

Timeline of Selected FDA Activities & Significant Events Addressing Opioid Misuse & Abuse

This document provides chronological information regarding FDA activities and significant events relating to opioids, including abuse and misuse. Below is a summary timeline of key events followed by a more extensive chronology, which includes selected additional actions and more detail about the items listed in the summary.

Summary Timeline: “At a Glance...”

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.

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](#) 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 designed to deter abuse.

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 On January 9, FDA issued a draft guidance document to assist industry in developing new formulations of opioid drugs with abuse-deterrent properties: [Guidance for Industry: Abuse-Deterrent Opioids –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

On January 24-25, FDA held a [meeting of its Drug Safety and Risk Management Advisory Committee](#) 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.

On February 7-8, FDA held a public hearing 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](#).

On 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.

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

On May 10, FDA responded to a citizen 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.

On July 29, FDA held the [Clinical Development Programs for Opioid Conversion: Public Workshop](#). 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](#). 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.

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.

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 and has 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), which were approved in April 2014.

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. 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.

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

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: 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 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.

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.

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.

On August 19, FDA approved [Troxyc 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. Troxyc 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. Troxyc 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.

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.

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.

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.

Detailed Timeline...

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.

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](#) 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.

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](#).)

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](#) designed to deter abuse associated with crushing the tablet.

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](#) (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*](#), a comprehensive action plan to address the national prescription drug abuse epidemic.

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

June: Oxecta (oxycodone hydrochloride) approved; the first immediate-release oxycodone tablet designed to deter abuse by resisting physical and chemical manipulation. It also includes a chemical to irritate the nose of abusers who try to snort the drug.

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), designed to deter abuse through resistance to physical and chemical manipulation of the drug.

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.

June: The Randomized Enrollment Study of Opioid Long-term use to eValuate Efficacy (RESOLVE) working group, under the auspices of ACTTION (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: ACTTION 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 ACTTION. 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.

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.

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.

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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: On January 9, FDA issued a draft guidance document 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](#), 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: On January 24-25, FDA held a [meeting of its Drug Safety and Risk Management Advisory Committee](#) 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: On February 7-8, FDA held a public hearing 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: On 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: On April 16, FDA took [multiple actions related to OxyContin](#).

May: 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.

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

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 9, FDA issued a [drug safety communication](#) on the possible risks of pain medicine use during pregnancy.

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 [final guidance](#) to assist industry in developing opioid drug products with potentially abuse-deterrent properties. "Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling" 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.

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 and 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, FDA announced that during the April 12 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 [Science Board to the FDA](#) heard about and discussed: (1) the role of opioids in pain management; (2) scientific challenges facing FDA in supporting the development of pain medications, including opioids, that have reduced risks of being abused; (3) scientific challenges facing FDA in seeking to understand the real-world use of opioids to treat pain, including the impact of opioids with potentially less risk for abuse; (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.

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 \(CNS\) 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.

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.

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.

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.

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