Regulatory History of Opana ER

Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee

March 13-14, 2017

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Outline

- Oxymorphone
- Approval History
- Reformulated Opana ER
- Citizen petition
- General extended-release/long-acting opioid analgesic information

Acronyms

- AC: Advisory committee
- CSA: Controlled Substance Act
- IR: Immediate-release
- ER: Extended-release
- ERLA: Extended-release/long-acting
- AD: abuse deterrent
- IN: intranasal
- RiskMap: Risk Minimization Action Plan
- REMS: Risk Evaluation and Mitigation Strategy

Oxymorphone

- Semisynthetic opioid analgesic
- Schedule II CSA
- Pure agonist, relatively selective for mu receptor
- Pharmacologic effects consistent with other mu opioid agonists
- Relatively low oral bioavailability ~ 10%
- Principally metabolized in liver
- Approximate potency (by IV route) compared to morphine is 10:1

History

- 1959–1960 Numorphan (Endo)
  - Parenteral oxymorphone 1 mg/mL
  - Immediate-release tablets
  - Rectal suppository- 5 mg
  - Relief of moderate-to-severe pain, preop medication, support of anesthesia, obstetrical analgesia, and relief of anxiety in patients with dyspnea associated with pulmonary edema due to left ventricular dysfunction
- Numorphan IR tablets voluntarily withdrawn from market 1982
  - Sponsor cited commercial reasons
  - Anecdotal reports of abuse by injection in 60's and 70's

History

- 2006
  - Opana (immediate-release tablets)
    - Relief of moderate-to-severe acute pain
  - Opana ER (extended-release tablets)
    - Management of moderate-to-severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time

2006 Approval

- Opana
  - 3 studies in post op pain, 2 orthopedic, 1 abdominal
  - 5 and 10 mg tablets
  - Dosing: 10-20 mg every 4-6 hours
  - Food effect: increase in Cmax and AUC ~40%
    - Take on an empty stomach

2006 Approval

- Original Opana ER
  - 2 double-blind, controlled trials in patients with moderate-severe chronic low back pain, 1 opioid naïve, 1 opioid tolerant
  - Safety data in >2000 subjects
  - 5, 10, 20, 40 mg tablets
  - 7.5, 15, and 30 mg dosage strengths added in 2008
  - Dosing:
    - Opioid naïve-5 mg Q 12 h
    - Opioid tolerant- convert from prior opioid
  - Food effect: increase Cmax ~ 50%-take on empty stomach
  - Not intended to be abuse deterrent: Swallow whole. Crushing, chewing, snorting, or injecting the dissolved product will result in uncontrolled delivery and pose significant risk that could result in overdose and death
  - Approval included Risk Minimization Action Plan (RiskMAP)

Reformulated Opana ER

- Supplemental NDA (sNDA) submitted in 2010
- Designed with physicochemical properties intended to make formulation resistant to physical and chemical manipulation for abuse by intranasal (IN) and intravenous (IV) routes
- Excipients include polyethylene oxide, which is included in a number of AD formulations, and is intended to:
  - Make tablets hard, difficult to crush
  - Form a viscous gel when tablets contact liquids

Reformulated Opana ER

- Submitted in vitro and in vivo studies that assessed AD properties
  - Agency determined did not support AD labeling
- Approved December, 2011 without AD labeling
- Approval included Risk Evaluation and Mitigation Strategy (REMS)
- Replaced original Opana ER over first few months of 2012
- Generic products to original Opana ER continue to be marketed
  - Currently no generic products referencing reformulated Opana ER

Citizen Petition

- Submitted by Endo in 2012
- Requested FDA make determination that original Opana ER was withdrawn from market due to safety concerns
- This would result in withdrawing generic products referencing original Opana ER
- Petition denied in 2013
  - Insufficient data to conclude original Opana ER posed increased risk of abuse compared to reformulated Opana ER
  - Refer to background package for details of Agency response to petition

Reformulated Opana ER

- sNDA submitted February, 2013 to request AD labeling language
- Included same studies as first sNDA plus preliminary post-marketing epidemiology data on Opana ER
- Not approved, insufficient data to support AD labeling

Reformulated Opana ER

- Resubmitted January 2016 requesting labeling for AD properties for IN abuse, as well as additional epidemiologic data on abuse patterns of Opana ER.
- Concurrently, reports of serious illnesses associated with IV abuse of Opana ER
- Agency concerns regarding shift of abuse from nasal to IV
- Advisory Committee meeting planned
- Supplement withdrawn by Sponsor, August, 2016 → AC cancelled
- Subsequently, three years of postmarketing data submitted to Agency to inform discussion at this AC
- Note: Sponsor not currently seeking AD labeling

ERLA Class Issues

- ERLA Opioid analgesic REMS
- ERLA Postmarketing requirements
- Opioid safety labeling changes

Thank You!


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In Vitro Abuse Deterrent Studies of Opana ER

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March 13-14, 2017
Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee

Overview

- This presentation will focus on interpretation of in vitro studies conducted by Endo and the FDA laboratories to evaluate the abuse deterrent properties of Opana ER.
- Only Particle Size Reduction and Small Volume Extraction (**SVE**) in vitro studies will be discussed in this presentation.
- The tablet manipulation techniques discussed today will be blinded and written in **bold red letters**.
  - For example, tools that are used to cut, crush, or grind the tablets will be represented with codes **A**- **W**. Temperatures used for the SVE of tablets will be coded as **T1**, **T2** and **T3**.

Overview

- Definitions:
  - **ADF** = Abuse-Deterrent Formulation
  - **Original Opana ER**= Original formulation of Opana ER
  - **Reformulated Opana ER**= Currently marketed formulation of Opana ER
  - **API** = Active Pharmaceutical Ingredient Oxymorphone HCl for Opana
  - **SVE**= Small Volume Extraction
  - **ER** = Extended Release

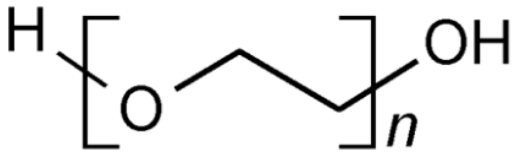
Formulation

- Reformulated Opana ER, Original Opana ER, and Opana IR all contain oxymorphone HCl, but differ in excipients. Of these, only Reformulated Opana ER contains polyethylene oxide (PEO).
- Examples of PEO containing products:
  - PEO is listed in nine extended release, controlled release, and sustained action tablets. All entries for PEO list oral route of administration.[1]
  - Some PEO containing ER products[2]: Arymo (morphine sulfate); Hysingla (hydrocodone bitartrate), Oxycontin (oxycodone HCl), Zohydro (hydrocodone bitartrate)

[1] FDA Inactive Ingredient Website

[2] Information from last approved labels in Drugs @ FDA

PEO



- PEO is a polymer of ethylene oxide.
- The number of oxyethylene groups (*n*) can vary from 2000 to 200,000
  - PEO is not a single molecule and can have a range of Molecular Weights (MW).
- PEO is a white to off-white powder available in different grades that vary in viscosity profile
- The viscosity of PEO is measured in isopropanol and water solutions

Particle Size Reduction

- Crushing and grinding studies included common physical manipulation techniques used by individuals who manipulate products. For example, tools **A, B, E, I, J, N-W**.
- Reformulated Opana ER was compared to Original Opana ER, OxyContin ADF and 2 generic Oxymorphone HCl ER products.
- In these studies, Reformulated Opana ER was more resistant to crushing and grinding than most of the comparators. Reformulated Opana ER was comparable to OxyContin ADF.
  - Tool **V** reduced the median particle size range of Reformulated Opana ER to <1 mm.

Small Volume Extraction (SVE)

- All SVE studies discussed in this presentation conducted with highest strength product (40 mg).
- SVE studies conducted with solvents **a** and **e**
- Reformulated Opana ER compared to OxyContin ADF, 2 generic Oxymorphone HCl ER products, and original Opana ER.
  - Only one set of conditions used to compare SVE of reformulated and original Opana ER.

Original and Reformulated Opana ER

- Particle Size Reduction
  - Tools **A, B, E** and **N** crushed or ground original Opana ER
  - Tool **B** flattened and tool **N** ground reformulated Opana ER
- SVE
  - Tablets manipulated with tool **B**. Extracted in 5 mL solvent **a**, 5 min at temperature **T2**. Withdrawn through **N3** needle.
  - Original Opana ER formed “highly viscous clotted gel”.
  - Reformulated Opana ER formed a hydrogel layer around tablet.

Entry	Product	Manipulation	Withdrawn	% API
1	Original Opana ER	crushed	0.3 g	0.4%
2	Reformulated Opana ER	flattened	4.23 g	26%

SVE Comparison of Products

- Same SVE conditions as previous slide: Tablets manipulated with tool **B**. Extracted in 5 mL solvent **a**, 5 min at Temperature **T2**. Withdrawn with needle **N3**.
- One set of conditions used for SVE of **B** manipulated tablets
- Reformulated Opana ER described as difficult to syringe.

Entry	Product	Manipulation	Withdrawn	% API
1	Reformulated Opana ER	flattened	4 mL	26-40%
2	OxyContin ADF	flattened	5 mL	42-46%
3	Generic Oxymorphone HCl ER*	crushed	2- 3 mL	66-74%
4	Generic Oxymorphone HCl ER *	crushed	4- 5 mL	61-80%

** Different manufacturers*

SVE of Manipulated Tablets

- Reformulated Opana ER manipulated with **V** was **not** syringeable through **N3** needle.
- Reformulated Opana ER manipulated with **W** was syringeable. Only 1 set of extraction conditions studied for **W** manipulated tablets.
  - Manipulation **W**: 1 mL of solvent **a** at **T2** withdrawn through **N1** needle 5 times. 39% of API extracted
  - Results from OxyContin ADF comparable

Pre-Treatment and SVE

- All tablets manipulated with **V** and extracted in 5 or 10 mL of solvents **a** and **e**. Pre-treatment conditions **P3**- **P8**.
- Pre-treatment did not impact median particle size range.
- 5 mL extract of reformulated Opana ER could not be filtered (solvents **a** or **e**). 67% API extracted from **P4** pre-treatment in solvent **a** (no filtration).
- Some 10 mL extracts (solvent **a**) were filterable. 50% of API extracted from **P4** pre-treatment and withdrawn through **N3** needle.
- 5 mL extracts (solvent **a**) filterable for both generic products through **N1** needle. 58% extracted with **P5** pretreatment.

FDA SVE

- FDA Laboratories studied syringeability of Reformulated Opana ER in solvent **a**.
- All samples below extracted at **T3**. Maximum API extracted at **T1** was 25%. All samples withdrawn through **N5** needle.
- Extractions in 2 mL more viscous, but all samples syringeable

	No Manipulation	Manipulated with Tool J
Condition	**API (%)**	**API (%)**
5 min, 2 mL	15	15
5 min, 5 mL	16	16
30 min, 2 mL	38	33
30 min, 5 mL	44	36

FDA SVE with Pre-Treatment

- Reformulated Opana ER pre-treated with condition **P4** and extracted with solvent **a** at **T3**. All samples withdrawn through **N5** needle.
- Samples described as “easily syringeable and filterable.”

	No Manipulation			Manipulated with Tool J			
Condition	**API (%)**	**API (mg)**	**Withdrawn (mL)**	**API (%)**	**API (mg)**	**Withdrawn (mL)**	**Mg/mL**
5 min, 2 mL	19	8	1.5	37	15	1.3	13.7
5 min, 5 mL	23	9	4.5	40	16	4.3	3.7
30 min, 2 mL	42	17	1.3	**72**	**29**	**1.0**	**29**
30 min, 5 mL	46	19	4.3	**79**	**32**	**4.1**	**7.8**

Conclusion

- Reformulated Opana ER was **resistant to crushing and grinding** by some common physical manipulation techniques.
- The API could be extracted from Reformulated Opana ER tablets in 5 mL of solvent **a**, and withdrawn into a needle.
- Endo SVE:
  - 40% API extracted (not pre-treated tablets) through **N3** needle.
- FDA SVE:
  - 44% API extracted (not pre-treated tablets) through **N5** needle. *Note- different set of conditions from Endo*.
  - 79% API extracted through **N5** needle(pre-treated and manipulated with tool **J**).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Intranasal Studies for Opana ER and Integration of In Vitro Findings

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March 13-14, 2017
FDA Joint Meeting of the Drug Safety
& Risk Management Advisory Committee (DSaRM)
and the
Anesthetic and Analgesic
Drug Products Advisory Committee (AADPAC)
Silver Spring, Maryland

Topics to be Discussed

- Pilot Intranasal Human Abuse Potential Study EN3288-113 submitted under NDA 201-655 for reformulated Opana ER.
- Pivotal Intranasal Human Abuse Potential Study EN3288-114 Submitted under NDA 201-655 for reformulated Opana ER
- Interpretation of study results in context of oxymorphone pharmacology and *in vitro* study findings

Subjective Measures

Drug Liking Visual Analog Scale (VAS) – 0-100-point Bipolar Scale (Primary Measure)

- Statement: "At this moment, my liking for this drug is"
- 0 = "Strong disliking" ; 50 = "Neither like nor dislike"; 100 = "Strong liking"

High VAS – 0–100-point Unipolar Scale (Secondary Measure)

- Statement: "At this moment, I am feeling high"
- 0 = "Not at all"; 100 = "Extremely"

Take Drug Again VAS - 0–100-point Bipolar Scale (Secondary Measure)

- Question: "Would you want to take the drug you just received again, if given the opportunity?"
- 0 = "Definitely not"; 50 = "Indifferent"; 100 = "Definitely so"

Overall Drug Liking VAS – 0-100-point Bipolar Scale (Secondary Measure)

- Statement: Overall, my liking for this drug is"
- 0 = "Strong Disliking"; 50 = "Neither like nor dislike";100 = "Strong liking"

Pharmacokinetics/Pharmacodynamic Parameters

Relevant Pharmacokinetic Parameters for Plasma Oxymorphone:

- Cmax – Maximum observed plasma concentration
- Tmax – Time at which which Cmax occurs

Relevant Pharmacodynamic (Subjective Measures) Parameters for Subjective Measures:

- Emax – Maximum (Peak) Effect
- TEmax – Time of Peak Effect

Pilot Study EN3288-113

- Randomized, double-blind, ascending-dose, placebo-controlled study using non-dependent, recreational opioid users.

- Purpose:
  - PILOT study to determine the safety and the dose response relationship of intranasal oxymorphone HCl powder for producing subjective reinforcing effects (i.e., Drug Liking)
  - Determination of dose to be used in pivotal study EN3288-114

- Study Subjects
  - Cohort 1 – 10 subjects – doses of 2.5 mg and 7.5 mg oxymorphone HCl
  - Cohort 2 – 9 subjects – doses of 5.0 mg and 10.0 mg oxymorphone HCl
  - 12 Subjects – Receive Placebo, 6 Subjects – Receive oxymorphone HCl doses

Pilot Study EN3288-113 – Emax of Subjective Measures

Subjective Measures (VAS)	Placebo (N = 12)	Mean Emax (SD) - Intranasal Oxymorphone HCl API			
		2.5 mg (N = 6)	5 mg (N = 6)	7.5 mg (N = 6)	10 mg (N = 6)
Bipolar Drug Liking	55.3 (10.7)	63.3 (16.5)	76.2 (15.8)	96.3 (4.8)	92.7 (7.9)
Unipolar High	16.8 (31.48)	31.5 (35.9)	62.8 (30.8)	98.8 (2.9)	93.8 (8.7)
Bipolar Take Drug Again	58.2 (16.8)	59.6 (14.9)	77.2 (14.1)	90.7 (10.6)	90.0 (12.2)
Bipolar Overall Drug Liking	55.0 (11.3)	61.4 (15.2)	74.8 (17.1)	89.0 (9.3)	83.8 (13.7)

With an increase in dose from 2.5 mg to 7.5 mg intranasal oxymorphone HCl API there was a dose-dependent increase in Emax of the four subjective measures. At the 7.5 mg dose, mean oxymorphone Cmax = 7.84 ng/mL, median Tmax = 0.25 Hours.

A dose of 7.5 mg reformulated OPANA ER and 7.5 mg Oxymorphone HCl API was selected for used in pivotal study EN3288-114.

Pivotal Study EN3288-114

- Randomized, double-blind, single-dose, placebo-controlled, 4-period, crossover design with Screening Phase, Qualitative Phase, Treatment Phase, and Follow-up.
- Non-dependent subjects who recreationally administer opioids intranasally.
- Intranasal Treatments
  - Reformulated Opana ER 7.5 mg Powder - Manipulated
  - Reformulated Opana ER Placebo Powder- Manipulated
  - Oxymorphone HCl 7.5 mg API Powder (Positive Control)
  - Placebo Powder (Lactose)
- Primary endpoint: Emax of Drug Liking VAS
- As part of the FDA review, statistical analyses of subjective measures were conducted by the CDER Office of Biostatistics using a mixed-effects model in which period, sequence, and treatment were fixed effects with subjects nested within sequence as a random effect.
- Primary comparison: ReformulatedOPANA ER 7.5 mg versus Oxymorphone HCl 7.5 mg
- Validation: Oxymorphone HCl 7.5 mg versus Placebo

Study EN3288-114 – Oxymorphone Plasma Pharmacokinetics

PK Parameter For Oxymorphone	Active Treatments	
	Manipulated Reformulated OPANA ER 7.5 mg (N = 43)	**Oxymorphone HCl API Powder 7.5 mg (N = 45)**
Mean (SD) Cmax (ng/mL)	2.84 (1.46)	6.03 (2.33)
Median Tmax (hours)	1.50	0.25

Study EN3288-114 – Emax of Subjective Measures

Subjective Measures VAS	Mean Emax (SD) - Intranasal Treatments (N =38)			
	OPANA ER 7.5 mg	OPANA ER Placebo	Oxymorphone HCl 7.5 mg	Placebo Powder
Bipolar Drug Liking	70.32 (16.20)	53.32 (8.69)	87.82 (10.33)	50.29 (0.65)
Unipolar High	45.29 (37.13)	9.24 (21.03)	83.00 (16.60)	2.47 (8.85)
Bipolar Take Drug Again	59.79 (24.40)	48.66 (17.26)	81.66 (17.55)	53.82 (15.25)
Bipolar Overall Drug Liking	60.66 (21.93)	51.71 (12.92)	81.79 (17.24)	53.34 (10.41)

Median TEmax: 2 Hours for reformulated OPANA ER, 1 Hour for Oxymorphone HCl

Intranasal administration of reformulated OPANA ER 7.5 mg produced statistically significant ($p<0.0001$) reductions in all four subjective measures compared to following intranasal administration of Oxymorphone HCl 7.5 mg. These results support a possible deterrent effect of OPANA ER to intranasal abuse.

Integration of Nasal Abuse Deterrence Studies with Oxymorphone Pharmacology and *In Vitro* Findings

- Study EN3288-114 predicts a reduction in intranasal abuse of reformulated OPANA ER, compared to original OPANA ER

- Oxymorphone has very low oral bioavailability (10%), thereby requiring larger doses (i.e., 40 mg) to produce significant subjective reinforcing effects when taken orally

- The dose response relationship of intravenous oxymorphone HCl for producing subjective effects is not known, but
  - In study EN3288-113, intranasal administration of 7.5 mg oxymorphone HCl resulted in high levels of subjective reinforcing effects.
  - Intranasal bioavailability of oxymorphone HCl in humans is not known, but it is likely less than 100%. Suggests that intravenous injection of 7.5 mg and possibly lower doses of oxymorphone HCl would produce subjective reinforcing effects.

Integration of Nasal Abuse Deterrence Studies with Oxymorphone Pharmacology and *In Vitro* Findings

- Category 1 studies conducted by FDA show that under selected conditions, using a single 40 mg reformulated OPANA ER tablet, solutions suitable for intravenous injection can be prepared containing sufficient oxymorphone concentrations (≥ 7.5 mg/mL) to produce subjective reinforcing effects.

- With limitations to oral and intranasal abuse of reformulated OPANA ER, individuals may be more likely to abuse OPANA ER by intravenous injection. Such abuse may be facilitated by the ability to manipulate reformulated OPANA to prepare solutions for intravenous injections and the potency of oxymorphone for producing subjective reinforcing effects via this route.

Conclusions

- The results of study EN3288-114, using the subjective measures of Drug Liking VAS, High VAS, Take Drug Again VAS, and Overall Drug Liking VAS, support a deterrent effect of reformulated OPANA ER to abuse by intranasal administration

- In vitro studies indicate the ability to manipulate reformulated OPANA ER tablets to produce solutions suitable for intravenous injection and likely to produce subjective reinforcing effects

- These findings, together with the low oral bioavailability of oxymorphone, might predict a shift to the intravenous route among some individuals who abuse Opana ER

Drug Utilization Patterns for Oxymorphone ER and Selected Opioid Analgesics, 2009-2015

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March 13-14, 2017

Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee

Outline

- Prescription Utilization Data
- Diagnoses Associated with Use
- Limitations
- Summary of Findings

Selected Opioid Products

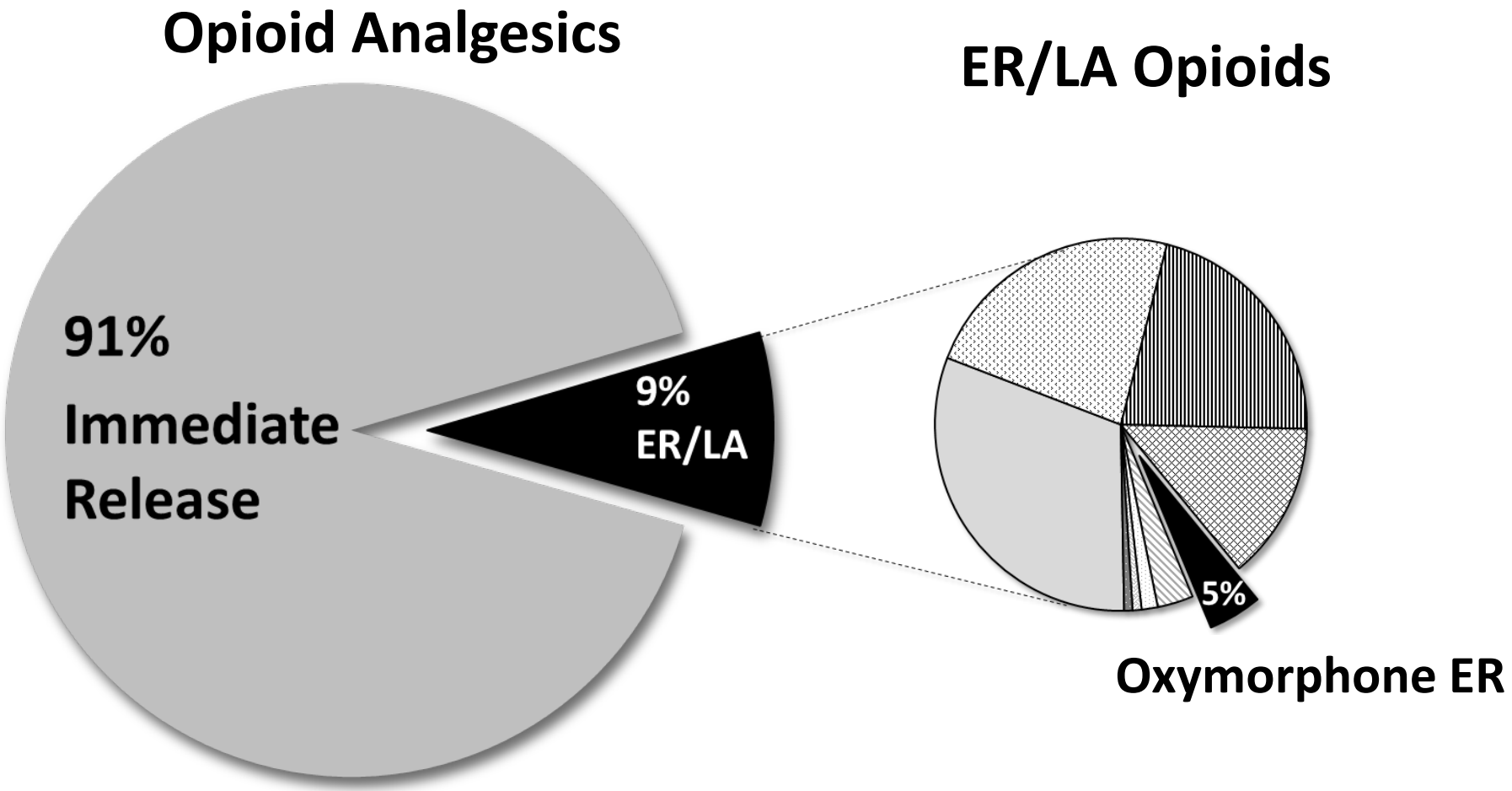
- **Extended-Release/Long-Acting (ER/LA) products:**
  - **Oral**
    - **Oxymorphone Extended-Release (ER)**
    - **Morphine ER**
    - **Oxycodone ER**
    - **Tapentadol ER**
    - **Hydrocodone ER**
    - **Hydromorphone ER**
    - **Methadone**
  - **Transdermal (TD)**
    - **Fentanyl TD**
    - **Buprenorphine TD**
- **Oral Immediate-Release (IR) products:**
  - **Oxymorphone IR**

Prescription Utilization Database

- **IMS Health, National Prescription Audit™ Database**
- **Measures prescriptions dispensed from outpatient retail pharmacies to patients**
- **Data are nationally projected to provide national estimates of utilization**

Opioid Analgesic Prescriptions

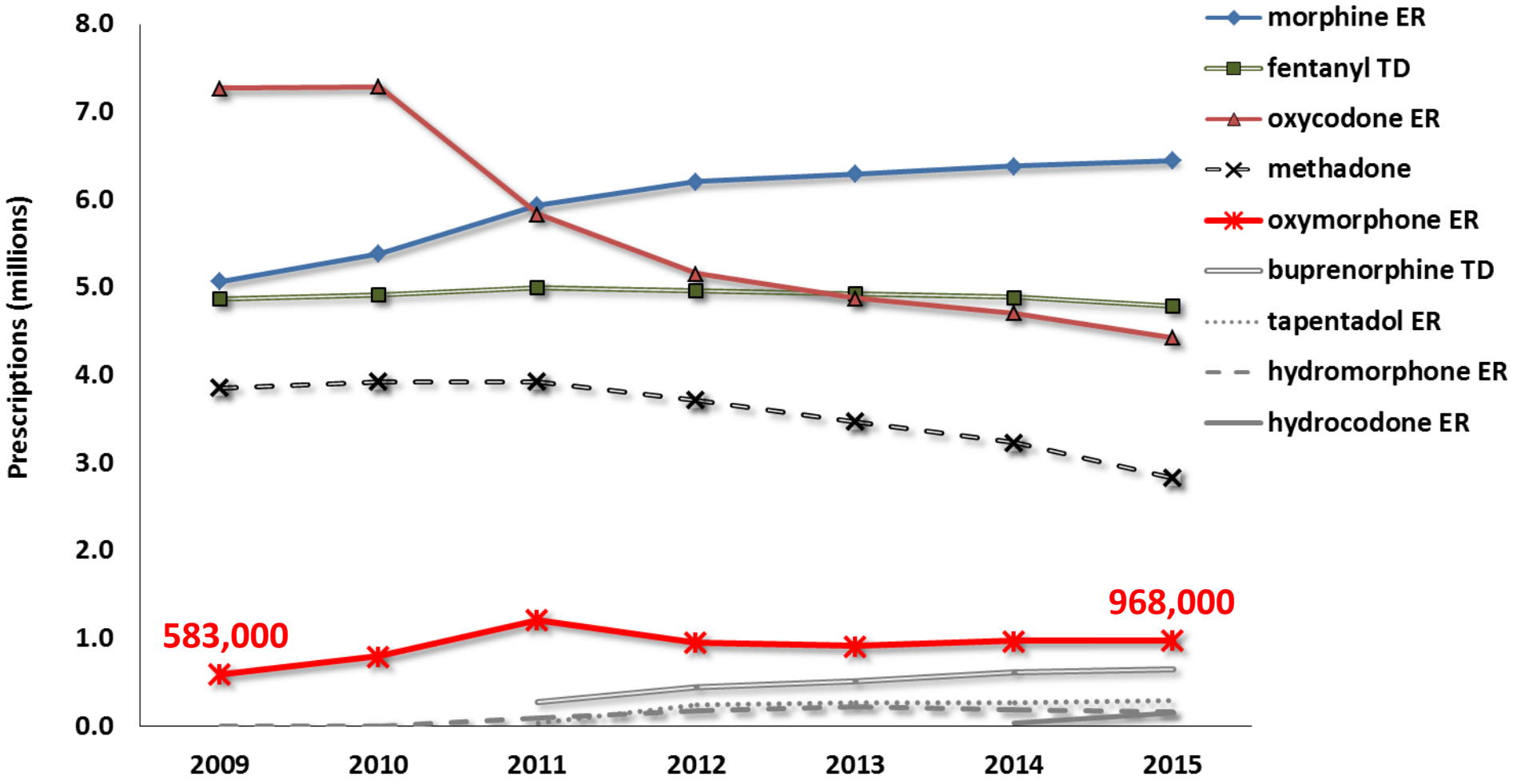
Nationally Estimated Number of Dispensed Prescriptions for Opioid Analgesics from U.S. Outpatient Retail Pharmacies in 2015



Source: IMS Health, National Prescription Audit™. Data extracted February 2017.

