

OPANA® ER (oxymorphone HCl) Benefit-Risk

March 13, 2017

Anesthetic & Analgesic Drug Products
Advisory Committee and
Drug Safety and Risk Management Advisory
Committee

Introduction

Harris Rotman, PhD

Vice President, US Regulatory Affairs
Endo Pharmaceuticals Inc.

Reformulated OPANA ER

- 2006 Original OPANA ER approved
- 2011 Reformulated OPANA ER approved
 - Only Reformulated OPANA ER available
 - Endo not currently seeking abuse-deterrent labeling

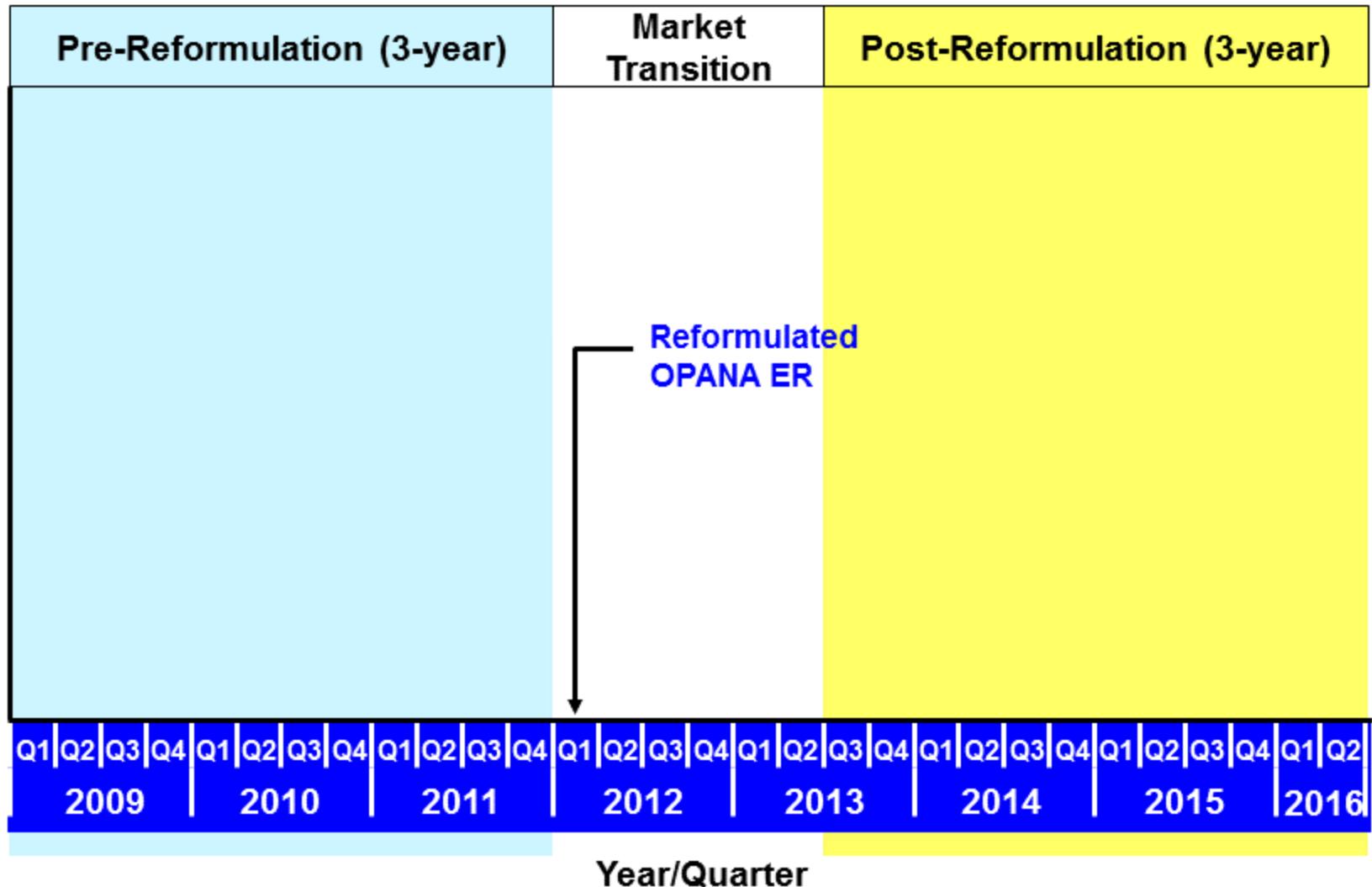
OPANA ER: Important Treatment Option for Chronic Pain Patients (Intended Use)

- Indication: Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
- Opioids are an important option
 - Patients have unique situations
 - Physicians need multiple opioid options

Opioid Abuse Evaluated Using Epidemiology Data

- Referred to as “Category 4” in FDA guidance finalized in 2015
- There are challenges inherent with evaluating abuse epidemiology data
 - Often conflicting analyses

Observational Epidemiology Studies Use a Pre-Post Design



OPANA ER Abuse Epidemiology Data Interpretation

- After reformulation of OPANA ER
 - Benefit-risk profile remains positive
 - Intranasal abuse lower
 - IV abuse increased, then stabilized in TN;
IV abuse stable or decreasing in other states
- Data limited by collection methodology
- Survey population may not represent those that choose to abuse opioids
- Provide insight for potential areas of investigation

OPANA ER Reformulated to Maintain ER Properties and Resist Crushing

- Polyethylene Oxide (PEO) formulation
- Extremely hard tablet resistant to crushing
 - Barrier to efforts to reduce particle size
- Gelling in aqueous solution
- PEO used for several ADF products
 - Approved: OxyContin[®], ArymoTM ER, Hysingla[®] ER

OPANA ER: ADF Labeling Timeline

- 2010:** Endo previously sought ADF labeling in the new formulation NDA
- 2013:** Endo submitted sNDA to obtain ADF labeling; FDA requested an intranasal abuse study
- 2016:** Endo submitted the intranasal abuse study and interim Category 4 studies requesting ADF labeling, but there was missing information in our Category 4 data
- 2016:** Endo withdrew the submission, as final Category 4 study results imminent

Endo Completed Category 1-3 Studies, and Post-Marketing Category 4 Studies

Category 1

Lab-based
in vitro
Manipulation &
Extraction
Studies

Category 2

Pharmacokinetic
Clinical Trial

Category 3

Human Abuse
Potential Clinical
Trial

Category 4

Postmarketing
Confirmation of
Reduction in
Abuse

- Physical & Chemical Manipulation Studies
- Route Specific Studies

- Study 114
(*Manipulated Intranasal*)

- NAVIPPRO®
- RADARS® Poison Center Program
- RADARS® Drug Diversion Program

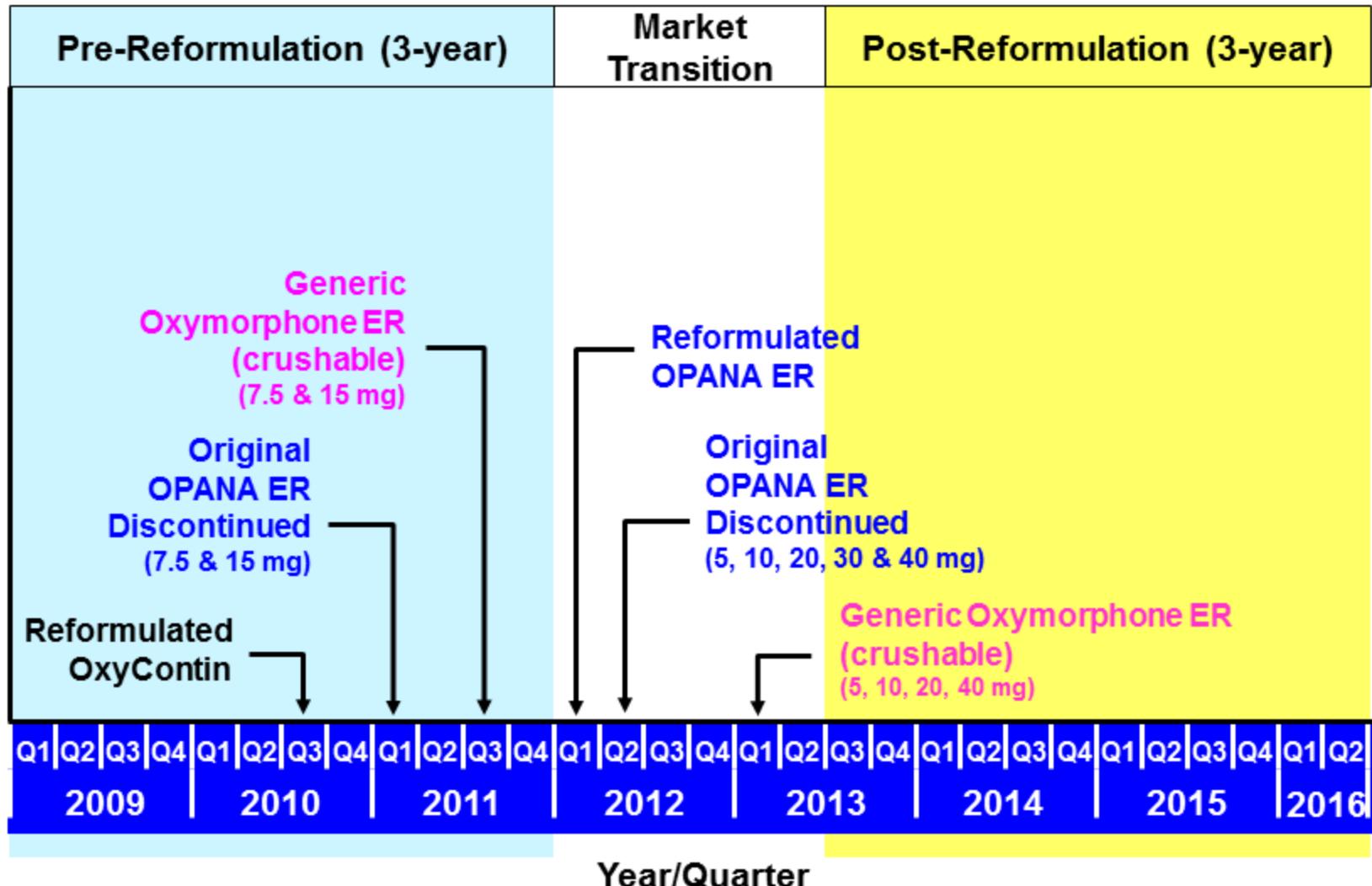
Hypothesis Generating

**Real World
Evidence**

Two Events Confound Epidemiology Interpretations for OPANA ER

1. Introduction of an abuse deterrent formulation of OxyContin® while original OPANA ER was on the market
2. Launch of generic oxymorphone products immediately before and after the introduction of Reformulated OPANA ER

Changing Environment Affected OPANA ER Abuse Patterns



OPANA ER Benefit-Risk Remains Favorable Following Reformulation

- Discuss benefits and safety of OPANA ER when used as intended in chronic pain patients
 - Oxymorphone has characteristics making it a meaningful choice for chronic pain
- Abuse patterns changed prior to and following the introduction of Reformulated OPANA ER, but cause-effect cannot be determined
- Overall positive benefit-risk profile unchanged

Agenda

Pain, Opioids and Personalized Medicine

Perry Fine, MD

Professor of Anesthesiology
Pain Research Center, School of Medicine
University of Utah

Category 1-3 Studies

Harris Rotman, PhD

Vice President, US Regulatory Affairs
Endo

Category 4: Post-marketing Epidemiology Studies

Neil Shusterman, MD

Chief Medical Officer
Endo

Understanding Complicated Observational Data

Alexander Walker, MD, DrPH

Former Chair of Department of Epidemiology
Harvard T.C. Chan School of Public Health

Benefit-Risk Assessment

Richard Dart, MD, PhD

Director, Rocky Mountain Poison & Drug Center
Executive Director, RADARS® System

Additional Experts

Stephen Butler, PhD

Chief Scientific Officer
Inflexxion

Gavril Pasternak, MD, PhD

Anne Burnet Tandy Chair of Neurology
Memorial Sloan Kettering Cancer Center
Professor of Neurology, Weill Medical School of Cornell University

Kerri Schoedel, PhD

Principal in Altreos Research Partners
Former Senior Director of Clinical Pharmacology,
INC Research, Toronto

Pain, Personalized Medicine and Opioid Therapy

Perry Fine, MD

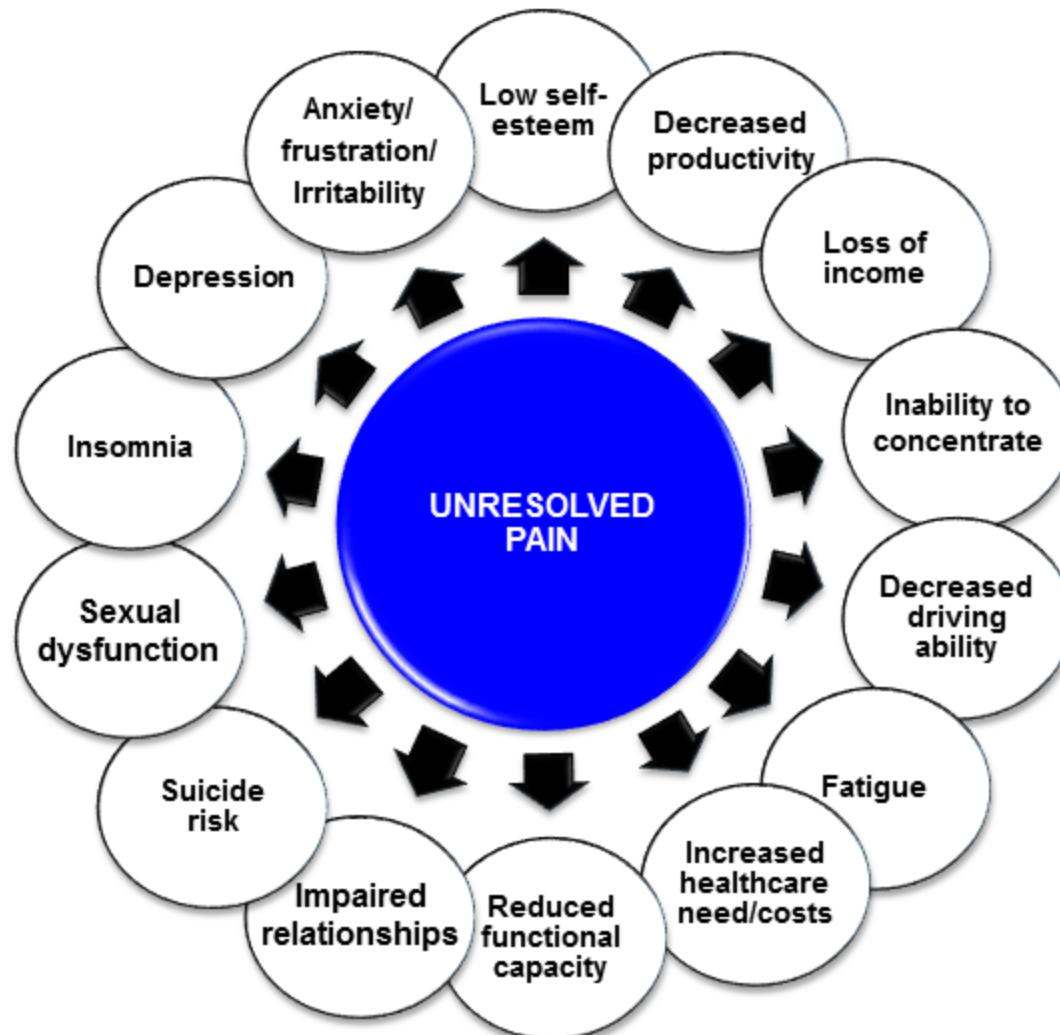
Professor of Anesthesiology

Pain Research Center, School of Medicine
University of Utah

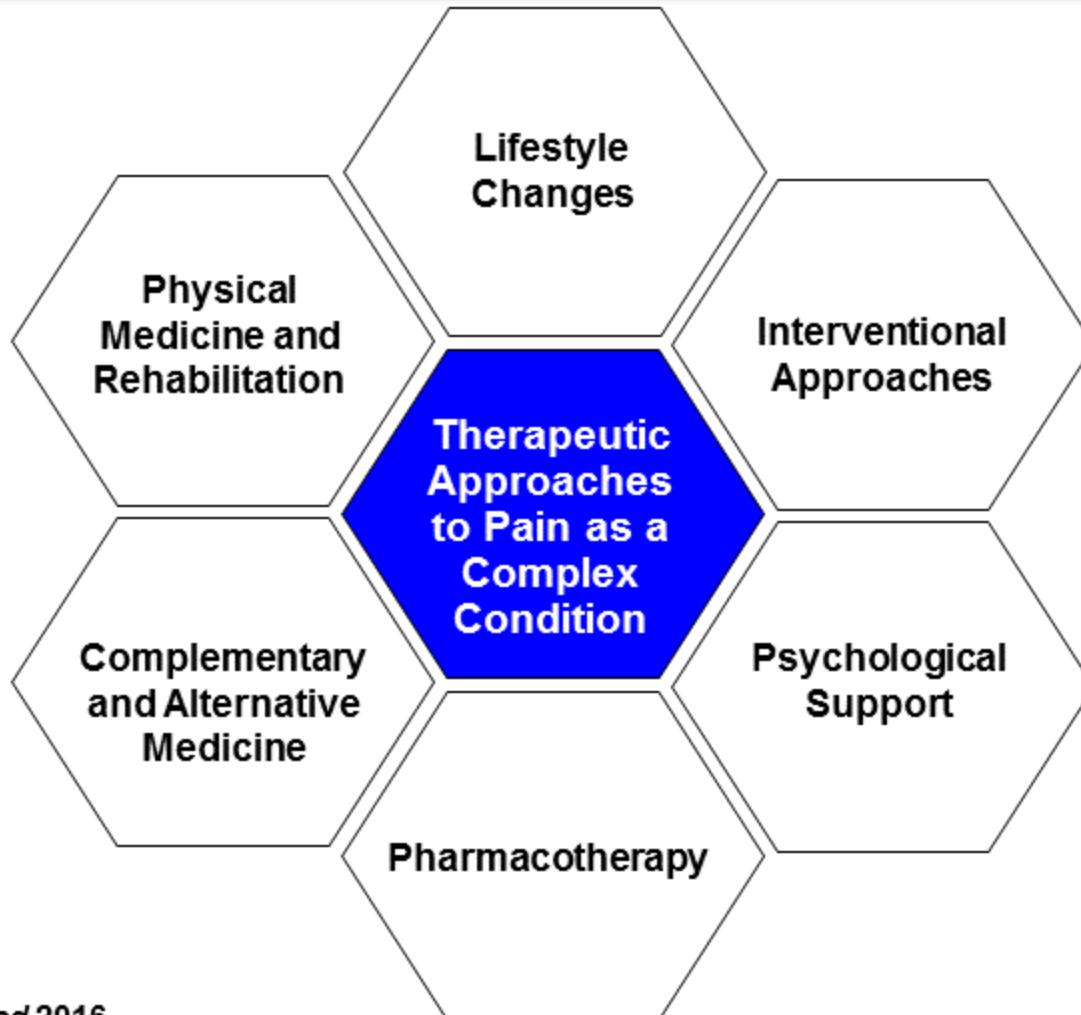
Key Points

- Severe intractable pain is a major public health problem
- Opioid therapy may be needed in selected patients to affect positive therapeutic outcomes
- Responses to opioids are highly variable, due to:
 - Variability in drug metabolism among diverse clinical populations
 - Potential drug-drug interactions
 - Receptor polymorphism
- A wide variety of opioids are needed - including oxymorphone - to optimize outcomes

Impact of Unrelieved Pain



Safe, Effective Pain Management Requires Comprehensive Assessment + Integrated Care



1. Gudin JA. *Postgrad Med* 2016
2. Tayeb BO. *Pain Med* 2016
3. CDC Guidelines, 2016

Personalized Medicine is Critical to Effective Pain Management

- “One size fits all” approach is a failing formula
- Unique social, cognitive, psychological, genetic circumstances¹
- PK PD variability of opioids relevant to pharmacogenetic differences in patients
- Currently requires “trial and error” or “N of 1” treatment design²
 - Matching drug characteristics and effects to patient characteristics and responses

1. Bottinger EP. *Mount Sinai J Med* 2007.

2. Offit K. *Hum Genet* 2011.

Reasons for Variable Responses

- People are not the same
 - Drug metabolism differs among diverse populations
 - Clinical factors influence drug effects
 - Polypharmacy
 - Variability in diseases and clinical condition over time
 - Genetic backgrounds differentially impact drug sensitivity

Drugs Are Not the Same: Unique Metabolic Profile of Oxymorphone

- Not a substrate for CYP450-based metabolism
- Pharmacogenetics and metabolism play an important role in analgesic efficacy and adverse effects
- Receptor polymorphism is well-established in opioid pharmacology gene splice variants coding for mu receptors determine dose-response^{1,2}
 - Opioids have both class and individual effects

1. Pasternak GW. *Clin J Pain* 2010.

2. Pergolizzi JV. *J Manag Care Pharm* 2014.

Variability in Opioid Responsiveness & Risk

- Therapeutic and adverse effects are a function of patient-specific factors¹
- Alternatives are necessary to account for these differences
 - Opioid rotation during initial titration and during ongoing treatment is a well established and necessary practice²

1. Benyamin R et al., *Pain Physician* 2008.

2. Fine PG et al., *J Pain Symptom Manage* 2009.

Case Study

- Middle age professional woman with severe neuropathic facial pain
- Modest benefits from non-opioid and opioid therapies
- Hospitalized 4 times for out-of-control pain and AEs
- Switched to IR, then ER oxymorphone with paroxetine (CYP2D6) and carbamazepine (CYP3A4)
- No ER or hospitalization in 12 months

Lesson from “the Trenches”

- No risk-free solutions
- Until such time that there is a class of drugs as efficacious and versatile as the opioids, clinicians need to learn how to select patients for opioid therapy, when indicated, and manage them as safely and effectively as possible.

Category 1

Lab-based *in vitro* Manipulation and Extraction Studies

Harris Rotman, PhD.

Vice President, US Regulatory Affairs
Endo Pharmaceuticals Inc.

Category 1: Lab-based *in vitro* Manipulation and Extraction Studies

Category 1

Lab-based
in vitro
Manipulation &
Extraction
Studies

Category 2

Pharmacokinetic
Clinical Trial

Category 3

Human Abuse
Potential Clinical
Trial

Category 4

Postmarketing
Confirmation of
Reduction in
Abuse

- Physical & Chemical Manipulation Studies
- Route Specific Studies

- Study 114
(Manipulated Intranasal)

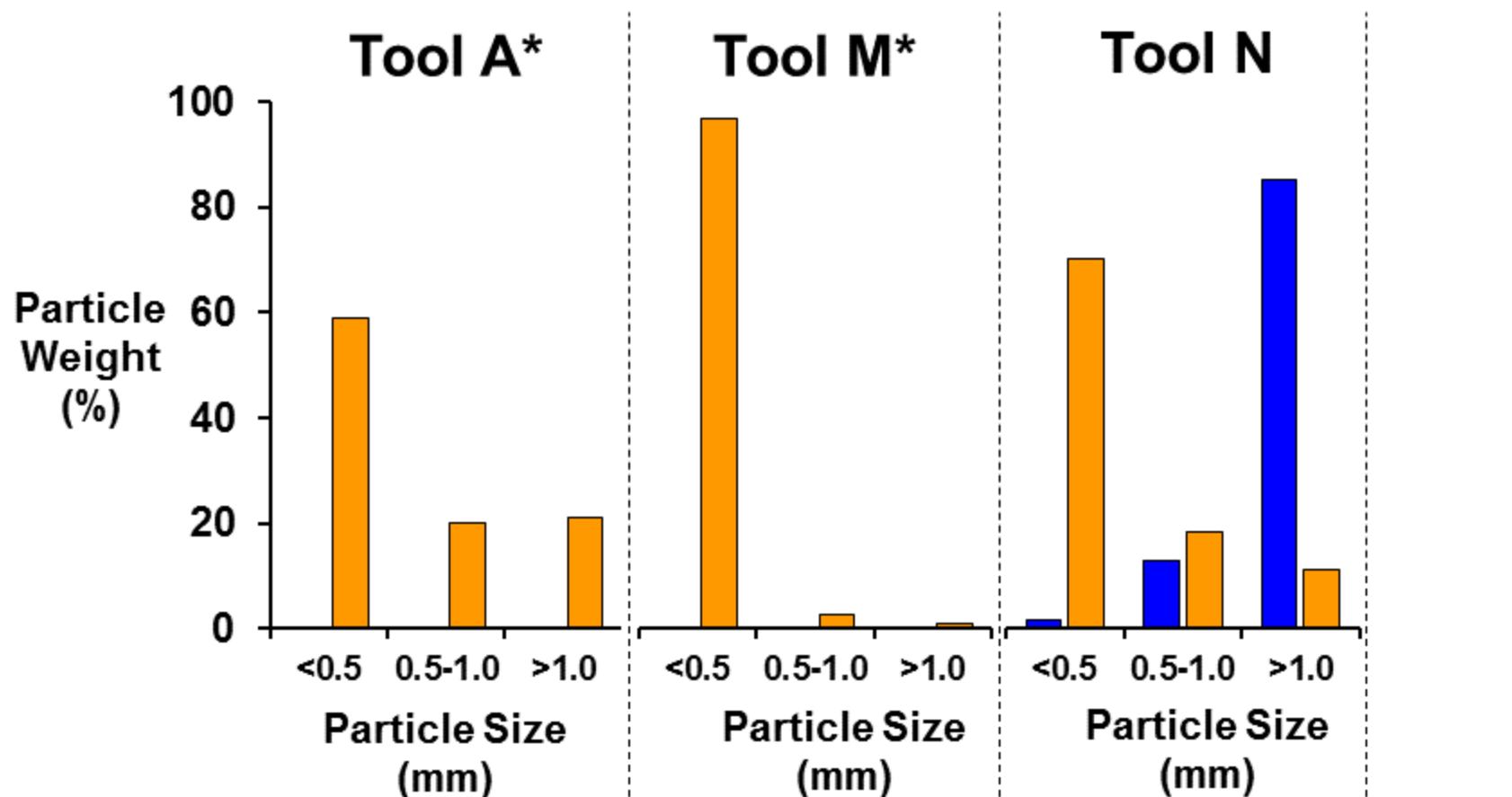
- NAVIPPRO®
- RADARS® Poison Center Program
- RADARS® Drug Diversion Program

