

# Oxycodone Extended-Release Tablets (IPC Oxy)

---

**July 26, 2017**

**Intellipharmaceuticals Corp.**

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

# Introduction

---

**Isa Odidi, MBA, PhD, DSc.,**

Co-Founder, Chairman, CEO and Co-Chief Scientific Officer  
Intellipharma Corp.

Adjunct Research Professor, Institute of Molecular Medicine, California

Professor of Pharmaceutical Technology, Toronto Institute of  
Pharmaceutical Technology, Canada

# Proposed IPC Oxy Indication

---

IPC Oxy is an opioid agonist indicated for pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in:

- Adults
- Opioid-tolerant pediatric patients  $\geq 11$  years of age who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent

# Regulatory Pathway and Dosage Strengths

---

- NDA under 505(b)(2) drug approval pathway using OxyContin as Reference Listed Drug (RLD)
- Category 1 studies compare IPC Oxy to Oxycontin
- Proposed dosage strengths: 10, 15, 20, 30, 40, 60 and 80 mg
- Bioequivalent to OxyContin
- No clinically significant food effect
- No dose dumping with alcohol

# IPC Oxy Formulated with Several Properties to Deter Abuse

	IPC Oxy	OxyContin
Resistance to physical manipulation	✓	✓
Resistance to chemical extraction	✓	✓
Gelling upon contact with liquid	✓	✓
Resistance to pre-treatment	✓	
Nasal irritant	✓	
Staining blue dye	✓	

# Results of Pre-Treatment with Internet Recipe Commonly Used to Defeat OxyContin

---



# Staining Blue Dye: Innovative Feature of IPC Oxy

---

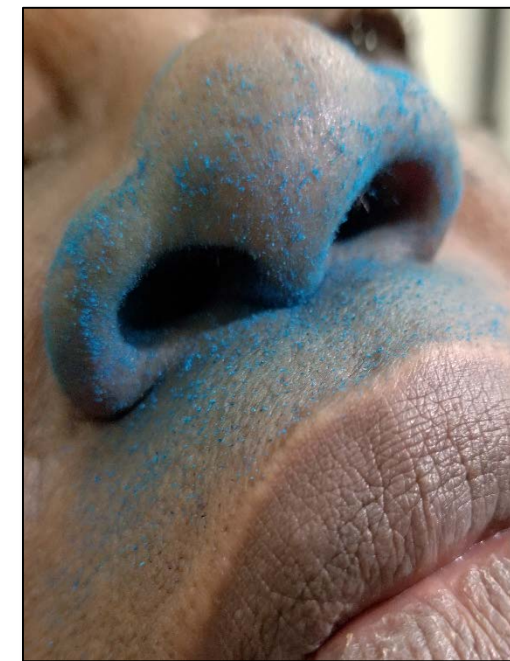
**Chewed**



**Crushed**



**Nasal**



**If chewed or crushed, IPC Oxy releases a staining blue dye**

# Rationale for Pursuing IV Abuse-Deterrent Label Only At This Time

---

- Make available to patients and physicians sooner
- Need for innovation and improvement over current ADFs
- OxyContin still being abused IV
- No ADF should be injected
- IPC Oxy difficult to prepare for injection
- Similar or superior IV abuse-deterrence vs. OxyContin



# Excipient Safety

---

- Blue dye and SLS do not pose safety risk when product taken as intended
- Limited data suggest excipients are safe when taken by non-intended routes
- IPC Oxy will include warnings against injection, crushing, snorting or tampering

# IPC Oxy Designed to Deter Abuse by Non-IV Routes

---

- Category 1 data suggest blue dye and nasal irritant may deter abuse by all routes
- HAP studies needed for explicit label
- Will seek to update label later

# Proposed Abuse-Deterrence Labeling Consistent with Current Level of Evidence

---

“... in vitro data demonstrate that [IPC Oxy] has physicochemical properties expected to deter intravenous abuse. However, abuse of these tablets by this route, as well as by the oral and intranasal routes, is still possible.”

# Proposed Label Warning

---

“If crushed or chewed [IPC Oxy] tablets release an intense blue dye that can stain skin, oral and nasal cavities.”

# Concern Regarding Injection of PEO-Based Abuse-Deterrent Formulations

---

- March 2017: Data suggested reformulated Opana ER associated with thrombotic thrombocytopenic purpura (TTP)-like illness
- FDA data suggested cause was IV injection of polyethylene oxide (PEO) in reformulated Opana ER<sup>1,2</sup>
- July 2017: Opana ER voluntarily withdrawn from the market
- FDA presented Thrombotic Microangiopath (TMA) cases (of which TTP is a subset) associated with Opana ER compared to other ADFs

1. FDA. Presentation on March 16-17, 2017. [www.fda.gov](http://www.fda.gov)

2. Hunt et al. 2017 *Blood* 2017;129:896-905

# Low Incidence of Thrombotic Microangiopathy (TMA) Associated With Injection of OxyContin

2011-2016 in U.S.	Opana ER	OxyContin
Case reports of TMA <sup>1</sup>	59	2
Prescriptions written	750,000	24,000,000
Rate per 100,000 prescriptions	7.9	< 0.01

# Expect IPC Oxy TMA-Related Safety Profile to be Similar to OxyContin

---

- Opana ER
  - Can be readily prepared for injection
  - Different type of PEO than OxyContin
- IPC Oxy
  - Same type of PEO as OxyContin
  - Suggests TMA-related safety profile similar or better than OxyContin

# Agenda

---

## Need for Abuse-Deterrent Opioid Analgesics

### **Richard Dart, MD, PhD**

Director, Rocky Mountain Poison and Drug Center  
Professor, University of Colorado  
Executive Director, RADARS® System

---

## Clinical Pharmacology

### **Beatrice Setnik, PhD**

Vice President, Scientific & Medical Affairs, INC Research  
Adjunct Professor, Department of Pharmacology & Toxicology,  
University of Toronto

---

## Category 1 Abuse-Deterrent Studies

### **Edward Cone, PhD**

Principal Scientist, PinneyAssociates  
Adjunct Professor, Johns Hopkins School of Medicine

---

## Public Health Perspective

### **Edward Sellers, MD, PhD**

Professor Emeritus, University of Toronto  
President and Principal, DL Global Partners Inc.

