Comments Regarding Category 3 Oral Study and Category 1 Smoking Study

James M. Tolliver, PhD
Pharmacologist
Controlled Substance Staff (CSS)
CDER/FDA

June 26, 2018
FDA Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety & Risk Management Advisory Committee (DSaRM)

Oral Study B4501016

- Randomized, double-blind, triple-dummy, placebo and active-controlled, single-dose, 4-way crossover design
- Evaluable Population: 46 non-dependent, recreational opioid users
- Treatments
  - Placebo
  - Remoxy ER Capsules, 40 mg, Intact
  - Remoxy ER Capsules, 40 mg, Chewed
  - Oxycodone HCl IR 40 mg Tablets, Crushed (Positive Control)
- Statistical analyses conducted by CDER Office of Biostatistics for pharmacodynamic measures.
- Primary Comparison: Remoxy 40 mg Chewed vs Oxycodone HCl IR 40 mg Crushed.

Pharmacodynamic Measures

(0 – 100 mm, Unipolar Scales)

- Drug Liking Visual Analogue Scale (VAS) (Primary Measure)
  - Respond to statement*: "At the moment, my liking for this drug is…"*
  - Anchors: Left "0: Not at All" Right "100: Extremely"

- High VAS (Primary Measure)
  - Respond to statement*: "I am feeling high …"*
  - Anchors: Left: "0: Not at All" Right: "100: Extremely"

- Take Drug Again VAS (Secondary Measure)
  - Respond to statement*: "I would take this drug again."*
  - Anchors: Left: "0: Definitely Not" Right: "100: Definitely So"

- Overall Drug Liking VAS (Secondary Measure)
  - Respond to statement*: "Overall, my liking for this drug is."*
  - Anchors: Left: "0: Not at All" Right: "100: Extremely"

Results of Primary Endpoints

Subjective Measure VAS	Primary Endpoint	LSmeans/Means*(SE) – Oral Treatments (N=46)			
		Remoxy 40 mg Intact	Remoxy 40 mg Chewed	Oxycodone HCl IR 40 mg Crushed	Placebo
Unipolar Drug Liking	Emax	26.6 (3.42)	63.0 (3.42)	69.9 (3.42)	11.7 (3.42)
	AUE 0-2hours*	17.7 (3.35)	72.1 (5.30)	99.4 (6.40)	11.6 (3.26)
Unipolar High	Emax*	24.0 (3.45)	63.1 (3.14)	70.7 (3.50)	12.0 (3.05)
	AUE 0-2hours*	15.0 (2.74)	69.6 (5.09)	102.0 (5.90)	12.1 (3.46)

Remoxy chewed and Oxycodone HCl IR crushed treatments resulted in maximum effects (Emax) and early experience (AUE0-2hours) higher than that produced by either placebo or Remoxy intact for Drug Liking and High. LS-Least Square.

Results of Primary Endpoints
(Primary Comparison)

- Emax of Drug Liking for Remoxy chewed is not smaller than that by Oxycodone HCl IR crushed (p=0.0533).

- Emax of High was smaller for Remoxy chewed compared to Oxycodone HCl IR (p=0.0043); however, there was a failure to demonstrate a minimum of 5% reduction in mean Emax of High for Remoxy chewed compared to Oxycodone HCl IR (p=0.06667).

- Remoxy chewed resulted in limited but, statistically significant reductions in AUE0-2hours compared to Oxycodone HCl IR crushed for both Drug Liking and High VAS (p<0.0001).

Results of Secondary Endpoints

Subjective Measures VAS at 24 Hours	LSmean Emax (SE) - Oral Treatments (N =46)			
	Remoxy 40 mg Intact	Remoxy 40 mg Chewed	Oxycodone HCl IR Crushed 40 mg	Placebo
Unipolar Take Drug Again	26.6 (4.50)	63.5 (4.30)	65.0 (4.90)	5.6 (2.45)
Unipolar Overall Drug Liking	23.6 (3.65)	60.5 (3.65)	64.3 (3.65)	6.0 (3.71)

For both Take Drug Again and Overall Drug Liking, the LSmean Emax of Remoxy chewed and Oxycodone HCL IR Crushed were greater than that produced by either placebo or Remoxy intact.

Results of Secondary Endpoints

(Primary Comparison)

- The LSmean Emax of 63.5 produced by Remoxy chewed was not statistically significantly smaller than LSmean of 65 following oxycodone HCl IR crushed for unipolar Take Drug Again VAS at 24 hours (p=0.4064).

- The LSmean of 60.5 following Remoxy chewed for unipolar Overall Drug Liking VAS at 24 hours was not statistically significantly smaller than that of 64.3 produced by Oxycodone HCl IR crushed (p=0.2165).

Conclusions from Oral Study

- With respect to the primary comparison of Remoxy chewed 40 mg versus Oxycodone HCl IR 40 mg crushed:
  - No statistically significance differences were found regard Emax for Drug Liking, Overall Drug Liking, or Take Drug Again VAS
  - Although statistically significant, the difference in Emax for High was limited raising the question of clinical relevance.
  - Early Drug Liking and High experience reflected in AUE0-2hours, was lower for Chewed Remoxy compared to Oxycodone HCI IR crushed.

- There are no data to support that limited differences in the early Drug Liking or High experience over the first 2 hours are clinically relevant findings consistent with possible abuse-deterrent effects, especially considering the Emax analyses for Drug Liking, High, Take Drug Again, and Overall Drug Liking in this study failed to demonstrate possible deterrent effects of Remoxy.

Category 1 Smoking Study

Manipulated Remoxy 40 mg Gel and 40 mg of active comparator were evaluated under protocol designated V1.

- Percent oxycodone recovered from vapor was limited constituting 3.8 (0.2 – 7.1) and 10.7 (8.9 – 12.2) from manipulated Remoxy gel and active comparator, respectively.
  - Overall this percentage difference is small representing a difference of 2.76 mg of oxycodone between the two samples.
- The 4.28 mg of oxycodone (10.7 x 40 mg) quantitated in the total collected vapor from comparator might be expected to produced subjective effects if all the vapor was inhaled.
  - Considering that individuals would be expected to only capture a small percentage of the vapor, it is not clear is any subjective effects would be obtained smoking the positive active comparator.

Category 1 Smoking Study
(Contribution of Triacetin)

- The contribution of triacetin, as an irritant to the respiratory tract and eyes, to an abuse-deterrent effect of Remoxy for inhalation (smoking) cannot be determined.
  - Confirmation of a significant irritant effect of triacetin could only come from documentation from human subjects smoking Remoxy. The administration of smoked Remoxy to human subjects for purposes of evaluating irritant or subjective effects cannot be ethically done.
  - Considering the limited amount of oxycodone recovered in the vapor it is not clear that the use of a triacetin as a potential aversive agent would be warranted.


