

## Timeline of Selected FDA Activities and Significant Events Addressing Substance Use and Overdose Prevention

This timeline provides chronological information about significant FDA activities related to substance use and overdose prevention. Included is a summary timeline of key events, followed by tabbed years that provide selected additional actions and more detail about the items listed in the summary.

### 1911-1999

#### 1911 to 1990s

Opioid pain medications were used primarily for acute pain and cancer pain. Studies showing inadequate treatment of chronic non-cancer pain by physicians lead to an increased use of opioids.

#### 1987

**May:** MS Contin, (morphine sulfate) approved; first formulation of an opioid pain medicine that allowed dosing every 12 hours instead of every 4 to 6 hours.

#### 1990

**August:** Duragesic (fentanyl transdermal system) approved; first formulation of an opioid pain medicine in a patch (sometimes referred to as a “skin patch”) that is changed every 3 days.

#### 1995

**December:** OxyContin (oxycodone controlled-release) approved; first formulation of oxycodone that allowed dosing every 12 hours instead of every 4 to 6 hours. OxyContin would soon become a focal point of opioid abuse issues that would continue to escalate into the late 2000s and beyond.

- At the time of approval, FDA believed the controlled-release formulation of OxyContin would result in *less* abuse potential, since the drug would be absorbed slowly and there would not be an immediate “rush” or high that would promote abuse. In part, FDA based its judgment on the prior marketing history of a similar product, MS Contin, a controlled-release formulation of morphine approved by FDA and used in the medical community since 1987 without significant reports of abuse and misuse.
- Also at the time of OxyContin’s approval, FDA product labeling warned of the danger of abuse of the drug and that crushing a controlled-release tablet followed by intravenous injection could result in a lethal overdose. There was no evidence to suggest at the time

that crushing the controlled-release capsule followed by oral ingestion or snorting would become widespread and lead to a high level of abuse.

## 1998

**November:** Actiq (fentanyl) approved; first pain medicine approved to treat cancer breakthrough pain but with additional safety concerns. Actiq was approved with a restricted distribution program to try to prevent 1) accidental exposure in children because the product looked like a lollipop, and 2) potential abuse. This drug would later become part of a category of opioids now known as transmucosal immediate-release fentanyl (TIRF) products. Transmucosal means that the dose of the drug is delivered across mucous membranes, such as inside the cheek, under the tongue, or in the nose.

## 2000-2004

### Early 2000s

Reports of overdose and death from prescription drug products, especially opioids, began to rise sharply, with OxyContin at the center of the problem. For instance, the number of people who admitted to using OxyContin for non-medical purposes increased dramatically from approximately 400,000 in 1999 to 1.9 million in 2002 and to 2.8 million in 2003.

By 2009, about 1.2 million emergency department (ED) visits were related to misuse or abuse of pharmaceuticals, an increase of more than 98% since 2004 and more than the number of ED visits related to use of illicit drugs such as heroin and cocaine. Most prominent among these prescription drug-related deaths and ED visits were opioid pain relievers (OPR), especially OxyContin.

FDA had worked with sponsors for more than a decade to implement risk management programs for a number of opioid products. However, data demonstrated that these programs did not adequately manage the risks of misuse, abuse, addiction, and overdose. More was needed.

## 2001

**January:** Beginning in 2001 and ongoing, inter-agency collaboration occurred to develop public education regarding prescription drug abuse. The involved agencies included FDA, SAMHSA, the Center for Substance Abuse Treatment (CSAT), and the National Institute on Drug Abuse (NIDA).

**March:** CSAT hosted a meeting with FDA and other federal agencies, including DEA, NIDA, and the Centers for Disease Control and Prevention (CDC).

**July:** Additional stronger warnings about the potential for misuse and abuse were added to the OxyContin label.

- To help prescribers choose patients who would benefit from using OxyContin, the indication for using the drug was changed from “moderate to severe pain where use of an opioid analgesic is needed for more than a few days” to “management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.”
- The label was also changed to say that OxyContin is not appropriate for “as needed” pain or in the immediate-post operative period if the pain is mild or not expected to persist for an extended period of time.
- A Boxed Warning was added to reinforce the most important warnings, and information in the DRUG ABUSE AND DEPENDENCE section was updated. OxyContin’s manufacturer, Purdue Pharma, agreed to implement a Risk Management Program (RMP) to try to reduce misuse and abuse of OxyContin and issued a Dear Healthcare Professional Letter about changes to the label.

## 2002

**January:** Patient Package Insert (PPI) approved for OxyContin. This is a document written for patients that provides information about how to safely use the drug.

**March:** Inter-Agency Working Group Meeting held to discuss OxyContin and other extended-release opioids and their abuse and diversion. FDA, DEA, NIDA, and SAMHSA involved.

## 2003

**January:** FDA issued a [Warning Letter](#) (PDF - 149KB) to OxyContin’s manufacturer, Purdue Pharma, for misleading advertisements. Among many other details, the warning specified that the ads left out and minimized the serious safety risks associated with OxyContin and promoted it for uses beyond those which had been proven safe and effective. Specifically, the letter pointed out that the advertisements failed to clearly present information from the product label’s Boxed Warning regarding the potentially fatal risks and the danger of abuse.

## 2005-2008

### 2006

**September:** PPI for Actiq converted to a Medication Guide (MG) due to heightened safety considerations. The conversion was to better ensure that each patient prescribed the drug was fully informed of its serious risks. In contrast to PPIs, MGs are required to be given to each patient when they fill a prescription.

**September:** Fentora (fentanyl buccal tablets), the second TIRF product, approved with an MG and RMP but not restricted distribution.

### 2007

**September:** FDA issued a Public Health Advisory for Fentora due to reports of medication errors resulting in adverse events and deaths.

**September:** The Food and Drug Administration Amendments Act (FDAAA) became law, providing the Agency with a wide array of new authority designed to enhance drug safety. One of these is the authority to require Risk Evaluation and Mitigation Strategies (REMS) in order to ensure the benefits of the drugs continue to outweigh their risks. REMS are intended to require manufacturers to implement various safety measures for certain drugs. This new law helped provide the basis for a future comprehensive REMS program for all FDA-approved Extended-Release (ER)/Long Acting (LA) opioid products (see 2009 through 2012 below).

**September:** FDA [announced](#) it would require companies to stop marketing any **unapproved** drug containing the opioid pain medication hydrocodone bitartrate (the active ingredient in the opioid sold under the familiar trade name Vicodin).

## 2008

Fentora's manufacturer, Cephalon, requested an expansion of the drug's indication to include patients with non-cancer breakthrough pain. An FDA Advisory Committee concluded that the existing RMP for the drug was not effective, and Cephalon was told that a REMS program would be required before the drug could be considered for a broader indication.

**February:** Fentora's label and MG were revised to strengthen warnings.

## 2009

**February:** FDA informed Cephalon that the RMP was not sufficient to ensure the safe use of Fentora for the already approved indication for treatment of breakthrough cancer pain and needed to be replaced by a REMS.

**March:** FDA met with manufacturers of ER/LA opioid pain medications to discuss the requirement for a class-wide, shared-system REMS, which is a single uniform program for all products in a drug class.

**April:** FDA partnered with SAMHSA to launch an [initiative](#) to help ensure the safe use of the opioid methadone, as this drug appeared to be responsible for a highly disproportionate number of overdoses and deaths in pain patients compared with all other opioids. (Methadone is best known as a treatment for addiction to and dependence on heroin and other narcotic pain medicines, but it is also prescribed to treat moderate-to-severe chronic pain.)

**May:** Among a variety of public and stakeholder meetings that occurred in 2009, FDA held a [large public meeting on May 27-28](#) where more than 100 people provided comments on their experiences with opioid drugs along with suggestions for a REMS targeting ER/LA opioid products. Groups that participated included patient advocacy organizations, prescriber organizations, pharmacy organizations, insurance providers, and other government agencies. In

addition, FDA solicited written comments through a public docket. (See [summary of comments](#) (PDF - 6MB).)

**July:** FDA approved Onsolis (fentanyl), the third TIRF for breakthrough cancer pain. It was approved with a REMS in place. At this point, FDA decided that a separate REMS for each TIRF product would create a great burden to patients, pharmacies, and prescribers and so began discussion of a single-shared REMS for all TIRF products.

FDA informed Cephalon in 2009 of the requirement to convert the RMP for Fentora and Actiq to a REMS.

**August:** Embeda (morphine sulfate and naltrexone extended-release tablets) approved. Naltrexone helps block the effects of opioids. Embeda was the first product approved combining an opioid pain medicine and opioid blocker since Talwin NX (pentazocine and naloxone) was approved in 1982. [Suboxone (buprenorphine and naloxone) sublingual tablets, approved in 2002, has an opioid blocker but is specifically for the treatment of opioid dependence, not for pain.]

**October:** Similar to actions in 2007 against makers of unapproved hydrocodone products, FDA [warned companies](#) they must stop marketing unapproved codeine sulfate tablets, a widely used opioid to treat pain.

**November:** FDA launched the [Safe Use Initiative](#) to create and facilitate public and private collaborations within the health care community, with a goal to reduce preventable harm from medication. Safe use of opioids is a primary focus of this ongoing effort.

**November:** The November 26, 2009, issue of *The New England Journal of Medicine* featured an article titled [A Difficult Balance – Pain Management, Drug Safety, and the FDA](#) by Janet Woodcock, M.D., director of FDA's Center for Drug Evaluation and Research (CDER). In the article, Dr. Woodcock discussed FDA's efforts to strike a balance between legitimate patient access to pain medications and managing the risks posed by various analgesics. She cited recent FDA actions on the over-the-counter pain reliever acetaminophen, the low-potency opioid propoxyphene, and high-potency opioids such as OxyContin.

**December:** FDA held a [stakeholder meeting on December 4](#) with the Industry Working Group (IWG), consisting of representatives from 22 pharmaceutical companies asked to help develop an effective opioid REMS program for a proposed class-wide opioid REMS. [IWG would be re-named REMS Program Companies (RPC) in August, 2011].

A significant percentage of deaths and overdose from opioids, especially from ER/LA opioids, results from theft of pain medicine from medicine cabinets and accidental exposure to the drugs. Since 2009, FDA has worked with DEA and other organizations to help [educate the public](#) on safe disposal of opioids when they are no longer needed for pain.

## 2010

**April:** FDA [approved a new formulation of OxyContin](#).

**July:** FDA held a [joint meeting](#) of its Anesthetic and Life Support Drugs Advisory Committee (ALSDAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee to discuss the Agency's proposal for a class-wide REMS for ER/LA opioid analgesics (for complete background information discussed at this meeting, see the [July 22-23, 2010, AC meeting](#) entry).

**September:** To improve clinical studies of pain medicines with the goal of advancing the development of novel, less abusable, safer, and more effective pain medicines, FDA announced a plan to establish a public-private partnership to conduct multiple scientific projects under the umbrella of the Analgesic Clinical Trial Translation, Innovations, Opportunities, and Networks (ACTION) Initiative. The University of Rochester (UR) was chosen for the contract to establish the infrastructure of the ACTION PPP initiative and to establish relationships with the key experts and organizations in the field.

**October:** FDA held a [joint Advisory Committee Meeting](#) (PDF - 149KB) (ALSDAC and DSaRM) on studies for demonstrating effectiveness of abuse-deterrent formulations on addiction, overdose, and death, with OxyContin and Embeda featured.

**October:** FDA held a meeting with TIRF sponsors and informed them that in order to decrease the burden on the healthcare system, they must form a single-shared REMS for these products. The Agency committed to working with the firms to assist in the regulatory aspects of developing this program. Regular meetings followed, after which the firms formed a working group, the Transmucosal Immediate-release Fentanyl REMS Industry Group (TRIG).

**November:** Separate from the developing REMS program but connected to FDA's overall effort toward safe use of opioids, FDA [recommended voluntary market withdrawal](#) of propoxyphene, sold under the familiar trade name Darvon. New data showed the drug could cause serious toxicity to the heart, even in therapeutic doses.

## 2011

**January:** Abstral (fentanyl) approved; the fourth TIRF product. This product was approved with a MG and REMS in place.

**April:** FDA supported the White House Office of National Drug Control Policy (ONDCP) report [Epidemic: Responding to America's Prescription Drug Abuse Crisis](#) (PDF - 306KB), a comprehensive action plan to address the national prescription drug abuse epidemic.

**June:** Oxecta (oxycodone hydrochloride) approved.

**June:** Lazanda (fentanyl) approved; the fifth TIRF product. This product was approved with a MG and REMS in place.

**September:** FDA provided funds through a one-year cooperative agreement grant to the University of South Carolina to develop a statewide collaboration to decrease rates of misuse, overuse, and abuse of opioids. This was to be accomplished through the detailing of information regarding prescription opioids and the use of state prescription drug monitoring programs (PDMPs) geared to individual physicians who are high volume prescribers of opioids.

**October:** As part of a three-year inter-agency agreement with the Department of Justice's Bureau of Justice Administration and in collaboration with the CDC, FDA provided funding to support efforts by the Prescription Drug Monitoring Program Center of Excellence at Brandeis University. The effort was to develop a national database of state PDMP data to be used for surveillance of emerging problems or concerns with scheduled drugs and to examine the impact of national, state and community initiatives implemented to curb misuse, overuse, and abuse of opioids.

**December:** FDA announced the approval of a new formulation of the ER/LA opioid OPANA ER (oxymorphone hydrochloride).

**December:** FDA approved a single-shared REMS system for all TIRF products (the "go-live" date would be March 2012). The industry working group (TRIG, see above) was encouraged to continue working to complete its single-shared TIRF REMS system. The Agency continued to provide regulatory input and review of TRIG's proposals throughout the year.

**December:** FDA began working to streamline the process for managing the TIRF single-shared REMS.

## 2012

**January:** Subsys (fentanyl sublingual spray) approved; the sixth TIRF product. It was approved directly into the single-shared TIRF REMS in anticipation of its upcoming "go live" date.

**January:** FDA awarded a Center of Excellence in Research Science and Innovation grant to the University of Maryland to examine the use and utility of Patient Prescriber Agreements in reducing prescription opioid abuse.

**March:** The single-shared TIRF REMS went "live," and FDA began work with TRIG to address patient access issues.

**April:** FDA hosted a scientific workshop to initiate a public discussion about the potential value of making naloxone available in the community to reduce the number of opioid overdose fatalities. In simple terms, naloxone, marketed under the trade name Narcan and others, reverses the effects of opioids.



**May:** FDA and the National Institutes of Health (NIH) Pain Consortium held a meeting on May 30-31, called *Assessment of Analgesic Treatment of Chronic Pain: A Scientific Workshop*, to review available data on the effectiveness of pain medications in the treatment of chronic non-cancer pain.

**September:** FDA awarded funding for up to three years for three cooperative agreement grants to examine strategies and interventions and their potential to impact opioid analgesic misuse and abuse. The following research topics were funded:

- Examine the prescribing habits of physicians who prescribe doses of opioids above 100 mg morphine equivalents per day and/or prescribe opioids in combination with benzodiazepines. Those prescribers will be targeted for educational and informational mailings, and the PDMP data will be examined for changes in prescribing habits post-education and over time.
- Examine the clinical use of different tools that can guide a clinician in prescribing opioids and reduce patient misuse, overuse, and abuse of opioids. All of the risk reduction strategies described are currently in use. They include 1) screening, brief intervention, and referral to treatment (SBIRT), 2) PDMPs, 3) REMS, 4) health insurer initiatives, and 5) treatment contracts. The study will survey approximately 1,300 prescribers (1,000 internists, 200 pain specialists and 100 addiction specialists) to gain an understanding of the knowledge, use, and perceptions of utility of these strategies.
- Estimate the incidence of urine drug testing (UDT) during the year following initiation of chronic opioid therapy (COT) and identify demographic, clinical, provider, and facility variables associated with the use of UDT within the national Veterans Affairs (VA) healthcare system. Use qualitative interviews with primary care providers to explore perceptions of barriers to UDT, appropriate care for patients who misuse opioids, and opportunities to coordinate treatment with substance abuse specialty care. Describe current clinical practice following an aberrant UDT result, including rates of follow-up assessments and treatment changes among patients who initiate COT for chronic pain.

