



The Honorable Maggie Hassan  
United States Senate  
Washington, D.C. 20510

Dear Senator Hassan:

Thank you for your letter, cosigned by Senator Edward Markey, to former Commissioner of Food and Drugs Scott Gottlieb and the U.S. Food and Drug Administration (FDA or the Agency), concerning the steps we are taking to address the opioid epidemic. FDA understands there is considerable public interest concerning the serious risks associated with opioid use and recognizes your concerns.

The Agency continues to take new steps to confront this crisis, while also paying careful attention to the needs of patients in accessing appropriate pain management. We have had a robust public debate over the years, engaging the pain and addiction communities, academia, health care professionals and policymakers on our framework for evaluating the benefit-risk considerations specific to prescription opioid analgesics that not only serves the patient community but the public health as a whole. Above all, our goal has been to ensure that our approval and other regulatory actions regarding opioids are science-based and that the agency's benefit-risk framework considers not only the outcomes of prescription opioid analgesics when used as prescribed but also the public health effects of inappropriate use.

The opioid crisis is one of the largest and most complex public health tragedies that our nation has ever faced. FDA is fully committed to looking closely at the opioid crisis, learning from what happened, and identifying missed opportunities. The Agency is proactively doing everything within our power to address the ongoing opioid crisis and applying these lessons to forcefully address future public health challenges.

We appreciate the opportunity to respond to your inquiry. Your questions are in bold, followed by FDA's responses.

**1. You referred to "past mistakes" in the statement you issued after the 60 Minutes report.**

**Specifically:**

- a. What are the past mistakes you were referring to?**
- b. When were these mistakes made?**
- c. For each past mistake identified, what actions has FDA taken in response?**

FDA is a deliberative, science-based agency. We calibrate our policy and regulatory actions carefully, based on rigorous scientific evidence that can often take many months and even years to collect. As we look back on our regulatory processes and decisions leading up to the opioid crisis, we can assure you that FDA followed the relevant rules and regulations, making decisions based on the best available data. With the benefit of hindsight, FDA has examined places where there are opportunities for process improvements, taken decisive steps in recent years, and has additional actions already underway for 2020. We are working to identify ways the Agency could have taken action more quickly and more forcefully. The agency is now taking a much more aggressive approach to rapid regulatory action that will allow us to respond more quickly as the opioid crisis continues to evolve.

One example of our commitment to this proactive strategy is our work on the Opioid Analgesic Risk Evaluation and Mitigation (OA REMS). While this REMS originally addressed only the extended-release and long-acting (ER/LA) opioid products, FDA expanded it in 2018 to cover the more commonly-prescribed immediate release products as well. Also, as of 2018, the OA REMS now requires that training on safe and appropriate use of opioids be made available not only to prescribers, but to all health care providers (HCPs) who are involved in the management of patients with pain, including nurses and pharmacists.

Another example of our commitment to a more proactive strategy is our use of label testing, where appropriate. We are cognizant of the need for prescribers to understand and comprehend our labeling language. This label testing strategy helps the agency anticipate misinterpretation, clarify messaging, and prevent misunderstanding before the agency takes regulatory action. For example, as part of a broader research program aimed at obtaining clearer understanding of knowledge, comprehension, attitudes, behaviors, and perceptions related to opioids, FDA's communications research team previously tested messages about the indicated use of extended-release and long-acting (ER/LA) opioids among healthcare professionals. This testing helped to inform the work done in 2013 to revise the ER/LA opioid label. In addition, FDA is currently testing prescriber's understanding of the labels given to abuse deterrent opioids. We are investigating whether abuse deterrent formulation (ADF) nomenclature is understood by prescribers and whether the ADF language should be changed, and if so, how.

A third example of our commitment to a more proactive strategy is our use of the Drug Safety Oversight Board (DSB) to obtain input from our federal partners (e.g. VA, DOD, CDC) on important safety-related opioid actions. For example, FDA discussed the opioid REMS and Medication Guide at DSB meetings in 2010 and 2013. FDA also worked with DSB members in 2013 on educational messaging about prescribing opioids for non-cancer pain.

Finally, consistent with the Comprehensive Addiction and Recovery Act of 2016, it has become FDA's general practice to obtain feedback from the relevant advisory committees prior to approving new opioid drug products. This helps ensure that the Agency's decision to approve, or not approve, an opioid is informed by a wide range of expert opinion from throughout the medical community.

Addressing the opioid crisis is a top priority for Secretary Azar and Commissioner Hahn as well as the entire Administration, and FDA is a key part of that effort. We are grateful for your

interest in this critical issue and look forward to working with you to ensure FDA’s effective and proactive response to this crisis.

- 2. Has the FDA conducted a review – either formal or informal – of the process surrounding its original 1995 approval of the OxyContin label and the 2001 change to the OxyContin label?**
  - a. If so, did such review find that the FDA followed all relevant rules and regulations?**
  - b. Specifically, did such review find that the required efficacy trials were conducted and that data from such trials was provided to the FDA for OxyContin at the 10mg, 20mg, 40mg, 80mg, and 160mg doses?**
  - c. If efficacy trials for each dose were not performed, why not?**

FDA has examined the original 1995 approval of OxyContin, the approvals of the supplemental applications for the 80-mg and 160-mg strengths, and the approval of the 2001 safety labeling change. All applicable statutes and regulations were followed.

#### ***1995 Approval of OxyContin (10 mg, 20 mg, and 40 mg strengths)***

OxyContin CR (oxycodone controlled-release) was approved on December 12, 1995 as 10 mg, 20 mg, and 40 mg tablet strengths for the, “management of moderate-to-severe pain where use of an opioid analgesic is appropriate for more than a few days.” Approval was based on efficacy findings from six controlled studies in approximately 500 patients with cancer pain, low back pain, or osteoarthritis (OA), with additional safety data in patients with cancer pain and patients with OA of up to 18 months or longer. The OA study was a double-blind, randomized, placebo-controlled trial in patients with moderate to severe pain due to osteoarthritis. Generally, these patients had pain judged to be inadequately controlled with non-opioid analgesics. Patients in the six studies required between 10 mg and 720 mg of oxycodone per day. Although the highest “strength” of the tablets studied in these trials was 40 mg, in many cases, patient doses were much higher. In separate studies, the pharmacokinetic data

<sup>1</sup> was also compared with immediate-release oxycodone and was comparable.

#### ***Approval of OxyContin 80 mg and 160 mg strengths***

The supplemental applications for 80 mg and 160 mg strengths of OxyContin, were approved on January 06, 1997, and March 15, 2000, respectively, using available efficacy and safety data, along with pharmacokinetic data. As noted above, patients in the original OxyContin studies received doses up to 720 mg per day. As a result, additional novel efficacy studies were not necessary.

Approval of the 80 mg strength was supported by a bioequivalence study that demonstrated that two 40 mg tablets delivered the same amount of oxycodone to the blood as one 80 mg tablet.

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<sup>1</sup> Pharmacokinetics is the disposition of drug in the body (that is, their absorption, distribution, metabolism, and elimination).

Approval of the 160 mg tablets was supported by a bioequivalence study that demonstrated that one 160 mg tablet delivered the same amount of oxycodone to the blood as two 80 mg tablets and four 40 mg tablets. Safety was supported by data from clinical studies submitted between December 1994 and January 1998. A total of 733 unique patients were enrolled in these studies. The sponsor organized the data from these patients into the following groups, based on maximum total daily dose of OxyContin: patients who received less than 160 mg/day (this group served as a control group), patients who received  $\geq 160$  mg/day, and within this group, there was a subset of patients who received a maximum daily dose of  $\geq 320$  mg/day. The overall safety profile of patients receiving doses of OxyContin of 160 mg/day or greater and those in the subset of this group receiving 320 mg/day or greater did not differ from the control group who received less than 160 mg/day. The labeling for the 160 mg strengths indicated that the dose was only appropriate for opioid-tolerant patients.