Reformulated OPANA ER vs Generic Non-ADF Oxymorphone

Category 1

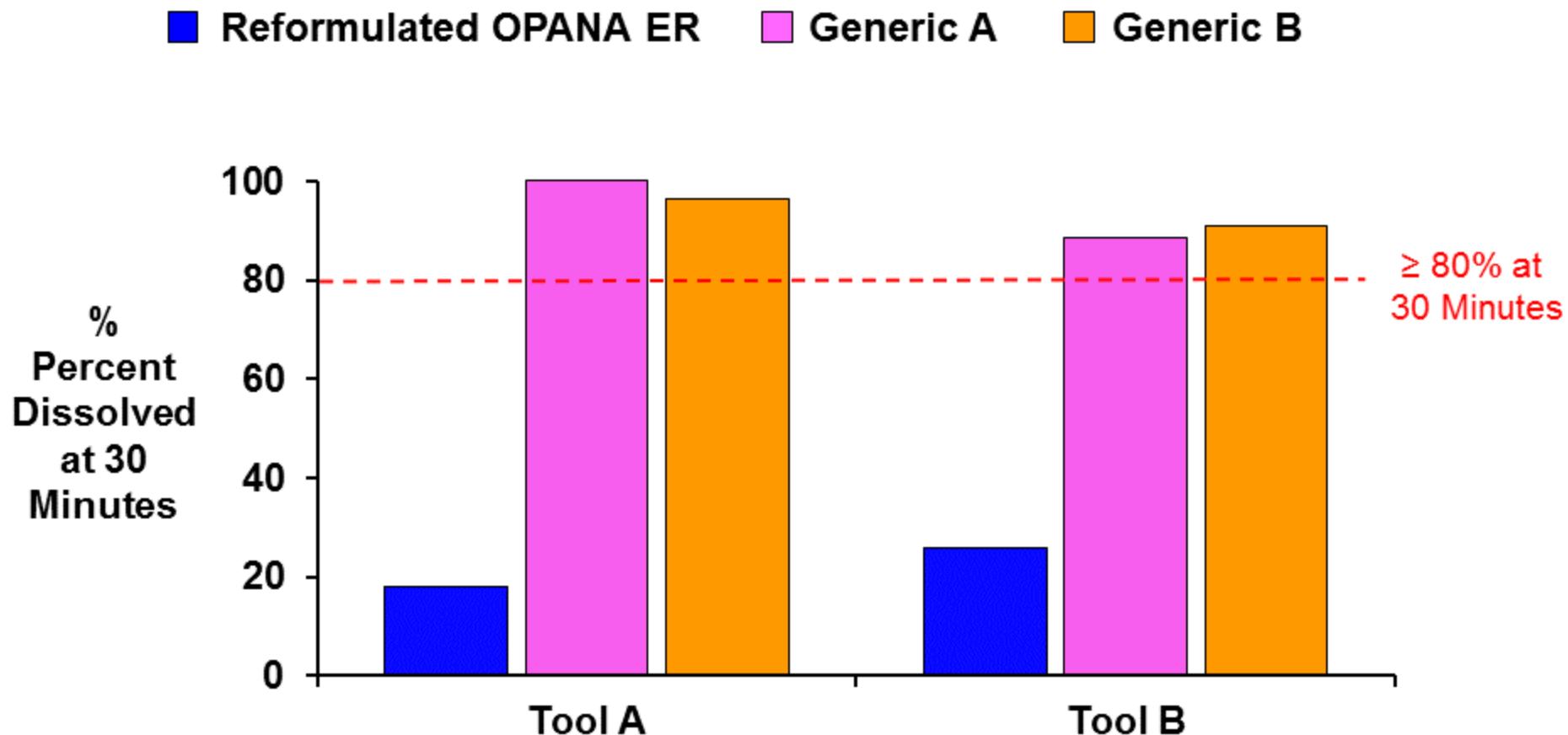
Reformulated OPANA ER Resists Reduction in Particle Size

■ Reformulated OPANA ER ■ Generic non-ADF Oxymorphone ER

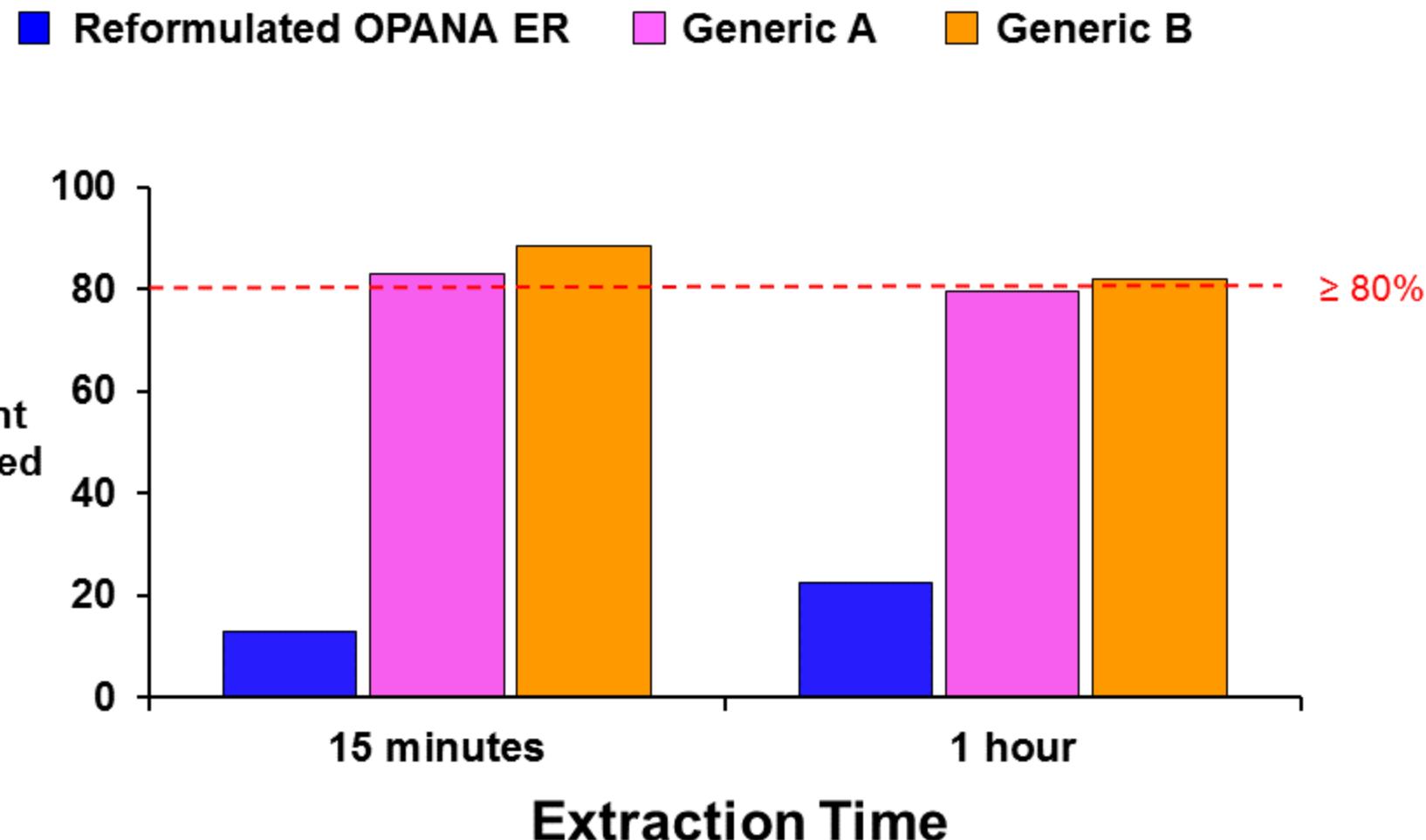


* No particles generated for Reformulated OPANA ER

Generic Products (Non-ADF Oxymorphone ER) Readily Convert to IR when Manipulated



Reformulated OPANA ER Had Lower Extraction Rate than Generic Non-ADF Oxymorphone ER



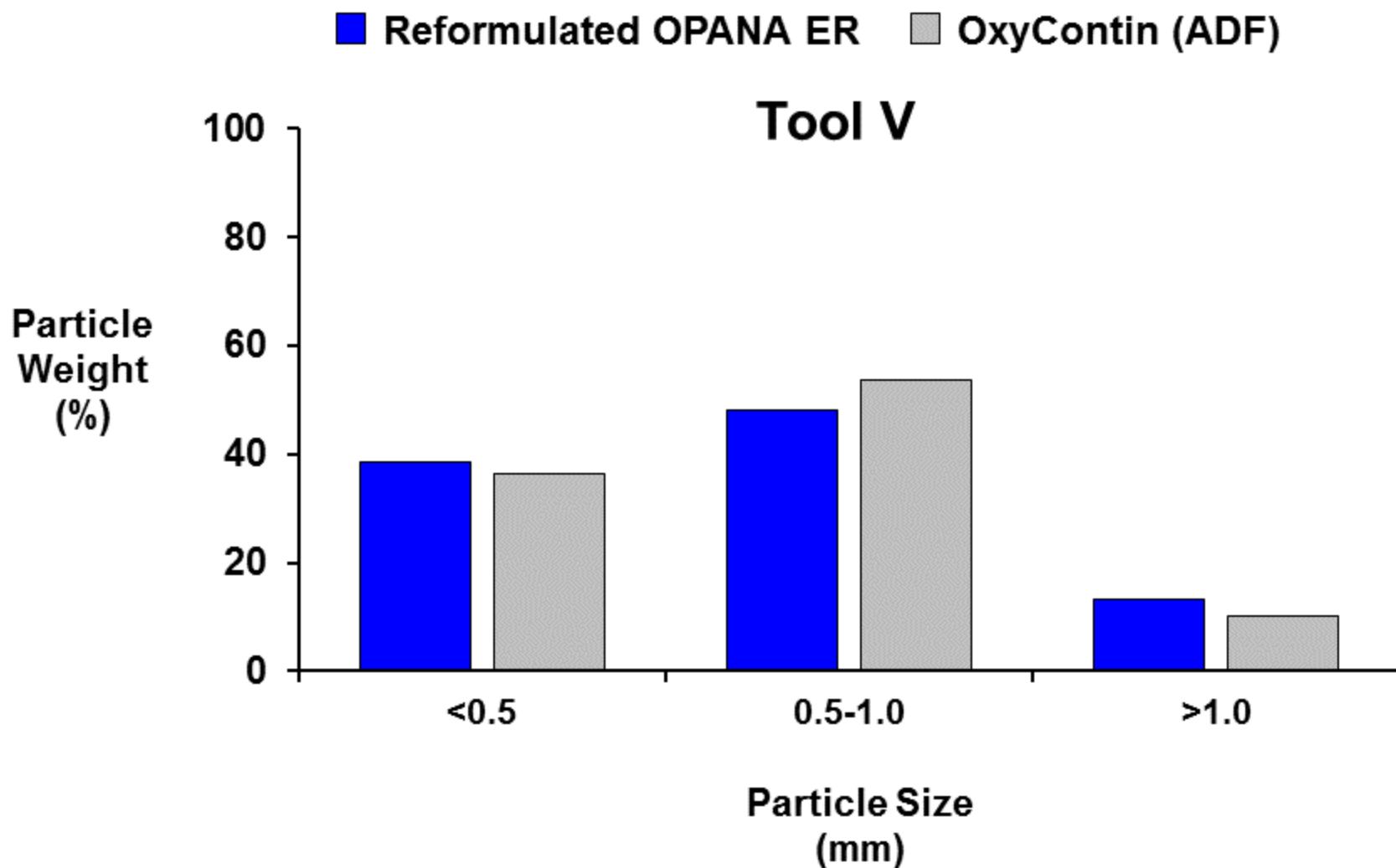
Reformulated OPANA ER had Lower Percent Extraction than Generic Oxymorphone

Tool	Solvent a (mL)	% API Extracted	
		Reformulated OPANA ER	Generics
Tool B	5 mL	26% - 40%	61% - 80%
Tool A	5 mL	N/A	79%
Tool V	3 mL	Not syringeable	N/A

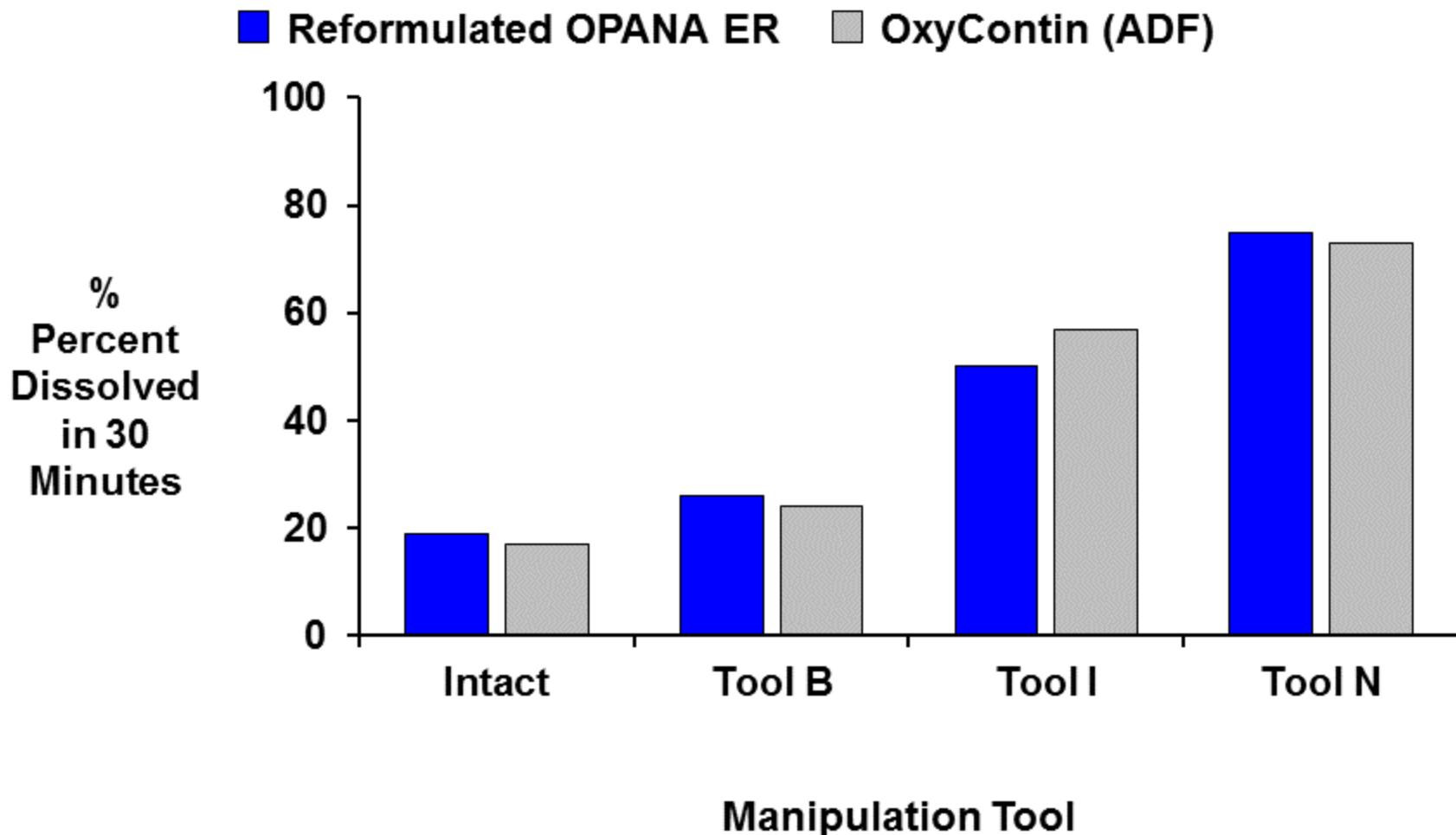
Reformulated OPANA ER vs OxyContin (ADF)

Category 1

Reformulated OPANA ER & OxyContin (ADF) Resist Particle Size Reduction

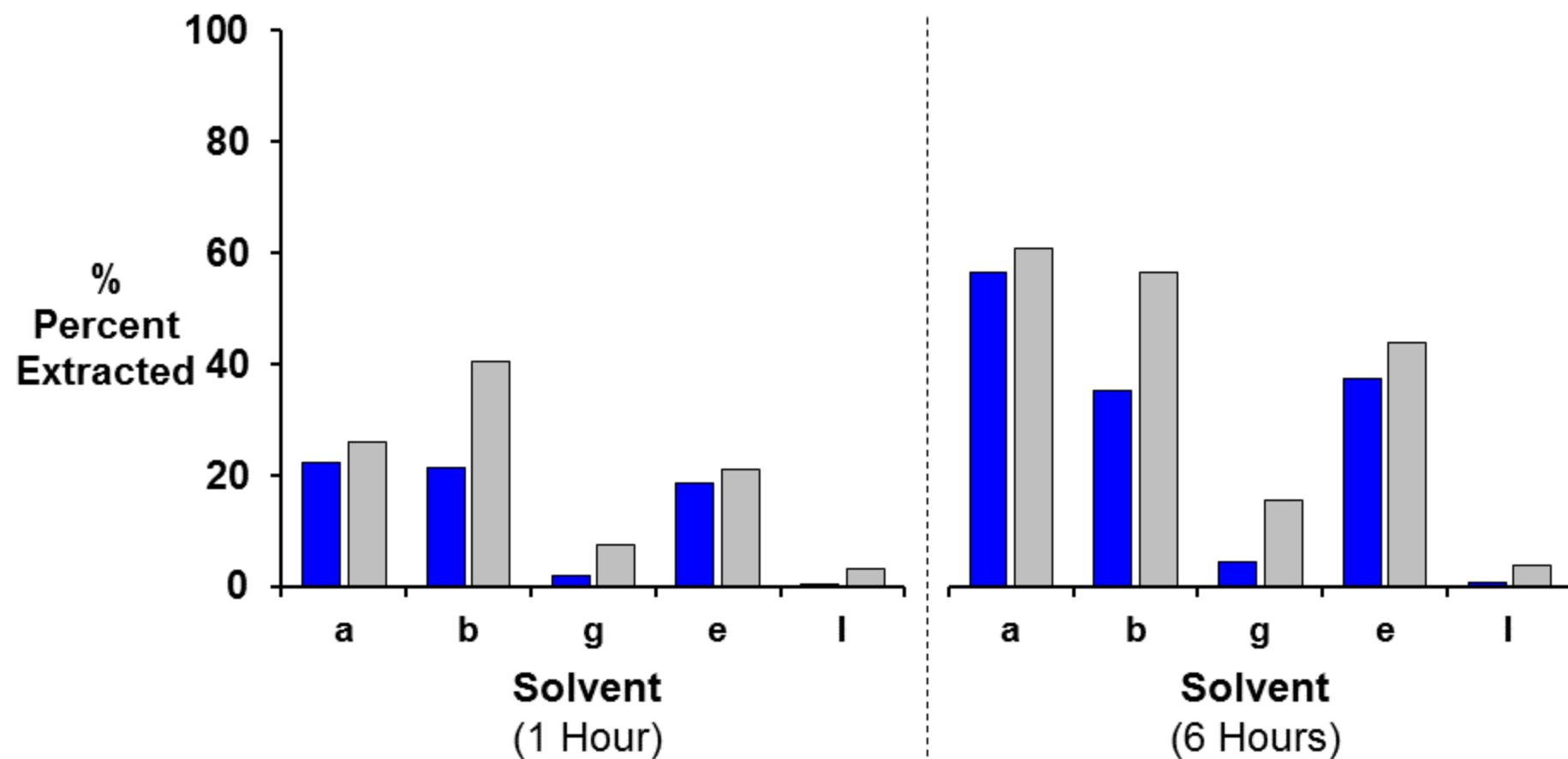


Reformulated OPANA ER & OxyContin (ADF) Have Similar *in vitro* Dissolution



Similar Extraction Rate in a Variety of Aqueous and Non-Aqueous Solvents

■ Reformulated OPANA ER ■ OxyContin (ADF)



Reformulated OPANA ER has Similar Extraction to OxyContin (ADF)

Tool	Solvent a (mL)	% API Extracted	
		Reformulated OPANA ER	OxyContin (ADF)
Tool V	3 mL	Not syringeable	Not syringeable
Tool B	5 mL	26% - 40%	42% - 46%
Tool I	2 mL, 5 times	39%	36%

Category 1 Testing Support ADF Properties of Reformulated OPANA ER

- Reformulated OPANA ER is more resistant to physical and chemical manipulations than generic oxymorphone ER
- Reformulated OPANA ER and OxyContin (ADF) demonstrate similar physical & chemical properties
 - Resist physical and chemical manipulations

Category 2 and 3 Intranasal PK and Abuse Potential Study

Category 2/3: PK and Human Abuse Potential Study for Intranasal Route of Abuse

Category 1

Lab-based
in vitro
Manipulation &
Extraction
Studies

Category 2

Pharmacokinetic
Clinical Trial

Category 3

Human Abuse
Potential Clinical
Trial

Category 4

Postmarketing
Confirmation of
Reduction in
Abuse

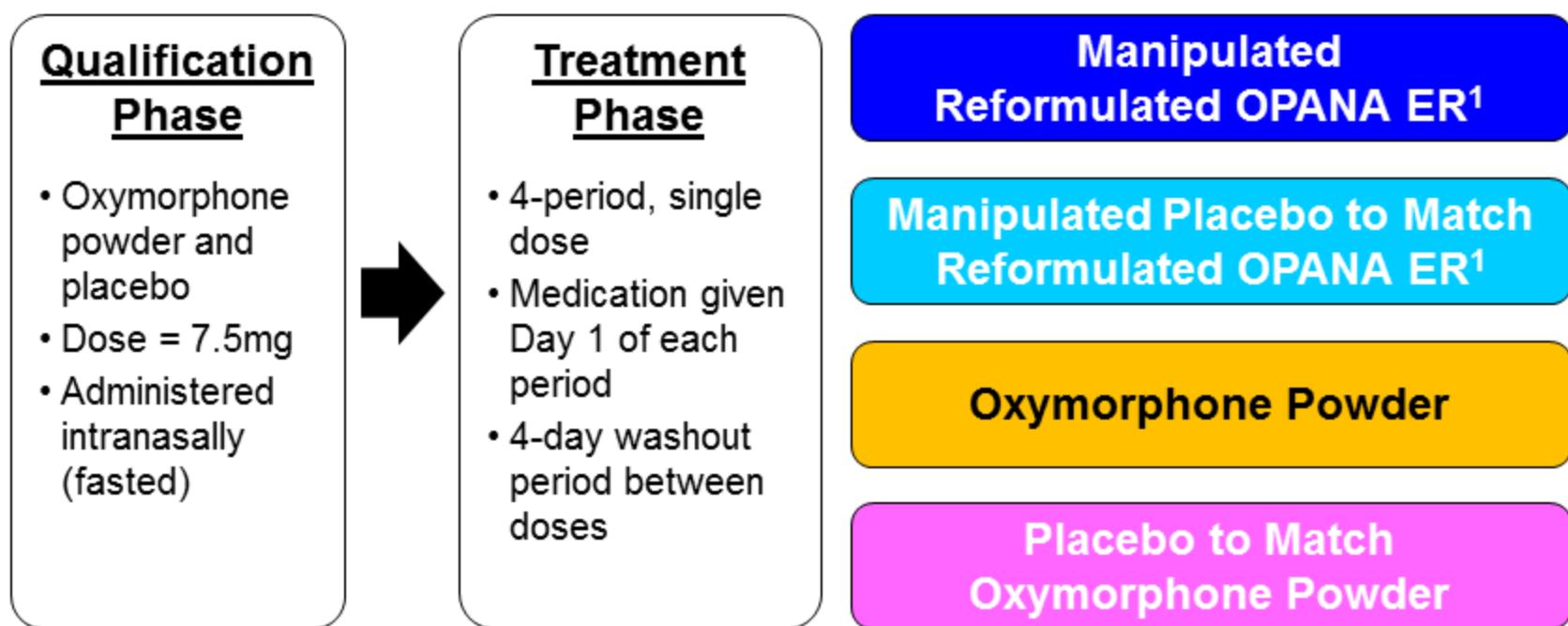
- Physical & Chemical Manipulation Studies
- Route Specific Studies

- **Study 114**
(*Manipulated Intranasal*)

- NAVIPPRO®
- RADARS® Poison Center Program
- RADARS® Drug Diversion Program

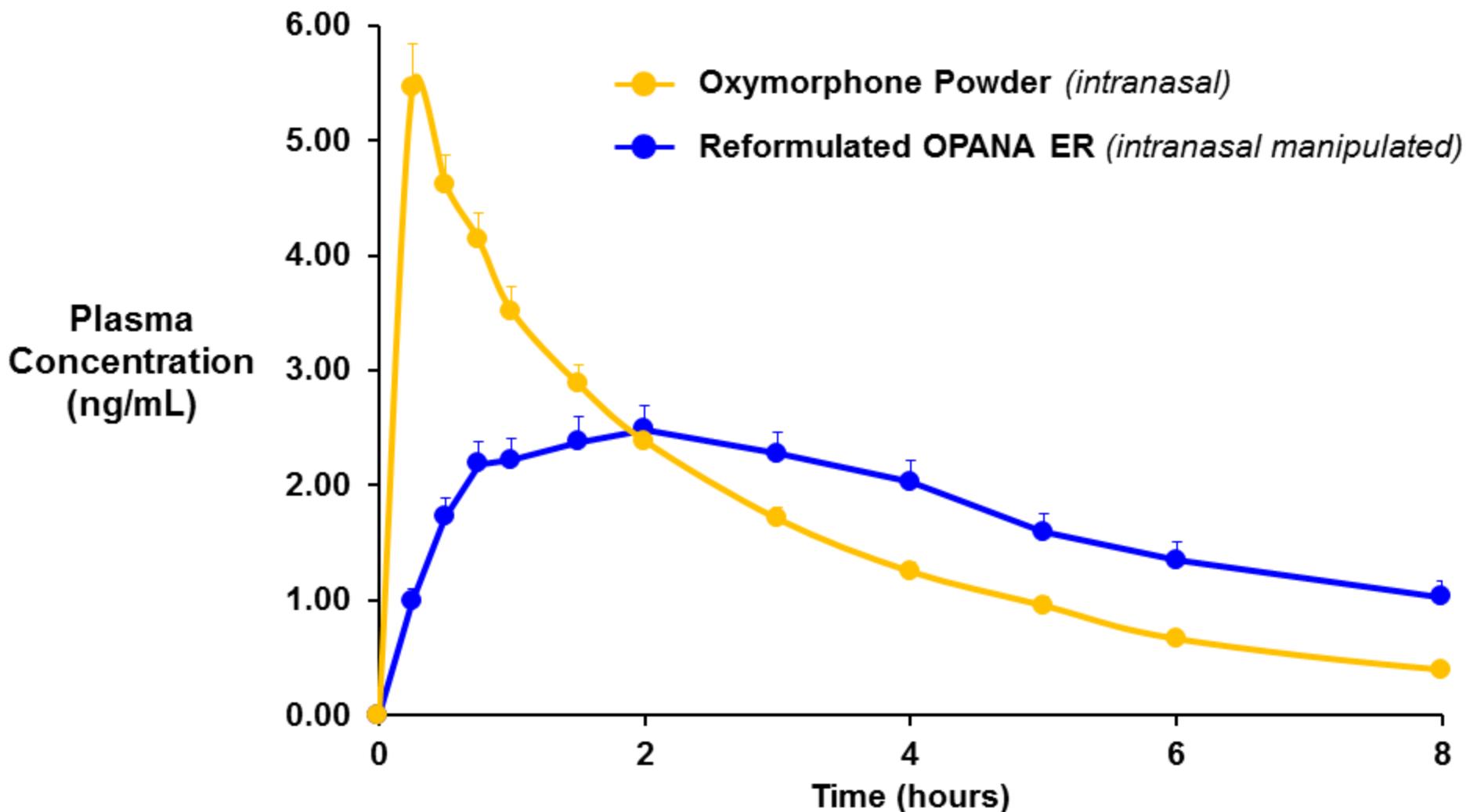
Study Design Consistent with Regulatory Guidelines for Abuse Deterrent Opioids