**June:** The Randomized Enrollment Study of Opioid Long-term use to eValuate Efficacy (RESOLVE) working group, under the auspices of ACTION (see September 2010 above), was established. Formation of this group was initiated based on the FDA-sponsored meeting held at NIH in May (see directly above) and on plans to develop protocols for clinical trials to assess the effectiveness of long-term use of opioid pain medicines.

**July:** FDA approved the [ER/LA opioids class REMS program](#). This program included new product labeling for ER/LA opioids and a requirement for manufacturers to develop and offer opioid training programs that prescribers can take on a voluntary basis.

**August:** ACTION established the Consortium for Addiction Research on Efficacy and Safety (CARES) to address challenges in addiction drug trials. The Abuse Liability Evaluation for Research, Treatment, and Training (ALERTT) project was also initiated under ACTION. This project was initiated with the intent to create a classification scheme and a risk assessment tool for use in clinical trials and for post-marketing adverse event reports to help identify incidents of drug abuse or emergence of drug addiction.



**October:** FDA and ACTION hosted a scientific workshop October 24-26 to discuss preclinical models and clinical study issues to find ways to improve analgesic drug discovery and development.

**October:** FDA scheduled a meeting of the [Drug Safety and Risk Management Advisory Committee](#) for October 29-30 to discuss the public health benefits and risks, including the potential for abuse, of drugs containing hydrocodone, either combined with other analgesics or as a cough suppressant. This meeting was postponed due to Hurricane Sandy.

**November:** FDA scheduled a meeting November 28-29 for ACTION's ALERTT project working group for stakeholders to discuss consensus recommendations and research studies on definitions, measures, and prediction tools for abuse liability.

**December:** FDA held a [December 7 meeting of the Anesthetic and Analgesic Drug Products Advisory Committee](#) to discuss the risks and benefits of new drug application, for hydrocodone bitartrate extended-release capsules, which would be the first single-entity hydrocodone-containing drug product. The committee voted against approval.

## 2013

**January:** FDA issued a draft guidance document, January 9, to assist industry in developing new formulations of opioid drugs with abuse-deterrent properties. The document, entitled [Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling](#) (PDF - 463KB), explains FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, how those studies will be evaluated by the agency, and what labeling claims may be approved based on the results of those studies.

**January:** FDA held a [January 24-25 meeting of its Drug Safety and Risk Management Advisory Committee](#) (PDF - 69KB) to discuss the public health benefits and risks, including the potential for abuse, of drugs containing hydrocodone either combined with other analgesics or as an antitussive. The Department of Health and Human Services (HHS) received a request from the Drug Enforcement Administration (DEA) for a scientific and medical evaluation and scheduling recommendation for drugs containing hydrocodone either combined with other analgesics or as an antitussive, in response to a citizen petition citing increasing reports of abuse related to these products. Currently, these products are Schedule III drugs under the Controlled Substances Act (CSA), and DEA is considering whether to reschedule the products to Schedule II, which would subject the products to more stringent requirements regarding storage, record keeping, and prescribing, such as limitations on oral prescriptions and refills. The committee voted in favor of rescheduling hydrocodone products from Schedule III controlled substances to Schedule II controlled substances.

**February:** FDA held public hearing on February 7 & 8 to obtain information -- particularly scientific evidence, such as study data or peer-reviewed analyses -- on issues pertaining to the use of opioid drugs in the treatment of chronic pain. [Impact of Approved Drug Labeling on Chronic Opioid Therapy: Part 15 Hearing](#).

**March:** March 1, in an [open letter](#) to prescribers, FDA and health professional organizations asked all prescribers of opioids to ensure they have thorough knowledge of the FDA-approved product labeling for the opioids they prescribe, and to ensure they have adequate training in opioid therapy. FDA also encouraged all prescribers to help curb our nation's opioid epidemic.

**April:** April 16, FDA took multiple actions related to [OxyContin](#).

**May:** May 10, FDA responded to a petition and decided that the original formulation of [Opana ER](#) (oxymorphone hydrochloride) Extended-Release Tablets was not withdrawn from the market for reasons of safety or effectiveness. As a result, generic versions of the original formulation can continue to be approved and marketed.

**July:** On July 29, FDA held the [Clinical Development Programs for Opioid Conversion; Public Workshop; Request for Comments](#). The scientific workshop was held to address public health concerns associated with the inclusion of equianalgesic opioid conversion tables in opioid product labeling.

**September:** On September 10, FDA announced a set of [significant measures to enhance the safe and appropriate use of extended-release and long-acting \(ER/LA\) opioids](#). These actions include class-wide safety labeling changes and new post-marketing requirements for all ER/LA opioid analgesics. FDA also responded to two citizen petitions regarding labeling of opioids.

**October:** FDA issued [Statement on Proposed Hydrocodone Reclassification from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research](#) on October 24.

## 2014

**April:** On April 3, FDA approved [Evzio \(naloxone hydrochloride injection\)](#) for the emergency treatment of known or suspected opioid overdose. Naloxone is a medication that rapidly reverses the effects of opioid overdose. Evzio is the first auto-injector designed to deliver a dose of naloxone outside of a healthcare setting.

**April:** On April 14, FDA finalized the [proposed class-wide safety labeling changes](#) for all extended-release and long-acting (ER/LA) opioid analgesics, and responded to two citizen petitions regarding labeling for neonatal opioid withdrawal syndrome (NOWS).

**July:** On July 23, FDA approved [Targiniq ER](#), an extended-release pain reliever that contains a combination of oxycodone and naloxone. Targiniq ER is the second extended-release/long-acting (ER/LA) opioid analgesic with FDA-approved labeling describing the product's abuse-deterrent properties.

**August:** On August 19, FDA approved revisions to the ER/LA Opioid Analgesics REMS to incorporate information from the ER/LA opioid analgesic safety labeling changes (SLCs) announced on September 10, 2013, and approved on April 16, 2014. The most significant changes were to clarify the approved indications for use and limitations of use, and to revise warnings, including boxed warnings.

**October:** On October 17, FDA approved new labeling for [Embeda](#) (morphine sulfate and naltrexone hydrochloride), an extended-release (ER) opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Embeda is the third ER opioid analgesic to be approved with labeling describing the product's abuse-deterrent properties consistent with the FDA's 2013 draft guidance, Abuse-Deterrent Opioids – Evaluation and Labeling. The new labeling includes a claim indicating that Embeda has properties that are expected to reduce oral and intranasal abuse when the product is crushed.

**November:** On November 20, FDA approved [Hysingla ER](#) (hydrocodone bitartrate), an extended-release (ER) opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Hysingla ER is the fourth ER opioid analgesic to be approved with labeling describing the product's abuse-deterrent properties consistent with the FDA's 2013 draft guidance for industry, Abuse-Deterrent Opioids – Evaluation and Labeling. Hysingla ER has properties that are expected to reduce, but not totally prevent, abuse of the drug when chewed and then taken orally, or crushed and snorted or injected.

## 2015

**January:** On January 30, FDA approved a modified formulation of Zohydro ER (hydrocodone bitartrate extended-release capsules). The FDA has not approved an abuse-deterrent labeling claim for Zohydro ER.

**April:** On April 1, FDA issued a [final guidance](#) to assist industry in developing opioid drug products with potentially abuse-deterrent properties.

**June:** On June 8-9, the FDA's [Risk Communication Advisory Committee](#) discussed approaches to communicating information about fetal effects in product labeling for methadone or buprenorphine maintenance therapy for opioid addiction, and about the maternal benefits and risks of treatment, to best enable patients and healthcare providers to make informed decisions about the use of these drugs during pregnancy.

**July:** On July 1-2, FDA, in collaboration with the National Institutes of Drug Abuse, the Centers for Disease Control and Prevention, the Substance Abuse and Mental Health Services Administration, and the Health Resources and Services Administration, held a [scientific workshop](#) to initiate a public discussion about issues surrounding the uptake of naloxone in certain medical settings – such as on ambulances and in association with prescriptions for opioids – as well as outside of conventional medical settings to reduce the incidence of opioid overdose fatalities. Discussions focused on which populations are at risk for opioid overdose; how public health groups can work together to use naloxone to reduce the risk of overdose; and legal, regulatory, logistical and clinical aspects related to making naloxone more widely available.

**August:** On August 13, FDA approved [OxyContin for certain pediatric patients](#) for pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative

treatment options are inadequate. This approval is limited to opioid-tolerant pediatric patients 11 and up who are already taking and tolerating a minimum daily dose of at least 20 mg oxycodone orally or its equivalent. These patients can be expected to remain on treatment with an opioid for several weeks or more.

**October:** On October 2, FDA approved [MorphaBond](#) (morphine sulfate), an extended-release (ER) opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. MorphaBond is the fifth ER opioid analgesic to be approved with labeling describing the product's abuse-deterrent properties consistent with the FDA's 2015 guidance for industry, Abuse-Deterrent Opioids – Evaluation and Labeling. MorphaBond has properties that are expected to reduce, but not eliminate, abuse of the drug when crushed and snorted or injected.

**November:** On November 18, FDA approved [Narcan nasal spray](#), the first FDA-approved nasal spray version of naloxone hydrochloride, a life-saving medication that can temporarily stop or reverse the effects of an opioid overdose, including an overdose from heroin.

## 2016

**February:** On February 4, FDA leaders, in response to the opioid abuse epidemic, called for a far-reaching action plan to reassess the agency's approach to opioid medications. The plan will focus on policies aimed at reversing the epidemic, while still providing patients in pain access to effective relief.

**February:** On February 4, FDA released five postmarketing (PMR) requirements announced on September 13, 2013, and replaced them with [11 PMRs \(10 postmarketing studies and one clinical trial\)](#) because the 10 postmarketing observational studies and one clinical trial include refined measures for assessing the known serious risks of misuse, abuse, addiction, overdose, and death.

**February:** On February 19, the FDA announced that during the April 12th meeting of the Pediatric Advisory Committee (PAC) they will present a framework of current plans for a 2-day joint meeting of the PAC, the Anesthetic and Analgesic Drug Products Advisory Committee, and the Drug Safety and Risk Management Advisory Committees. This joint meeting is scheduled for September 15 and 16, 2016 and during this meeting the FDA will be calling on a broad range of independent experts with real-world experience to provide recommendations on how to address the unique needs of children in pain.

**March:** On March 1, the FDA convened the [Science Board](#) to hear about and discuss a range of pressing issues related to the current opioid epidemic, including: (1) the role of opioids in pain management; (2) scientific challenges facing FDA in supporting the development of pain medications (3) scientific challenges facing FDA in seeking to understand the real-world use of opioids to treat pain (4) the role that FDA plays as a part of a larger Federal, State and local response to the challenges of providing appropriate pain treatment while reducing opioid abuse; and (5) postmarket surveillance activities related to opioids.

**March:** On March 22, FDA announced required [class-wide safety labeling changes for immediate-release \(IR\) opioid pain medications](#). Among the changes, the FDA is requiring a new boxed warning about the serious risks of misuse and abuse, which can lead to addiction, overdose and death. The FDA is also requiring several additional safety labeling changes across all prescription opioid products to include additional information on the risk of these medications.

**March:** On March 24, FDA issued a draft guidance titled “[General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products](#).” This guidance recommends studies a generic applicant should conduct so FDA can evaluate the abuse deterrence of certain generic opioid drug products and help ensure that generic versions of approved opioids with abuse-deterrent formulations (ADFs) are no less abuse-deterrent than the brand named drug.

**April:** On April 26, FDA approved [Xtampza ER](#) (oxycodone), an extended-release (ER) opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. Xtampza ER is the sixth ER opioid analgesic to be approved with labeling describing the product’s abuse-deterrent properties consistent with the FDA’s 2015 guidance for industry, Abuse-Deterrent Opioids – Evaluation and Labeling. Xtampza ER has properties that are expected to reduce, but not eliminate, abuse of the drug when crushed and snorted or injected.

**May:** On May 3-4, FDA convened a [joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee](#) to discuss results from assessments of the extended-release and long-acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategies (REMS). The committees provided comments as to whether this REMS with Elements to Assure Safe Use (ETASU) assures safe use, is not unduly burdensome to patient access to the drugs, and to the extent practicable, minimizes the burden to the healthcare delivery system.

**May:** On May 26, FDA announced required [safety labeling changes for methadone and buprenorphine products](#) when used by pregnant women for medication-assisted treatment (MAT) of opioid use disorder to ensure providers have complete information about the benefits and risks of these products.

**May:** On May 26, FDA approved [Probuphine](#), the first buprenorphine implant for the maintenance treatment of opioid dependence. Probuphine, an implant designed to provide a constant, low level of buprenorphine for six months, should be used in patients who are already stable on low-to-moderate doses of other forms of buprenorphine and as part of a complete treatment program that includes counseling and psychosocial support.

**August:** On August 19, FDA approved [Troxyca ER](#) (oxycodone hydrochloride and naltrexone hydrochloride extended-release capsules), an extended-release (ER) opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. Troxyca ER is the seventh ER opioid analgesic to be approved with labeling describing the product’s abuse-deterrent properties consistent with the FDA’s 2015 guidance for industry, Abuse-Deterrent Opioids – Evaluation and Labeling.

Troxyca ER has properties that are expected to reduce, but not eliminate, abuse of the drug when crushed and then taken orally, snorted, or injected.

**August:** On August 31, FDA announced required class-wide changes to drug labeling to help inform health care providers and patients of the [serious risks associated with the combined use of certain opioid medications and a class of central nervous system depressant drugs called benzodiazepines](#). Among the changes, the FDA is requiring boxed warnings and Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines with information about the serious risks, including extreme sleepiness, respiratory depression, coma and death, associated with using these medications at the same time.

**September:** On September 15-16, the FDA convened a [joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee](#) to discuss the appropriate development plans for establishing the safety and efficacy of prescription opioid analgesics for pediatric patients, including obtaining pharmacokinetic data and the use of extrapolation.

**October:** On October 5, the FDA convened a [joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management](#) to discuss naloxone products intended for use in the community, specifically the most appropriate dose or doses of naloxone to reverse the effects of life-threatening opioid overdose in all ages, and the role of having multiple doses available in this setting. The committees also discussed the criteria prescribers will use to select the most appropriate dose in advance of an opioid overdose event and the labeling to inform this decision, if multiple doses are available.

**October:** On October 31 – November 1, the FDA held a public meeting, [Pre-Market Evaluation of Abuse-Deterrent Properties of Opioid Drug Products](#), to discuss scientific and technical issues relating to formulation development and pre-market evaluation of opioid drug products with abuse-deterrent properties. The meeting was intended to give FDA the opportunity to discuss, and seek public input from stakeholders on, the approach to testing FDA recommended in its draft guidance General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products. The meeting also provided an opportunity to discuss FDA's efforts to develop standardized in vitro testing methodologies for evaluating the abuse deterrence of opioid drug products.

**December:** On December 16, the FDA approved several safety labeling changes (SLCs) about the serious risks of prescription opioid analgesics and opioids approved for medication assisted treatment (MAT) of opioid addiction including [class-wide SLCs for immediate-release \(IR\) opioid pain medications, SLCs for methadone and buprenorphine products](#), and [class-wide SLCs about the serious risks associated with the combined use of certain opioid medications with benzodiazepines or other central nervous system \(CNS\) depressants](#).



## 2017

**January:** On January 9, FDA approved [Arymo ER](#) (morphine sulfate extended-release tablets), an extended-release (ER) opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. Arymo ER is the eighth ER opioid analgesic to be approved with labeling describing the product's abuse-deterrent properties consistent with the FDA's 2015 guidance for industry, Abuse-Deterrent Opioids – Evaluation and Labeling. Arymo ER is formulated to give it physicochemical properties expected to make abuse by injection difficult.

**January:** On January 17, FDA approved [Vantrela ER](#) (hydrocodone bitartrate extended-release tablets), an extended-release (ER) opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. Vantrela ER is the ninth ER opioid analgesic to be approved with labeling describing the product's abuse-deterrent properties consistent with the FDA's 2015 guidance for industry, Abuse-Deterrent Opioids – Evaluation and Labeling. The physical and chemical properties of Vantrela ER are expected to make intravenous (injection) abuse difficult and are expected to reduce, but not eliminate, abuse by nasal and oral routes. However, abuse of Vantrela ER by these routes is still possible.