### ***2001 OxyContin Safety-related Labeling Changes***

Prompted by the Agency's growing concerns about OxyContin misuse and abuse, FDA requested safety-related changes to the OxyContin labeling to strengthen the warnings about the potential for misuse and abuse and to narrow the approved indication for use to a more appropriate patient population. The revised labeling, which also included addition of a Boxed Warning to reinforce critical safety messages, and updates to the *Drug Abuse and Dependence*, and *Adverse Events* sections, was approved in July 2001.

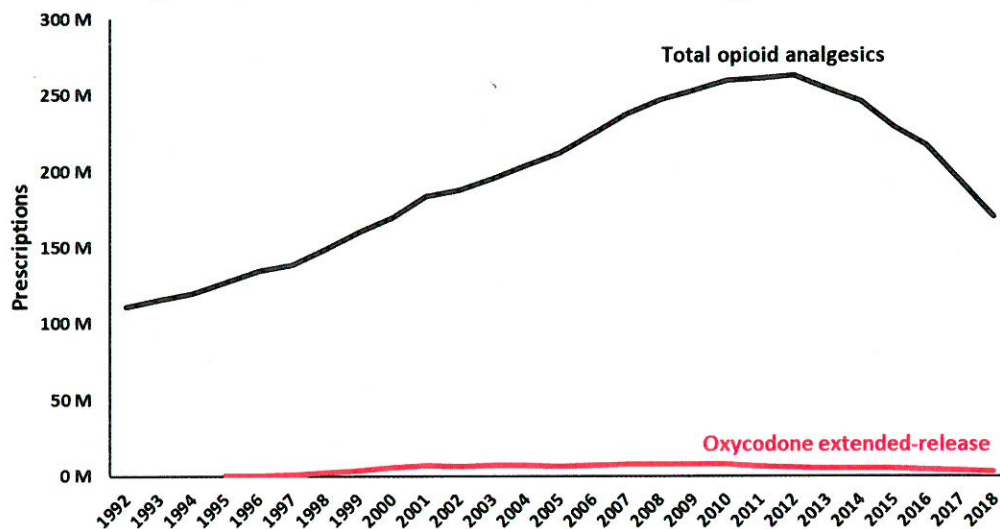
Recent press reports have described the 2001 labeling change as *broadening* the indication to include chronic, long-term use; however, this is not correct. As previously described, when OxyContin was approved in 1995 it was not limited to the treatment of acute pain or otherwise limited in its duration of use. Chronic or long-term use (in appropriate situations), with no maximum duration, was always part of the approved use of OxyContin. Therefore, the change to the OxyContin labeling in 2001 *narrowed* the indication (and intended patient population) from where use is needed for "more than a few days," to the treatment of pain where a "continuous, around-the-clock opioid analgesic is needed for an extended period of time." The indication was also changed to clarify that OxyContin is not appropriate for "as needed dosing" (PRN), or in the immediate post-operative period if pain is mild or not expected to persist for an extended period of time. Additionally, stronger warnings about the potential for misuse and abuse and a Boxed Warning were also added to the OxyContin labeling in 2001.

In addition, the Agency worked with the sponsor to implement a Risk Management Program aimed at reducing misuse and abuse of OxyContin, and issued a letter to prescribers, pharmacists and other healthcare professionals (a "Dear Healthcare Professional Letter") to alert them about the safety updates to the label. The letter explained that the labeling had been revised in response to reports of OxyContin misuse and abuse and highlighted the changes to reinforce the appropriate patient population for whom the product is intended and to strengthen the warnings about the potential for misuse, and abuse.

The exact effect of the 2001 labeling changes and other risk management efforts on prescribing of OxyContin is difficult to clearly distinguish since there are many influences that impact prescribing by healthcare practitioners. Given this, it is extremely difficult to isolate the effect of

a single regulatory action or other intervention against the backdrop of the many concurrent efforts and the evolving landscape of the opioid crisis. Figure 1 shows the estimated annual number of total opioid analgesic prescriptions dispensed compared to prescriptions dispensed for oxycodone extended-release tablets. As a close-up of Figure 1, Figure 2 shows the annual number of extended-release oxycodone prescriptions dispensed in U.S. outpatient pharmacies and covers the time period since 1995, including the years prior to and following the 2001 labeling change. As can be seen from this figure, oxycodone ER (brand and generic) prescriptions rapidly rose until 2001. For at least 4 years after the labeling change – at a time when prescription opioid use was rising – the number of prescriptions dispensed for oxycodone ER was generally flat, with the number of oxycodone ER prescriptions making up a very small and decreasing fraction of prescriptions since 2010. The 2001 labeling change and related actions discussed above may have contributed to a slowing of the rapidly increasing number of prescriptions for oxycodone ER (brand and generic) OxyContin. However, whether the pattern that would have occurred in the absence of these actions is not knowable.

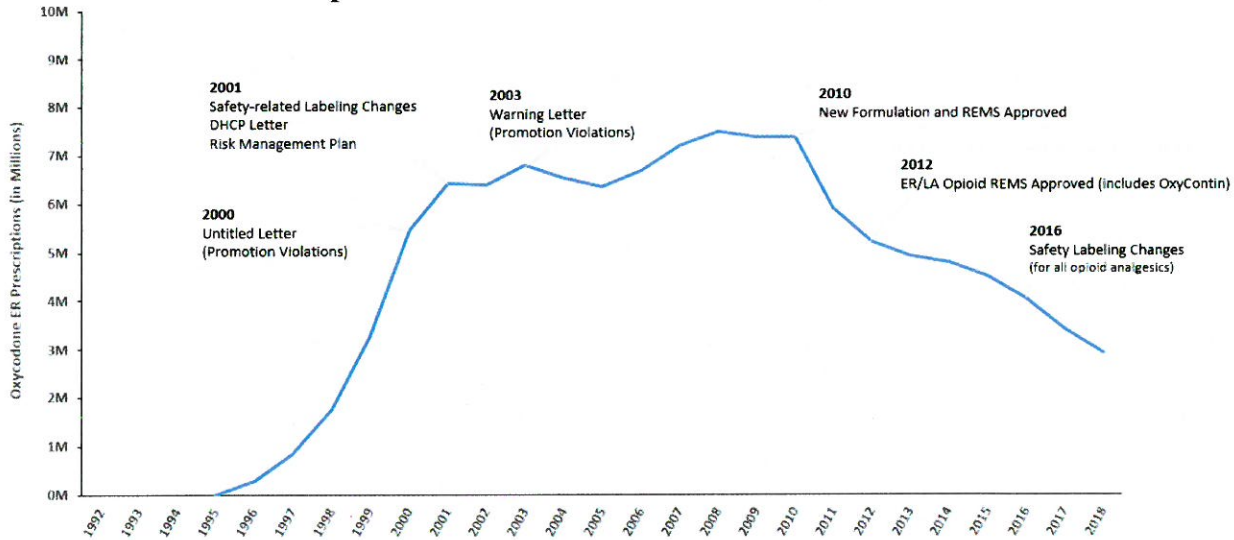
**Figure 1. Estimated Number of Prescriptions Dispensed for Opioid Analgesics vs. Oxycodone Extended-Release<sup>1</sup> from U.S. Outpatient Pharmacies<sup>2</sup>**



<sup>1</sup> Oxycontin and other oxycodone ER products, including generic products

<sup>2</sup> Source: IQVIA National Prescription Audit. 1992-2018. Extracted March 2019. Includes outpatient retail and mail-order/specialty pharmacies. Does not include opioid-containing products used as part of medication-assisted treatment for opioid dependence, opioid-containing cough/cold products, or compounded bulk powder prescriptions. There have been changes in the underlying data and methodology of the proprietary database, IQVIA NPA, including a change to manage prescription claims that are voided or reversed historically adjusted to January 2017, data prior to January 2017 have not been adjusted to this new methodology; therefore, changes over time must be interpreted in the context of the changes in methodology. For example, an estimated 2% of total prescription claims for oxycodone ER dispensed from U.S. retail pharmacies appears to have been voided or reversed in 2017.

