



## **Recent Advances in Opioid Abuse Deterrent Formulations (ADF)**

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### **Disclosure**

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- Consultant/Independent Contractor:  
Collegium, Eaglet, Millennium Labs, Quest Diagnostic
- Honoraria: AZ, Daiichi, Pernix, St. Judd (Abbott)



## Learning Objectives

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- Summarize the current trends in opioid abuse, including the source of abused opioids and the various ways opioids are abused
- Explain the FDA's criteria for an opioid having the product label "abuse deterrent"
- Differentiate between current and pipeline technologies for abuse deterrence



## Agenda

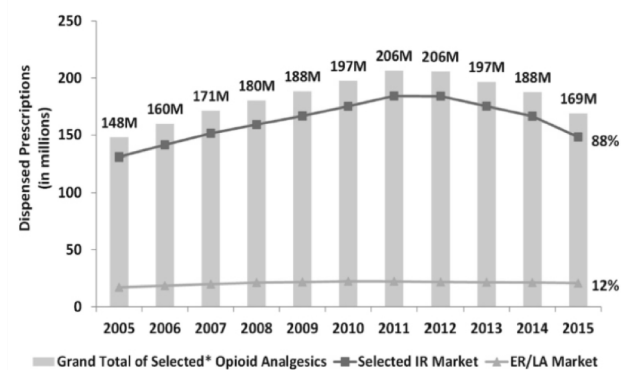
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- Scope of Opioid Abuse, Misuse and Diversion
- Common Clinician Abuse Misconceptions
- Current Abuse Deterrent Strategies
- Future Pipeline Technologies
- Conclusion



## Healthcare Prescription Trends

- Opioid Sales increased almost 4x 1999 – 2008
- Noncancer Pain represents 20% of Primary Care visits
  - Opioid prescriptions Increased 170% from 2000 – 2010
  - Around 1 in 5 with pain received opioid prescription
- Current trends are decreasing prescriptions
  - MME 782 mg down to 640 mg (per capita)
  - 2015 still 3x MME compared to 1999



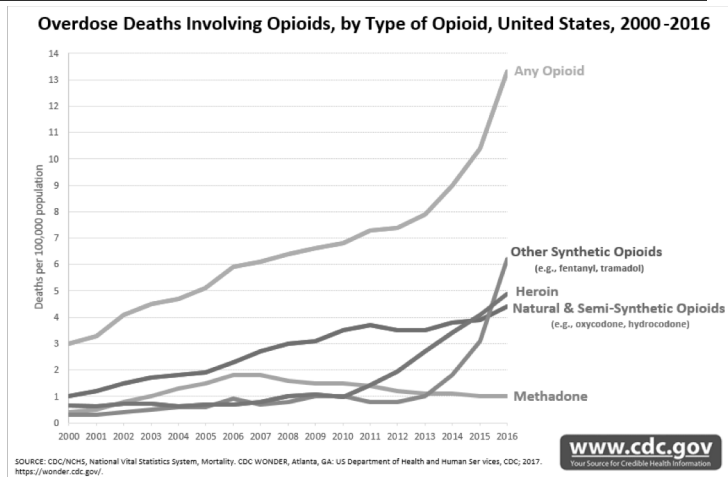
ER/LA opioid molecules include buprenorphine transdermal patch, fentanyl transdermal patch, hydrocodone ER, hydromorphone ER, morphine ER, oxycodone ER, oxymorphone ER, tapentadol ER, and methadone (all approved and marketed ER/LAs at the time). IR opioid molecules include hydrocodone IR combination analgesics (hydrocodone in combination with acetaminophen, ibuprofen, or aspirin), oxycodone IR combination analgesics (oxycodone in combination with acetaminophen, ibuprofen, or aspirin), oxycodone IR, hydromorphone IR, morphine IR, tapentadol IR, and oxymorphone IR. Buprenorphine indicated for medication-assisted treatment is not included.

1. Daubresse M, Chang HY, Yu Y, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000–2010. *Med Care*. 2013;51(10):870–878.
2. Centers for Disease Control and Prevention, (CDC). Vital signs: Overdoses of prescription opioid pain relievers—United States, 1999–2008. *MMWR Morb Mortal Wkly Rep*. 2011;60(43):1487–1492.
3. Guy GP, Jr, Zhang K, Bohm MK, et al. Vital signs: Changes in opioid prescribing in the United States, 2006–2015. *MMWR Morb Mortal Wkly Rep*. 2017;66(26):697–704.
4. Staffa. *Overview of the prescription opioid epidemic and the FDA activities to address it*. Presentation at DIA/FDA statistics forum; 2017.

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## Scope of Problem

- Opioid related harms have continued to increase
- Between 1999 – 2016 an est. 200,000 Americans died from opioid poisoning
- Fentanyl and synthetics increasingly associated with overdose deaths



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2017. <https://wonder.cdc.gov/>

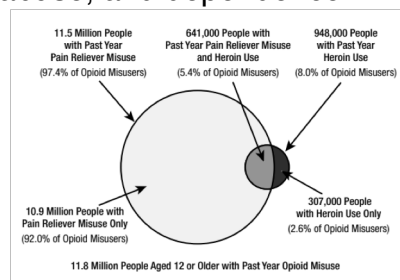
**www.cdc.gov**  
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1. Hedegaard H, Warner M, Minino AM. Drug overdose deaths in the United States, 1999–2016. *NCHS Data Brief*. 2017;(294):1–8.
2. O'Donnell J, Gladden RM, Mattson CL, Kariisa M. Notes from the field: Overdose deaths with carfentanyl and other fentanyl analogs detected – 10 states, July 2016–June 2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(27):767–768.