**April:** On April 20, FDA announced the [restricted the use of codeine and tramadol medicines in children](#) because these medicines carry serious risks, including slowed or difficult breathing and death, which appear to be a greater risk in children younger than 12 years, and should not be used in these children. These medicines should also be limited in some older children. The FDA also recommended against the use of codeine and tramadol medicines in breastfeeding mothers due to possible harm to their infants.

**April:** On April 20, the FDA approved [RoxyBond](#) (oxycodone hydrochloride), an opioid analgesic indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. RoxyBond is the first immediate-release opioid analgesic approved with labeling describing its abuse-deterrent properties consistent with the FDA's 2015 Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling. Based on laboratory studies, RoxyBond tablets are resistant to certain forms of manipulation such as crushing, grinding, or otherwise extracting oxycodone from the tablet that are typically used to make opioids easier to abuse by the nasal and intravenous routes.

**April:** On April 27, FDA held an [expert roundtable](#) for healthcare professionals to discuss their experiences with the use of cough suppressants in children (<18 years of age), particularly opioid containing antitussive products, as well as the data available to support recommendations made by various professional societies regarding the treatment of cough in children.

**May:** On May 9-10, FDA held a public meeting, [Training Health Care Providers on Pain Management and Safe Use of Opioid Analgesics – Exploring the Path Forward](#), to obtain input on issues and challenges associated with Federal efforts to support training on pain management and the safe prescribing, dispensing, and patient use of opioids (safe use of opioids) for health care providers.



**May:** On May 10, FDA released the "[FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain](#)" (draft revisions to the Blueprint), which broadens the current Blueprint to include information on pain management, including the principles of acute and chronic pain management; non-pharmacologic treatments for pain; and pharmacologic treatments for pain (both non-opioid analgesic and opioid analgesic).

**June:** On June 8, FDA requested that [Endo Pharmaceuticals remove its opioid pain medication, reformulated Opana ER \(oxymorphone hydrochloride\), from the market](#) based on its concern that the benefits of the drug may no longer outweigh its risks.

**July:** On July 6, the JAMA Viewpoint article by Dr. Scott Gottlieb and Dr. Janet Woodcock entitled, "[Marshaling FDA Benefit-Risk Expertise to Address the Current Opioid Abuse Epidemic](#)," was published.

**July:** On July 6, following the FDA's request, Endo announced that it would [voluntarily remove reformulated Opana ER](#) from the market.

**July:** On July 10-11, FDA held a public meeting, [Data and Methods for Evaluating the Impact of Opioid Formulations with Properties Designed to Deter Abuse in the Postmarket Setting: A Scientific Discussion of Present and Future Capabilities](#), to discuss ways to improve the analysis and interpretation of existing data, as well as to discuss opportunities and challenges for collecting and/or linking additional data to improve national surveillance and research capabilities in this area.

**July:** On July 13, the National Academies of Science, Engineering, and Medicine release the [consensus report](#), commissioned by the FDA, which outline the state of the science regarding prescription opioid abuse and misuse, as well as the evolving role that opioids play in pain management.

**September:** On September 11, FDA held a [Pediatric Advisory Committee meeting](#) to discuss the use of prescription opioid products containing hydrocodone or codeine for the treatment of cough in pediatric patients. The discussion included current practice for the treatment of cough in children and benefit-risk considerations regarding the use of prescription opioid products in pediatric patients.

**September:** On September 20, FDA [advised](#) that the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS). The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks. Careful medication management by health care professionals can reduce these risks.

**September:** On September 28, after determining that a REMS is necessary for IR opioid analgesics to ensure that the benefits of these drugs continue to outweigh the risks, [FDA sent letters to IR opioid analgesic manufacturers](#) informing them that their products that are intended

to be used in the outpatient setting will be subject to the same REMS requirements as the ER/LA opioid analgesics.

**November:** On November 21, FDA issued a final guidance titled “[General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products](#).” This guidance recommends studies, including comparative in vitro and pharmacokinetic studies, that the potential abbreviated new drug application (ANDA) applicant should conduct and submit to FDA in an ANDA to demonstrate that a generic solid oral opioid drug product is no less abuse-deterrent than its reference listed drug with respect to all potential routes of abuse.

**November:** On November 30, FDA approved [Sublocade](#), the first once-monthly injectable buprenorphine product for the treatment of moderate-to-severe opioid use disorder in adult patients who have initiated treatment with a transmucosal (absorbed through mucus membrane) buprenorphine-containing product. It is indicated for patients that have been on a stable dose of buprenorphine treatment for a minimum of seven days.

**December:** On December 11-12, FDA hosted a [public workshop regarding the role of packaging, storage, and disposal options](#) within the larger landscape of activities aimed at addressing abuse, misuse, or inappropriate access of prescription opioid drug products; guiding principles and considerations for the design of packaging, storage, and disposal options for opioids; integrating packaging, storage, and disposal options into existing health care and pharmacy systems, including both open and closed health care systems; data needs and how to address challenges in assessing the impact of packaging, storage, and disposal options in both the premarket and postmarket settings; and ways in which FDA could encourage the development and assessment of packaging, storage, and disposal options for opioids that have the potential to enhance opioid safety.

## 2018

**January:** On January 11, FDA announced that it is requiring [safety labeling changes for prescription cough and cold medicines containing codeine or hydrocodone](#) to limit the use of these products to adults 18 years and older because the risks of these medicines outweigh their benefits in children younger than 18. The agency is also requiring the addition of safety information about the risks of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing to the Boxed Warning of the drug labels for prescription cough and cold medicines containing codeine or hydrocodone.

**January:** On January 11, FDA Commissioner, Scott Gottlieb, M.D., announced the [2018 Strategic Policy Roadmap](#), which provides an overview of some of the key priorities the agency will pursue advance FDA’s public health mission. Part of the Roadmap is reducing misuse and abuse of opioid drugs through the Opioid Policy Work Plan.

**January:** On January 24, FDA and the Federal Trade Commission [posted joint warning letters](#) to the marketers and distributors of 12 opioid cessation products, for illegally marketing unapproved products with claims about their ability to help in the treatment of opioid addiction and withdrawal.

**January:** On January 30, FDA held a public hearing, [“Opioid Policy Steering Committee: Prescribing Intervention—Exploring a Strategy for Implementation,”](#) to receive stakeholder input on how FDA might, under its REMS authority, improve the safe use of opioid analgesics by curbing overprescribing to decrease the occurrence of new addictions and limit misuse and abuse of opioid analgesics.

**January:** On January 30, FDA announced [limits to packaging for anti-diarrhea medicine Loperamide](#) (Imodium) to encourage safe use.

**January:** On January 30, FDA posted the revised Blueprint, [“Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain,”](#) which broadens the current Blueprint to include information on pain management, including the principles of acute and chronic pain management; non-pharmacologic treatments for pain; and pharmacologic treatments for pain. (It is important to note that the revised Blueprint will not be considered final until the Opioid Analgesic Risk Evaluation and Mitigation Strategy is approved.)

**February:** On February 14, FDA held a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the new drug application for [Hydexor](#) (proposed tradename), a fixed-dose combination oral tablet, submitted by Charleston Laboratories, Inc., that contains hydrocodone, acetaminophen, and promethazine, for the short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting. The committees also discussed the abuse potential of this non-abuse-deterrent product and whether it should be approved.

**February:** On February 15, through a cooperative agreement with the FDA, the Duke-Margolis Center hosted a public workshop, [“Strategies for Promoting the Safe Use and Appropriate Prescribing of Prescription Opioids,”](#) to examine the landscape of health system and payer interventions to promote safe and appropriate prescribing of opioids; discuss how health systems and payers are using data and health IT tools to support interventions; discuss how health system approaches were implemented, barriers to their adoption, and potential unintended consequences of adoption; and discuss how to build an evidence base to support existing health system and payer interventions as well as how success may be defined and measured.

**March:** On March 27, FDA held a meeting of the Psychopharmacologic Drugs Advisory Committee to discuss the new drug application for [lofexidine hydrochloride](#), submitted by US WorldMeds, LLC, for mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment.

**April:** On April 17, FDA is hosting a public meeting on [Patient-Focused Drug Development for Opioid Use Disorder \(OUD\)](#), in collaboration with National Institute of Drug Abuse (NIDA). In addition to NIDA, FDA is also working closely with patient advocacy and community organizations to encourage participation from individuals with OUD. This meeting aligns with FDA’s ongoing work aimed at reducing the impact of opioid abuse and addiction.

**April:** On April 20, FDA issued the draft guidance, “[Opioid Dependence: Developing Buprenorphine Depot Products for Treatment](#),” which reflects the agency’s current thinking regarding drug development and trial design issues relevant to the study of depot buprenorphine products (i.e. modified-release products for injection or implantation).

**May:** On May 16, FDA approved [Lucemyra](#) (lofexidine hydrochloride), the first non-opioid treatment for the mitigation of withdrawal symptoms associated with abrupt discontinuation of opioids.

**May:** On May 22, FDA convened a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the new drug application for [buprenorphine sublingual spray](#), submitted by INSYS Development Company, Inc., for the treatment of moderate-to-severe acute pain where the use of an opioid analgesic is appropriate. The committees will also be asked to discuss whether this product should be approved.

**May:** On May 30, FDA launched an [innovation challenge](#) to spur development of medical devices – including digital health and diagnostics – that target pain, addiction and diversion.

**June:** On June 1, FDA sent [safety labeling change notification letters](#) to drug companies with approved opioid analgesic products intended for use in an outpatient setting, which require the companies to include new safety information regarding the Opioid Analgesic REMS in the Boxed Warning and Warnings and Precautions sections of prescribing information due to a general lack of awareness of the REMS among all opioid analgesic prescribers.

**June:** On June 5, FDA [took action](#) against 53 websites marketing unapproved opioids as part of a comprehensive effort to target illegal online sales.

**June:** On June 14, FDA approved [first generic versions of Suboxone sublingual film](#).

**June:** On June 26, FDA convened a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the new drug application for [oxycodone extended-release capsules](#), submitted by Pain Therapeutics, with the proposed indication of the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The product is intended to have abuse-deterrent properties based on its physicochemical properties. The committees will be asked to discuss whether the data submitted by the Applicant are sufficient to support labeling of the product with the properties expected to deter abuse.

**June:** On June 27, FDA convened internet stakeholders, government entities, academic researchers, and advocacy groups at a one-day [Online Opioid Summit](#) to discuss ways to collaboratively take stronger action in combatting the opioid crisis by reducing the availability of illicit opioids online.

**July:** On July 9, FDA hosted a public meeting on [Patient-Focused Drug Development for chronic pain](#) to hearing patients' perspectives on chronic pain, views on treatment approaches, and challenges or barriers to accessing treatments for chronic pain.

**August:** On August 3, FDA convened a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss results from assessments of the [transmucosal immediate-release fentanyl \(TIRF\) medicines' risk evaluation and mitigation strategy \(REMS\)](#), approved in December 2011. The TIRF REMS requires that healthcare providers who prescribe TIRF medicines for outpatient use are specially certified, that pharmacies that dispense TIRF medicines for inpatient and outpatient use are specially certified, and that completion of the prescriber-patient agreement form occurs prior to dispensing TIRF medicines for outpatient use. The Agency will seek the committees' assessment as to whether this REMS with elements to assure safe use (ETASU) assures safe use, is not unduly burdensome to patient access to the drugs, and to the extent practicable, minimizes the burden to the healthcare delivery system. The Agency will also seek the committees' input on any possible modifications to the TIRF REMS goals and requirements, as well as input on the adequacy of the evaluations conducted in the REMS assessments to determine whether the TIRF REMS goals are being met.

**August:** On August 6, FDA issued the draft guidance for industry, [“Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Medication-Assisted Treatment,”](#) which is intended to assist sponsors in developing drugs for medication-assisted treatment of opioid use disorder (OUD) and addresses the clinical endpoints acceptable to demonstrate effectiveness of such drugs.

**August:** On August 22, FDA [awarded a contract](#) to the National Academies of Sciences, Engineering, and Medicine (NASEM) to help advance the development of evidence-based guidelines for appropriate opioid analgesic prescribing for acute pain resulting from specific conditions or procedures.

**August:** On August 28, FDA [took action](#) against 21 websites marketing unapproved opioids as part of agency's effort to target illegal online sales

**September:** On September 7, FDA [approved a new dosage strength](#) of buprenorphine and naloxone sublingual film as maintenance treatment for opioid dependence

**September:** On September 18, FDA approved the [Opioid Analgesic REMS](#).

**September:** On September 20, through a cooperative agreement with the FDA, the Duke Margolis Center for Health Policy convened a [public workshop](#), “Expanding Access to Effective Treatment for Opioid Use Disorder: Provider Perspectives on Reducing Barriers to Evidence-Based Care.”

**September:** On September 27-28, FDA's Office of Women's Health, in collaboration with CDER and CTP, hosted a [2-day public meeting](#), “Opioid and Nicotine Use, Dependence, and Recovery: Influences of Sex and Gender.”

**October:** On October 11, FDA convened a [meeting of the Anesthetic and Analgesic Drug Products Advisory Committee](#) to discuss new drug application 210730, for oliceridine 1 milligram/milliliter injection, submitted by Trevena, Inc., for the management of moderate-to-severe acute pain in adult patients for whom an intravenous opioid is warranted. The committee also discussed the efficacy and safety data and benefit-risk considerations.

**October:** On October 12, FDA convened a [meeting of the Anesthetic and Analgesic Drug Products Advisory Committee](#) to discuss new drug application 209128, sufentanil sublingual tablets, submitted by AcclRx Pharmaceuticals, Inc., for the management of moderate-to-severe acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adult patients in a medically supervised setting. The committee also discussed risk-benefit considerations and whether this product should be approved.

**November:** On November 1, FDA convened a [joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee](#) to discuss efficacy, safety and risk-benefit profile of new drug application 210417 for buprenorphine and samidorphan sublingual tablets, submitted by Alkermes, Inc., for adjunctive treatment of major depressive disorder.

**November:** On November 2, FDA approved [first oral sufentanil pain medication](#) for use in a medically supervised setting.

**November:** On November 14, FDA convened a [joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee](#) to discuss new drug application 209774, for an immediate-release oral tablet formulation of oxycodone, which is intended to resist common methods of physical or chemical manipulation and to deter intravenous and intranasal abuse, submitted by SpecGx Inc., for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The committees also determined whether the Applicant adequately demonstrated that the abuse-deterrent properties of the proposed product are sufficient to include this information in the product label, and whether the product should be approved.

**November:** On November 15, FDA convened a [meeting of the Anesthetic and Analgesic Drug Products Advisory Committee](#) to discuss the assessment of opioid analgesic sparing outcomes in clinical trials of acute pain. The committee also commented on the trial design and endpoints of these studies and how to determine the clinical relevance of the results.

**December:** On December 17-18, FDA convened a [joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee](#) to provide input and advice on strategies to increase the availability of naloxone products intended for use in the community. The committees were asked to consider various options for increasing access to naloxone, weighing logistical, economic, and harm reduction aspects and whether naloxone should be co-prescribed with all or some opioid prescriptions to reduce the risk of overdose death. Because of the potential, significant costs and burdens that may be associated with naloxone co-prescribing (e.g., economic costs to consumers and health



systems, adjusting to manufacturing volume growth, drug shortages), the committees were also asked to consider the potential burdens that may be associated with naloxone co-prescribing for all or some prescription opioid patients.

## 2019

**January:** On January 17, FDA [announced](#) the results of unprecedented work to design, test, and validate the key labeling requirements necessary to approve an over-the-counter (OTC) version of naloxone, including posting [two model Drug Facts labels \(DFLs\) and the supporting FDA review](#). Overall, the study demonstrated that the model DFL was well-understood by consumers and is acceptable for use by manufacturers in support of their OTC naloxone development programs.

**February:** On February 6, FDA issued the final guidance, [“Opioid Use Disorder: Developing Depot Buprenorphine Products for Treatment,”](#) which reflects the agency’s current thinking regarding drug development and trial design issues relevant to the study of depot buprenorphine products (i.e. modified-release products for injection or implantation).