**Figure 2. Estimated Number of Oxycodone Extended-Release<sup>1</sup> Prescriptions Dispensed from U.S. Outpatient Pharmacies – With Notable FDA Actions Taken<sup>2</sup>**



<sup>1</sup> Oxycotin and other oxycodone ER products, including generic products

<sup>2</sup> Source: IQVIA National Prescription Audit. 1992-2018. Extracted March 2019. Includes outpatient retail and mail-order/specialty pharmacies. There have been changes in the underlying data and methodology of the proprietary database, IQVIA NPA, including a change to manage prescription claims that are voided or reversed historically adjusted to January 2017, data prior to January 2017 have not been adjusted to this new methodology; therefore, changes over time must be interpreted in the context of the changes in methodology.

**Figure 2**

The following actions are noted in Figure 2:

- May 2000:** FDA issued an *Untitled Letter* to Purdue Pharma (Purdue), citing violations in OxyContin promotion related to misleading efficacy and safety presentations.
- July 2001:** FDA approved safety-related updates to the OxyContin labeling that included for example, a narrowing of the indication and addition of a Boxed Warning and other strengthened warnings about the potential for misuse and abuse. The Agency also worked with Purdue to implement a Risk Management Program aimed at reducing misuse and abuse of OxyContin and to issue a letter to healthcare professionals (a “Dear Healthcare Professional (DHCP) Letter”) to alert them about the safety updates to the label.
- Jan. 2003:** FDA issued a *Warning Letter* to Purdue, citing violations in OxyContin promotion related to misleading efficacy and safety presentations, including a failure to clearly present information from the label’s Boxed Warning regarding the potentially fatal risks and danger of abuse.
- April 2010:** FDA approved a new formulation of OxyContin, designed to help discourage abuse by snorting or injecting. The new formulation was approved with a Risk Evaluation and Mitigation Strategy (REMS) that included a Medication Guide

for patients and a requirement to make training available to prescribers on the appropriate use of opioid analgesics in the treatment of pain.

- July 2012:** FDA approved a REMS for all members of the class of extended-release/long-acting (ER/LA) opioid analgesics (which includes Oxycontin). The ER/LA Opioid Analgesic REMS – now known as the Opioid Analgesic REMS and includes IR products – required drug companies to make education programs available to prescribers based on the FDA REMS Education Blueprint (now known as the FDA Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain<sup>2</sup>).
- Dec. 2016:** FDA approved several safety labeling changes to all opioid analgesics (ER/LA and immediate-release), including changes to help inform patients and prescribers about the serious risks associated the combined use of certain opioid medications with benzodiazepines or other central nervous system depressants.

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FDA has always taken into consideration how changes in labeling, or other actions we take, may affect prescriber behavior, including potential unintended consequences. We do not have evidence that prescribers misinterpreted the 2001 narrowing of the indication to be an expansion of the approved duration of use. Further, it does not appear that there was any notable increase in the overall number of oxycodone ER prescriptions dispensed as a result of the 2001 change.

Aggressive marketing practices by pharmaceutical companies may have affected prescriber behavior, as did the unintended consequences of efforts to address patient pain by a number of organizations in the 1990s. In 1996, the American Pain Society coined the term *fifth vital sign* in the context of quality of care, meaning pain should be measured and treated. This concept was soon incorporated into the Veterans Health Administration (VHA) patient care toolkit (which outlined an extensive process for assessing and treating pain), and the practice guidelines of The *Joint Commission*<sup>3</sup> (formerly known as JCAHO), the Agency for Healthcare Research and Quality (AHRQ), and other specialty groups. Pain scores, and patient satisfaction with the pain treatment they received became routine elements of clinical evaluation in doctor's offices, clinics, and hospitals across the country and remain so today. In addition, practices such as giving prescriptions for relatively large numbers of opioid tablets at post-procedure hospital discharge—when either fewer tablets of an opioid, or use of a non-opioid analgesic, would have been sufficient—contributed to the problem, as these tablets could have been diverted and inappropriately used by family members or others. And finally, the disturbing reality that there are individuals who will intentionally prescribe and dispense opioids inappropriately for financial gain underscores the complex factors that contribute to the opioid crisis, the challenges of isolating the consequences of individual regulatory actions, and the importance of shared responsibility and action across multiple government agencies and private organizations.

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<sup>2</sup> [https://www.accessdata.fda.gov/drugsatfda\\_docs/rems/Opioid\\_analgesic\\_2018\\_09\\_18\\_FDA\\_Blueprint.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/rems/Opioid_analgesic_2018_09_18_FDA_Blueprint.pdf)

<sup>3</sup> [https://www.jointcommission.org/assets/1/6/Pain\\_Std\\_History\\_Web\\_Version\\_05122017.pdf](https://www.jointcommission.org/assets/1/6/Pain_Std_History_Web_Version_05122017.pdf)

**3. Since the 1995 approval of OxyContin, how many adverse events reports involving deaths has FDA received?**

**a. How many adverse event reports involving deaths were received by FDA for individuals younger than 21 years old?**

From 1995 through November 3, 2019, FDA received 29,071 reports in the FDA Adverse Event Reporting System (FAERS) database with an outcome of death associated with OxyContin. We note, however, that report counts may include duplicate reports for the same patient from multiple reporters (e.g., manufacturer, family member, physician, pharmacist, nurse), or an unrelated report. An example of an unrelated report includes a report describing a prior medical history of OxyContin use, that did not describe current OxyContin use during the time of death or as the cause of death. Furthermore, establishment of a causal association between a drug and an event is not a requirement prior to submission of a report to FDA or entry of a report into FAERS. Through FDA’s ongoing review of FAERS reports associated with opioid-containing products, we are aware that many of the reports with a fatal outcome are related to a wide range of opioid-containing products, including OxyContin. These reports, which date back as far as 1999, describe both medical and non-medical use of opioid-containing products. Because multiple substances are often detected and reported in drug overdose deaths (i.e., one person often will be found to have had several different substances in his body when he died), and little additional clinical information is provided in these reports, it is not possible to meaningfully attribute these deaths exclusively to any one substance or product.

It is important to note that FAERS does not receive reports for every adverse event that occurs with a product, particularly well-known adverse events, leading to a general under-reporting of adverse events. Therefore, FAERS report counts for misuse/abuse and overdose death cannot be used to determine the incidence of abuse or overdoses or trends over time. However, FAERS can be a useful tool for identifying new characteristics of how products are misused or abused and adverse events related to that misuse and abuse, such as with Opana ER.<sup>4</sup>

We continue to monitor the safety profile of OxyContin and have not identified any new safety concerns or trends within the FAERS data.