- Randomized, double-blind, placebo-controlled crossover design



1. Reformulated OPANA ER and matching placebo manipulated using tool V

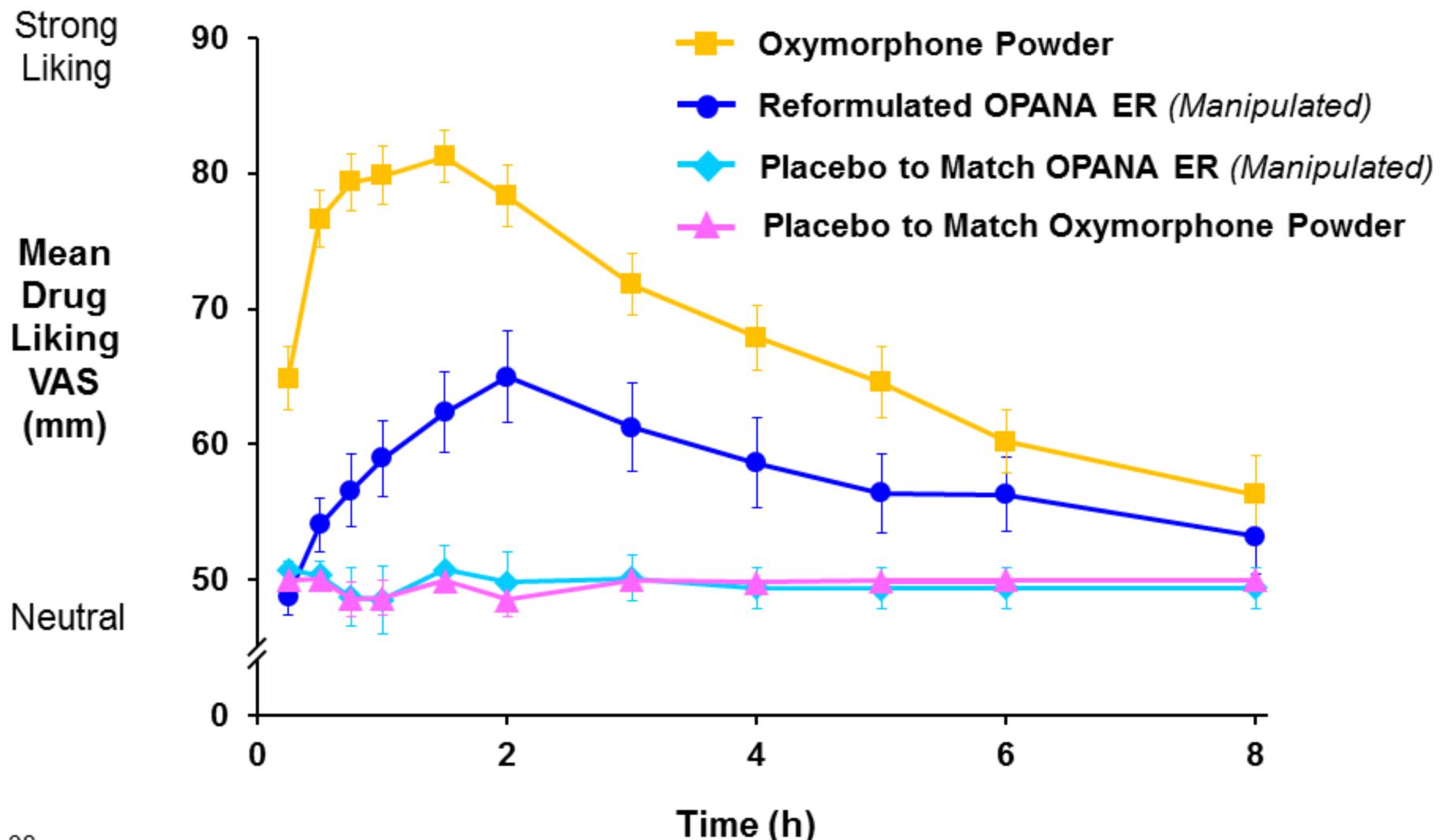
Manipulated Reformulated OPANA ER Retains ER Properties Following Intranasal RoA



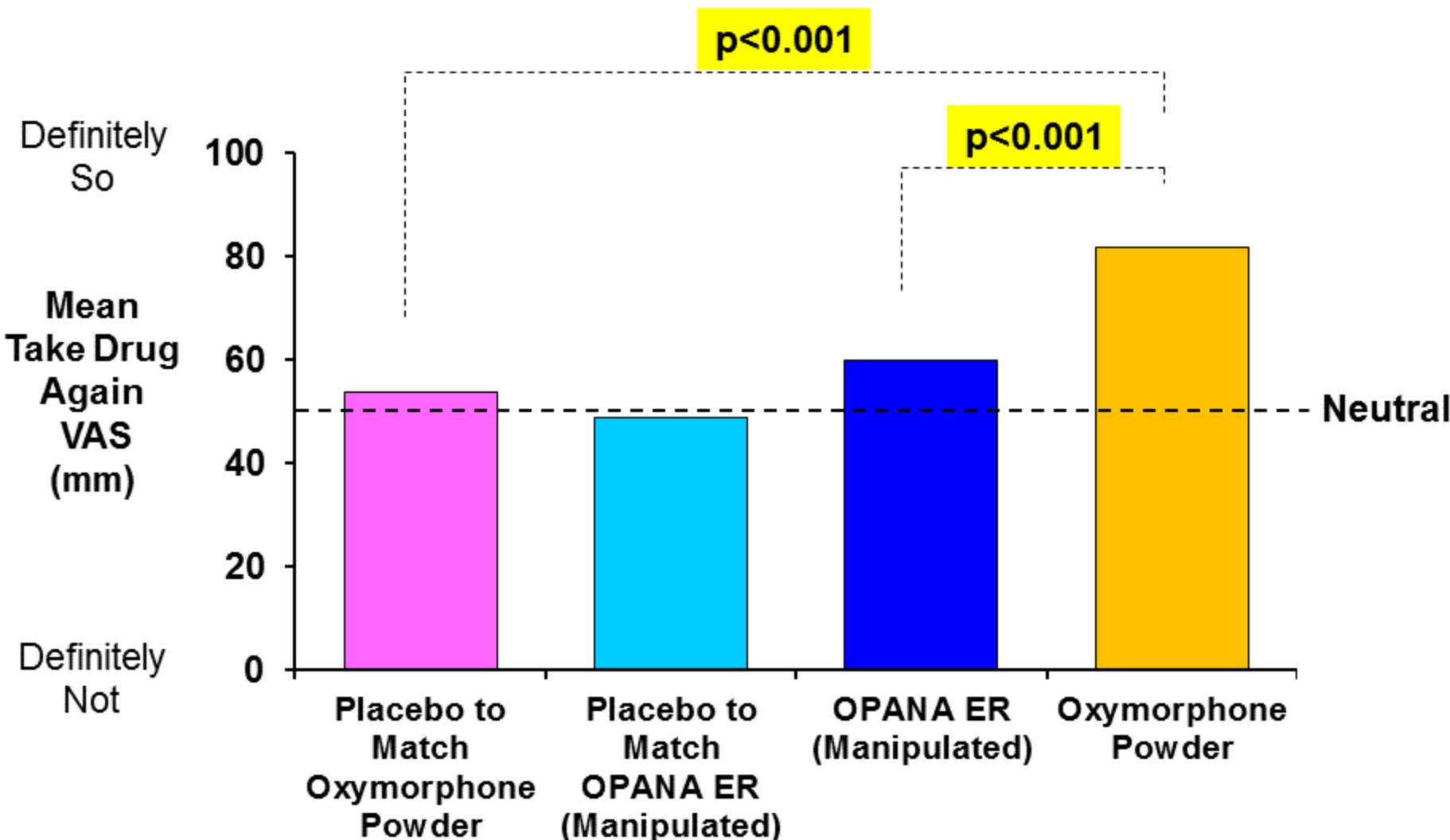
Category 3: Drug Liking Endpoints to Measure Pharmacodynamics Effects

- Primary endpoint
 - E_{max} of Drug Liking Visual Analog Scale (VAS)
- Primary comparison
 - Manipulated Reformulated OPANA ER vs. oxymorphone powder

Lower Drug Liking for Manipulated Reformulated OPANA ER than Oxymorphone Powder



Lower “Take Drug Again” for Manipulated Reformulated OPANA ER Compared to Oxymorphone Powder



Reformulated OPANA ER Retains Extended Release Properties Following Manipulation

- PK shows lower C_{max} and delayed T_{max} compared to oxymorphone powder
- Significantly lower drug liking effects compared to oxymorphone powder
- Intranasal PK/PD study met prespecified endpoints

Post-Marketing Observational Data: Category 4 Abuse Epidemiology

Neil Shusterman, MD
Chief Medical Officer
Endo Pharmaceuticals Inc.

Evaluation of Opioid Abuse Comes From 3 Epidemiology Sources

Data Source	Primary Epidemiology	Secondary Epidemiology
National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®)	Substance Abuse Treatment	
Researched Abuse Diversion and Addiction-Related Surveillance System (RADARS®)	Poison Center	Drug Diversion

NAVIPPRO® Study Design

- Cross-sectional, observational, post-market data
- Data from Addiction Severity Index Multimedia Version (ASI-MV) from 2009-2016
 - 459,240 interviews / 1,084 sites / 40 states
 - 4,984 mentions of OPANA ER
- Two denominators –
 - per 100 ASI-MV assessments
 - per 10,000 tablets dispensed

NAVIPIPRO® Pre-Specified Primary Objectives

- Compare abuse of Reformulated OPANA ER by alternate routes of administration to
 - Historic control - original OPANA ER
 - Concurrent control - generic oxymorphone ER
- Alternate routes of administration – combined endpoint of intranasal or intravenous
- Compare abuse of Reformulated OPANA ER to historic control and concurrent control by individual routes of
 - Intranasal
 - Intravenous

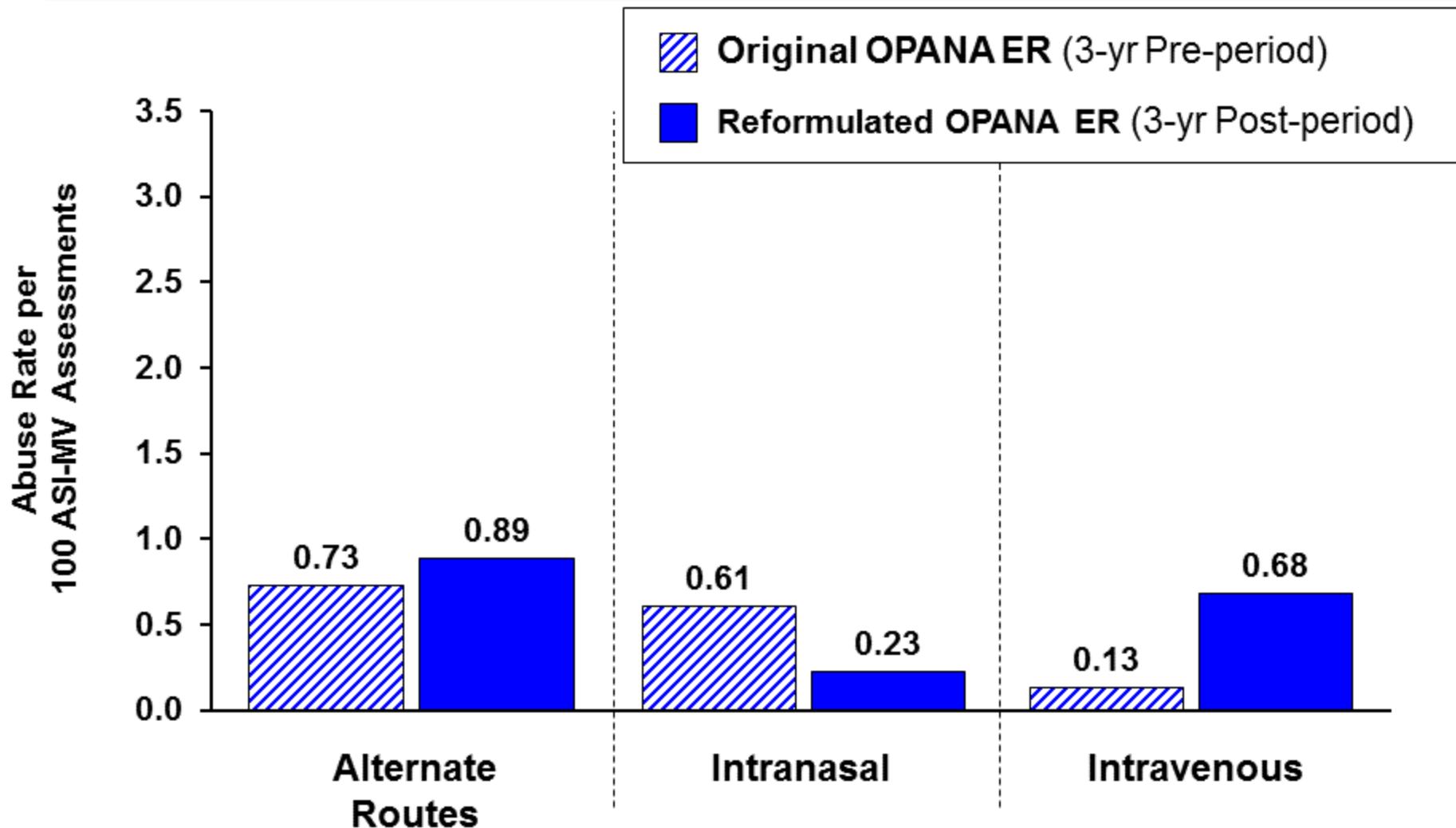
NAVIPPRO® Limitations

- Convenience sample
- No direct abuse-related outcomes
- Sampling is non-random
 - Not nationally representative
- Sampling changes over time
- Self-reported responses subject to recall bias
- Accuracy and honesty cannot be verified

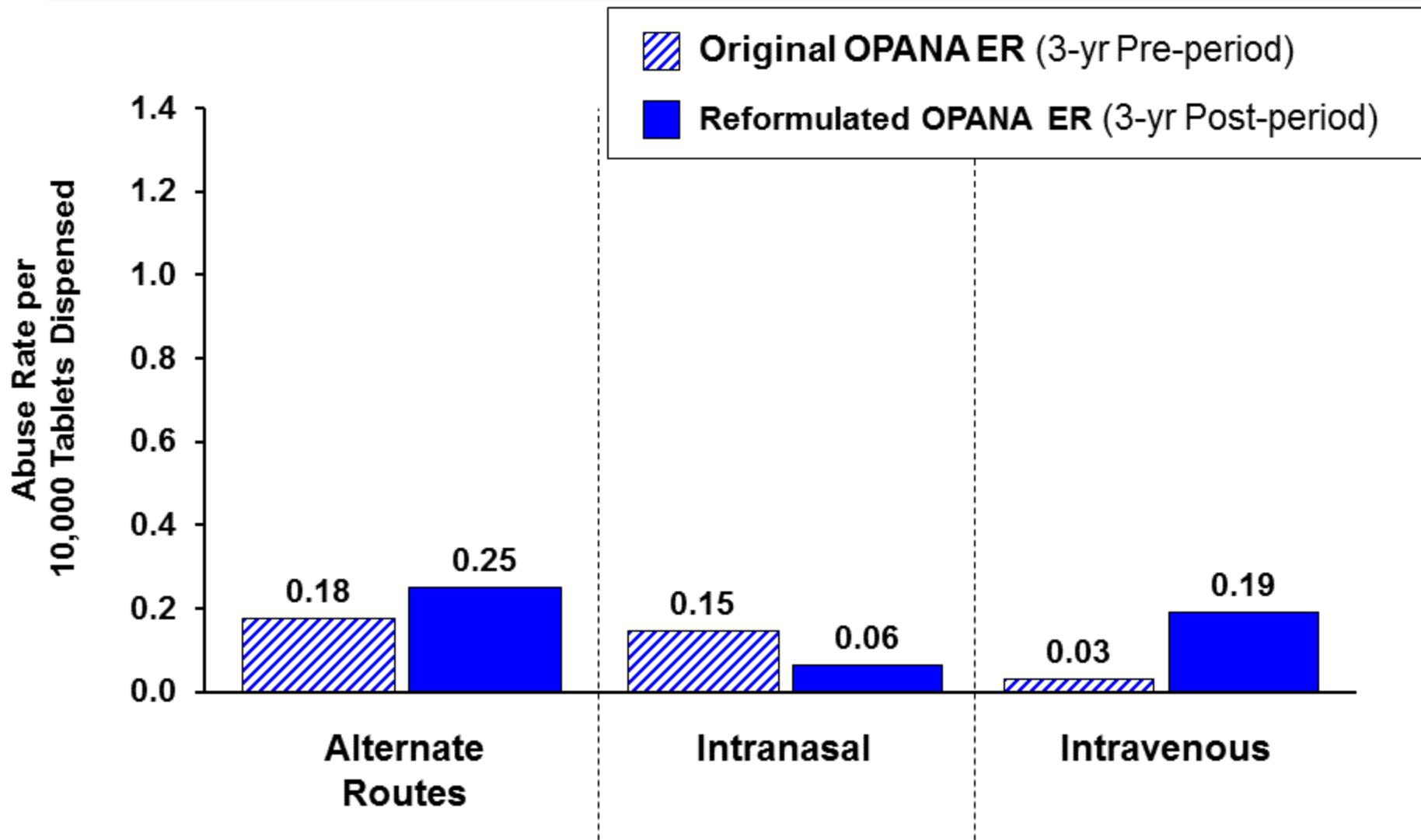
All Sites Included in NAVIPPRO® Prespecified Primary Analysis

- Fixed site was prespecified sensitivity analysis
- Fixed site pattern of results comparable to all sites

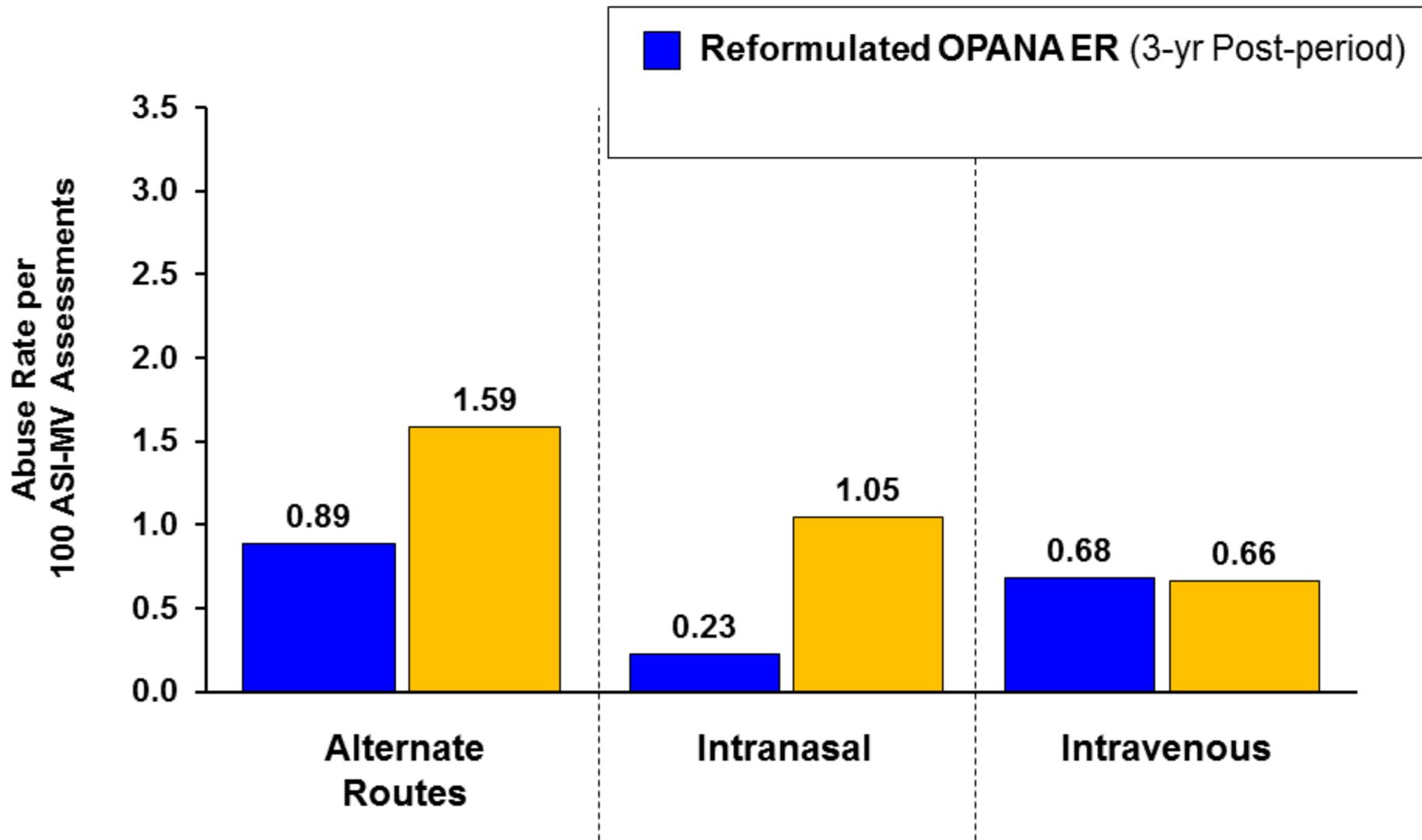
NAVIPIPRO®: Abuse Prevalence by Route of Administration (100 ASI-MV)



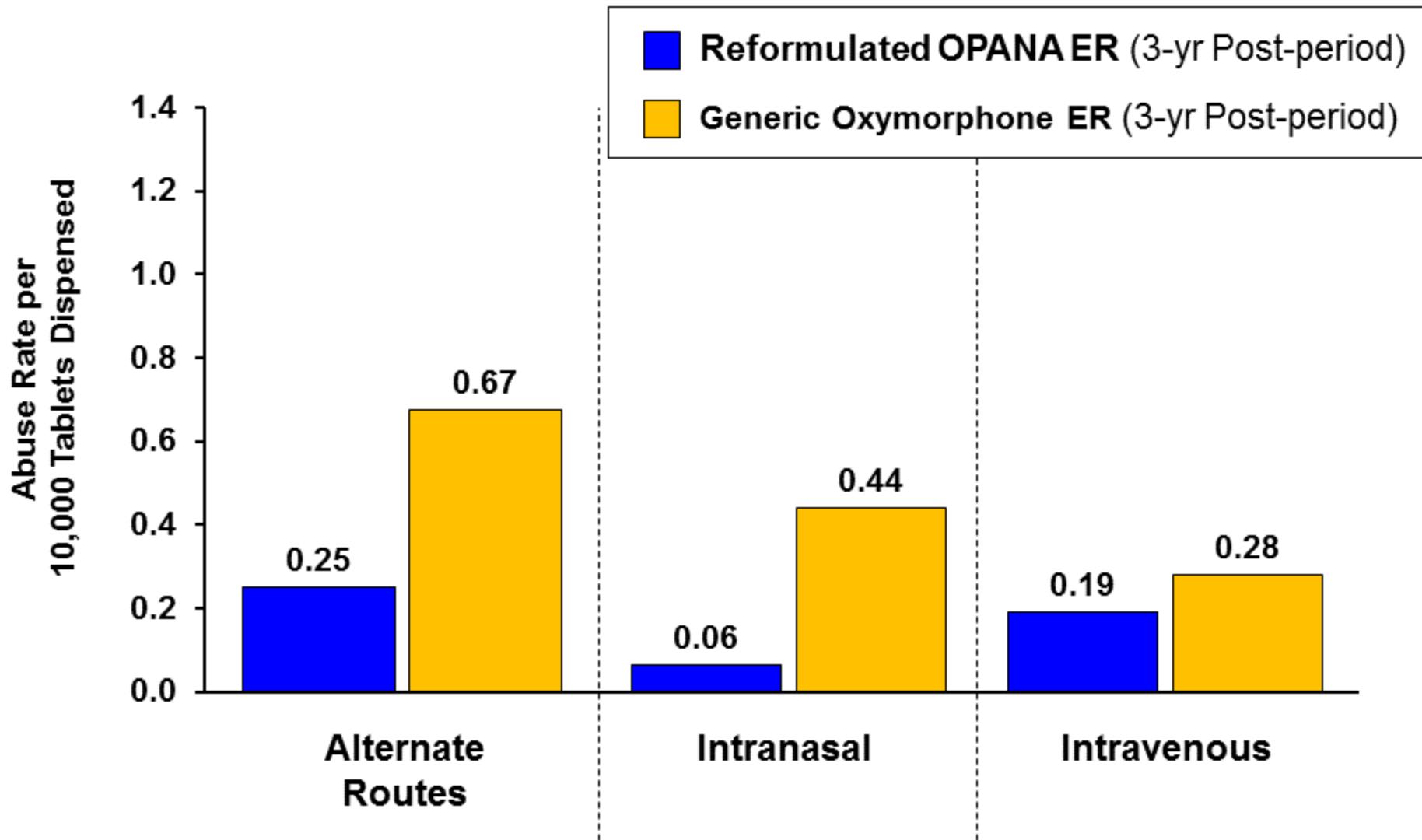
NAVIPPRO®: Abuse Prevalence by Route of Administration (10,000 Tablets Dispensed)