**February:** On February 12, FDA [announced](#) ongoing efforts to stop the spread of illicit opioids, further secure the U.S. drug supply chain and forcefully confront opioid epidemic.

**March:** On March 19, FDA [took action](#) against marketer of unapproved products claiming to treat addiction, chronic pain and other serious conditions.

**March:** On March 27, FDA [announced](#) new steps to strengthen agency’s safety requirements aimed at mitigating risks associated with transmucosal immediate-release fentanyl products.

**April:** On April 2, FDA took [new enforcement actions](#) as part of the agency’s ongoing effort to combat the illegal online sales of opioids.

**April:** On April 2, FDA hosted internet stakeholders, thought leaders, government entities, academic researchers, and advocacy groups at its second [Online Opioid Summit](#).

**April:** On April 9, FDA announced harm reported from sudden discontinuation of opioid pain medicines and [required label changes](#) to guide prescribers on gradual, individualized tapering.

**April:** On April 19, FDA [approved first generic naloxone nasal spray](#) to treat opioid overdose.

**April:** On April 25, FDA launched a [public education campaign](#) to encourage safe removal of unused opioid pain medicines from homes.

**May:** On May 30, FDA opened a public docket to request information on requiring [fixed-quantity blister packaging for certain opioid pain medicines](#) to help decrease unnecessary exposure to opioids.



**June:** On June 11-12, FDA convened a [joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee](#) to seek input on the clinical utility and safety concerns associated with the higher range of opioid analgesic dosing (both in terms of higher strength products and higher daily doses) in the outpatient setting. The FDA is interested in better understanding current clinical use; situations that may warrant use of higher doses of opioid analgesics; and the magnitude and frequency of harms associated with higher doses of opioid analgesics relative to lower doses, as well as optimal strategies for managing these risks while ensuring access to appropriate pain management for patients.

**June:** On June 20, FDA issued draft guidance, [“Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework,”](#) which describes the application of the benefit-risk assessment framework that the agency uses in evaluating applications for opioid analgesic drugs and summarizes the information that can be supplied by opioid analgesic drug applicants to assist the agency with its benefit-risk assessment, including considerations about the broader public health effects of these products in the context of this crisis.

**July:** On July 2, FDA [warned](#) repackers distributing pharmaceutical ingredients, including opioids, for putting consumers at risk with significant violations of manufacturing quality standards.

**September:** On September 17, FDA held a public hearing, [“Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction,”](#) to receive stakeholder input on the approval process for new opioids and how FDA might best consider the existing armamentarium of therapies, among other factors, in reviewing applications for new opioids to treat pain.

**September:** On September 20, FDA issued a [statement](#) on the agency’s continued efforts to increase availability of all forms of naloxone to help reduce opioid overdose deaths.

**September:** On September 20, FDA [announced](#) the approval of new packaging for brand-name over-the-counter loperamide to help curb abuse and misuse.

**September:** On September 26, FDA held a [joint meeting](#) of the Pediatric and Drug Safety and Risk Management Advisory Committees 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), and to discuss pediatric data considerations for opioid analgesics labeling and Pediatric Research Equity Act studies for opioids generally, using Opana IR as an example.

**September:** On September 30, FDA and DEA [warn](#) website operators illegally selling opioids

**October:** On October 24, FDA outlined the [agency’s first year accomplishments](#) implementing SUPPORT Act authorities to address the opioids crisis

**November:** On November 26, FDA [issued warning letter](#) for products illegally marketed for the treatment of health conditions, including opioid withdrawal symptoms

**December:** On December 11, FDA [issued warning letter](#) for not including the most serious risks in advertisement for medication-assisted treatment drug

**December:** On December 19, the National Academies of Sciences, Engineering, and Medicine released a [consensus report](#), commissioned by the FDA, on framing opioid prescribing guidelines for acute pain.

## 2020

**January:** On January 14, FDA convened a [joint meeting](#) of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the new drug application (NDA) for oxycodol, a new molecular entity full mu-opioid receptor agonist, submitted by Nektar Therapeutics, for the management of chronic low back pain in adult patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The committees were asked to discuss the safety and efficacy data as well as the overall risk-benefit profile of the product.

**January:** On January 15, FDA convened a [joint meeting](#) of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee. During the morning session, the committees discussed the NDA for tramadol 44 milligrams (mg) and celecoxib 56 mg tablet, which contains a fixed-dose combination of an opioid and a non-steroid anti-inflammatory drug, submitted by Esteve Pharmaceuticals, S.A., for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The committees were asked to discuss the safety and efficacy data as well as the overall risk-benefit profile of the product.

During the afternoon session, the committees discussed the NDA for an extended-release oral tablet formulation of oxycodone, submitted by Intellipharma Corp., for the management of moderate-to-severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The product has been formulated with properties intended to deter abuse, and the applicant has submitted data to support these abuse-deterrent properties for this product. The committees were asked to discuss whether the applicant has demonstrated abuse-deterrent properties for their product that would support labeling, as well as the overall risk-benefit profile of the product.

**June:** On June 8, FDA and the National Telecommunications and Information Administration (NTIA) are [launching a 120-day pilot](#) to help reduce the availability of unapproved opioids illegally offered for sale online.

**July:** On July 23, the FDA issued a [Drug Safety Communication](#) announcing that the agency is requiring the drug manufacturers for all opioid pain relievers and medicines to treat OUD to add new recommendations about naloxone to the prescribing information to help ensure that health

care professionals discuss the availability of naloxone and assess each patient's need for a naloxone prescription when opioid pain relievers or medicines to treat OUD are being prescribed or renewed. In addition, the agency recommended that health care professionals consider prescribing naloxone to patients at increased risk of opioid overdose, regardless of whether they are receiving a prescription for an opioid pain reliever or medicine to treat OUD. These may include people with a current or past diagnosis of OUD or who have experienced a previous opioid overdose.

**August:** On August 6, the FDA approved a prior approval supplemental new drug application that provides for a [shelf life extension](#) for Narcan (naloxone hydrochloride) nasal spray from the current 2-year shelf-life to 3 years and updates to the labeling.

**August:** On August 7, the FDA approved [Olinvyk \(oliceridine\)](#), an opioid agonist for the management of moderate to severe acute pain in adults, where the pain is severe enough to require an intravenous opioid and for whom alternative treatments are inadequate.

**September:** On September 1, the FDA awarded a [cooperative agreement](#) to support the development of an evidence-based clinical practice guideline for the management of acute dental pain.

**September:** On September 10-11, the FDA convened a [joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee](#) to discuss the results of required postmarketing studies (Postmarketing Requirements 3051-1, 3051-2, 3051-3, and 3051-4) that evaluated the effect of the reformulation of OxyContin (oxycodone hydrochloride extended-release tablets, manufactured by Purdue Pharma L.P., NDA 022272) on abuse, misuse, and fatal and non-fatal overdose, associated with OxyContin. The committees discussed whether these studies, in concert with other information from the published literature, have demonstrated that the reformulated OxyContin product has resulted in a meaningful reduction in these outcomes. The committees also discussed the broader public health impact of OxyContin's reformulation.

**October:** On October 2, the FDA published the final guidance for industry, [Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Treatment](#), which is intended to help sponsors develop drugs for treatment of opioid use disorder (OUD). This guidance addresses clinical endpoints acceptable for demonstrating effectiveness of such drugs.

**November:** On November 2, the FDA convened a [joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee](#) to discuss the new drug application for Hydexor, a fixed-dose combination oral tablet, submitted by Ōlas Pharma, Inc., that contains hydrocodone, acetaminophen, and promethazine, for the short-term (not to exceed 3 days) management of acute post-operative pain severe enough to require an opioid analgesic and the prevention of opioid-induced nausea and vomiting in patients who are at risk for or have a history of nausea and vomiting.

**December:** On December 23, the FDA [finalized modifications](#) to the transmucosal immediate-release fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) to address the

persistence of concerning prescribing practices and improve the agency's ability to monitor for adverse events and ensure safe use of these medicines.

## 2021

**February:** On February 1, the FDA provided an [update on the pilot program](#) with the National Telecommunications and Information Administration (NTIA) and three domain name registries to help reduce the availability of unapproved opioids illegally offered for sale online.

**February:** On February 16, the FDA issued a [warning letter](#) to AcelRx Pharmaceuticals, Inc. for the false and misleading promotion of Dsuvia (sufentanil sublingual tablet), a potent opioid analgesic.

**March:** On March 1, the FDA approved [Hydrocodone bitartrate \(reference listed drug: Hysingla ER\)](#), the first FDA-approved generic opioid with an [abuse-deterrent formulation \(ADF\)](#)—meaning the product has properties that are expected to reduce, though not totally prevent, abuse of the drug when chewed and then taken orally or crushed and snorted or injected.

**March:** On March 24, the FDA issued a white paper, [Introduction to FDA's Opioid Systems Model](#), which introduces FDA's opioid systems modeling effort, discusses potential uses of the model, provides an overview of the model's scope and structure, highlights preliminary areas for potential policy analysis and outlines on-going work.

**April:** On April 15, the FDA held the public workshop, [Morphine Milligram Equivalents: Current Applications and Knowledge Gaps, Research Opportunities, and Future Directions](#), to bring stakeholders together to discuss the scientific basis of morphine milligram equivalents (MMEs) with the goals of providing an understanding of the science and data underlying existing MME calculations for opioid analgesics, discussing the gaps in these data, and discussing future directions to refine and improve the scientific basis of MME applications.

**April:** On April 29, the FDA approved [morphine sulfate injection](#), an opioid analgesic for the management of severe pain for which alternative treatments are inadequate.

**April:** On April 30, the FDA approved a higher dose [naloxone hydrochloride nasal spray](#) product to treat opioid overdose.

**June:** On June 2, the FDA approved [morphine sulfate oral solution](#) and [morphine sulfate tablets](#), opioid analgesics for the management of severe pain in adult and pediatric patients for whom other pain relief options are inadequate.

**July:** On July 12-13, through a cooperative agreement with the FDA, the Duke-Margolis Center hosted a public workshop, [Safe Use of Benzodiazepines: Clinical, Regulatory, and Public Health Perspectives](#), to bring together regulators, academic researchers, clinicians, patient advocates, and other stakeholders to discuss epidemiological and abuse liability data, patient and clinician

perspectives and experiences, and gaps in data and understanding about the safe use of benzodiazepines.

**July:** On July 12, the *PAIN* Journal article by Dr. John Farrar entitled, "[Evaluating the stability of opioid efficacy over 12 months in patients with chronic noncancer pain who initially demonstrate benefit from extended release oxycodone or hydrocodone](#)," was published.

**July:** On July 21, the FDA issued a Consumer Update, [Accidental Exposures to Fentanyl Patches Continue to Be Deadly to Children](#), to warn, patients, caregivers, and health care professionals about the dangers of accidental exposure to the fentanyl patch, and the need to properly store and dispose of the product.

**September:** On September 9, the FDA hosted internet stakeholders, government entities, academia, and other important stakeholders at its third [Online Opioid Summit](#).

**October:** On October 15, the FDA approved a single-dose [naloxone hydrochloride injection](#) product to treat opioid overdose.

**October:** On October 15, the FDA approved [Seglentis \(celecoxib and tramadol hydrochloride\)](#), a combined opioid agonist and nonsteroidal anti-inflammatory, for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

**October:** On October 18, through a cooperative agreement with the FDA, the Reagan-Udall Foundation hosted a public workshop, [A Practical Research Agenda for Treatment Development for Stimulant Use Disorder](#), to discuss a proposed practical research agenda that focused on innovation in clinical trial design and candidate endpoints for the evaluation of potential treatments for stimulant use disorder.

## 2022

**January:** On January 12, the FDA issued a [Drug Safety Communication](#) warning of reported dental problems associated with medicines containing buprenorphine that are dissolved in the mouth. The dental problems include tooth decay, cavities, oral infections, and loss of teeth, and have been reported even in patients with no history of dental issues. The agency required a new warning about the risk of dental problems be added to the prescribing information and the patient [Medication Guide](#) for all buprenorphine-containing medicines dissolved in the mouth.

**February:** On February 9, the FDA published the draft guidance for industry, [Development of Non-Opioid Analgesics for Acute Pain](#), which is intended to provide recommendations to companies developing non-opioid analgesics for acute pain lasting up to 30 days, typically in response to some form of tissue injury, such as trauma or surgery. This guidance supports the [HHS Overdose Prevention Strategy](#).

**February:** On February 15, the FDA convened a [joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee](#) to discuss new drug application 213231, for tramadol hydrochloride injection, submitted by Avenue Therapeutics, Inc., for the management of moderate to moderately severe pain in adults in a medically supervised healthcare setting. The committees also discussed the clinical relevance of tramadol hydrochloride injection (an opioid intended for management of acute pain in a medically supervised healthcare setting), when its onset of action is delayed, and its proposed dosing is a fixed-dosing regimen.

**February:** On February 28, the FDA approved a military-usage and chemical incident response indication for a [naloxone hydrochloride auto-injector](#) product to treat opioid overdose.

**March:** On March 29, through a cooperative agreement with the FDA, the Reagan-Udall Foundation hosted a public meeting, [Naloxone Access: Answering Questions](#), to explore some of the most frequently asked questions about access to naloxone, a drug used to reverse opioid overdoses.

**April:** On April 4-5, through a cooperative agreement with the FDA, the Duke-Margolis Center hosted a public workshop, [Identifying Key Competencies for Opioid Prescriber Education](#), which focused on identifying gaps in the content of existing opioid prescriber education offerings and core competencies that should be included in educational content for opioid prescribers and other healthcare providers, including prescriber education under a Risk Evaluation and Mitigation Strategy (REMS).

**April:** On April 20, FDA [published](#) a Federal Register notice seeking public comment on a potential change that would require opioid analgesics used in outpatient settings to be dispensed with prepaid mail-back envelopes and that pharmacists provide patient education on safe disposal of opioids.

**May:** On May 31, the FDA, in collaboration with Harvard University and Massachusetts General Hospital, published the research article, [Modeling the evolution of the US opioid crisis for national policy development](#), which discusses FDA's initiative to develop a data-driven, national-level simulation model of the opioids system, named SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects) and includes baseline projections of the opioid crisis – opioid misuse rates, prevalence of opioid use disorder and overdose deaths – over the next ten years, across different scenarios.

**June:** On June 21, FDA [approved the second generic naloxone intranasal spray](#) to treat opioid overdose.

**June:** On June 27, the FDA, in collaboration with Harvard University and Massachusetts General Hospital, published the research article, [Reducing opioid use disorder and overdose deaths in the United States: A dynamic modeling analysis](#), which discusses FDA's initiative to develop a data-driven, national-level simulation model of the opioids system, named SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects) and describes an initial



analysis of 11 high-level interventions and the effects that SOURCE projects those interventions may have on the crisis.

**June:** On June 30, the FDA, in collaboration with the Federal Trade Commission, issued warning letters to four companies selling unapproved kratom products and one company selling essential oils for the treatment or cure of opioid use disorder and withdrawal symptoms. The companies that received warning letters are: [Herbsens Botanicals](#), [Klarity Kratom](#), [Kratom Exchange](#), [Omni Consumer Products LLC d/b/a YoKratom](#) and [MONQ, LLC](#).

**August:** On August 23, the FDA issued a [warning letter](#) to the operator of 25 websites illegally selling unapproved and misbranded opioids and benzodiazepines to U.S. consumers in violation of the Federal Food, Drug, and Cosmetic Act.

**August:** On August 30, the FDA announced the establishment of the [FDA Overdose Prevention Framework](#). The framework details FDA's vision to undertake impactful, creative actions to prevent drug overdoses and reduce deaths through initiatives and activities nested within four priorities: (1) supporting primary prevention by eliminating unnecessary initial prescription drug exposure and inappropriate prolonged prescribing; (2) encouraging harm reduction through innovation and education; (3) advancing development of evidence-based treatments for substance use disorders; and (4) protecting the public from unapproved, diverted or counterfeit drugs presenting overdose risks. The Overdose Prevention Framework supports the [HHS Overdose Prevention Strategy](#).

**September:** On September 12, the FDA awarded a [cooperative agreement](#) to support an evidence-based clinical practice guideline for the safe tapering of benzodiazepines.