## Scope of Problem

- 2016 – Prescription and illicit opioids caused > 40,000 deaths
- Over 1000 Emergency Department visits daily for prescription opioid abuse
- Estimated \$78.5 Billion annually for overdose, abuse, and dependence
- National Drug Use and Health Survey 2016
  - 11.5 million (Age >12) misused prescription pain reliever in last year
  - 948,000 used heroin



1. Hedegaard H, Warner M, Minino AM. Drug overdose deaths in the united states, 1999-2016. *NCHS Data Brief*. 2017;(294):1-8.
2. Substance Abuse and Mental Health Services Administration. Highlights of the 2011 drug abuse warning network (DAWN) findings on drug-related emergency department visits. <https://www.samhsa.gov/data/sites/default/files/DAWN127/DAWN127/sr127-DAWN-highlights.pdf>. 2013.
3. Florence CS, Zhou C, Luo F, Xu L. The economic burden of prescription opioid overdose, abuse, and dependence in the united states, 2013. *Med Care*. 2016;54(10):901-906.
4. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the united states: Results from the 2016 national survey on drug use and health (HHS publication no. SMA 17-5044, NSDUH series H-52). . 2017. <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf>.

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## Multiple Concomitant Actions

- U.S. National Public Health Emergency Declaration – October 2017
- Centers for Disease Control Opioid Treatment Guidelines – March 2016
- Multiple States Expanding Prescription Drug Monitoring Programs
- Multiple Legislative Mandates on prescribing and monitoring
- FDA Guidance on Abuse Deterrent Formulation of Opioids – 2015
- Opioid Education requirements from FDA
- Increased access for Medication-assisted Treatment of Opioid Addiction
- Greater Naloxone access
- Good Samaritan Laws when treating opioid overdose
- Drug Take-back days and safe disposal

1. Hargan, Eric D. (Acting Secretary). Determination that a public health emergency exists. <https://www.hhs.gov/sites/default/files/opioid%20PHE%20Declaration-no-sig.pdf>. 2017.
2. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain - united states, 2016. *MMWR Recomm Rep*. 2016;65(1):1-49.
3. Wickramatilake S, Zur J, Mulvaney-Day N, Klimo MC, Selmi E, Harwood H. How states are tackling the opioid crisis. *Public Health Rep*. 2017;132(2):171-179.
4. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids —evaluation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. 2015.

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## Definitions

### ▪ Misuse (inappropriate use)

Use in any way not directed by a doctor, including:

- use without a prescription of one's own
- use in greater amounts, more often, or longer than told to take a drug
- use in any other way not directed by a doctor

### ▪ Abuse (use for psychological or non-therapeutic physiological effect)

One or more of the following:

- problems at work, home, and school because of use of the drug
- regularly using the drug and then doing something physically dangerous
- repeated trouble with the law because of use of the drug
- continued use of the drug despite problems with family or friends.

### ▪ Non-medical Use (outdated term – pre 2015 NSDUH data)

Use without a prescription of the individual's own or simply for the experience or feeling the drugs caused



1. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality. Results from the 2013 national survey on drug use and health: Summary of national findings. <https://www.samhsa.gov/data/sites/default/files/NSDUHresultsPDFWHHTML2013/Web/NSDUHresults2013.pdf>. 2014.
2. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the united states: Results from the 2016 national survey on drug use and health (HHS publication no. SMA 17-5044, NSDUH series H-52). 2017. <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf>.

## Definitions

### ▪ Dependence (>3 criteria met)

1. spent a lot of time engaging in activities related to use of the drug
2. used the drug in greater quantities or for a longer time than intended
3. developed tolerance to the drug
4. made unsuccessful attempts to cut down on use of the drug
5. continued to use the drug despite physical health or emotional problems associated with use
6. reduced or eliminated participation in other activities because of use of the drug
7. experienced withdrawal symptoms when respondents cut back or stopped using the drug

### ▪ Diversion

Illegal distribution of prescription drugs



1. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the united states: Results from the 2016 national survey on drug use and health (HHS publication no. SMA 17-5044, NSDUH series H-52). 2017. <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf>.
2. U.S Department of Health and Human Services, Centers for Medicare and Medicaid Services. Partners in integrity. what is a prescriber's role in preventing the diversion of prescription drugs? <https://www.cms.gov/medicare-medicare-coordination/fraud-prevention/medicaid-integrity-education/provider-education-toolkits/downloads/prescriber-role-drugdiversion.pdf>. Accessed July 8, 2018.

## Patient Risk Stratification

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- History & Physical Exam
  - Risks for abuse, misuse and diversion
  - Screening Instruments (ORT, SOAP-R)
  - Psychosocial and Family History
- Benefit to Harm considerations
- Toxicology Testing
- Prescription Drug Monitoring Programs
- Review of relevant medical records
- Abuse deterrent opioid formulations



1. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009;10(2):113-130.
2. Webster L, St BM, McCarberg B, Passik SD, Panchal SJ, Voth E. Current status and evolving role of abuse-deterrent opioids in managing patients with chronic pain. *Journal of opioid management*. 2011;7(3):235-245.