ER/LA Opioid Analgesic Prescriptions

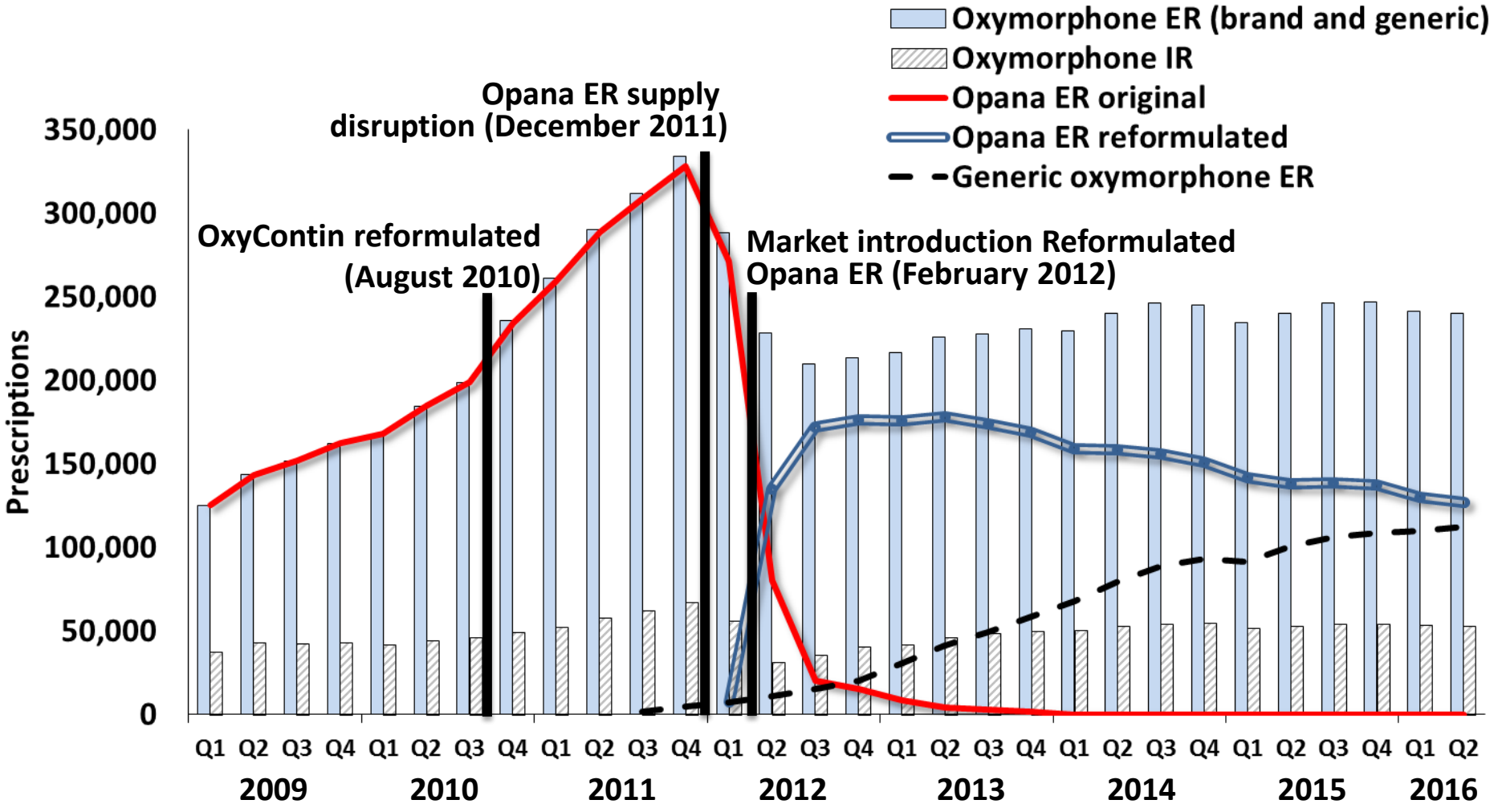
Nationally Estimated Number of Dispensed Prescriptions for Extended-Release/Long-Acting (ER/LA) Opioid Analgesics from U.S. Outpatient Retail Pharmacies



Source: IMS Health, National Prescription Audit™. Data extracted September 2016.

Oxymorphone Prescriptions

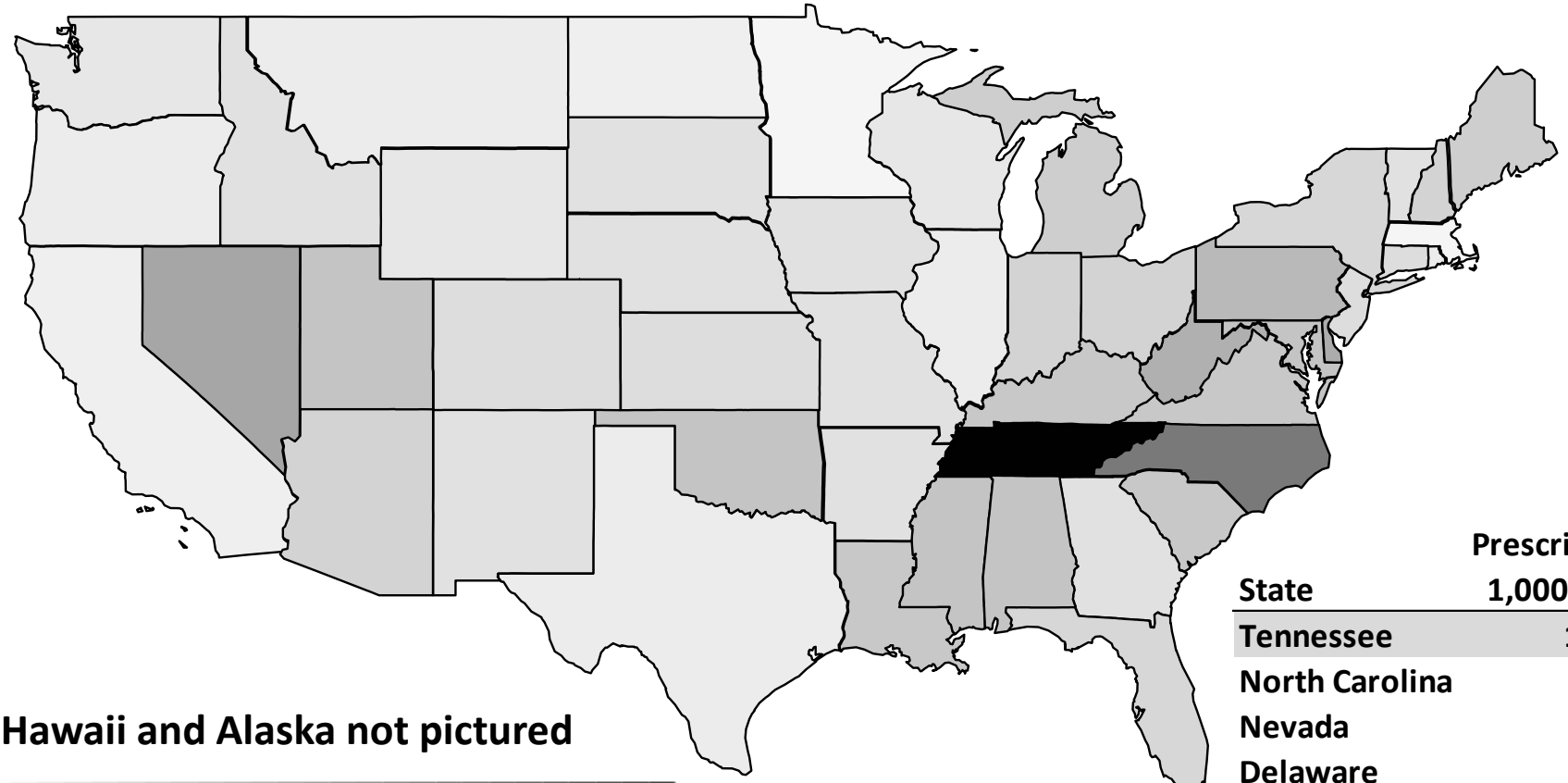
Nationally Estimated Number of Dispensed Prescriptions for Oxymorphone ER and Oxymorphone IR products from U.S. Outpatient Retail Pharmacies



Source: IMS Health, National Prescription Audit™. Data Extracted September 2016.

Oxymorphone ER Prescriptions in U.S.

Nationally Estimated Number of Dispensed Prescriptions per 1,000 U.S. State Residents* for Brand and Generic Oxymorphone ER Products from Outpatient Retail Pharmacies in 2015



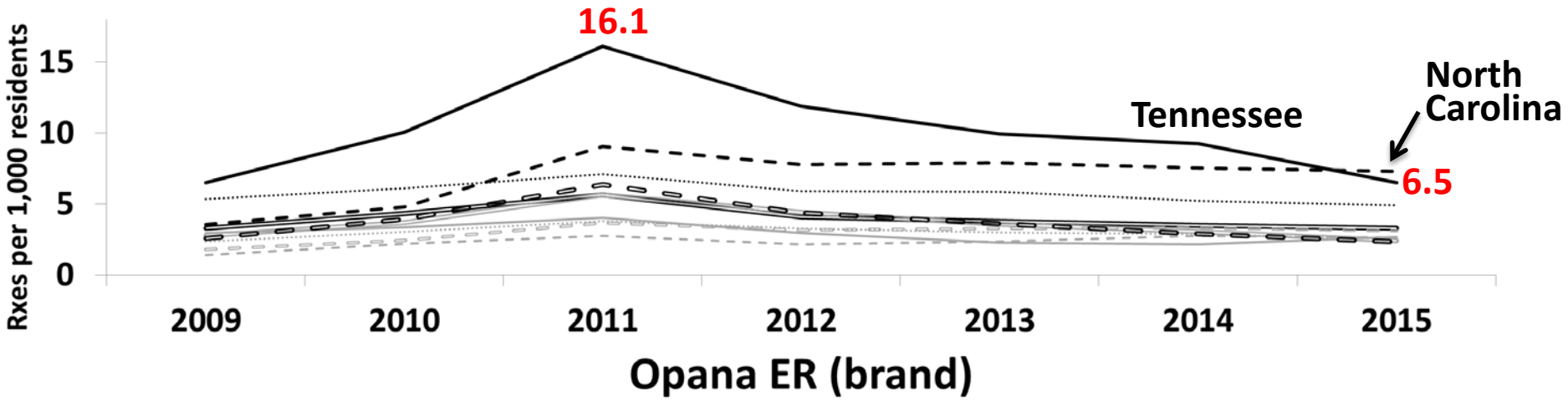
*Hawaii and Alaska not pictured

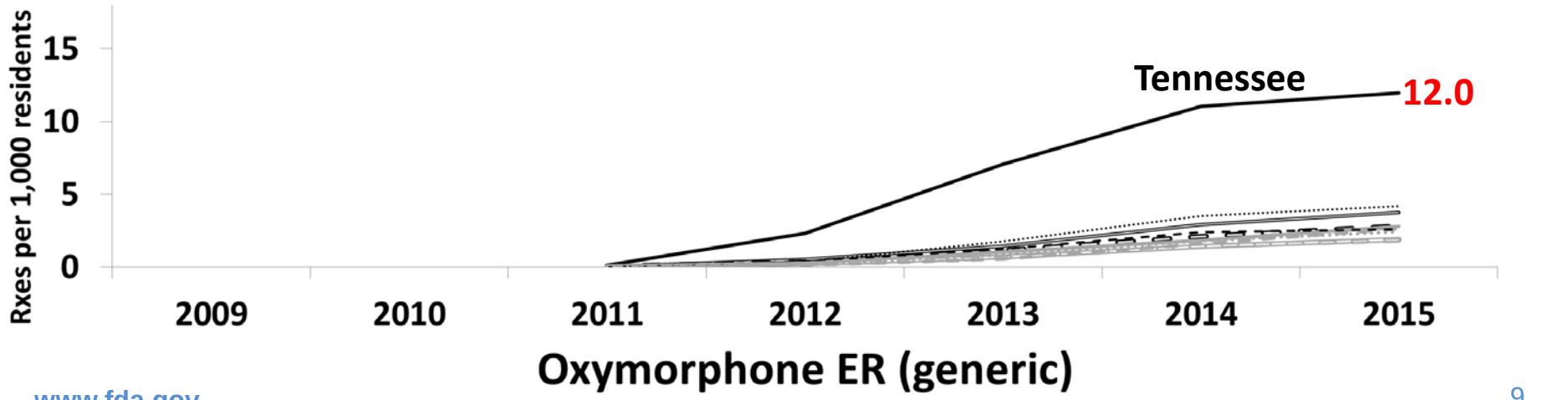
State	Prescriptions per 1,000 residents
Tennessee	18.5
North Carolina	9.9
Nevada	6.7
Delaware	6.3
West Virginia	5.9

Sources: IMS Health, National Prescription Audit™. Data extracted July 2016.
U.S. Census Data, www.census.gov. Data extracted February 2017.

Oxymorphone ER Prescriptions by State

Nationally Estimated Number of Dispensed Prescriptions per 1,000 Residents for Brand and Generic Oxymorphone ER Products from U.S. Outpatient Retail Pharmacies, by Top States





Sources: IMS Health, National Prescription Audit™. Data extracted July 2016. U.S. Census Data, www.census.gov.

U.S. Office-Based Physician Survey Data

- inVentiv Health TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel
- Monthly survey of 3,200 office-based physicians
- Data are nationally projected to reflect national prescribing patterns
- Data provide insight into prescriber intent

Diagnoses Associated with Selected Opioids

Diagnosis Categories Associated with Drug Use Mentions of Selected Opioids as Reported on U.S. Office-Based Physician Surveys, Stratified by Drug, 2011-2015, Aggregated

	Oxymorphone ER	Oxymorphone IR	Oxycodone ER	Morphine ER
Diseases of the musculoskeletal system & connective tissue	77%	56%	65%	68%
Diseases of the nervous system & sense organs	11%	16%	15%	13%
Injury & poisoning	3%	11%	5%	3%
Neoplasms	1%	5%	5%	8%
All other categories	8%	12%	10%	8%

Source: inVentiv TreatmentAnswers ™ and TreatmentAnswers with Pain Panel™. Data extracted October 2016.

Limitations

- Only outpatient retail pharmacy utilization was assessed
- Diagnoses data were not linked to dispensed prescriptions
- Diagnoses data were derived from surveys of office-based physician practices

Summary of Findings

- Oxymorphone ER comprised 5% of the ER/LA opioid market in 2015
- Utilization of Opana ER peaked in 2011 then declined through second quarter of 2016
- Utilization of oxymorphone ER varied by state
- Oxymorphone ER use:
  - 77% associated with musculoskeletal pain
  - Diagnosis patterns were similar to those of oxymorphone IR, morphine ER and oxycodone ER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Opana ER Adverse Event Reports: Non-Oral Abuse and Thrombotic Microangiopathy

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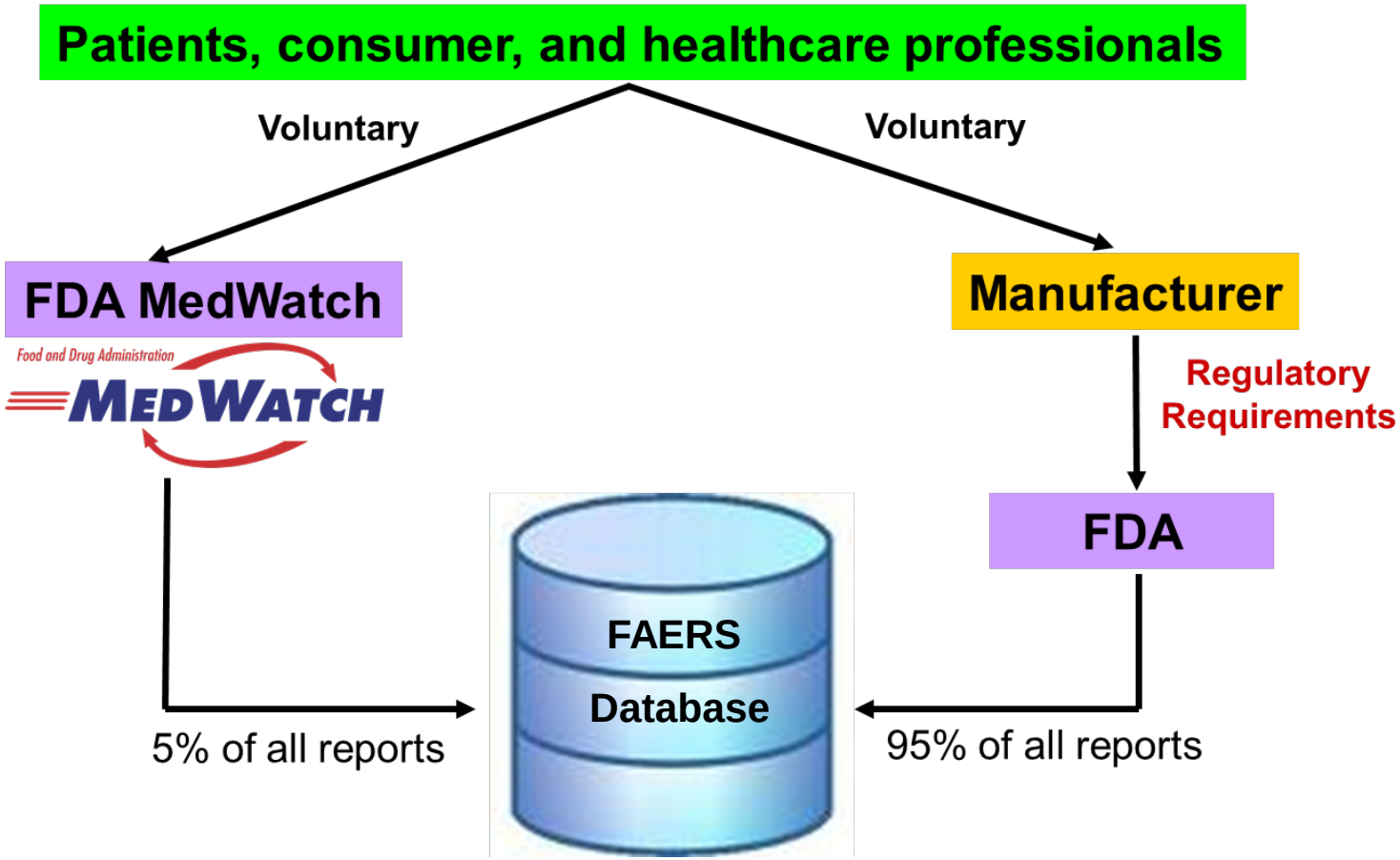
Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee
March 13-14, 2017

Outline

- FDA Adverse Event Reporting System (FAERS) Overview
- Non-oral abuse
- Thrombotic microangiopathy (TMA)
- Summary

FDA ADVERSE EVENT REPORTING SYSTEM

How Postmarketing Reports Get to FDA



FAERS Strengths

- Computerized database
- > 13 million reports since 1968
- Includes all U.S. marketed products
- Includes all uses (both approved and off-label use)
- Includes broad patient populations
- Detection of events not seen in clinical trials
- Detection of events with rare background rate
- Identification of reporting trends, possible risk factors, at risk populations

FAERS Limitations

- Causal relationship between a product and event is not required for reporting to the FDA
- Quality of reports is variable – information is limited in some reports
- Misclassification of reports
- Duplicate reports
- Under-reporting – not every adverse event is reported
- FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population

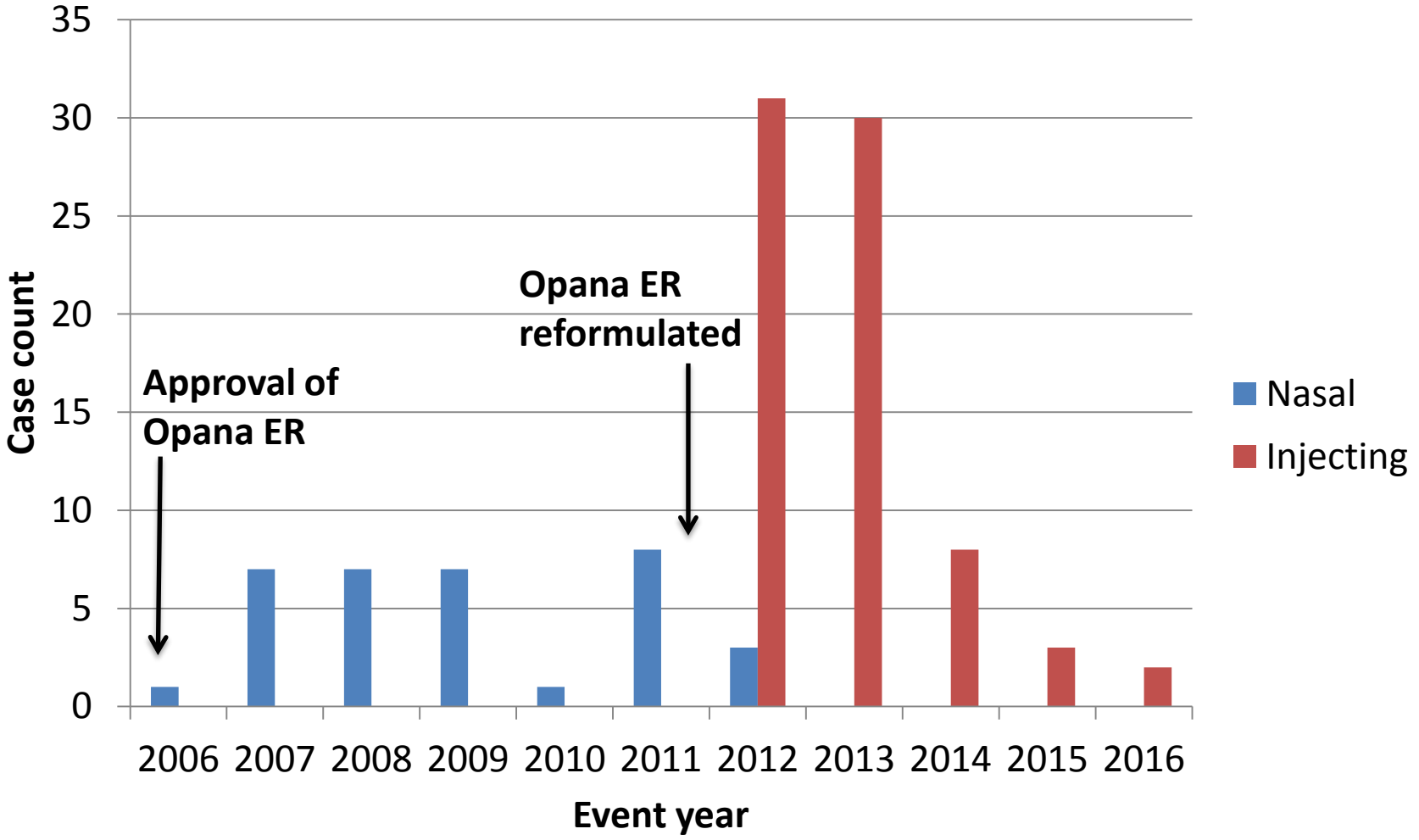
Opana ER and Non-Oral Abuse

- Purpose: qualitatively assess reports of non-oral abuse before and after Opana ER reformulation
- FAERS search
  - Opana ER
  - Event date: approval* - June 1, 2016
  - All adverse events
  - Narrative keywords: inhal, insuffl, inject, intravenous, nasal, smoke, and snort

Non-Oral Abuse: FAERS Case Series			
	Before reformulation*	After reformulation*	Total
Case count	31	77	108

* Original Opana ER was approved on June 22, 2006, and reformulated Opana ER was approved December 9, 2011.