Unfortunately, there is no national data source that provides data on all overdoses or deaths involving OxyContin or any other specific opioid product. For example, national data derived from death certificates can, at best, identify certain drugs or drug groups (e.g., “opioids” or “oxycodone”) involved in an overdose death. FDA has been conducting and supporting projects, as well as requiring industry to conduct studies, linking multiple population-based data sources to better understand the risk of overdose and death among those dispensed specific opioid products such as OxyContin.

**Question 3a. How many adverse event reports involving deaths were received by FDA for individuals younger than 21 years old?**

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<sup>4</sup> <https://www.fda.gov/media/103654/download>



From 1995 through November 3, 2019, FDA has received 668 reports with an outcome of death associated with OxyContin in those with a reported age less than 21 years old. In September 2019 FDA convened a meeting of its Pediatric Advisory Committee and Drug Safety and Risk Management Advisory Committee to discuss the pediatric-focused safety review for OxyContin (oxycodone hydrochloride) extended-release tablets, as mandated by the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144). Such reviews are routinely discussed at public advisory committee meetings.

FDA approved OxyContin in 2015 for use in opioid-tolerant pediatric patients 11 years of age and older who are already receiving and tolerating opioids for at least 5 consecutive days with a minimum of 20 mg per day of oxycodone orally or its equivalent for at least two days immediately preceding dosing with OxyContin. At the September 26, 2019 Pediatric Advisory Committee meeting,<sup>5</sup> FDA presented results from its routine safety reviews, which described patterns of utilization of OxyContin among pediatric patients in the outpatient retail pharmacy setting and evaluated postmarketing adverse event reports with a serious outcome for OxyContin in pediatric patients. In addition, as part of FDA's approval of OxyContin for use in opioid-tolerant patients 11 years of age and older, the Agency required the sponsor to conduct two postmarketing studies (PMRs) in the pediatric population: enhanced pharmacovigilance (PMR 2923-1) and a drug utilization study (PMR 2923-2), to provide detailed clinical data on prescribing and use of OxyContin in children. PMR 2923-1 requires that the sponsor analyze postmarketing spontaneous adverse events in children. The FDA reviews (see link above) also describe the goals and status of these PMRs.

FDA evaluated all U.S. pediatric (ages 0 to <17) postmarketing adverse event reports with a serious outcome for OxyContin in the FAERS database from August 13, 2015, approval date of the pediatric labeling, through December 31, 2018.<sup>6</sup> When reports are submitted to FDA by the manufacturer, the manufacturer determines the outcome. Of the 89 reports reviewed, only eight cases, primarily in the 11 to <17 year age group, mentioned prescribed OxyContin use for post-surgical pain management (n=3) or pain management associated with a medical condition (n=5). Six of these cases reported the subsequent development of drug addiction. Overall, the most frequently reported adverse events in the 11 to <17 year age group were drug addiction and drug abuse, and in the 0 to <11 year age group were accidental overdose and accidental exposures. We identified 13 cases with a fatal outcome within this review. These fatal reports are further described in the September 26, 2019 advisory committee briefing document.<sup>7</sup> No new safety signals or increased severity or frequency of any labeled adverse events attributable to OxyContin use in the pediatric population were identified. FDA did not determine that any

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<sup>5</sup> Link to the background materials, <https://www.fda.gov/advisory-committees/pediatric-advisory-committee/fda-briefing-materials-september-26-2019-joint-meeting-pediatric-and-drug-safety-risk-management>, as well as the slides presented by FDA at the meeting <https://www.fda.gov/advisory-committees/pediatric-advisory-committee/presentations-september-26-2019-joint-meeting-pediatric-and-drug-safety-and-risk-management-advisory>

<sup>6</sup> The following outcomes qualify as "serious": death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, or other event that may jeopardize the patient and may require medical or surgical intervention.

<sup>7</sup> <https://www.fda.gov/media/131025/download>

regulatory action was needed, and continues to conduct routine pharmacovigilance of OxyContin. The Advisory Committees concurred with this conclusion.

**4. Did FDA require efficacy trials for its approval of Roxicodone 15mg and 30mg oxycodone tablets in 2000? If not, why were efficacy trials not required?**

The new drug application (NDA) for Roxicodone IR (oxycodone HCl) 15 mg and 30 mg tablets was approved pursuant to the 505(b)(2) approval pathway.<sup>8</sup> For approval, that application relied upon the Agency's previous finding of safety and effectiveness for Percodan (which is an oxycodone-containing product with more than 50 years of marketing experience and safety data) and published scientific literature relevant to oxycodone.

The 505(b)(2) approval pathway is one of two abbreviated approval pathways that were added to the FD&C Act (the Act) with the passage of the 1984 Hatch-Waxman Amendments.<sup>9</sup> For approval, a 505(b)(2) NDA must meet the statutory standard of safety and substantial evidence of effectiveness. For a 505(b)(2) NDA at least some of the information required for approval comes from one or more studies that were not conducted by or for the applicant and for which it does not have a right of reference or use. The 505(b)(2) approval pathway permits an applicant to rely on FDA's previous finding of safety and/or effectiveness for a previously approved drug as long as requirements for approval are met, including those regarding patent certifications. This approach is intended to encourage innovation by allowing applicants to avoid conducting studies that are not scientifically necessary.

Typically, the sources of information relied upon by a 505(b)(2) applicant include published scientific literature and/or FDA's finding of safety and/or effectiveness for an approved drug. To rely on these sources, the 505(b)(2) applicant must demonstrate sufficient similarity between the applicant's proposed product and the relied-upon approved drug or product described in the scientific literature to justify reliance on the existing information (the scientific justification is commonly referred to as the "bridge"). For reliance on an approved drug, the bridge is typically accomplished by bioavailability or bioequivalence (BA/BE) studies that compare similarity between the proposed drug product and the relied-upon approved drug.

Most 505(b)(2) applications consist of changes to a previously approved drug, such as a difference in strength, dosage form, or route of administration. Depending on the nature of the differences between the two drugs, FDA may require additional information, including new clinical trials, to support efficacy, safety, or both.

From both scientific and regulatory standpoints, the information submitted in support of the Roxicodone IR 505(b)(2) NDA, including the demonstration of bioequivalence to establish a scientific bridge to justify reliance on the Agency's previous finding for Percodan, was

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<sup>8</sup> A 505(b)(2) application is an NDA submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use.

<sup>9</sup> The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417). The second abbreviated pathway is the pathway for approval of generic drugs and is codified at section 505(j) of the FD&C Act.

determined to be adequate to support findings of safety and effectiveness for Roxycodone IR, as both Roxycodone IR and Percodan contain oxycodone as an analgesic and are titrated to effect and tolerability in the clinical treatment of pain. The application also included a body of published literature relevant to oxycodone. Thus, in the case of Roxycodone IR, it was determined that the applicant had provided sufficient information to support a finding of safety and effectiveness for the product without the need for new clinical trials.

- 5. In the FDA Briefing Document for the Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee & Drug Safety and Risk Management Advisory Committee held on June 26, 2018, FDA indicated that the safety and efficacy of oxycodone ER was based on bioequivalence to immediate release Roxycodone. On what basis did FDA come to the conclusion that extended release and immediate release oxycodone are bioequivalent?**
- a. If studies demonstrating safety and efficacy of Roxycodone were not performed, is it appropriate for FDA to assume that a drug bioequivalent to Roxycodone is safe and effective?**

The product discussed at the June 26, 2018, AADPAC and DSaRM meeting, Remoxy ER (oxycodone) extended-release capsules, was submitted as a 505(b)(2) application that relied on FDA's finding of safety and effectiveness for Roxycodone IR. FDA has not approved Remoxy ER. For that reason, it is premature to discuss whether Remoxy ER may meet the statutory standard for approval.