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## Common Clinician Abuse Misconceptions



## Select Misconceptions

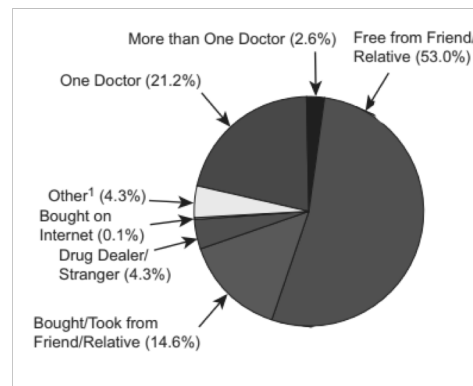
- **Misconception:** Source of opioids for abuse:
  - Majority of abuse is in patients receiving their own prescriptions
  - Doctor shopping is a common way opioids are obtained for nonmedical use or misuse
  - Most reported misuse is individuals trying to “get high”
- **Misconception:** Routes of abuse:
  - Tampering of opioids represents a minority of abusers
  - Changing the route (e.g. snorting oral tablets) is uncommon
- **Misconception:** Abuse deterrent formulation of opioids:
  - ADF are less addictive
  - ADF cannot be abused



Volkow ND, McLellan AT. Opioid abuse in chronic pain—misconceptions and mitigation strategies. *N Engl J Med*. 2016;374(13):1253-1263.

## 2013 Source of Opioids for Nonmedical Use (>12yo)

- Final year survey asked about only "nonmedical" use:
  - use without a prescription of the individual's own or simply for the experience or feeling the drugs caused
  - 6.5 million nonmedical users
  - 76.2% obtained **WITHOUT** a prescription
  - Greatest source (53%) was Diverted from Friends and Family
  - 2.6% Doctor Shopping



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality. Results from the 2013 national survey on drug use and health: Summary of national findings. <https://www.samhsa.gov/data/sites/default/files/NSDUHResultsPDEWHTML2013/Web/NSDUHResults2013.pdf>. 2014.

## 2016 Source of Opioids for Misuse (>12yo)

- Surveyed about misuse, not non-medical use

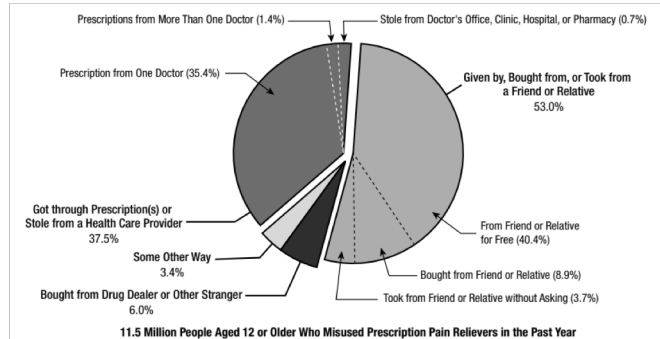
- use in any way not directed by a doctor, including use without a prescription of one's own; use in greater amounts, more often, or longer than told to take a drug; or use in any other way not directed by a doctor.

- 11.5 million misusers

- 62.5% obtained WITHOUT prescription

- Greatest source (53%) was Diverted from Friends and Family

- 1.4% Doctor shopping

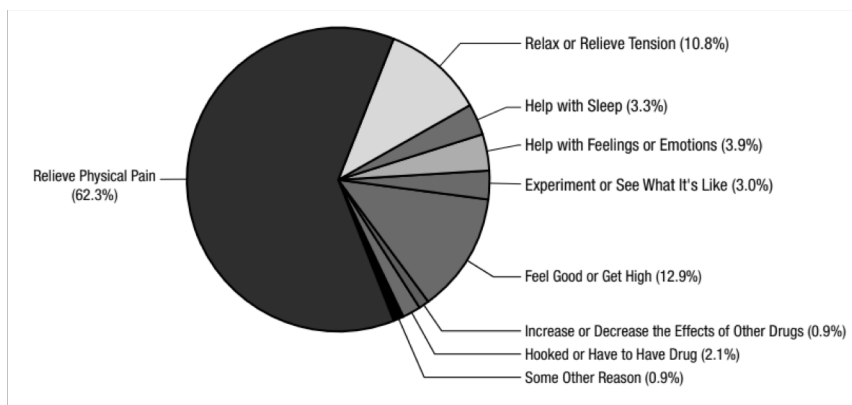


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Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the united states: Results from the 2016 national survey on drug use and health (HHS publication no. SMA 17-5044, NSDUH series H-52). 2017. <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf>

## 2016 Reason for Most Recent Opioid Misuse (>12yo)

- >2 million misusers took specifically to feel good, get high, experiment or were "hooked"



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Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the united states: Results from the 2016 national survey on drug use and health (HHS publication no. SMA 17-5044, NSDUH series H-52). 2017. <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf>



## Diversion

- Primary source of opioid for misuse
  - mostly from Friends and Family (53%)
- West Virginia Example:
  - Overdose death data:
    - 63% of deaths from pharmaceutical diversion
    - Deaths in 18-24 y.o. were 91% from diversion
    - 95% involved nonmedical route of exposure



1. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the united states: Results from the 2016 national survey on drug use and health (HHS publication no. SMA 17-5044, NSDUH series H-52). 2017. <https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf>

2. Hall AJ, Logan JE, Toblin RL, et al. Patterns of abuse among unintentional pharmaceutical overdose fatalities. *JAMA*. 2008;300(22):2613-2620.