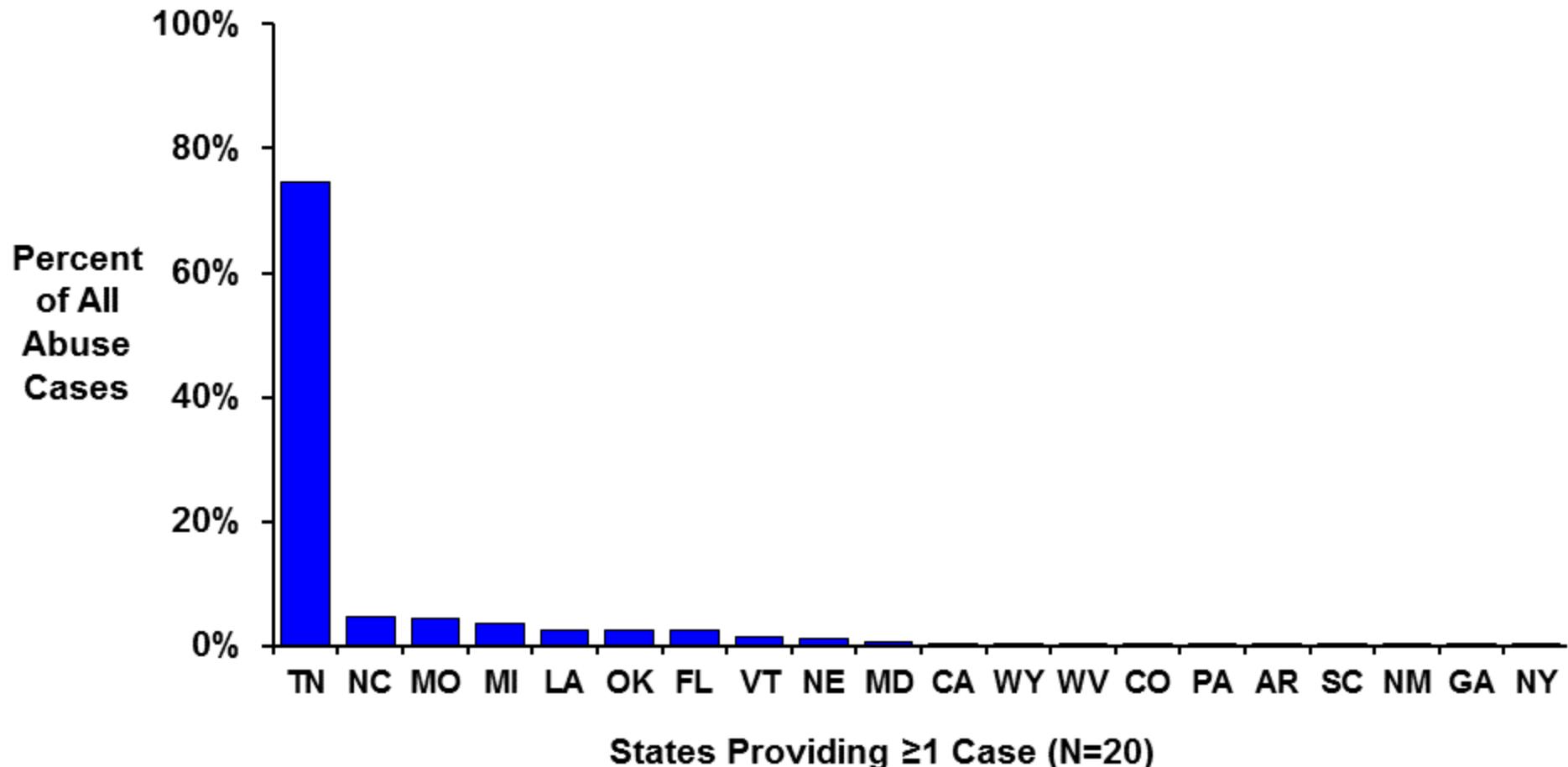
NAVIPPPRO[®]: Abuse Prevalence by Route of Administration (100 ASI-MV)



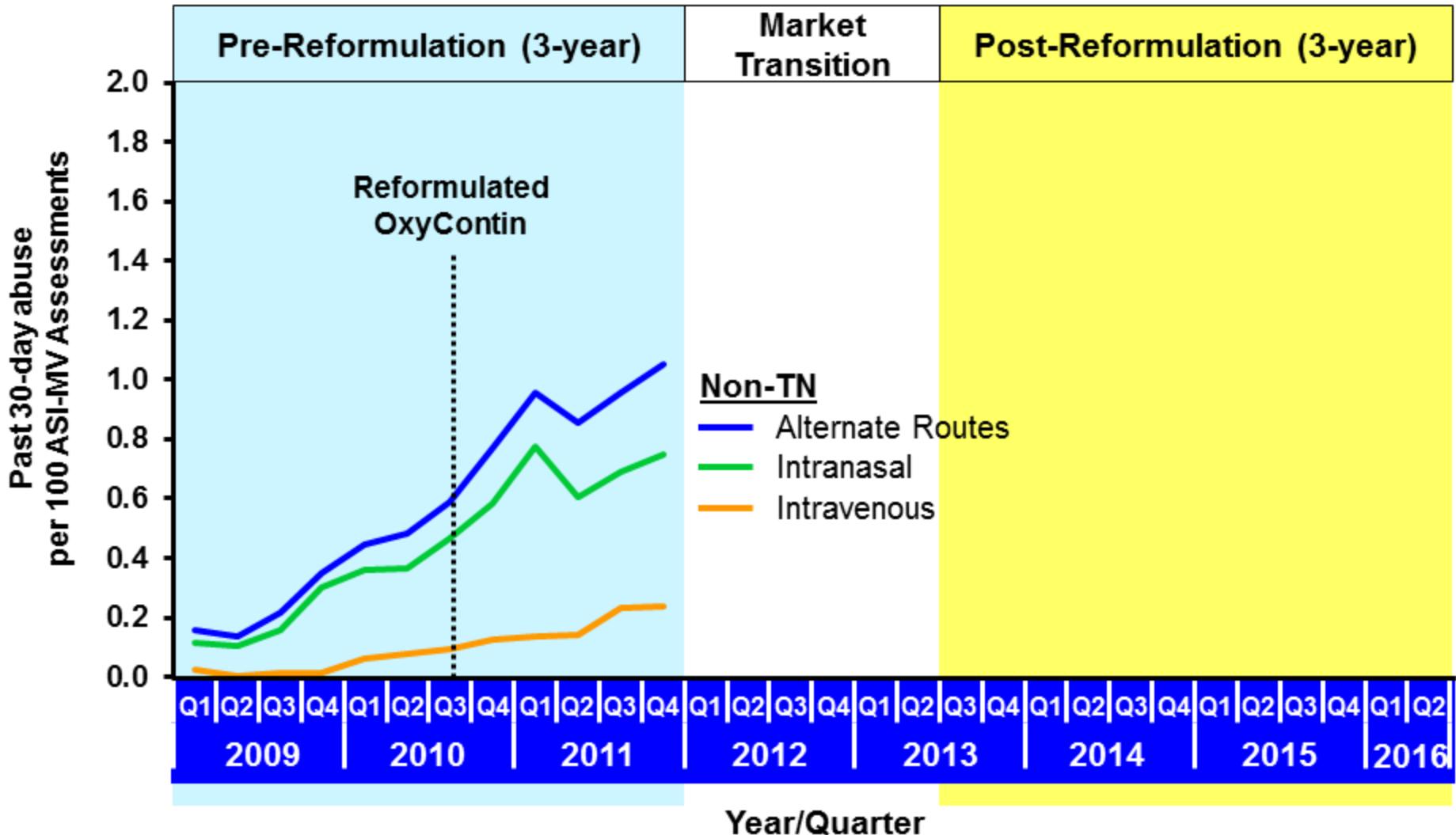
NAVIPPRO®: Abuse Prevalence by Route of Administration (10,000 Tablets Dispensed)



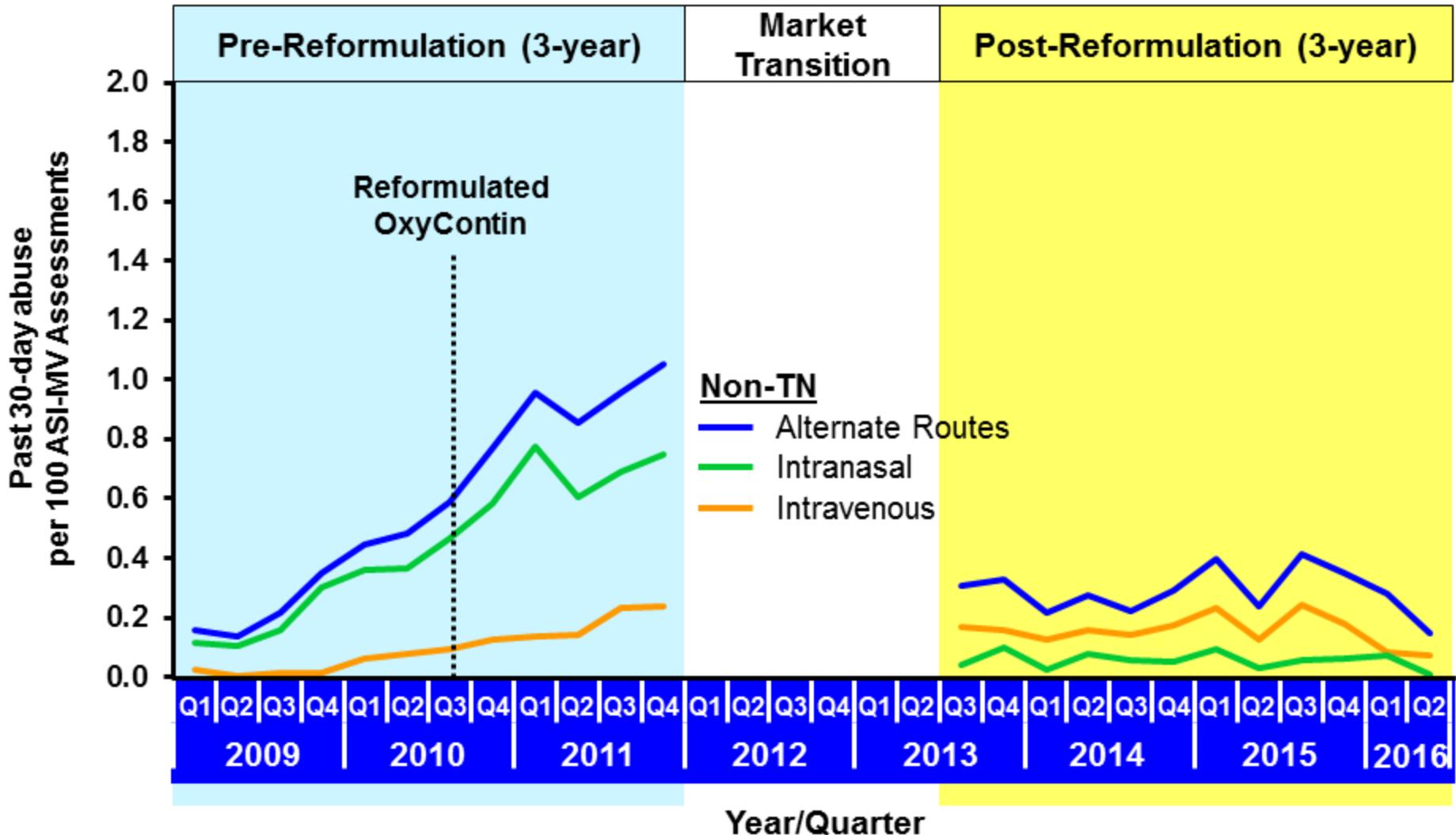
Tennessee Accounted for 75% of Reports for Reformulated OPANA ER



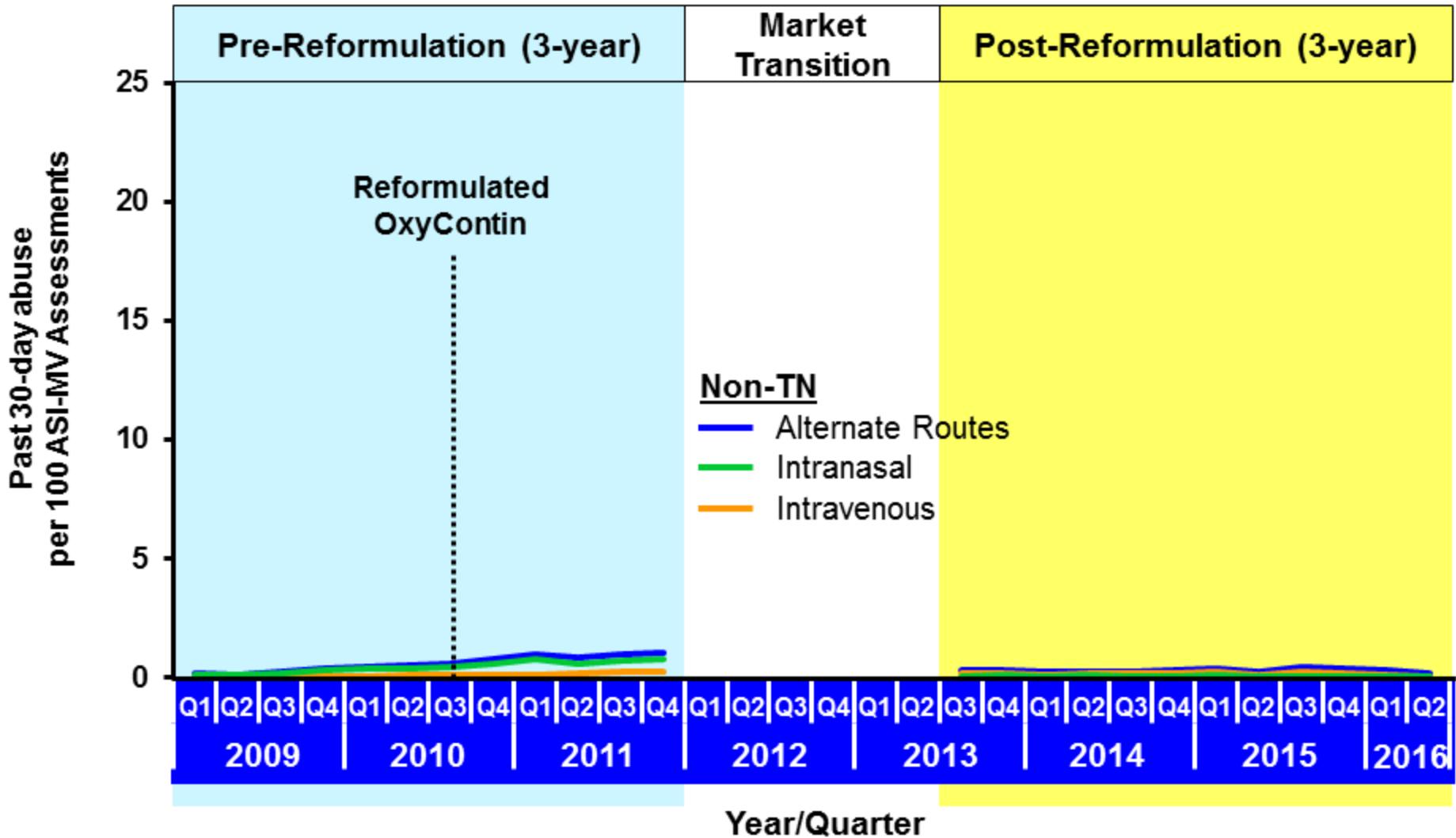
NAVIPPRESS®: OPANA ER Rate of Abuse by Route of Administration (Non-Tennessee)



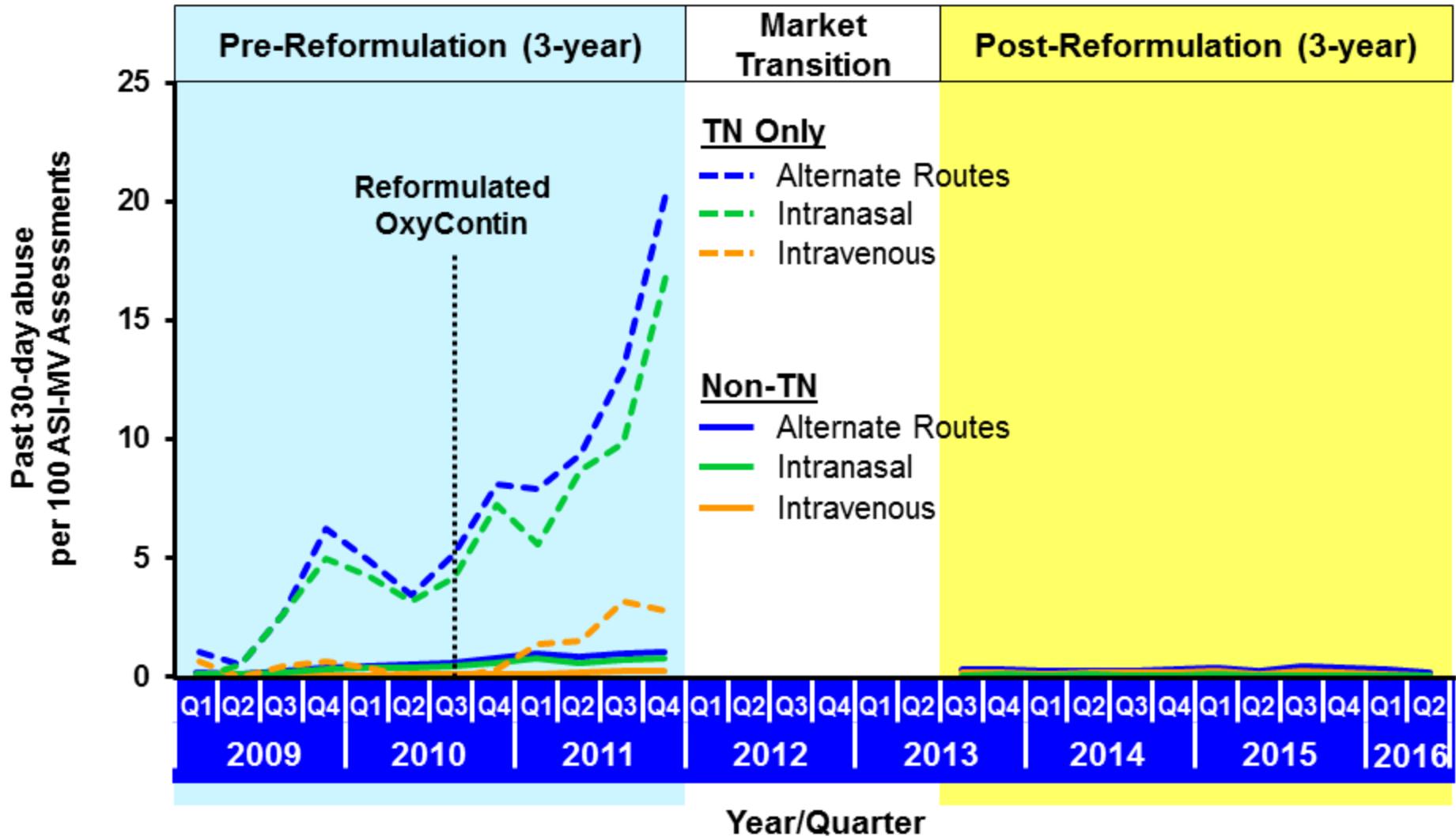
NAVIPPRESS®: OPANA ER Rate of Abuse by Route of Administration (Non-Tennessee)



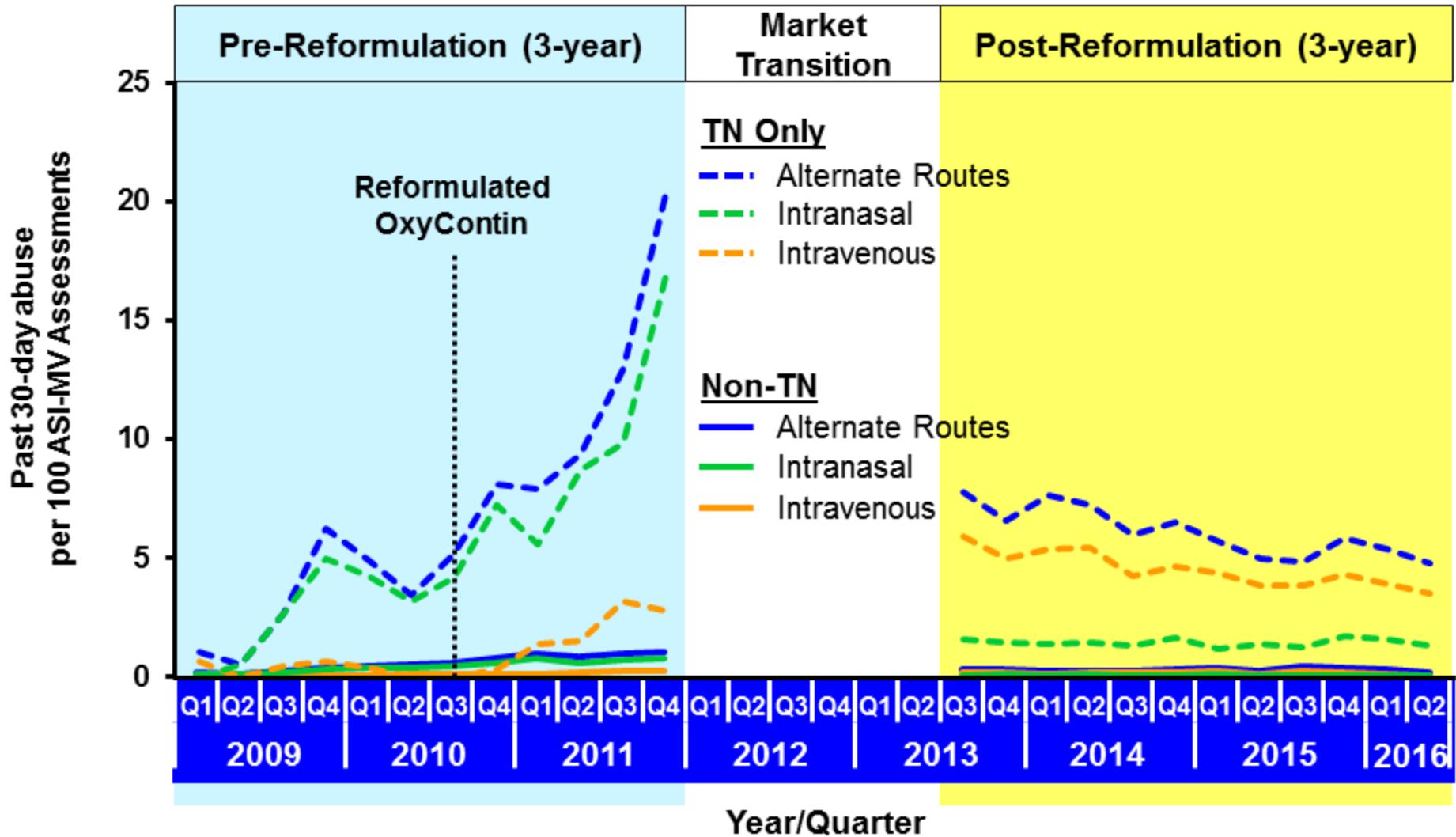
NAVIPPRO®: OPANA ER Rate of Abuse by Route of Administration (Non-Tennessee)



NAVIPPRO®: OPANA ER Rate of Abuse by Route of Administration (TN & Non-TN)



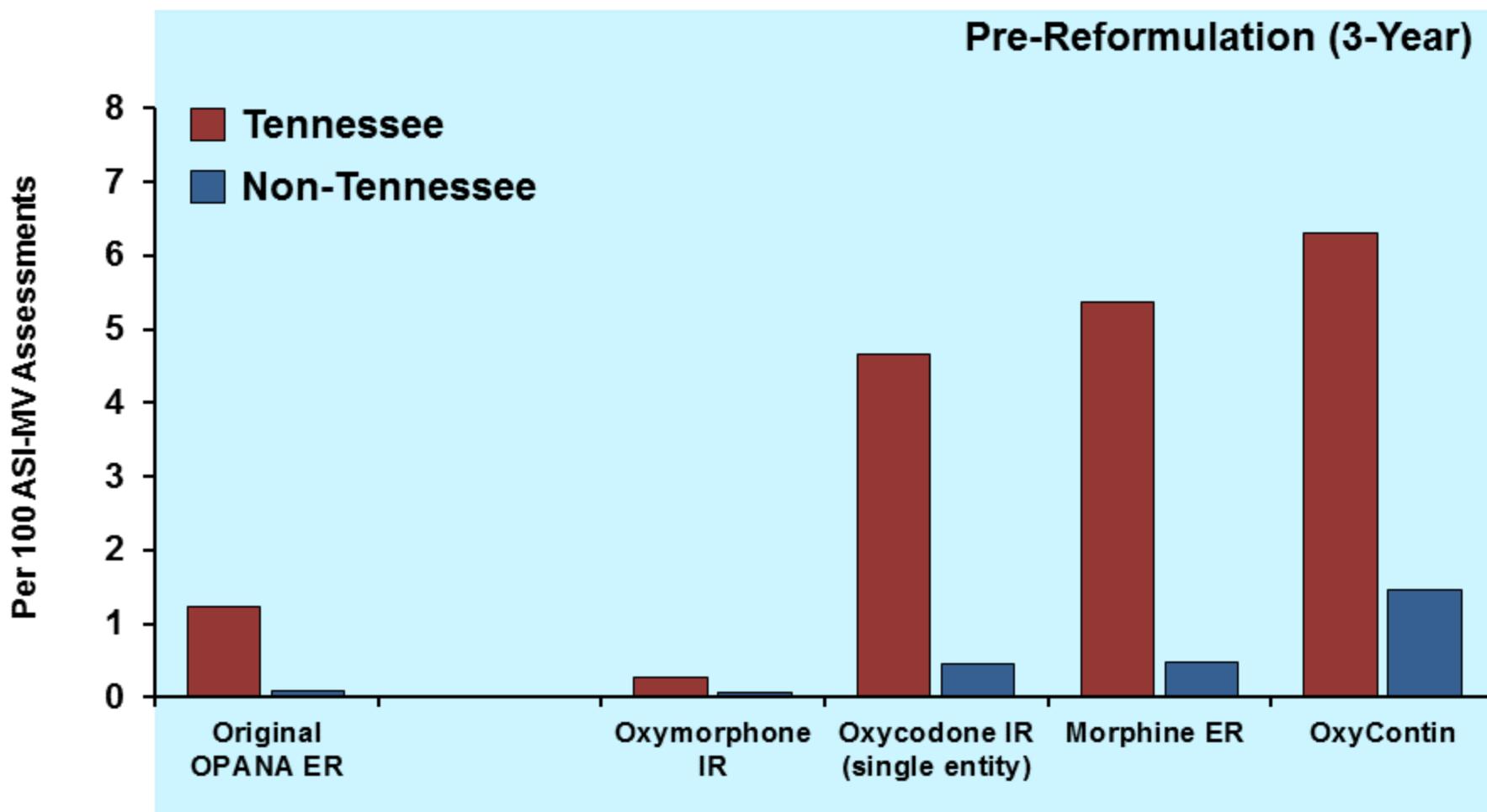
NAVIPPROM[®]: OPANA ER Rate of Abuse by Route of Administration (TN & Non-TN)