**September:** On September 15, the FDA awarded a [cooperative agreement](#) to support the development of an evidence-based clinical practice guideline for the management of post-operative pain in obstetric patients. The purpose of this guideline is to promote appropriate opioid prescribing in obstetric patients who have undergone surgery.

**September:** On September 22, the FDA published the immediately-in-effect guidance, [Exemption and Exclusion from Certain Requirements of the Drug Supply Chain Security Act \(DSCSA\) for the Distribution of FDA-Approved Naloxone Products During the Opioid Public Health Emergency](#), which is intended to clarify the scope of the public health emergency (PHE) exclusion and exemption under the [DSCSA](#) as they apply to the distribution of FDA-approved naloxone products to harm reduction programs during the opioid PHE. This guidance supports the [FDA Overdose Prevention Framework](#).

**September:** On September 30, the FDA [published an update](#) on actions the agency has taken to align with the National Academies for Sciences, Engineering, and Medicine's (NASSEM) recommendations regarding *Opioid Approval and Monitoring by the FDA*.

**October:** On October 11, through a cooperative agreement with the FDA, the Duke-Margolis Center hosted a public workshop, [Challenges and Opportunities for REMS Integration, Innovation, and Modernization](#), to solicit feedback from key stakeholders on a Risk Evaluation and Mitigation Strategies (REMS) integration prototype.



**November:** On November 8, the FDA issued an [alert to health care professionals](#) warning of possible xylazine inclusion in fentanyl, heroin, and other illicit drug overdoses, as naloxone may not be able to reverse its effects and the FDA is aware of increasing reports of serious side effects from individuals exposed to fentanyl, heroin, and other illicit drugs contaminated with xylazine.

**November:** On November 15, the FDA [issued a Federal Register notice](#) to alert application holders of certain prescription naloxone drug products aware of the agency's preliminary assessment and the possibility that the agency may make a conclusive determination, through approval of a nonprescription naloxone drug product, that such products are safe and effective for use without a prescription.

**November:** On November 28, the FDA held a [stakeholder call](#) to discuss naloxone access and affirm the agency's commitment to support the efforts of harm reduction groups to acquire FDA-approved naloxone products.

## 2023

**January:** On January 30, the *Drug and Alcohol Dependence* Journal article co-authored by FDA entitled, "[Concordance between controlled substance receipt and post-mortem toxicology in opioid-detected overdose deaths: A statewide analysis](#)," was published.

**February:** On February 13, the *Pharmacoepidemiology and Drug Safety* Journal article authored by FDA entitled, "[The impact of hydrocodone rescheduling on utilization, abuse, misuse, and overdose deaths](#)," was published.

**February:** On February 15, the FDA convened a [joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee](#) to discuss supplemental new drug application 208411/S-006, for NARCAN (naloxone hydrochloride) nasal spray, indicated for nonprescription treatment of known or suspected opioid overdose.

**February:** On February 16, the FDA [published the results](#) of Ohio State University's [External Review of FDA Regulation of Opioid Analgesics](#). The review analyzed the FDA's implementation of the 2017 National Academies for Sciences, Engineering, and Medicine's (NASEM) recommendations along with key regulatory policies and decisions, including labeling.

**February:** On February 28, the FDA [announced an action](#) to restrict the unlawful entry of xylazine active pharmaceutical ingredients and finished dosage form drug products into the United States.

**March:** On March 7, the FDA [approved a naloxone intranasal spray](#) to treat opioid overdose.

**March:** On March 8-9, through a cooperative agreement with the FDA, the Reagan-Udall Foundation for the FDA hosted a public meeting, [Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose](#), to explore the

evolving context surrounding fatal overdoses and discuss epidemiological trends, drug supply changes, public health interventions to manage overdose, and drug development opportunities.

**March:** On March 16, the FDA published the draft guidance for industry, [Development of Local Anesthetic Drug Products With Prolonged Duration of Effect](#), which is intended to provide the agency's recommendations for assisting developers in generating the data necessary to support different indications and labeling claims for these drugs.

**March:** On March 29, the FDA [approved the first over-the-counter naloxone nasal spray](#), thereby expanding access and availability of the first-line treatment used for opioid overdose.

**March:** On March 30, the FDA held a [stakeholder call](#) to discuss expanding access to naloxone following the approval of the first over-the-counter naloxone nasal spray.

**April:** On April 3, the FDA [announced](#) it is requiring manufacturers of opioid analgesics dispensed in outpatient settings to make prepaid mail-back envelopes available to outpatient pharmacies and other dispensers as an additional opioid analgesic disposal option for patients.

**April:** On April 13, the FDA issued a [Drug Safety Communication](#) and a [statement](#) announcing several updates to the prescribing information for immediate-release and extended-release/long-acting opioid analgesics. The updates also included a new warning about opioid-induced hyperalgesia, which is a condition where opioids cause an increase in pain (hyperalgesia) or an increased sensitivity to pain (allodynia).

**April:** On April 19, the FDA convened a [joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee](#) to discuss postmarketing requirement (PMR) 3033-11, issued to application holders of new drug applications for extended-release and long-acting opioid analgesics to evaluate long-term efficacy of opioid analgesics and the risk of opioid-induced hyperalgesia.

**May:** On May 9, the FDA and the Substance Abuse and Mental Health Services Administration issued a [joint letter](#) to health care providers intended to clarify buprenorphine prescribing recommendations.

**May:** On May 10-11, through a cooperative agreement with the FDA, the Reagan-Udall Foundation for the FDA hosted a public meeting, [Considerations for Buprenorphine Initiation and Maintenance Care](#), to explore real-world experiences and scientific evidence for buprenorphine initiation strategies as well as medication dosing and management during continued treatment across different care settings.

**May:** On May 11, the FDA issued a [Drug Safety Communication](#) and a [statement](#) announcing updates for amphetamine and methylphenidate products, a class of stimulant medications used to treat attention deficit/hyperactivity disorder (ADHD) and other disorders, to standardize prescribing information. The updates intend to inform patients, caregivers and health care professionals of risks associated with their medications, and address misuse and abuse (also called nonmedical use), addiction, and overdose information.

**May:** On May 22, the FDA [approved a nalmefene intranasal spray](#) to treat opioid overdose.

**May:** On May 23, the FDA [approved an extended-release buprenorphine injection](#) to treat moderate to severe opioid use disorder.

**June:** On June 8, the FDA hosted internet stakeholders, regulatory organizations, academia, and other important stakeholders at its fourth [Online Controlled Substances Summit](#), (formerly the “Online Opioid Summit”).

**June:** On June 20-21, the FDA announced the opening of two Notice of Funding Opportunities (NOFOs) to encourage applications to support the development of evidence-based, clinical practice guidelines for the management of [acute low back pain](#), and [acute postoperative pain in patients who have undergone diagnostic and procedural laparoscopic abdominal surgeries](#). These NOFOs support the FDA’s primary prevention priority under the [Overdose Prevention Framework](#).

**June:** On June 23, the FDA [announced](#) issuance of its first draft guidance presenting considerations to industry for designing clinical trials for psychedelic drugs, [Psychedelic Drugs: Considerations for Clinical Investigations](#). The guidance intends to highlight fundamental considerations to researchers investigating the use of psychedelic drugs for potential treatment of medical conditions, including psychiatric or substance use disorders.

**June:** On June 26-27, the FDA participated in the National Academies of Sciences, Engineering, and Medicine’s public workshop, [Defining and Evaluating In-Home Drug Disposal Systems for Opioid Analgesics](#). The workshop provided an opportunity for stakeholders to examine in-home drug disposal options, with a focus on removing unused opioid analgesics from the home.

**July:** On July 6, the FDA [approved the first generic application for naltrexone extended-release injectable suspension](#), indicated to treat alcohol and opioid use disorder.

**July:** On July 18, the FDA [approved the first generic over-the-counter naloxone nasal spray](#) to treat opioid overdose.

**July:** On July 27, the FDA announced issuance of a draft guidance to help facilitate innovation in devices intended to treat opioid use disorder, [Clinical Considerations for Studies of Devices Intended to Treat Opioid Use Disorder](#). The guidance will help sponsors design clinical studies to evaluate these devices, and further [FDA’s Overdose Prevention Framework](#) goal of advancing evidence-based treatment for those with substance use disorders.

**July:** On July 28, the FDA [approved the second branded over-the-counter naloxone nasal spray](#) to treat opioid overdose.

**August:** On August 25, the American Dental Association Science and Research Institute, the University of Pittsburgh School of Dental Medicine, and the Center for Integrative Global Oral Health at the University of Pennsylvania School of Dental Medicine issued a [new clinical practice guideline detailing dental pain management strategies for children](#). The development of this guideline was funded by an FDA-provided grant following an FDA-commissioned report by the National Academies of Science, Engineering, and Medicine that recommended that the guideline be developed.

**September:** On September 15, the FDA awarded cooperative agreements to support the development of two evidence-based clinical practice guidelines: one for the management of [acute low back pain](#), and another for the management of acute postoperative pain in patients who have undergone diagnostic and procedural [laparoscopic abdominal surgeries](#).

## Summary Timeline

**1995.** OxyContin (oxycodone controlled-release) approved; first formulation of oxycodone that allowed dosing every 12 hours instead of every 4 to 6 hours.

**1998.** Actiq (fentanyl) approved; first pain medicine approved to treat cancer breakthrough pain, but with additional safety measures.

**Early 2000s.** Reports of overdose and death from prescription pain drugs, especially OxyContin, began to rise sharply.

**2001.** OxyContin label was changed to add and strengthen warnings about the drug's potential for misuse and abuse.

**2003.** FDA issued a [Warning Letter](#) (PDF - 149KB) to OxyContin's manufacturer for misleading advertisements.

**2007.** FDA Amendments Act granted FDA authority to require for certain drugs specified safety measures known as Risk Evaluation and Mitigation Strategies (REMS).

**2009.** FDA held several public and stakeholder meetings, including [May 27-28 public meeting](#) and [December 4 stakeholder meeting](#), to discuss opioid risks, misuse, and abuse.

FDA partnered with U.S. Substance Abuse and Mental Health Services Administration (SAMHSA) to launch an [initiative](#) to help ensure the safe use of the opioid methadone.

FDA launched the [Safe Use Initiative](#) to reduce preventable harm by medications, including opioids.

FDA began working with U.S. Drug Enforcement Administration (DEA) and others to help educate the public on [safe disposal](#) of opioids.

**2010.** FDA [approved](#) a new formulation of OxyContin.

FDA held [joint advisory committee meeting](#) to discuss its proposal for a class-wide REMS for Extended-Release (ER)/Long acting (LA) opioids, such as OxyContin.

**2011.** FDA [approved](#) REMS for transmucosal immediate-release fentanyl (TIRF) products, such as Actiq.

**2012.** FDA implemented the [ER/LA opioids REMS program](#), which includes voluntary training for prescribers.

**2013.** On January 9, FDA issued a draft guidance to assist industry in developing new formulations of opioid drugs with abuse-deterrent properties: [Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling](#) (PDF - 463KB).

FDA held a [January 24-25 meeting of its Drug Safety and Risk Management Advisory Committee](#) (PDF - 69KB) to discuss the public health benefits and risks, including the potential for abuse, of drugs containing hydrocodone either combined with other analgesics or as an antitussive.

FDA held a public hearing on February 7-8 to obtain information on issues pertaining to the use of opioid drugs in the treatment of chronic pain. Impact of Approved Drug Labeling on Chronic Opioid Therapy: Part 15 Hearing.

In an [open letter](#) to prescribers on March 1, FDA and health professional organizations asked all prescribers of opioids to ensure they have thorough knowledge of the FDA-approved product labeling for the opioids they prescribe, and to ensure they have adequate training in opioid therapy. FDA also encouraged all prescribers to help curb our nation's opioid epidemic.

On April 16, FDA took multiple actions related to [OxyContin](#).

On May 10, FDA responded to a petition and decided that the original formulation of [Opana ER](#) (oxymorphone hydrochloride) Extended-Release Tablets was not withdrawn from the market for reasons of safety or effectiveness. As a result, generic versions of the original formulation can continue to be approved and marketed.

FDA held the [Clinical Development Programs for Opioid Conversion; Public Workshop: Request for Comments](#) on July 29. The scientific workshop was held to address public health concerns associated with the inclusion of equianalgesic opioid conversion tables in opioid product labeling.

On September 10, FDA announced a set of [significant measures to enhance the safe and appropriate use of extended-release and long-acting \(ER/LA\) opioids](#), including class-wide safety labeling changes and new post-marketing requirements for all ER/LA opioid analgesics. FDA also responded to two citizen petitions regarding labeling of opioids.

On October 24, FDA issued [Statement on Proposed Hydrocodone Reclassification from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research](#).

**2014.** On April 3, FDA approved [Evzio \(naloxone hydrochloride injection\)](#) for the emergency treatment of known or suspected opioid overdose. Naloxone is a medication that rapidly reverses the effects of opioid overdose. Evzio is the first auto-injector designed to deliver a dose of naloxone outside of a healthcare setting.

On April 14, FDA finalized the [proposed class-wide safety labeling changes](#) for all extended-release and long-acting (ER/LA) opioid analgesics, and responded to two citizen petitions regarding labeling for neonatal opioid withdrawal syndrome (NOWS).

On July 23, FDA approved [Targiniq ER](#), an extended-release pain reliever that contains a combination of oxycodone and naloxone. Targiniq ER is the second extended-release/long-acting (ER/LA) opioid analgesic with FDA-approved labeling describing the product's abuse-deterrent properties.

On August 19, FDA approved revisions to the ER/LA Opioid Analgesics REMS to incorporate information from the ER/LA opioid analgesic safety labeling changes (SLCs) announced on September 10, 2013, and approved on April 16, 2014. The most significant changes were to clarify the approved indications for use and limitations of use, and to revise warnings, including boxed warnings.

On October 17, FDA approved new labeling for [Embeda](#) (morphine sulfate and naltrexone hydrochloride), an extended-release (ER) opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Embeda is the third ER opioid analgesic to be approved with labeling describing the product's abuse-deterrent properties consistent with the FDA's 2013 draft guidance, Abuse-Deterrent Opioids – Evaluation and Labeling. The new labeling includes a claim indicating that Embeda has properties that are expected to reduce oral and intranasal abuse when the product is crushed.

On November 20, FDA approved [Hysingla ER](#) (hydrocodone bitartrate), an extended-release (ER) opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Hysingla ER is the fourth ER opioid analgesic to be approved with labeling describing the product's abuse-deterrent properties consistent with the FDA's 2013 draft guidance for industry, Abuse-Deterrent Opioids – Evaluation and Labeling. Hysingla ER has properties that are expected to reduce, but not totally prevent, abuse of the drug when chewed and then taken orally, or crushed and snorted or injected.

**2015. January:** On January 30, FDA approved a modified formulation of Zohydro ER (hydrocodone bitartrate extended-release capsules). The FDA has not approved an abuse-deterrent labeling claim for Zohydro ER.

April: On April 1, FDA issued a final guidance to assist industry in developing opioid drug products with potentially abuse-deterrent properties. [Guidance for Industry: Abuse-Deterrent Opioids](#)” (PDF - 227KB) explains the FDA's current thinking about the studies that should be conducted to demonstrate that a given formulation has abuse-deterrent properties, makes recommendations about how those studies should be performed and evaluated, and discusses what labeling claims may be approved based on the results of those studies.

August: On August 13, FDA approved [OxyContin for certain pediatric patients](#) for pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative



treatment options are inadequate. This approval is limited to opioid-tolerant pediatric patients 11 and up who are already taking and tolerating a minimum daily dose of at least 20 mg oxycodone orally or its equivalent. These patients can be expected to remain on treatment with an opioid for several weeks or more.

On October 2, FDA approved [MorphaBond](#) (morphine sulfate), an extended-release (ER) opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. MorphaBond is the fifth ER opioid analgesic to be approved with labeling describing the product's abuse-deterrent properties consistent with the FDA's 2015 guidance for industry, Abuse-Deterrent Opioids – Evaluation and Labeling. MorphaBond has properties that are expected to reduce, but not eliminate, abuse of the drug when crushed and snorted or injected.