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Review of Recent Epidemiologic Data on Use, Misuse and Abuse of Oxycodone

REMOXY ER® Advisory Committee
June 26, 2018

Mallika Mundkur, MD, MPH
Division of Pharmacovigilance II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Considering public health impact in opioid drug approvals

- NASEM, 2017: "Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use"
  - "Integrating public health considerations into [FDA's] regulation of opioids—including its approval decisions on new opioids—would be consistent with both its past practice and a generally accepted understanding of its statutory authority."
  - "Public health considerations may include how the availability or use of the product will affect an unintended population or the broad public health impact resulting from the aggregated effects on patients taking the drug."

Objectives of epidemiology review

- Review data on **utilization** of oxycodone-containing products and comparator drugs
- Review epidemiologic data on **misuse/abuse** of oxycodone-containing products and comparator drugs to inform public health risk/benefit assessment
- No post-market data have been submitted to the FDA that support a meaningful effect of ADFs on reductions in abuse, misuse, or related adverse clinical outcomes in the community– published studies attempting to evaluate these outcomes will not be reviewed

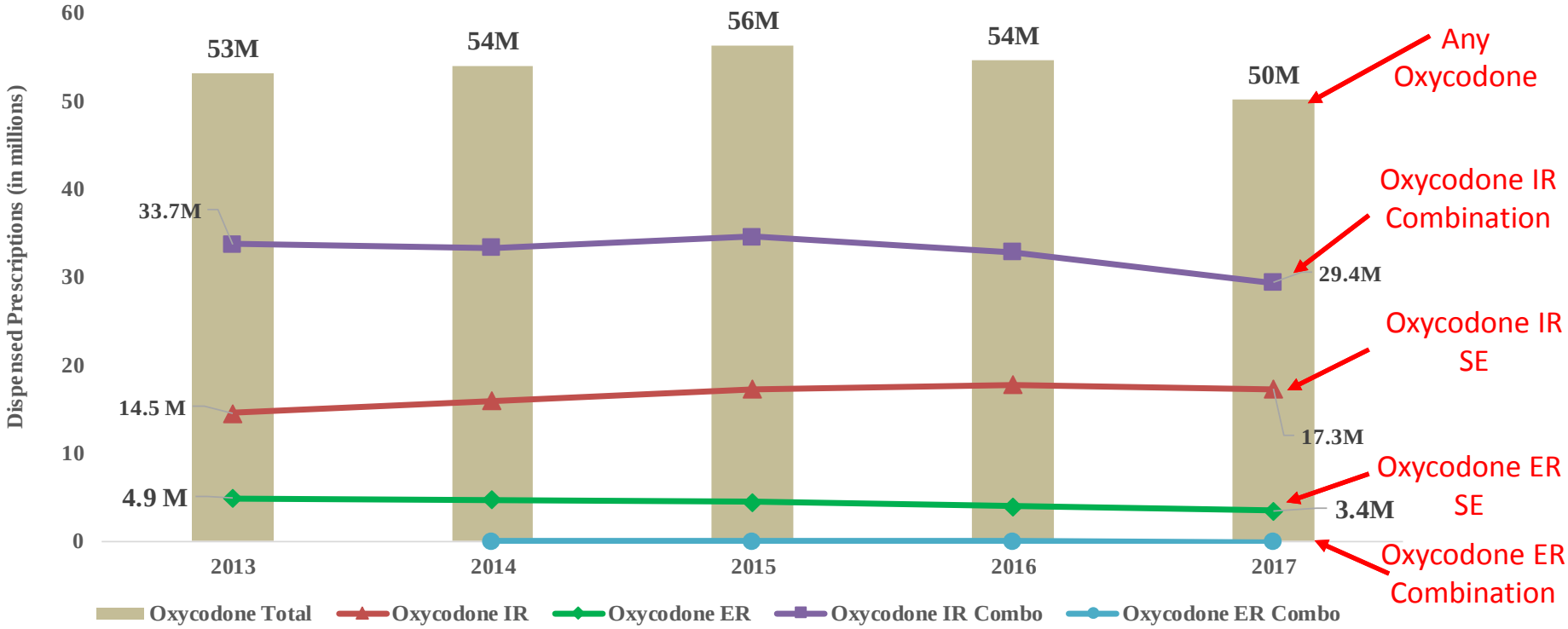
Objectives of epidemiology review

- Utilization
  - How frequently are specific oxycodone products dispensed in the US?
  - Among ER/LA* products, which are the most frequently dispensed products?
  - Among products intended to deter abuse, which are the most frequently dispensed?
  - What are the trends in dispensing for any of the above?