---



# Additional Responder

---

**Toxicology**

**William Brock, PhD**

Brock Scientific Consulting

---

# Need for Abuse-Deterrent Opioid Analgesics

---

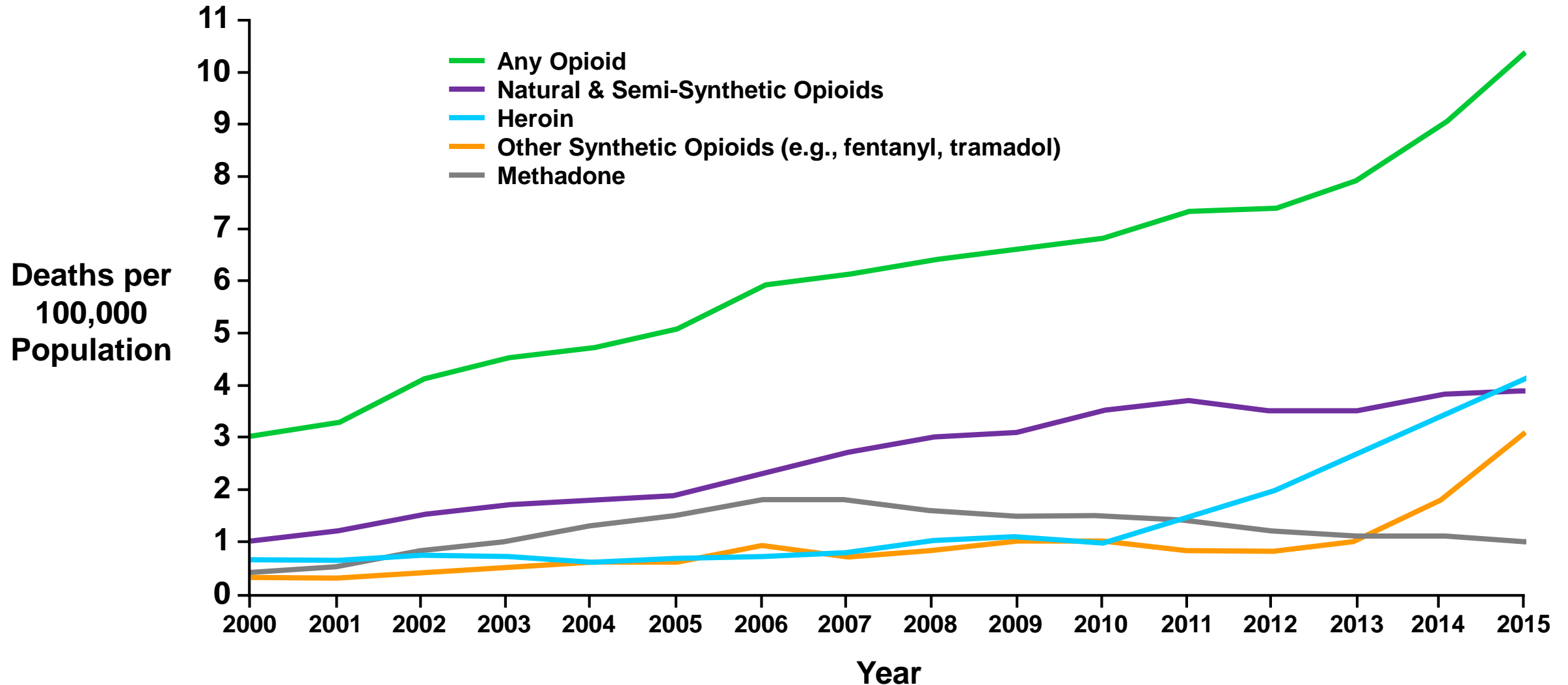
## **Richard C Dart, MD, PhD**

Director, Rocky Mountain Poison & Drug Center

Professor of Emergency Medicine, University of Colorado School of Medicine

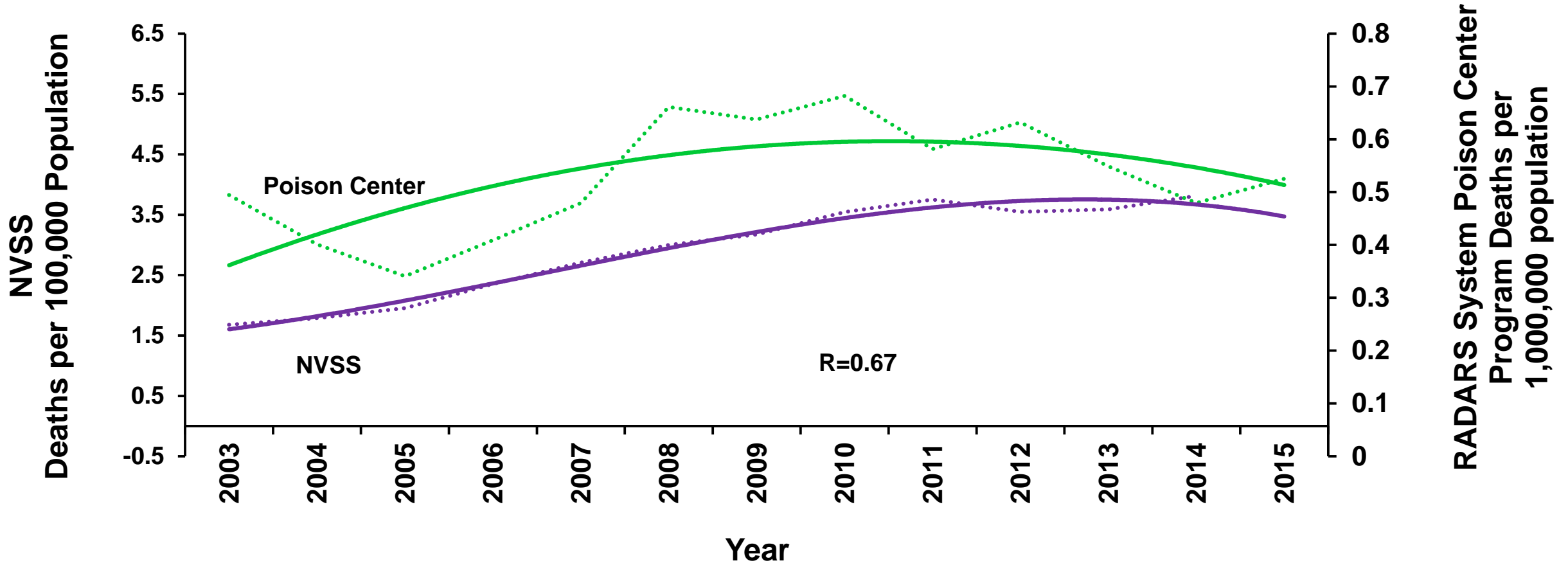
Executive Director, RADARS<sup>®</sup> System

# Deaths from Prescription Opioids Remain at Historic High



# 15-20% of Deaths Reported to Poison Center Involve Injection

## Natural & Semisynthetic Opioids, 2003 to 2015



\*\*T40.2 Natural and semisynthetic opioids: oxycodone, morphine, hydromorphone, oxymorphone, others

\*\*RADARS System opioids: oxycodone, hydrocodone, morphine, hydromorphone, and oxymorphone. Deaths include cases followed to a known medical outcome whose death was related to the reported exposure

# IV Route Increases Risk of Serious Health Consequences

---

- Risk of death or major adverse effect in the RADARS Poison Center program 2.6 [2.0, 3.4] times greater when the IV route is involved
- 6% of HIV diagnoses and 10% of AIDS cases attributed to IV drug use in 2015<sup>1</sup>
- Other health risks of injection
  - Hepatitis C<sup>2</sup>
  - Endocarditis<sup>3,4</sup>
  - Blood clots<sup>5</sup>

1. CDC. HIV Surveillance Report, 2015;27

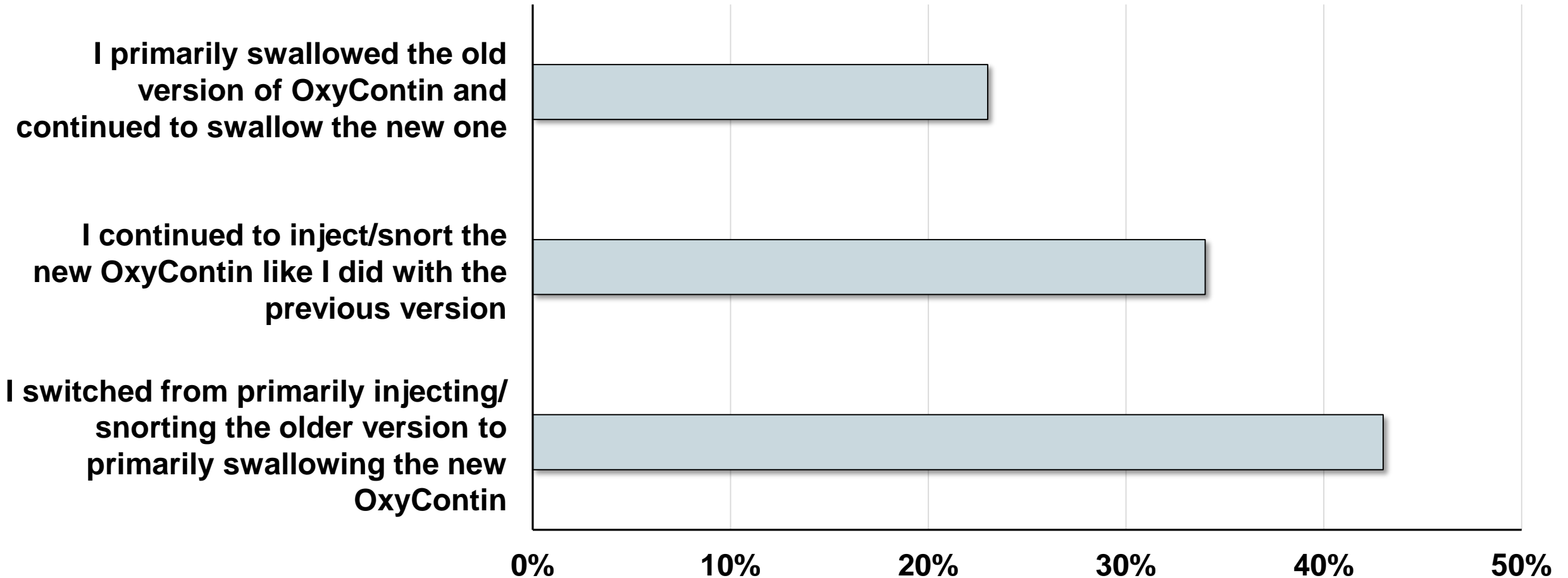
2. Bruneau et al. *Addiction* 2012;107:1318-27

3. Ronan & Herzig. *Health Affairs* 2016;35:832-7

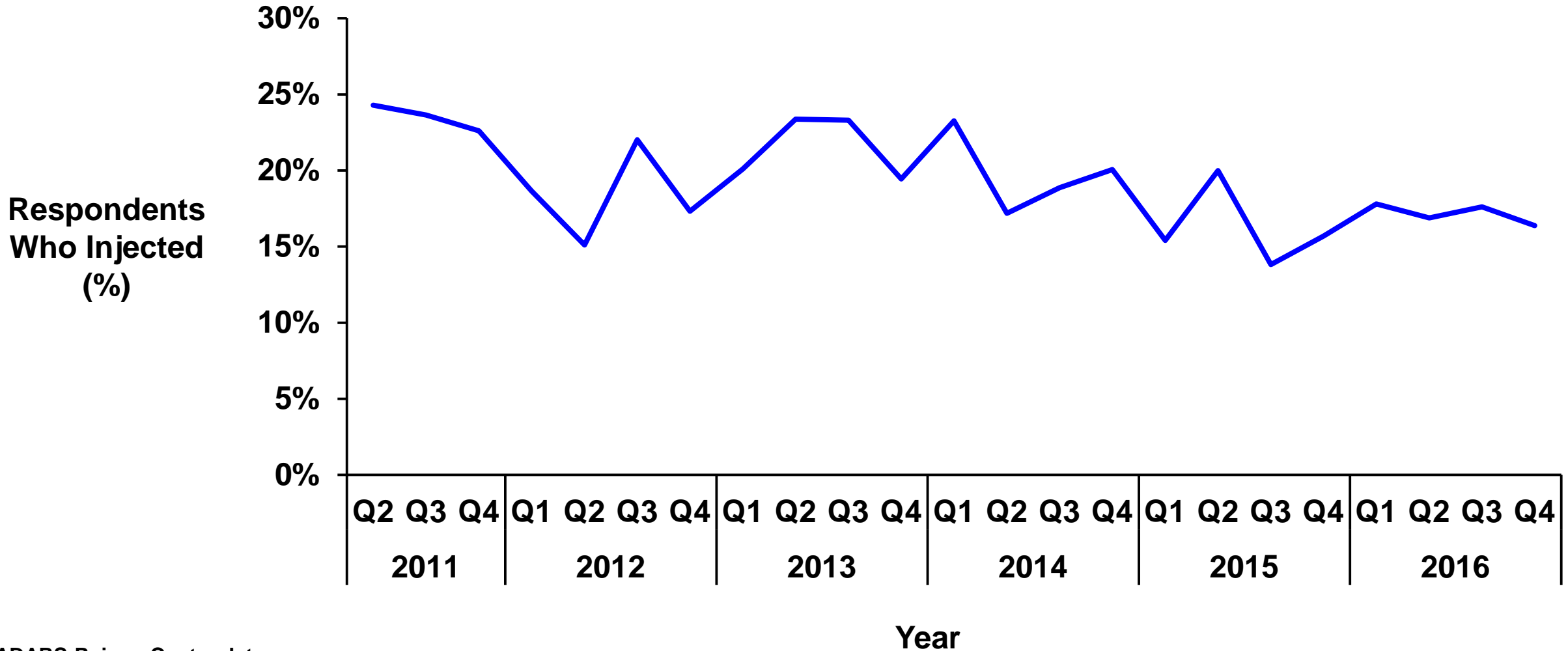
4. Gordon & Lowy. *NEJM* 2005;353:1945-54

5. McLean et al. *Harm Reduct J* 2009;6:37

# RAPID Data Show Some OxyContin Abusers Continued to Snort or Inject After Reformulation



# Non-Oral Abuse Persists Despite OxyContin Reformulation



# How Can ADFs Make Positive Impact on Different Types of Individuals?

---

## Pain Patient

- Decrease likelihood of crushing drug to increase effects
- Deter transition to intranasal and IV abuse