As a general matter, as noted in response to the previous question, the 505(b)(2) pathway permits FDA to approve NDAs that rely on published literature or on the Agency's finding of safety and effectiveness for another drug product, provided that such reliance is scientifically justified and the 505(b)(2) applicant complies with the applicable statutory requirements including those regarding patent certification. Generally, a scientific bridge between an extended-release formulation of a drug and an immediate-release formulation of a drug can be established through information such as a relative bioavailability study, which shows the systemic absorption of the two drugs.

Also, please see our response to the previous question explaining why the approval of Roxycodone IR in the absence of new clinical trials was appropriate.

- 6. In the years since 2001, has the FDA at any time formally or informally considered removing chronic pain from the label of opioid products? Have any offices at FDA or any staff involved in the review of opioid products at the FDA ever recommended removing chronic pain from the label of opioid products?**

First, as explained in our response to question 2, long-term use was not *added* to the OxyContin labeling in 2001; rather, long-term use has been part of the approved conditions of use for OxyContin from the time of its approval in 1995.

A small number of opioid analgesics are, in fact, indicated for treatment of acute pain only. This is based on the kind of indication requested by the sponsor and the type of clinical studies conducted. However, we are not aware of any FDA staff or offices ever having recommended that opioid analgesics, as a class, be limited to acute-use only.<sup>10</sup> Please see our response to question 11 regarding the basis for our conclusion that opioid analgesics, as a class, are appropriate, in certain circumstances, for long-term use.

Notably, in March 2017, a company submitted a citizen petition asking FDA to “revoke approval” of opioid analgesic drug products for chronic use and immediate-release opioid analgesic labeling supporting use for the treatment of chronic pain, and asking FDA to require that immediate-release opioid analgesic labeling state that the indication is for acute pain for a limited duration.<sup>11</sup> The agency is in the process of considering the issues raised in that petition. Please see our response to question 11 for additional information about the specific steps we are taking to consider the issues raised in that petition.

- 7. The CDC, DOD/VA, and American Academy of Neurology have said that the risks of opioid therapy for chronic conditions such as headache, fibromyalgia, and chronic low back pain likely outweigh the benefits.**
- a. Does the FDA agree with this assessment?**
  - b. If so, has the FDA taken any action as a result?**
  - c. Is any additional action being considered?**

Clinical guidelines are important to assist healthcare providers with their clinical decisions. They often are based on a combination of data from well-controlled clinical trials, clinical experience, and expert opinion. Treatment guidelines such as those developed by the groups listed above would not be included in product labeling; however, we acknowledge that these guidelines exist and understand that prescribers likely will follow those that are relevant to their practice.

We are aware that opioids are not first line therapy for headache, fibromyalgia, and chronic low back pain.<sup>12</sup> When prescribers are making a decision to use opioids in an individual patient, all of the potential risks and benefits must be weighed by the prescriber and discussed with their patient. Further, as described in the indication for all opioid analgesics used in the outpatient setting, patients should be prescribed opioids only if alternative treatment options are inadequate.

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<sup>10</sup> We note in this regard that FDA reviewers are not only encouraged, but required, to express their views and concerns during the application review process. This approach, formalized as the Equal Voice Initiative, helps spur scientific debate and ensure that all scientific and regulatory experts provide input before decisions are made. For further information, see, e.g., CDER Manual of Policies and Procedures “Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions” (available at <https://www.fda.gov/media/79353/download>).

<sup>11</sup> Docket FDA-2017-P-1359, at <https://www.regulations.gov/docket?D=FDA-2017-P-1359>.

<sup>12</sup> We note that there have been positive studies conducted in patients with chronic low back pain in whom non-opioid analgesics were not effective, and those studies have supported the approval of some opioids.

- 8. The CDC and VA/DoD have warned against prescribing opioids at doses that exceed 90mg morphine equivalents per day.**
  - a. Does the FDA agree with this assessment?**
  - b. If so, has the FDA taken any action as a result?**
  - c. Has the FDA contemplated any labeling changes that would reflect this warning?**
  - d. Is any other action being considered?**

The 2016 CDC opioid guidelines include warnings against prescribing opioids at doses that exceed 90mg morphine equivalents (MME) per day. CDC has since advised against misapplication of the guidelines, including raising awareness about specific issues that could put patients at risk.<sup>13,14</sup>

FDA has expressed concerns about the use of a specific dose of opioids as a “bright line” to identify risk. Our review of the data examining the relationship between daily opioid analgesic dose and risk of overdose deaths shows a linearly increasing relationship – that is, increasing daily dose clearly increases risk for opioid overdose, but, the data do not suggest a threshold below which opioid use is “safe” and above which it is “too risky”.<sup>15</sup> Multiple patient factors that have an association with opioid overdose (e.g., mental health diagnoses, family history of substance use disorder)<sup>16,17,18,19</sup> may have as strong or stronger association than the magnitude of association for a higher-dose vs. lower-dose opioid analgesic prescription. In other words, factors such as mental health diagnoses or family history of substance use may be more closely related to risk of overdose than the dose a patient is taking.

FDA supports individualizing therapy, using careful assessment of the benefits and risks of a therapeutic regimen for an individual patient. VA and DOD have also recognized the need for individualized therapy. More recently, the HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics<sup>20</sup> was published to further clarify the need to judiciously provide individualized therapy, including slow tapering of opioids, transition to other opioid analgesics such as buprenorphine, as well as recognition that there may

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<sup>13</sup> <https://www.cdc.gov/media/releases/2019/s0424-advises-misapplication-guideline-prescribing-opioids.html>

<sup>14</sup> <https://www.nejm.org/doi/full/10.1056/NEJMp1811473>

<sup>15</sup> <https://onlinelibrary.wiley.com/doi/full/10.1002/pds.4366>

<sup>16</sup> Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med.* 2011;171(7):686-691.

<sup>17</sup> Turner BJ, Liang Y. Drug Overdose in a Retrospective Cohort with Non-Cancer Pain Treated with Opioids, Antidepressants, and/or Sedative-Hypnotics: Interactions with Mental Health Disorders. *J Gen Intern Med.* 2015;30(8):1081-1096.

<sup>18</sup> Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. *BMJ.* 2015;350:h2698.

Garg RK, Fulton-Kehoe D, Franklin GM. Patterns of Opioid Use and Risk of Opioid Overdose Death Among Medicaid Patients. *Med Care.* 2017;55(7):661-668.

<sup>19</sup> Oliva EM, Bowe T, Tavakoli S, et al. Development and applications of the Veterans Health Administration's Stratification Tool for Opioid Risk Mitigation (STORM) to improve opioid safety and prevent overdose and suicide. *Psychol Services.* 2017;14(1):34-49.