FAERS Cases of Non-Oral Abuse of Opana ER Reporting Event Dates



Thrombotic Microangiopathy

- Arteriolar and capillary thrombosis with characteristic abnormalities in the endothelium and vessel wall
  - Microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and frequently organ injury
- Primary TMA syndromes include thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) among others
- Acquired TTP: 2.9 cases per 1 million per year
- Treatment: Supportive care, plasmapheresis for TTP

George JN, Nester CM. N Engl J Med 2014;371:654-66.

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 62 / No. 1
January 11, 2013

Thrombotic Thrombocytopenic Purpura (TTP)–Like Illness Associated with Intravenous Opana ER Abuse — Tennessee, 2012

Case Definition for TMA

1. Known injection of Opana ER
2. A) Diagnosis of TMA
   - Including TTP or HUS

   OR

   B) Thrombocytopenia AND anemia with evidence of hemolysis.
   - Red cell fragmentation on peripheral smear (e.g., schistocytes), elevated lactate dehydrogenase (LDH), elevated reticulocyte count (without evidence of blood loss) or elevated total bilirubin (without evidence of hepatitis).
3. Absence of an alternative etiology for TMA in the report

Thrombotic Microangiopathy

- FAERS search
  - Opana ER
  - Reports initially received: approval* – June 1, 2016
    - MedDRA (version 19.0) high level group terms:
      - Coagulopathies and bleeding diatheses, Haemolyses and related conditions, Haematological disorders, and Platelet disorders

TMA: FAERS Case Series	
Review Period	**FAERS Cases**
Dec 2011* – Mar 2013	**29**
Mar 2013 – Jun 2016	**30**

* Reformulated Opana ER was approved December 9, 2011

FAERS Cases of TMA with Injection of Opana ER Received from March 27, 2013 to June 1, 2016 (n=30)

Sex	Male (15)	Female (15)	
Age	Mean: 32 years	Median: 28 years	Range: 19 – 52 years
Reporter's State	NC (17); AR (3); SC (3); TN (3); PA (2); FL (1); Unknown (1)		
Initial FDA Received Year	2013	8	
	2014	17	
	2015	4	
	2016	1	
Event Year	2013	8	
	2015	1	
	Unknown	21	
Serious Outcomes* (n=29)	Death	1	
	Hospitalization	27	
	Life-threatening	4	
	Other serious	25	

* Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

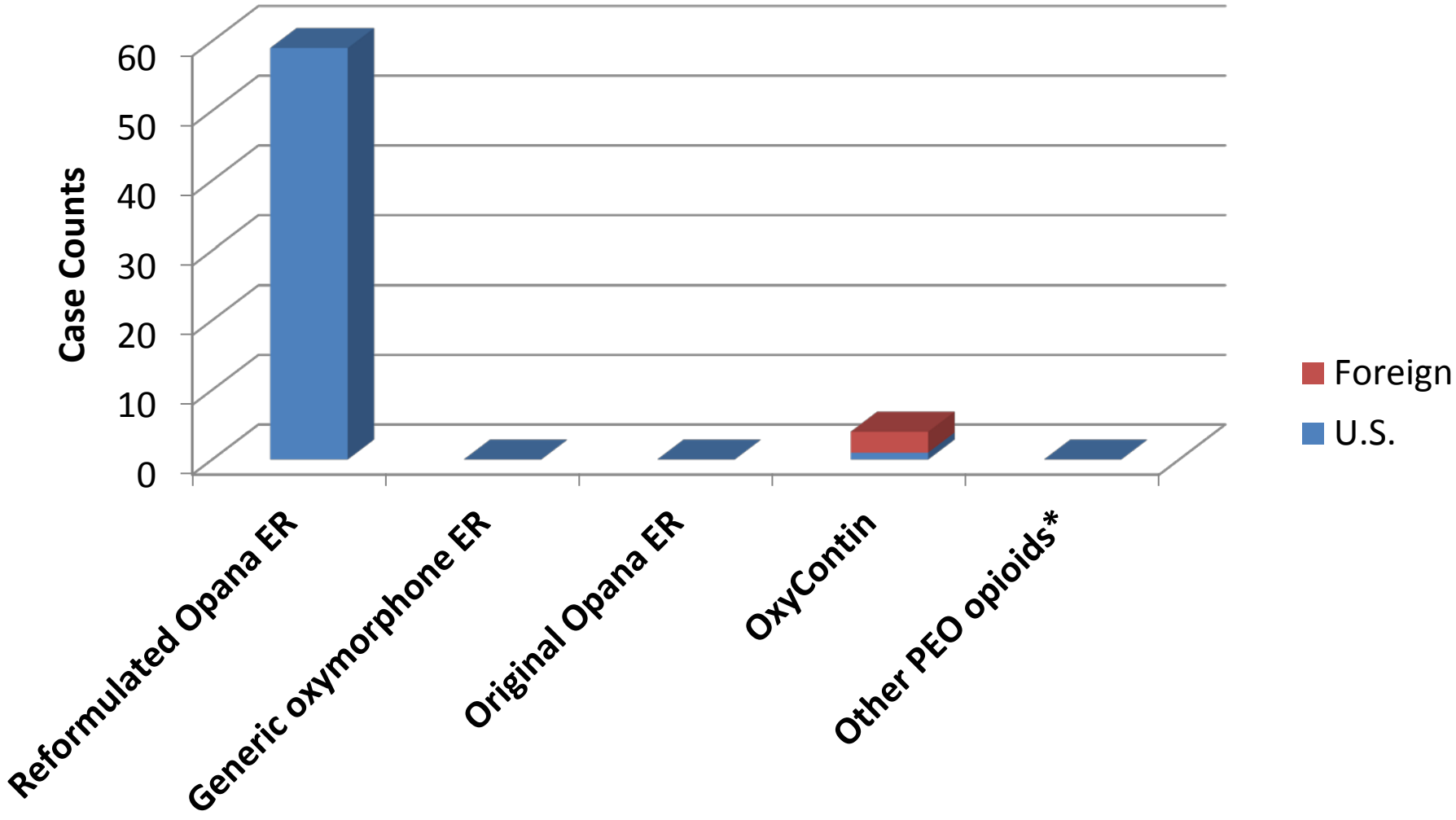
FAERS Cases of TMA with Injection of Opana ER Received from March 27, 2013 to June 1, 2016 (n=30)

Platelet Count on Admission (n=21)	Median: 65 x 10^3/µL Range: 5 – 135 x 10^3/µL
Serum Creatinine on Admission (n=16)	Mean: 3.75 mg/dL Median: 1.94 mg/dL Range: 0.4 – 14.4 mg/dL
Hemoglobin on Admission (n=7)	Median: 8.4 g/dL Range: 5.8 – 11.2 g/dL
Treatment (n=25)*	Plasmapheresis (9) Hemodialysis (4) Platelet transfusion (1) Supportive care (13) Splenectomy (1)
ADAMTS13 (n=13)	Median: 66% Range: 23 – 105%
LDH (n=15)	Median: 554 U/L Range: 294 – 4000 U/L
Schistocytes	Present (10) Not reported (20)

ADAMTS13 = A Disintegrin And Metalloprotease with a ThromboSpondin type 1 motif, member 13

* Some cases reported one or more treatments

FAERS Cases of TMA Associated with Injection of Opioids



* Hysingla ER, Nucynta ER, and Zohydro ER

FAERS Case Report

- A 43-year-old female with a previous history of substance abuse presented with abdominal pain to a hospital in eastern Tennessee.
- Laboratory evaluation showed thrombocytopenia, and schistocytes with LDH elevation, indicating hemolysis.
- Treatment included two courses of plasma exchange; a subsequent assay of her ADAMTS13 activity was normal.
- Later, she reported intravenous injection of OxyContin 60 mg six days prior to admission.
  - "She removed the hard shell, dissolved the contents in water and heated and then pulled up the substance with a syringe through a cigarette filter. It was then intravenously injected."
- Denied Opana ER abuse and reported only one instance of intravenous drug injection.

Summary

- Non-oral abuse of Opana ER before and after reformulation
  - Shift in route of abuse from nasal to injection following reformulation
- FAERS continues to receive reports of TMA associated with injection of reformulated Opana ER

Mechanisms Underlying Thrombotic Microangiopathy Associated with Intravenous Opana ER Abuse

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U.S. Food and Drug Administration

March 13-14, 2017

Joint Meeting of the Drug Safety and Risk Management Advisory Committee (DSaRM)
and the
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

CBER's Involvement

Chava Kimchi-Sarfaty (OTAT/CBER)

Expertise in ADAMTS13, VWF and TTP

Paul Buehler (OBRR/CBER)

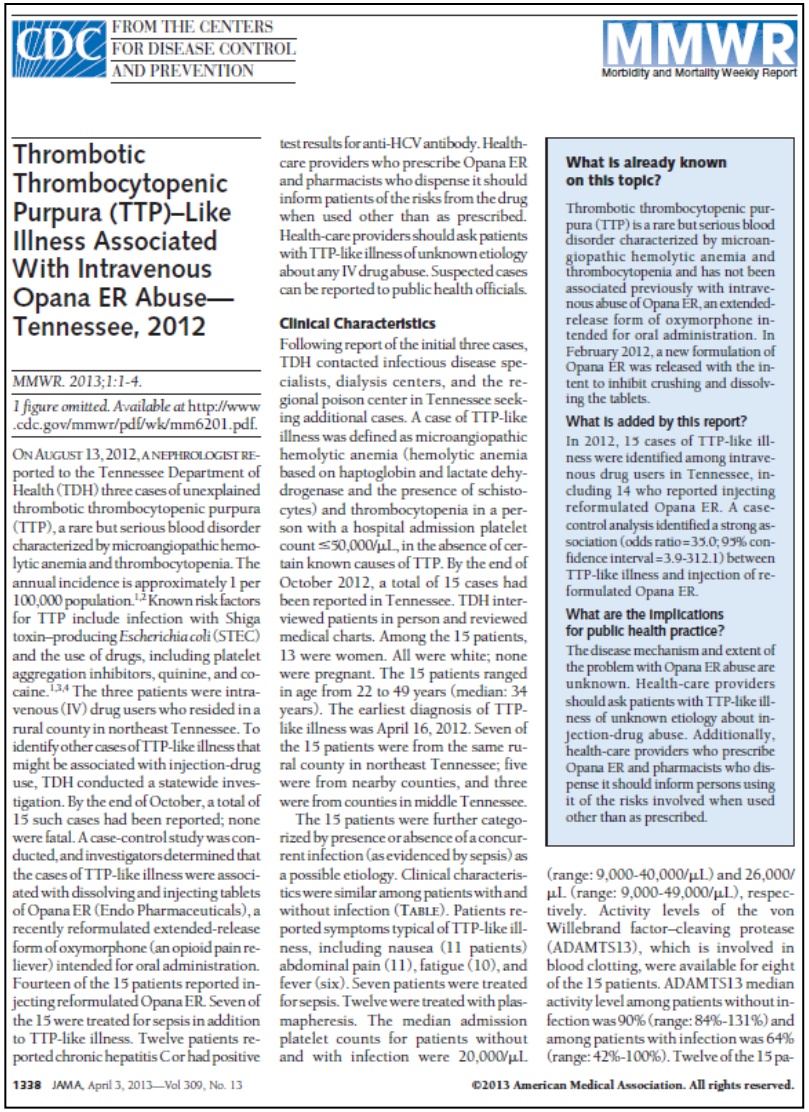
Expertise in toxicology & hemolysis/cell free hemoglobin

"TTP-like illness"

Judith Racoosin (DAAAP/CDER)

Neil Shusterman (Endo)

Paulozzi, Leonard J (CDC)



CDC FROM THE CENTERS FOR DISEASE CONTROL AND PREVENTION

MMWR Morbidity and Mortality Weekly Report

Thrombotic Thrombocytopenic Purpura (TTP)–Like Illness Associated With Intravenous Opana ER Abuse—Tennessee, 2012

MMWR. 2013;1:1-4.

1 figure omitted. Available at http://www.cdc.gov/mmwr/pdf/wk/mm6201.pdf.

ON AUGUST 13, 2012, A NEPHROLOGIST REported to the Tennessee Department of Health (TDH) three cases of unexplained thrombotic thrombocytopenic purpura (TTP), a rare but serious blood disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia. The annual incidence is approximately 1 per 100,000 population.[1,2] Known risk factors for TTP include infection with Shiga toxin–producing *Escherichia coli* (STEC) and the use of drugs, including platelet aggregation inhibitors, quinine, and cocaine.[1,3,4] The three patients were intravenous (IV) drug users who resided in a rural county in northeast Tennessee. To identify other cases of TTP-like illness that might be associated with injection-drug use, TDH conducted a statewide investigation. By the end of October, a total of 15 such cases had been reported; none were fatal. A case-control study was conducted, and investigators determined that the cases of TTP-like illness were associated with dissolving and injecting tablets of Opana ER (Endo Pharmaceuticals), a recently reformulated extended-release form of oxymorphone (an opioid pain reliever) intended for oral administration. Fourteen of the 15 patients reported injecting reformulated Opana ER. Seven of the 15 were treated for sepsis in addition to TTP-like illness. Twelve patients reported chronic hepatitis C or had positive test results for anti-HCV antibody. Healthcare providers who prescribe Opana ER and pharmacists who dispense it should inform patients of the risks from the drug when used other than as prescribed. Health-care providers should ask patients with TTP-like illness of unknown etiology about any IV drug abuse. Suspected cases can be reported to public health officials.

Clinical Characteristics

Following report of the initial three cases, TDH contacted infectious disease specialists, dialysis centers, and the regional poison center in Tennessee seeking additional cases. A case of TTP-like illness was defined as microangiopathic hemolytic anemia (hemolytic anemia based on haptoglobin and lactate dehydrogenase and the presence of schistocytes) and thrombocytopenia in a person with a hospital admission platelet count ≤50,000/µL, in the absence of certain known causes of TTP. By the end of October 2012, a total of 15 cases had been reported in Tennessee. TDH interviewed patients in person and reviewed medical charts. Among the 15 patients, 13 were women. All were white; none were pregnant. The 15 patients ranged in age from 22 to 49 years (median: 34 years). The earliest diagnosis of TTP-like illness was April 16, 2012. Seven of the 15 patients were from the same rural county in northeast Tennessee; five were from nearby counties, and three were from counties in middle Tennessee.

The 15 patients were further categorized by presence or absence of a concurrent infection (as evidenced by sepsis) as a possible etiology. Clinical characteristics were similar among patients with and without infection (TABLE). Patients reported symptoms typical of TTP-like illness, including nausea (11 patients) abdominal pain (11), fatigue (10), and fever (six). Seven patients were treated for sepsis. Twelve were treated with plasmapheresis. The median admission platelet counts for patients without and with infection were 20,000/µL (range: 9,000-40,000/µL) and 26,000/µL (range: 9,000-49,000/µL), respectively. Activity levels of the von Willebrand factor–cleaving protease (ADAMTS13), which is involved in blood clotting, were available for eight of the 15 patients. ADAMTS13 median activity level among patients without infection was 90% (range: 84%-131%) and among patients with infection was 64% (range: 42%-100%). Twelve of the 15 pa-

What is already known on this topic?

Thrombotic thrombocytopenic purpura (TTP) is a rare but serious blood disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia and has not been associated previously with intravenous abuse of Opana ER, an extended-release form of oxymorphone intended for oral administration. In February 2012, a new formulation of Opana ER was released with the intent to inhibit crushing and dissolving the tablets.

What is added by this report?

In 2012, 15 cases of TTP-like illness were identified among intravenous drug users in Tennessee, including 14 who reported injecting reformulated Opana ER. A case-control analysis identified a strong association (odds ratio=33.0; 95% confidence interval=3.9-312.1) between TTP-like illness and injection of reformulated Opana ER.

What are the implications for public health practice?

The disease mechanism and extent of the problem with Opana ER abuse are unknown. Health-care providers should ask patients with TTP-like illness of unknown etiology about injection-drug abuse. Additionally, health-care providers who prescribe Opana ER and pharmacists who dispense it should inform persons using it of the risks involved when used other than as prescribed.

1338 JAMA, April 3, 2013—Vol 309, No. 13

Name	Cause	Initial Management
Hereditary disorders		
ADAMTS13 deficiency mediated TMA (also called TTP)	Homozygous or compound heterozygous *ADAMTS13* mutations	Plasma infusion
Complement-mediated TMA	Mutations in *CFH*, *CFI*, *CFB*, *C3*, *CD46*, and other complement genes	Plasma infusion or exchange, anti-complement agent
Metabolism-mediated TMA	Homozygous mutations in *MMACHC*	Vitamin B_{12}, betaine, Folinic acid
Coagulation-mediated TMA	Homozygous mutations in *DGKE*; mutations in *PLG* and *THBD*	Plasma infusion
Acquired disorders		
ADAMTS13 deficiency mediated TMA (also called TTP)	Autoantibody inhibition of ADAMTS13	Plasma exchange, immunosuppression
Shiga toxin-mediated TMA	Enteric infection with a Shiga toxin-secreting strain of *E. coli* or *Shigella*	supportive care
Drug-mediated TMA- immune reaction	Quinine and possibly other drugs, with multiple cells affected by drug-dependent antibodies	Removal of drug, supportive care
Drug-mediated TMA- toxic dose-related reaction	Multiple potential mechanisms (e.g., VEGF inhibition)	Removal of drug, supportive care
Complement-mediated TMA	Antibody inhibition of complement factor H	Plasma exchange, immunosuppression, anticomplement agent

Primary Thrombotic Microangiopathy (TMA) Syndromes

Common pathological features

- vascular damage manifested by arteriolar and capillary thrombosis

Common clinical features

- microangiopathic hemolytic anemia
- thrombocytopenia
- organ injury

Adapted from:
George JN, Nester CM. N Engl J Med 2014;371:654-666.

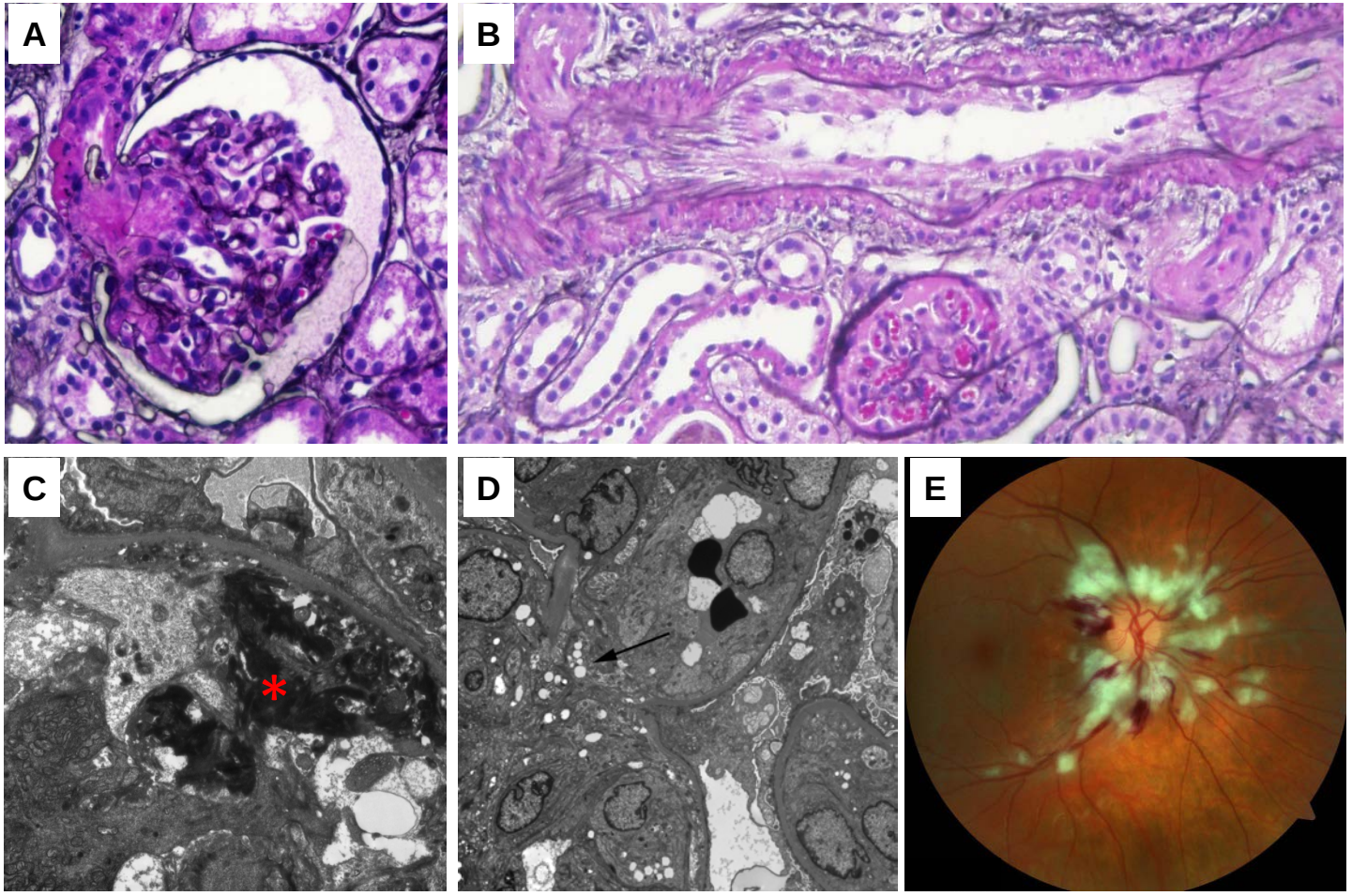
3 Patients with TMA Following Intravenous Abuse of Opana ER: Clinical Characteristics & Laboratory Abnormalities

Dr. James Tumlin, University of Tennessee College of Medicine

	Patient 1	Patient 2	Patient 3
Age (years)	24	28	48
Gender	female	male	female
Presenting symptoms	numbness of extremities, vision loss	angina, dyspnea, abdominal pain, vision loss	angina, dyspnea, abdominal pain, diarrhea, numbness of extremities, vision loss
Treatment	5X plasma exchange	9X plasma exchange	5X plasma exchange
WBC (4.5-11 k/µL)	12.6	23.3	WNL
Hemoglobin (13.5-17.5 g/dL)	11.2	7.7	7.7
Hematocrit (35-50 %)	31.9	22.8	23.3
Platelet count (150-450 k/µL)	43	18	20
Creatinine (0.6-1.3 mg/dL)	WNL	2.2	1.6
LDH (140-280 U/L)	1507	1981	2584
Haptoglobin (30-200 mg/dL)	undetectable	undetectable	undetectable
ADAMTS13	66%	64%	ND
D-Dimer (≤0.5 µg/mL)	0.97	ND	ND
Troponin I (<0.01 ng/mL)	6.14	4.95	12.83

Adapted from: Hunt, R. et al. A mechanistic investigation of thrombotic microangiopathy associated with intravenous abuse of Opana ER. Blood, doi:10.1182/blood-2016-08-736579 (2016)

Patient Kidney Biopsies and Retinal Fundus Photograph Following Intravenous Abuse of Opana ER



Adapted from: Hunt, R. et al. A mechanistic investigation of thrombotic microangiopathy associated with intravenous abuse of Opana ER. Blood, doi:10.1182/blood-2016-08-736579 (2016)

Can TMA Be Generated in Animals Injected with the Inert Ingredients Found in Opana ER?