- Misuse/Abuse

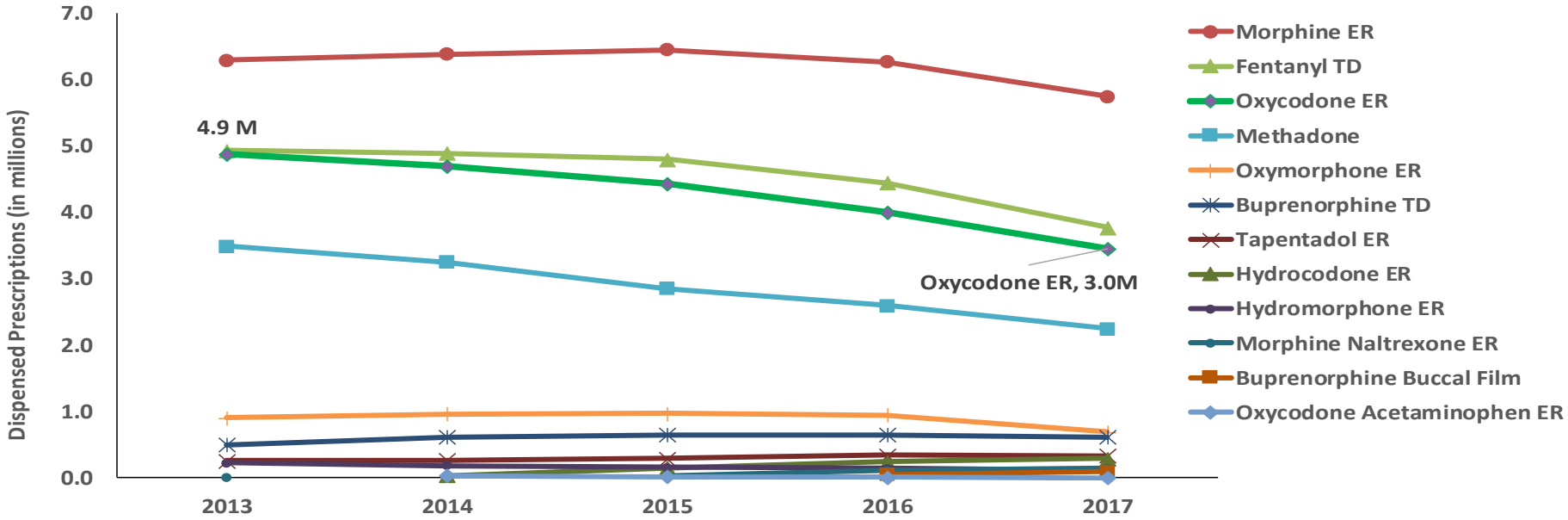
*ER/LA, Extended-Release/Long-Acting

50 million oxycodone prescriptions in 2017, IR >>>ER



Data Source: IQVIA, National Prescription Audit™, Years 2013-2017. Data Extracted April 2018. File: 2018-504 NPA Remoxy.xlsx
IR, Immediate-Release formulations include oral solid tablets/capsules and oral liquids; ER/LA Extended-Release/Long-Acting
SE, single-substance entity

Among ER/LA opioid analgesics: oxycodone ER 20% of dispensed prescriptions



Source: IQVIA, National Prescription Audit™, Years 2013-2017. Data Extracted April 2018. File: 2018-504 NPA Remoxy.xlsx

[1] Zohydro Approved October 2013; Hysingla November 2014

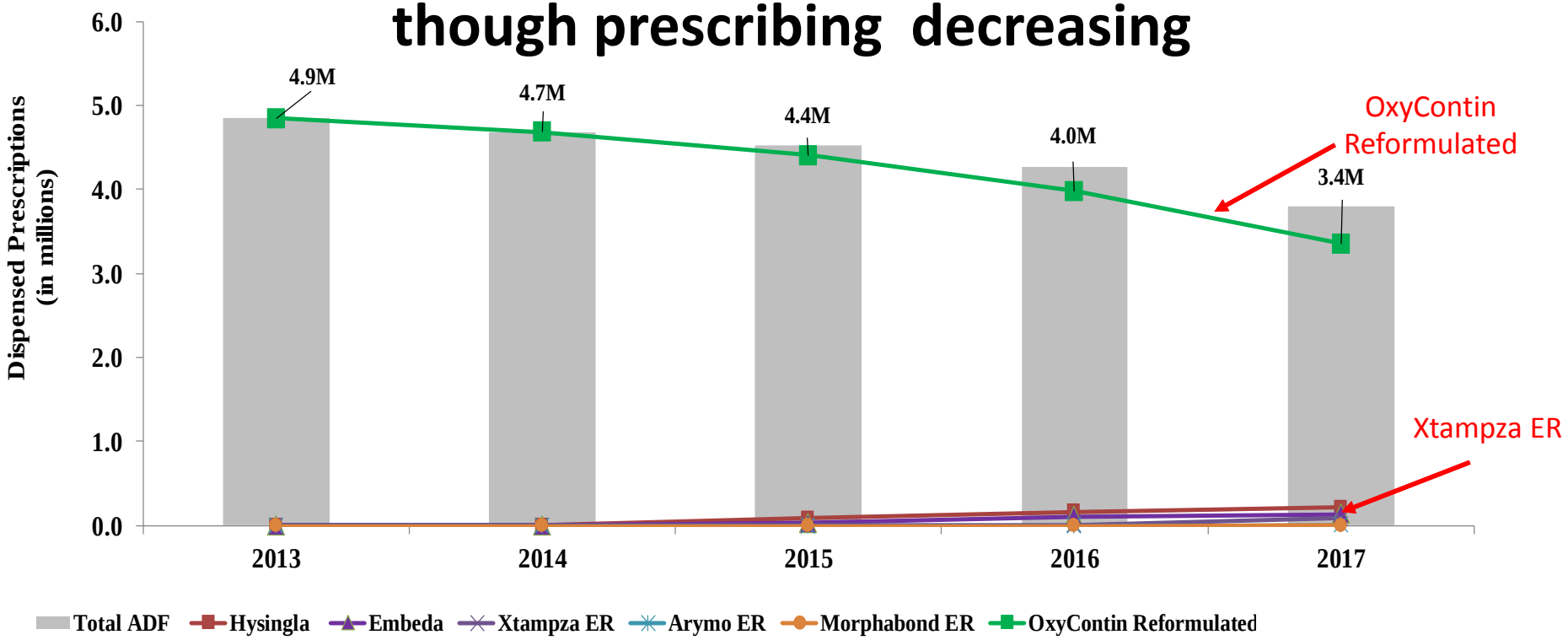
[2] Embeda was withdrawn from the market in March 2011 because of stability issues. It was approved with a manufacturing supplement in November 2013.

[3] Belbuca Approved October 2015

[4] Xartemis XR Approved March 2014

[5] Opana ER was withdrawn from the market in July 2017 following FDA's withdrawal request

Reformulated Oxycodone ER accounts for majority of dispensed ADF products, though prescribing decreasing



Source: IQVIA, National Prescription Audit™, Years 2009-2017. Data Extracted February 2018.
*ADF Products not marketed during study period: RoxyBond (Oxycodone IR) - Approved 04/2017; Targiniq ER (oxycodone/naloxone ER) Approved 07/2014; Troxyca ER (Oxycodone/naltrexone ER) - Approved 08/2016; Vantrela ER (Hydrocodone ER) - Approved 01/2017

Summary: Utilization

- In 2017, ~50 million prescriptions for oxycodone were dispensed at outpatient retail pharmacies in the US
  - Dispensed prescriptions peaked in 2015 (~56 million dispensed prescriptions) with subsequent decline
  - Oxycodone IR was dispensed much more frequently than oxycodone ER
  - Oxycodone ER represented less than 8% of all dispensed prescriptions for oxycodone
- Among ER/LA opioids, oxycodone ER constituted 20% of all dispensed prescriptions
- Among ADF products specifically, 88% of dispensed prescriptions in 2017 were for reformulated oxycodone ER
  - Over the period 2013-2017, dispensing of reformulated oxycodone ER has decreased steadily from 4.9 to 3.4 million prescriptions per year

ADF, Abuse-Deterrent Formulation; IR, Immediate-Release; ER, Extended-Release; ER/LA, Extended-Release or Long-Acting

Objectives of epidemiology review

- Utilization

- Misuse/Abuse
  - What is the current scale of misuse/abuse of prescription opioids?
  - Which are the most frequently abused opioids?
  - What are common routes of abuse for opioids, including available abuse-deterrent formulations?
  - What is the magnitude of morbidity and mortality associated with oxycodone-containing products versus comparator drugs?