<sup>20</sup> [https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage\\_Reduction\\_Discontinuation.pdf](https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf)

be some patients who are unable to taper or discontinue opioid analgesic therapy.<sup>21</sup> Data are lacking on the effect opioid dose tapering (particularly forced tapers) has on patients' risk of overdose. Additionally, studies suggest that high variability in a patient's opioid analgesic dose may be a more important contributor to risk of overdose than the average daily dose. Variability in dose, such as large and/or fluctuating increases or decreases in a patient's opioid dose, was associated with a greater risk of opioid overdose, after adjusting for average recent opioid analgesic daily dose and other patient medical and demographic factors, among patients treated with opioid analgesics for  $\geq 90$  days for chronic, non-cancer pain.<sup>22</sup> Other studies also show that opioids produce drug liking and reinforcing effects across a range of doses, consistent with their known abuse liability.<sup>23,24</sup>

FDA held a public advisory committee meeting, on June 11-12, 2019, to discuss concerns that have been raised about the safety of the higher-range doses of opioid analgesics. Specifically, there are safety concerns associated with both higher strength products and higher daily doses of opioid analgesics, both in patients and in others who may have access to these drugs. However, many patients and healthcare professionals state that higher-strength opioid analgesics are a necessary part of effective pain management for some patients. FDA is focused on striking the right balance between reducing the rate of new addiction while providing appropriate access to those patients in need of pain management. The Agency has heard the concerns expressed by patients with chronic pain about their need for continued access to necessary pain medication, the fear of being stigmatized as an addict, challenges in finding healthcare professionals willing to prescribe opioid analgesics, and tragically, for some patients, suicidal thoughts or actual suicide because of intractable pain.<sup>25</sup>

FDA also recently funded a research project to study the effect of opioid analgesic deprescribing (i.e., tapering and/or discontinuing) on patient outcomes, including suicidality, completed suicide, and overdose, and to explore these associations for different tapering patterns and in different patient subgroups. The study completion date is planned for 2022.<sup>26</sup>

- 9. At the request of the FDA, the National Academies of Sciences, Engineering, and Medicine in 2017 released its Strategies for Reducing the Opioid Epidemic, which included a new framework for considering the approval and removal of opioid products that takes into account the public health impact. You said that you would be implementing this framework.**
- a. What specific steps has the FDA taken to implement this framework?**
  - b. Has the FDA considered using the framework to seek removal of opioid products from the market, other than Opana?**

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<sup>21</sup> <https://www.fda.gov/drugs/drug-safety-and-availability/fda-identifies-harm-reported-sudden-discontinuation-opioid-pain-medicines-and-requires-label-changes>

<sup>22</sup> <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2730786>

<sup>23</sup> <https://www.sciencedirect.com/science/article/pii/S037687160800197X?via%3Dihub>

<sup>24</sup> <https://www.nature.com/articles/1301479>

<sup>25</sup> For more information about this advisory committee meeting, including meeting materials and transcripts, please visit our website: <https://www.fda.gov/advisory-committees/advisory-committee-calendar/june-11-12-2019-joint-meeting-drug-safety-and-risk-management-advisory-committee-and-anesthetic-and>.

<sup>26</sup> <https://www.fda.gov/media/132314/download>

The 2017 NASEM report contained multiple recommendations regarding FDA’s framework for making regulatory decisions regarding opioids. Among other things, NASEM recommended that FDA’s benefit-risk framework appropriately take into account the public health impact of opioid drug products. In fact, FDA has long endeavored to consider the risks associated with these products, including the risks associated with abuse and misuse, by patients and non-patients alike, when weighing the risks of these products against their benefits. Of course, FDA also continually evaluates the manner in which it does so to ensure that its decisions are consistent with our public health mission as well as the current scientific understanding of the role that opioid drug products play in the evolving landscape of the opioid crisis.

On June 20, 2019, FDA issued a new draft guidance for industry Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework (draft guidance),<sup>27</sup> which describes the application of the benefit-risk assessment framework that the Agency uses in evaluating new drug applications for opioid analgesic drugs and summarizes the information that should be supplied by sponsors of opioid analgesic drug applications to facilitate the Agency’s benefit-risk assessment. FDA developed the draft guidance based on our statutory authorities and in light of the NASEM report’s recommendations. The draft guidance devotes particular attention to those recommendations concerning the need to properly account for the public health impact of opioid analgesics within FDA’s benefit-risk framework. As explained in the draft guidance: FDA assesses risks and benefits of all drugs in the context of the use indicated in the labeling. However, because of the widespread misuse and abuse of prescription opioid analgesic drugs, for this class of drugs, FDA also considers the broader public health effect of opioid analgesic drugs; this involves consideration of the risks related to misuse, abuse, opioid use disorder, accidental exposure, and overdose, for both patients and others. Likewise, FDA considers any properties of a drug expected to mitigate these risks.

Accordingly, the draft guidance contains a section explaining in detail what data and information we recommend that sponsors submit related to the expected public health impact of candidate opioid analgesics, including impacts associated with anticipated inappropriate use, as well as how FDA intends to consider such data and information within the context of its overall benefit-risk assessment. This guidance can be found at the following link:  
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/opioid-analgesic-drugs-considerations-benefit-risk-assessment-framework-guidance-industry>.

In addition, FDA held a Part 15 hearing, on September 17, 2019, to further discuss the Agency’s benefit-risk assessment of opioid analgesics, including the manner in which risks of misuse and abuse of these products factor into the benefit-risk assessment. This hearing included a discussion of whether an applicant for a new opioid analgesic should be required to demonstrate that its product has an advantage over existing drugs in order to be approved and, if so, what new authorities the FDA would need to impose such a requirement. The hearing also addressed whether new preapproval incentives (in addition to existing incentives, such as breakthrough designation) are needed to better support and encourage development of all therapeutics – opioid or non-opioid drugs, biological products or devices – intended to treat pain or addiction. More information about this Part 15 hearing can be found at: <https://www.fda.gov/drugs/development->

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<sup>27</sup> This draft guidance, when finalized, will represent the current thinking of the FDA on this topic.

*approval-process-drugs/standards-future-opioid-analgesic-approvals-and-incentives-new-therapeutics-treat-pain-and-addiction.*

We also plan to issue additional guidance that will outline appropriate clinical endpoints and clinical trial approaches for the development of non-opioid drugs for use in the treatment of acute and chronic pain.

**Question 9b. Has the FDA considered using the framework to seek removal of opioid products from the market, other than Opana?**

In 2005, the manufacturer of Palladone (hydromorphone hydrochloride) ER capsules agreed to FDA's request to suspend sales and marketing of the product in the United States. The Agency concluded that the overall risk versus benefit profile of Palladone was unfavorable due to a potentially fatal interaction with alcohol.<sup>28</sup>

**10. Last month, you said that the FDA will require drug companies to initiate studies on whether prescription opioids are effective for treating chronic pain. The FDA has already repeatedly claimed that it would require post-market studies, including in 2013, when the FDA said it would require studies on the safety of opioids for treating chronic pain. What is the status of these post-market studies?**

On September 10, 2013, FDA issued letters to each ER/LA opioid analgesic NDA holder, requiring five PMRs under section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) —four observational studies and one clinical trial.<sup>29</sup> The purposes of the PMRs are to assess the known serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of ER/LA opioid analgesics.

FDA established an Opioid PMR Steering Committee to provide CDER management-level leadership on operational and strategic decisions concerning the implementation of the PMR project. Similarly, the ER/LA NDA holders came together to form the Opioid PMR Consortium (OPC), consisting of one to four representatives from each company. The FDA Opioid PMR Steering Committee held monthly meetings with the OPC from October 2013 through September 2014 and has continued to meet quarterly since 2014.

During the protocol development phase, FDA hosted a public meeting<sup>30</sup> to obtain stakeholder input on the design and conduct of protocols needed to fulfill the PMRs. The five proposed

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<sup>28</sup> *Information for Healthcare Professionals: Hydromorphone Hydrochloride Extended-Release Capsules (marketed as Palladone)*, available at <https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/information-healthcare-professionals-hydromorphone-hydrochloride-extended-release-capsules-marketed>.