## Nonmedical Routes and Tampering

- Purpose of manipulating prescription opioids:
  - Enhance psychoactive effects
  - Accelerated onset of action and peak exposure
  - Defeating extended release opioids for dose dumping
- Common Tampering strategies:
  - Crushing tablets or oral/intranasal use
  - Liquefying in preparation for injection



1. Green JL, Bucher Bartelson B, Le Lait MC, et al. Medical outcomes associated with prescription opioid abuse via oral and non-oral routes of administration. *Drug Alcohol Depend*. 2017;175:140-145.

2. Katz N, Dart RC, Bailey E, Trudeau J, Osgood E, Paillard F. Tampering with prescription opioids: Nature and extent of the problem, health consequences, and solutions. *Am J Drug Alcohol Abuse*. 2011;37(4):205-217.

## Routes of Abuse

### Oral

- 66-97% of abusers
- Swallow whole (most common)
- Crush/Chew



### Inhalation

- 6-52% of abusers
- Crush/Snorting
- Crush/Smoke



### Injection

- 0.5-28% of abusers
- Intravenous
- Intramuscular
- Subcutaneous



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Katz N, Dart RC, Bailey E, Trudeau J, Osgood E, Paillard F. Tampering with prescription opioids: Nature and extent of the problem, health consequences, and solutions. *Am J Drug Alcohol Abuse*. 2011;37(4):205-217.

## History of Abuse Deterrent Opioids

CDC Testifies to Senate Subcommittee on Crime and Drug:

"... drug manufacturers should modify opioid painkillers so that they are more difficult to tamper with and/or combine them with agents that block the effect of the opioid if it is dissolved and injected."

FDA produces draft guidance to industry on abuse deterrent opioid

2008

2010

2013

2015

FDA Approves reformulated OxyContin with Abuse Deterrent Label

FDA publishes "Abuse-Deterrent Opioids — Evaluation and Labeling: Guidance for Industry"

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Generation Rx: The Abuse of Prescription and Over-the-Counter Drugs: Hearings before the Committee of the Judiciary, Joint Subcommittee on Crime and Drug and Caucus on International Narcotic Control, Senate, 110<sup>th</sup> Cong., (March 12, 2008) (Testimony of Leonard J. Paulozzi, M.D., M.P.H). [https://www.judiciary.senate.gov/imo/media/doc/paulozzi\\_testimony\\_03\\_12\\_08.pdf](https://www.judiciary.senate.gov/imo/media/doc/paulozzi_testimony_03_12_08.pdf)  
U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

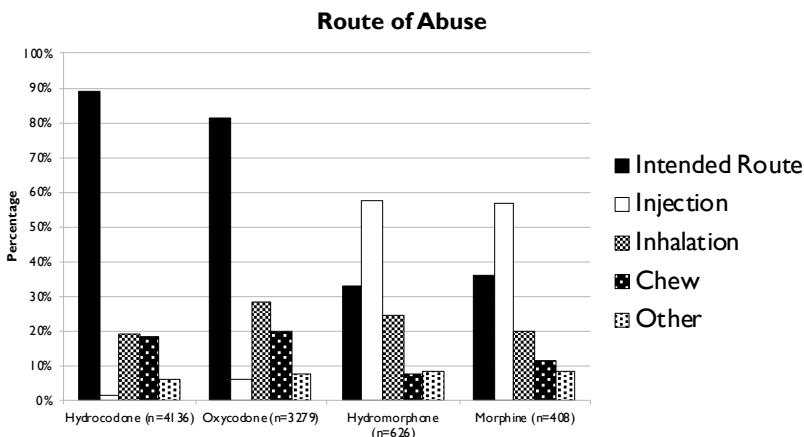
## Reported Route of Abuse (2009)

### ■ Treatment Admissions

- 34 States
- 464 Facilities
- 59,792 admissions

### ■ Tampering reported

- 45% Hydrocodone
- 62% Oxycodone
- 98% Hydromorphone
- 96% Morphine



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Butler SF, Black RA, Cassidy TA, Dailey TM, Budman SH. Abuse risks and routes of administration of different prescription opioid compounds and formulations. *Harm Reduct J.* 2011;8:29.

## Drug Specific Route Variations in Abuse

Preferred Route of Abuse ↑

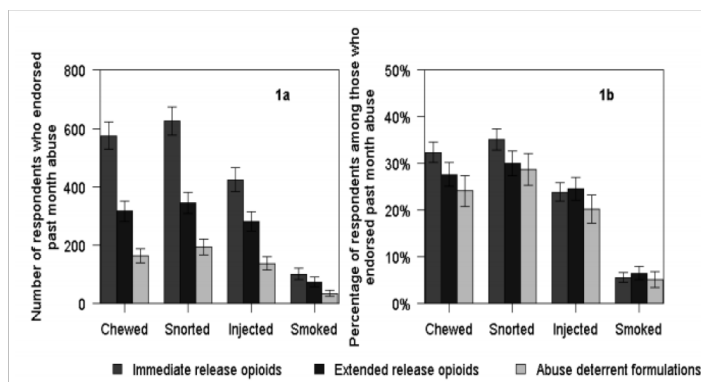
Intended Route	Injection	Inhalation	Chew
Hydrocodone	Morphine	Oxymorphone	Oxycodone
Oxycodone	Hydromorphone	Oxycodone	Hydrocodone
Oxymorphone	Oxymorphone	Hydromorphone	Fentanyl
Morphine	Fentanyl	Morphine	Morphine
Hydromorphone	Oxycodone	Hydrocodone	Oxymorphone
Fentanyl	Hydrocodone	Fentanyl	Hydrocodone

**PainWeek**

Butler SF, Black RA, Cassidy TA, Dailey TM, Budman SH. Abuse risks and routes of administration of different prescription opioid compounds and formulations. *Harm Reduct J.* 2011;8:29.