On November 18, FDA approved [Narcan nasal spray](#), the first FDA-approved nasal spray version of naloxone hydrochloride, a life-saving medication that can temporarily stop or reverse the effects of an opioid overdose, including an overdose from heroin.

**2016. February:** On February 4, FDA leaders, in response to the opioid abuse epidemic, called for a far-reaching action plan to reassess the agency's approach to opioid medications. The plan will focus on policies aimed at reversing the epidemic, while still providing patients in pain access to effective relief.

On February 4, FDA released five postmarketing (PMR) requirements announced on September 13, 2013, and replaced them with [11 PMRs \(10 postmarketing studies and one clinical trial\)](#) because the 10 postmarketing observational studies and one clinical trial include refined measures for assessing the known serious risks of misuse, abuse, addiction, overdose, and death.

On February 19 the FDA announced that during the April 12th meeting of the Pediatric Advisory Committee (PAC) they will present a framework of current plans for a 2-day joint meeting of the PAC, the Anesthetic and Analgesic Drug Products Advisory Committee, and the Drug Safety and Risk Management Advisory Committees. This joint meeting is scheduled for September 15 and 16, 2016 and during this meeting the FDA will be calling on a broad range of independent experts with real-world experience to provide recommendations on how to address the unique needs of children in pain.

March: On March 1, the FDA convened the [Science Board](#) to hear about and discuss a range of pressing issues related to the current opioid epidemic, including: (1) the role of opioids in pain management; (2) scientific challenges facing FDA in supporting the development of pain medications (3) scientific challenges facing FDA in seeking to understand the real-world use of opioids to treat pain (4) the role that FDA plays as a part of a larger Federal, State and local response to the challenges of providing appropriate pain treatment while reducing opioid abuse; and (5) postmarket surveillance activities related to opioids.

On March 22, FDA announced required [class-wide safety labeling changes for immediate-release \(IR\) opioid pain medications](#). Among the changes, the FDA is requiring a new boxed warning about the serious risks of misuse and abuse, which can lead to addiction, overdose and

death. The FDA is also requiring several additional safety labeling changes across all prescription opioid products to include additional information on the risk of these medications.

On March 24, FDA issued a draft guidance titled “[General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products](#).” This guidance recommends studies a generic applicant should conduct so FDA can evaluate the abuse deterrence of certain generic opioid drug products and help ensure that generic versions of approved opioids with abuse-deterrent formulations (ADFs) are no less abuse-deterrent than the brand named drug.

April: On April 26, FDA approved [Xtampza ER](#) (oxycodone), an extended-release (ER) opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. Xtampza ER is the sixth ER opioid analgesic to be approved with labeling describing the product’s abuse-deterrent properties consistent with the FDA’s 2015 guidance for industry, Abuse-Deterrent Opioids – Evaluation and Labeling. Xtampza ER has properties that are expected to reduce, but not eliminate, abuse of the drug when crushed and snorted or injected.

May: On May 3-4, FDA convened a [joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee](#) to discuss results from assessments of the extended-release and long-acting (ER/LA) Opioid Analgesics Risk Evaluation and Mitigation Strategies (REMS). The committees provided comments as to whether this REMS with Elements to Assure Safe Use (ETASU) assures safe use, is not unduly burdensome to patient access to the drugs, and to the extent practicable, minimizes the burden to the healthcare delivery system.

On May 26, FDA announced required [safety labeling changes for methadone and buprenorphine products](#) when used by pregnant women for medication-assisted treatment (MAT) of opioid use disorder to ensure providers have complete information about the benefits and risks of these products.

On May 26, FDA approved [Probuphine](#), the first buprenorphine implant for the maintenance treatment of opioid dependence. Probuphine, an implant designed to provide a constant, low level of buprenorphine for six months, should be used in patients who are already stable on low-to-moderate doses of other forms of buprenorphine and as part of a complete treatment program that includes counseling and psychosocial support.

August: On August 19, FDA approved [Troxyca ER](#) (oxycodone hydrochloride and naltrexone hydrochloride extended-release capsules), an extended-release (ER) opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. Troxyca ER is the seventh ER opioid analgesic to be approved with labeling describing the product’s abuse-deterrent properties consistent with the FDA’s 2015 guidance for industry, Abuse-Deterrent Opioids – Evaluation and Labeling. Troxyca ER has properties that are expected to reduce, but not eliminate, abuse of the drug when crushed and then taken orally, snorted, or injected.

On August 31, FDA announced required class-wide changes to drug labeling to help inform health care providers and patients of the [serious risks associated with the combined use of certain opioid medications and a class of central nervous system depressant drugs called benzodiazepines](#). Among the changes, the FDA is requiring boxed warnings and Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines with information about the serious risks, including extreme sleepiness, respiratory depression, coma and death, associated with using these medications at the same time.

September: On September 15-16, the FDA convened a [joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, the Drug Safety and Risk Management Advisory Committee, and the Pediatric Advisory Committee](#) to discuss the appropriate development plans for establishing the safety and efficacy of prescription opioid analgesics for pediatric patients, including obtaining pharmacokinetic data and the use of extrapolation.

October: On October 5, the FDA convened a [joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management](#) to discuss naloxone products intended for use in the community, specifically the most appropriate dose or doses of naloxone to reverse the effects of life-threatening opioid overdose in all ages, and the role of having multiple doses available in this setting. The committees also discussed the criteria prescribers will use to select the most appropriate dose in advance of an opioid overdose event and the labeling to inform this decision, if multiple doses are available.

On October 31 – November 1, the FDA held a public meeting, [Pre-Market Evaluation of Abuse-Deterrent Properties of Opioid Drug Products](#), to discuss scientific and technical issues relating to formulation development and pre-market evaluation of opioid drug products with abuse-deterrent properties. The meeting was intended to give FDA the opportunity to discuss, and seek public input from stakeholders on, the approach to testing FDA recommended in its draft guidance General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products. The meeting also provided an opportunity to discuss FDA's efforts to develop standardized in vitro testing methodologies for evaluating the abuse deterrence of opioid drug products.

December: On December 16, the FDA approved several safety labeling changes (SLCs) about the serious risks of prescription opioid analgesics and opioids approved for medication assisted treatment (MAT) of opioid addiction including [class-wide SLCs for immediate-release \(IR\) opioid pain medications](#), [SLCs for methadone and buprenorphine products](#), and [class-wide SLCs about the serious risks associated with the combined use of certain opioid medications with benzodiazepines or other central nervous system \(CNS\) depressants](#).

**2017.** On January 9, FDA approved [Arymo ER](#) (morphine sulfate extended-release tablets), an extended-release (ER) opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. Arymo ER is the eighth ER opioid analgesic to be approved with labeling describing the product's abuse-deterrent properties consistent with the FDA's 2015 guidance for industry, Abuse-

Deterrent Opioids – Evaluation and Labeling. Arymo ER is formulated to give it physicochemical properties expected to make abuse by injection difficult.

On January 17, FDA approved [Vantrela ER](#) (hydrocodone bitartrate extended-release tablets), an extended-release (ER) opioid analgesic to treat pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate. Vantrela ER is the ninth ER opioid analgesic to be approved with labeling describing the product's abuse-deterrent properties consistent with the FDA's 2015 guidance for industry, Abuse-Deterrent Opioids – Evaluation and Labeling. The physical and chemical properties of Vantrela ER are expected to make intravenous (injection) abuse difficult and are expected to reduce, but not eliminate, abuse by nasal and oral routes. However, abuse of Vantrela ER by these routes is still possible.

On April 20, FDA announced the [restricted the use of codeine and tramadol medicines in children](#) because these medicines carry serious risks, including slowed or difficult breathing and death, which appear to be a greater risk in children younger than 12 years, and should not be used in these children. These medicines should also be limited in some older children. The FDA also recommended against the use of codeine and tramadol medicines in breastfeeding mothers due to possible harm to their infants.

On April 20, the FDA approved [RoxyBond](#) (oxycodone hydrochloride), an opioid analgesic indicated for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. RoxyBond is the first immediate-release opioid analgesic approved with labeling describing its abuse-deterrent properties consistent with the FDA's 2015 Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling. Based on laboratory studies, RoxyBond tablets are resistant to certain forms of manipulation such as crushing, grinding, or otherwise extracting oxycodone from the tablet that are typically used to make opioids easier to abuse by the nasal and intravenous routes.

On April 27, FDA held an [expert roundtable](#) for healthcare professionals to discuss their experiences with the use of cough suppressants in children (<18 years of age), particularly opioid containing antitussive products, as well as the data available to support recommendations made by various professional societies regarding the treatment of cough in children.

On May 9-10, FDA held a public meeting, [Training Health Care Providers on Pain Management and Safe Use of Opioid Analgesics – Exploring the Path Forward](#), to obtain input on issues and challenges associated with Federal efforts to support training on pain management and the safe prescribing, dispensing, and patient use of opioids (safe use of opioids) for health care providers.

On May 10, FDA released the "[FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain](#)" (draft revisions to the Blueprint), which broadens the current Blueprint to include information on pain management, including the principles of acute and chronic pain management; non-pharmacologic treatments for pain; and pharmacologic treatments for pain (both non-opioid analgesic and opioid analgesic).

On June 8, FDA requested that [Endo Pharmaceuticals remove its opioid pain medication, reformulated Opana ER \(oxymorphone hydrochloride\), from the market](#) based on its concern that the benefits of the drug may no longer outweigh its risks.

On July 6, the JAMA Viewpoint article by Dr. Scott Gottlieb and Dr. Janet Woodcock entitled, "[Marshaling FDA Benefit-Risk Expertise to Address the Current Opioid Abuse Epidemic](#)," was published.

On July 6, following the FDA's request, Endo announced that it would [voluntarily remove reformulated Opana ER](#) from the market.

On July 10-11, FDA held a public meeting, [Data and Methods for Evaluating the Impact of Opioid Formulations with Properties Designed to Deter Abuse in the Postmarket Setting: A Scientific Discussion of Present and Future Capabilities](#), to discuss ways to improve the analysis and interpretation of existing data, as well as to discuss opportunities and challenges for collecting and/or linking additional data to improve national surveillance and research capabilities in this area.

On July 13, the National Academies of Science, Engineering, and Medicine release the [consensus report](#), commissioned by the FDA, which outline the state of the science regarding prescription opioid abuse and misuse, as well as the evolving role that opioids play in pain management.

On September 11, FDA held a [Pediatric Advisory Committee meeting](#) to discuss the use of prescription opioid products containing hydrocodone or codeine for the treatment of cough in pediatric patients. The discussion included current practice for the treatment of cough in children and benefit-risk considerations regarding the use of prescription opioid products in pediatric patients.

On September 20, FDA [advised](#) that the opioid addiction medications buprenorphine and methadone should not be withheld from patients taking benzodiazepines or other drugs that depress the central nervous system (CNS). The combined use of these drugs increases the risk of serious side effects; however, the harm caused by untreated opioid addiction can outweigh these risks. Careful medication management by health care professionals can reduce these risks.

On September 28, after determining that a REMS is necessary for IR opioid analgesics to ensure that the benefits of these drugs continue to outweigh the risks, [FDA sent letters to IR opioid analgesic manufacturers](#) informing them that their products that are intended to be used in the outpatient setting will be subject to the same REMS requirements as the ER/LA opioid analgesics.

On November 21, FDA issued a final guidance titled "[General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products](#)." This guidance recommends studies, including comparative in vitro and pharmacokinetic studies, that the potential abbreviated new drug application (ANDA) applicant should conduct and submit to FDA in an

ANDA to demonstrate that a generic solid oral opioid drug product is no less abuse-deterrent than its reference listed drug with respect to all potential routes of abuse.

On November 30, FDA approved [Sublocade](#), the first once-monthly injectable buprenorphine product for the treatment of moderate-to-severe opioid use disorder in adult patients who have initiated treatment with a transmucosal (absorbed through mucus membrane) buprenorphine-containing product. It is indicated for patients that have been on a stable dose of buprenorphine treatment for a minimum of seven days.

On December 11-12, FDA hosted a [public workshop regarding the role of packaging, storage, and disposal options](#) within the larger landscape of activities aimed at addressing abuse, misuse, or inappropriate access of prescription opioid drug products; guiding principles and considerations for the design of packaging, storage, and disposal options for opioids; integrating packaging, storage, and disposal options into existing health care and pharmacy systems, including both open and closed health care systems; data needs and how to address challenges in assessing the impact of packaging, storage, and disposal options in both the premarket and postmarket settings; and ways in which FDA could encourage the development and assessment of packaging, storage, and disposal options for opioids that have the potential to enhance opioid safety.

**2018.** On January 11, FDA announced that it is requiring [safety labeling changes for prescription cough and cold medicines containing codeine or hydrocodone](#) to limit the use of these products to adults 18 years and older because the risks of these medicines outweigh their benefits in children younger than 18. The agency is also requiring the addition of safety information about the risks of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing to the Boxed Warning of the drug labels for prescription cough and cold medicines containing codeine or hydrocodone.

On January 11, FDA Commissioner, Scott Gottlieb, M.D., announced the [2018 Strategic Policy Roadmap](#), which provides an overview of some of the key priorities the agency will pursue advance FDA's public health mission. Part of the Roadmap is reducing misuse and abuse of opioid drugs.

On January 24, FDA and the Federal Trade Commission [posted joint warning letters](#) to the marketers and distributors of 12 opioid cessation products, for illegally marketing unapproved products with claims about their ability to help in the treatment of opioid addiction and withdrawal.

On January 30, FDA held a public hearing, [“Opioid Policy Steering Committee: Prescribing Intervention—Exploring a Strategy for Implementation.”](#) to receive stakeholder input on how FDA might, under its REMS authority, improve the safe use of opioid analgesics by curbing overprescribing to decrease the occurrence of new addictions and limit misuse and abuse of opioid analgesics.

On January 30, FDA announced [limits to packaging for anti-diarrhea medicine Loperamide \(Imodium\)](#) to encourage safe use.



On January 30, FDA posted the revised Blueprint, [“Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain,”](#) which broadens the current Blueprint to include information on pain management, including the principles of acute and chronic pain management; non-pharmacologic treatments for pain; and pharmacologic treatments for pain. (It is important to note that the revised Blueprint will not be considered final until the Opioid Analgesic Risk Evaluation and Mitigation Strategy is approved.)

On February 14, FDA held a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the new drug application for [Hydexor](#) (proposed tradename), a fixed-dose combination oral tablet, submitted by Charleston Laboratories, Inc., that contains hydrocodone, acetaminophen, and promethazine, for the short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting. The committees also discussed the abuse potential of this non-abuse-deterrent product and whether it should be approved.

On February 15, through a cooperative agreement with the FDA, the Duke-Margolis Center hosted a public workshop, [“Strategies for Promoting the Safe Use and Appropriate Prescribing of Prescription Opioids,”](#) to examine the landscape of health system and payer interventions to promote safe and appropriate prescribing of opioids; discuss how health systems and payers are using data and health IT tools to support interventions; discuss how health system approaches were implemented, barriers to their adoption, and potential unintended consequences of adoption; and discuss how to build an evidence base to support existing health system and payer interventions as well as how success may be defined and measured.

On March 27, FDA held a meeting of the Psychopharmacologic Drugs Advisory Committee to discuss the new drug application for [lofexidine hydrochloride](#), submitted by US WorldMeds, LLC, for mitigation of symptoms associated with opioid withdrawal and facilitation of completion of opioid discontinuation treatment.

On April 17, FDA is hosting a public meeting on [Patient-Focused Drug Development for Opioid Use Disorder \(OUD\)](#), in collaboration with National Institute of Drug Abuse (NIDA). In addition to NIDA, FDA is also working closely with patient advocacy and community organizations to encourage participation from individuals with OUD. This meeting aligns with FDA’s ongoing work aimed at reducing the impact of opioid abuse and addiction.

On April 20, FDA issued the draft guidance, [“Opioid Dependence: Developing Buprenorphine Depot Products for Treatment,”](#) which reflects the agency’s current thinking regarding drug development and trial design issues relevant to the study of depot buprenorphine products (i.e. modified-release products for injection or implantation).