<sup>29</sup> <https://wayback.archive-it.org/7993/20180726173705/https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf>

<sup>30</sup> <https://wayback.archive-it.org/7993/20170111082950/http://www.fda.gov/Drugs/NewsEvents/ucm384489.htm>



protocols discussed at the public meeting subsequently evolved into eleven inter-related studies with refined measures for assessing the known serious risks of misuse, abuse, addiction, overdose and death. On February 3, 2016, FDA issued a letter to each ER/LA opioid analgesic sponsor, titled “Release From Postmarketing Requirement; New Postmarketing Requirement”<sup>31</sup> and replaced the five existing PMRs with eleven PMRs (ten postmarketing studies and one clinical trial). The current status (as of November 2019) of the ER/LA PMRs is available on FDA’s website at <https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm>. Eight studies are completed (3033-3, 4, 5, 6, 7, 8, 9, 10) and two studies are ongoing (3033-1 and 3033-2). The clinical trial (3033-11) to assess the risk of hyperalgesia associated with long-term opioid use is being redesigned given the original 2013 study’s inability to recruit. The 2013 study design that was initially agreed upon to fulfill this PMR required that patients on long-term opioid analgesics be tapered off the opioid. Because of changes in opioid prescribing and reimbursement guidelines, patients who might have been eligible for the study were concerned about having access to their medication after study completion. As a result, the ER/LA NDA holders were unable to enroll sufficient patients in the study. A new protocol to assess the risk of hyperalgesia is currently under review by FDA.

At the same time, FDA is considering next steps given FDA’s new PMR authorities under the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act. We are currently analyzing the existing data on long-term opioid use to identify areas where more data are needed. The information derived from this analysis will help inform the objectives and design of a new long-term effectiveness study we intend to require, and help us understand how best to consider questions related to hyperalgesia.

For additional information on the completed studies, the OPC has six published manuscripts that describe the studies and their findings (see Appendix).

**11. When the FDA called for post-market studies in 2013, Director of the Center for Drug Evaluation and Research Janet Woodcock wrote, that "FDA is not aware of adequate and well-controlled studies of opioid use longer than 12 weeks" and that the FDA was thus exercising its authority to require "opioid drug sponsors to conduct PMRs to assess the known serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of opioid analgesics." Title 21, Sec. 314.126 of the Code of Federal Regulations states "adequate and well-controlled investigations provide the primary basis for determining if there is 'substantial evidence' to support the claims of effectiveness." What is the legal justification for the FDA's current label for extended-release opioids if the agency acknowledged in 2013 that such "adequate and well-controlled" studies did not exist?**

Randomized, controlled clinical trials of 12-weeks’ duration have served as the basis for a determination of long-term efficacy for other classes of drugs in many chronic or lifelong conditions, such as diabetes, high blood pressure, and depression. The effectiveness of opioid analgesics for treatment of chronic pain has been well established through numerous 12-week randomized, placebo-controlled trials followed by 12-month open-label extension studies, in

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<sup>31</sup> <https://www.fda.gov/media/95546/download>

addition to centuries of clinical experience. Randomized trials combined with open-label extension studies tell us that there is a population of chronic pain patients who benefit from long-term opioid therapy, and that these benefits are maintained for this population over time.

FDA agrees that additional long-term studies are needed to augment our understanding of the risks and benefits of long-term opioid use and allow us to better inform prescribers and patients about the safe and appropriate use of opioids for treatment of chronic pain. For example, the results of the new long-term effectiveness study discussed in response to question 10 above could improve our understanding of long-term efficacy for those patients who continue to require opioid analgesics for chronic pain and provide more information about those who do not respond to treatment. This could lead to additional information for prescribers about how to identify which of their patients could be expected to benefit from long-term opioid use and which may not, and how to safely discontinue the opioid analgesic for the non-responders.

Finally, FDA has engaged researchers at the University of Pennsylvania (UPenn) to evaluate the long-term efficacy of chronic opioid use in chronic pain patients using the existing opioid clinical trial data in FDA's database. Under this contract, academics at the University of Pennsylvania have extracted, harmonized, merged, and pooled patient-level raw data from Phase 2 and 3 analgesic clinical trials archived at the FDA. Analyses of the data are still underway. FDA is looking forward to sharing this information with you and your offices once UPenn completes and publishes its analyses. The results of these analyses are expected to augment the Agency's understanding of the long-term efficacy of FDA approved opioids in chronic pain patients.

FDA fully recognizes the difficulties inherent in balancing the needs of patients who suffer from chronic pain—whether related to cancer or to non-cancer causes—with the need to limit inappropriate prescribing and use. We held a patient-focused drug development workshop in 2018 and heard first-hand about the devastating impact that inadequately-treated chronic pain has on the lives of patients. Robust evidence shows that chronic pain itself, regardless of type, is an important independent risk factor for suicidality, as chronic pain patients are at least twice as likely to report suicidal behaviors or to complete suicide.<sup>32</sup> In a national sample from the Veterans Health Administration, among patients discontinued from long-term opioid therapy for chronic pain, nearly 12% had documented suicidal ideation and suicidal self-directed violence in the year following discontinuation.<sup>33</sup> More information about the workshop can be found at: <https://www.fda.gov/drugs/news-events-human-drugs/public-meeting-patient-focused-drug-development-chronic-pain>.

**12. The enriched enrollment randomized withdrawal (EERW) study design for opioid analgesics is a clinical trial methodology that limits inclusion to patients who tolerate opioids and are likely to be physiologically dependent on opioids after taking them in an**

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<sup>32</sup> Racine, M. Chronic pain and suicide risk: A comprehensive review. *Progress in Neuropsychopharm and Biological Psychiatry* 2018; 87:269-280

<sup>33</sup> Demidenko MI, et. al., Suicidal ideation and suicidal self-directed violence following clinician-initiated prescription opioid discontinuation among long-term opioid users, *General Hospital Psychiatry* 47 (2017) 29–35

**open-label phase. Critics have called this methodology scientifically unsound and have said that it amounts to cooking the books.**

- a. In 2013, the Washington Post reported on a group known as IMMPACT, which held meetings that pharmaceutical companies paid tens of thousands of dollars to participate in and advised the FDA on clinical trials. In a presentation entitled, "The Impact of IMMPACT," former chief of the FDA's analgesic division Bob Rappaport touted "A New Successful Trial Design" that resulted from the IMMPACT meetings. Was the "new successful trial design" that emerged from the IMMPACT meetings EERW?**
- b. Have any offices at FDA or any staff involved in the review of opioid products at the FDA ever raised concerns about the EERW study design?**
- c. Has FDA ever convened an advisory committee meeting to discuss and vote on the appropriateness of using EERW?**
- d. Opioid dependent pain patients switched to placebo are likely to experience withdrawal symptoms. How are double-blind requirements maintained when patients are switched from a drug with a noticeable psychoactive effect to placebo and when withdrawal symptoms are experienced?**
- e. If increased pain sensitivity and worsening of pain are common during opioid withdrawal, is it fair to assume that opioid dependent patients switched to placebo in an EERW study will have an increase in pain?**
- f. In light of these concerns, will FDA consider convening an advisory committee meeting to review and vote on the appropriateness of EERW designed for opioid approvals?**

Randomized withdrawal trial design is a form of enrichment design, and this type of trial has been used as a part of drug development for over thirty years in a range of therapeutic classes with a goal of improving the efficiency of the assessment of drugs for potential approval. FDA recently published a final guidance on this type of trial to assist industry in developing enrichment strategies for use in clinical investigation as a part of drug development.<sup>34</sup> Importantly, enrichment designs, including randomized withdrawal studies, are the prospective use of patient-specific factors to select a study population in which detection of a drug effect, if one is in fact present, is more likely than it would be in an unselected population. In the case of opioids, there are a number of side-effects that are related to the dose that can limit the ability of patients to remain enrolled in trials including nausea, vomiting, headache, constipation, and pruritus (itching). Enrichment design studies use an open-label titration phase to identify patients that are able to tolerate these side-effects, followed by a randomized withdrawal phase which allows for an assessment of efficacy in opioid-tolerant patients by randomizing them to continued opioid therapy or to placebo. The result is a trial that provides information in the population of patients who tolerate the drug about the safety and efficacy of the opioid being studied. When drawing conclusions from such a trial, it is important to identify the population that was enrolled in the study and the number of patients unable to tolerate the drug. The number of subjects who are unable to tolerate the drug during the open-label titration portion of the study is part of the information reported in labeling, so that prescribers are aware that a similar proportion of their patients may not be able to tolerate the drug.