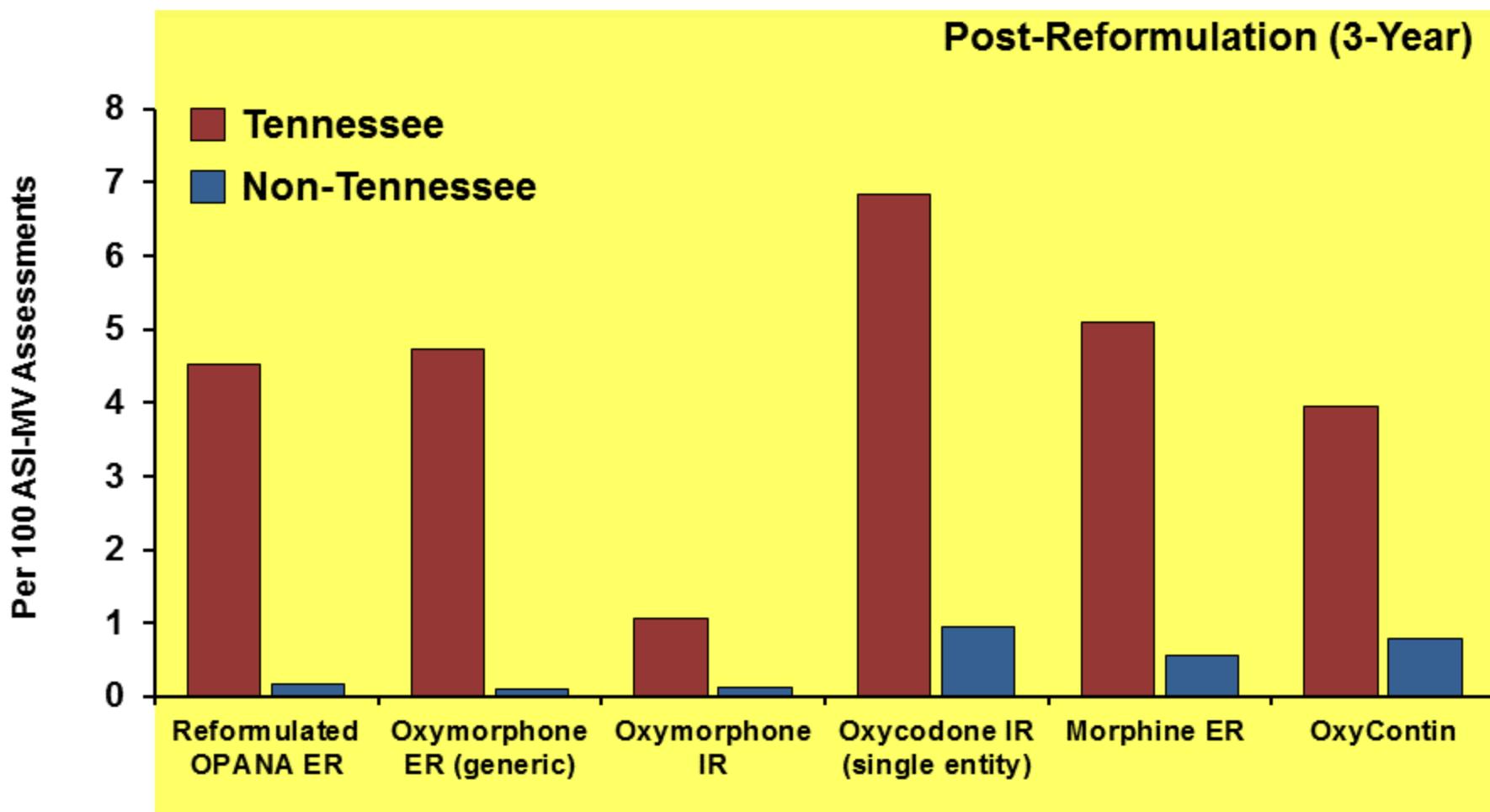
Tennessee Abuse Pattern is Distinctly Different From Non-Tennessee

- Noted in initial NAVIPPRO® ASI-MV publication from 2008¹
- Tennessee intravenous abuse rate is not specific for OPANA ER

Rate of Intravenous Abuse High in TN Prior to Reformulation of OPANA ER



Rate of Intravenous Abuse in TN Remained High Following OPANA ER Reformulation



TN Addiction Population Different from Other States

Grouping	Tennessee Only		Non-Tennessee	
	Pre Reformulated OPANA ER (n = 400)	Post Reformulated OPANA ER (n = 1250)	Pre Reformulated OPANA ER (n = 1170)	Post Reformulated OPANA ER (n = 425)
Drug Treatment Setting				
Residential / Inpatient	67%	89%	29%	41%
Outpatient / Non-Methadone	18%	8%	44%	20%
Methadone / LAAM	1%	0%	7%	6%
Corrections	2%	< 1%	14%	20%
Other	13%	4%	5%	13%
Missing	0%	0%	0%	0%
History of Prescription Opioids Injection				
Number Injected (≥ 1 Rx Opioid)	48%	81%	46%	72%

Summary of NAVIPPRO® Data

- Abuse of OPANA ER increased during the pre-period
- In the post-period compared to the pre-period:
 - Tennessee: Intravenous abuse was higher although levels of alternate routes and intranasal abuse were lower
 - Intravenous abuse was high for a number of opioids
 - Outside of TN: alternate route and intranasal abuse was lower and intravenous abuse was similar

RADARS® Post-marketing Studies

RADARS® Poison Center

RADARS® Drug Diversion

RADARS® Poison Center

- Data from US poison centers covering 48 states
 - > 90% of US population
 - Nationally representative of PC calls
- Callers seeking advice / help about potentially toxic exposures, including opioids
- Detect product-specific prescription drug abuse and misuse including outcomes
- > 2.3 million exposure calls per year
- Incidence-based analyses
 - Per 100,000 population
 - Per 100,000 tablets

RADARS® Poison Center: Primary Objectives

Determine if rates of OPANA ER mentions:

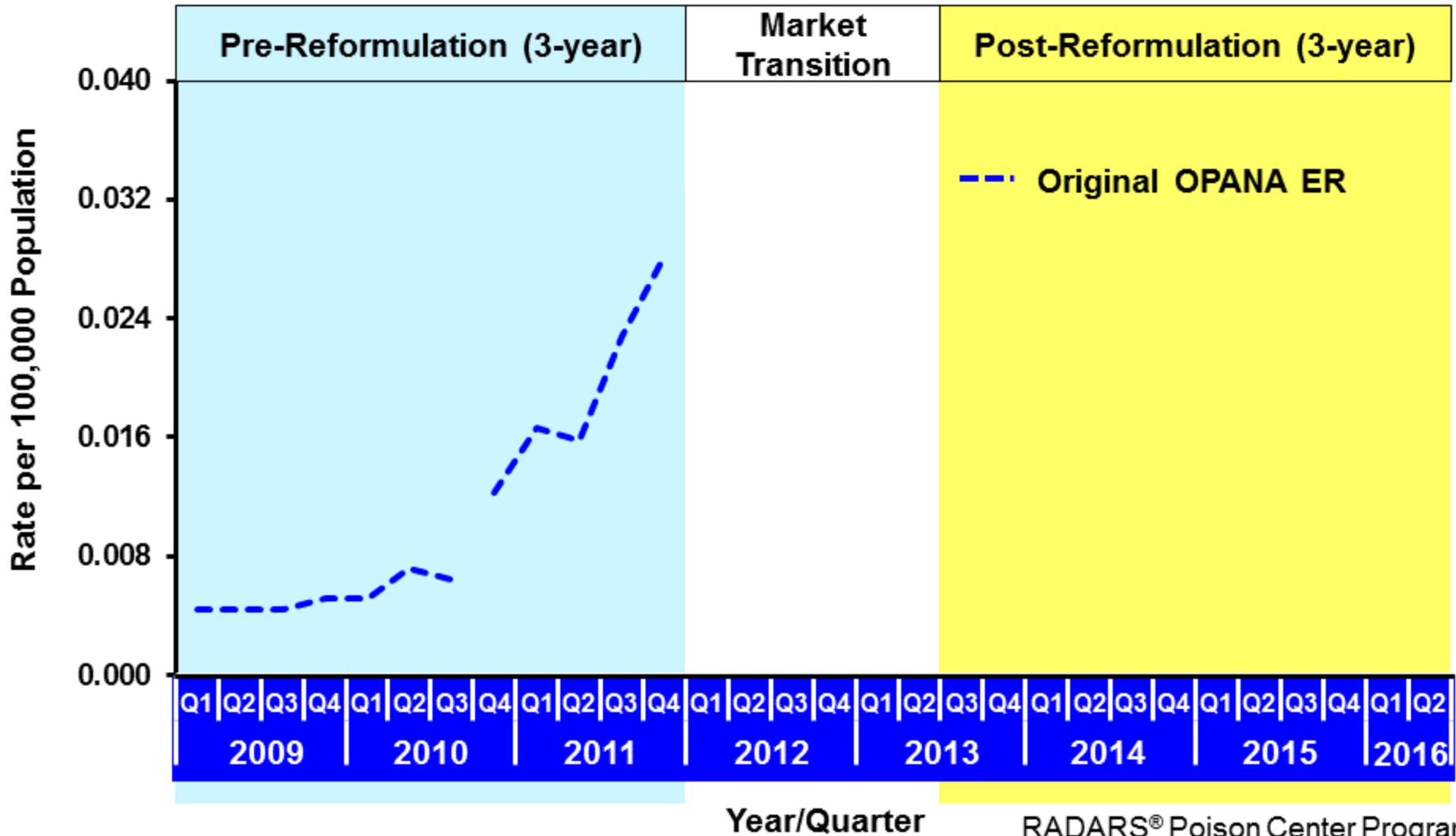
- by intentional abuse
- resulting in major outcome or death
- through non-oral routes of administration
- resulting in overdose

were lower following the introduction of
Reformulated OPANA ER compared to the pre-
period

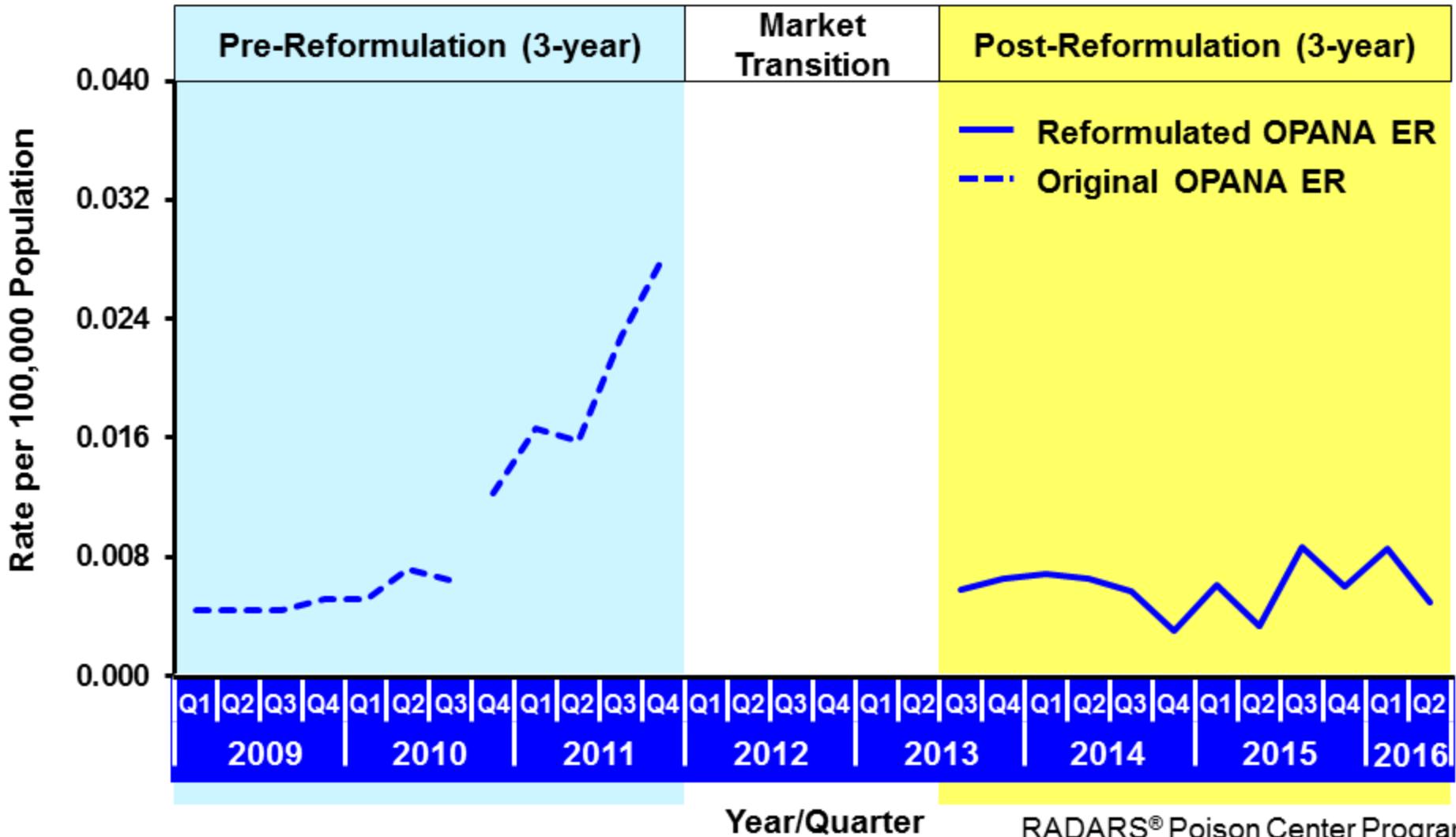
RADARS® Poison Center: Limitations

- Spontaneous reports subject to bias
- Rates underestimated due to limited reporting
- Difficult to accurately identify toxic exposure
 - If can't accurately ID product, listed as "not otherwise specified" (NOS)

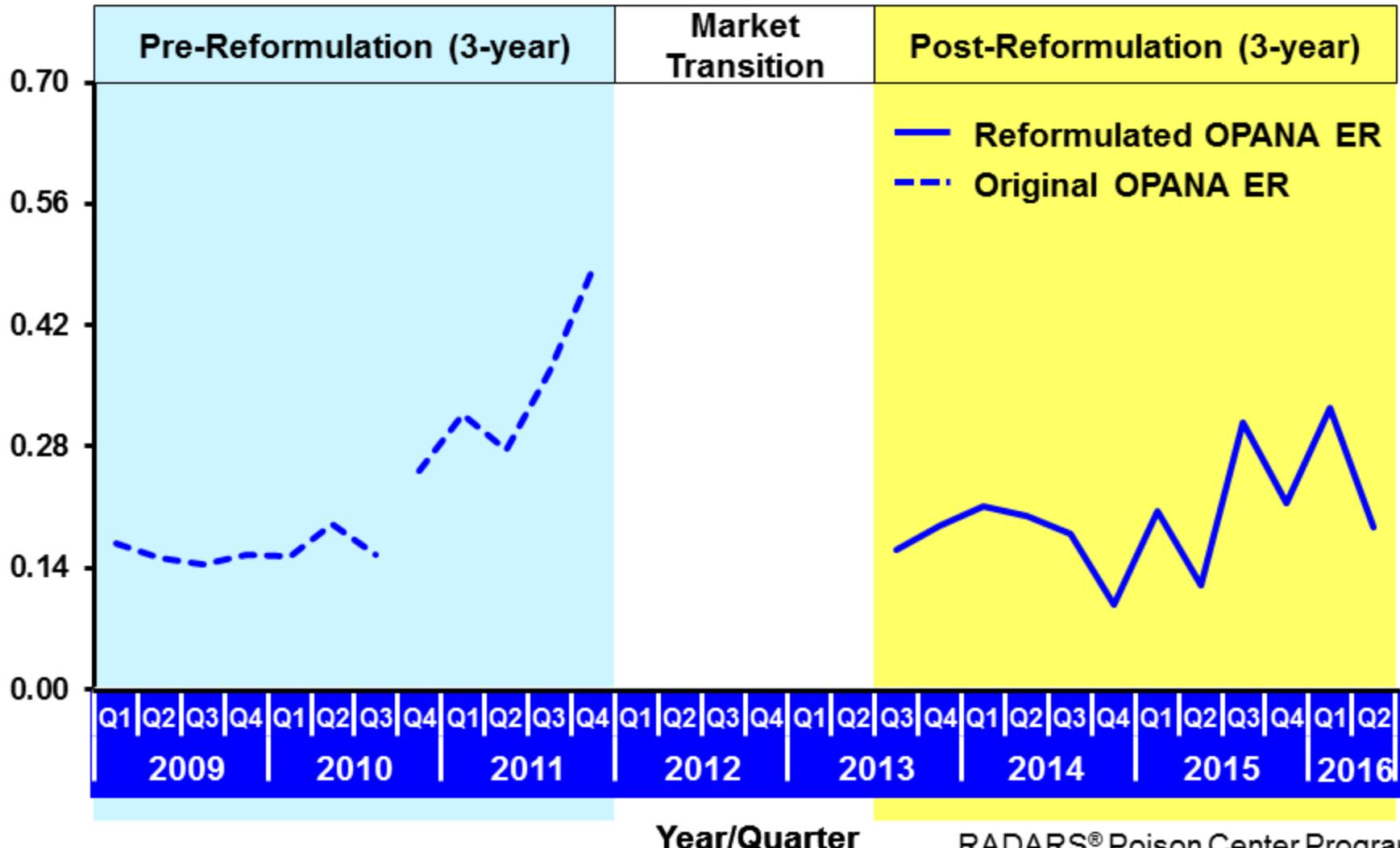
RADARS® Poison Center: Increase of Intentional Abuse During Pre-Period



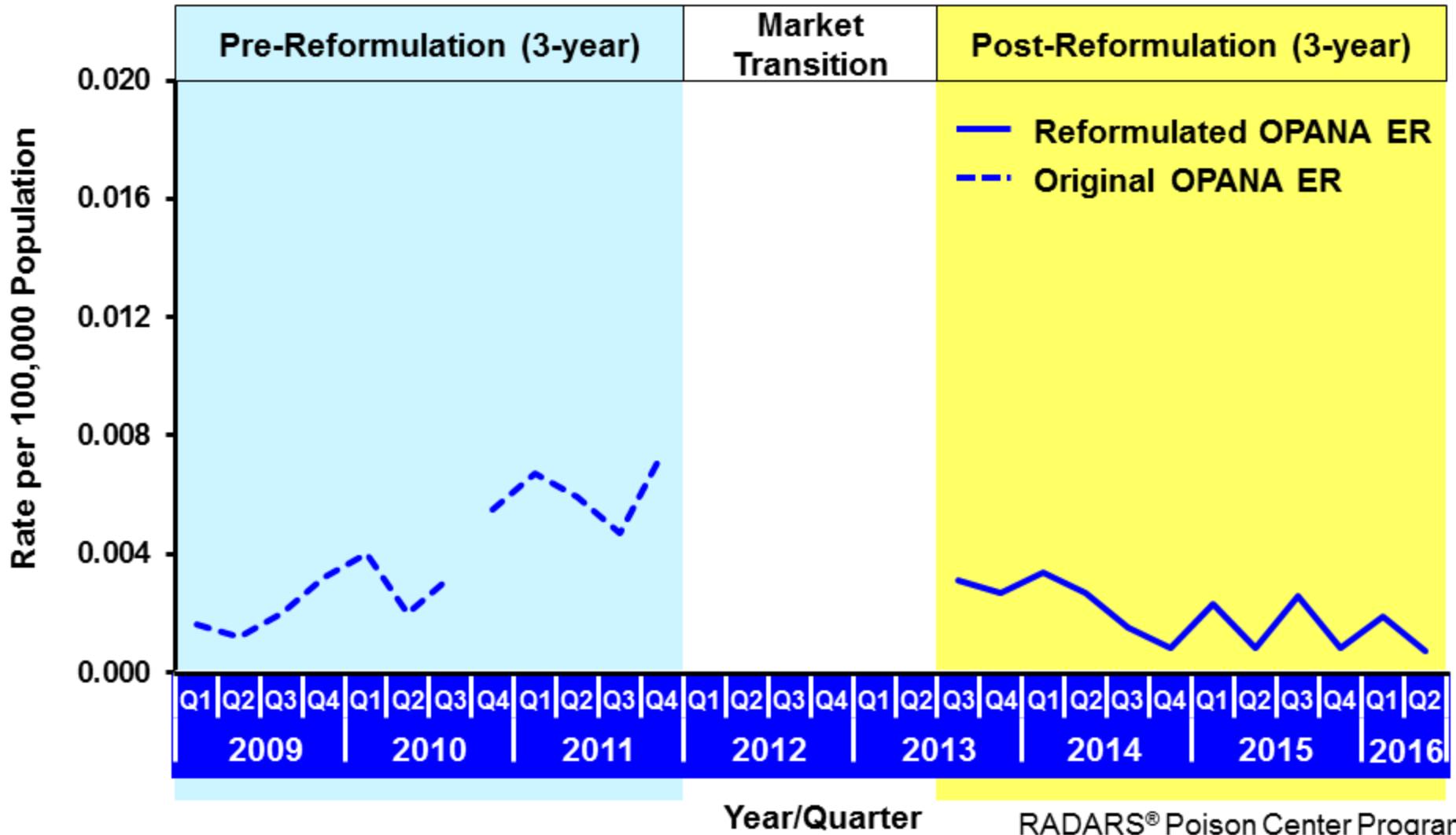
RADARS® Poison Center: Rate of Intentional Abuse Mentions During Pre- and Post-Period



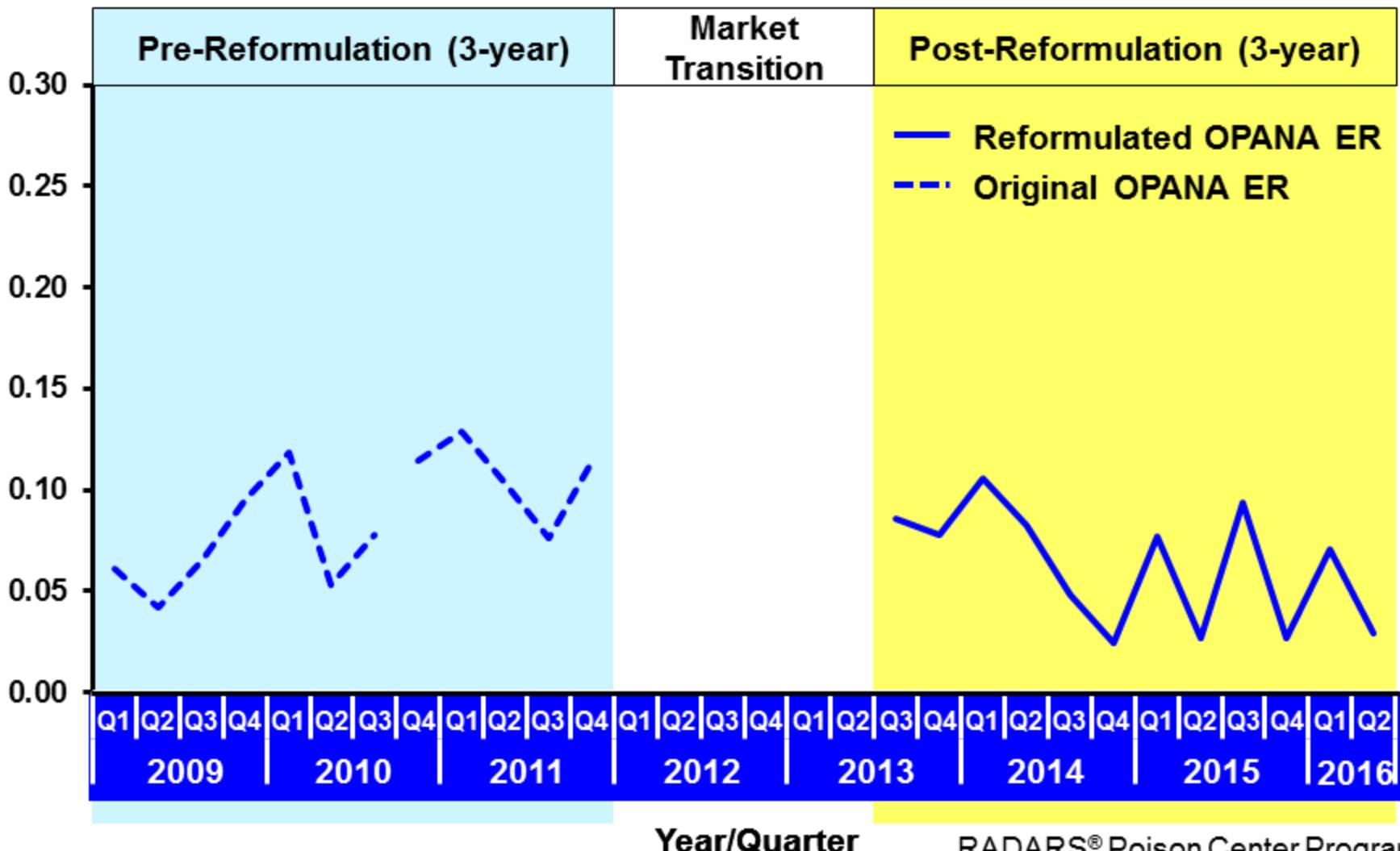
RADARS® Poison Center: Rate of Intentional Abuse Mentions During Pre- and Post-Period (100,000 Dosage Units)



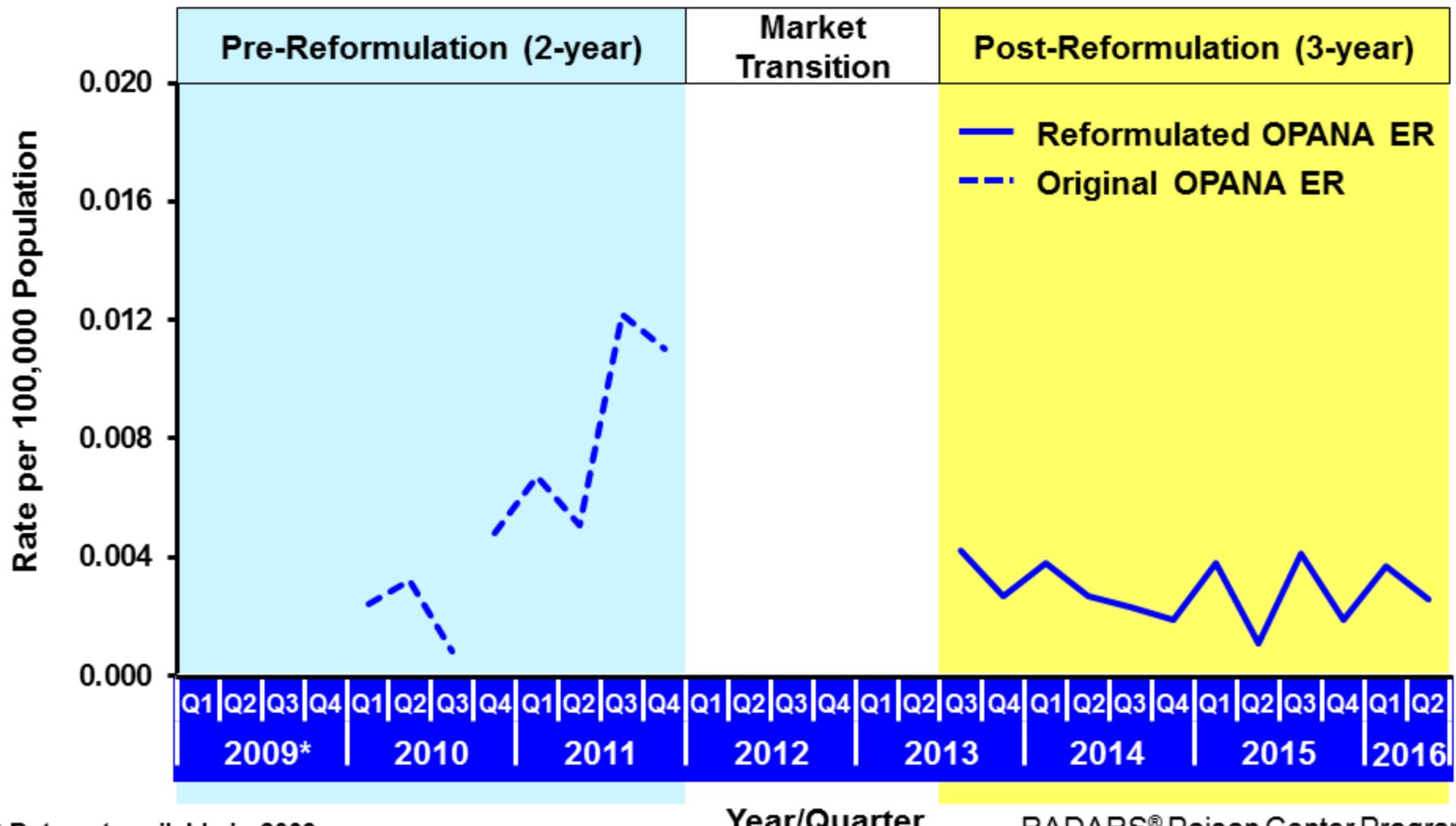
RADARS® Poison Center: Rate of Death & Major Outcomes During Pre- and Post-Periods