On May 16, FDA approved [Lucemyra](#) (lofexidine hydrochloride), the first non-opioid treatment for the mitigation of withdrawal symptoms associated with abrupt discontinuation of opioids.

On May 22, FDA convened a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the new drug application for [buprenorphine sublingual spray](#), submitted by INSYS Development Company, Inc., for the treatment of moderate-to-severe acute pain where the use of an opioid analgesic is appropriate. The committees will also be asked to discuss whether this product should be approved.

On May 30, FDA launched an [innovation challenge](#) to spur development of medical devices – including digital health and diagnostics – that target pain, addiction and diversion.

On June 5, FDA [took action](#) against 53 websites marketing unapproved opioids as part of a comprehensive effort to target illegal online sales.

On June 14, FDA approved [first generic versions of Suboxone sublingual film](#).

On June 26, FDA convened a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the new drug application for [oxycodone extended-release capsules](#), submitted by Pain Therapeutics, with the proposed indication of the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The product is intended to have abuse-deterrent properties based on its physicochemical properties. The committees will be asked to discuss whether the data submitted by the Applicant are sufficient to support labeling of the product with the properties expected to deter abuse.

On June 27, FDA convened internet stakeholders, government entities, academic researchers, and advocacy groups at a one-day [Online Opioid Summit](#) to discuss ways to collaboratively take stronger action in combatting the opioid crisis by reducing the availability of illicit opioids online.

On July 9, FDA hosted a public meeting on [Patient-Focused Drug Development for chronic pain](#) to hearing patients' perspectives on chronic pain, views on treatment approaches, and challenges or barriers to accessing treatments for chronic pain.

On August 3, FDA convened a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss results from assessments of the [transmucosal immediate-release fentanyl \(TIRF\) medicines' risk evaluation and mitigation strategy \(REMS\)](#), approved in December 2011. The TIRF REMS requires that healthcare providers who prescribe TIRF medicines for outpatient use are specially certified, that pharmacies that dispense TIRF medicines for inpatient and outpatient use are specially certified, and that completion of the prescriber-patient agreement form occurs prior to dispensing TIRF medicines for outpatient use. The Agency will seek the committees' assessment as to whether this REMS with elements to assure safe use (ETASU) assures safe use, is not unduly burdensome to patient access to the drugs, and to the extent practicable, minimizes the burden to the healthcare delivery system. The Agency will also seek the committees' input on any possible modifications to the TIRF REMS goals and requirements, as well as input on the

adequacy of the evaluations conducted in the REMS assessments to determine whether the TIRF REMS goals are being met.

On August 6, FDA issued the draft guidance for industry, [“Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Medication-Assisted Treatment,”](#) which is intended to assist sponsors in developing drugs for medication-assisted treatment of opioid use disorder (OUD) and addresses the clinical endpoints acceptable to demonstrate effectiveness of such drugs.

On August 22, FDA [awarded a contract](#) to the National Academies of Sciences, Engineering, and Medicine (NASEM) to help advance the development of evidence-based guidelines for appropriate opioid analgesic prescribing for acute pain resulting from specific conditions or procedures.

On August 28, FDA [took action](#) against 21 websites marketing unapproved opioids as part of agency’s effort to target illegal online sales

On September 7, FDA [approved a new dosage strength](#) of buprenorphine and naloxone sublingual film as maintenance treatment for opioid dependence

On September 18, FDA approved the [Opioid Analgesic REMS](#).

On September 20, through a cooperative agreement with the FDA, the Duke Margolis Center for Health Policy convened a [public workshop](#), “Expanding Access to Effective Treatment for Opioid Use Disorder: Provider Perspectives on Reducing Barriers to Evidence-Based Care.”

On September 27-28, FDA’s Office of Women’s Health, in collaboration with CDER and CTP, hosted a [2-day public meeting](#), “Opioid and Nicotine Use, Dependence, and Recovery: Influences of Sex and Gender.”

On October 11, FDA convened a [meeting of the Anesthetic and Analgesic Drug Products Advisory Committee](#) to discuss new drug application 210730, for oliceridine 1 milligram/milliliter injection, submitted by Trevena, Inc., for the management of moderate-to-severe acute pain in adult patients for whom an intravenous opioid is warranted. The committee also discussed the efficacy and safety data and benefit-risk considerations.

On October 12, FDA convened a [meeting of the Anesthetic and Analgesic Drug Products Advisory Committee](#) to discuss new drug application 209128, sufentanil sublingual tablets, submitted by AcelRx Pharmaceuticals, Inc., for the management of moderate-to-severe acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, in adult patients in a medically supervised setting. The committee also discussed risk-benefit considerations and whether this product should be approved.

On November 1, FDA convened [a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee](#) to discuss efficacy, safety and risk-benefit profile of new drug application 210417 for buprenorphine and

samidorphan sublingual tablets, submitted by Alkermes, Inc., for adjunctive treatment of major depressive disorder.

On November 2, FDA approved [first oral sufentanil pain medication](#) for use in a medically supervised setting.

On November 14, FDA convened a [joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee](#) to discuss new drug application 209774, for an immediate-release oral tablet formulation of oxycodone, which is intended to resist common methods of physical or chemical manipulation and to deter intravenous and intranasal abuse, submitted by SpecGx Inc., for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The committees also determined whether the Applicant adequately demonstrated that the abuse-deterrent properties of the proposed product are sufficient to include this information in the product label, and whether the product should be approved.

On November 15, FDA convened a [meeting of the Anesthetic and Analgesic Drug Products Advisory Committee](#) to discuss the assessment of opioid analgesic sparing outcomes in clinical trials of acute pain. The committee also commented on the trial design and endpoints of these studies and how to determine the clinical relevance of the results.

**2019.** On January 17, FDA [announced](#) the results of unprecedented work to design, test, and validate the key labeling requirements necessary to approve an over-the-counter (OTC) version of naloxone, including posting [two model Drug Facts labels \(DFLs\) and the supporting FDA review](#). Overall, the study demonstrated that the model DFL was well-understood by consumers and is acceptable for use by manufacturers in support of their OTC naloxone development programs.

On February 6, FDA issued the final guidance, [“Opioid Use Disorder: Developing Depot Buprenorphine Products for Treatment.”](#) which reflects the agency’s current thinking regarding drug development and trial design issues relevant to the study of depot buprenorphine products (i.e. modified-release products for injection or implantation).

On February 12, FDA [announced](#) ongoing efforts to stop the spread of illicit opioids, further secure the U.S. drug supply chain and forcefully confront opioid epidemic.

On March 19, FDA [took action](#) against marketer of unapproved products claiming to treat addiction, chronic pain and other serious conditions.

On March 27, FDA [announced](#) new steps to strengthen agency’s safety requirements aimed at mitigating risks associated with transmucosal immediate-release fentanyl products.

On April 2, FDA took [new enforcement actions](#) as part of the agency’s ongoing effort to combat the illegal online sales of opioids.

On April 2, FDA hosted internet stakeholders, thought leaders, government entities, academic researchers, and advocacy groups at its second [Online Opioid Summit](#).

On April 9, FDA announced harm reported from sudden discontinuation of opioid pain medicines and [required label changes](#) to guide prescribers on gradual, individualized tapering.

On April 19, FDA [approved first generic naloxone nasal spray](#) to treat opioid overdose.

On April 25, FDA launched a [public education campaign](#) to encourage safe removal of unused opioid pain medicines from homes.

On May 30, FDA opened a public docket to request information on requiring [fixed-quantity blister packaging for certain opioid pain medicines](#) to help decrease unnecessary exposure to opioids.

On June 11-12, FDA convened a [joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee](#) to seek input on the clinical utility and safety concerns associated with the higher range of opioid analgesic dosing (both in terms of higher strength products and higher daily doses) in the outpatient setting. The FDA is interested in better understanding current clinical use; situations that may warrant use of higher doses of opioid analgesics; and the magnitude and frequency of harms associated with higher doses of opioid analgesics relative to lower doses, as well as optimal strategies for managing these risks while ensuring access to appropriate pain management for patients.

On June 20, FDA issued draft guidance, [“Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework,”](#) which describes the application of the benefit-risk assessment framework that the agency uses in evaluating applications for opioid analgesic drugs and summarizes the information that can be supplied by opioid analgesic drug applicants to assist the agency with its benefit-risk assessment, including considerations about the broader public health effects of these products in the context of this crisis.

On July 2, FDA [warned](#) repackers distributing pharmaceutical ingredients, including opioids, for putting consumers at risk with significant violations of manufacturing quality standards.

On September 17, FDA held a public hearing, [“Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction,”](#) to receive stakeholder input on the approval process for new opioids and how FDA might best consider the existing armamentarium of therapies, among other factors, in reviewing applications for new opioids to treat pain.

On September 20, FDA issued a [statement](#) on the agency’s continued efforts to increase availability of all forms of naloxone to help reduce opioid overdose deaths.

On September 20, FDA [announced](#) the approval of new packaging for brand-name over-the-counter loperamide to help curb abuse and misuse.

On September 26, FDA held a [joint meeting](#) of the Pediatric and Drug Safety and Risk Management Advisory Committees 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), and to discuss pediatric data considerations for opioid analgesics labeling and Pediatric Research Equity Act studies for opioids generally, using Opana IR as an example.

On September 30, FDA and DEA [warn](#) website operators illegally selling opioids.

On October 24, FDA outlined the [agency's first year accomplishments](#) implementing SUPPORT Act authorities to address the opioids crisis.

On November 26, FDA [issued warning letter](#) for products illegally marketed for the treatment of health conditions, including opioid withdrawal symptoms.

On December 11, FDA [issued warning letter](#) for not including the most serious risks in advertisement for medication-assisted treatment drug.

On December 19, the National Academies of Sciences, Engineering, and Medicine released a [consensus report](#), commissioned by the FDA, on framing opioid prescribing guidelines for acute pain.

**2020.** On January 14, FDA convened a [joint meeting](#) of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss the new drug application (NDA) for oxycodone, a new molecular entity full mu-opioid receptor agonist, submitted by Nektar Therapeutics, for the management of chronic low back pain in adult patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. The committees were asked to discuss the safety and efficacy data as well as the overall risk-benefit profile of the product.

On January 15, FDA convened a [joint meeting](#) of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee. During the morning session, the committees discussed the NDA for tramadol 44 milligrams (mg) and celecoxib 56 mg tablet, which contains a fixed-dose combination of an opioid and a non-steroid anti-inflammatory drug, submitted by Esteve Pharmaceuticals, S.A., for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The committees were asked to discuss the safety and efficacy data as well as the overall risk-benefit profile of the product.

During the afternoon session, the committees discussed the NDA for an extended-release oral tablet formulation of oxycodone, submitted by Intellipharma Corp., for the management of moderate-to-severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The product has been formulated with properties intended to deter abuse, and the applicant has submitted data to support these abuse-deterrent properties for this



product. The committees were asked to discuss whether the applicant has demonstrated abuse-deterrent properties for their product that would support labeling, as well as the overall risk-benefit profile of the product.

On June 8, FDA and the National Telecommunications and Information Administration (NTIA) are [launching a 120-day pilot](#) to help reduce the availability of unapproved opioids illegally offered for sale online.

On July 23, the FDA issued a [Drug Safety Communication](#) announcing that the agency is requiring the drug manufacturers for all opioid pain relievers and medicines to treat OUD to add new recommendations about naloxone to the prescribing information to help ensure that health care professionals discuss the availability of naloxone and assess each patient's need for a naloxone prescription when opioid pain relievers or medicines to treat OUD are being prescribed or renewed. In addition, the agency recommended that health care professionals consider prescribing naloxone to patients at increased risk of opioid overdose, regardless of whether they are receiving a prescription for an opioid pain reliever or medicine to treat OUD. These may include people with a current or past diagnosis of OUD or who have experienced a previous opioid overdose.

On August 6, the FDA approved a prior approval supplemental new drug application that provides for a [shelf life extension](#) for Narcan (naloxone hydrochloride) nasal spray from the current 2-year shelf-life to 3 years and updates to the labeling.

On August 7, the FDA approved [Olinvyk \(oliceridine\)](#), an opioid agonist for the management of moderate to severe acute pain in adults, where the pain is severe enough to require an intravenous opioid and for whom alternative treatments are inadequate.

On September 1, the FDA awarded a [cooperative agreement](#) to support the development of an evidence-based clinical practice guideline for the management of acute dental pain.

On September 10-11, the FDA convened a [joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee](#) to discuss the results of required postmarketing studies (Postmarketing Requirements 3051-1, 3051-2, 3051-3, and 3051-4) that evaluated the effect of the reformulation of OxyContin (oxycodone hydrochloride extended-release tablets, manufactured by Purdue Pharma L.P., NDA 022272) on abuse, misuse, and fatal and non-fatal overdose, associated with OxyContin. The committees discussed whether these studies, in concert with other information from the published literature, have demonstrated that the reformulated OxyContin product has resulted in a meaningful reduction in these outcomes. The committees also discussed the broader public health impact of OxyContin's reformulation.

On October 2, the FDA published the final guidance for industry, [Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Treatment](#), which is intended to help sponsors develop drugs for treatment of opioid use disorder (OUD). This guidance addresses clinical endpoints acceptable for demonstrating effectiveness of such drugs.

On November 2, the FDA convened a [joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee](#) to discuss the new drug application for Hydexor, a fixed-dose combination oral tablet, submitted by Ölas Pharma, Inc., that contains hydrocodone, acetaminophen, and promethazine, for the short-term (not to exceed 3 days) management of acute post-operative pain severe enough to require an opioid analgesic and the prevention of opioid-induced nausea and vomiting in patients who are at risk for or have a history of nausea and vomiting.

On December 23, the FDA [finalized modifications](#) to the transmucosal immediate-release fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) to address the persistence of concerning prescribing practices and improve the agency's ability to monitor for adverse events and ensure safe use of these medicines.

**2021.** On February 1, the FDA provided an [update on the pilot program](#) with the National Telecommunications and Information Administration (NTIA) and three domain name registries to help reduce the availability of unapproved opioids illegally offered for sale online.

On February 16, the FDA issued a [warning letter](#) to AcelRx Pharmaceuticals, Inc. for the false and misleading promotion of Dsuvia (sufentanil sublingual tablet), a potent opioid analgesic.

On March 1, the FDA approved [Hydrocodone bitartrate \(reference listed drug: Hysingla ER\)](#), the first FDA-approved generic opioid with an [abuse-deterrent formulation \(ADF\)](#)—meaning the product has properties that are expected to reduce, though not totally prevent, abuse of the drug when chewed and then taken orally or crushed and snorted or injected.

On March 24, the FDA issued a white paper, [Introduction to FDA's Opioid Systems Model](#), which introduces FDA's opioid systems modeling effort, discusses potential uses of the model, provides an overview of the model's scope and structure, highlights preliminary areas for potential policy analysis and outlines on-going work.

On April 15, the FDA held the public workshop, [Morphine Milligram Equivalents: Current Applications and Knowledge Gaps, Research Opportunities, and Future Directions](#), to bring stakeholders together to discuss the scientific basis of morphine milligram equivalents (MMEs) with the goals of providing an understanding of the science and data underlying existing MME calculations for opioid analgesics, discussing the gaps in these data, and discussing future directions to refine and improve the scientific basis of MME applications.

On April 29, the FDA approved [morphine sulfate injection](#), an opioid analgesic for the management of severe pain for which alternative treatments are inadequate.

On April 30, the FDA approved a higher dose [naloxone hydrochloride nasal spray](#) product to treat opioid overdose.

On June 2, the FDA approved [morphine sulfate oral solution](#) and [morphine sulfate tablets](#), opioid analgesics for the management of severe pain in adult and pediatric patients for whom other pain relief options are inadequate.

On July 12-13, through a cooperative agreement with the FDA, the Duke-Margolis Center hosted a public workshop, [Safe Use of Benzodiazepines: Clinical, Regulatory, and Public Health Perspectives](#), to bring together regulators, academic researchers, clinicians, patient advocates, and other stakeholders to discuss epidemiological and abuse liability data, patient and clinician perspectives and experiences, and gaps in data and understanding about the safe use of benzodiazepines.