## Novice / Recreational Abuser

- Decrease likelihood of crushing drug to increase effects
- Deter transition to intranasal and IV abuse

## Advanced Abuser

- Make dangerous routes of abuse more difficult with that ADF product



# Why More ADF Options?

---

- IV abuse of oxycodone ER continues
- Improved ADF options needed to address vulnerabilities in easily abusable products and current ADFs
- FDA Guidance anticipated innovation and incremental improvement of opioids with abuse deterrent properties

# Clinical Pharmacology

---

## **Beatrice Setnik, PhD**

VP of Medical and Scientific Affairs for INC Research Early Phase  
Adjunct Professor, Department of Pharmacology & Toxicology,  
University of Toronto

# Clinical Pharmacology Overview

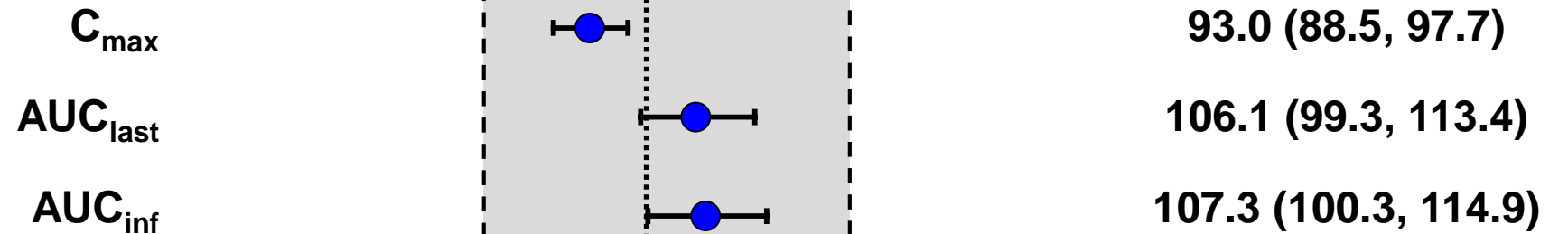
---

- Bioequivalence
- Dose proportionality
- Food effect

# Demonstrated Bioequivalence to OxyContin (10 mg)

## IPC Oxy vs OxyContin (10 mg - Fasted)

Study 1878, N=31



## IPC Oxy vs OxyContin (10 mg - Fed)

Study 1879, N=29



40 50 60 70 80 90 100 110 120 130 140 150 160

LS Mean Ratios (%)  
(90% CI Range)

# Demonstrated Comparable Bioavailability to OxyContin at Higher Dose (80 mg)

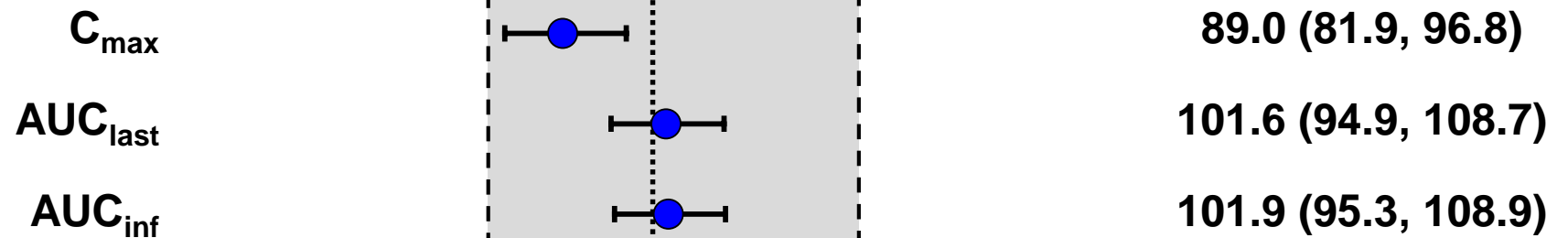
## IPC Oxy vs OxyContin (80 mg - Fasted)

Study 656-15, N=30



## IPC Oxy vs OxyContin (80 mg - Fed)

Study 655-15, N=29



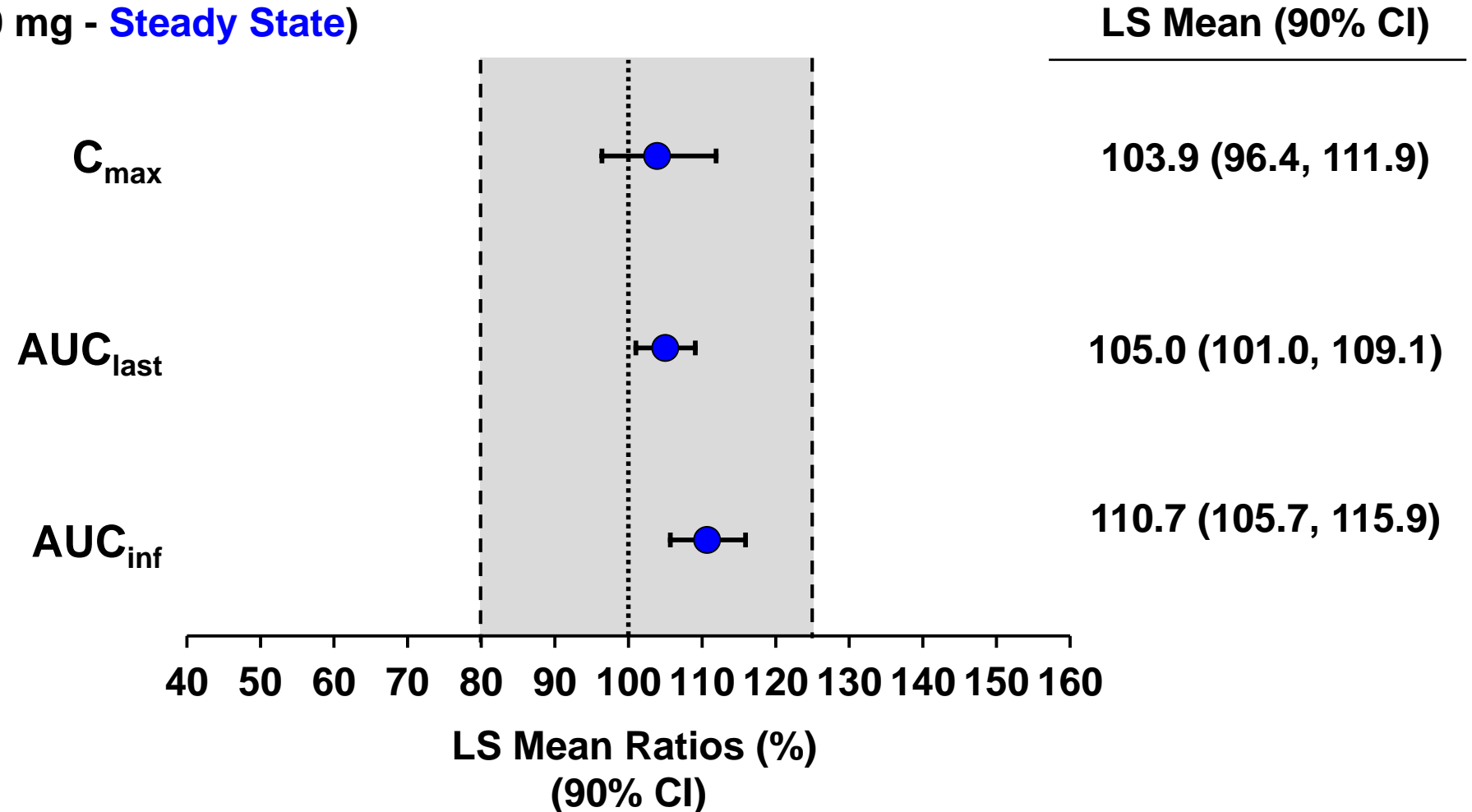
40 50 60 70 80 90 100 110 120 130 140 150 160

LS Mean Ratios (%)  
(90% CI Range)