Placebo powder of
Opana ER inert ingredients

- **HMW PEO**
- hypromellose
- macrogol
- alpha-tocopherol
- citric acid

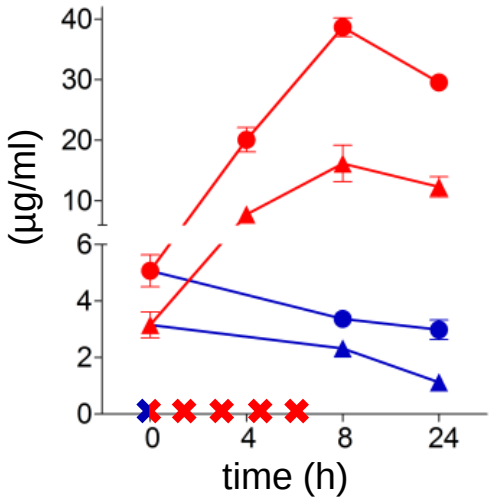
solubilize

Hartley guinea pig

Inert ingredient
dosing groups

- 5X 0.3 mg/kg
- 5X 0.1 mg/kg
- 1X 0.3 mg/kg
- 1X 0.1 mg/kg
- Control

Plasma PEO
concentration



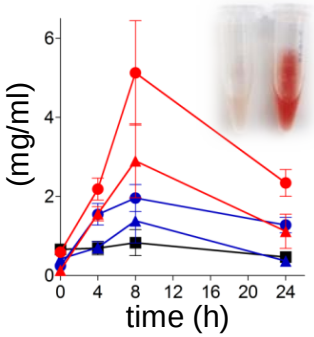
= injection

Signs of TMA In Peripheral Blood Following IV Administration of Inactive Ingredients in Guinea Pigs

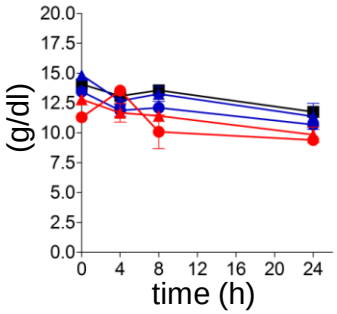
Inactive ingredient dosing groups

- 5X 0.3 mg/kg
- 5X 0.1 mg/kg
- 1X 0.3 mg/kg
- 1X 0.1 mg/kg
- Control

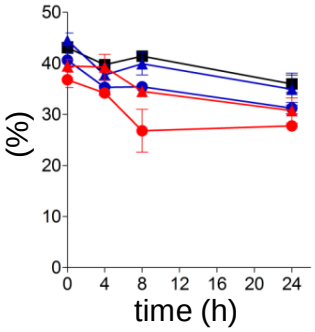
Plasma free Hb



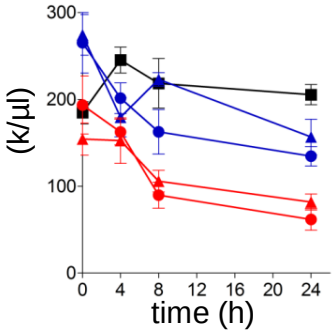
RBC Hb



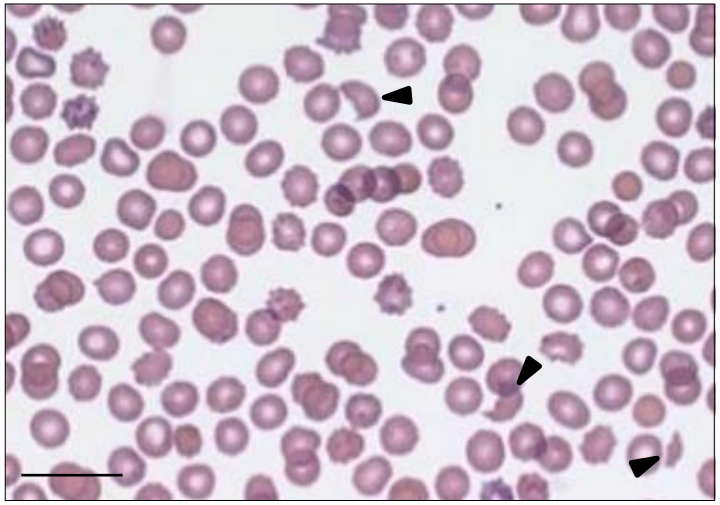
Hematocrit



Platelet count

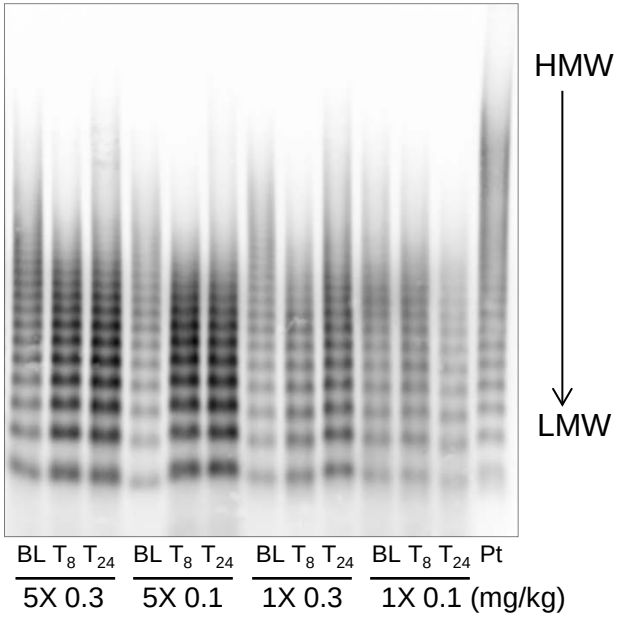


Peripheral blood smear



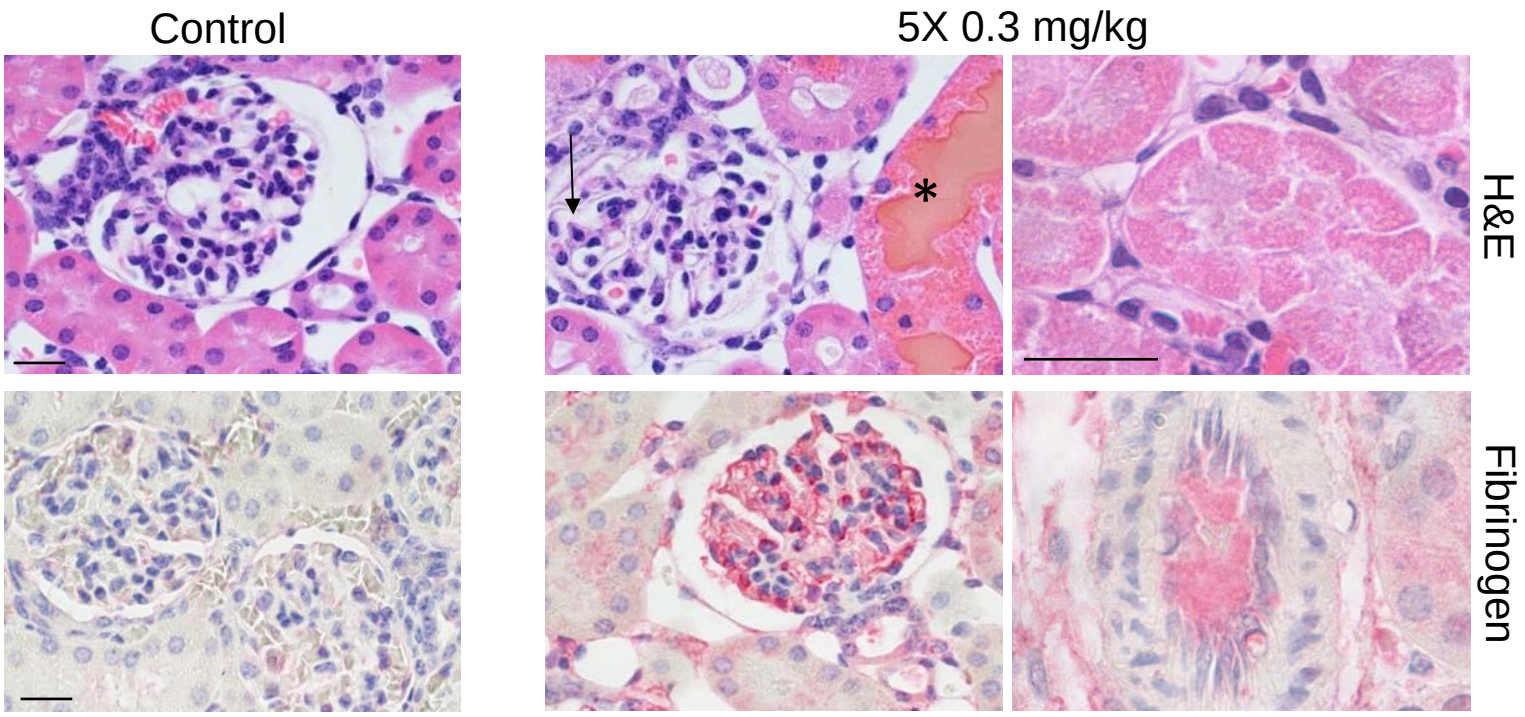
5X 0.1 mg/kg treated animal

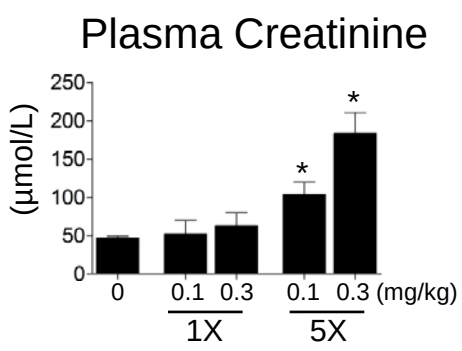
VWF multimer profile

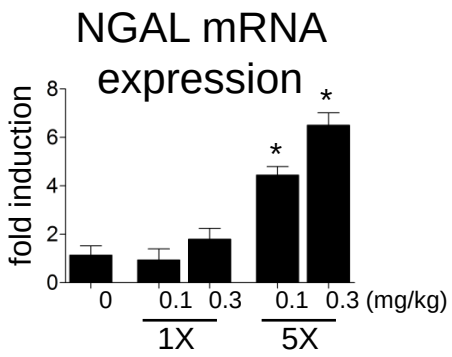


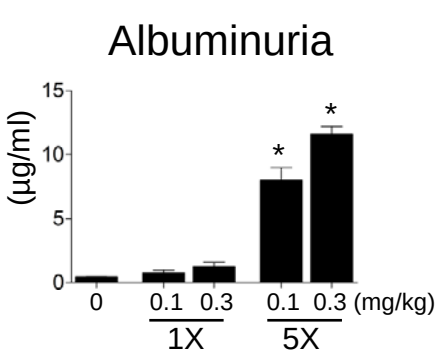
Adapted from: Hunt, R. et al. A mechanistic investigation of thrombotic microangiopathy associated with intravenous abuse of Opana ER. Blood, doi:10.1182/blood-2016-08-736579 (2016)

Acute Renal Injury Following IV Administration of Inactive Ingredients in Guinea Pigs



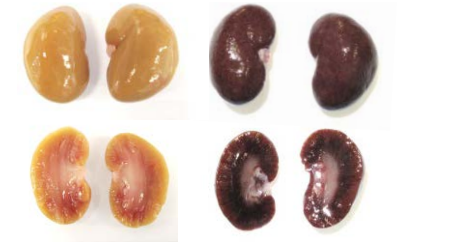


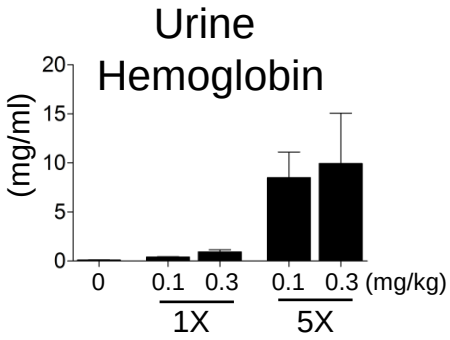


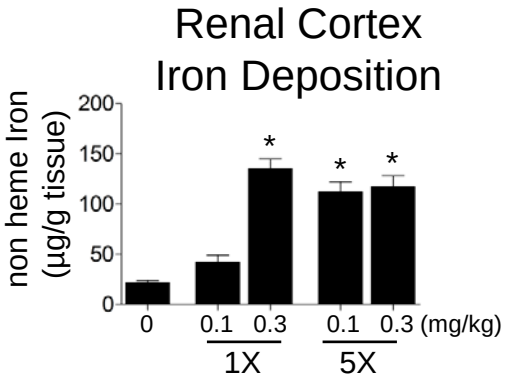


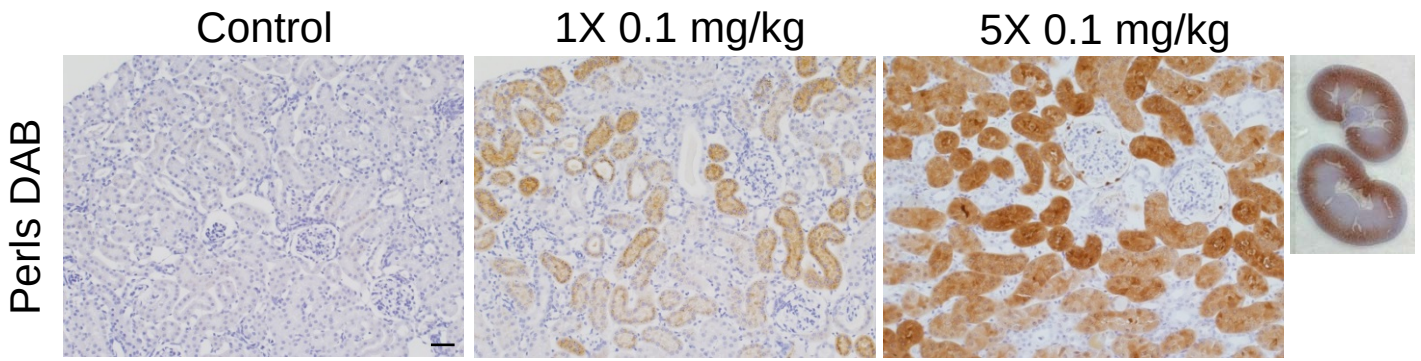
Adapted from: Hunt, R. et al. A mechanistic investigation of thrombotic microangiopathy associated with intravenous abuse of Opana ER. Blood, doi:10.1182/blood-2016-08-736579 (2016)

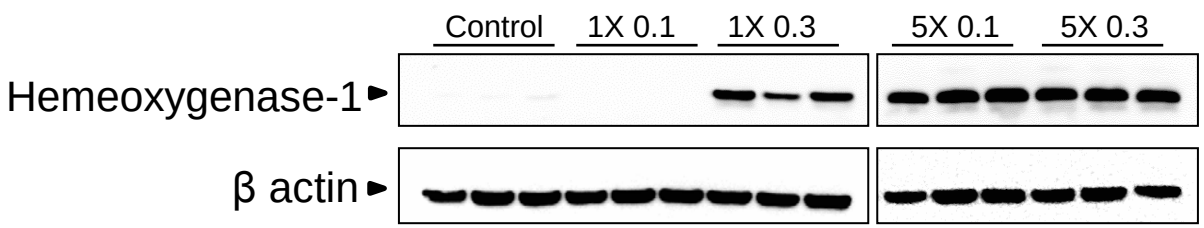
Renal Iron Deposition Following IV Administration of Inactive Ingredients in Guinea Pigs

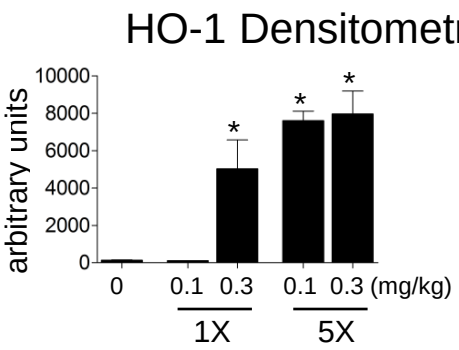






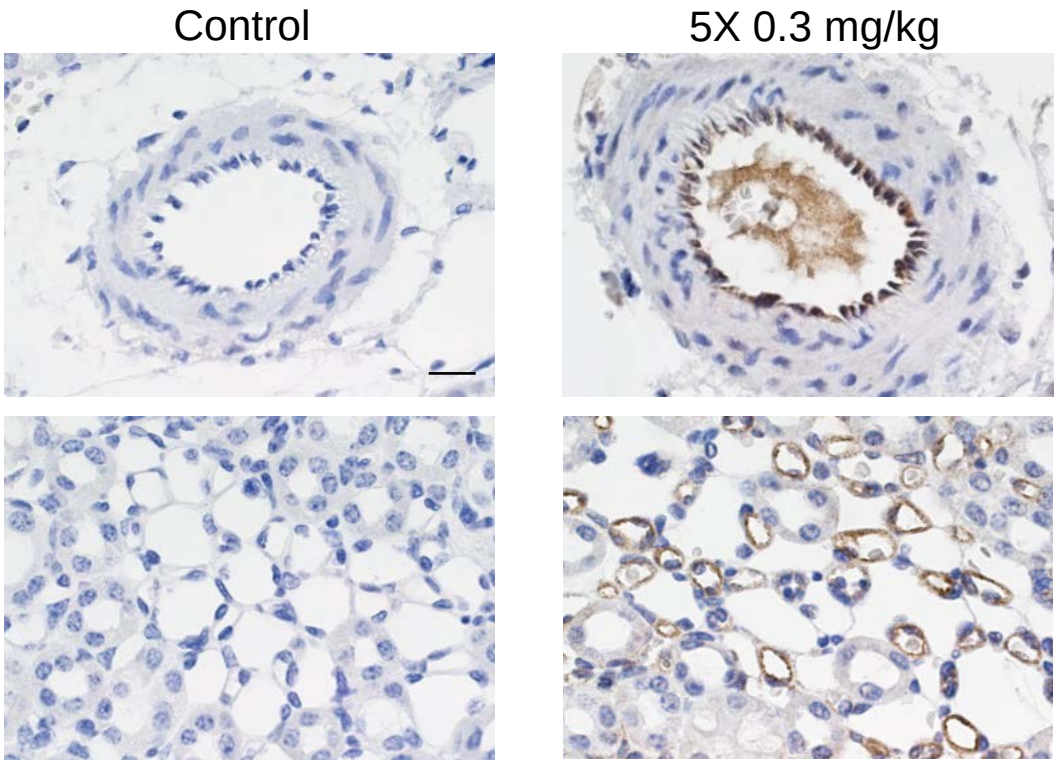


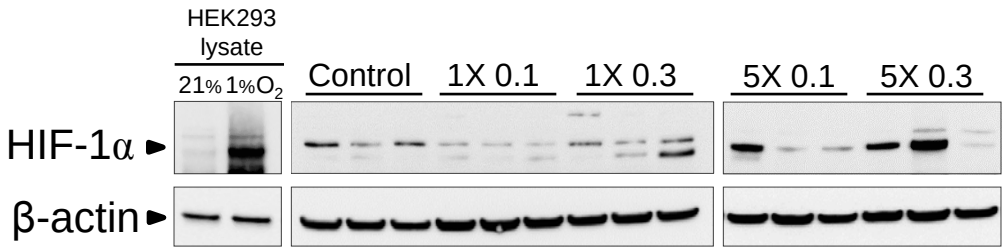


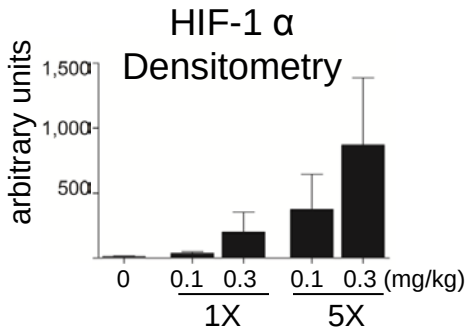


Adapted from: Hunt, R. et al. A mechanistic investigation of thrombotic microangiopathy associated with intravenous abuse of Opana ER. Blood, doi:10.1182/blood-2016-08-736579 (2016)

Identification of HMW PEO in the Small Arteries & Microvasculature of the Kidney







Conclusions

- **A mechanistic link exists between the constituents of the Opana ER tablet and cases of thrombotic microangiopathy (TMA):**
  i. Dose-dependent intravascular hemolysis and kidney injury occurred following IV injection of the inert ingredients
  ii. Driven primarily by HMW PEO

- **Determinants of likelihood for thrombotic microangiopathy in humans:**
  i. dose and frequency of injection
  ii. method?

Unanswered questions

- **Reasons for apparent higher rates of TMA associated with IV Opana ER abuse vs other opioids formulated with HMW PEO:**
  tablet –specific vs. external factors

- **Best treatment approach:**
  supportive care alone vs. plasma exchange therapy

Acknowledgements

Ayla Yalamanoglu (OBRR/CBER)
Jin Hyen Baek (OBRR/CBER)
Paul W. Buehler (OBRR/CBER)
Chava Kimchi-Sarfaty (OTAT/CBER)

Neil Shusterman

James Tumlin

Peter Miller

Agnes B. Fogo
Haichun Yang

Statistical Considerations for Evaluating the Abuse-Related Outcomes of Reformulated Opana ER

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Office of Biostatistics
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee
March 13—14, 2017

Outline

- **Observational Studies**
- **Statistical Considerations**
  - **Data quality**
  - **Estimability***
  - **Causality***
  - **Interpretation**
- **Summary**

*Kunthel By, Ph.D.
Important Statistical Considerations in the Evaluation of Post-market Studies to Assess Whether Opioids With Abuse-Deterrent Properties Result in Reduced Abuse In the Community (paper under review)

Outline

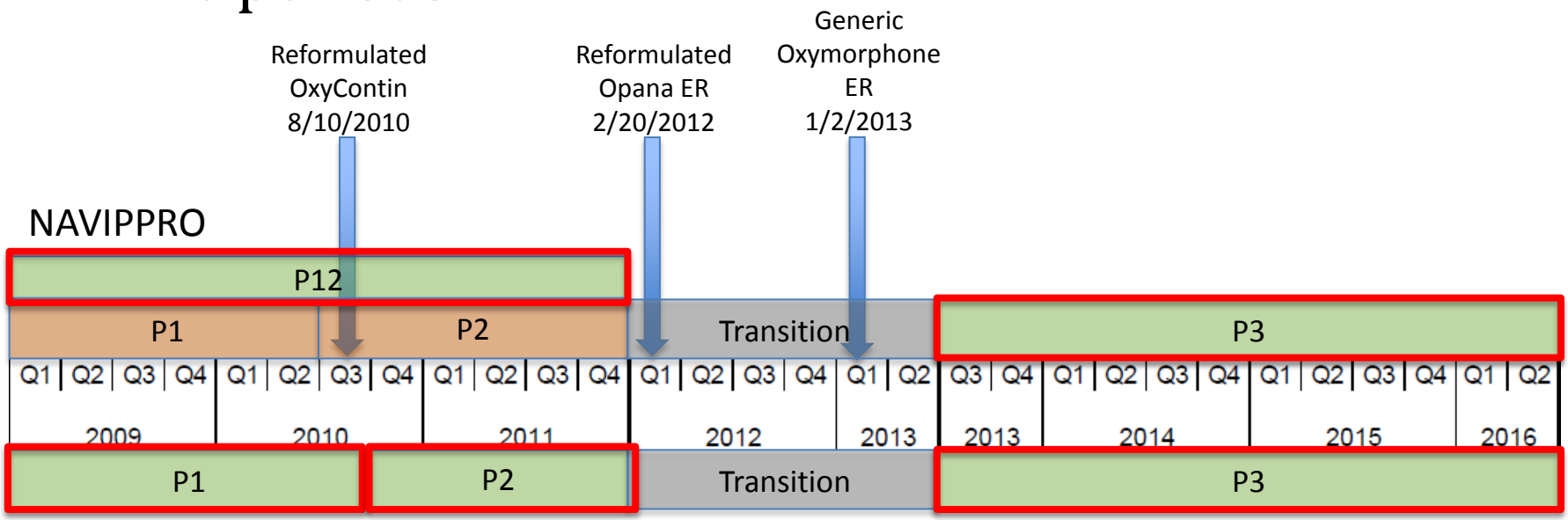
- **Observational Studies**

- Statistical Considerations
  - Data quality
  - Estimability
  - Causality
  - Interpretation

- Summary

Observational Studies

- Two formal observational studies
  - NAVIPPRO
  - RADARS PC
- Time periods



Obs. Studies: NAVIPPRO

- Primary Comparisons
  - P12 vs. P3 abuse measures of Opana ER
  - P3 Opana ER vs. P3 comparator abuse measures
- Outcomes
  - Overall abuse
  - Alternate routes abuse
  - Route specific abuse
- Denominators
  - Prevalence: per 100 assessments
  - Tb rate: per 10,000 dosage units (tablets/pills) dispensed

P12 = Three-year period before Opana ER reformulation (three-year pre period)
P3 = Time period after Opana ER reformulation (post period)

Obs. Studies: RADARS PC

- Primary Comparisons
  - P1 vs. P2, P2 vs. P3 abuse measures of Opana ER
  - P1 vs. P3 changes between Opana ER and comparators
- Outcomes
  - Intentional abuse
  - Death and major medical outcome
  - Overdose
- Denominators
  - Prevalence: per 100,000 population
  - Tb rate: per 10,000 dosage units dispensed
  - Rx rate: per 1,000 prescriptions dispensed

P1 = Time period before OxyContin reformulation
P2 = Time period after OxyContin reformulation and before Opana ER reformulation
P3 = Time period after Opana ER reformulation

Outline

- Observational studies
- Statistical Considerations
  - **Data quality:** Does the data measure what it is supposed to measure?
  - Estimability
  - Causality
  - Interpretation
- Summary

Outline

- Observational studies
- Statistical Considerations
  - Data quality
  - **Estimability:** Can the data be used to make inference about the population?
  - Causality
  - Interpretation
- Summary

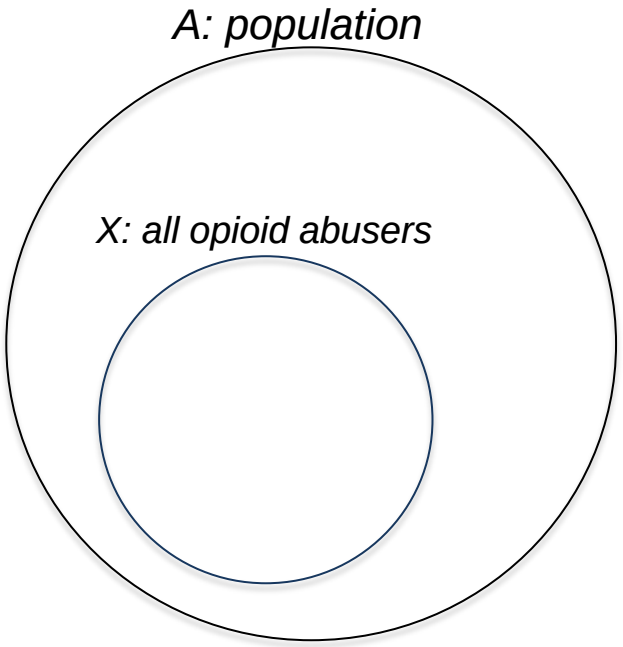
Estimability

- Can the data be used to make statements about the extent of overall abuse of Opana ER, in absolute or relative terms, in the underlying population?

- Can the data be used to make statements about shifts in the pattern of Opana ER abuse from the nasal to the intravenous route of abuse after reformulation?