RADARS® Poison Center: Rate of Death & Major Outcomes during Pre- and Post-Periods (100,000 Dosage Units)



RADARS® Poison Center: Rate of Intentional Non-Oral Abuse During Pre- and Post-Periods

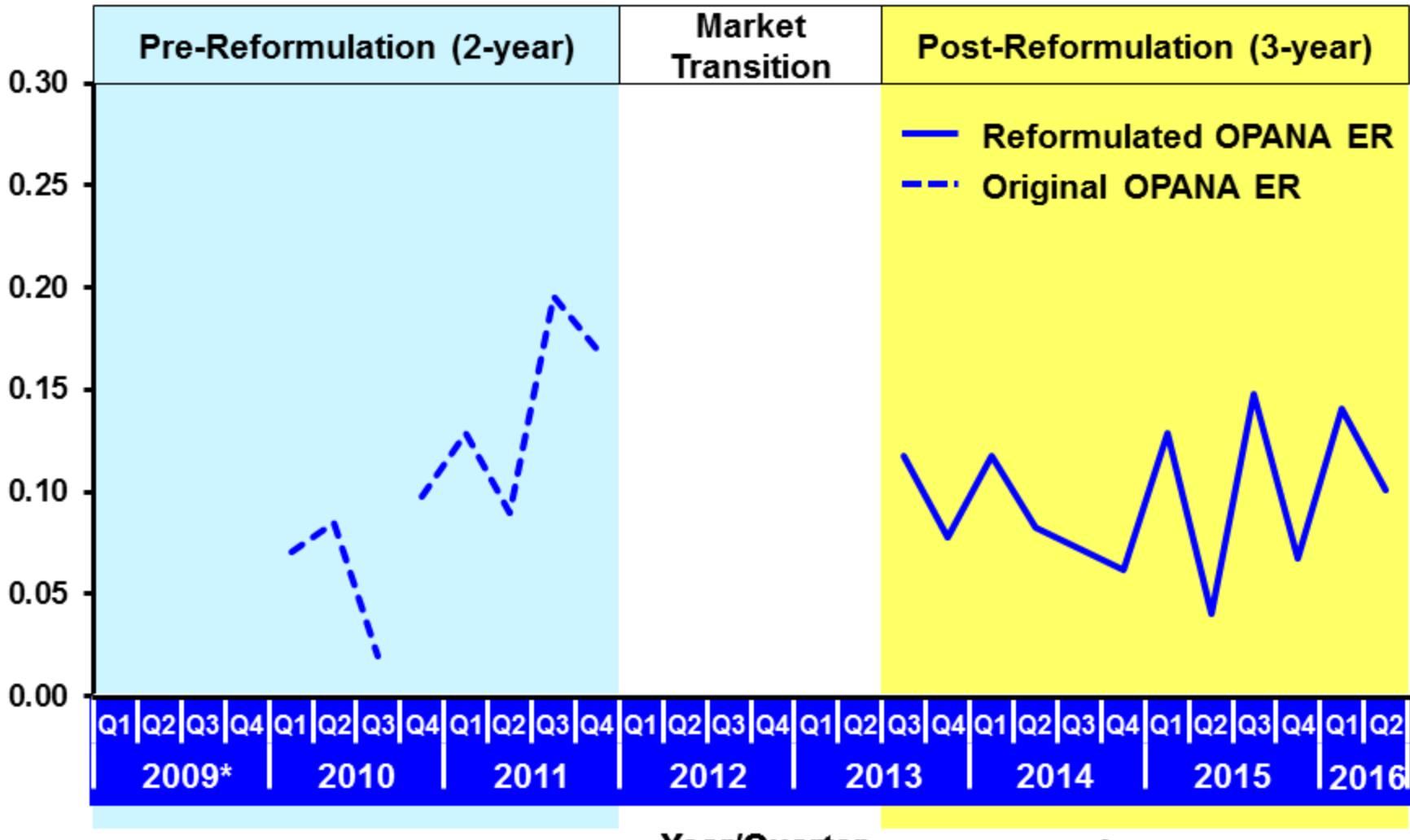


* Data not available in 2009

Year/Quarter

RADARS® Poison Center Program

RADARS® Poison Center: Rate of Intentional Non-Oral Abuse During Pre- and Post-Periods (100,000 Dosage Unit)

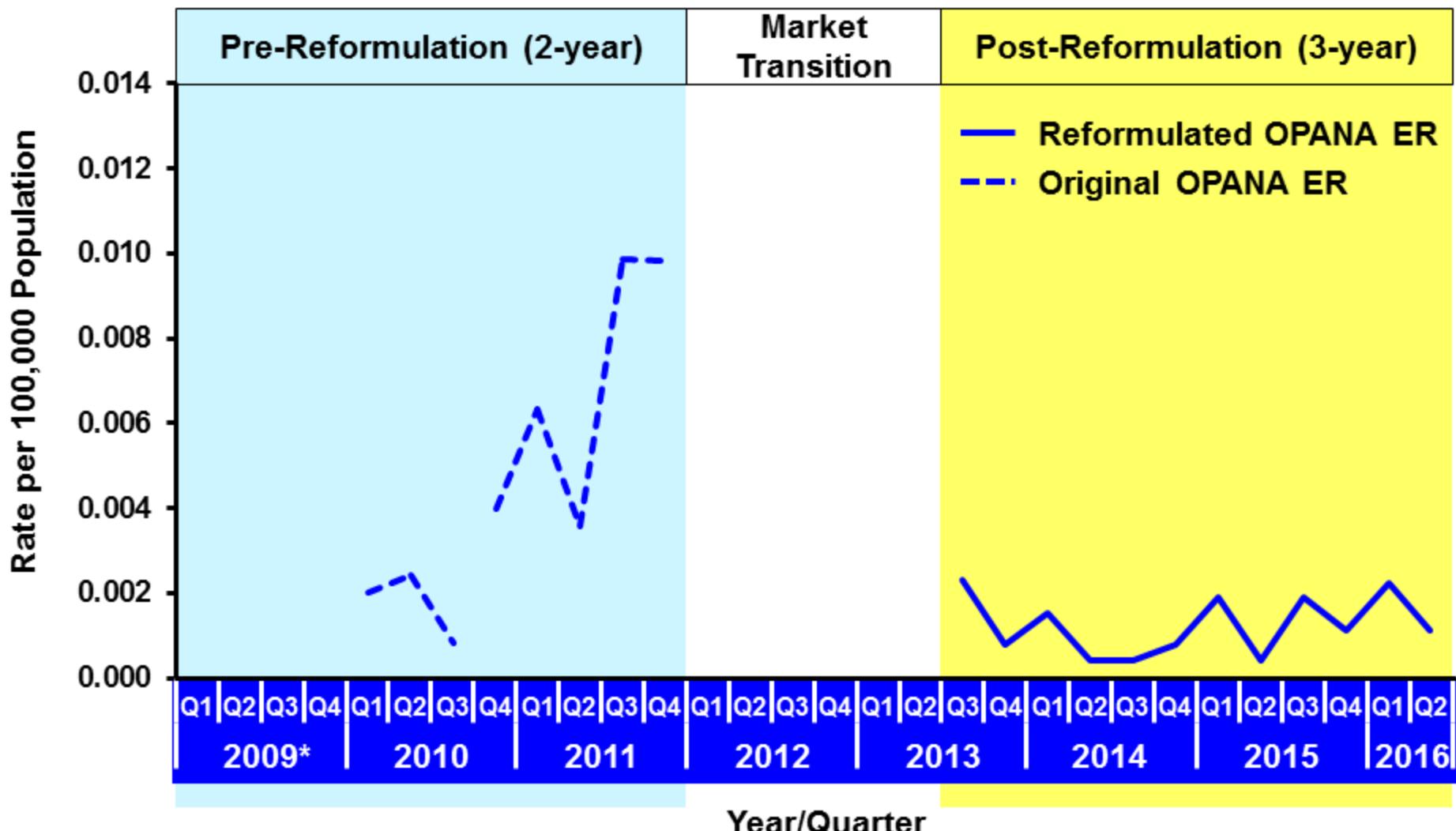


* Data not available in 2009

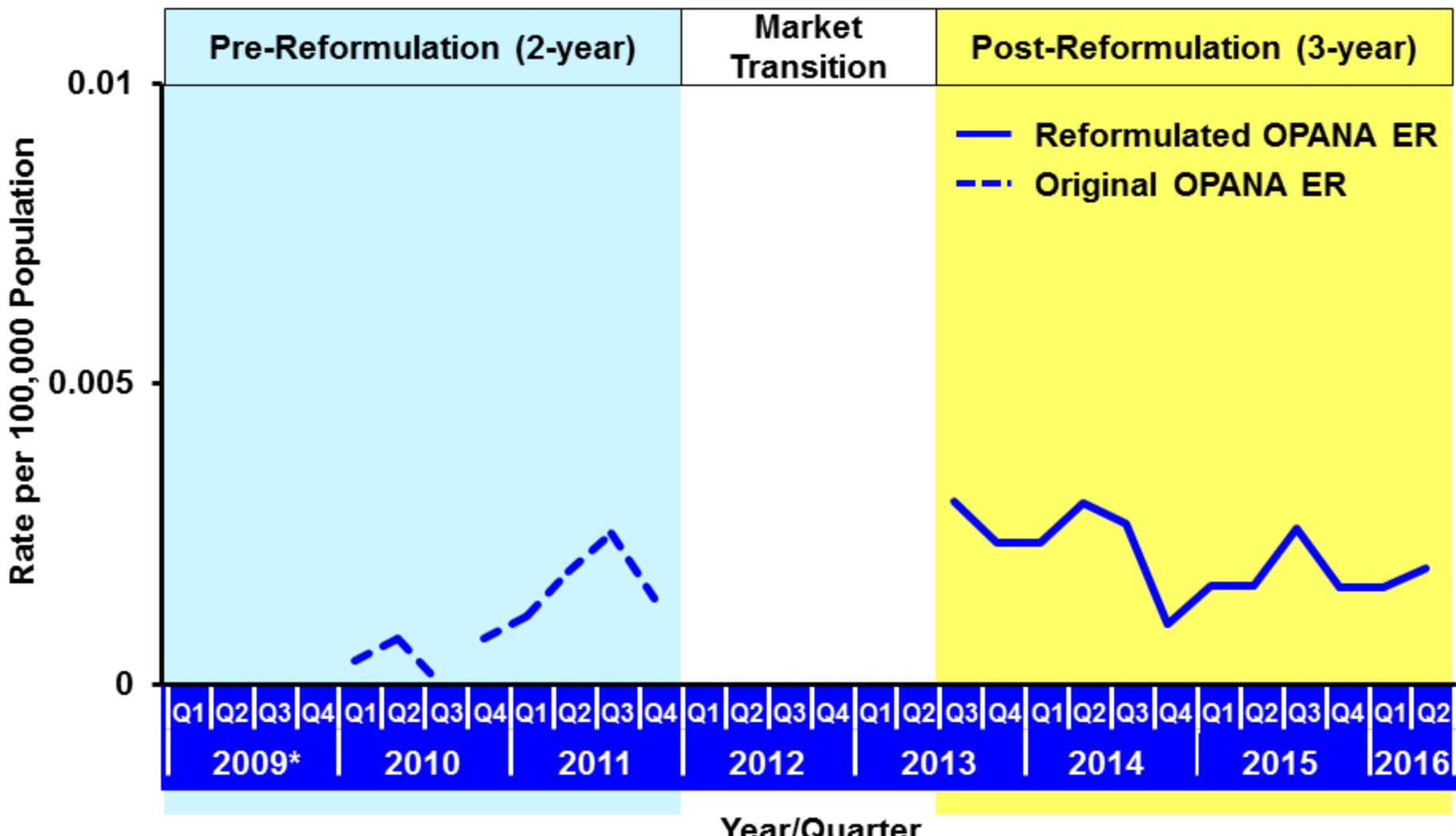
Year/Quarter

RADARS® Poison Center Program

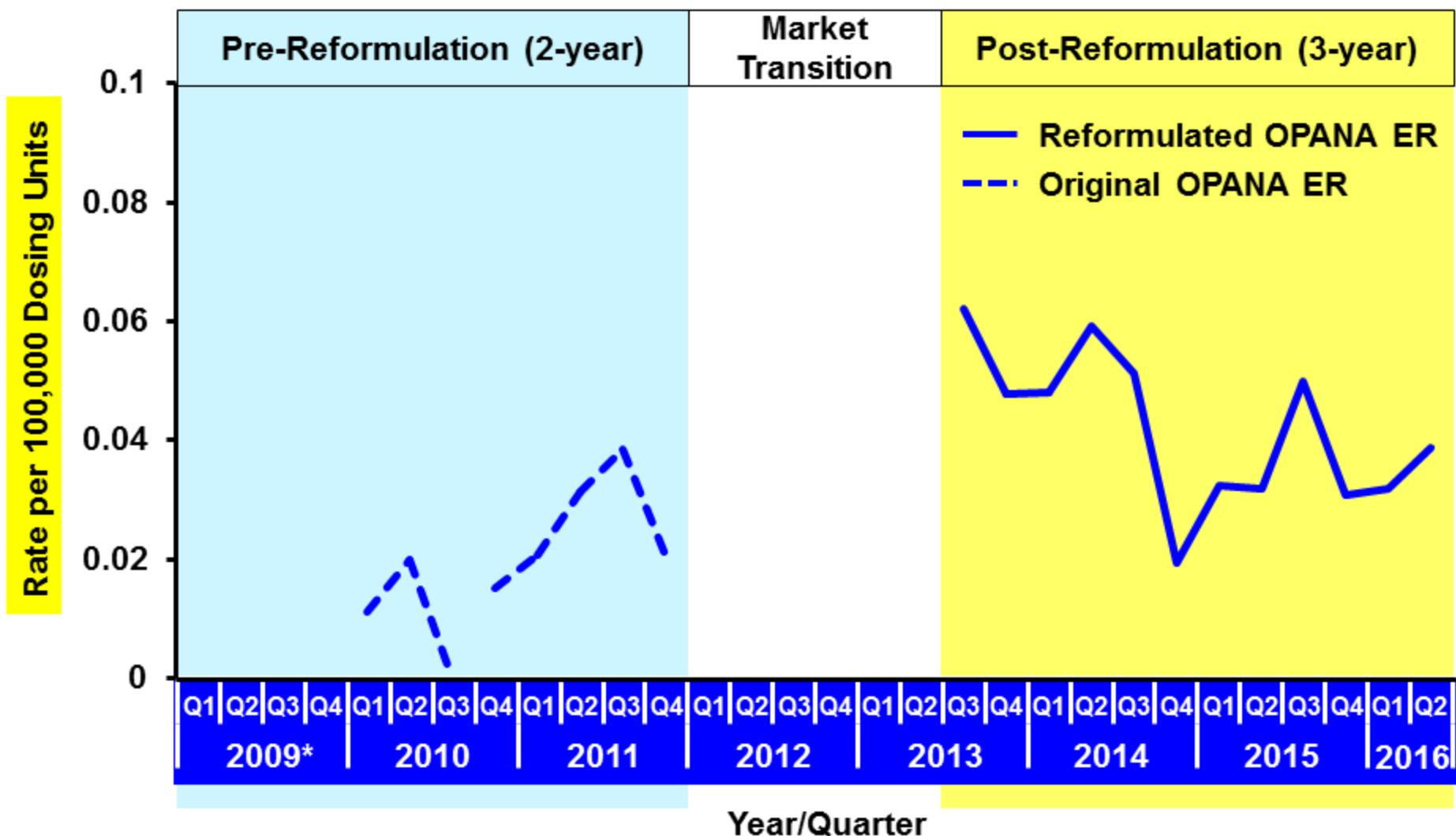
RADARS® Poison Center: Rate of Intentional Intranasal Abuse, Pre- and Post-Periods



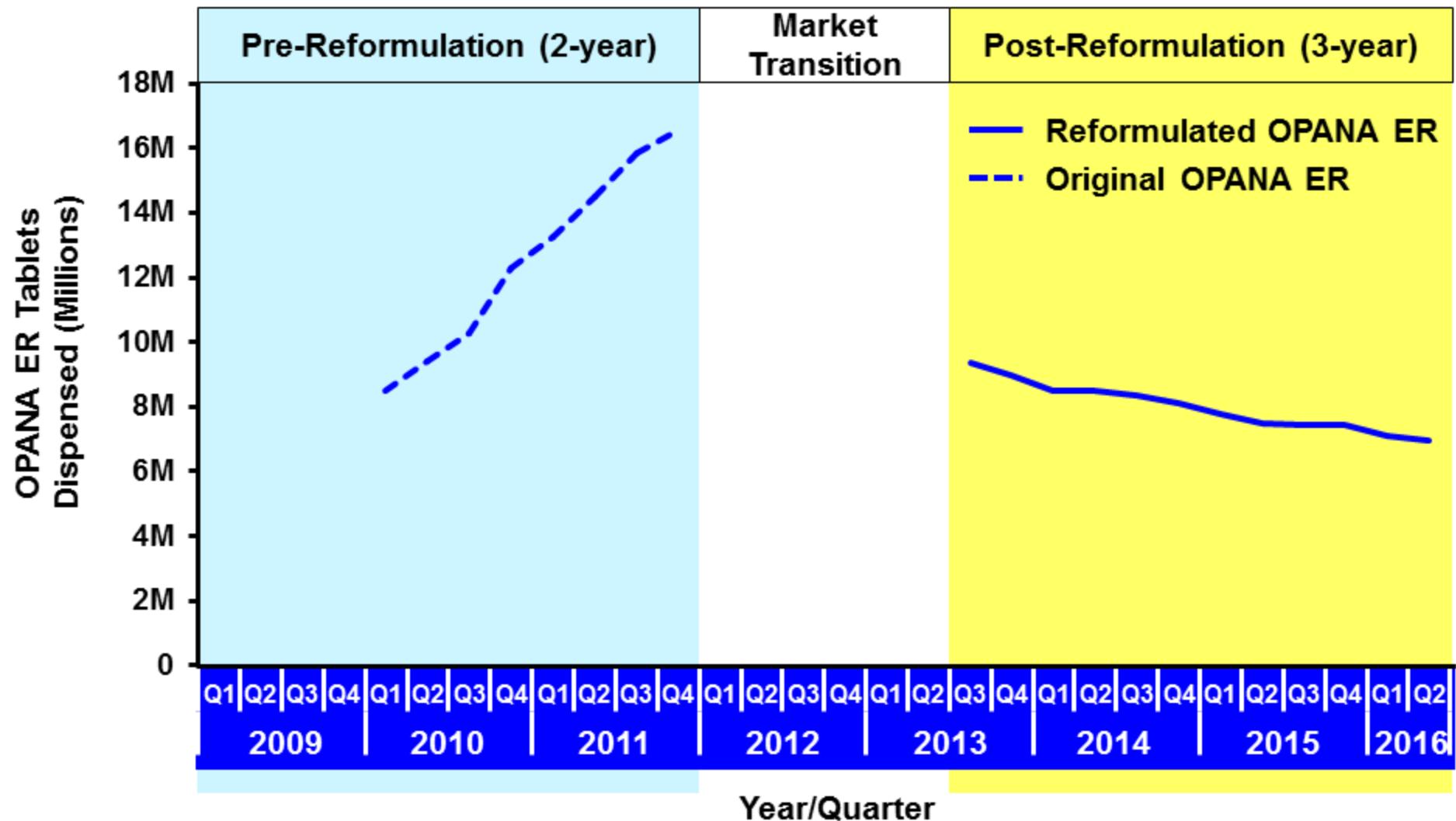
RADARS® Poison Center: IV Abuse Rates for OPANA ER are Not Increasing



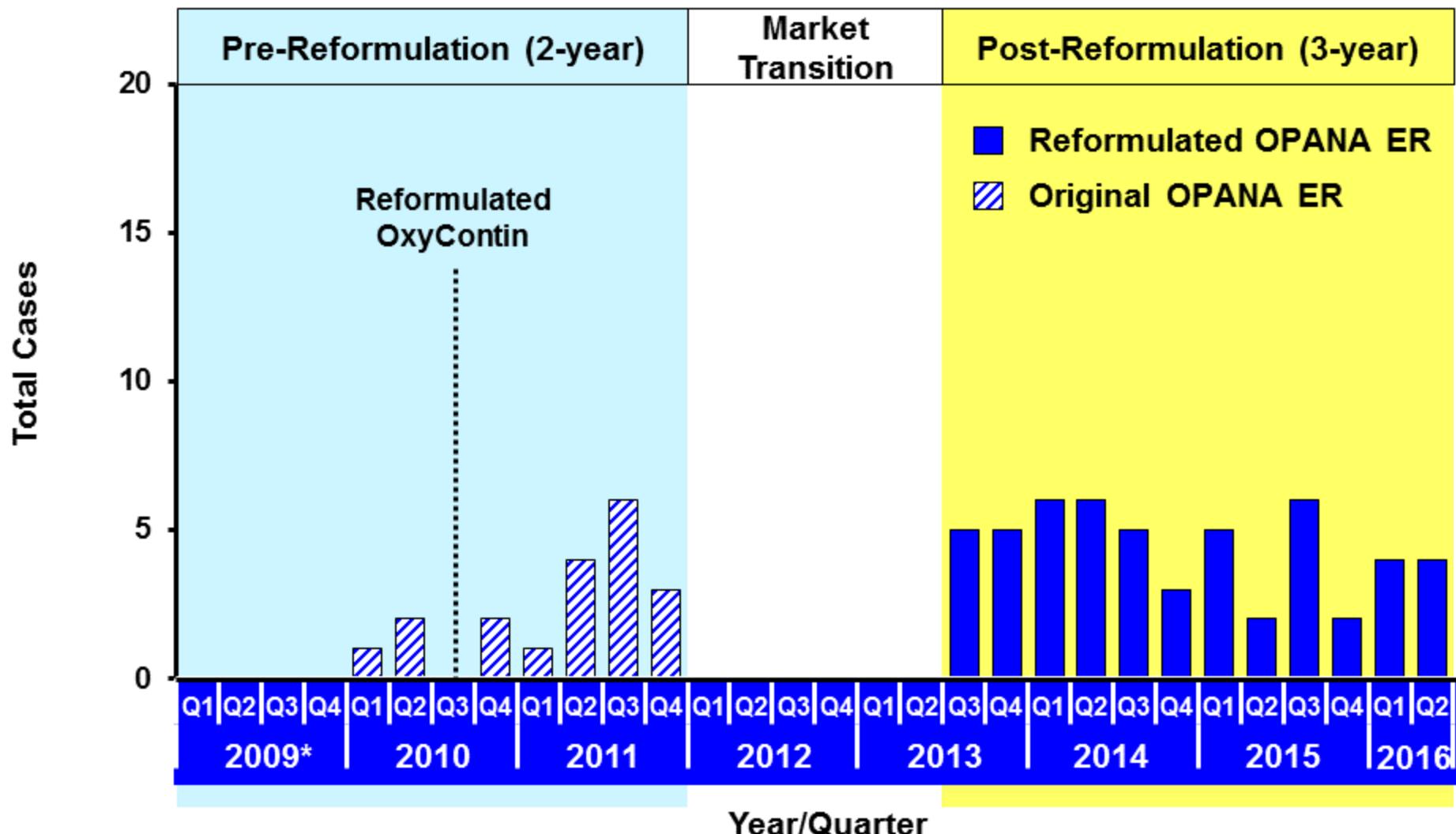
RADARS® Poison Center: IV Abuse Rates for OPANA ER are Not Increasing (100,000 Dosage Unit)



Number of Dispensed OPANA ER Tablets – Rise and Fall



RADARS® Poison Center: Number of IV Injection Cases Not Increasing



RADARS® Poison Center: Summary of Data

- OPANA ER abuse increased throughout the pre-period, particularly after the introduction of reformulated OxyContin
- Rates of intentional abuse, death and major medical outcomes, non-oral abuse, and overdose were lower for OPANA ER during the post-period compared to the pre-period

RADARS® Post-marketing Studies

RADARS® Poison Center

RADARS® Drug Diversion

RADARS® Drug Diversion

- Supportive epidemiological study
- Examines differences in diversion rates before and after Reformulated OPANA ER introduction
- Prevalence-based analysis:
 - Per 100,000 population