# Multiple Dose Study (80 mg)

## IPC Oxy vs OxyContin (80 mg - Steady State)

Study 80-184, N=24



# Dose Proportionality Design (Study 80-185)

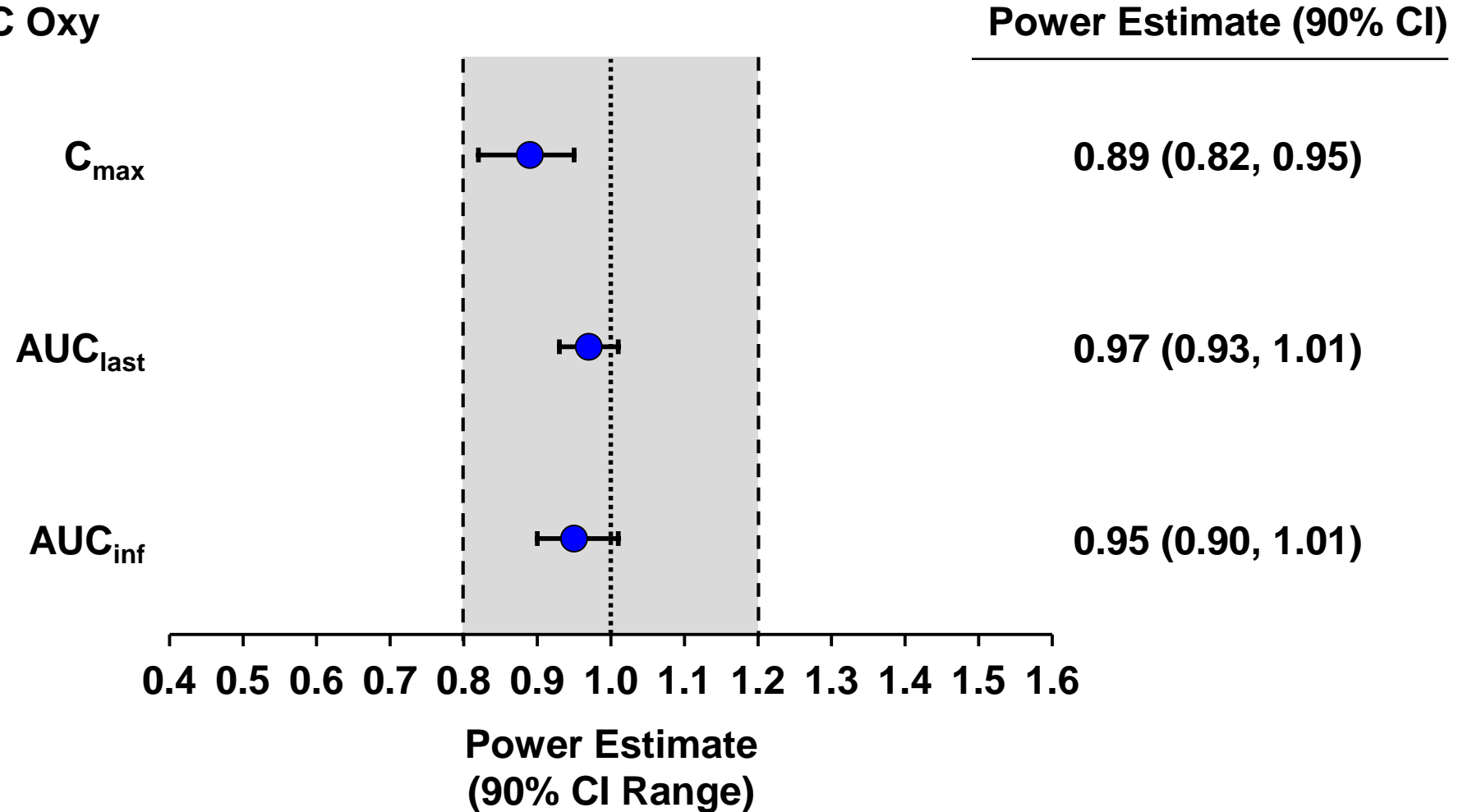
---

- Randomized, 7-periods, crossover, open label, laboratory-blind
- Single oral doses
  - 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg
- Blood samples taken up to 24 hours post-dosing
- Healthy adult subjects under fasted conditions
  - Males 18-50 years
- 22 subjects completed

# Dose Proportional Between All 7 Doses

## Dose Proportionality of IPC Oxy

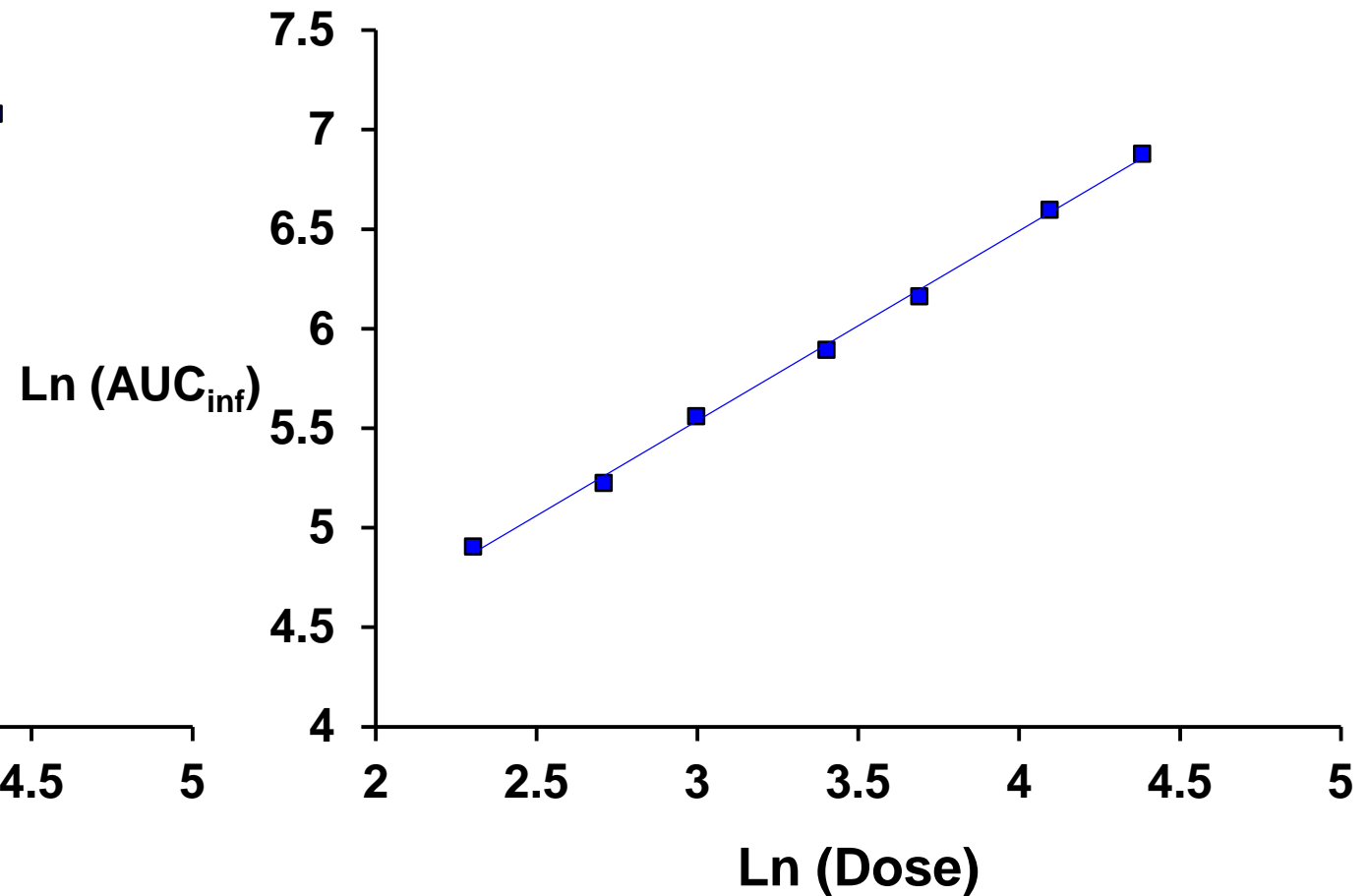
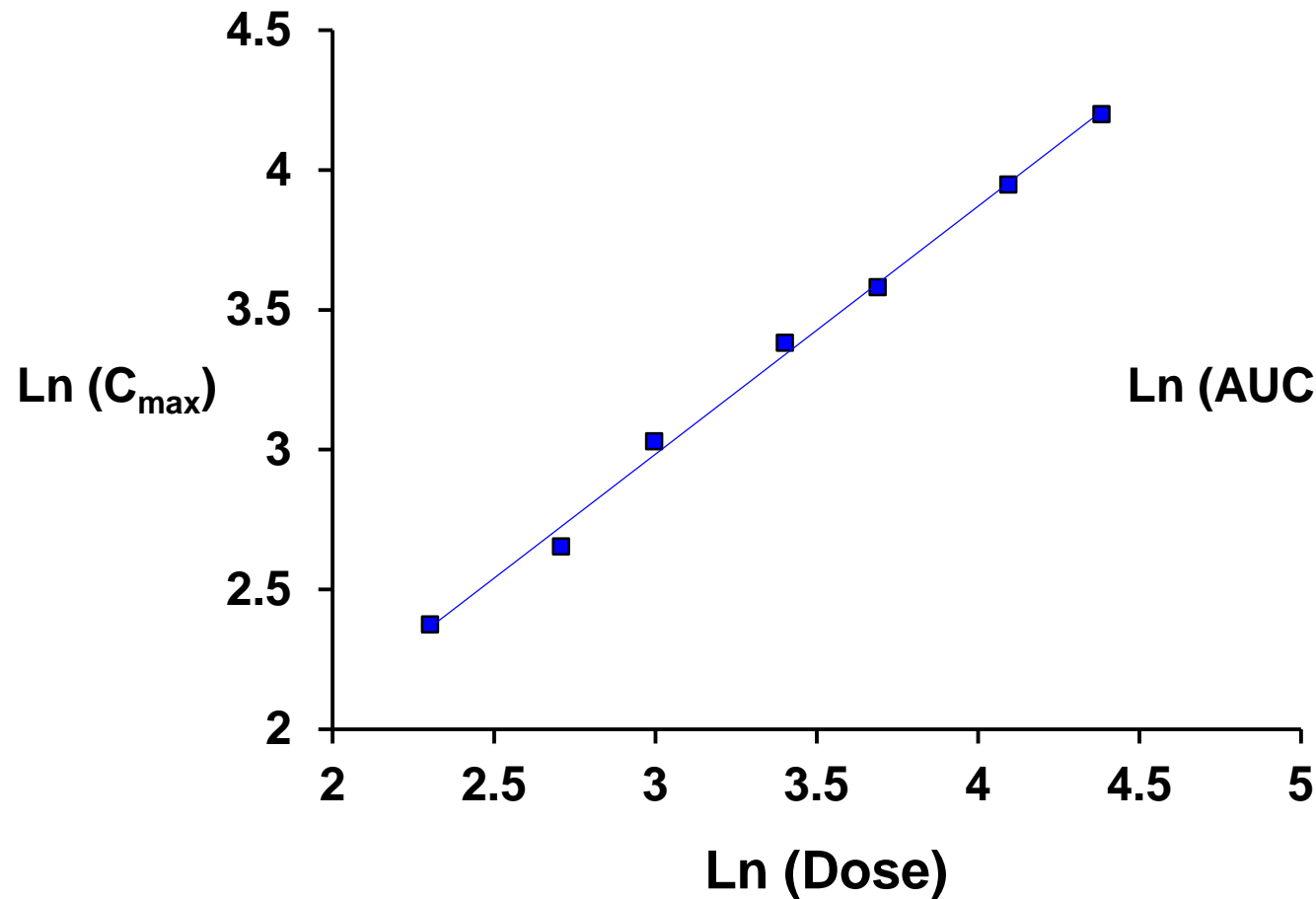
Study 80-185, N=22