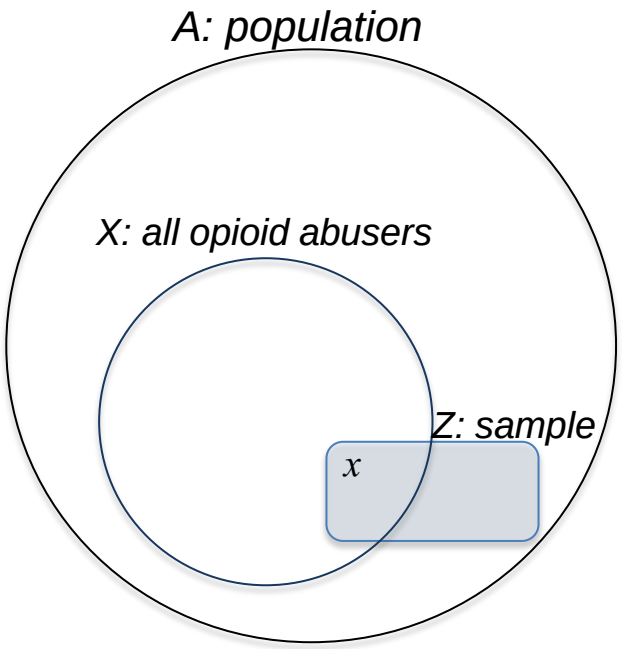
Estimability

- Population data---ideal
  - Count the number in *A*
  - Count the number in *X*
  - Compute and compare the prevalences in P1 (pre period) and P3 (post period)



Estimability

- Study data---surveillance sample
  - Not random in either study
  - Captures a small fraction of population
  - Catchment area changes over time
  - Surveillance questionnaire may change over time



- Can we estimate some abuse-related quantities in the population using data from the sample?

Estimability: Prevalence

- Population prevalence
  - Pre period $P_0 = \frac{\#\text{ of abusers in the } \mathbf{pre} \text{ period in } X}{\#\text{ of individuals in the } \mathbf{pre} \text{ period in } A}$
  - Post period $P_1 = \frac{\#\text{ of abusers in the } \mathbf{post} \text{ period in } X}{\#\text{ of individuals in the } \mathbf{post} \text{ period in } A}$
- Sample prevalence
  - Pre period $p_0 = \frac{\#\text{ of abusers in the } \mathbf{pre} \text{ period in } x}{\#\text{ of individuals in the } \mathbf{pre} \text{ period in Z}}$
  - Post period $p_1 = \frac{\#\text{ of abusers in the } \mathbf{post} \text{ period in } x}{\#\text{ of individuals in the } \mathbf{post} \text{ period in } Z}$

Estimability: Prevalence

- $p_0 \stackrel{?}{=} P_0$ and $p_1 \stackrel{?}{=} P_1$

- ***Assumption 1***

  Selection into the sample is independent of the substance being abused.

- Sample plausibility: ~~Assumption 1~~

  If individuals who abuse Opana ER tend to interact more with treatment centers than abusers of other opioids

Estimability: Ratios

- Post vs pre prevalence ratio
  - Population: $\mathrm{RP} = \frac{P_1}{P_0}$
  - Sample: $\mathrm{rp} = \frac{p_1}{p_0}$

- $rp \stackrel{?}{=} RP$

- ***Assumption 2.***

  If selection into the sample depends on the substances being abused, then the nature of the dependence does not change over time.

Estimability: Ratios

- Sample plausibility: ~~Assumption 2~~
  - If treatment sites were added or dropped in the post period in areas with more or less Opana ER abuse

Table 4: States with double-digit changes in the number ASI-MV sites from the pre to the post period

State	Total ASI-MV sites pre period	Total ASI-MV sites post period	Opana ER abuse prev. pre period
Tennessee	26	38	8.52%
Florida	16	39	0.73%
Michigan	9	50	0.68%
Missouri	43	70	0.48%
Oklahoma	57	67	0.18%
New Mexico	131	17	0.10%
Wyoming	15	30	0.00%

  - If policy changes that encouraged or discouraged people to be assessed by NAVIPPRO in the post period

Estimability: Ratio-Ratio

Measures the relative post-pre change between drug d and Opana ER

- Population: $RRP_d = \frac{RP_d}{RP_{Op}}$

- Sample: $rrp_d = \frac{rp_d}{rp_{Op}}$

Estimability: Ratio-Ratio

- $rrp_d \stackrel{?}{=} RRP_d$

- ***Assumption 3.***

  If selection into the sample depends on the substances being abused, and the nature of the dependence changes over time, then the change in the dependence is the same for Opana ER and the comparator opioid.

Estimability: Ratio-Ratio

- Sample plausibility: ~~Assumption 3~~

  If dramatic changes in number of assessments in some states + these states have different opioid abuse prevalences

Table 5: Number (percentage) of assessments in states that contributed more than 10% of ASI-MV data in the pre and the post period in NAVIPPRO study

State	Pre Period N = 206,417	Post Period N = 168,078
Missouri	11,869 (5.8%)	24,818 (14.8%)
North Carolina	33,679 (16.3%)	20,246 (12.1%)
New Mexico	56,667 (27.5%)	5,038 (3.0%)
Oklahoma	18,815 (9.1%)	22,105 (13.2%)
Tennessee	4,724 (2.3%)	20,294 (12.1%)

Source: created by reviewer using submitted NAVIPPRO data

Estimability: Change in ROA

For the ROA change in the sample to reflect relevant ROA change in the underlying population, we need:

1. Selection into the sample is independent of the ROA;
2. If selection into the sample depends on the ROA, then the nature of the dependence does not change over time;
3. If selection into the sample depends on the ROA and the nature of the dependence changes over time, then the change in the dependence is the same for Opana ER and the comparator opioid.

ROA = route of abuse

Outline

- **Observational studies**
- **Statistical Considerations**
  - **Data quality**
  - **Estimability**
  - **Causality:** Can the estimated effects be attributed to the reformulation?
  - **Interpretation**
- **Summary**

Causality

- External factors may vary the abuse pattern
  - DEA efforts to reduce opioid abuse
  - Law enforcement, education efforts to reduce abuse
  - FDA Risk Evaluation and Mitigation Strategies
  - Social trends, availability and cost of alternate drugs

- How to separate the effect due to reformulation?

Causality

Change in Opana ER
- Reformulation
- Secular trends

versus

Change in Comparators
- Secular trends

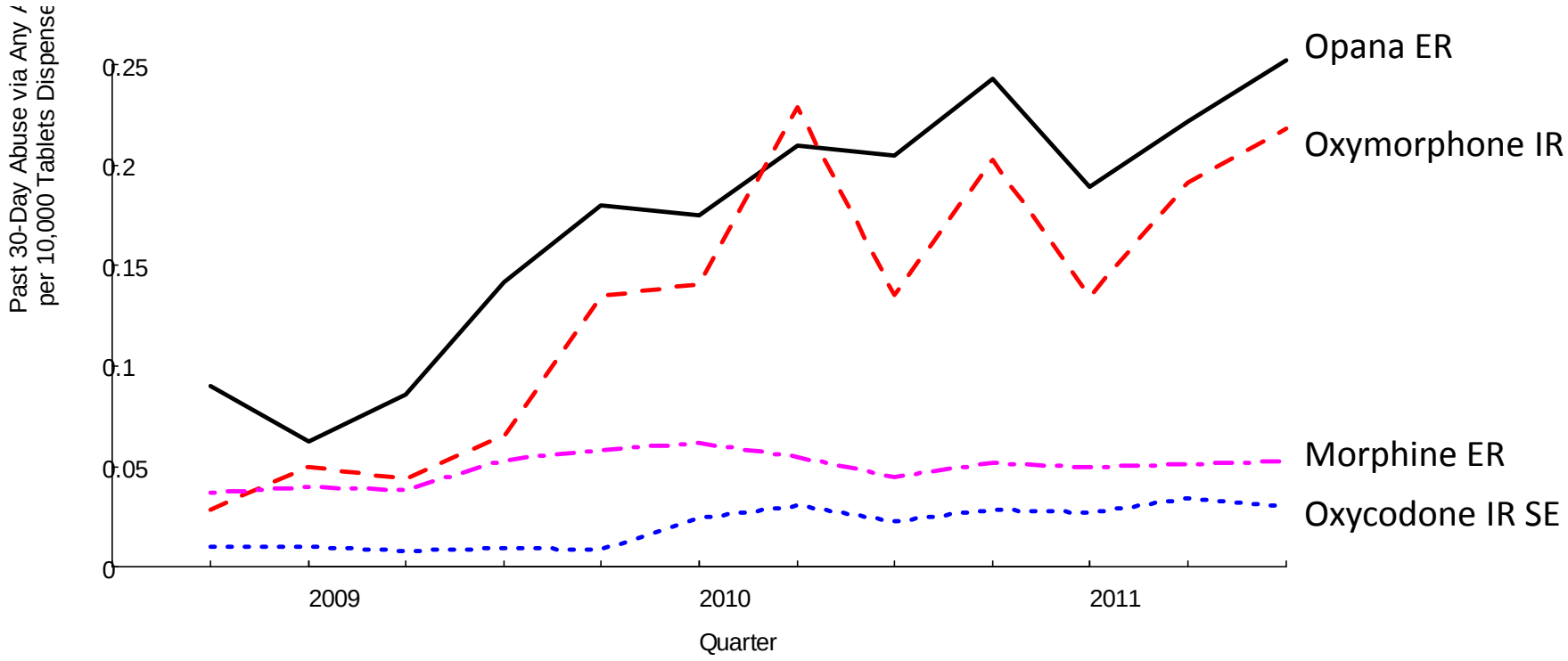
Change in Opana ER
- Reformulation

- Similarity
  - In the pre period
  - In the post period
    - Affected by external factors similarly over time
  - Different from Opana ER **only** in reformulation

- Verify similarity in surveillance samples
  - Abuse rates
  - Abuse rate trends
  - Abuse through specific ROA

Causality

- Pre period overall abuse
  - Opana ER, oxymorphone IR similar, high Tb rate
  - Morphine ER, oxycodone IR SE similar, low Tb rates



Outline

- **Observational studies**
- **Statistical Considerations**
  - **Data quality**
  - **Estimability**
  - **Causality**
  - **Interpretation:** How do we interpret the observed effects in the context of
    - Data quality (covered by Dr. McAninch later)
    - Estimability
    - Causality
- Summary

Interpretation

- Time periods considered: P1 and P3
  - More homogeneity between Opana ER and comparators
  - P2 may present another aspect of time period before Opana ER reformulation

- Comparisons
  - Opana post vs pre ratios: *rp* and *rr*
  - Opana vs comparators ratio-ratio: *rrp* and *rrr*

Interpretation

- Comparators
  - NAVIPPRO

    morphine ER, oxycodone IR SE, oxymorphone IR, generic oxymorphone ER
  - RADARS PC

    morphine ER

- ***Assumption 4.***

  The abuse pattern of generic oxymorphone ER in the pre period, if it existed, should have been exactly or approximately the same as the abuse pattern of Opana ER in the pre period.

Interpretation: NAVIPPRO

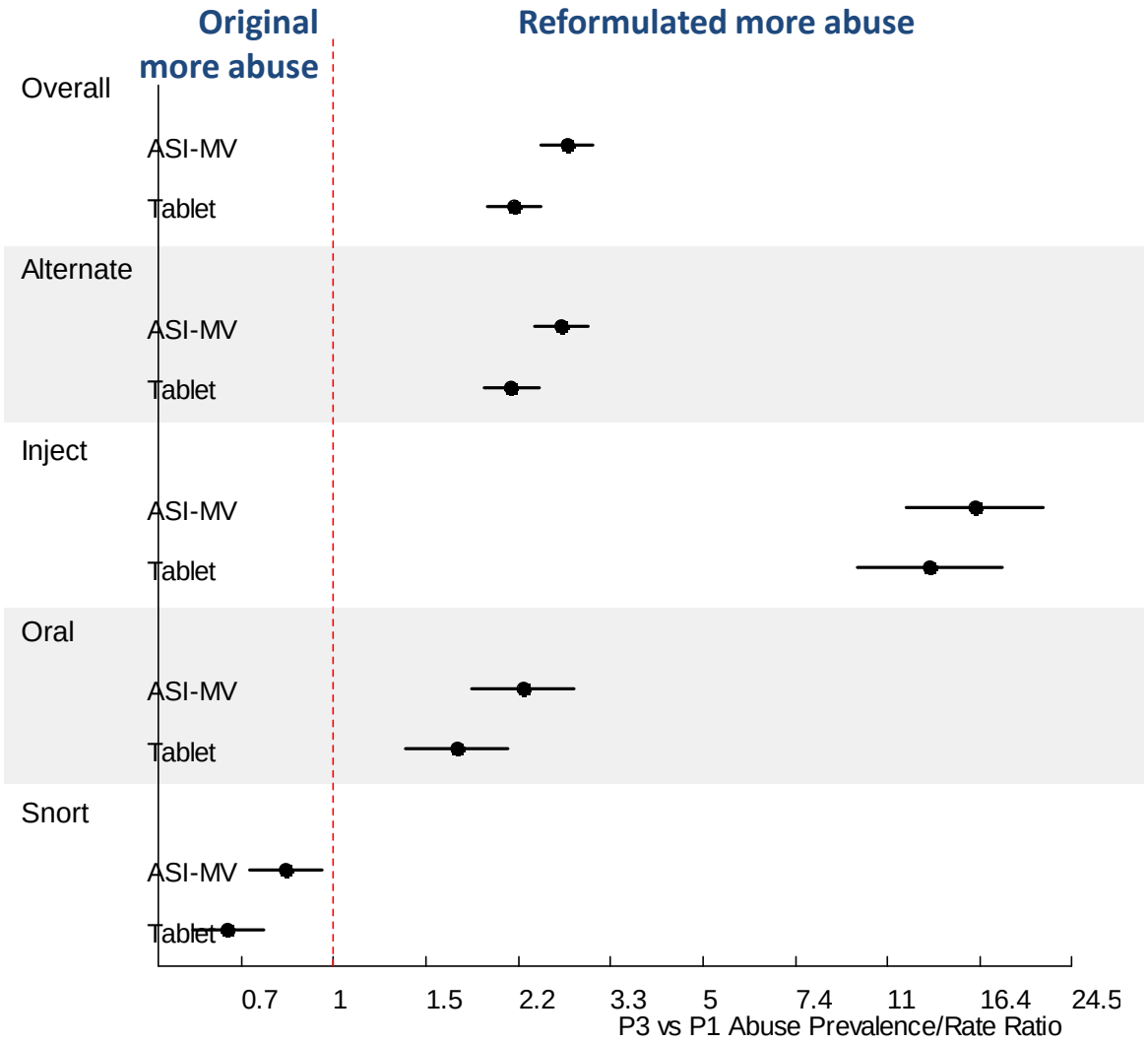


Figure 1: Prevalence/rate ratio of past 30-day overall abuse of Opana ER comparing P3 to P1.

Interpretation: NAVIPPRO

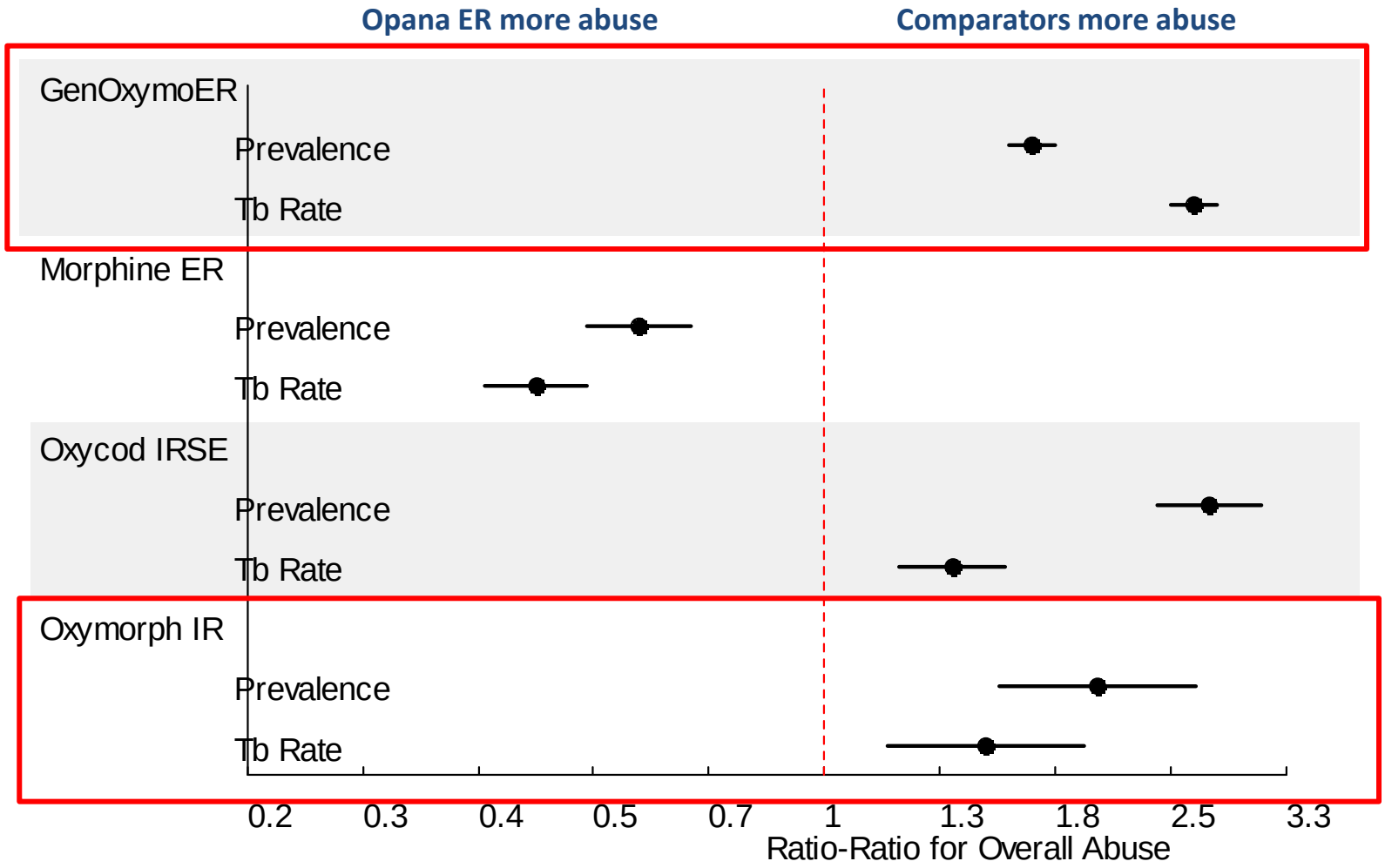


Figure 2: Ratio-ratio comparison between comparators and Opana ER (P3 vs P1) of past 30-day **overall abuse**.

Interpretation: NAVIPPRO

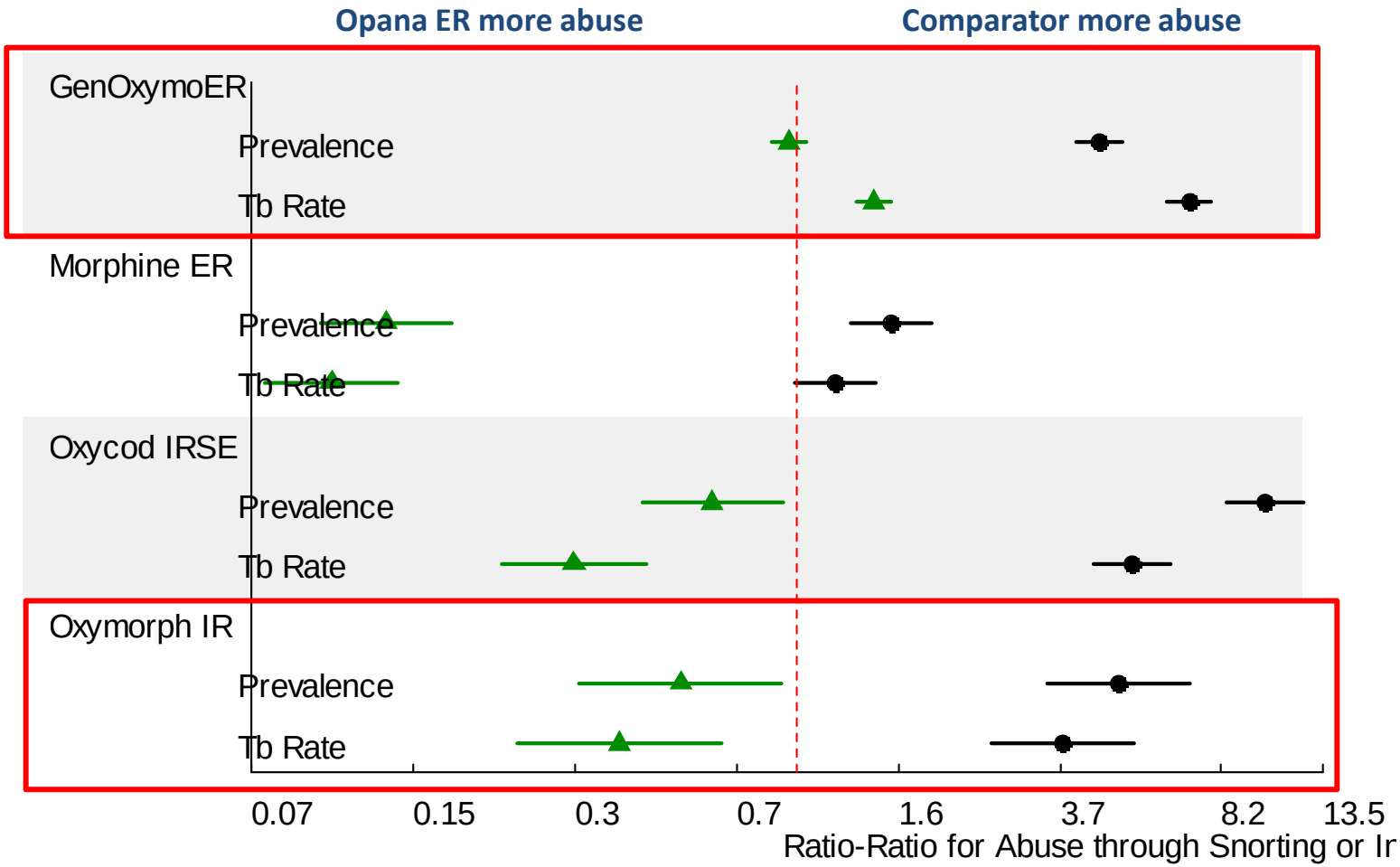


Figure 3: Ratio-ratio comparison between comparators and Opana ER (P3 vs P1) of past 30-day abuse through **injection (in green)** and **snorting (in black)**.

Interpretation: RADARS PC

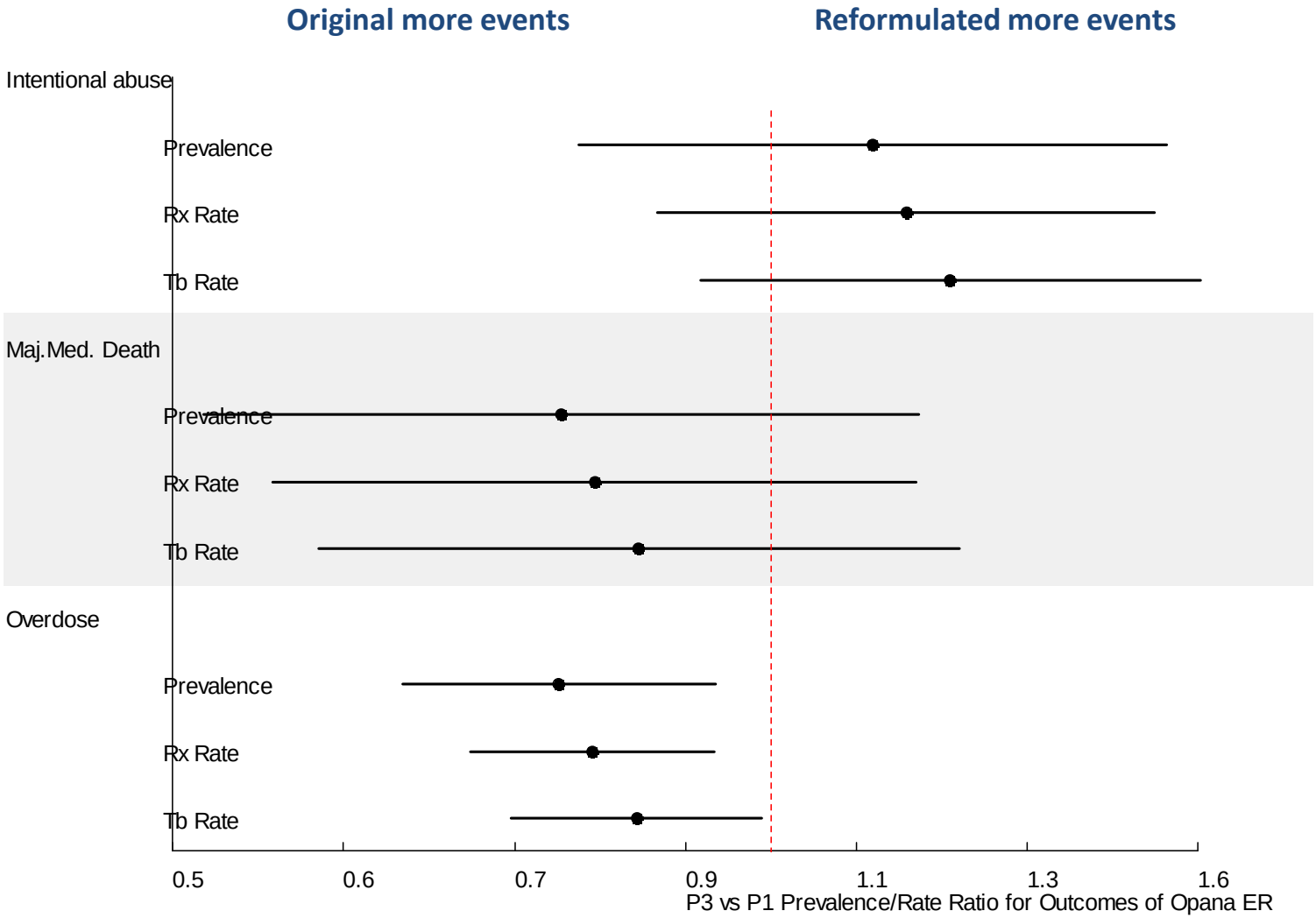


Figure 4: Prevalence/rate ratio of past 30-day abuse outcomes of Opana ER comparing P3 to P1.

