drug manufacturer assessments and work with drug manufacturers to obtain missing information; (3) to develop and implement a plan to identify, develop, and to validate, and assess REMS components; and (4) clarify expectations for sponsors' assessments in FDA assessment plans. The statuses of the open recommendations were current as of April 2020.

<sup>38</sup> The third-party administrator of the TIRF REMS conducts the surveys. The administrator stated that confidence intervals were 53.2 percent to 64.5 percent for prescriber results, and 41.2 percent to 52.8 percent for pharmacist results.

<sup>39</sup> FDA, *Review of the fifth (48 month, October 29, 2014 to October 28, 2015) Risk Evaluation and Mitigation Strategy (REMS) Assessment Report for Transmucosal Immediate Release Fentanyl (TIRF) Agents*, p. 89, December 4, 2017.

<sup>40</sup> Data submitted by the TIRF manufacturers showed that 3.9 percent of deaths occurred in patients taking the drug off-label, 53.5 percent occurred in patients taking the drug for unknown indications, and only 42.6 percent occurred in patients taking the drug for cancer-related indications.

<sup>41</sup> The drug manufacturers' analyses were done by each individual TIRF drug. The range represents the opioid nontolerance variability across drugs.

<sup>42</sup> FDA used its FDA Adverse Event Reporting System (FAERS). The FAERS data has limitations, such as there being no certainty that the drug in question caused the adverse event and the system not capturing every adverse event or prescription error. FDA told us that it has not found FAERS to be an effective tool to assess drug utilization patterns over time.

<sup>43</sup> FDA, *Review of the sixth (60 month, October 29, 2015 to October 28, 2016) Risk Evaluation and Mitigation Strategy (REMS) Assessment Report for Transmucosal Immediate Release Fentanyl (TIRF) Agents*, p. 50, September 28, 2016.

<sup>44</sup> FDA told us that it eventually realized these data were inflated when analyzing the 84-month assessment, which was outside the scope of our review. The inflated numbers did not change the veracity of the conclusions that FDA drew based on its analysis at the time.

<sup>45</sup> Alexander, G. Caleb, et al., *Testimony for the Record Submitted to the U.S. Food and Drug Administration for the Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee*, Docket No. FDA-2018-N-1917, August 3, 2018. The same researchers published their findings the following year. See Rollman, Jeffrey Eric, et al., "Assessment of the FDA Risk Evaluation and Mitigation Strategy for Transmucosal Immediate-Release Fentanyl Products," *Journal of the American Medical Association*, Volume 321, Number 7, February 19, 2019.

<sup>46</sup> Transcript for the Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee, August 3, 2018, pp. 334-347.

<sup>47</sup> *Ibid.*, p. 292.

<sup>48</sup> Heyward, James, et al., "Evaluation of the Extended-Release/Long-Acting Opioid Prescribing Risk Evaluation and Mitigation Strategy Program by the US Food and Drug Administration: A Review," *Journal of the American Medical Association*, published online December 31, 2019. Accessed at <https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2757791?resultClick=1> on January 7, 2020.

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<sup>49</sup> The 24-month reviews for both REMS were the first to contain detailed data to address the goals.

<sup>50</sup> At an FDA advisory committee meeting on May 4, 2016, the vote was nearly unanimous in favor of mandatory training for prescribers of ER/LA opioids. See <https://www.fda.gov/media/100444/download>, accessed on February 11, 2020. FDA decided not to take the recommendation of the advisory committee, citing burden to the health care industry.

<sup>51</sup> *State of Oklahoma vs. Purdue Pharma*, No. CJ-2017-816 (filed August 26, 2019). Accessed at <https://nondoc.com/2019/08/26/read-the-full-johnson-johnson-opioid-ruling-from-judge-thad-balkman/> on December 20, 2019.

<sup>52</sup> A drug may be deemed to be misbranded if it is subject to a REMS and the drug manufacturer fails to comply with a requirement of the REMS. FD&C Act § 502(y). Misbranded drugs may not be introduced into, delivered, or received into interstate commerce. FD&C Act § 301 (a) and (c).

<sup>53</sup> Drug manufacturers that violate REMS requirements may be subject to civil monetary penalties of up to \$250,000 per violation. Civil monetary penalties are not to exceed \$1 million in a single proceeding. Civil monetary penalties may increase to \$10 million for continued violations. FD&C Act § 303(f)(4)(A).

<sup>54</sup> Press Release, Department of Justice, "Founder and Four Executives of Insys Therapeutics Convicted of Racketeering Conspiracy," May 3, 2019. Accessed at <https://www.justice.gov/usao-ma/pr/founder-and-four-executives-insys-therapeutics-convicted-racketeering-conspiracy> on June 30, 2020.