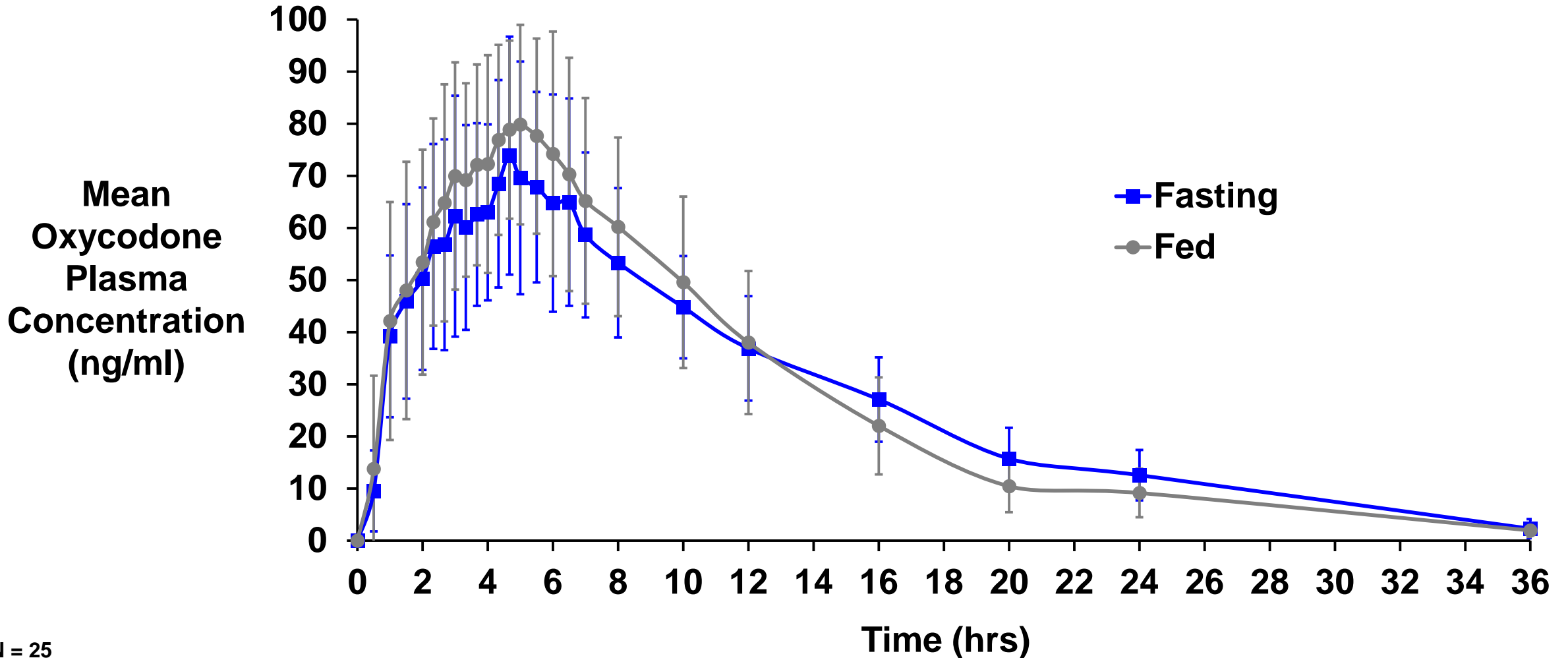


# Least Square Means (Study 80-185)

---



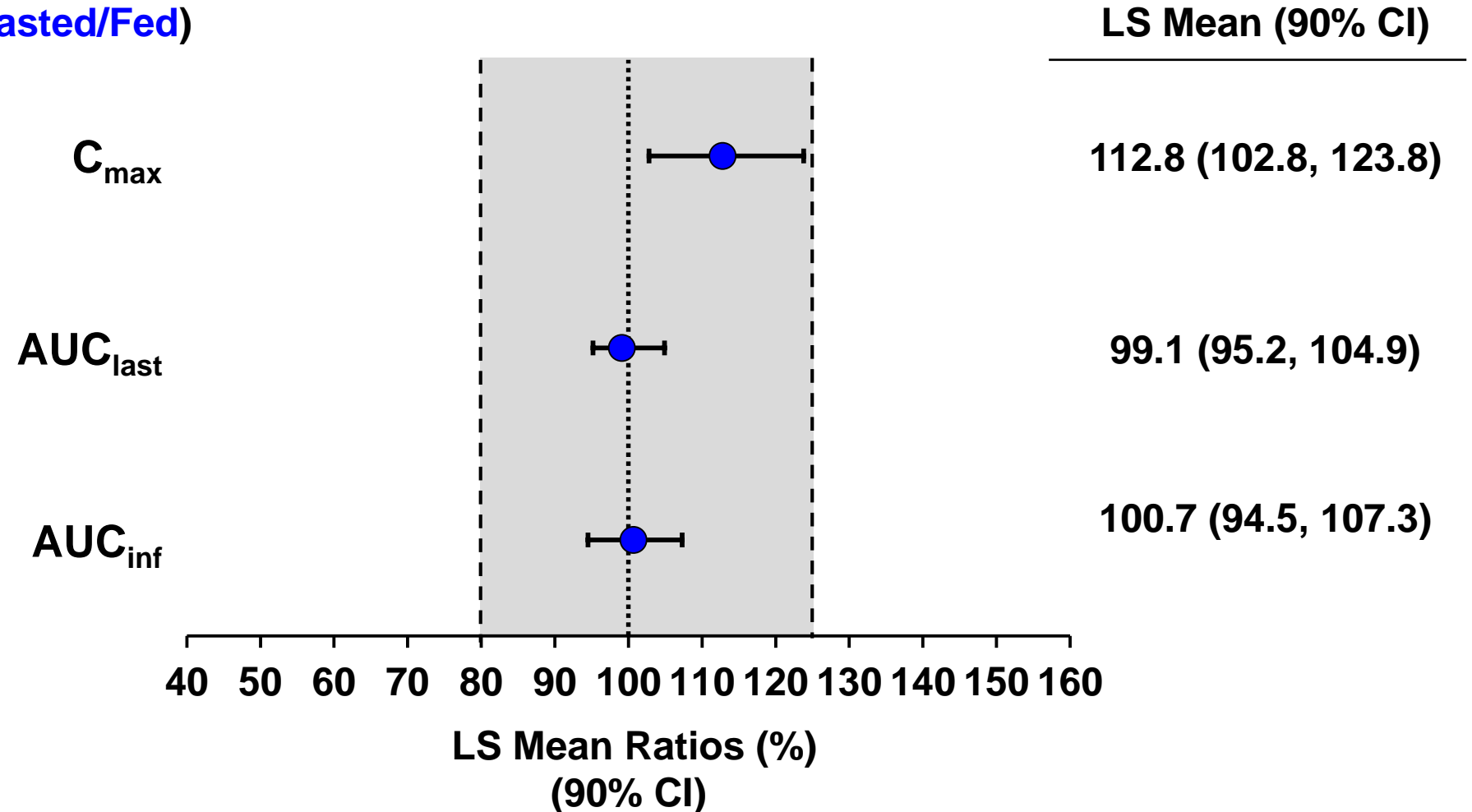
# No Clinically Significant Food Effect (Study 80-186)



# No Clinically Significant Food Effect

## Food Effect of IPC Oxy (Fasted/Fed)

Study 80-186, N=25



# Clinical Pharmacology Summary

---

- Bioequivalent to OxyContin
  - Supports approval of 505(b)(2) application
  - Well-established safety and efficacy profile
- Demonstrated dose proportionality between all doses
- Patients can take medication without regards to meals

# Category 1 Abuse-Deterrent Studies

---

**Edward Cone, PhD**

Principal Scientist, PinneyAssociates

Adjunct Professor, Johns Hopkins School of Medicine

# In Vitro Studies Evaluated Physical and Chemical Abuse-Deterrent Properties of IPC Oxy

---

- Conducted in accordance with 2015 FDA Guidance
- OxyContin used as abuse-deterrent comparator
- Selection of tools, solvents and conditions
  - Exploratory phase to manipulate using common practices
  - Standardization phase to select “worst-case” scenarios
- Range of conditions include common methods used by abusers, and extreme laboratory manipulations

# Overview of Category 1 Studies

---

- Particle Size Reduction
- Syringeability / Injectability and Small Volume Extraction
- Large Volume Extraction
- Alcohol Dose Dumping
- Manipulated Tablet Dissolution
- Dye Elimination
- Simulated Smoking / Vaporization

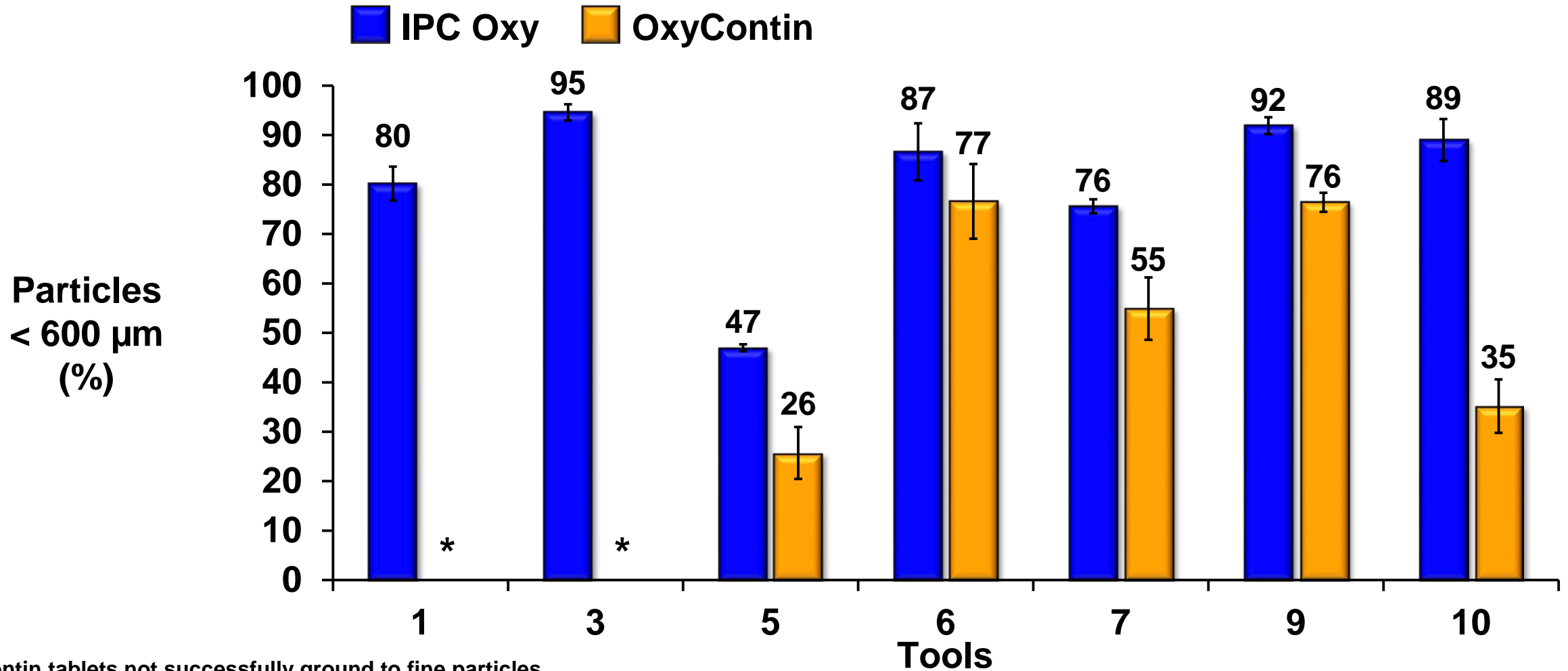
# Particle Size Reduction Methods

---

- 10 household tools chosen as representative of cutting, crushing, grating, and grinding
- Tools applied to both IPC Oxy and OxyContin by trained laboratory technicians
- Particle size measured using sieve tray
- API assessed for each range of particle sizes