Interpretation: RADARS PC

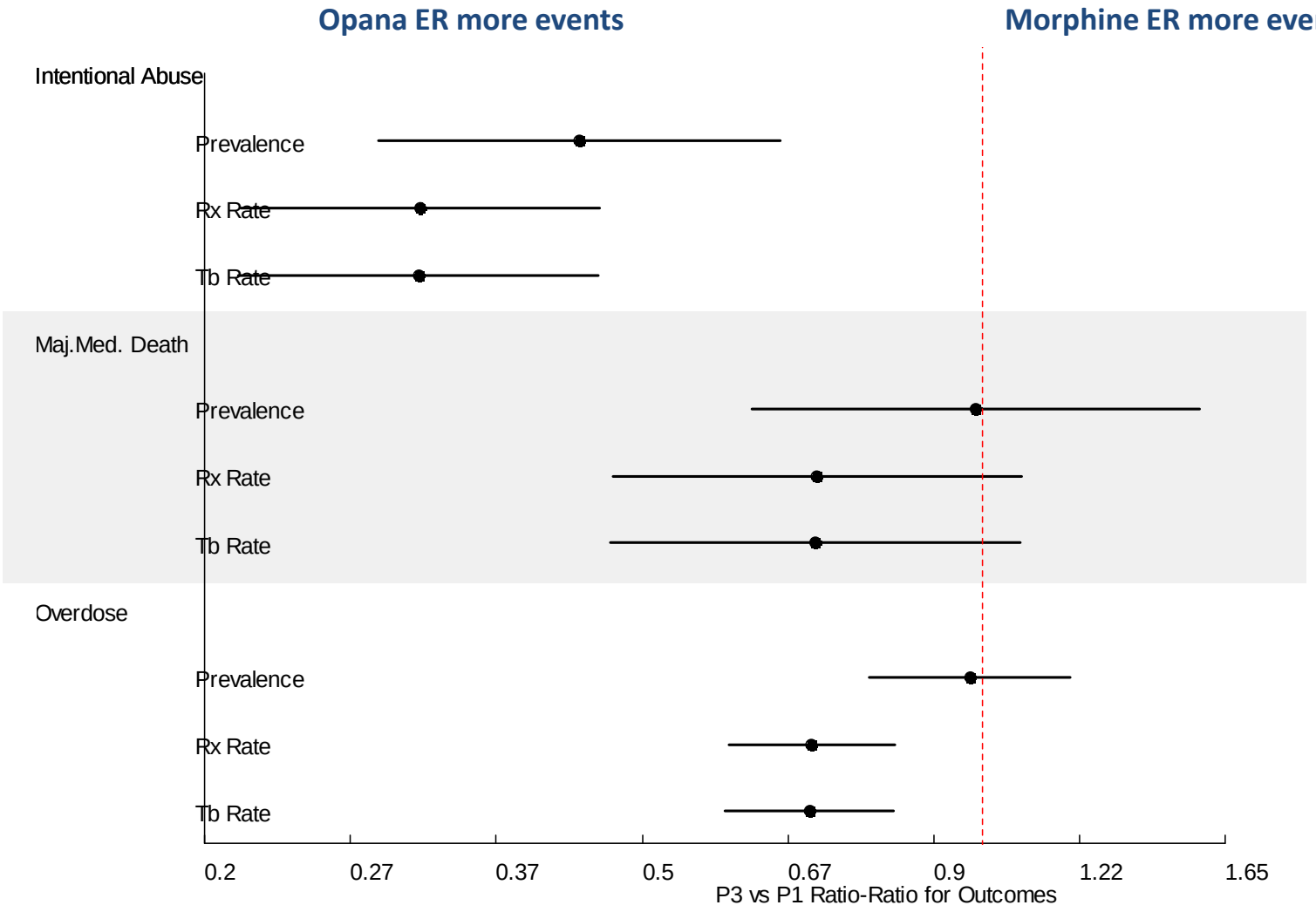


Figure 5: Ratio-ratio comparison between morphine ER and Opana ER (P3 vs P1) of intentional abuse, major medical outcomes/death, and overdose.

Outline

- Observational studies
- Statistical Considerations
  - Data quality
  - Estimability
  - Causality
  - Interpretation
- Summary

Summary

- Estimability
  - No population data
  - No probability sample from a well define population
  - Assumptions of sample selection
- Causality
  - No cohort followed over time
  - Assumption of similarity
- Interpretation
  - In the context of estimability, causality and data quality


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Review of Postmarketing Epidemiologic Data on Opana ER and Selected Comparators

Jana McAninch, MD, MPH, MS
Division of Epidemiology II
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee
March 13-14, 2017

Presentation Outline

1. Submitted formal epidemiologic studies
   - National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) study
   - Researched Abuse, Diversion and Addiction-Related Surveillance Poison Center (RADARS® PC) study
2. Other population data
   - National Survey on Drug Use and Health
   - RADARS Treatment Center Program
3. Overall conclusions

NAVIPPRO® Study

- Self-reported drugs abused in past 30 days in a sample of individuals assessed for substance abuse triage and treatment planning in the U.S.

NAVIPPRO® Study Methods
Measurement of abuse outcomes

Addiction Severity Index—Multimedia Version, (ASI-MV®): screen shot of oxymorphone questions at beginning of post-period

If respondent endorses use of a product, directed to series of questions to determine route and if use was non-medical ("abuse")

Source: NAVIPPRO® Final Study Report, submitted by Endo Pharmaceuticals December 21, 2016

NAVIPPRO® Study Methods

Measurement of abuse outcomes

- **Route of abuse (ROA) profile** = Proportion of people abusing a drug who report abusing it via specific routes

- **Abuse prevalence** = Abuse mentions for a drug per 100 assessments

- **Tablet-adjusted abuse rate** = Abuse mentions for a drug per 10,000 tablets dispensed

Factors that might influence prescribing patterns and trends

- Product reformulation
- Drug shortages
- Availability of generics
- Advertising
- Use of prescription drug monitoring programs
- Law enforcement actions (e.g., "pill mill" crackdowns)

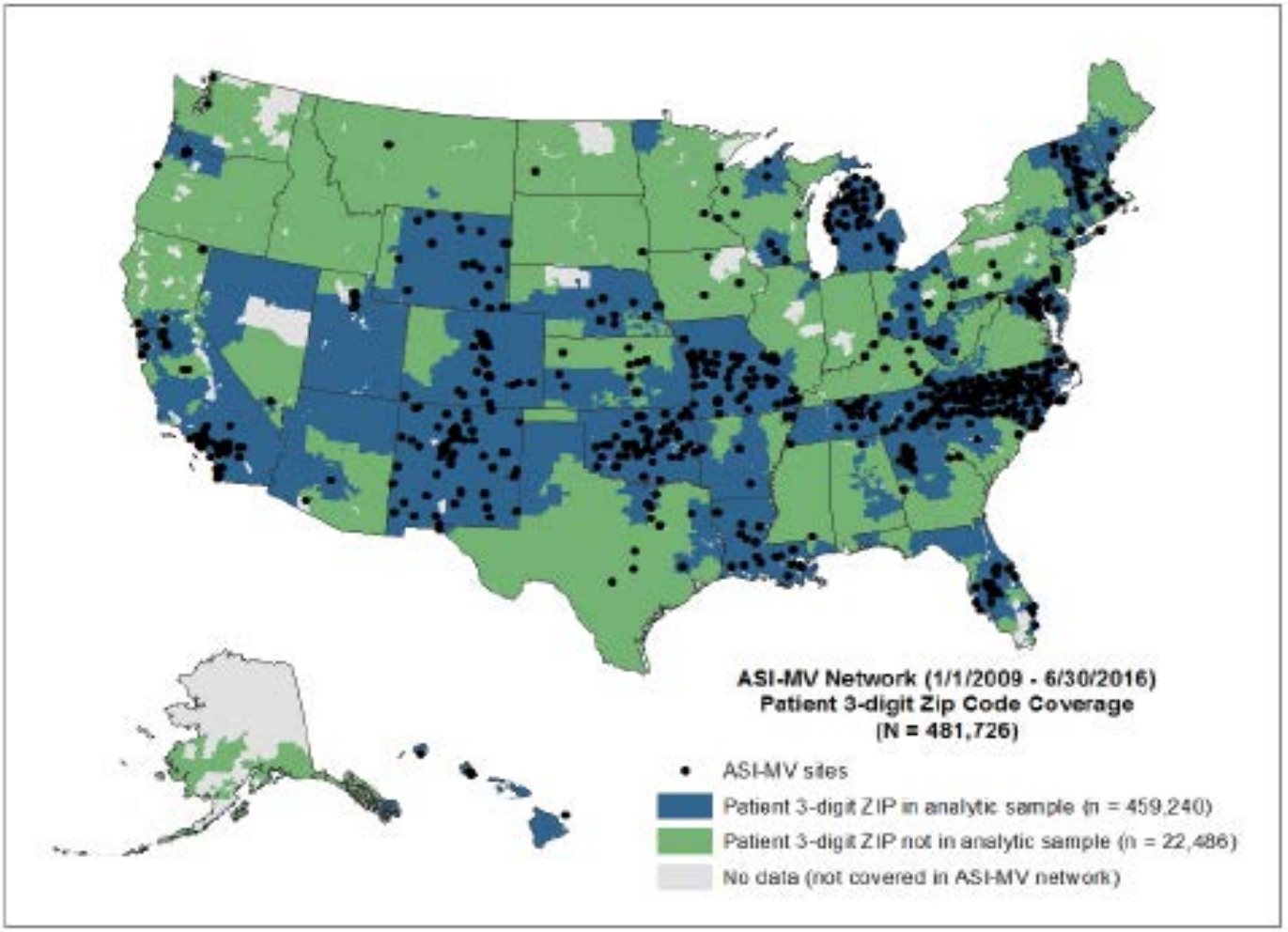
NAVIPPRO® Study Methods

The "counterfactual" and use of comparators

- "How did Opana ER abuse patterns change after its reformulation, compared to what *would have* happened without the reformulation?"
- Comparators and trend analyses help isolate effect of reformulation from secular drug abuse trends, changes in study population, effects of other interventions.
- Generic oxymorphone ER products, in particular, might provide a clue to what would have happened to Opana ER abuse without reformulation

NAVIPPRO® Study Methods

Sampling and Study Population



Source: NAVIPPRO® Final Study Report, submitted by Endo Pharmaceuticals December 21, 2016

NAVIPPRO® Study Methods

Sampling and Study Population

Selected States	Total Number of Sites		Total Number of Assessments	
	3-year Pre-period	3-year Post-period	3-year Pre-period	3-year Post-period
Tennessee	26	38	4,695	20,964
New Mexico	131	17	56,791	5,056
West Virginia	5	7	2,411	247
Kentucky	0	2	0	10
Utah	3	4	406	333
Indiana	0	0	0	0

Source: Table generated by reviewer using data from NAVIPPRO® Final Study Report, submitted by Endo Pharmaceuticals December 21, 2016

NAVIPPRO® Study Methods
Sampling and Study Population

- **Focus on "fixed" set of sites participating in every quarter**
  - Stabilizes sampling frame
  - Mitigates bias due to changes in geographic distribution and type of site

  But…
  - Reduces power and generalizability (53 sites, 15 states)
  - Does NOT account for external factors affecting likelihood that someone abusing is assessed
- **Looking separately at Tennessee and non-Tennessee sites also valuable**

NAVIPPRO® Study Results

	Number of sites		Number of assessments		Number of Opana ER* abuse cases	
	3-year Pre-period	3-year Post-period	3-year Pre-period	3-year Post-period	3-year Pre-period	3-year Post-period
Overall network	687	644	206,466	168,078	1,570	1,675*
Tennessee only	26	38	4,695	20,964	400	1,250
Non-Tennessee	661	605	201,771	147,114	1,170	425
Fixed sites only	**53**	**53**	**46,851**	**50,285**	**304**	**523**

Source: Table generated by reviewer using data from NAVIPPRO® Final Study Report, submitted by Endo Pharmaceuticals December 21, 2016

*Original Opana ER in pre-period and reformulated Opana ER in post-period.

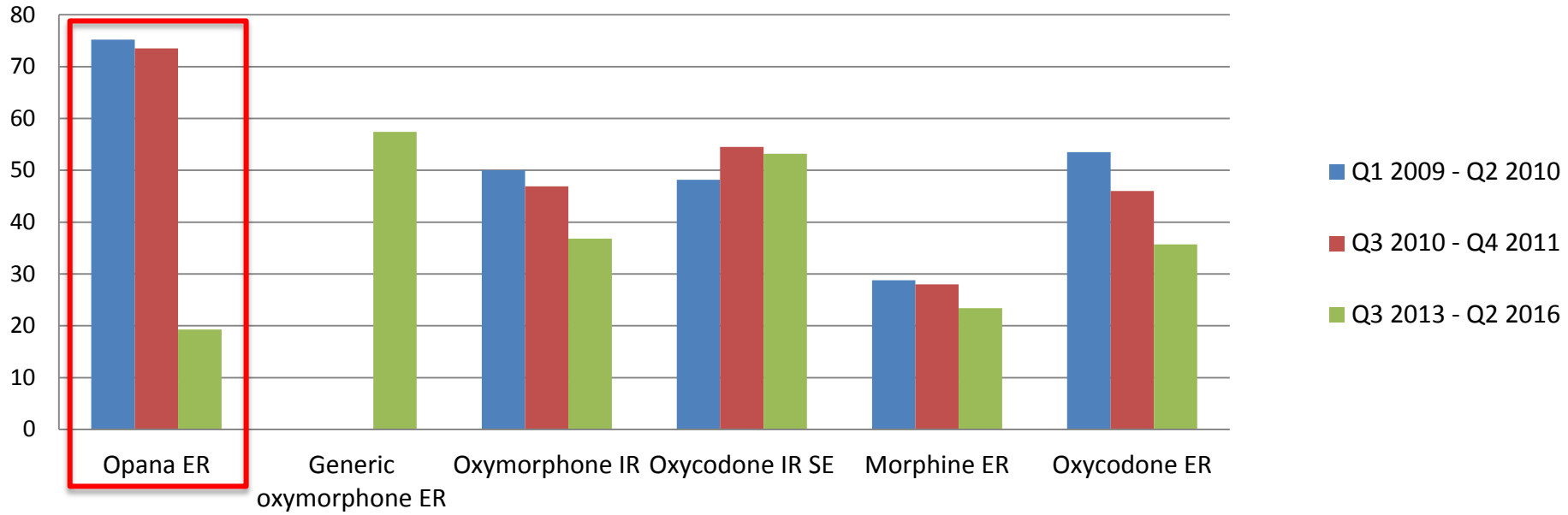
*** In addition to 1,675 reformulated Opana ER abuse reports, 532 original Opana ER abuse reports in post-period (not included in pre-post analyses)**

- Residual supply or counterfeit original Opana ER?
- Respondent reported lifetime abuse?
- Reformulated Opana ER, generic oxymorphone ER, oxymorphone IR, or other opioid misidentified as original Opana ER?

NAVIPPRO® Study Results

ROA Profile for Opana ER* and comparators across three time periods

Percent of past 30-day abusers of each drug who reported abusing it via NASAL route, fixed site sample



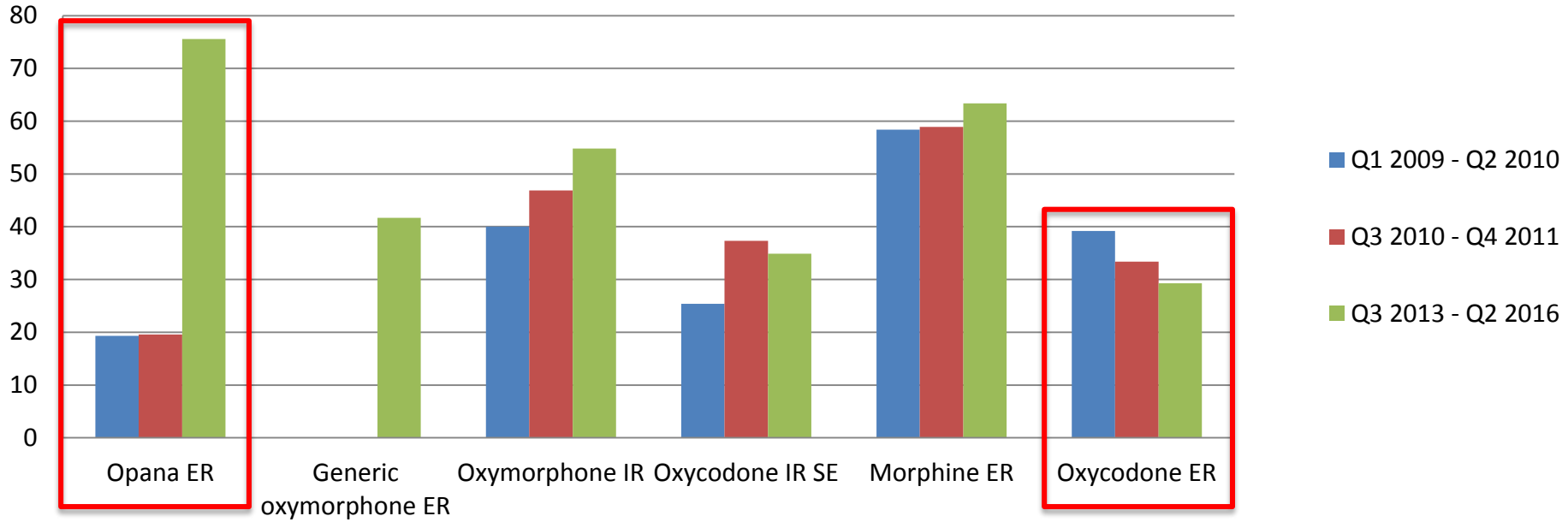
* Original Opana ER in first two time periods, reformulated Opana ER in third time period

Source: Figure generated by reviewer using data from NAVIPPRO® Final Study Report, submitted by Endo Pharmaceuticals December 21, 2016

NAVIPPRO® Study Results

ROA Profile for Opana ER* and comparators across three time periods

Percent of past 30-day abusers of each drug who reported abusing it via INJECTION, fixed site sample



* Original Opana ER in first two time periods, reformulated Opana ER in third time period

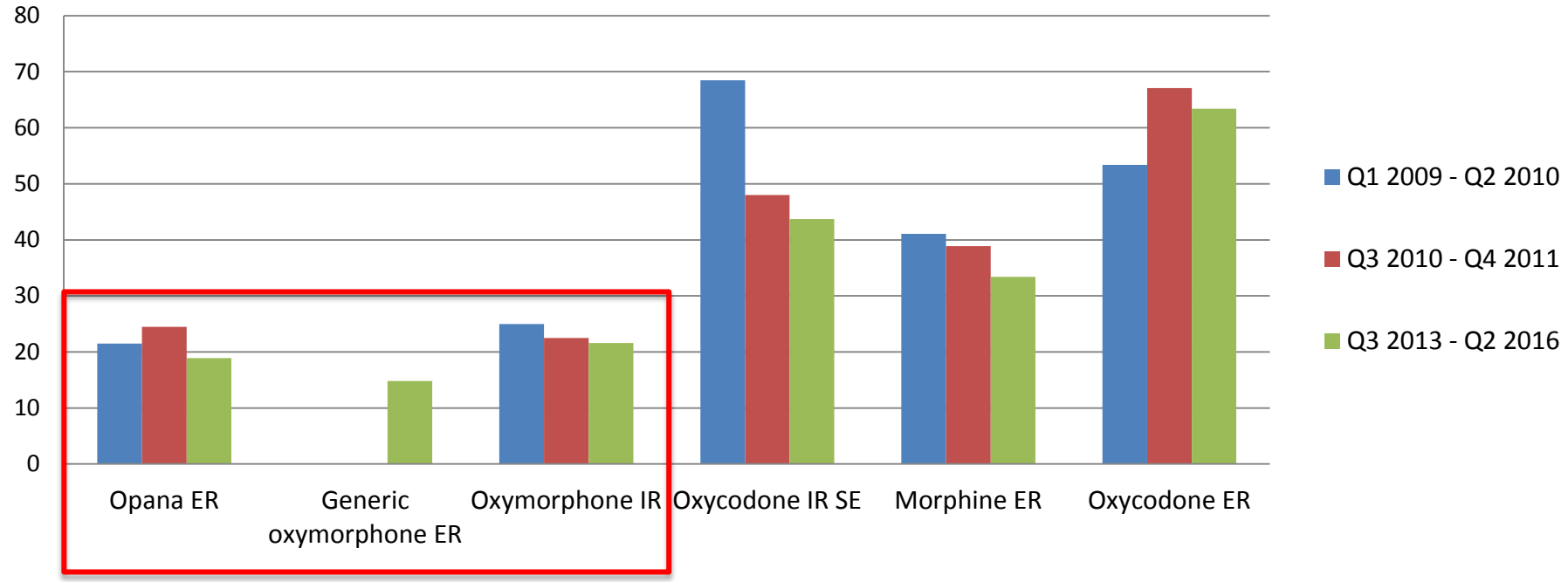
Source: Figure generated by reviewer using data from NAVIPPRO® Final Study Report, submitted by Endo Pharmaceuticals December 21, 2016

- Opana ER's shift toward injection seen in both Tennessee and non-Tennessee subsamples

NAVIPPRO® Study Results

ROA Profile for Opana ER* and comparators across three time periods

Percent of past 30-day abusers of each drug who reported abusing it via the ORAL route, fixed site sample



* Original Opana ER in first two time periods, reformulated Opana ER in third time period

Source: Figure generated by reviewer using data from NAVIPPRO® Final Study Report, submitted by Endo Pharmaceuticals December 21, 2016

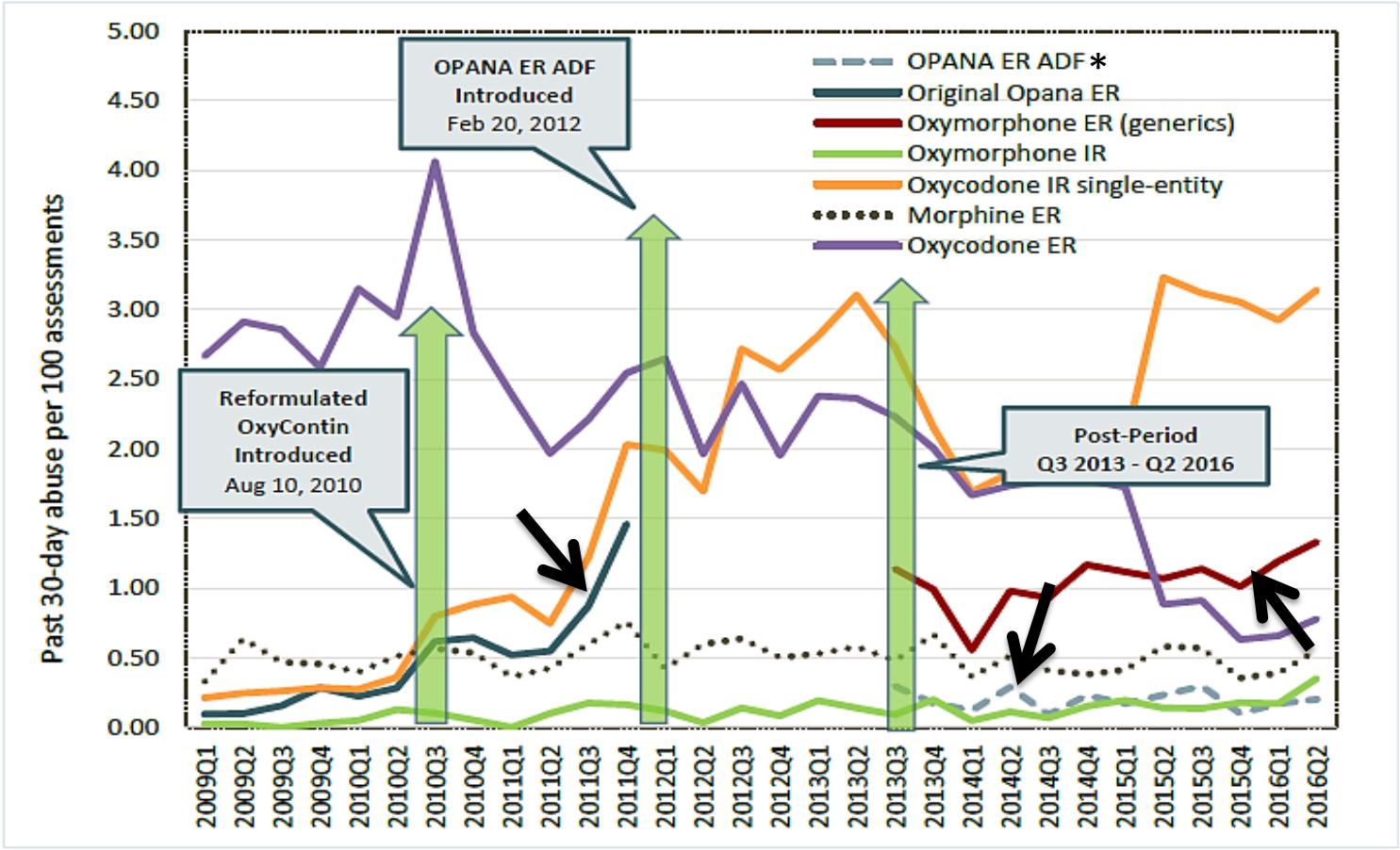
NAVIPPRO® Study Results

Changes in route-specific abuse prevalence and tablet-adjusted rates

- Also must examine changes in route-specific abuse levels in the overall study population, *not only among those who abuse each product*.
- Very challenging, because of potential for
  - Sampling bias—fixed site and stratified analyses again useful
  - Misclassification bias—post-period oxymorphone rates may be underestimated
  - Confounding by secular trends—comparators important