Definitions of misuse/abuse

- **Misuse:** the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse

- **Abuse:** the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect

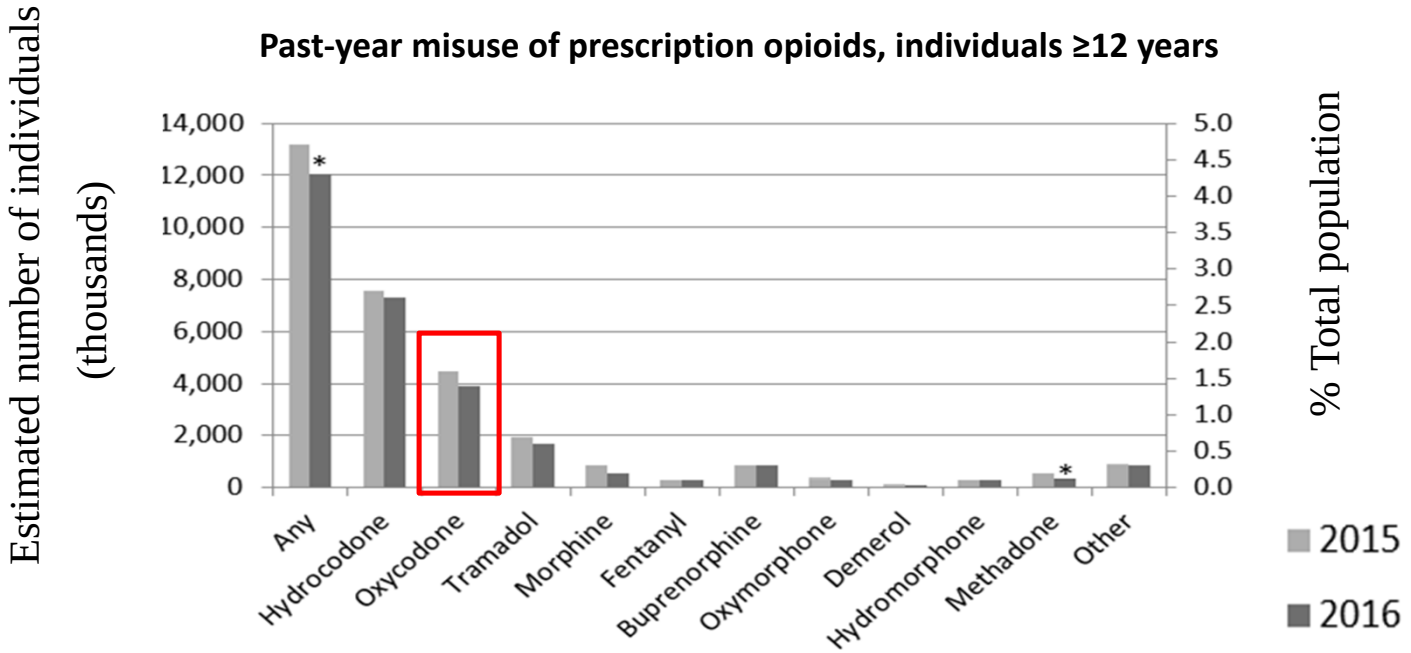
Food and Drug Administration [Internet]. "Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry" [updated 2015 Apr; cited 2018 May 10.] Available from: https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf.

Data sources included

- NSDUH- National Survey on Drug Use and Health, 2016
- NEISS-CADES- National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance, 2016
- AAPCC NPDS- American Association of Poison Control Centers, National Poison Data System, 2012-2015
- RADARS® TCP- Researched Abuse, Diversion and Addiction-Related Surveillance Treatment Center Program, 2016
- LITERATURE/NAVIPPRO™- National Addictions Vigilance Intervention and Prevention Program, 2012-2015
- NVSS-M and DIM- National Vital Statistics System-Mortality and Drug Involved Mortality Data for Overdose Deaths, 2010-2015

Scale of Misuse/Abuse

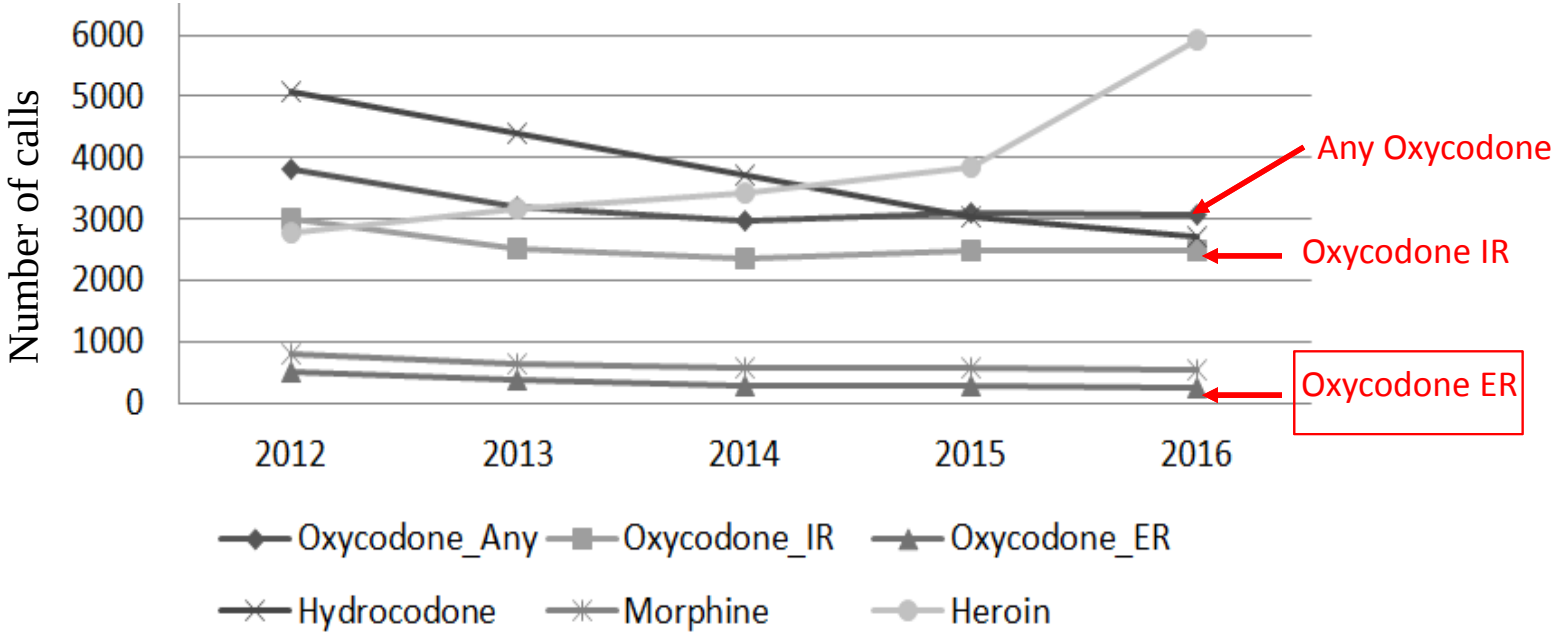
Oxycodone was misused* by ~3.9 million individuals in the US during the year 2016 (NSDUH)