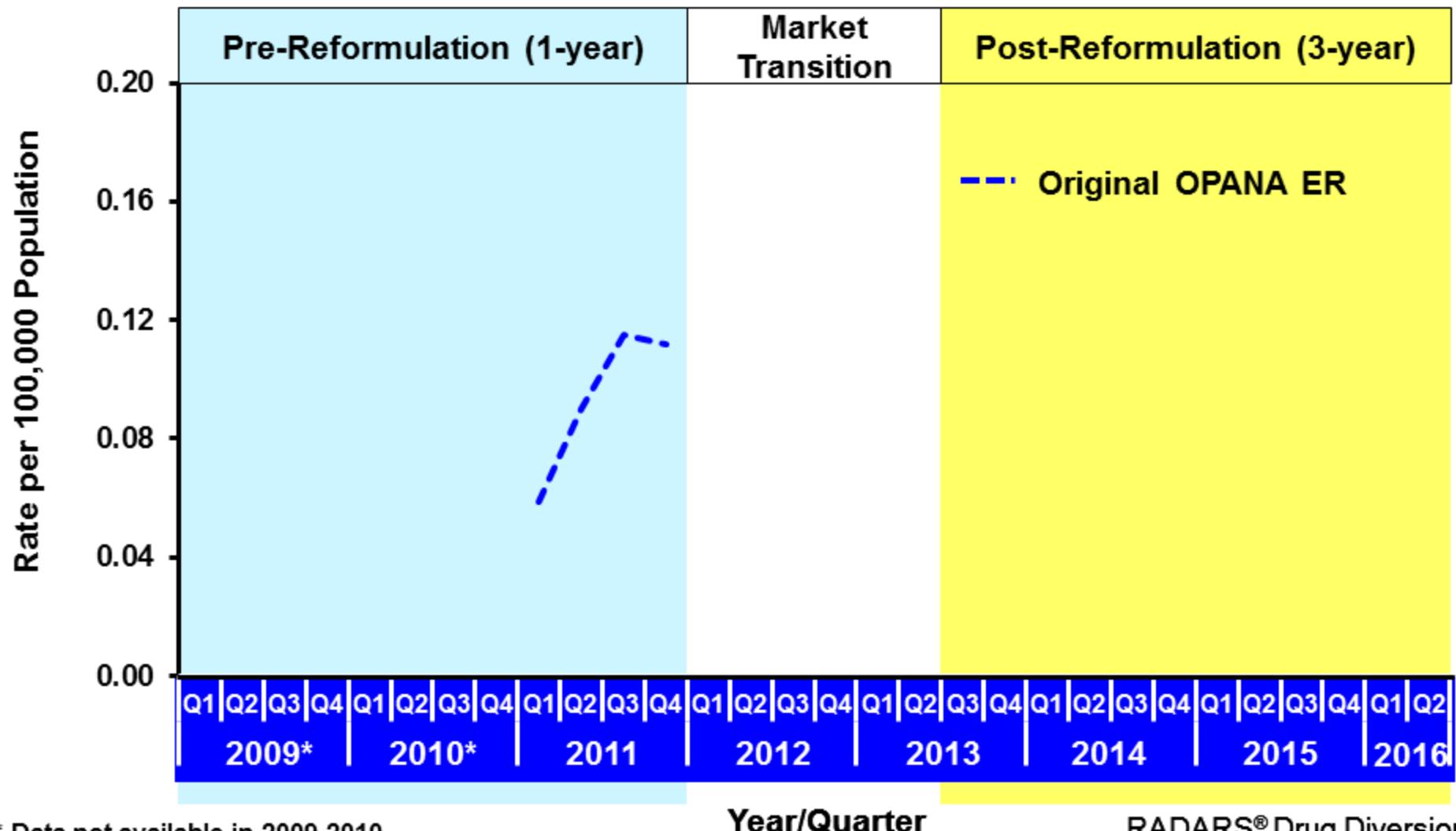
RADARS® Drug Diversion

- Collects reports of prescription drugs found outside of controlled distribution channels
 - Reported by law enforcement
 - Samples from 110 participating agencies in 45 states within US
- Number of cases may reflect drug desirability
- Diversion decline support abuse deterrence
- Inclusion of oxymorphone data started in 2011

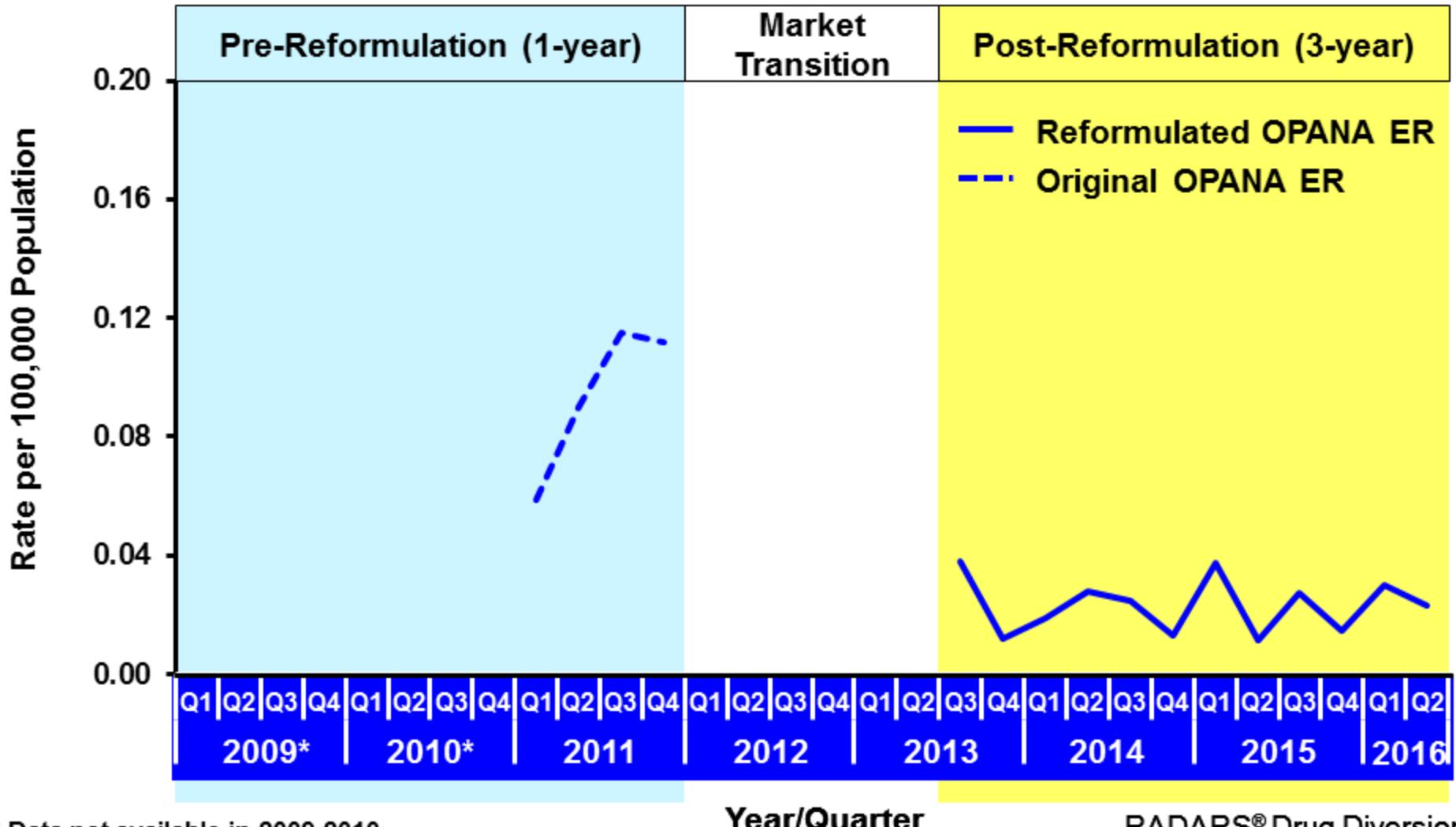
RADARS® Drug Diversion: Limitations

- Drug diversion investigators not randomly drawn from pool of all possible officers
- Investigations may vary between calendar quarters
- Data do not distinguish route of abuse

RADARS® Drug Diversion: Increased with OPANA ER During Baseline Period



RADARS® Drug Diversion: Decline Following Introduction of Reformulated OPANA ER



RADARS® Drug Diversion: Supports Less Desirability With Reformulated OPANA ER

- Increased investigations with original OPANA ER in 2011
- Decreased investigations following introduction of Reformulated OPANA ER
- Decrease suggests less desirability of Reformulated OPANA ER

Conclusions From Post-Marketing Epidemiology Studies & Safety

NAVIPPRO®

RADARS® Poison Center

RADARS® Drug Diversion

Concordant Epidemiologic Findings

- Increased abuse of original OPANA ER from 2009 to 2011, primarily as intranasal abuse
- Coincident with the introduction of Reformulated OPANA ER
 - Intranasal abuse was lower
 - IV abuse increased in TN, but not in other states
 - Law enforcement reports of diversion were lower
- Consistency across multiple epidemiology methods
 - NAVIPPRO®
 - RADARS® Poison Center
 - RADARS® Drug Diversion
- Reformulated OPANA ER has not increased IV abuse rates observed with original formulation in 2011

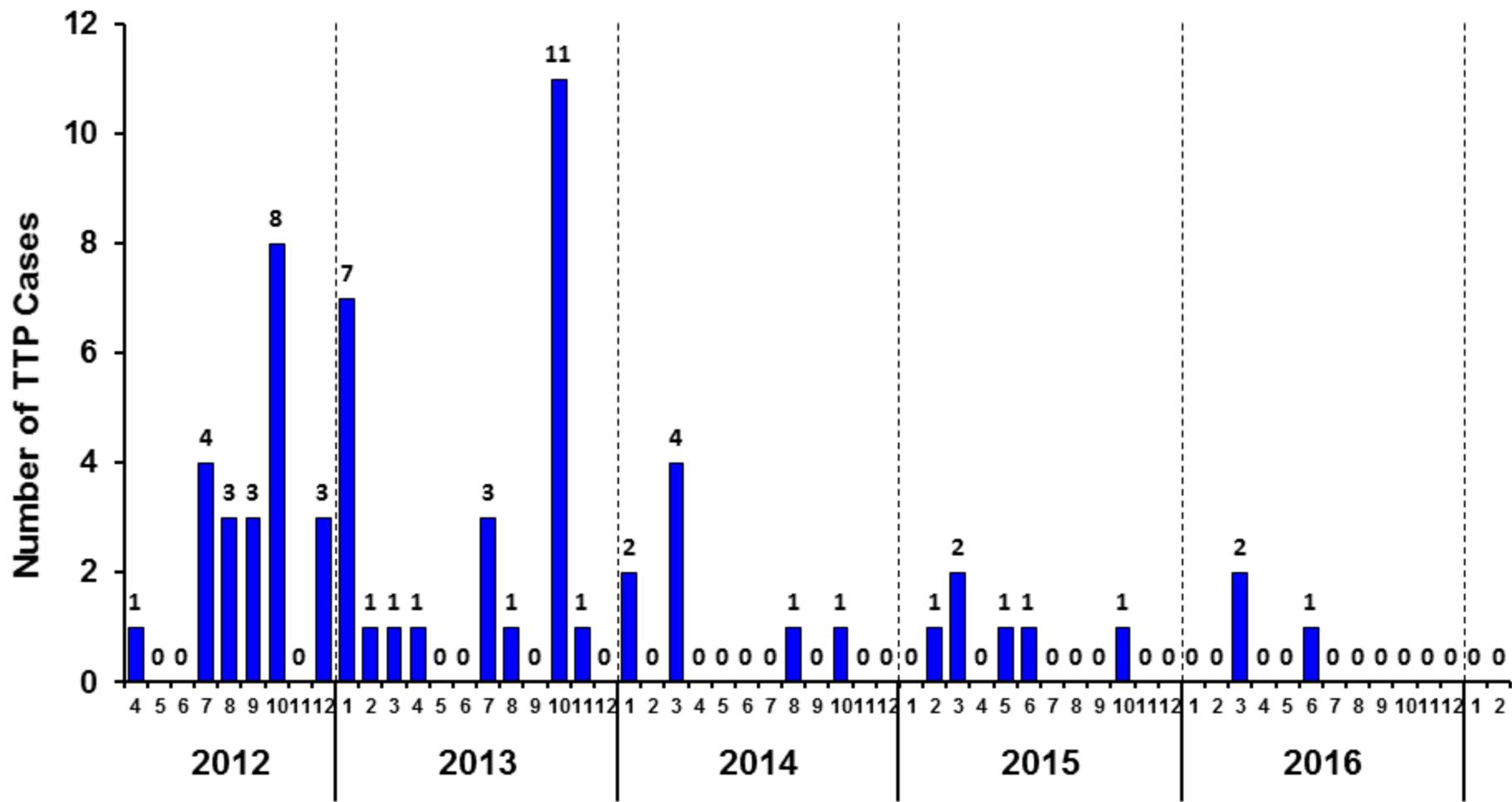
Post-Marketing Pharmacovigilance

- Thrombotic Thrombocytopenic Purpura (TTP) in Tennessee
- HIV in Indiana

Reports of Thrombotic Thrombocytopenic Purpura (TTP) and Response

- Aug 2012: 5 cases of TTP reported from Tennessee
 - Associated with IV injection of OPANA ER tablets
- Endo response
 - Promptly informed FDA and met with federal and state officials
 - Discussions with sales representatives
 - Contacted local anti-drug organization
 - Worked with law enforcement
 - Maintained contact with local HCPs treating patients

Cases of TTP



TTP Associated with IV Administration of Polyethylene Oxide (PEO)

- PEO - listed in FDA's database of inactive ingredients for oral administration
- Potential link to inactive ingredient
 - Animal investigations – IV administration of PEO can recapitulate some TTP features
- Reported with IV administration of OxyContin (ADF) tablets
- Should be considered IV administration risk of any oral pharmaceutical containing PEO

Needle Sharing Leads to HIV Outbreak in March 2015

- Health emergency declared - Scott County, IN
 - Outbreak of HIV due to needle sharing among a group of abusers of IV drugs
- Various health agencies (e.g., CDC, Indiana State DOH) intervened to stop spread of HIV
- Oxymorphone ER most prevalent abused drug
 - Both brand and generic were identified
- Heroin, methamphetamine, cocaine, and oxycodone were also being abused IV¹

Endo Committed to Understanding IV Abuse & Assisting Communities

- Conduct ethnographic study
- New 3-year program with targeted interventions:
 - Conduct parent coaching trainings
 - Pilot mobile texting parent support program
 - Toll Free Hotline for families / patients
 - Media awareness campaign
 - Increase in law enforcement outreach
 - Increase in local treatment center outreach
 - Increase outreach with local communities leaders
- Continued monitoring of NAVIPPRO® and RADARS®

Decision-Making with Incomplete Observational Data

Alexander Walker, MD, DrPH

Former Chair of Department of Epidemiology
Harvard T.C. Chan School of Public Health

Epidemiologist's Approach to NAVIPPRO and RADARS

- Public health decisions time sensitive, often made before all data are in
- Information – less complete, less accurate, less representative than study designed from scratch
 - Still tells a coherent story

We Can't Always Measure What We Want to Measure

- Quantification of drug abuse – based on ratios
- Available sources provide crude measures, i.e., National Survey on Drug Abuse and Health
 - Limited information on specific drugs available prior to 2015
- No real numerator at product-specific level
 - No estimates of diversion for specific entities
 - No census estimates of deaths associated with individual products

Substitutes are Used if Populations are Not Directly Observable

- Registry
- Monitoring programs
- Spontaneous reports
- Counts in a relevant subset, e.g. poison center calls or deaths

Proxy Denominators for Abuse Prevalence or Overdose Incidence

- Population (RADARS)
 - Poison center overdose events
- Persons entering rehab (NAVIPPRO)
 - Represent abuser community
- Number of tablets dispensed (RADARS and NAVIPPRO)
 - Product-specific denominator adjustments
- None leads to direct estimate of incidence or prevalence
 - Look for consistent pattern of results with multiple approximate measures

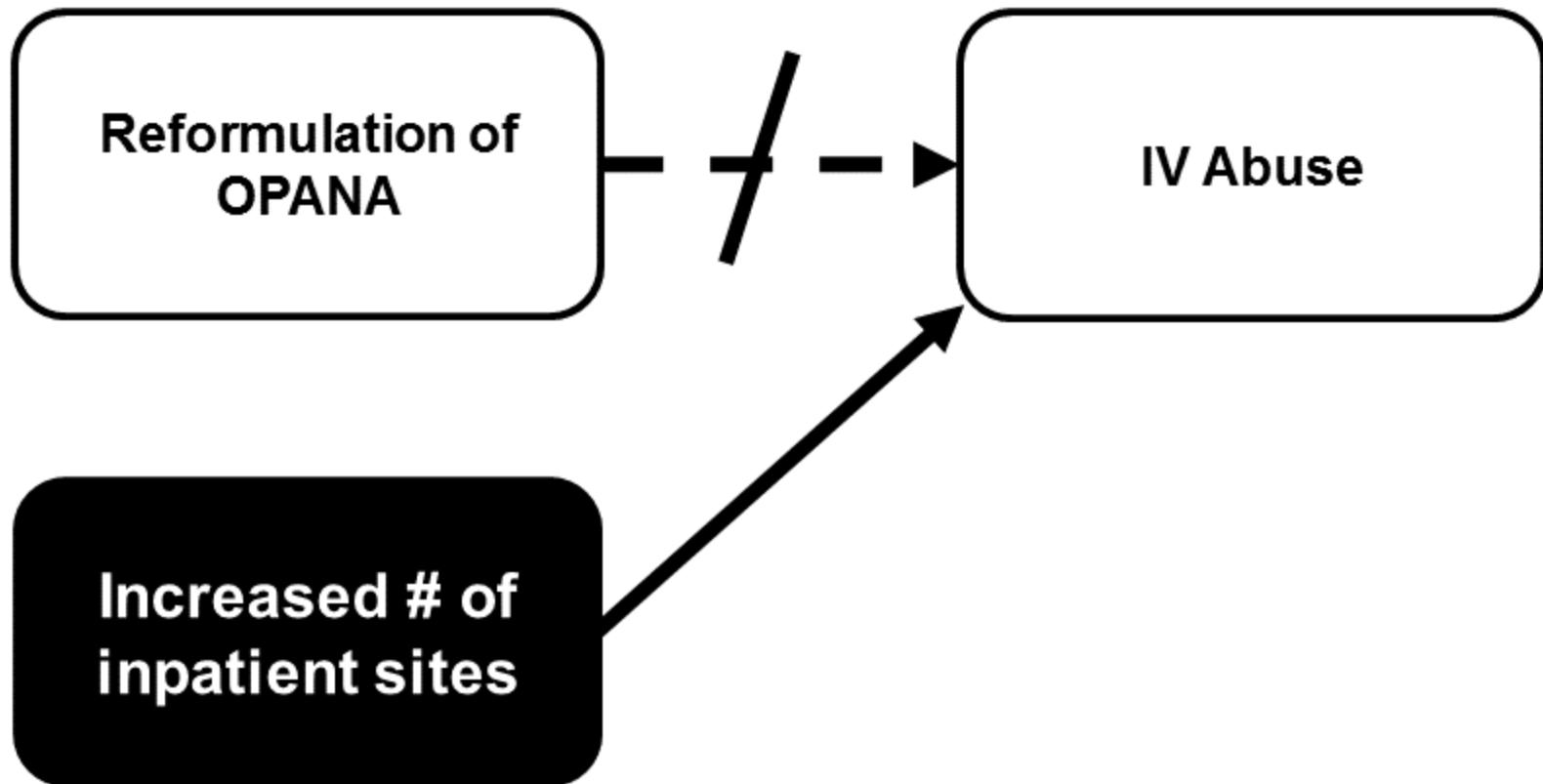
Regional Tablets Sold are not a Measure of Regional Tablets Diverted

"Prescription-adjusted abuse was estimated ... using quarterly total dosage units associated with the individual home 3-digit ZIP code areas ... in order to approximate 'local availability.'" ¹

Tablets sold fails as denominator on regional level

- Two-thirds of diverted drugs come from drug dealers¹
- Illegal movement will tend to
 - Inflate event-to-tablet ratios in areas of high demand
 - Diminish the same ratios in levels of low demand

Confounding = “Ecological Fallacy”



Fixed Sites Analysis May Not Generalize to Broader Population

- Holding population constant across pre- and post-periods partially addresses shift
 - Pre-specified fixed sites sensitivity analysis performed
 - Sites must have ≥ 1 ASI-MV each quarter
- Only 26% of the full data set
- Only 2 Tennessee sites
 - 85% of Reformulated OPANA ER reports
- Restricted data set may not generalize

Confronting the Challenges of Proxy Measures and the Ecological Fallacy

- Decisions must be made on incomplete data
- Interpretation requires that we consider processes that generated the data
- My own view on reformulation of OPANA ER
 - Has deterred intranasal abuse
 - Has had limited effect on IV abuse
- Tennessee is an important anomaly
 - Not likely to be resolved today
 - Not a basis for national decisions

Benefit-Risk Assessment of Opana ER

Richard Dart, MD, PhD

RADARS® System

Rocky Mountain Poison & Drug Center

Professor, University of Colorado

How Can We Measure Abuse Behavior?

- Abusers seek to hide their behavior
- Measured when abusers choose or forced to reveal themselves
 - Acute events and poison center cases
 - Law enforcement of drug transaction
 - Substance treatment
 - Voluntary disclosure

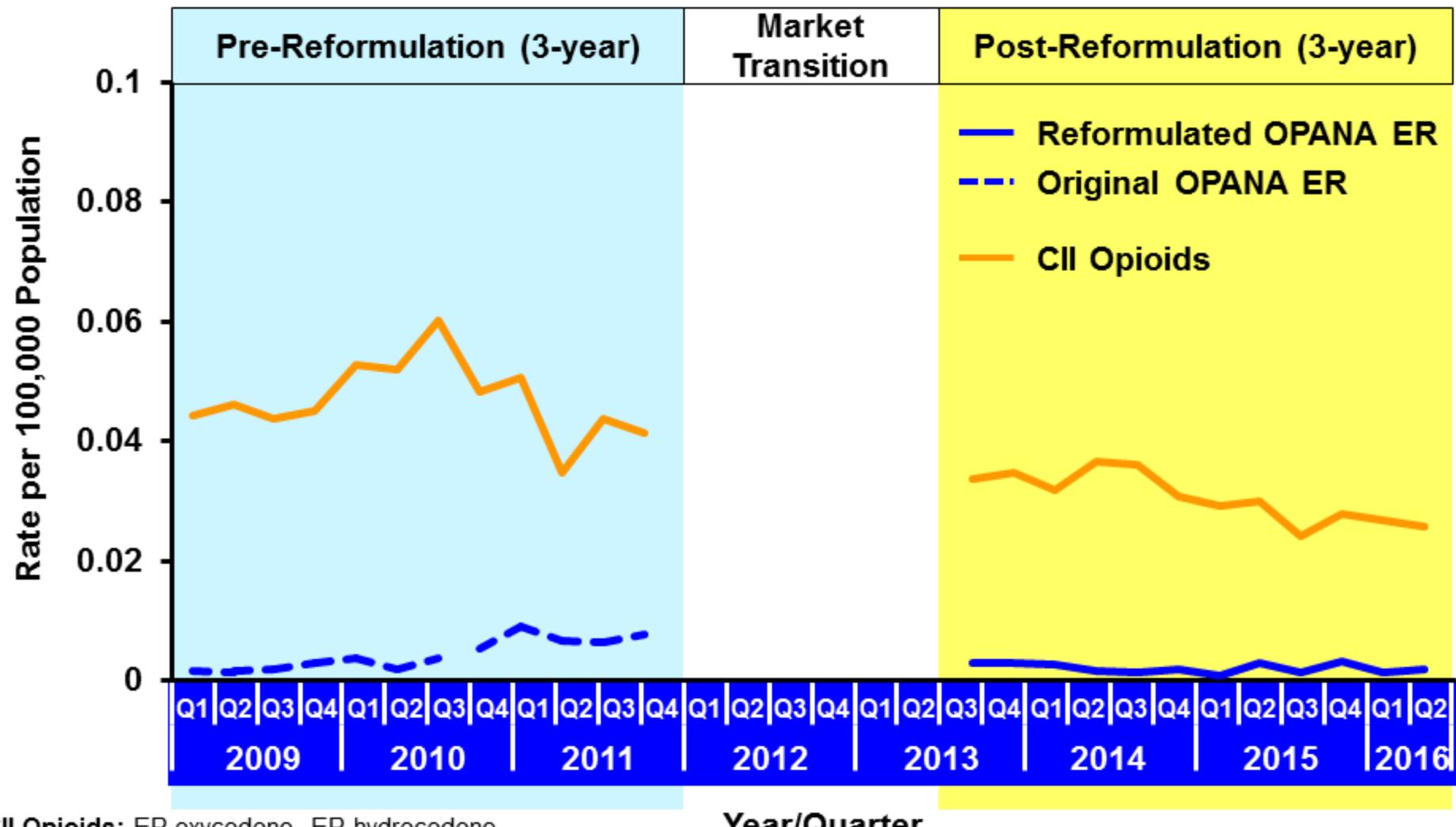
Challenges of Post-Marketing Surveillance

- Individual programs do not include every geographic region
- Spontaneous reporting susceptible to bias
- Self-reporting involves recall bias
- Cannot make direct causal links between outcomes and drugs
- Respondents accuracy cannot be verified
- Dramatic increase in abuse prevalence for all comparators

Benefits and Risks of Regulatory Action of Reformulated OPANA ER

- Benefits
 - Opioid analgesics needed for chronic pain that does not respond to alternative treatments
 - Multiple opioids with different characteristics are needed to address multiple patient needs
- Risks
 - All opioid drugs abused
 - Overdose, addiction, death
- Is Reformulated OPANA ER different?