On July 12, the *PAIN* Journal article by Dr. John Farrar entitled, "[Evaluating the stability of opioid efficacy over 12 months in patients with chronic noncancer pain who initially demonstrate benefit from extended release oxycodone or hydrocodone](#)," was published.

On July 21, the FDA issued a Consumer Update, [Accidental Exposures to Fentanyl Patches Continue to Be Deadly to Children](#), to warn, patients, caregivers, and health care professionals about the dangers of accidental exposure to the fentanyl patch, and the need to properly store and dispose of the product.

On September 9, the FDA hosted internet stakeholders, government entities, academia, and other important stakeholders at its third [Online Opioid Summit](#).

On October 15, the FDA approved a single-dose [naloxone hydrochloride injection](#) product to treat opioid overdose.

On October 15, the FDA approved [Seglentis \(celecoxib and tramadol hydrochloride\)](#), a combined opioid agonist and nonsteroidal anti-inflammatory, for the management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

On October 18, through a cooperative agreement with the FDA, the Reagan-Udall Foundation hosted a public workshop, [A Practical Research Agenda for Treatment Development for Stimulant Use Disorder](#), to discuss a proposed practical research agenda that focused on innovation in clinical trial design and candidate endpoints for the evaluation of potential treatments for stimulant use disorder.

**2022. January:** On January 12, the FDA issued a [Drug Safety Communication](#) warning of reported dental problems associated with medicines containing buprenorphine that are dissolved in the mouth. The dental problems include tooth decay, cavities, oral infections, and loss of teeth, and have been reported even in patients with no history of dental issues. The agency required a new warning about the risk of dental problems be added to the prescribing information and the patient [Medication Guide](#) for all buprenorphine-containing medicines dissolved in the mouth.

**February:** On February 9, the FDA published the draft guidance for industry, [Development of Non-Opioid Analgesics for Acute Pain](#), which is intended to provide recommendations to companies developing non-opioid analgesics for acute pain lasting up to 30 days, typically in

response to some form of tissue injury, such as trauma or surgery. This guidance supports the [HHS Overdose Prevention Strategy](#).

On February 15, the FDA convened a [joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee](#) to discuss new drug application 213231, for tramadol hydrochloride injection, submitted by Avenue Therapeutics, Inc., for the management of moderate to moderately severe pain in adults in a medically supervised healthcare setting. The committees also discussed the clinical relevance of tramadol hydrochloride injection (an opioid intended for management of acute pain in a medically supervised healthcare setting), when its onset of action is delayed, and its proposed dosing is a fixed-dosing regimen.

On February 28, the FDA approved a military-usage and chemical incident response indication for a [naloxone hydrochloride auto-injector](#) product to treat opioid overdose.

**March:** On March 29, through a cooperative agreement with the FDA, the Reagan-Udall Foundation hosted a public meeting, [Naloxone Access: Answering Questions](#), to explore some of the most frequently asked questions about access to naloxone, a drug used to reverse opioid overdoses.

**April:** On April 4-5, through a cooperative agreement with the FDA, the Duke-Margolis Center hosted a public workshop, [Identifying Key Competencies for Opioid Prescriber Education](#), which focused on identifying gaps in the content of existing opioid prescriber education offerings and core competencies that should be included in educational content for opioid prescribers and other healthcare providers, including prescriber education under a Risk Evaluation and Mitigation Strategy (REMS).

On April 20, FDA [published](#) a Federal Register notice seeking public comment on a potential change that would require opioid analgesics used in outpatient settings to be dispensed with prepaid mail-back envelopes and that pharmacists provide patient education on safe disposal of opioids.

**May:** On May 31, the FDA, in collaboration with Harvard University and Massachusetts General Hospital, published the research article, [Modeling the evolution of the US opioid crisis for national policy development](#), which discusses FDA's initiative to develop a data-driven, national-level simulation model of the opioids system, named SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects) and includes baseline projections of the opioid crisis – opioid misuse rates, prevalence of opioid use disorder and overdose deaths – over the next ten years, across different scenarios.

**June:** On June 21, FDA [approved the second generic naloxone intranasal spray](#) to treat opioid overdose.

On June 27, the FDA, in collaboration with Harvard University and Massachusetts General Hospital, published the research article, [Reducing opioid use disorder and overdose deaths in the](#)

[United States: A dynamic modeling analysis](#), which discusses FDA's initiative to develop a data-driven, national-level simulation model of the opioids system, named SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects) and describes an initial analysis of 11 high-level interventions and the effects that SOURCE projects those interventions may have on the crisis.

On June 30, the FDA, in collaboration with the Federal Trade Commission, issued warning letters to four companies selling unapproved kratom products and one company selling essential oils for the treatment or cure of opioid use disorder and withdrawal symptoms. The companies that received warning letters are: [Herbsens Botanicals](#), [Klarity Kratom](#), [Kratom Exchange](#), [Omni Consumer Products LLC d/b/a YoKratom](#) and [MONQ, LLC](#).

**August:** On August 23, the FDA issued a [warning letter](#) to the operator of 25 websites illegally selling unapproved and misbranded opioids and benzodiazepines to U.S. consumers in violation of the Federal Food, Drug, and Cosmetic Act.

On August 30, the FDA announced the establishment of the [FDA Overdose Prevention Framework](#). The framework details FDA's vision to undertake impactful, creative actions to prevent drug overdoses and reduce deaths through initiatives and activities nested within four priorities: (1) supporting primary prevention by eliminating unnecessary initial prescription drug exposure and inappropriate prolonged prescribing; (2) encouraging harm reduction through innovation and education; (3) advancing development of evidence-based treatments for substance use disorders; and (4) protecting the public from unapproved, diverted or counterfeit drugs presenting overdose risks. The Overdose Prevention Framework supports the [HHS Overdose Prevention Strategy](#).

**September:** On September 12, the FDA awarded a [cooperative agreement](#) to support an evidence-based clinical practice guideline for the safe tapering of benzodiazepines.

On September 15, the FDA awarded a [cooperative agreement](#) to support the development of an evidence-based clinical practice guideline for the management of post-operative pain in obstetric patients. The purpose of this guideline is to promote appropriate opioid prescribing in obstetric patients who have undergone surgery.

On September 22, the FDA published the immediately-in-effect guidance, [Exemption and Exclusion from Certain Requirements of the Drug Supply Chain Security Act \(DSCSA\) for the Distribution of FDA-Approved Naloxone Products During the Opioid Public Health Emergency](#), which is intended to clarify the scope of the public health emergency (PHE) exclusion and exemption under the [DSCSA](#) as they apply to the distribution of FDA-approved naloxone products to harm reduction programs during the opioid PHE. This guidance supports the [FDA Overdose Prevention Framework](#).

On September 30, the FDA [published an update](#) on actions the agency has taken to align with the National Academies for Sciences, Engineering, and Medicine's (NASEM) recommendations regarding *Opioid Approval and Monitoring by the FDA*.

**October:** On October 11, through a cooperative agreement with the FDA, the Duke-Margolis Center hosted a public workshop, [Challenges and Opportunities for REMS Integration](#),

[Innovation, and Modernization](#), to solicit feedback from key stakeholders on a Risk Evaluation and Mitigation Strategies (REMS) integration prototype.

**November:** On November 8, the FDA issued an [alert to health care professionals](#) warning of possible xylazine inclusion in fentanyl, heroin, and other illicit drug overdoses, as naloxone may not be able to reverse its effects and the FDA is aware of increasing reports of serious side effects from individuals exposed to fentanyl, heroin, and other illicit drugs contaminated with xylazine.

On November 15, the FDA [issued a Federal Register notice](#) to alert application holders of certain prescription naloxone drug products aware of the agency's preliminary assessment and the possibility that the agency may make a conclusive determination, through approval of a nonprescription naloxone drug product, that such products are safe and effective for use without a prescription.

On November 28, the FDA held a [stakeholder call](#) to discuss naloxone access and affirm the agency's commitment to support the efforts of harm reduction groups to acquire FDA-approved naloxone products.

**2023. January:** On January 30, the *Drug and Alcohol Dependence* Journal article co-authored by FDA entitled, "[Concordance between controlled substance receipt and post-mortem toxicology in opioid-detected overdose deaths: A statewide analysis](#)," was published.

**February:** On February 13, the *Pharmacoepidemiology and Drug Safety* Journal article authored by FDA entitled, "[The impact of hydrocodone rescheduling on utilization, abuse, misuse, and overdose deaths](#)," was published.

On February 15, the FDA convened a [joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee](#) to discuss supplemental new drug application 208411/S-006, for NARCAN (naloxone hydrochloride) nasal spray, indicated for nonprescription treatment of known or suspected opioid overdose.

On February 16, the FDA [published the results](#) of Ohio State University's [External Review of FDA Regulation of Opioid Analgesics](#). The review analyzed the FDA's implementation of the 2017 National Academies for Sciences, Engineering, and Medicine's (NASSEM) recommendations along with key regulatory policies and decisions, including labeling.

On February 28, the FDA [announced an action](#) to restrict the unlawful entry of xylazine active pharmaceutical ingredients and finished dosage form drug products into the United States.

**March:** On March 7, the FDA [approved a naloxone intranasal spray](#) to treat opioid overdose.

On March 8-9, through a cooperative agreement with the FDA, the Reagan-Udall Foundation for the FDA hosted a public meeting, [Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose](#), to explore the evolving context surrounding fatal overdoses and discuss epidemiological trends, drug supply changes, public health interventions to manage overdose, and drug development opportunities.



On March 16, the FDA published the draft guidance for industry, [Development of Local Anesthetic Drug Products With Prolonged Duration of Effect](#), which is intended to provide the agency's recommendations for assisting developers in generating the data necessary to support different indications and labeling claims for these drugs.

On March 29, the FDA [approved the first over-the-counter naloxone nasal spray](#), thereby expanding access and availability of the first-line treatment used for opioid overdose.

On March 30, the FDA held a [stakeholder call](#) to discuss expanding access to naloxone following the approval of the first over-the-counter naloxone nasal spray.

**April:** On April 3, the FDA [announced](#) it is requiring manufacturers of opioid analgesics dispensed in outpatient settings to make prepaid mail-back envelopes available to outpatient pharmacies and other dispensers as an additional opioid analgesic disposal option for patients.

On April 13, the FDA issued a [Drug Safety Communication](#) and a [statement](#) announcing several updates to the prescribing information for immediate-release and extended-release/long-acting opioid analgesics. The updates also included a new warning about opioid-induced hyperalgesia, which is a condition where opioids cause an increase in pain (hyperalgesia) or an increased sensitivity to pain (allodynia).

On April 19, the FDA convened a [joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee](#) to discuss postmarketing requirement (PMR) 3033-11, issued to application holders of new drug applications for extended-release and long-acting opioid analgesics to evaluate long-term efficacy of opioid analgesics and the risk of opioid-induced hyperalgesia.

**May:** On May 9, the FDA and the Substance Abuse and Mental Health Services Administration issued a [joint letter](#) to health care providers intended to clarify buprenorphine prescribing recommendations.

On May 10-11, through a cooperative agreement with the FDA, the Reagan-Udall Foundation for the FDA hosted a public meeting, [Considerations for Buprenorphine Initiation and Maintenance Care](#), to explore real-world experiences and scientific evidence for buprenorphine initiation strategies as well as medication dosing and management during continued treatment across different care settings.

On May 11, the FDA issued a [Drug Safety Communication](#) and a [statement](#) announcing updates for amphetamine and methylphenidate products, a class of stimulant medications used to treat attention deficit/hyperactivity disorder (ADHD) and other disorders, to standardize prescribing information. The updates intend to inform patients, caregivers and health care professionals of risks associated with their medications, and address misuse and abuse (also called nonmedical use), addiction, and overdose information.

On May 22, the FDA [approved a nalmefene intranasal spray](#) to treat opioid overdose.

On May 23, the FDA [approved an extended-release buprenorphine injection](#) to treat moderate to severe opioid use disorder.

**June:** On June 8, the FDA hosted internet stakeholders, regulatory organizations, academia, and other important stakeholders at its fourth [Online Controlled Substances Summit](#), (formerly the “Online Opioid Summit”).

On June 20-21, the FDA announced the opening of two Notice of Funding Opportunities (NOFOs) to encourage applications to support the development of evidence-based, clinical practice guidelines for the management of [acute low back pain](#), and [acute postoperative pain in patients who have undergone diagnostic and procedural laparoscopic abdominal surgeries](#). These NOFOs support the FDA’s primary prevention priority under the [Overdose Prevention Framework](#).

On June 23, the FDA [announced](#) issuance of its first draft guidance presenting considerations to industry for designing clinical trials for psychedelic drugs, [Psychedelic Drugs: Considerations for Clinical Investigations](#). The guidance intends to highlight fundamental considerations to researchers investigating the use of psychedelic drugs for potential treatment of medical conditions, including psychiatric or substance use disorders.

On June 26-27, the FDA participated in the National Academies of Sciences, Engineering, and Medicine’s public workshop, [Defining and Evaluating In-Home Drug Disposal Systems for Opioid Analgesics](#). The workshop provided an opportunity for stakeholders to examine in-home drug disposal options, with a focus on removing unused opioid analgesics from the home.

**July:** On July 6, the FDA [approved the first generic application for naltrexone extended-release injectable suspension](#), indicated to treat alcohol and opioid use disorder.

On July 18, the FDA [approved the first generic over-the-counter naloxone nasal spray](#) to treat opioid overdose.

On July 27, the FDA announced issuance of a draft guidance to help facilitate innovation in devices intended to treat opioid use disorder, [Clinical Considerations for Studies of Devices Intended to Treat Opioid Use Disorder](#). The guidance will help sponsors design clinical studies to evaluate these devices, and further [FDA’s Overdose Prevention Framework](#) goal of advancing evidence-based treatment for those with substance use disorders.

On July 28, the FDA [approved the second branded over-the-counter naloxone nasal spray](#) to treat opioid overdose.

**August:** On August 25, the American Dental Association Science and Research Institute, the University of Pittsburgh School of Dental Medicine, and the Center for Integrative Global Oral Health at the University of Pennsylvania School of Dental Medicine issued a [new clinical practice guideline detailing dental pain management strategies for children](#). The development of this guideline was funded by an FDA-provided grant following an FDA-commissioned report by the National Academies of Science, Engineering, and Medicine that recommended that the guideline be developed.

**September:** On September 15, the FDA awarded cooperative agreements to support the development of two evidence-based clinical practice guidelines: one for the management of [acute low back pain](#), and another for the management of acute postoperative pain in patients who have undergone diagnostic and procedural [laparoscopic abdominal surgeries](#).

## Acronyms List

### **ACTION**

Analgesic Clinical Trial Translation, Innovations, Opportunities and Networks

### **ALERTT**

Abuse Liability Evaluation for Research, Treatment, and Training

### **ALSDAC**

Anesthetic and Life Support Drugs Advisory Committee

### **CARES**

Consortium for Addiction Research on Efficacy and Safety

### **CDC**

Centers for Disease Control and Prevention

### **CDER**

Center for Drug Evaluation and Research

### **COT**

Chronic Opioid Therapy

### **CSAT**

Center for Substance Abuse Treatment

### **DEA**

Drug Enforcement Administration

### **DSaRM**

Drug Safety and Risk Management Advisory Committee

### **ER**

Extended Release

### **FDA**

Food and Drug Administration

**FDAAA**

Food and Drug Administration Amendments Act

**IWG**

Industry Working Group

**LA**

Long Acting

**MG**

Medication Guide

**NIDA**

National Institute on Drug Abuse

**ONDCP**

Office of National Drug Control Policy

**OPR**

Opioid Pain Relievers

**PDMP**

Prescription Drug Monitoring Program

**PPI**

Patient Package Insert

**REMS**

Risk Evaluation and Mitigation Strategies

**RESOLVE**

Randomized Enrollment Study of Opioid Long-term use to evaluate Efficacy

**RMP**

Risk Management Program

**SAMHSA**

Substance Abuse and Mental Health Services Administration

**SBIRT**

Screening, Brief Intervention and Referral to Treatment

**TIRF**

Transmucosal Immediate-Release Fentanyl

**TRIG**

Transmucosal Immediate-Release Fentanyl REMS Industry Group

**UDT**

Urine Drug Testing

**VA**

Veterans Affairs