Data Source: National Survey on Drug Use and Health (NSDUH), 2016

*NSDUH definition of "misuse" encompasses use of a drug in any mode other than as medically directed, including but not limited to abuse

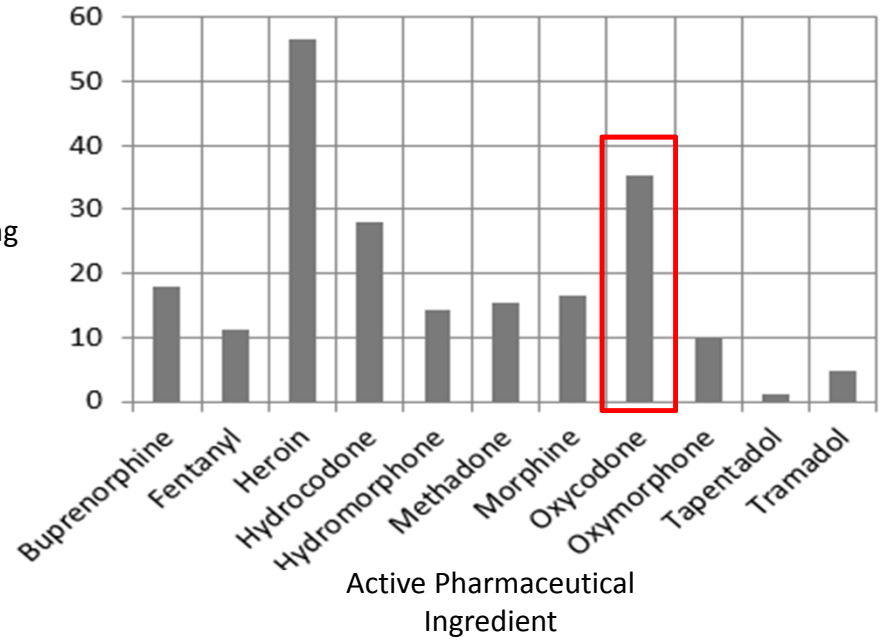
Over the period 2012-2016, intentional exposure calls* to PCCs involving oxycodone > 3000/yr (NPDS)



Data Source: American Association of Poison Control Centers (AAPCC)/National Poison Data System (NPDS); IR, Immediate-Release; ER, Extended-Release; PCCs, Poison Control Centers *restricted to individuals ≥12 years

Relative Frequency of Abuse, Specific Products

35% of individuals entering treatment for OUD in 2016 reported past-month abuse of oxycodone; IR > ER (RADARS® TCP)

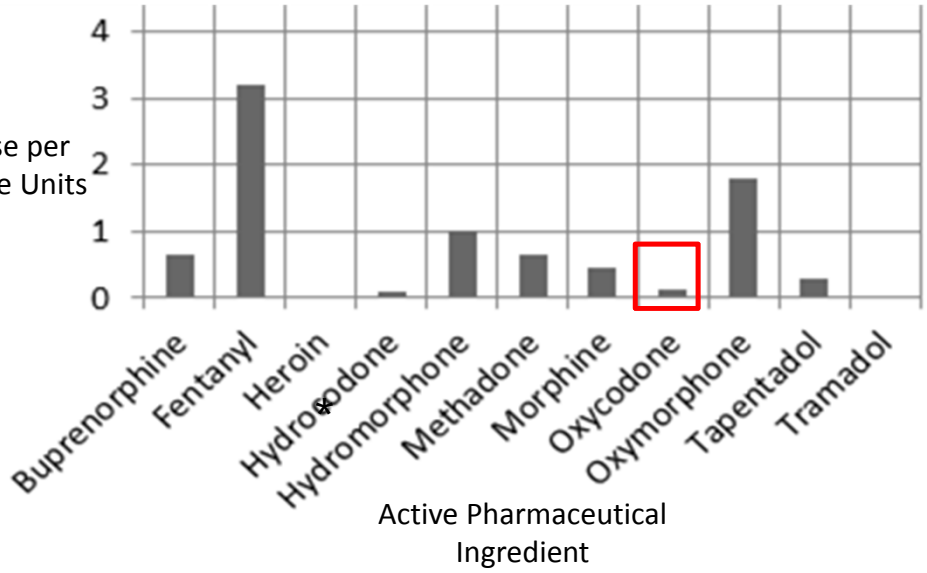


Oxycodone IR:
22% report past-month abuse

Oxycodone ER:
15% report past-month abuse

Data Source: Researched Abuse, Diversion and Addiction-Related Surveillance Treatment Center Program (RADARS® TCP); OUD, opioid use disorder

The relative frequency of oxycodone abuse versus other products changes after adjusting for utilization(RADARS® TCP)



Oxycodone IR:
abuse rate- **0.09** individuals endorsing past-month abuse per 100,000 dosage units dispensed

Oxycodone ER:
abuse rate- **0.89** individuals endorsing past-month abuse per 100,000 dosage units dispensed

Data Source: Researched Abuse, Diversion and Addiction-Related Surveillance Treatment Center Program (RADARS® TCP);
IR, immediate-release; ER, extended-release
*Heroin could not be adjusted for prescription volume, but is retained on graph for consistency

Routes of Abuse

Routes of Abuse

Author	Data Source	Opioid Category (# individuals endorsing abuse)	Oral	Snort	Inject	Chew	Smoke
Cassidy, 2017	NAVIPPRO™	ADF ER/LA (n = *NR)*	60%	20-30%	30%	*NR*	*NR*
Severtson, 2017	RADARS® TCP- SKIP	ADF ER/LA (n = 675)	*NR*	20-30%	20%	25%	5%
Butler, 2013	NAVIPPRO™	Oxycodone ER (Reformulated) (n = 1,705)	76%	25%	16%	*NR*	4%
Vietri, 2014*	US National Wellness Survey, sample	All prescription Opioids (n = 251)	91%	38%	32%	38%	34%