RADARS Poison Center: Outcomes of OPANA ER Abuse are Not Worsening

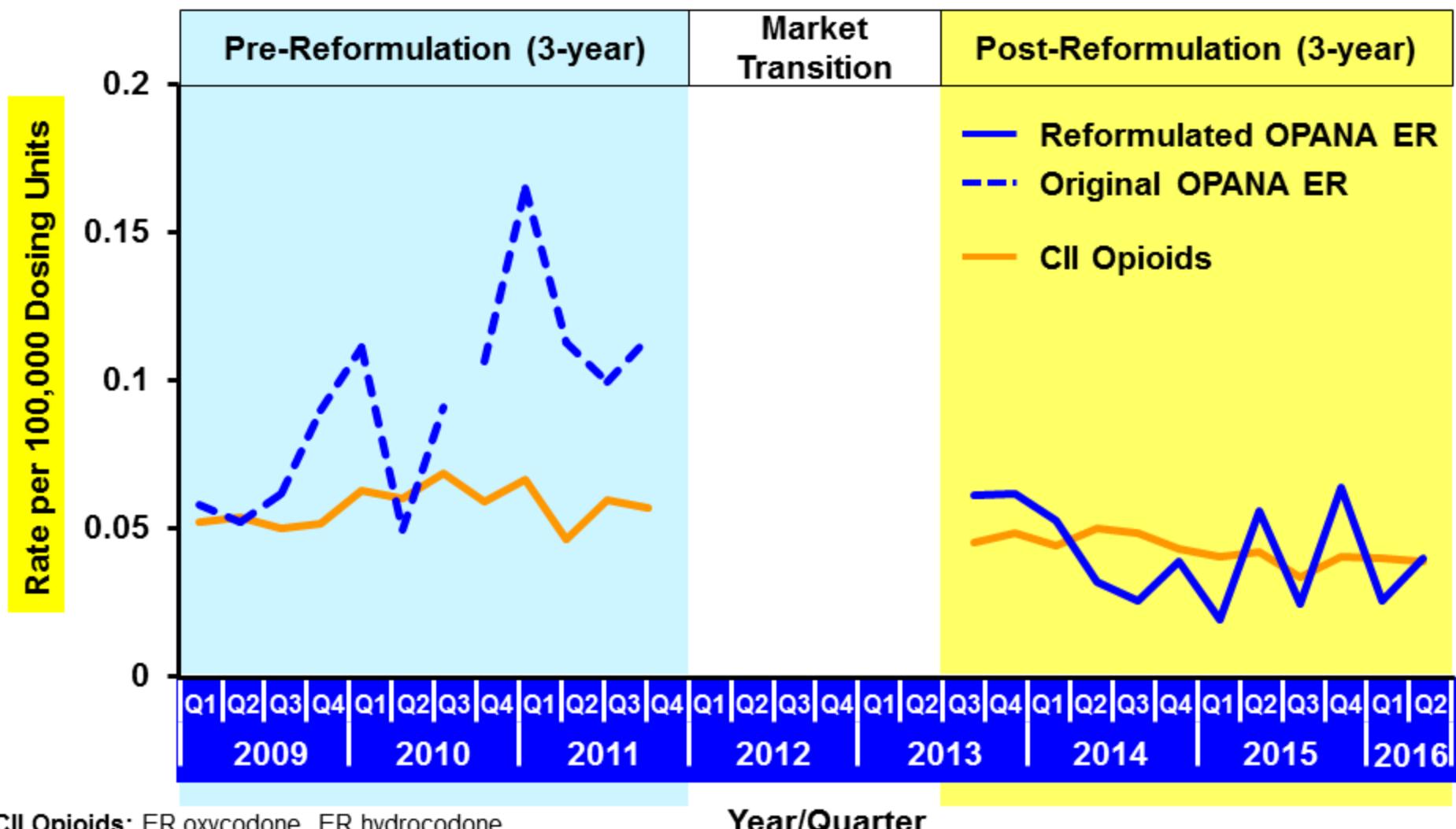


CII Opioids: ER oxycodone, ER hydrocodone, ER morphine, ER hydromorphone, and tapentadol ER

Year/Quarter

RADARS® Poison Center Program

RADARS Poison Center: Outcomes of OPANA ER Abuse are Not Worsening (100,000 Dosage Unit)

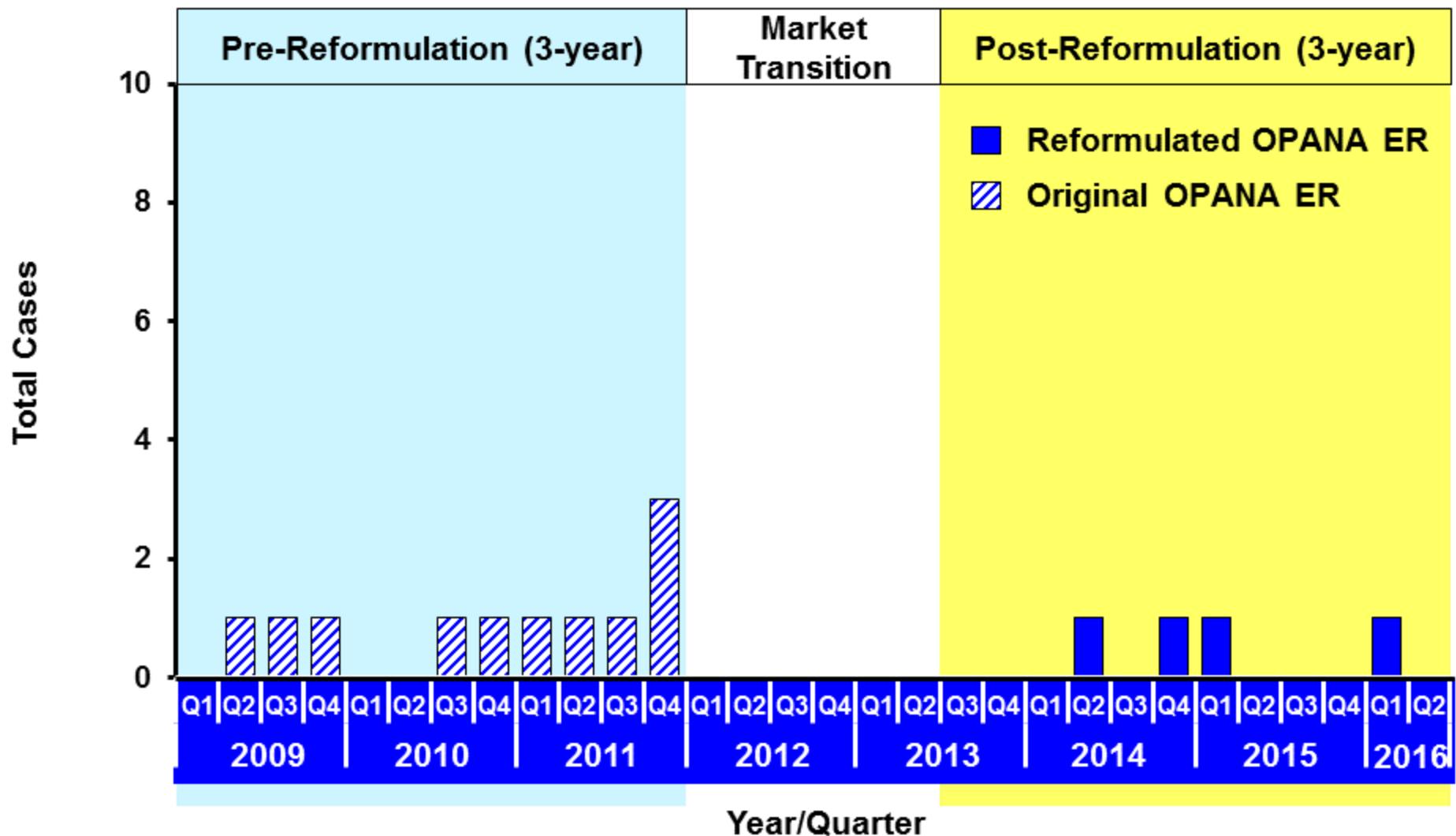


CII Opioids: ER oxycodone, ER hydrocodone, ER morphine, ER hydromorphone, and tapentadol ER

Year/Quarter

RADARS® Poison Center Program

OPANA ER Deaths are Low and Not Increasing in Poison Centers



Risks of OPANA ER Similar to Other ER/LA Opioids

- All opioids carry risks
 - OPANA ER: small portion of total abuse cases
 - OPANA ER: risks similar to other ER/LAs
- Rates of abuse are similar to other opioid analgesics since reformulation
- Consistent trends observed in 3 different programs (PC, DD, ASI-MV)
- Reformulated OPANA ER: physical / chemical barriers likely decrease attractiveness for abuse

OPANA ER Should Remain Available for Patients with Chronic Pain

- OPANA ER data show no new net harm
 - Not worse than other opioid analgesics
- OPANA ER provides consistent and predictable 12-hour pain relief
- Diversion and abuse similar to other opioids
- Interventions may be needed in specific locations, but not appropriate for entire US
- Removal of OPANA ER would be major burden to patients with no evidence of net gain

OPANA® ER (oxymorphone HCl) Benefit-Risk

March 13, 2017

Anesthetic & Analgesic Drug Products
Advisory Committee and
Drug Safety and Risk Management Advisory
Committee

Back-Up Slides

NAVIIPPRO: Selected Demographic Characteristics

Selected Demographic Characteristics		Total Analytic Sample (N=459,240)	Original OPANA ER Abusers Pre-Period (n=1,570)	Reformulated OPANA ER Abusers Post-Period (n=1,675)
Age	21 to 34	50.4	71.4	69.4
	35 to 54	36.3	12.4	23.1
Gender	Male	63.8	50.7	45.6
	Female	36.2	49.3	54.3
Race	White	59.4	91.7	93.5
	Black	18.9	1.5	1.8
	Hispanic	15.2	5	2
	Other	6.5	1.8	2.7
Education	Less than high school	28.4	26.1	27.9
	High school degree	41.8	44.3	45.6
	Some college	23.8	26.8	21.7
	College degree	3.9	2	2.6
Self-Reported Pain Problem	Yes	32.6	50.9	58
	No	67.3	49	41.9
	Unknown/ Missing	< 1.0	< 1.0	< 1.0
Chronic Medical Problem	Yes	30	30	38
	No	69.7	69.7	61.9
	Unknown/ Missing	< 1.0	< 1.0	< 1.0
Criminal Justice-Required Substance Abuse Treatment	Yes	58.7	25	26.7

Metabolic Pathways of Common Opioids

Opioid	Phase I Metabolism	Phase II Metabolism
Codeine	CYP2D6 & CYP3A	UGT2B7
Hydrocodone	CYP2D6 & CYP3A	UGT1A3, UGT2B2, dihydromorphine ketone reductase
Oxycodone	CYP3A & CYP2D6	UGT2B7
Methadone	CYP3A, CYP2B6, CYP2D6, CYP2C9 ^a , CYP2C19 ^a	
Tramadol	CYP3A & CYP2D6	
Fentanyl	CYP3A	
Morphine	(CYP3A) ^a	UGT2B7
Hydromorphone		UGT1A3 & UGT2B7
Oxymorphone		UGT2B7

^a Minor pathways/clinical significance unknown

Adapted from: Smith HS. Mayo Clin Proc. 2009; Fredheim CM, Acta Anaesthesiol Scand. 2008

Thrombotic Thrombocytopenic Purpura (TTP) in OPANA ER and OxyContin

- TTP has been reported with reformulated OxyContin containing PEO
- FAERS Database contains 6 cases of TTP with OxyContin
- Literature reports 2 cases of TTP with OxyContin

Thrombotic Thrombocytopenic Purpura (TTP) and OxyContin – FAERS 6 Cases

Event Date	Location	Gender	Age	Primary Suspect Drug	Route	Secondary Suspect Drugs	Concomitant Drugs	Outcome	Published
6-Jun-14	Australia	M	56	OxyContin	Intravenous	None	Diazepam Sertraline Cannabis	Hospitalized	Yes (Med J Aust 2015)
1-Apr-14	Australia	F	29	OxyContin	Intravenous	None	Acetaminophen Desenlafaxine Vitamin B9	Hospitalized	Yes (Clin Kid J 2016)
21-Oct-15	Australia	M	28	OxyContin	Intravenous	None	None	Hospitalized Life Threatening	No
27-Feb-15	Canada	F	19	Oxycodone	Unknown	Diclofenac	Amitriptyline Celecoxib Fentanyl Pregabalin	Other	No
6-Apr-12	US	F	-	OxyContin	Oral	None	None	Hospitalized	No
26-Sep-12	US	F	27	Oxycodone	Unknown	None	None	Hospitalized Life Threatening	No

NAVIPPRO: Distribution of OPANA ER Abuse Cases, ASI-MV Assessments and Number of Opioid Prescriptions by State

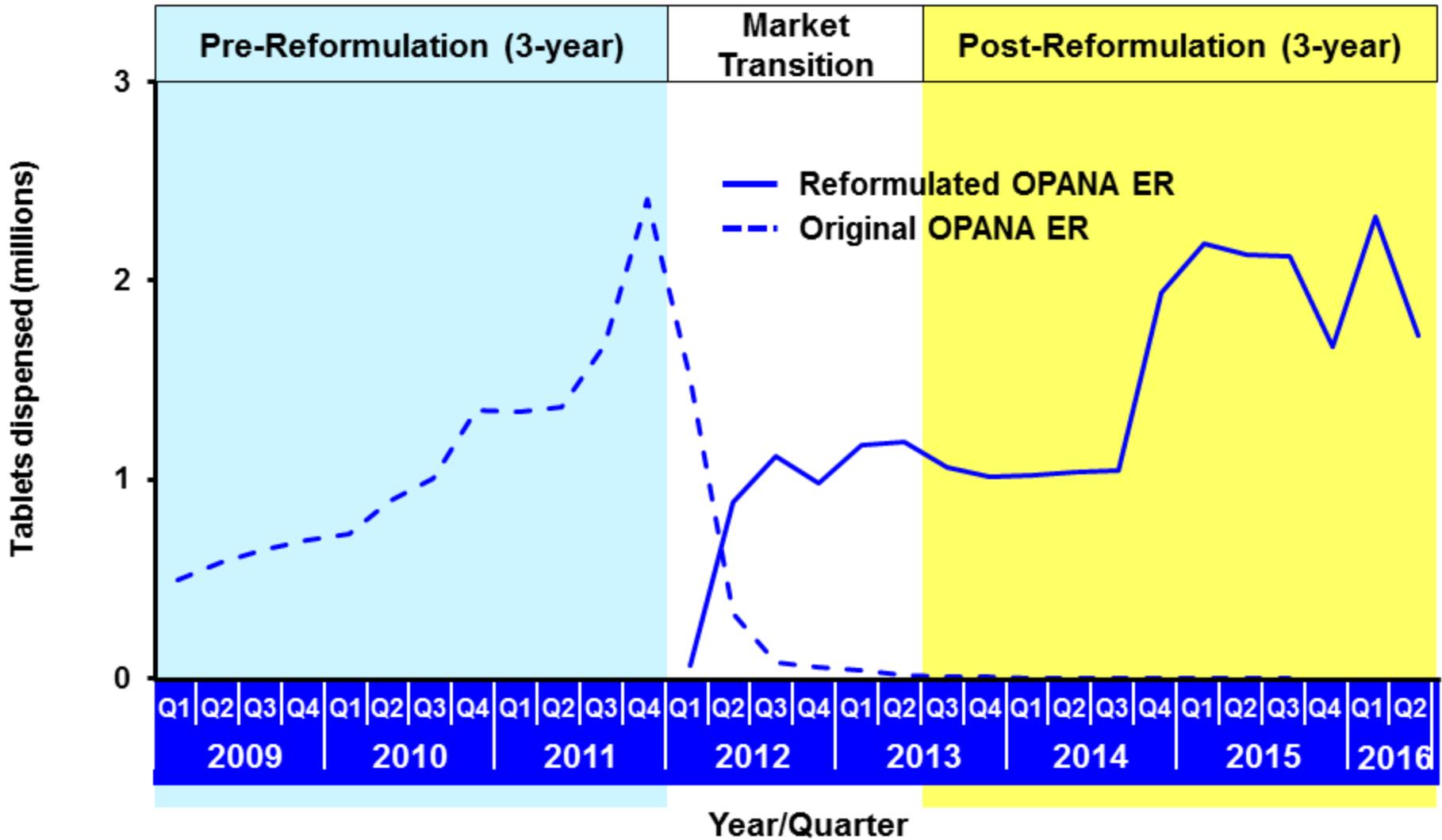
VR-143

	Tennessee	North Carolina
Opioid Prescriptions	19,281,864	16,495,810
Prescription Opioid Abusers	10,432	2,542
ASI-MV Sites	38	125
ASI-MV Assessments	20,964	20,284
OPANA ER Abuse Cases	1250	80
OPANA ER Abuse Cases (% Total)	74.6%	4.8%

Why TN Experience is an Anomaly and Not a Sentinel Occurrence

- IV abuse of nearly all opioids very high for some time without appreciable spread
- Very particular abuse ecology
 - Complicated set of factors
- Pockets of increased IV drug use occurring in other locations around the country have not led to OPANA ER signals

NAVIPPRO: OPANA ER Tablets Dispensed (TN)



RADARS Poison Center: Comparison of OPANA ER and OxyContin (Population-adjusted)

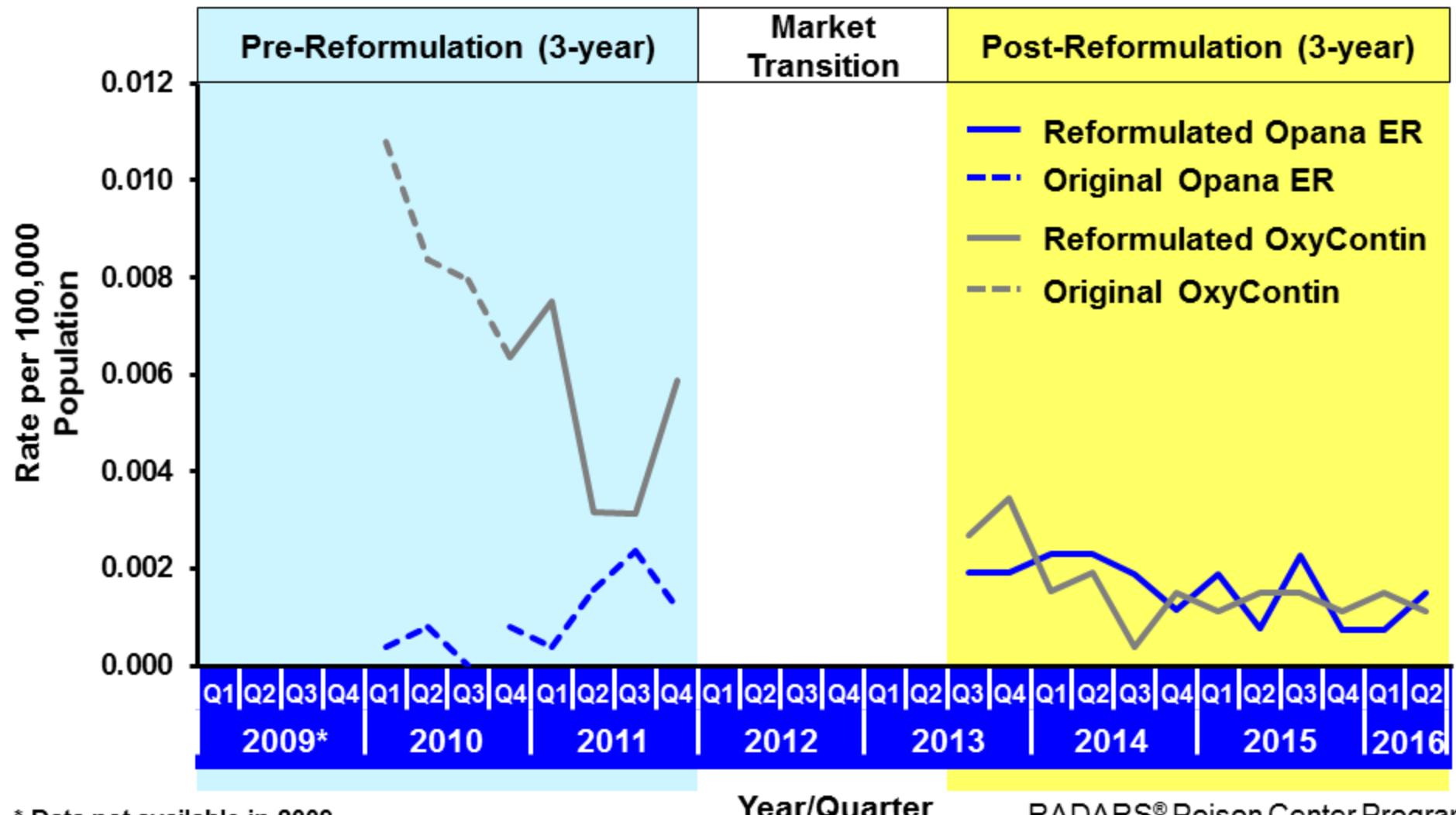


Table 2-3: Extraction Results for Reformulated OPANA ER, 40-mg Tablets – 5 mL

Pretreatment	Sample Type	Solvent 'a'			Solvent 'e'		
		Filterable/ Needle Size ^a	Extraction Solution (mL)	% Extracted ^b	Filterable / Needle Size ^a	Extraction Solution (mL)	% Extracted ^b
P3	Intact/Heated/Grated	No / N3	2.2, 3.3, 2.5	36.6, 59.3, 43.2 ^c 46.7	No / N4	3.1, 3.1	59.0, 56.0 57.5
	Grated/Heated	No / N3	3.1, 2.8	59.0, 52.2 55.6	No / N4	3.0, 2.8	54.9, 52.8 53.9
P4	Intact/Heated/Grated	No / N3	2.3, 2.0	38.0, 34.1 36.1	No / N4	3.4, 3.0	69.1, 60.8 65.0
	Grated/Heated	No / N3	4.1, 3.0, 4.3	69.8, 51.6, 78.4 ^c 66.6	No / N3	3.1, 3.0	59.6, 59.6 59.6
P6	Intact/Heated/Grated	No / N4	3.5, 3.5	60.1, 58.8 59.5	No / N4	2.7, 3.0	51.8, 60.6 56.2
	Grated/Heated	No / N4	3.1, 3.3	51.0, 54.8 52.9	No / N4	2.8, 3.1	55.3, 57.8 56.6
P7	Intact/Heated/Grated	No / N3	1.8, 2.6	28.1, 37.5 32.8	Not tested		
	Grated/Heated	No / N3	3.0, 3.1	51.6, 56.1 53.9	Not tested		
P8	Intact/Heated/Grated	No / N4	3.4, 3.4	63.4, 61.9 62.7	No / N4	2.7, 2.8	51.6, 54.4 53.0
	Grated/Heated	No / N3	2.1, 2.8, 2.1	36.4, 50.4, 38.0 ^c 41.6	No / N4	1.5, 2.2., 2.3	29.5, 48.6, 44.2 ^c 40.8

^a Needle size results represent the smallest bore needle used to collect >1 mL extraction solution.

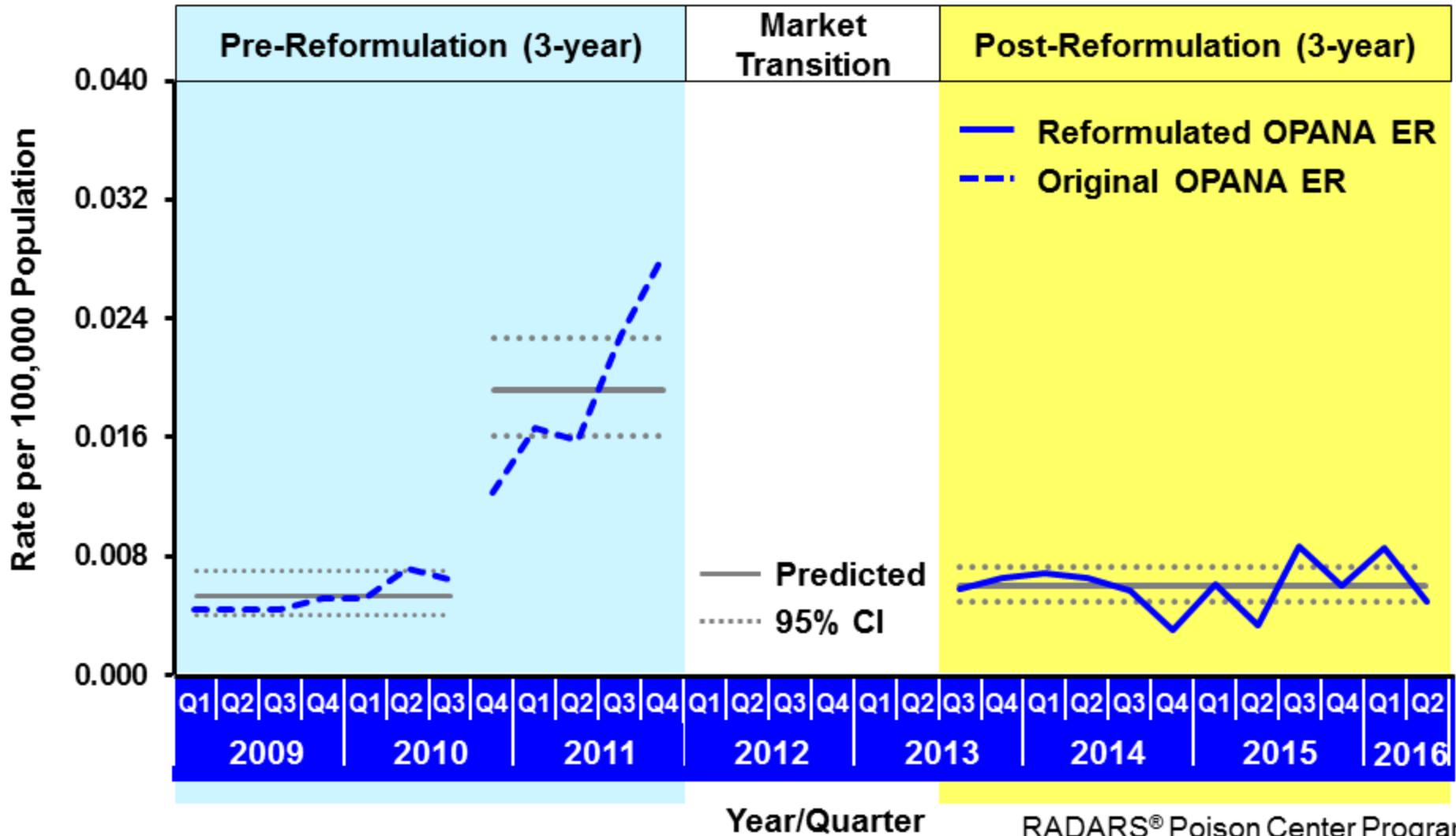
^b Individual results reported, average result in bold.

^c Additional sample preparation and extraction performed due to variability of the duplicate results.

Factors Affecting Syringeability/Extractability

- Particle Size of Sample
- Volume of Liquid
- Duration
- Temperature
- Agitation
- Needle Size
- Filter Type

RADARS® Poison Center: Rate of Intentional Abuse Mentions During Pre- and Post-Period



NAVIPPRO®: Abuse Prevalence by Alternate Routes of Administration (100 ASI-MV)

Tennessee vs Non-Tennessee

	Pre-Period	Post-Period	Percent Change from Pre- to Post- Period (%)	Percent Change 95% CI
Tennessee Only				
Original OPANA ER	8.26	N/A	N/A	N/A
Reformulated OPANA ER	N/A	5.69	-31.1	(-38.4, -22.9)
Non-Tennessee				
Original OPANA ER	0.54	N/A	N/A	N/A
Reformulated OPANA ER	N/A	0.24	-55.9	(-61.0, -50.1)

NAVIPPRO®: Abuse Prevalence by Intranasal Route of Administration (100 ASI-MV)

Tennessee vs Non-Tennessee

	Pre-Period	Post-Period	Percent Change from Pre- to Post-Period (%)	Percent Change 95% CI
Tennessee Only				
Original OPANA ER	7.12	N/A	N/A	N/A
Reformulated OPANA ER	N/A	1.47	-79.4	(-82.4, -75.9)
Non-Tennessee				
Original OPANA ER	0.45	N/A	N/A	N/A
Reformulated OPANA ER	N/A	0.06	-87.0	(-89.6, -83.8)

NAVIPPRO®: Abuse Prevalence by Intravenous Route of Administration (100 ASI-MV)

Tennessee vs Non-Tennessee

	Pre-Period	Post-Period	Percent Change from Pre- to Post-Period (%)	Percent Change 95% CI
Tennessee Only				
Original OPANA ER	1.24	N/A	N/A	N/A
Reformulated OPANA ER	N/A	4.53	264.6	(177.4, 379.1)
Non-Tennessee				
Original OPANA ER	0.10	N/A	N/A	N/A
Reformulated OPANA ER	N/A	0.16	56.1	(28.7, 89.4)