## Routes of Abuse (2017)

- RADARS data from 48 States
- >60% of IR/ER opioids reported tampering
- (ADF only OxyContin®, Hysingla® ER, and EMBEDA®)
- Snorting was most frequent



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Severtson SG, Olsen HA, Ellis MS, Cicero TJ, Green JL, Dart RC. Prevalence of chewing, snorting, injecting, and smoking prescription opioid tablets/capsules among individuals entering treatment for an opioid use disorder. *RADARS® System Technical Report*. 2017, Q1. [https://www.radars.org/system/publications/2017%201Q%20QTR\\_1.pdf](https://www.radars.org/system/publications/2017%201Q%20QTR_1.pdf).

FDA Guidance to Industry 2015

## Current Abuse Deterrent Strategies

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## FDA Guidance to Industry on ADF (2015)

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*“One potentially important step towards the goal of creating safer opioid analgesics has been the development of opioids that are formulated to deter abuse.”*

*“FDA considers the development of these products a high public health priority.”*

*“FDA encourages additional scientific and clinical research that will advance the development and assessment of abuse-deterrent technologies.”*



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

## Important Considerations

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- Technology do not yet deter most common form of abuse – swallowing whole products
- Abuse deterrent products do not mean the products can't be abused
- Products must still provide opioid when prescribed



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

## FDA Categories of Abuse Deterrent Technology

- Physical/Chemical barrier
  - Agonist/antagonist combination
  - Aversion
  - New molecular entities and prodrugs
  - Delivery system
  - Combination
  - Novel approaches
- All current technologies



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

## Physical/Chemical Barriers

- Prevent:
  - Chewing
  - Crushing
  - Cutting
  - Grating
  - Grinding
- Add gelling agents
- Resist solvents like water, simulated biological media, alcohol, or other organic solvents
- Limit drug release following mechanical manipulation or change the physical form of a drug



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

## Current forms of Physical/Chemical Barriers

- Polyethylene glycol (PEO)
  - Does not fracture under mechanical stress
  - Viscous in water with poor syringeability
  - Insoluble in most household products
- Superabsorbents
  - Technology exposed only with tampering
  - Absorb large quantities of water
- Fat/Wax Coating
  - Prevent extraction from low solubility in ethanol
  - Crush resistance
  - Control drug release



1. Zhang F, McGinity JW. Properties of sustained-release tablets prepared by hot-melt extrusion. *Pharm Dev Technol.* 1999;4(2):241-250.
2. Shah M, Difalco R, inventors; ABUSE DETERRENT PHARMACEUTICAL LLC. Abuse Resistant Drugs, Method of Use and Method of Making. February 19, 2009.
3. Walid A. Habib, Ehab Hamed, Manuel A. Vega Zepeda, inventors. Abuse resistant drug formulation. patent 8445018. May 21, 2013.

## Agonist/Antagonist Combinations

- Add antagonist to interfere with, reduce, or defeat euphoria
- Antagonist can be sequestered and release upon manipulation



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

## Current forms of Chemical Barriers

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- Addition of antagonist (naloxone or naltrexone)
  - Oral first pass metabolism effects all but 2% of naloxone
  - Non-oral (intranasal/inject) blocks opioid effects
- Sequestered antagonist (naloxone or naltrexone)
  - Antagonist not absorbed when taken orally
  - Manipulation/tampering of product releases antagonist



Maincent J, Zhang F. Recent advances in abuse-deterrent technologies for the delivery of opioids. *Int J Pharm.* 2016;510(1):57-72.

## Aversion

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- Add substances to produce an unpleasant effect if manipulated or used at a dosage higher than directed
- For example:
  - Irritate nasal mucosa if ground and snorted



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.



## Delivery System

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- Drug release designs or method of drug delivery to resist abuse
- For example:
  - Sustained-release depot injectable formulations
  - Subcutaneous implant



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

## Clinical Studies

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- Must have a meaningful impact on overall abuse of the product
- Must be scientifically rigorous
  - Laboratory-based in vitro manipulation and extraction studies (Category 1)
  - Pharmacokinetic studies (Category 2)
  - Clinical abuse potential studies (Category 3)
  - Postmarket (Category 4)



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

## Laboratory Manipulation and Extraction Studies (Category 1)

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- Evaluate ease at which ADF can be defeated or compromised
  - Crushing
  - Chewing
  - Cutting
  - Mixing (Dose dumping with Alcohol)
  - Separating opioid antagonist
  - Defeating controlled release
  - Preparing for alternate routes of administration



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

## Laboratory Manipulation and Extraction Studies (Category 1)

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- Consider readily available items and particle size:
  - Spoons, cutters, coffee grinders
  - Heat/cold effects
  - Solubility
  - pH effects
  - Solvents:
    - Water, vinegar, ethanol, isopropanol, acetone, mineral spirits



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

## Pharmacokinetic Studies (Category 2)

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- Compare intact to manipulated formulations
- Consider risk to subjects based on excipients
- Only subjects with history of nasal abuse of opioids should be recruited for nasal studies
- Consider food and alcohol consumption effects