ADF ER/LA, Abuse-Deterrent Formulation Extended Release/Long-Acting; *NR*, Not Reported *study identified by the sponsor

Routes of Abuse

- From a sample of patients entering treatment for opioid or substance use disorder reporting past-month abuse of ADF ER/LA product*
  - Oral abuse most common (60-76%)
  - Snorting (20-30%)
  - Injection (16-30%)
  - Smoking (4-5%)
- From a sample of patients in the general population reporting past 3-month abuse of any prescription opioid*
  - Oral abuse most common (91%)
  - Snorting (38%)
  - Injection (32%)
  - Smoking (34%)

ADF ER/LA, Abuse-Deterrent Formulation Extended Release/Long-Acting; *estimates may not be nationally representative

Morbidity and Mortality

During 2016, an estimated 105,771 ED visits in the US involved harms from oxycodone (NEISS-CADES)

Opioid Analgesic Product	Cases	Annual Estimate		
	No.	No.	%	95% CI
Non-medical Use* (Total Estimate = 129,862 ED Visits)				
Oxycodone-containing Product	751	51,204	39.4	(32.8 - 46.0)
Hydrocodone-containing Product	194	16,745	12.9	(7.2 - 18.6)
Morphine-containing Product	108	7,532	5.8	(4.0 - 7.6)
Therapeutic Use (Total Estimate = 106,066 ED Visits)				
Oxycodone-containing Product	532	38,396	36.2	(27.1 - 45.3)
Hydrocodone-containing Product	260	24,250	22.9	(14.9 - 30.8)
Morphine-containing Product	116	8,863	8.4	(6.2 - 10.5)
Self-harm Attempt (Total Estimate = 39,012 ED Visits)				
Oxycodone-containing Product	210	16,171	41.5	(31.9 - 51.0)
Hydrocodone-containing Product	127	9,268	23.8	(16.7 - 30.8)
Morphine-containing Product	23	1,889	4.8	(2.7 - 7.0)

Data Source: National Electronic Injury Surveillance System (NEISS-CADES) 2016; table provided by CDC Division of Healthcare Quality Promotion;ED, Emergency Department

*Non-medical use includes pharmaceutical abuse, therapeutic misuse, and overdoses without indication of intent

43% of ED visits with non-medical use of oxycodone required admission/transfer/observation (NEISS-CADES)

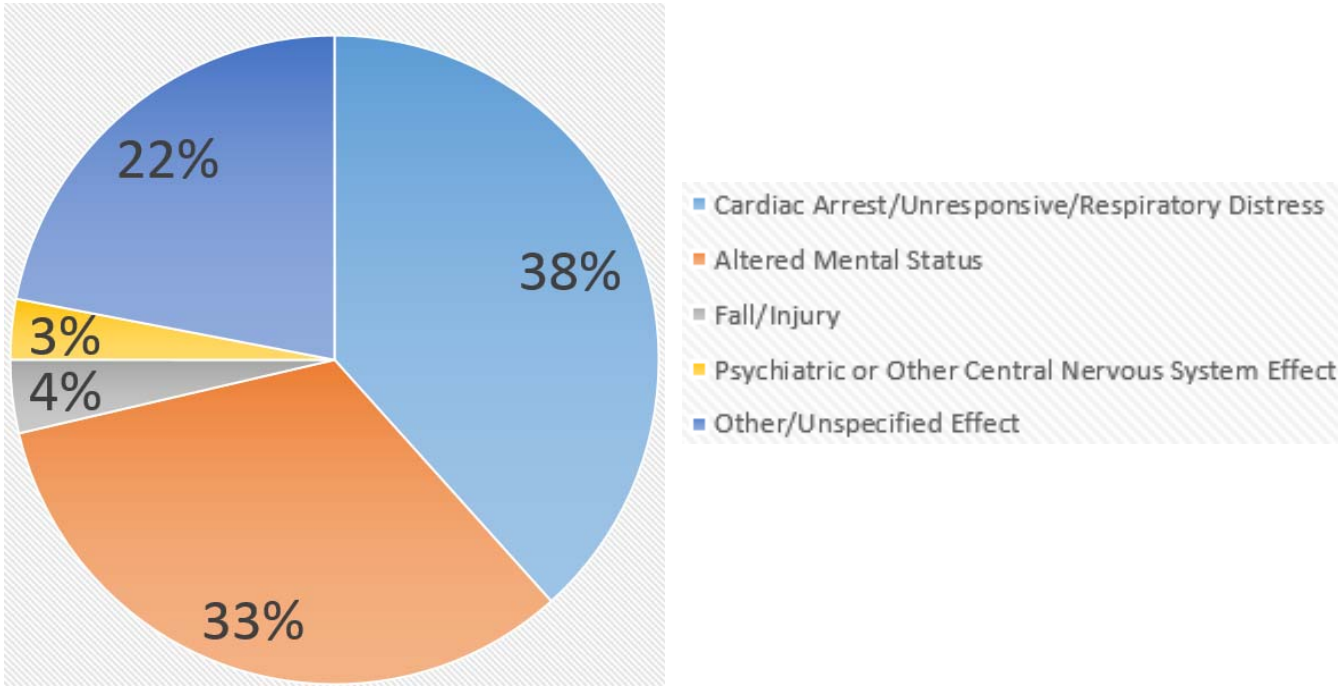
Case Characteristic	Cases	Annual Estimate		
ED Visits for Non-medical Use* of Oxycodone-containing products (N= 51,204)	No.	No.	%	95% CI
Disposition				
Admitted, Transferred, or Held for Observation	304	22,208	43.4	(32.6 - 54.2)
Treated/Released or Left Against Medical Advice	447	28,997	56.6	(45.8 - 67.4)
Implicated Oxycodone Product				
Single-ingredient Oxycodone	425	28,529	55.7	(46.8 - 64.6)
Oxycodone in Combination with Acetaminophen	334	22,970	44.9	(35.7 - 54.0)
Concurrent substance use				
>1 Prescription Opioid	116	7,538	14.7	(9.9 - 19.6)
Benzodiazepine	248	16,241	31.7	(26.3 - 37.2)
Illicit Drug(s) or Alcohol	388	24,725	48.3	(44.1 - 52.5)

Data Source: NEISS-CADES 2016; table provided by CDC Division of Healthcare Quality Promotion;
*Non-medical use includes pharmaceutical abuse, therapeutic misuse, and undetermined intent of use