# IPC Oxy Yielded More Particles < 600 $\mu\text{m}$ Across All Tools

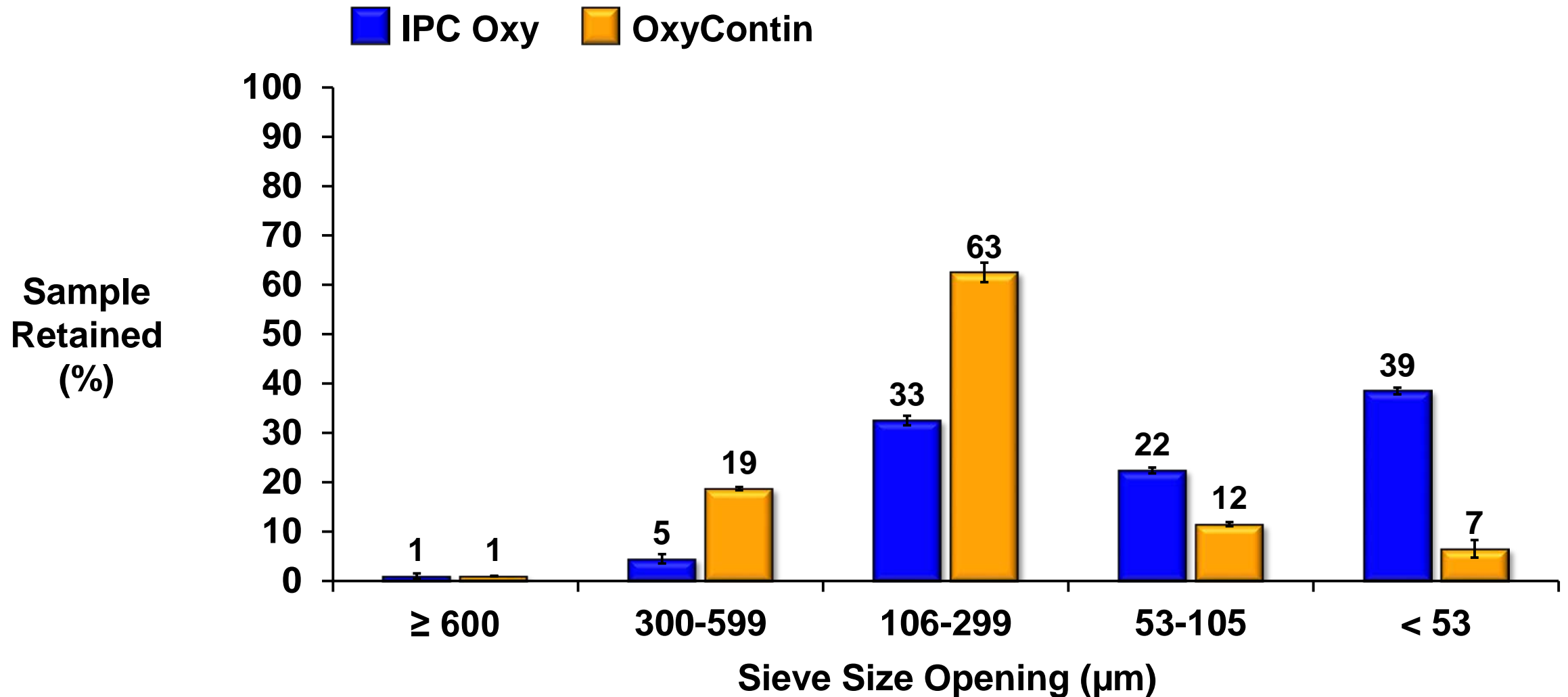


\* OxyContin tablets not successfully ground to fine particles

Tools 2, 4, 8: Sieve analysis not completed because tablets were not successfully manipulated to fine particles

Error Bars = SD; Experiment performed in triplicates

# Optimal Particle Size Reduction Method Reduced 99% of IPC Oxy and OxyContin to <600 Microns



# Overview of Category 1 Studies

---

- Particle Size Reduction
- **Syringeability / Injectability and Small Volume Extraction**
- Large Volume Extraction
- Alcohol Dose Dumping
- Manipulated Tablet Dissolution
- Dye Elimination
- Simulated Smoking / Vaporization

# Common Methods for Preparing Solid Oral Dosage for IV Injection

---

- Grind tablet
- Extract with 1-2 mL water in spoon
- May or may not heat with a lighter
- Syringe using cotton or cigarette filter using 27-29 gauge needle



# Most ADFs Designed to Resist Common Methods for IV Abuse

---

- Studies evaluated common and extreme methods to overcome gelling properties
- IPC Oxy and OxyContin produce highly viscous gel when subjected to liquid
- IPC Oxy formulated to enhance gelling even if subjected to large volume or pre-treatment
- Cotton filter used to prevent needle clogging
- Studies started with largest needle, then progressed to smaller sizes

# Standard Syringeability / Injectability Studies Conducted to Simulate Common Abuser Practices

---

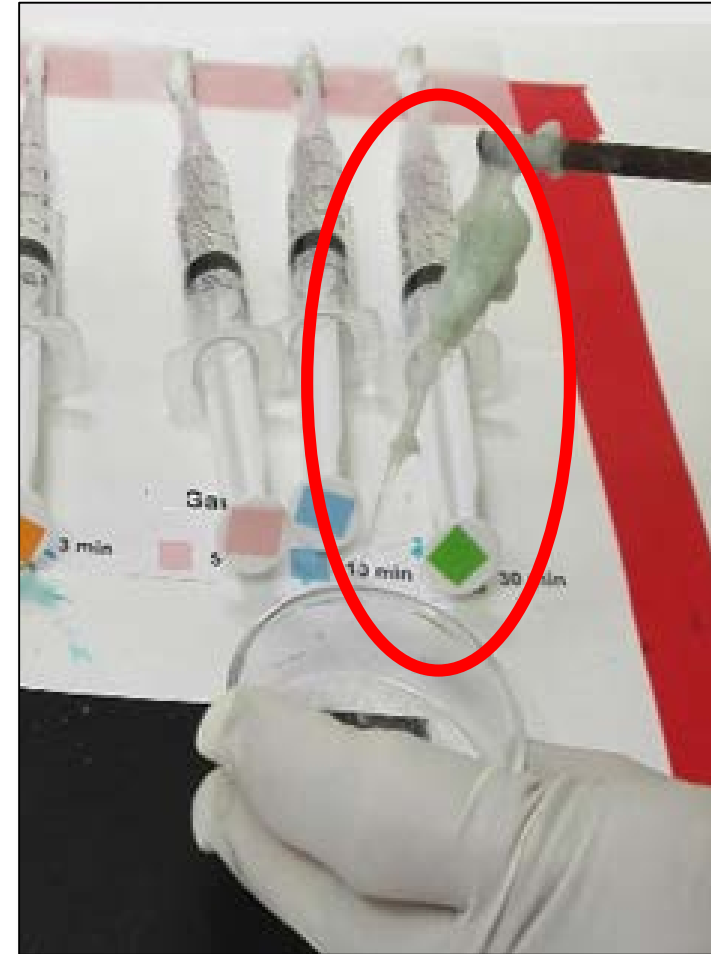
- Single dose of Tablet Form B
  - Volumes 1, 2, 3, 4 or 6
  - Extracted in Solvents 1 or 2
  - Incubation up to 30 min
  - Agitation A or C
  - Temperatures A or B
- No conditions yielded suitable amount of injectable oxycodone ( $\geq 20\%$ )
  - Supports IPC Oxy and OxyContin IV abuse-deterrent properties

# Pictures of Abuse-Deterrence with Standard Methods

## IPC Oxy



## OxyContin



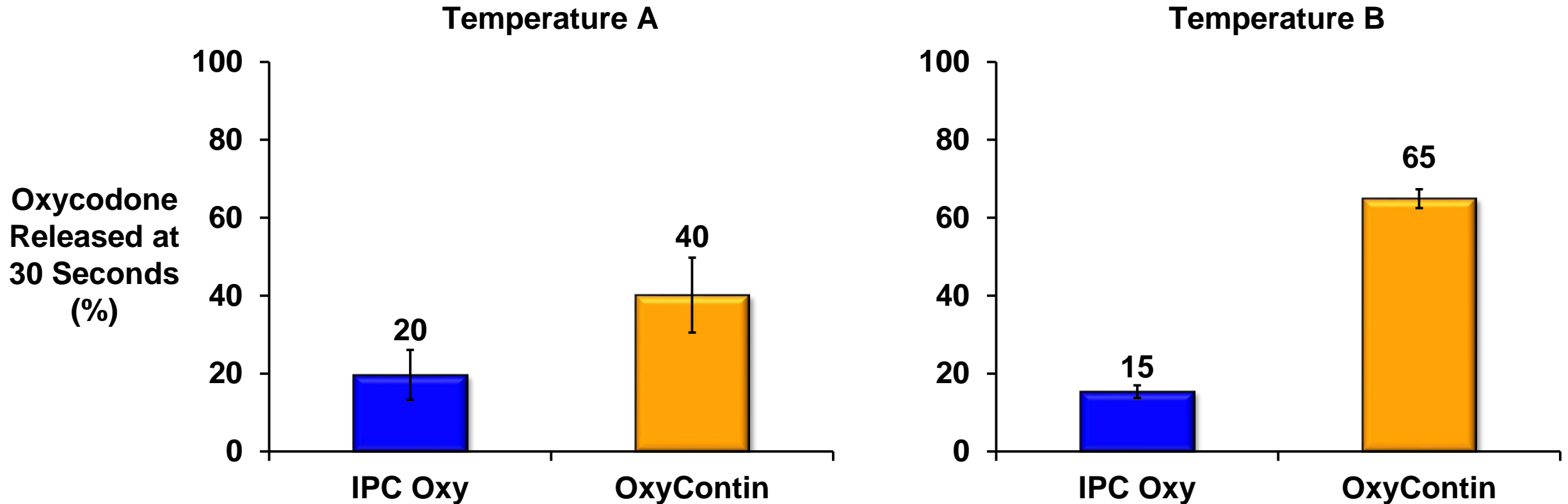
# Additional Studies Conducted Using Recipe from Drug Abuse Websites to Defeat ADFs