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

## Clinical Abuse Potential Studies (Category 3)

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- Blinding
  - Note: Subjects are recreational drug users
- Pre-qualification Phase
  - Subjects must be able to differential placebo and active opioid
- Assessment Phase
  - ADF compared to positive control
  - Positive control compared to placebo



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

## Clinical Abuse Potential Studies (Category 3)

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- Subjects
  - Must be opioid-experienced, recreational drug users, generally not physically dependent
- Route of Administration, Dose Selection, Manipulation Mode, and Sample Preparation
  - Based on epidemiological data for relevant route of abuse
  - Subject safety: Excipients may not be safe for IV use



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

## Clinical Abuse Potential Studies (Category 3)

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- Outcome measures
  - Visual Analogue Scales
    - Drug liking
    - Good effects
    - Bad effects
    - Likelihood to take drug again
  - Profile of Mood States
- Statistical Analysis



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

## Postmarket Studies (Category 4)

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- Does the ADF result in *meaningful* reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death
- FDA provides some guidance on study ideas



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

## Labeling

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- Label should reflect abuse-deterrent properties, as supported by data, and that abuse is still possible
- Limit data on ADF as demonstrated in premarketing studies and predictive quality
- Postmarket data, when available, should be added to labeling
- Label should describe specific routes of abuse that the product has been developed to deter
- Label may need revisions with new data



U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Abuse-deterrent opioids — valuation and labeling guidance for industry. <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf>. Updated 2015.

## Opioid Products with ADF in Label FDA Approval Dates

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- OXYCONTIN (oxycodone): New Formulation 2010
  - Physical/Chemical
- TARGINIQ ER (Oxycodone with Naloxone): July 23, 2014
  - Agonist/Antagonist
- EMBEDA (Morphine with Naltrexone): New Label October 17, 2014
  - Agonist/Antagonist
- HYSINGLA ER (Hydrocodone): November 20, 2014
  - Physical/Chemical
- MORPHABOND (Morphine): October 2, 2015
  - Physical/Chemical
- XTAMPZA ER (Oxycodone): April 26, 2016
  - Physical/Chemical
- ARMYO ER (Morphine): January 9, 2017
  - Physical/Chemical
- ROXYBOND (Oxycodone IR): April 20, 2017
  - Physical/Chemical



U.S. Food and Drug Administration Center for Drug Evaluation and Research. Postmarket drug safety information for patients and providers - abuse-deterrent opioid analgesics. <https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm600788.htm>. Updated 2018.

## Opioids without ADF Labeling, but have some ADF Properties

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- Exalgo
- Nucynta ER
- Oxaydo/Oxceta
- Xartemis XR
- Zohydro ER with BeadTek



## Category 4 Studies

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- No ADF has category 4 studies in product label
- Category 4 studies must demonstrate meaningful reductions in abuse, misuse, and related adverse clinical outcomes, including addiction, overdose, and death
- Reformulated OxyContin was approved in 2010
- No Category 4 label, but published studies have monitored postmarket abuse trends



## Reformulated OxyContin Postmarket Study

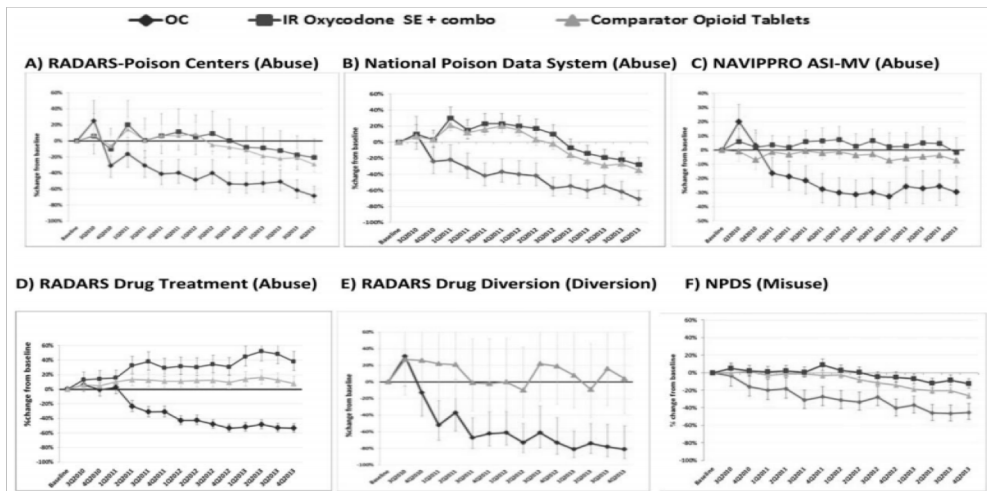
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- Abuse:
  - 48% decrease in National Poison Center surveillance systems
  - 32% decrease in national drug treatment system
  - 27% decrease in individuals prescribed OxyContin
- Doctor-shopping:
  - 50% decrease
- Overdose Fatalities:
  - 65% decrease (reported to manufacturer)
- Decreases larger for non-oral abuse



Coplan PM, Chilcoat HD, Butler SF, et al. The effect of an abuse-deterrent opioid formulation (OxyContin) on opioid abuse-related outcomes in the postmarketing setting. *Clin Pharmacol Ther.* 2016;100(3):275-286.