~19,600 ED visits in the US with non-medical use of oxycodone resulted in cardiac arrest, respiratory failure/distress or non-responsiveness (NEISS-CADES)

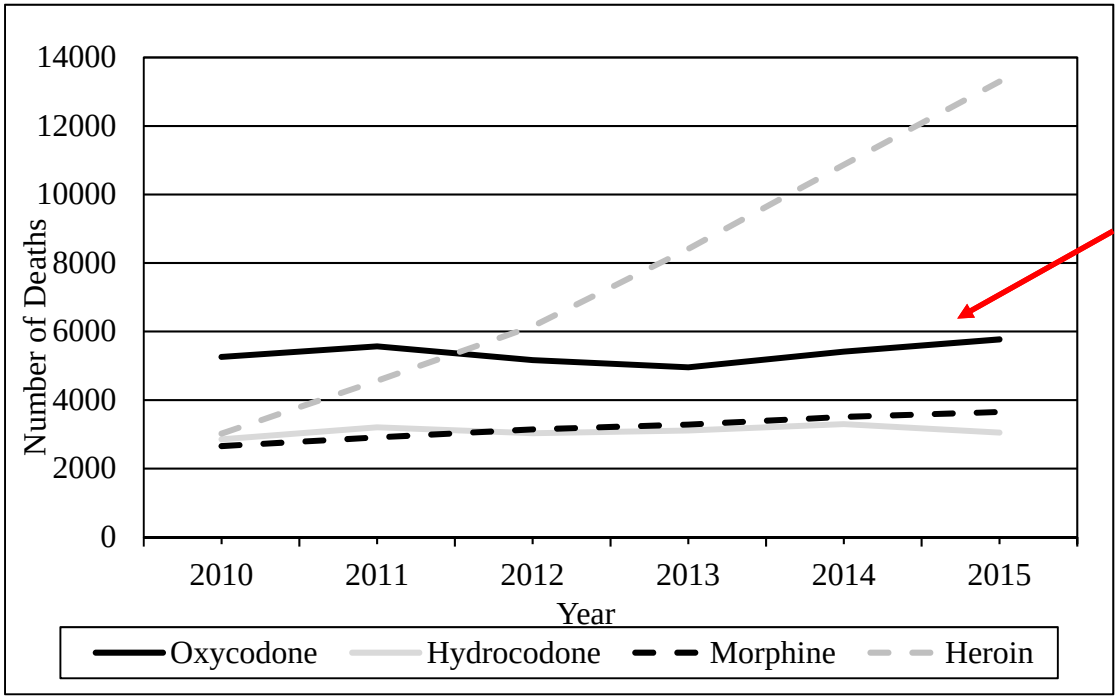
Non-medical use of oxycodone

N= 51,204 ED visits in the US



Data Source: NEISS-CADES 2016;
ED, Emergency Department

Over the period 2010-2015, oxycodone-involved deaths totaled 32,128; > 5000 deaths/year (NVSS-M/DIM)



Rates of oxycodone-involved death have not declined

Data Source: National Vital Statistics System-Mortality (NVSS-M) /Drug Involved Mortality (DIM)

Summary: Misuse/Abuse

- Scale of Misuse/Abuse
  - In 2016, 3.9 million individuals in the general population reported past-year misuse of oxycodone-containing products (NSDUH 2016)
  - Greater than 3000 calls/year placed to poison control centers reported intentional exposure to oxycodone-containing products (NPDS 2012-2016)
  - 35% of individuals entering treatment for opioid use disorder reported past-month abuse of oxycodone-containing products (RADARS® TCP, 2016)
- Abuse of Specific Products
  - Past-month abuse of oxycodone IR products was more frequent than for oxycodone ER products- 22% of respondents vs. 15% (RADARS® TCP, 2016)
  - Adjusting for prescription volume, past-month abuse of oxycodone ER products appeared more frequent than oxycodone IR products- 0.89 vs. 0.09 endorsements per 100,000 prescriptions (RADARS®, 2016)

Summary: Misuse/Abuse

- Routes of Abuse
  - AD ER/LA opioid analgesics- oral abuse 60%, snorting 20-30%, injection 30% (Cassidy et al., 2017; NAVIPPRO™)
- Morbidity/Mortality
  - 40% of ED visits in 2016 that involved non-medical use of oxycodone-containing products required admission/hospitalization/transfer (NEISS-CADES, 2016)
  - An estimated 19,600 ED visits with non-medical use of oxycodone-containing products involved patients experiencing cardiac arrest, respiratory failure/distress or non-responsiveness (NEISS-CADES, 2016)
  - Over the period 2010-2015, an estimated 32,128 deaths involved oxycodone (NVSS-M/DIM, 2010-2015)

Key Limitations of Data Sources

- NSDUH
  - Survey biases: recall, response, social desirability
- NPDS
  - Presumed under-capture of exposures with serious outcomes (i.e., death) where calls to poison control centers considered futile
  - Less reliable for estimates of trend
- RADARS® TCP/NAVIPPRO™
  - Findings from the included treatment centers may not be broadly generalizable or nationally representative of patients entering treatment for opioid use disorder
  - Product misclassification may occur (self-report)

Key Limitations of Data Sources

- NEISS-CADES
  - Does not include cases that result in death before or during ED evaluation
  - Potential for misclassification of products (e.g., oxycodone single ingredient vs. oxycodone combination)
  - Only includes acute opioid harms resulting in an ED visit; does not include visits for opioid withdrawal, seeking treatment/detoxification, or inadequate therapy

- NVSS-M/DIM
  - Reliance on literal text of death certificate likely to miss proportion of opioid-related deaths that do not contain an ingredient or product in the literal text

Conclusions

- Oxycodone-containing products are frequently dispensed in the US, with oxycodone ER products representing the majority of the ADF market
- Oxycodone-containing products are among the most frequently misused and abused prescription opioid products per population, with high levels of abuse possibly driven by wide utilization in the general population
- Products intended to deter abuse, such as reformulated oxycodone ER, are commonly abused by several routes, though most commonly oral, followed by snorting and injection
- Despite the growing popularity of illicit opioids, oxycodone-containing products continue to be involved with high morbidity and mortality in the US

Review Team

- Tamra Meyer, PhD, MPH- OSE/DEPI-Drug Abuse
- Jana McAninch, MD, MPH, MS- OSE/DEPI-Drug Abuse
- Judy Staffa, PhD, RPh- OSE
- Daniel Bak, PharmD- OSE/DEPI-Drug Use
- Sara Karami, PhD, MPH - OSE/DEPI-DMAT
- Celeste Mallama, PhD- OSE/ORISE fellow
- Sara Camilli, PharmD- OSE/DPV