---

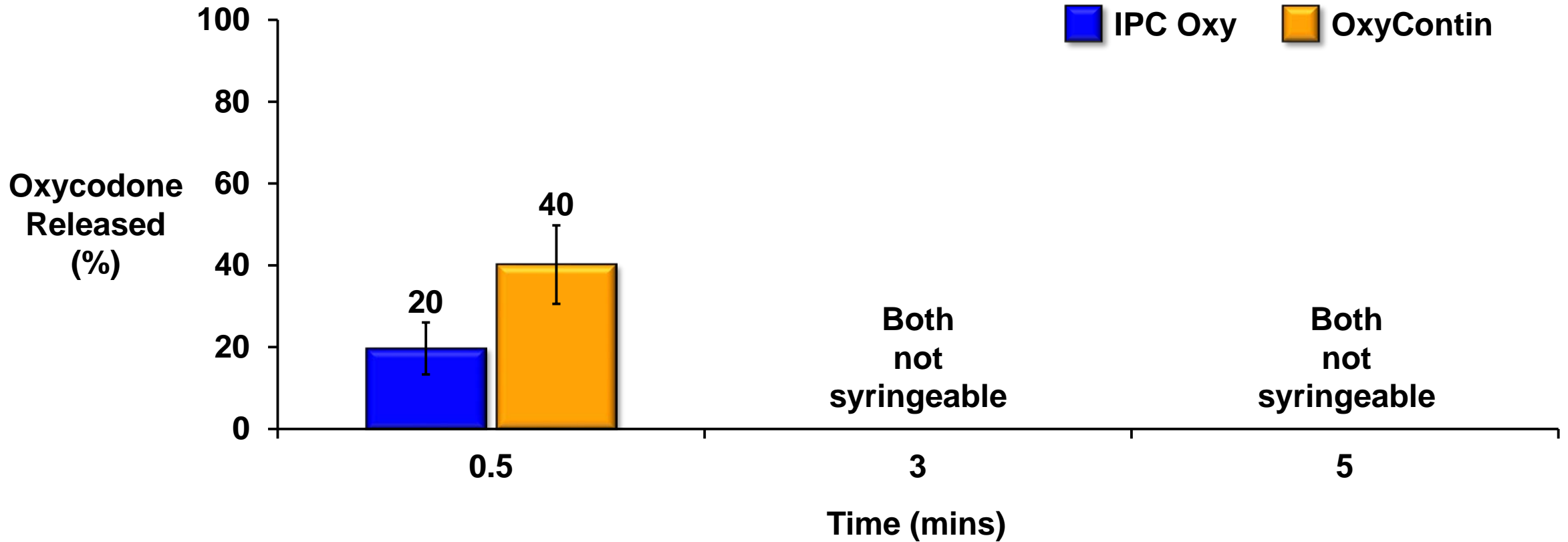
- Drug abuse websites offer instructions for how to defeat gelling properties of ADFs
- Most typical manipulation involves Pre-treatment D
- Studies for IPC Oxy and OxyContin evaluated:
  - Pre-treatment D
  - Tablet Form B
  - Volumes 1, 2 or 3
  - Solvent 1
  - Agitation A
  - Temperature A or B



# Syringeability of Pre-Treated Tablet Form B Lower with IPC Oxy than OxyContin in Volume 1



# Neither Product Syringeable with Longer Incubation Time



Tablet Form B, Pre-Treatment D, Volume 1, Solvent 1, Agitation A, Temperature A, Needle Gauge A  
Experiment performed in triplicates

# Overview of Category 1 Studies

---

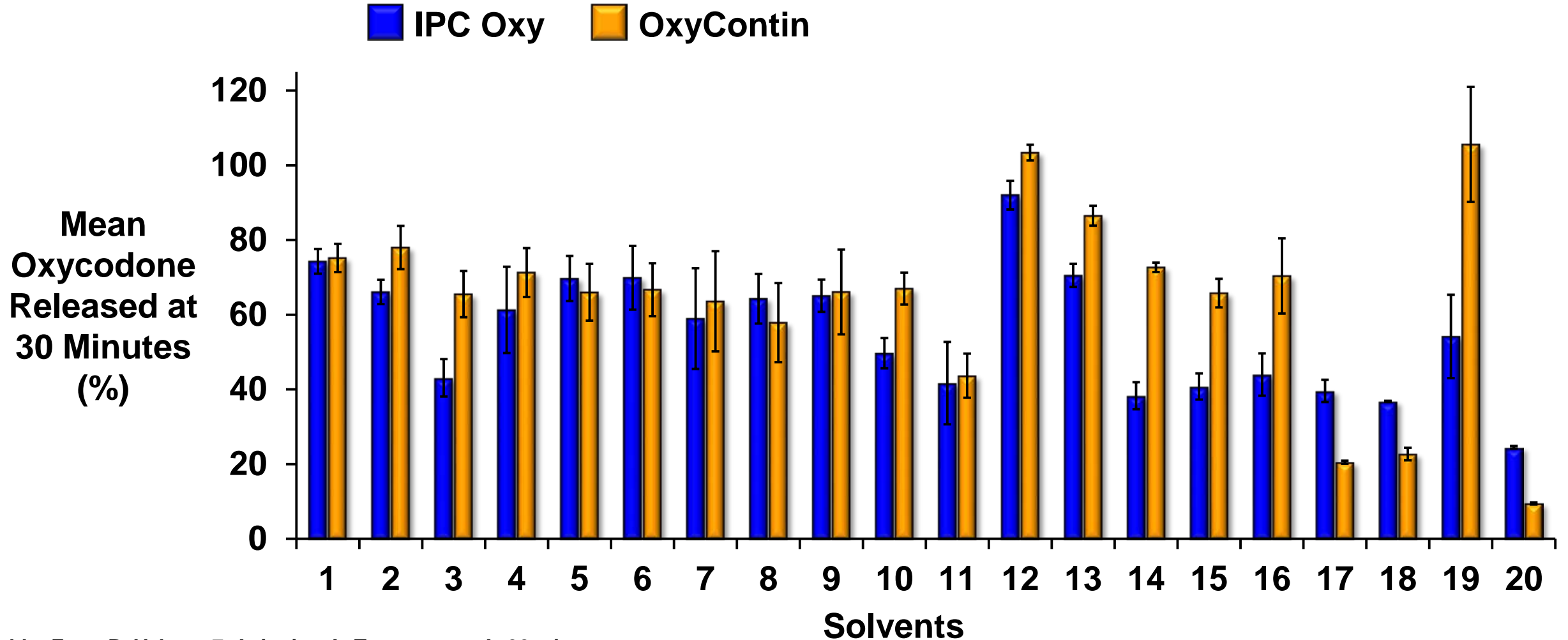
- Particle Size Reduction
- Syringeability / Injectability and Small Volume Extraction
- **Large Volume Extraction**
- Alcohol Dose Dumping
- Manipulated Tablet Dissolution
- Dye Elimination
- Simulated Smoking / Vaporization

# Large Volume Extraction Methods

---

- Evaluate extractability of oxycodone from IPC Oxy and OxyContin tablets
  - Variety of 20 household and advanced solvents
  - Range of pH and polarity; protic and aprotic
- Experiments conducted with different agitation conditions and modifications to temperature

# Large Volume Extraction Similar Between IPC Oxy and OxyContin in Tablet Form B



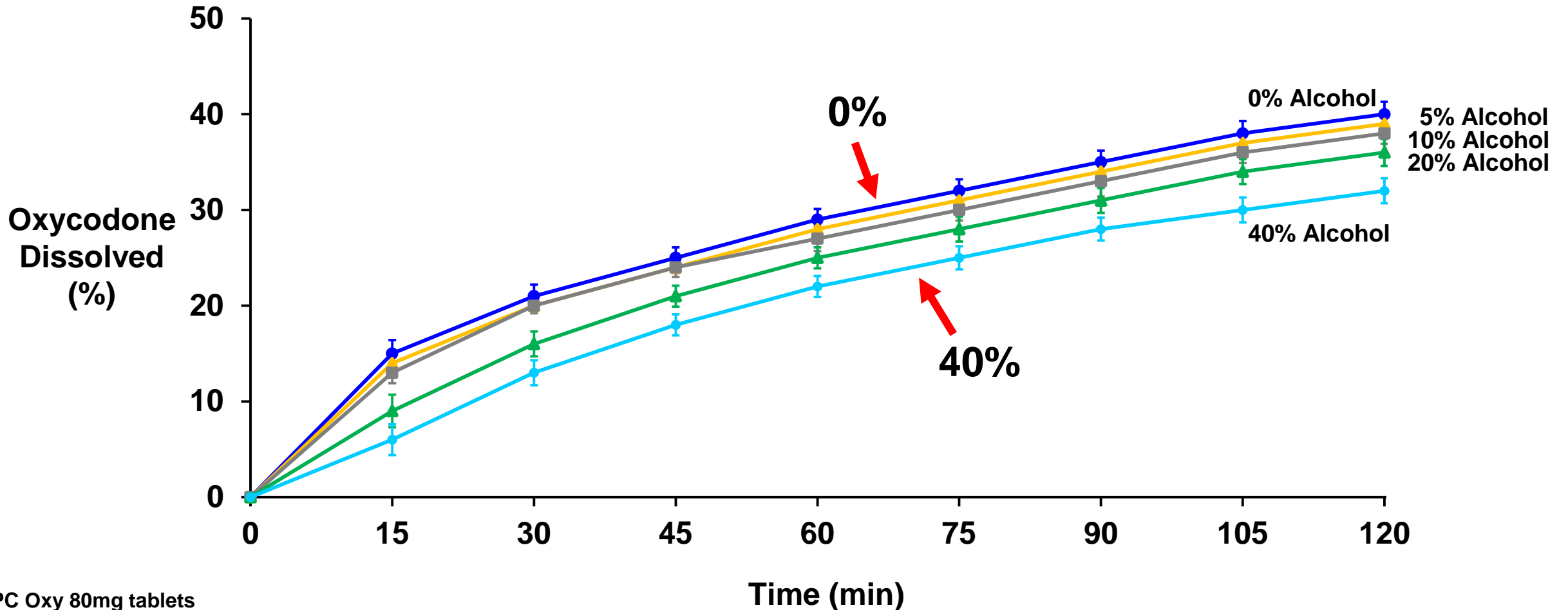
Tablet Form B, Volume 7, Agitation A, Temperature A, 30 minutes  
Error Bars = SD; Experiment performed in triplicates