NAVIPPRO® Study Results
Nasal abuse prevalence

Quarterly past 30-day nasal abuse prevalence per 100 assessments, fixed sites sample



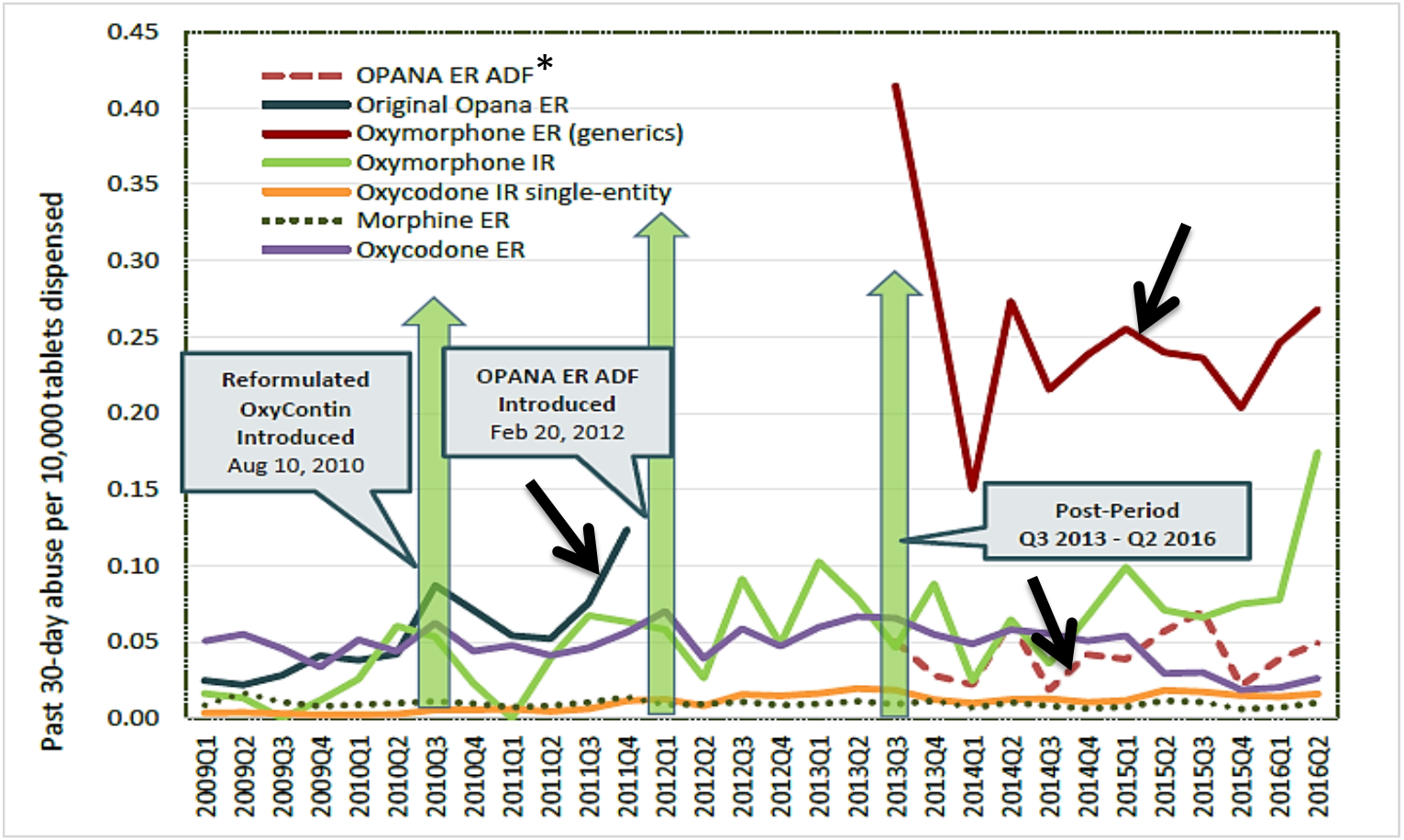
*Reformulated Opana ER is referred to in the NAVIPPRO study as "OPANA ER ADF."

Source: NAVIPPRO® Final Study Report, submitted by Endo Pharmaceuticals December 21, 2016

NAVIPPRO® Study Results

Tablet-adjusted **nasal** abuse rates

Quarterly past 30-day nasal abuse rates per 10,000 tablets dispensed, fixed sites sample



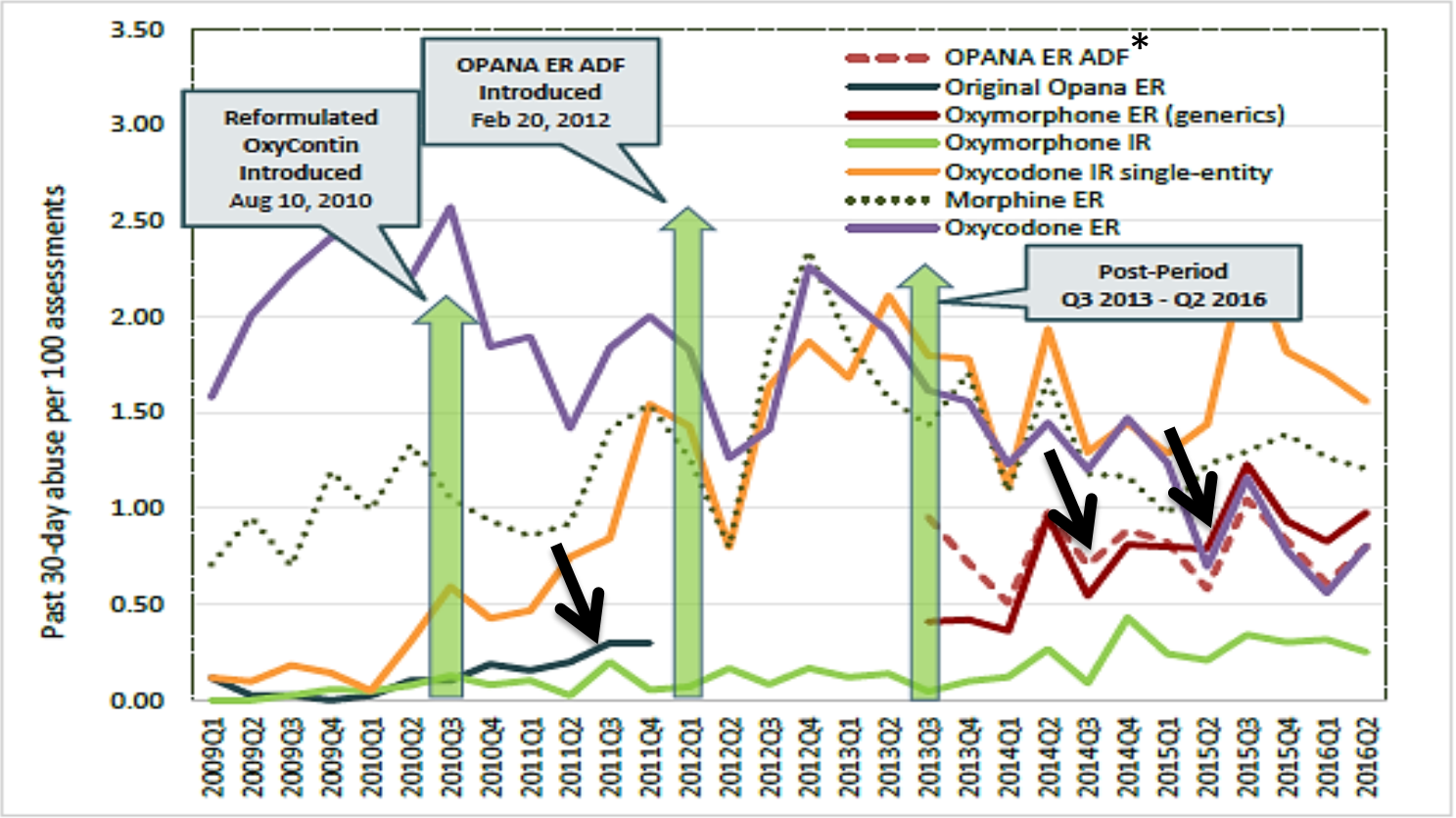
*Reformulated Opana ER is referred to in the NAVIPPRO study as "OPANA ER ADF."

Source: NAVIPPRO® Final Study Report, submitted by Endo Pharmaceuticals December 21, 2016

NAVIPPRO® Study Results

Injection abuse prevalence

Quarterly past 30-day injection abuse prevalence per 100 assessments, fixed sites sample



*Reformulated Opana ER is referred to in the NAVIPPRO study as "OPANA ER ADF."

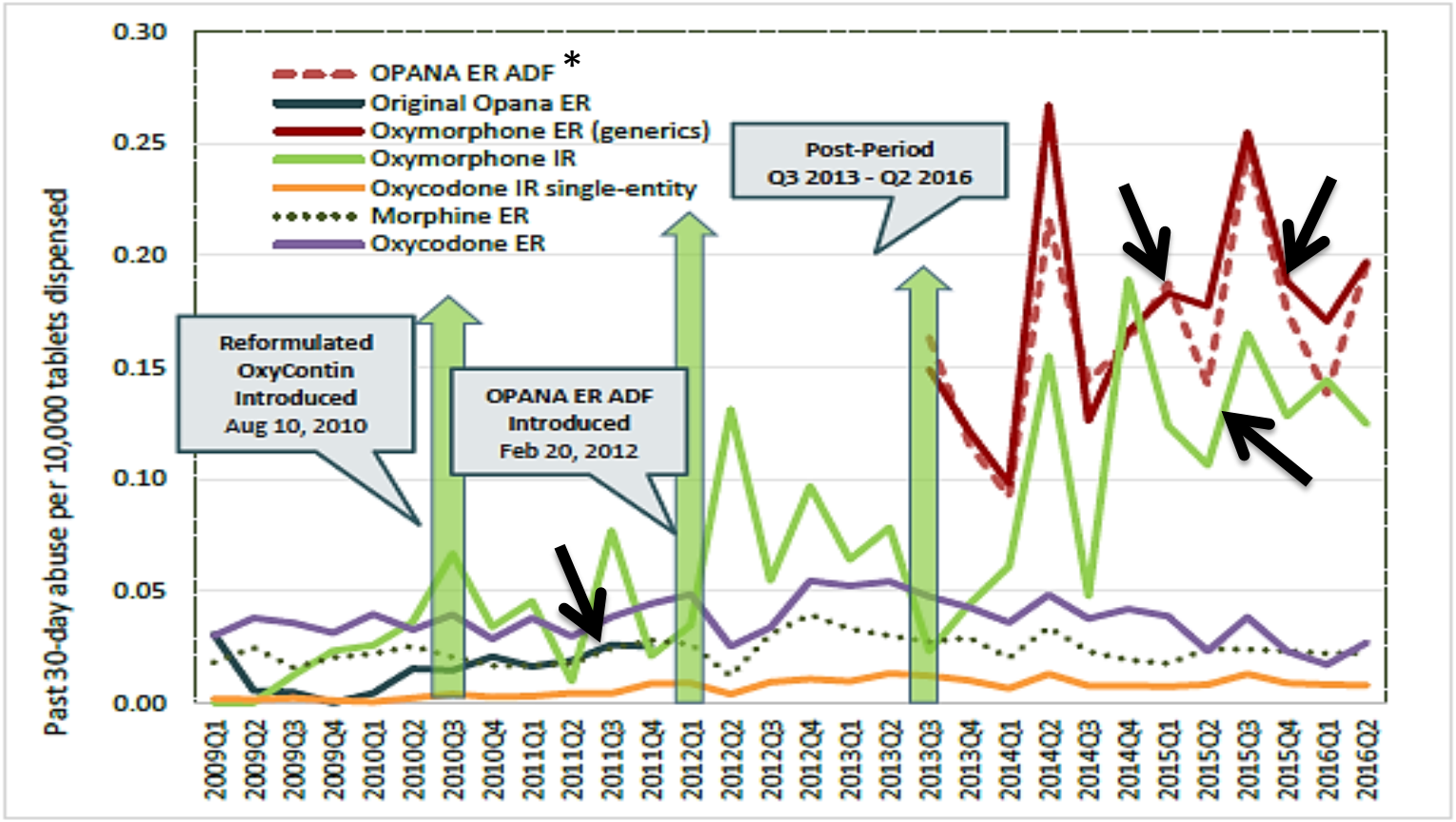
Source: NAVIPPRO® Final Study Report, submitted by Endo Pharmaceuticals December 21, 2016

- **Stratified analyses suggest Tennessee is largely driving increases in Opana ER injection abuse prevalence**

NAVIPPRO® Study Results

Tablet-adjusted **injection** abuse rates

Quarterly past 30-day injection abuse rates per 10,000 tablets dispensed, fixed sites sample



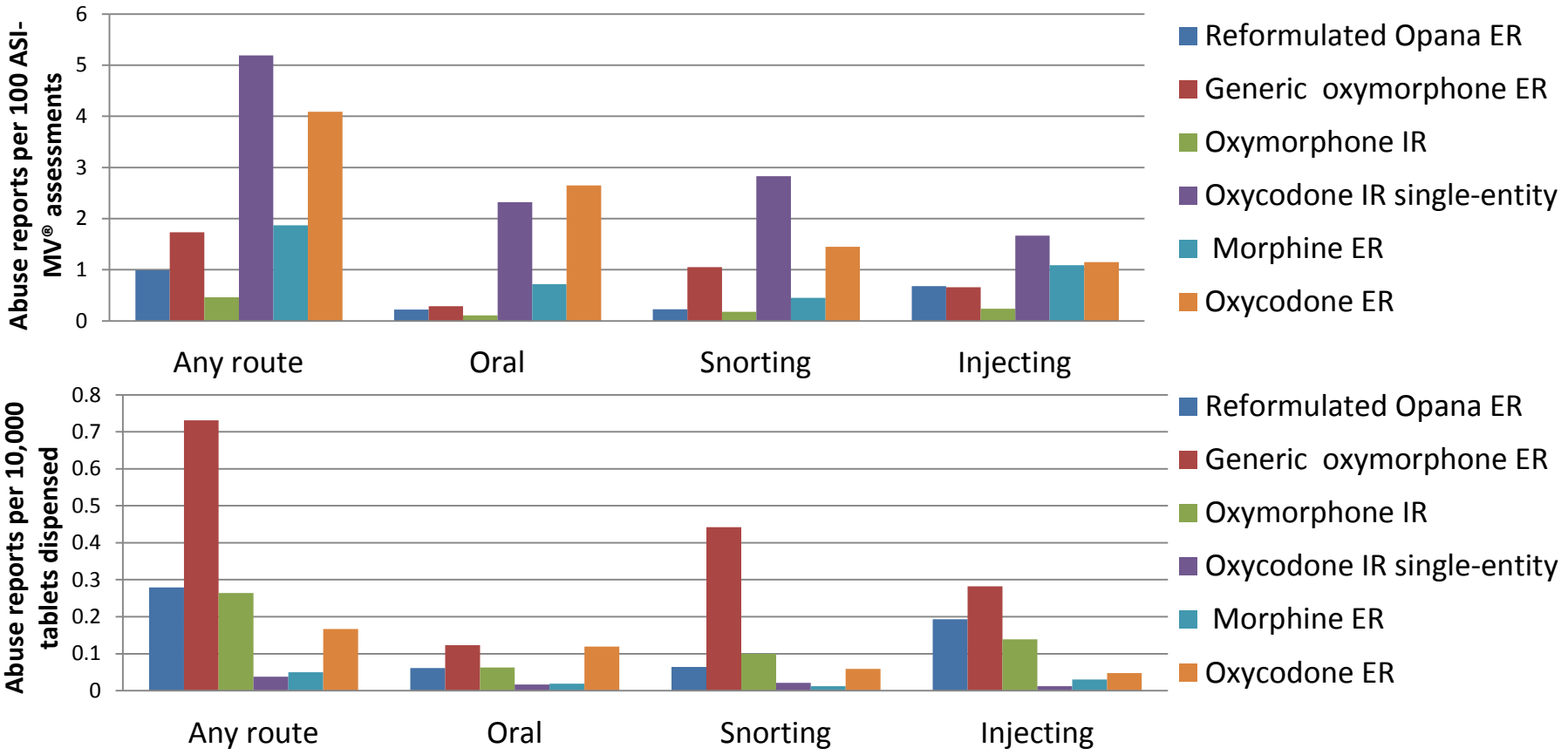
*Reformulated Opana ER is referred to in the NAVIPPRO study as "OPANA ER ADF."

Source: NAVIPPRO® Final Study Report, submitted by Endo Pharmaceuticals December 21, 2016

NAVIPPRO® Study Results

Post-period Abuse Comparisons*

Past 30-day abuse reports per 100 ASI-MV® assessments (top panel) and per 10,000 tablets (bottom panel) using the full sample, post-period only



Source: Figure generated by reviewer using data from NAVIPPRO® Final Study Report, submitted by Endo Pharmaceuticals December 21, 2016

***Caveats: Non-representative sample, and potential product misclassification**

NAVIPPRO® Study Summary

1. After Opana ER reformulation, shift from snorting to injecting, among abusers of this drug
   - Seen in fixed site, Tennessee, and non-Tennessee samples
   - Not seen for comparator opioids
2. Decrease in Opana ER nasal abuse rates after reformulation—difficult to determine magnitude
3. Increase in Opana ER injection abuse rates
   - Began before reformulation
   - Seen in fixed site analyses, but varied geographically (Tennessee driving increases)
   - Similar injection abuse rates for generic oxymorphone ER in post-period

NAVIPPRO® Study Summary

- During the post-period,
  - Overall and route-specific abuse prevalence highest for IR and ER oxycodone
  - Adjusting for prescribed availability,
    - Generic oxymorphone ER had highest overall and nasal abuse rates
    - Generic oxymorphone ER and reformulated Opana ER had highest injection abuse rates, followed by oxymorphone IR
- Must consider non-representative sampling and potential product misclassification

RADARS Poison Center (PC) Study

Data from spontaneous calls to regional U.S. poison centers, covering over 90% of the U.S. population.

RADARS® PC Study Methods

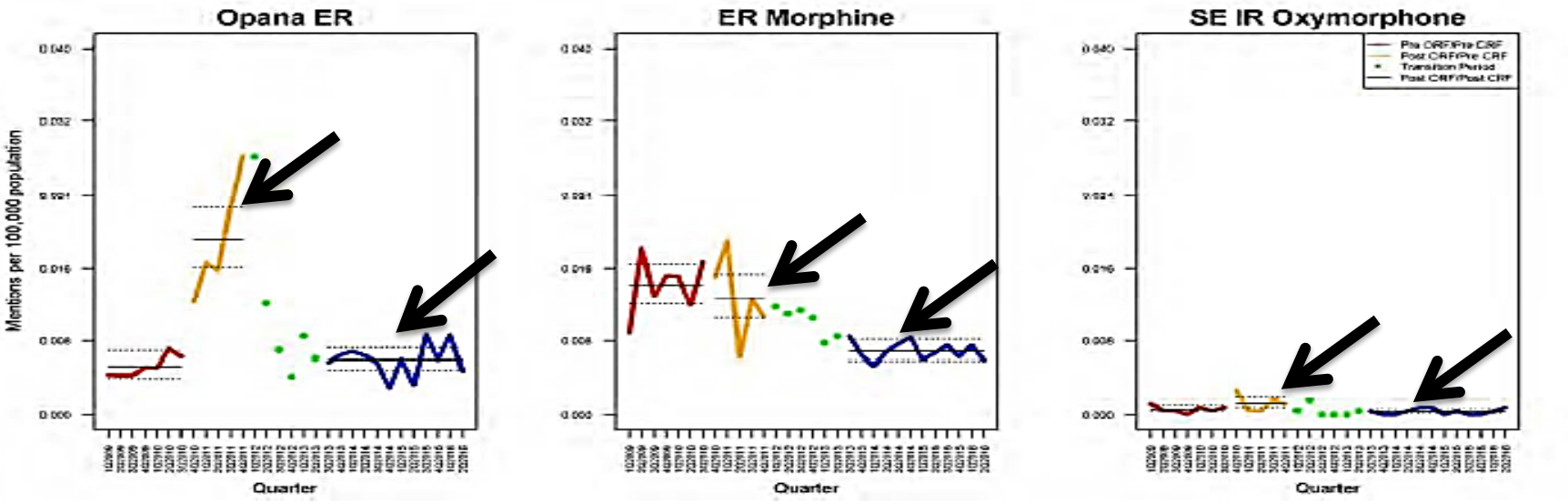
- Study periods
  - **Pre-ORF*/Pre-CRF*:** 1Q2009 – 3Q2010
  - **Post-ORF/Pre-CRF:** 4Q2010 – 4Q2011
  - **Transition:** 1Q2012 – 2Q2013
  - **Post-ORF/Post-CRF:** 3Q2013 – 2Q2016
- Outcomes
  - Population- and utilization-adjusted exposure call rates
    - Intentional abuse (with routes)
    - "Overdoses"
    - Calls resulting in major medical outcome or death

In this study, *ORF = reformulated OxyContin; CRF = reformulated Opana ER "crush-resistant formula"

RADARS ® PC Study Results

Change in intentional abuse call rates for Opana ER, ER Morphine, and IR oxymorphone

Mean intentional abuse exposure call rates per 100,000 population covered, 1Q2009 – 2Q2016



Source: RADARS Poison Center System Final Study Report, submitted by Endo Pharmaceuticals November 28, 2016

- **Only <u>six</u> intentional abuse calls mentioning a generic ER oxymorphone product during post-period**

RADARS® PC Study Results

ROA Profile: Opana ER abuse calls involving inhalation/nasal and injection routes

	INHALATION/ NASAL CASES (N)	INJECTION CASES (N)	TOTAL ABUSE CASES (N)**	% VIA INHALATION/ NASAL ROUTE	% VIA INJECTION ROUTE
Pre-period (1Q2010* - 4Q2011)	98	19	290	34%	7%
Post-period (3Q2013 - 2Q2016)	39	53	190	21%	29%

* RADARS® PC program began collecting information on route of administration in Q1 2010

**Approximately 20% missing data on route.

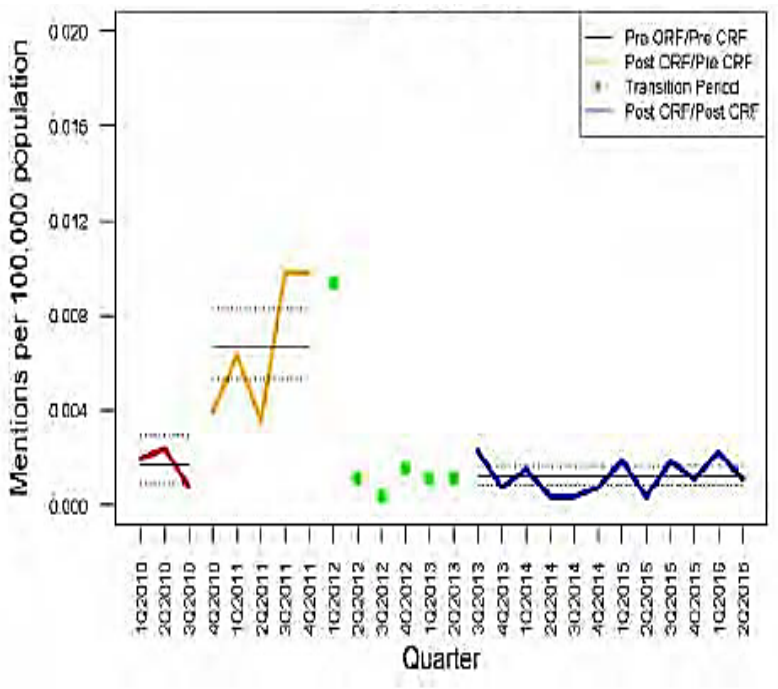
Source: Table generated by reviewer, using data from RADARS Poison Center System Final Study Report and updated response to June 1, 2016 FDA Information request, submitted by Endo Pharmaceuticals November 28, 2016

- Similar shift from inhalation to injection not seen for ER oxycodone after OxyContin reformulated

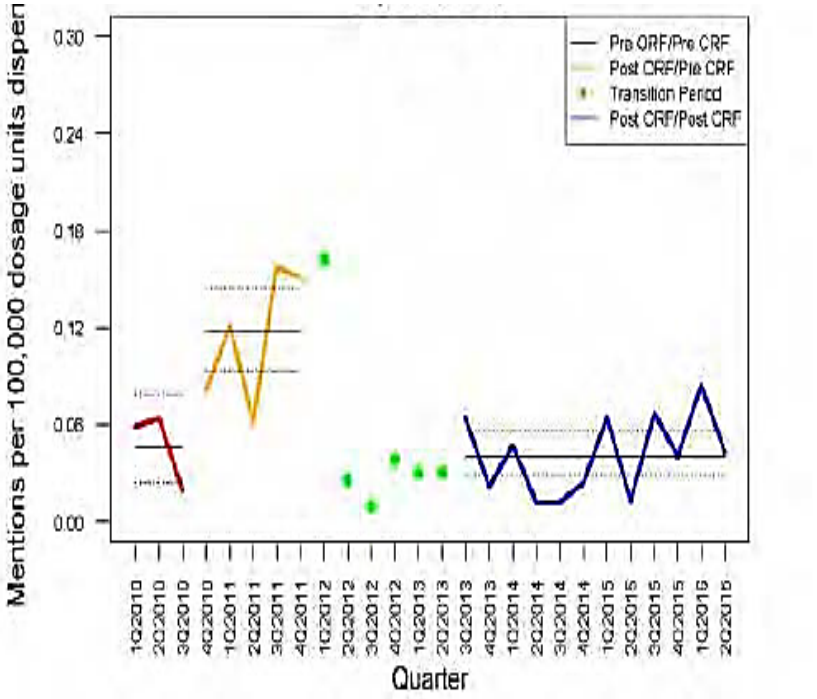
RADARS® PC Study Results

Change in Opana ER inhalation/nasal abuse call rates

Mean rates of Opana ER intentional abuse calls involving the inhalation/nasal route, per 100,000 population, 1Q2010 –2Q2016