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<sup>34</sup> "Enrichment Strategies for Clinical Trials to Support Determination of Effectiveness of Human Drugs and Biological Products" (March 2019).

**Question 12a. In 2013, the Washington Post reported on a group known as IMMPACT, which held meetings that pharmaceutical companies paid tens of thousands of dollars to participate in and advised the FDA on clinical trials. In a presentation entitled, "The Impact of IMMPACT," former chief of the FDA's analgesic division Bob Rappaport touted "A New Successful Trial Design" that resulted from the IMMPACT meetings. Was the "new successful trial design" that emerged from the IMMPACT meetings EERW?**

It is not clear what type of trial design Dr. Rappaport was referring to. As discussed above, enrichment designs have been used in a variety of therapeutic areas for many years prior to this meeting, including analgesic trials.

**Question 12b. Have any offices at FDA or any staff involved in the review of opioid products at the FDA ever raised concerns about the EERW study design?**

We are aware of no employee of FDA who has raised concerns about the use of randomized withdrawal study designs. Similarly, no comments were received regarding this issue when the recently-finalized Enrichment Guidance was in draft form.

**Question 12c. Has FDA ever convened an advisory committee meeting to discuss and vote on the appropriateness of using EERW?**

While no advisory committee has been convened to discuss the appropriateness of randomized withdrawal designs, EERW studies have been presented at advisory committee meetings. Enrichment designs are widely accepted as a standard approach to use under appropriate circumstances.

**Question 12d. Opioid dependent pain patients switched to placebo are likely to experience withdrawal symptoms. How are double-blind requirements maintained when patients are switched from a drug with a noticeable psychoactive effect to placebo and when withdrawal symptoms are experienced?**

Maintaining blinding to treatment when some of the trial participants are switched to placebo is managed by slow tapering and making rescue medications, including immediate-release opioids, available to patients as needed. To further reduce the effects of any early withdrawal symptoms, efficacy assessments are based on outcomes measured 12 weeks following the withdrawal. The difference in the amount of pain at the end of the study is used to make a determination of efficacy.

**Question 12e. If increased pain sensitivity and worsening of pain are common during opioid withdrawal, is it fair to assume that opioid dependent patients switched to placebo in an EERW study will have an increase in pain?**

See the answer to ‘d’. Opioid tapers during clinical trials are conducted over a long enough duration so that withdrawal symptoms, including pain, are minimized. Furthermore, assessments are conducted during the randomized withdrawal phase to measure for symptoms of opioid withdrawal. These assessments include the Clinical Opioid Withdrawal Scale and the Subjective Opioid Withdrawal Scale.

**Question 12f. In light of these concerns, will FDA consider convening an advisory committee meeting to review and vote on the appropriateness of EERW designed for opioid approvals?**

FDA believes that this form of enriched trial design is a standard strategy to employ as a part of efficient clinical drug development.

FDA has tried to find approaches that assure availability of opioids to patients in need of these drugs to manage their pain, while working towards solutions that can reduce the misuse and abuse of these drugs. For example, as you are aware, in 2012 FDA approved a REMS for the extended-release/long acting opioid analgesics that was broadened in 2016 to all opioid analgesics intended for outpatient use and focuses on providing training to prescribers on appropriate pain management including the use of opioid and non-opioid analgesics. We are now seeing an overall decrease in opioid prescriptions, likely related to many factors including changing guidelines, efforts by government agencies, including FDA, and changing practice behavior by healthcare providers. Efforts to develop abuse- deterrent formulations (ADFs) to inhibit abuse (such as reducing snorting or intravenous injection) have been another area of focus; however, whether ADFs have impacted the incidence of misuse and abuse and, importantly, serious outcomes such as overdoses, remains to be determined.

As you know, the opioid crisis is one of the largest and most complex public health tragedies that our nation has ever faced, and advancing efforts to address this crisis is one of the FDA’s top priorities. Additional information on FDA’s efforts in combatting the opioid crisis, including actions taken to better inform practitioners and patients of the risks associated with opioids through FDA-required labeling, is available on FDA’s website:

*<https://www.fda.gov/drugs/information-drug-class/timeline-selected-fda-activities-and-significant-events-addressing-opioid-misuse-and-abuse/>*. We remain steadfast in our work to address the ongoing challenge of opioid abuse and misuse.

Please do not hesitate to contact us again if you have further questions. An identical response has been sent to Senator Markey.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Woodcock', written in a cursive style.

Janet Woodcock, MD

Director

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

**Appendix**

## Manuscripts

PMR	Title	Authors	Journal and Date
3033-6	Identifying and classifying opioid-related overdoses: A validation study.	Green CA, Perrin NA, Hazlehurst B, Janoff SL, DeVeugh-Geiss A, Carrell DS, Grijalva CG, Liang C, Enger CL, Coplan PM.	Pharmacoepidemiol Drug Saf. 2019 Apr 24. <a href="#">PDF Here</a>
3033-6	Development of an algorithm to identify inpatient opioid-related overdoses and oversedation using electronic data.	Green CA, Hazlehurst B, Brandes J, Sapp DS, Janoff SL, Coplan PM, DeVeugh-Geiss A.	Pharmacoepidemiol Drug Saf. 2019 May 16. <a href="#">PDF Here</a>
3033-6	Using natural language processing of clinical text to enhance identification of opioid-related overdoses in electronic health records data.	Hazlehurst B, Green CA, Perrin NA, Brandes J, Carrell DS, Baer A, DeVeugh-Geiss A, Coplan PM.	Pharmacoepidemiol Drug Saf. 2019 Jun 19 <a href="#">PDF Here</a>
3033-8	Possible Opioid Shopping and its Correlates.	Walker AM, Weatherby LB, Cepeda MS, Bradford D, Yuan Y	Clin J Pain. 2017 Nov. <a href="#">Article Available Here</a>
	Information on Doctor and Pharmacy Shopping for Opioids Adds Little to the Identification of Presumptive Opioid Abuse Disorders in Health Insurance Claims Data	Walker AM, Weatherby LB, Cepeda MS, Bradford D	Substance Abuse and Rehabilitation. 2019 Aug. <a href="#">Article Available Here</a>
3033-10	Medical record-based ascertainment of behaviors suggestive of opioid misuse, diversion, abuse, and/or addiction among individuals showing evidence of doctor/pharmacy shopping	Esposito DB, Cepeda MS, Lyons JG, Yin R, Lanes S	J Pain Res. 2019 Jul 24. <a href="#">Article Available Here</a>