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Remoxy ER: Multidisciplinary Review

NDA 022324 – Oxycodone ER Capsules

Lisa Wiltrout, MD

Medical Officer

Division of Anesthesia, Analgesia, and Addiction Products

Office of Drug Evaluation II

Office of New Drugs

Center for Drug Evaluation and Research

Outline

1. Abuse-deterrent opioid formulations (ADFs): Goals vs. Reality
2. Remoxy ER: Summary of clinical trial data
3. Remoxy ER: Abuse deterrence (AD) findings
4. Excipient Safety and ADFs

Goals For ADFs

A successful ADF does the following:

- delivers a consistent and effective dose of opioid when used as labeled
- can be expected to, or actually does, result in a reduction in abuse by making it more difficult to abuse by one or more relevant routes

Reality with ADFs

1. ADFs are NOT abuse proof and do NOT prevent addiction.

2. We have approved ten opioid analgesic products labeled with AD properties in accordance with the FDA Guidance.

3. AD labeling is based on data from premarket studies –
   a. Category 1 (In vitro studies)
   b. Category 2 (Pharmacokinetic (PK) studies)
   c. Category 3 (Clinical abuse potential studies)

Reality with ADFs

4. AD labeling is found in Section 9.2 of the prescribing information.

5. All FDA approved ADFs have postmarket requirements to conduct additional studies (Category 4 studies).

6. To date, no postmarket data have been submitted to the FDA that support a meaningful effect of ADFs on reductions in abuse, misuse, or related adverse clinical outcomes in the community.

Remoxy ER Clinical Trial Data

- Efficacy: Study PTI-821-CO, conducted under Special Protocol Assessment, provides substantial evidence of efficacy for the proposed indication.

- Safety: A database of 873 subjects and 1379 patients shows that Remoxy ER, taken as directed, has a safety profile typical of an extended-release opioid.

Remoxy ER AD Findings

- Oral route - Human Abuse Potential (HAP) study fails to demonstrate AD.
- Intranasal (IN) route - HAP study demonstrates that subjects experienced less drug liking and less willingness to take drug again with use of Remoxy ER under the conditions tested.
- Smoking route - This route generally not considered a relevant route of abuse.
- Intravenous (IV) route - Category 1 studies yielded different results between the Applicant and the FDA lab.

FDA Lab Category 1 Study Results

Remoxy ER/Manipulation Method RM11
No pretreatment

Extraction Solvent	Extraction Time & Volume	Needle Gauge	% LC	AVG % LC	SD	% RSD	Injectable amount (mg)	AVG Injectable amount (mg)	SD	% RSD
Solvent S20	Time F & Volume B	A	61.5	66.8	11.3	17.0	12.3	14.9	2.3	0.2
			79.8				15.5			
			59.0				16.9			
	Time H & Volume B	A	69.8	71.7	4.7	6.5	18.6	15.5	3.7	0.2
			68.3				16.4			
			77.0				11.5			

%LC – percent label claims; %RSD – percent relative standard deviation

FDA Lab Category 1 Study Results

Remoxy ER - Pretreatment C and Temperature G

Manipulation Method RM11											
Ext. Solvent, Time & Volume	Preheat Time	Needle Gauge	% LC	AVG % LC	SD	% RSD	Injectable amount (mg)	AVG Injectable amount (mg)	SD	% RSD
Solvent S20, Time F & Volume B	Time D	A	74.5 61.9 81.7	72.7	10.0	13.8	15.1 15.8 18.0	16.3	1.5	9.1
	Time F	A	83.2 83.9 83.2	83.4	0.4	0.5	20.6 15.6 17.0	17.7	2.6	0.1
	Time H	D	82.1 84.8 81.9	82.9	1.7	2.0	28.6 29.9 28.6	29.0	0.7	0.0

Ext. Solvent – extraction solvent; %LC – percent label claims; %RSD – percent relative standard deviation

Implications of FDA Lab Results

- Oxycodone can be extracted from Remoxy ER for IV use.
- Extracted oxycodone may potentially be shared among IV drug users.
- Sharing may lead to associated public health risks, such as blood-borne illnesses.

Prior Agency Approach to Excipient Safety

- Excipients in drug products are assessed for safety for the intended route(s) of administration
  - FDA guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf
- Drugs intended for parenteral administration cannot contain coloring agents (i.e., dyes) per USP Chapter <1>
- In the past, the Agency did not require an assessment of oral drug product excipient safety via IV or other unintended routes

Postmarket Experience with ADFs

Unanticipated outcomes have occurred with the introduction of ADFs to the market (recent example is Opana ER) –

- Data supporting a shift from one route of abuse to another more dangerous route of abuse - from nasal to IV
- Excipient-related adverse events associated with ADF abuse by unintended routes of administration, i.e., thrombotic microangiopathy with IV use of manipulated Opana ER
- HIV and Hepatitis C in drug users who were sharing manipulated Opana ER

Current Agency Approach to Excipient Safety

The Agency approach to excipient safety has now changed …

- We require sponsors to provide a safety assessment of the potential adverse effects and risks associated with abuse of the final drug product.
  - Consists of in vitro assessments, literature review, or nonclinical studies
- An adequate assessment of the potential risks associated with non-oral abuse of the final drug product formulation is needed to determine the complete risk:benefit profile of the drug product.
- We include potential excipient-related adverse events from abuse of ADFs in Section 9.2 of the prescribing information. (Note, warning about talc in MS Contin prescribing information precedes the development of ADFs.)

Limitations of the Remoxy ER Excipient Safety Assessment

- The Applicant only assayed for known Remoxy ER excipients and the expected degradants
- Basic, typical forms of manipulation were used for the extraction conditions
- The “worst case” IV abuse simulation conditions from the Category 1 studies were not used
- Excipient safety using the “worst case” conditions remains unknown

Summary

1. Data support the safety and efficacy of Remoxy ER for the proposed indication as an extended-release/long-acting opioid analgesic.
2. The AD data for Remoxy ER meet current standards for AD labeling by the intranasal route.
3. The AD data for Remoxy ER do NOT meet current standards for AD labeling by the oral route.
4. Our data do not support smoking as a relevant route of abuse for oxycodone.
5. Category 1 data from the FDA lab demonstrate that oxycodone suitable for IV use can be extracted from Remoxy ER under certain conditions.
6. The Applicant's assessment of excipient risk from abuse of the final drug product is incomplete.


FDA
U.S. FOOD & DRUG
ADMINISTRATION