Mean rates of Opana ER intentional abuse calls involving the inhalation/nasal route, per 100,000 dosing units, 1Q2010 –2Q2016

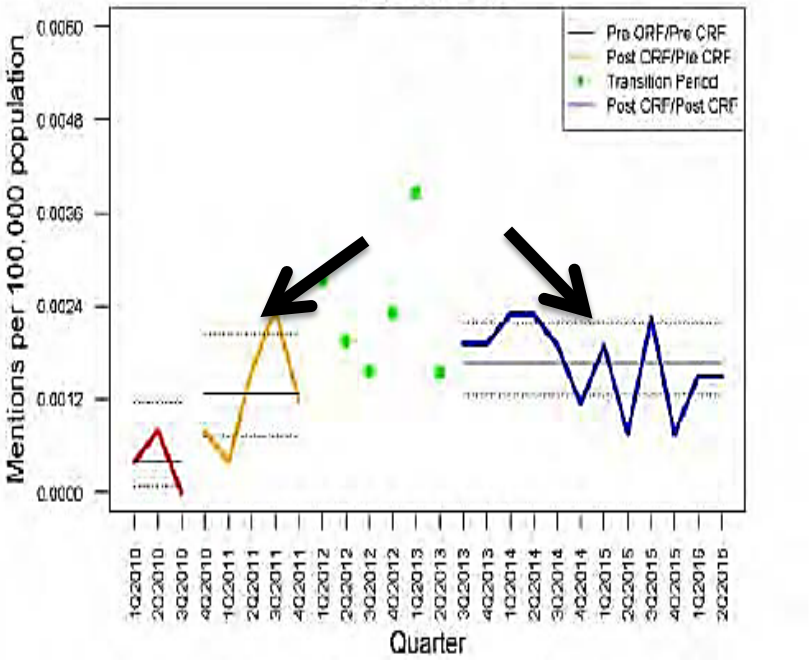


Source: updated response to June 1, 2016 FDA Information request, submitted by Endo Pharmaceuticals November 28, 2016

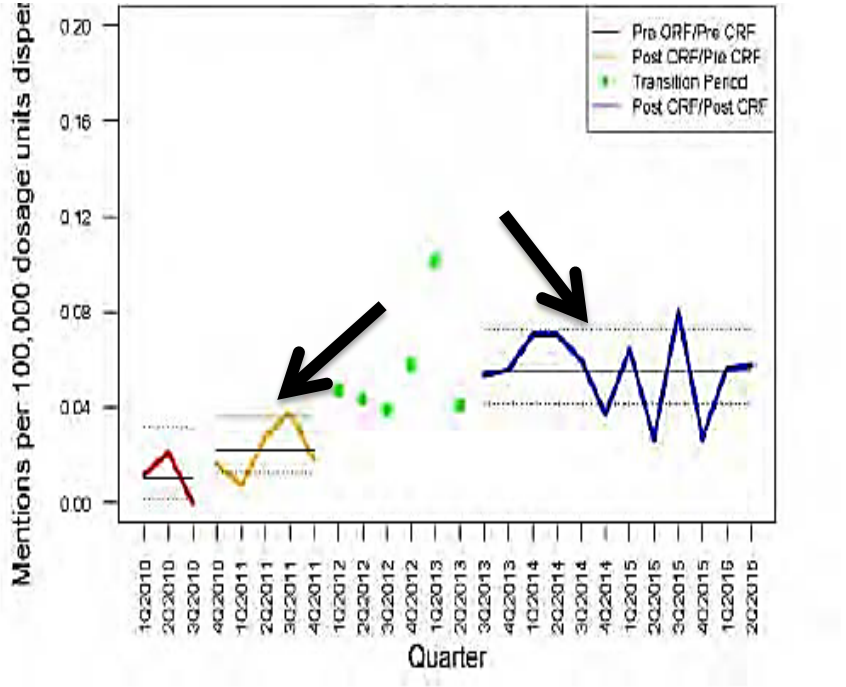
RADARS® PC Study Results

Change in Opana ER injection abuse call rates

Mean rates of Opana ER intentional abuse calls involving the injection route, per 100,000 population, 1Q2010 –2Q2016



Mean rates of Opana ER intentional abuse calls involving the injection route, per 100,000 dosing units, 1Q2010 –2Q2016



Source: updated response to June 1, 2016 FDA Information request, submitted by Endo Pharmaceuticals November 28, 2016

RADARS® PC Study

Opana ER Intentional Abuse Call Rates,* by state (Top Ten), 1Q 2009 – 2Q 2016

State	Rate per 100,000 Population (95% CI)	Rate per 100,000 tablets (95% CI)
West Virginia	4.1 (3.2, 5.1)	1.4 (1.1, 1.7)
Kentucky	2.4 (1.9, 2.9)	1.5 (1.2, 1.8)
Tennessee	1.3 (1.0, 1.6)	0.2 (0.2, 0.3)
Indiana	0.8 (0.6, 1.0)	0.5 (0.4, 0.6)
Pennsylvania**	0.6 (0.4, 0.8)	0.2 (0.1, 0.3)
Virginia	0.5 (0.4, 0.7)	0.4 (0.3, 0.5)
Ohio**	0.5 (0.4, 0.6)	0.2 (0.2, 0.3)
Maryland	0.4 (0.3, 0.6)	0.3 (0.2, 0.5)
Oklahoma	0.4 (0.2, 0.6)	0.2 (0.1, 0.3)
Nevada	0.3 (0.1, 0.7)	0.2 (0.1, 0.9)

*Represents total rate for entire time period

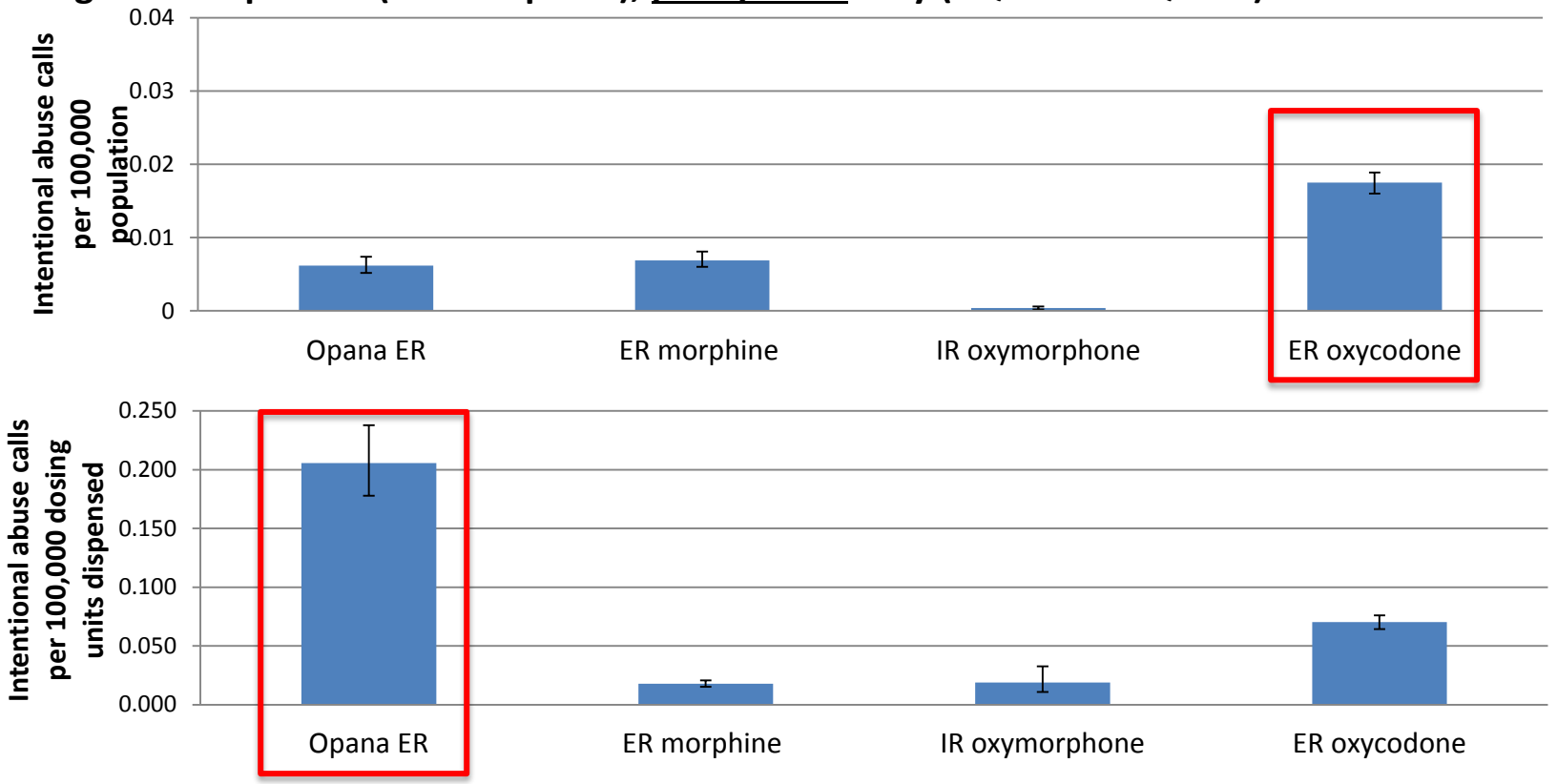
**Indicates only part of the state was covered for all quarters from Q1 2009 - Q2 2016

Source: Table generated by reviewer using data from response to FDA information request, submitted by Endo Pharmaceuticals February 23, 2017

RADARS® PC Study Results

Post-period Comparisons

Intentional abuse call rates (any route) per 100,000 population (top panel) and per 100,000 dosing units dispensed (bottom panel), post-period only (3Q2013 – 2Q2016)



Source: Table generated by reviewer, using data from RADARS Poison Center System Final Study Report, submitted by Endo Pharmaceuticals November 28, 2016

- **Generic oxymorphone ER reported as Opana ER??**
- **If dispensed generic oxymorphone ER tablets were included in Opana ER utilization-adjusted denominator, would still remain highest**

RADARS® PC Study Summary

- Following Opana ER's reformulation:
  - Shift in Opana ER abuse calls from inhalation/nasal to injection
  - Opana ER inhalation/nasal abuse call rates decreased significantly
  - Utilization-adjusted Opana ER injection abuse call rates increased significantly
- Utilization-adjusted Opana ER abuse call rates higher than other opioids analyzed
- Geographic heterogeneity in Opana ER abuse call rates—highest rates in Appalachian states and Indiana
- Limitations:
  - Misclassification of generics?
  - Like spontaneous adverse event reports, capture unknown proportion of actual abuse—do not represent true prevalence

Other Postmarketing Data

National Survey on Drug Use and Health (NSDUH)

- Large nationally-representative household survey
- Provides national estimates of use/misuse of prescription pain relievers
- Pill photo cards used to identify products
- 2015 survey redesign allows comparisons of past-year use and misuse across opioid subgroups
- Definitions:
  - **Any Use** = (a) use of one's own prescription medication as directed by a doctor OR (b) misuse
  - **Misuse** = use in any way not directed by a doctor

NSDUH

Estimated Use and Misuse of Prescription Pain Relievers* among Persons Age 12 Years or older, 2015

	Any Use in Past year: N, in thousands (S.E.**)	Misuse in Past Year: N, in thousands (S.E.)	Misuse among Past Year Any Users: % (S.E.)
Hydrocodone	58,261 (688)	7,193 (229)	12.3 (0.38)
Oxycodone	27,873 (503)	4,258 (169)	15.2 (0.57)
Tramadol	18,573 (440)	1,794 (124)	9.7 (0.63)
Morphine	7,205 (257)	697 (64)	9.7 (0.87)
Fentanyl	1,997 (138)	299 (42)	15.0 (2.05)
Demerol®	1,434 (125)	106 (23)	7.4 (1.59)
Oxymorphone	1,329 (114)	384 (49)	28.9 (3.44)
Hydromorphone	2,484 (161)	261 (39)	10.5 (1.55)

*Methadone and buprenorphine are not included, as these categories include products used to treat opioid use disorders

**S.E. = Standard Error

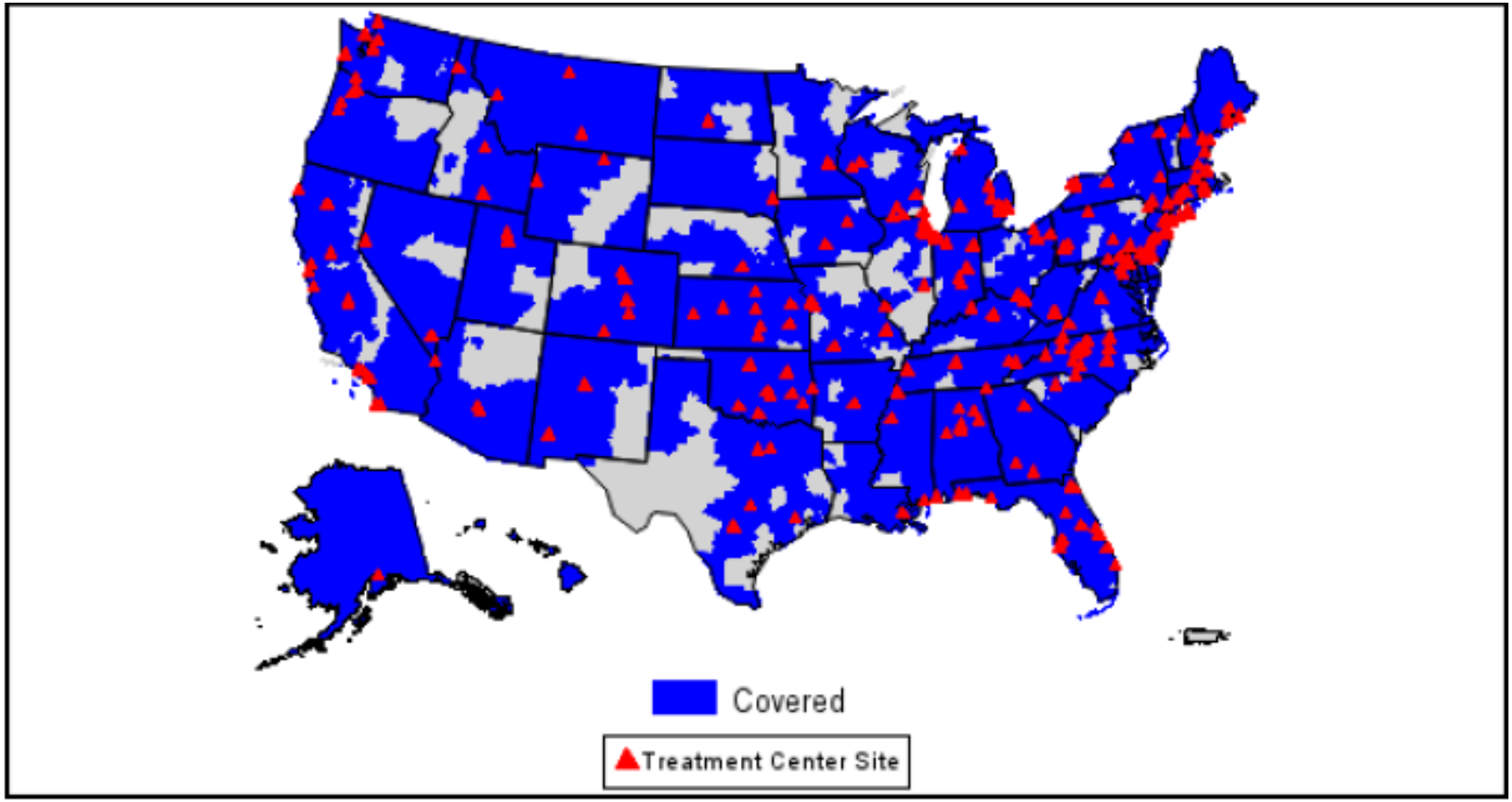
Source: Table generated by reviewer using data from "Results from the 2015 NSDUH: Detailed Tables," Substance Abuse and Mental Health Services Administration Center for Behavioral Health Statistics and Quality, September 8, 2016

RADARS® Treatment Center Data

- Data analyses newly commissioned by FDA to help understand Opana/oxymorphone abuse, especially discrepant findings regarding generics
- RADARS® Treatment Center Program surveys individuals entering treatment for opioid use disorder, asking what drugs used “to get high” (abused) in past month
- Began collecting data on
  - Opana (IR), Opana ER, generic oxymorphone in Q2 2011
  - Injection route in 3Q 2011
  - Other routes in 3Q 2015

RADARS® Treatment Center Data

Participating centers and 3-digit ZIP code coverage, July 2013 – June 2016



- Approximately 27,000 completed surveys (July 2013 – June 2016)

Source: "Drug Specific Report—Route of Abuse Patterns for Opana Extended Release and Selected Comparator Opioids among Individuals Entering Treatment for Opioid Addiction: RADARS® System Report"

RADARS® Treatment Center Data

Survey instrument (3Q 2013 version): Oxymorphone section

OXYMORPHONE Used to get high	Used in past month to get high	Injected in past month
FORMULATION UNKNOWN		
Oxymorphone, type unknown	☐	☐
TABLETS – IMMEDIATE RELEASE (IR)		
Opana® tablets	☐	☐
Oxymorphone IR tablets, not listed above	☐	☐
Oxymorphone IR tablets, not sure of name	☐	☐
TABLETS – EXTENDED RELEASE (ER)		
Opana ER® tablets	☐	☐
Oxymorphone ER tablets, not listed above	☐	☐
Oxymorphone ER tablets, not sure of name	☐	☐

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RADARS® Treatment Center Data

Post-period comparisons (Q3 2013 – Q2 2016)

	Respondents reporting past-month abuse of drug: N (%)	Past-month abuse rate per 100,000 dosage units dispensed
Opana (IR)	1741 (6.4%)	210.1 ??
Opana ER	1042 (3.9%)	1.5
Other ER oxymorphone	386 (1.4%)	0.8
Other IR oxymorphone	517 (1.9%)	1.3
ER morphine	1828 (6.8%)	0.2
ER oxycodone	4363 (16.2%)	0.9
ER hydromorphone	423 (1.6%)	3.2
IR oxycodone	6579 (24.4%)	0.1

Source: Table generated by reviewer using data from "Drug Specific Report—Route of Abuse Patterns for Opana Extended Release and Selected Comparator Opioids among Individuals Entering Treatment for Opioid Addiction: RADARS® System Report"

- **Opana (IR) rates not plausible — suggest some misidentification of other oxymorphone products, including Opana ER, as Opana**

RADARS® Treatment Center Data

Injection abuse of Opana ER

	Before Opana ER reformulation (Q3 2011 – Q4 2011)	After Opana ER reformulation (Q3 2013 – Q2 2016)
Percent of past-month Opana ER abusers who inject it	17.2% (13.2%, 21.2%)	38.1% (35.1%, 41.1%)
Percent of respondents reporting past-month injection abuse of Opana ER	0.8% (0.6%, 1.0%)	1.5% (1.3%, 1.6%)
Opana ER injection abuse rate, per 100,000 dosage units dispensed, for Opana ER (95% C.I.)	0.18 (0.14, 0.23)	0.57 (0.52, 0.63)

Source: Table generated by reviewer using data from "Drug Specific Report—Route of Abuse Patterns for Opana Extended Release and Selected Comparator Opioids among Individuals Entering Treatment for Opioid Addiction: RADARS® System Report"

- Increases in injection not unique to Opana ER
- Proportion of surveys from Tennessee stable (2.3% in pre-period, 2.6% in post-period)

Conclusions

"The art of epidemiologic reasoning is to draw sensible conclusions from imperfect data."[1]

1. George Comstock. *Am J Epidemiology*, 1990

Conclusions

Shift in route of abuse profile

- Data are compelling that reformulation caused **shift from nasal to injection route** among those abusing Opana ER
  - Temporally associated with reformulation
  - Consistent finding in multiple data sources and populations
  - Shift of this magnitude not seen for comparators
  - Biological plausibility
    - Nasal abuse deterrence experimental study findings
    - Ability to prepare suitable solution for injection
    - Very low oral bioavailability—if snorting becomes more difficult, IV may be perceived as best option

Conclusions

Changes in abuse rates in the population

- Reformulation appears to have reduced Opana ER nasal abuse in the population
- Opana ER injection abuse increased during study period—unclear whether increases greater than if hadn't been reformulated
  - Increases started prior to reformulation
  - Post-period injection rates similar to generic oxymorphone ER and oxymorphone IR (NAVIPPRO study)
  - Limited geographic areas (e.g., Appalachia) appear to be driving increases and high post-period injection rates

Conclusions

Comparisons with other opioids

- Multiple studies suggest
  - Opana ER and other oxymorphone products represent small fraction of overall opioid use and abuse
  - Relative to prescribed availability, Opana ER and other oxymorphone products may be relatively likely to be abused or misused, but varies geographically
- NAVIPPRO study suggests
  - Generic oxymorphone ER has high nasal abuse rates
  - Reformulated Opana ER and generic oxymorphone ER both have high injection abuse rates, with only slightly lower rates for oxymorphone IR
  - Geographic variation and non-representative sampling complicate interpretation

Conclusions

Risks associated with Opana ER injection

- **Thrombotic microangiopathy (TTP-like illness)**
  - Biological model for PEO as causal agent
  - Why not seen in Scott County, Indiana and rarely seen with other PEO-containing opioids?
  - **Different preparation techniques? Different PEO molecular weight?**
- **Transmission of blood borne pathogens (e.g., HIV)**
  - Factors driving need for multiple shared injections
    - Short duration of effect and intensity of withdrawal
    - Need for increased solvent and “rinse shots”
    - Sharing of pills, equipment
  - **Excess risk for reformulated Opana ER vs. ER oxymorphone vs. oxymorphone?**

Thank you.

DEPI-Drug Use
Backup Slide Shown

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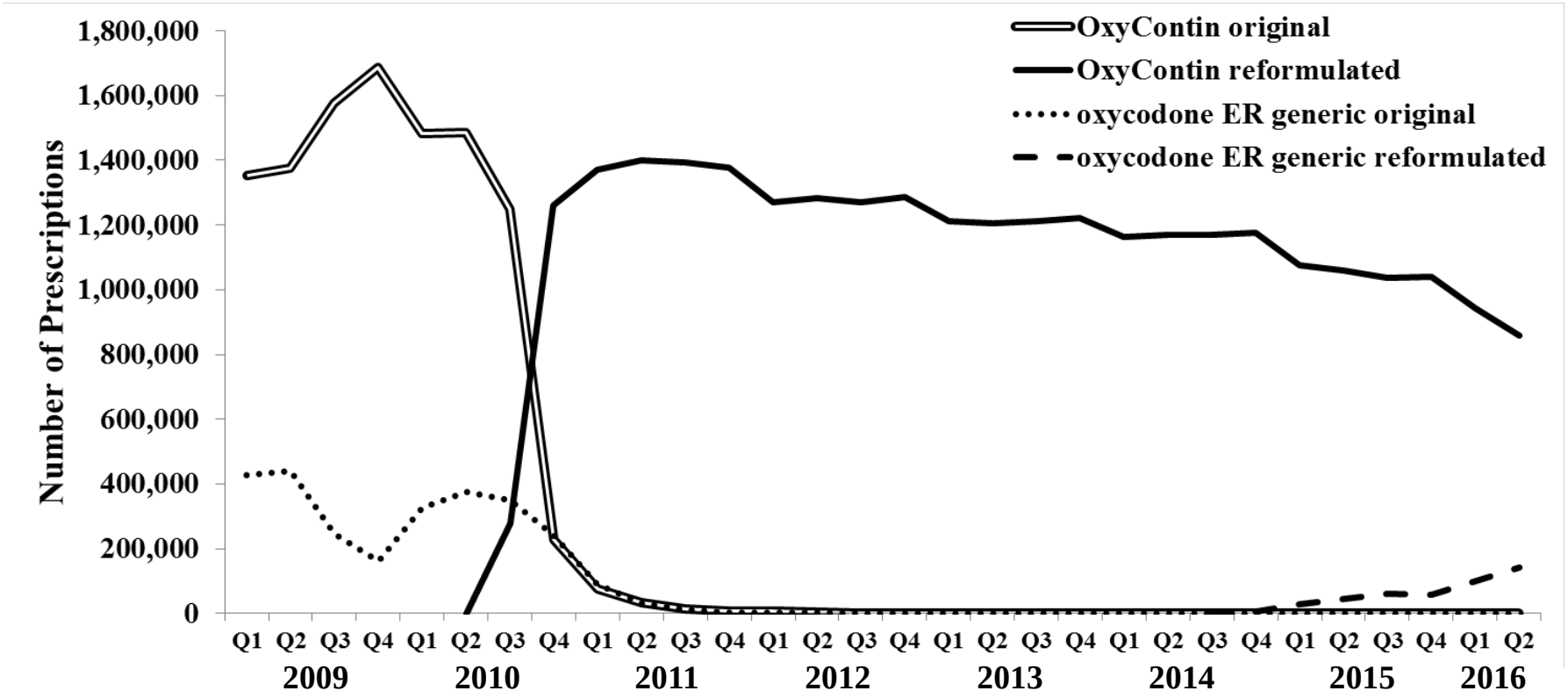
FDA Center for Drug Evaluation and Research

March 13-14, 2017

Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee

Notice of Correction

FDA Briefing Document: Correction to Figure 3, Page 188



- **Graph displays a correction to 2010, Quarter 3 data for generic oxycodone ER only.**
- **Table 3 in Appendix C on page 286 will also be removed, this table was included in error. Please disregard Table 3 and refer to the corrected graph above.**

Source: IMS Health, National Prescription Audit™ . 2009-2016. Extracted September 2016.