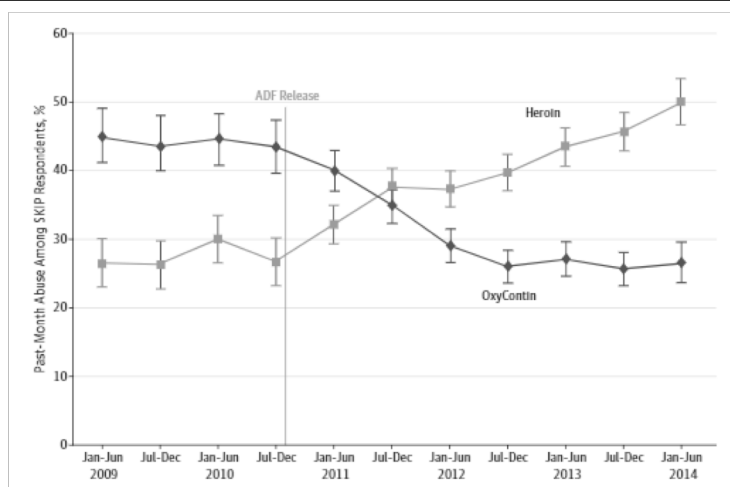
## Trends in abuse, diversion, and misuse for extended release oxycodone (OC) and comparator opioids



**PainWeek**

Coplan PM, Chilcoat HD, Butler SF, et al. The effect of an abuse-deterrent opioid formulation (OxyContin) on opioid abuse-related outcomes in the postmarketing setting. *Clin Pharmacol Ther.* 2016;100(3):275-286.

## Before & after Reformulated OxyContin and Heroin Past Month Use

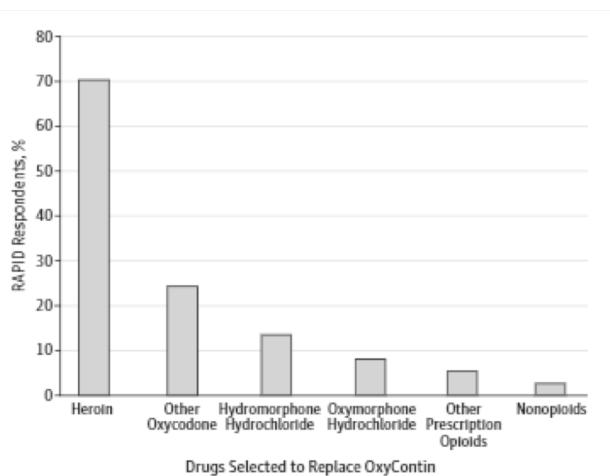


**PainWeek**

Cicero TJ, Ellis MS. Abuse-deterrent formulations and the prescription opioid abuse epidemic in the united states: Lessons learned from OxyContin. *JAMA Psychiatry.* 2015;72(5):424-430.



## Drugs Selected to Replace Reformulated OxyContin

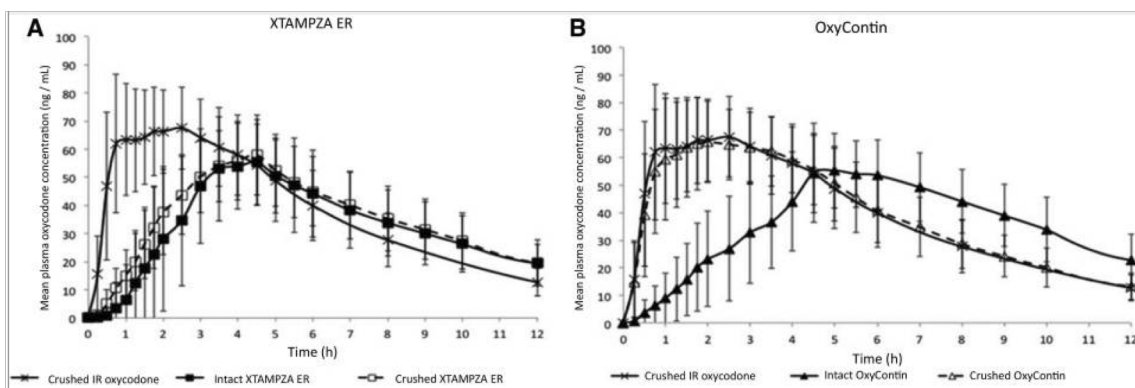


**PainWeek**

Cicero TJ, Ellis MS. Abuse-deterrent formulations and the prescription opioid abuse epidemic in the united states: Lessons learned from OxyContin. *JAMA Psychiatry*. 2015;72(5):424-430.

## Variations in ADF Properties Oxycodone Example

- Xtampza ER vs. Reformulated OxyContin Pharmacokinetics
- Xtampza ER retained ER properties when crushed



**PainWeek**

Gudin J, Levy-Cooperman N, Kopecky EA, Fleming AB. Comparing the effect of tampering on the oral pharmacokinetic profiles of two extended-release oxycodone formulations with abuse-deterrent properties. *Pain Med*. 2015;16(11):2142-2151.

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## Pipeline Technologies




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## Novel Physical Barriers

- Sucrose acetate isobutyrate (SAIB)
  - Viscous liquid with thermal stability and is water insoluble
  - Resists extraction with ethanol
  - Poor syringeability
  - Crush and freezing resistant
  - New formulations with oxycodone base or salt
- Superabsorbent-based technology
  - Cross-linked acrylic polymers which swell in liquid or pH >6
  - Hard gel results in slower drug release
  - Crush resistant
  - Poor syringeability
  - Unpleasant to inhale



1. Su Yum, Grant Schoenhard, Arthur Tipton, John Gibson, John Middleton, inventor; Durect Corp, assignee. Oral drug delivery system. patent US20040161382A1. August 19, 2004.
2. Miloud Rahmouni, Angela Ferrada, Fouzia Souhli, Sonia Gervais, Vinayak Sant, Damon Smith, Frederic Duffayet, Shams Rustom, Ali El-Jammal, Jean-Michel Ndong, Bobby-Ernest Boursiquot, Ali Bichara, inventor; Paladin Labs (Barbados) Inc, Paladin Labs Inc, Paladin Labs Europe Ltd, assignee. Misuse preventative, controlled release formulation. patent US8691270B2. April 4, 2014.

## Novel Physical Barriers

- Lipid-based products
  - Add crush resistance to hydrocodone HCL microparticles
  - Crush resistance and extraction resistance of levorphanol
- Ceramic nanoparticles
  - Contain hollow core for drug delivery
  - Resist crushing/grinding
  - May prevent ingestion, inhalation, and injection abuse
- Foam forming agents
  - Surfactants, organic acids, and polymers to trap gases and produce foam
  - Foam in nasal passages results in coughing and prevent repeat exposure
  - Foam resists injection



1. Florence Guimberteau FD, inventor; Flamel Technologies SA, assignee. Anti-misuse microparticulate oral pharmaceutical form, patent US8652529B2. February 8, 2014.
2. Rudi Moerck, Bruce Sabacky, Timothy Spitzer, Jan Prochazka, Douglas Ellsworth, inventor; Moerck Rudi E, Sabacky Bruce J, Spitzer Timothy M, Jan Prochazka, Douglas Ellsworth, assignee. Ceramic structures for prevention of drug diversion, patent US20060127486A1. June 15, 2006.
3. James Emigh, Andrew Reddick, Ron Spivey, inventor; Acura Pharmaceuticals Inc, assignee. Methods and compositions for deterring abuse of orally administered pharmaceutical products, patent US20060177380A1. August 10, 2006.

## Novel Chemical Barriers

- Ion exchange resins (IERs)
  - Have been used for taste marking and sustained release
  - Chemical and physical requirements for drug release (less dose dumping)
  - Drug release dependent on environment in GI tract to reducing abuse



- Ketan Mehta, Yu-Hsing Tu, Alivia Chaudhuri, Ashok Perumal, inventor; Tris Pharma Inc, assignee. Abuse resistant opioid drug-ion exchange resin complexes having hybrid coatings, patent US8202542B1. June 19, 2012.

## Novel Prodrug Technology

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- Prodrugs are inactive and require biologic activation for desired effect
- Many pharmaceuticals are prodrugs since they may improve:
  - Pharmacokinetics
  - Solubility
  - Bioavailability
  - Stability
- Requirements for bioconversion are inherently abuse deterrent



Maincent J, Zhang F. Recent advances in abuse-deterrent technologies for the delivery of opioids. *Int J Pharm*. 2016;510(1):57-72.

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## Considerations of ADF on Abuser



## Opana ER Removed from U.S. Market (June 8, 2017)

- This is the first time the agency [FDA] has taken steps to remove a currently marketed opioid pain medication from sale due to the **public health consequences of abuse.**
- *“The abuse and manipulation of reformulated Opana ER by injection has resulted in a serious disease outbreak. When we determined that the product had dangerous unintended consequences, we made a decision to request its withdrawal from the market. This action will protect the public from further potential for misuse and abuse of this product.”*

Janet Woodcock, M.D.  
Director of the FDA’s Center for  
Drug Evaluation and Research.



Food and Drug Administration Office of the Commissioner. Press announcements - FDA requests removal of opana ER for risks related to abuse. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm562401.htm>. Updated 2017.

## Opana ER Studies Leading to Removal

- Thrombotic Thrombocytopenia Purpura (TTP)
  - Tennessee (2012) – 15 cases, no deaths
  - Mechanism unclear – High Molecular Weight PEO considered
- HIV – Indiana Study (Scott County)
  - Indiana (2015) – no TTP
  - 148 Participants included
    - IV Abuse 89% Opana ER, 17% Heroin, 3% Other
    - Typically shared pill with 2-4 people citing cost
    - Injected 3-7x/day and 2-4 injections each time (rinse shots)
  - Infectious disease:
    - 57% HIV, 90 % Hepatitis C

*“They're like, plastic. Real hard. Well, I shot too, but I, mostly I would snort it. But, and then, when you couldn't snort it at all. I started shooting it.” - Abuser*



1. Hunt R, Yalmanoglu A, Tumlin J, et al. A mechanistic investigation of thrombotic microangiopathy associated with IV abuse of opana ER. *Blood*. 2017;129(7):896-905.
2. John T. Brooks, Centers for Disease Control. CDC outbreak investigations involving OPANA® ER. At Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee. 2014. <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM547237.pdf>

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## Conclusions



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## Conclusions

- Balancing legitimate use and abuse is challenging but critical
- Diversion remains significant source of opioid in abuse and overdose
- No opioid is abuse proof
- Abuse by manipulation of opioids for oral, inhalation and injection is not insignificant
- ADF is only one component of risk management with opioids
- ADF must balance safety to both patient and potential abuser
- Important differences exists between technologies for ADF
- Novel strategies are relevant in improving opioid safety