# Overview of Category 1 Studies

---

- Particle Size Reduction
- Syringeability / Injectability and Small Volume Extraction
- Large Volume Extraction
- **Alcohol Dose Dumping**
- Manipulated Tablet Dissolution
- Dye Elimination
- Simulated Smoking / Vaporization

# Consumption of Alcohol with IPC Oxy Does Not Lead to Dose Dumping in Dissolution Condition A



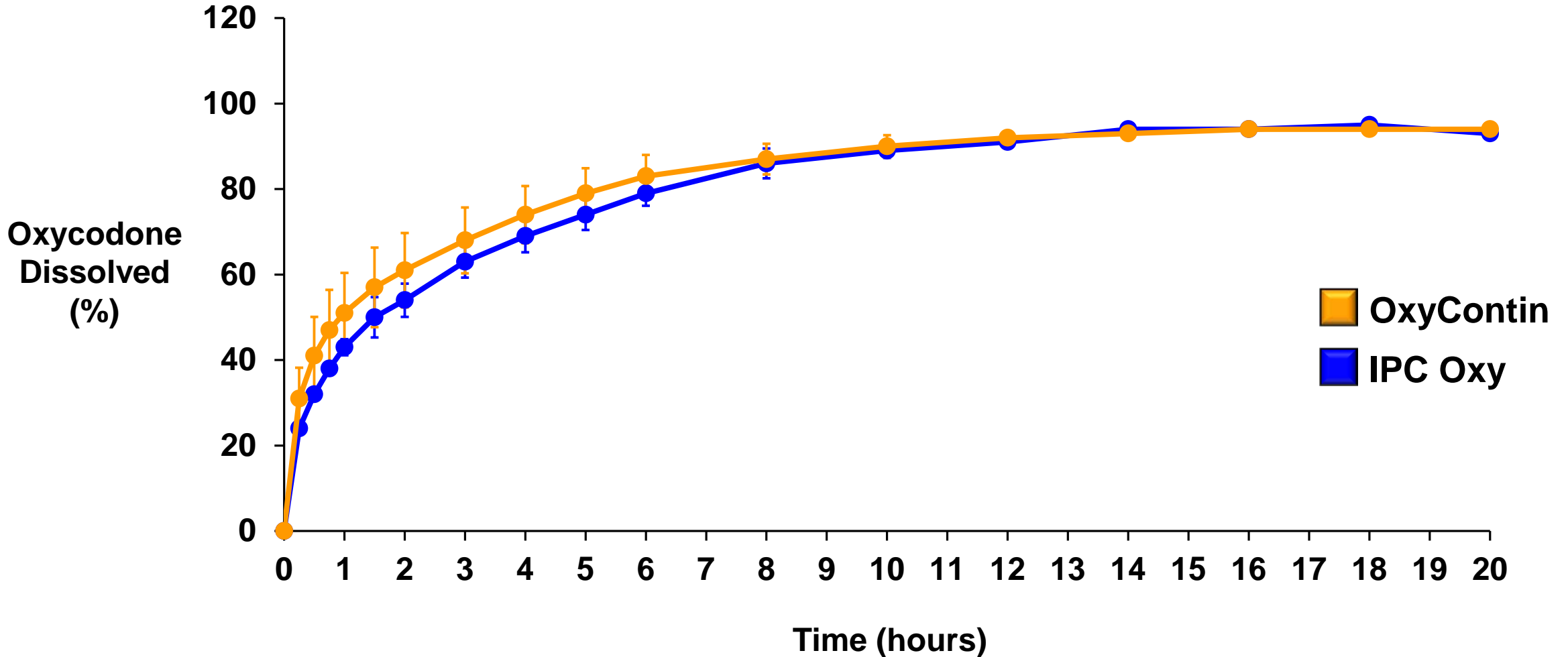
# Overview of Category 1 Studies

---

- Particle Size Reduction
- Syringeability / Injectability and Small Volume Extraction
- Large Volume Extraction
- Alcohol Dose Dumping
- **Manipulated Tablet Dissolution**
- Dye Elimination
- Simulated Smoking / Vaporization

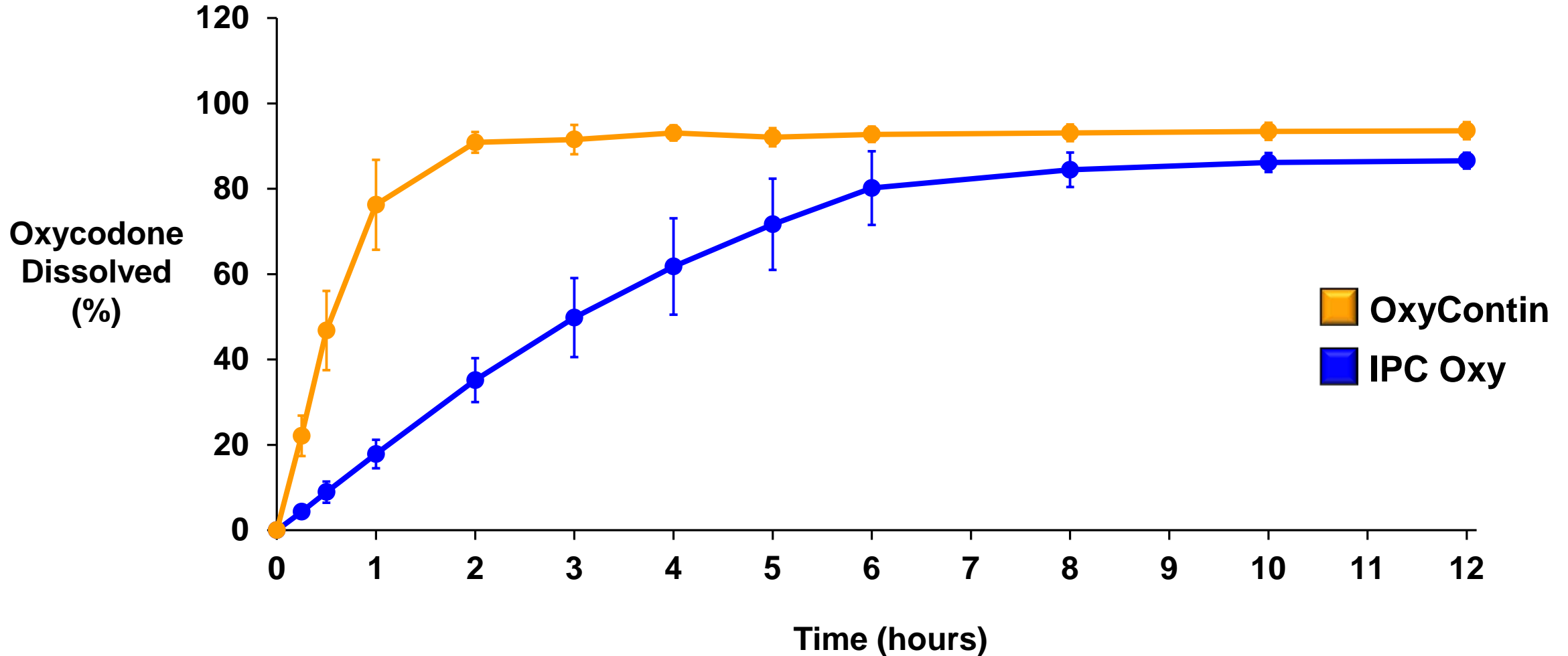


# Similar Dissolution Profile of IPC Oxy and OxyContin Under Tablet Form B in Dissolution Condition A



Tablet Form B, Pre-Treatment A, Dissolution Condition A  
Error Bars = SD; Experiment performed with 6 replicates

# Slower Oxycodone Release After Pre-Treatment G with IPC Oxy Than OxyContin



Tablet Form A, Pre-Treatment G, Dissolution Condition C  
Error Bars = SD; Experiment performed with 6 replicates

# Overview of Category 1 Studies

---

- Particle Size Reduction
- Syringeability / Injectability and Small Volume Extraction
- Large Volume Extraction
- Alcohol Dose Dumping
- Manipulated Tablet Dissolution
- **Dye Elimination**
- Simulated Smoking / Vaporization

# Single Solvent Dye Elimination Not Successful

Solvent	Initial Color	Average Oxycodone Recovery (Color)	
		Filtrate	Residue
Solvent 11	Blue	89.6% (Blue)	8.8% (Light Blue)
Solvent 13	Blue	96.7% (Blue)	0.2% (Deep Blue)
Solvent 18	Blue	97.3% (Blue)	0.6% (Deep Blue)
Solvent 23	Blue	44.8% (Blue)	43.3% (Light Blue)
Solvent 20	Blue	38.0% (Colorless)	52.3% (Deep Blue)
Solvent 24	Blue	0.0% (Colorless)	76.8% (Deep Blue)

# Overview of Category 1 Studies

---

- Particle Size Reduction
- Syringeability / Injectability and Small Volume Extraction
- Large Volume Extraction
- Alcohol Dose Dumping
- Manipulated Tablet Dissolution
- Dye Elimination
- **Simulated Smoking / Vaporization**

# Simulated Smoking Studies of IPC Oxy and OxyContin

Method	Oxycodone Vapor	
	IPC Oxy	OxyContin
Block heater (SD)	6% (0.2)	7% (0.9)
Bunsen burner (SD)	8% (1.1)	11% (0.9)

- Neither method considered efficient route of administration

# Summary of IPC Oxy Category 1 Studies

---

- Small IPC Oxy particles led to increased gelling and did not increase oxycodone extraction vs OxyContin
- Oxycodone could not be effectively separated from blue dye with single-step chemical extractions
- IPC Oxy and OxyContin similar IV abuse-deterrence under standard conditions
- IPC Oxy resists pre-treatments that defeat OxyContin
- Large volume extraction was comparable to OxyContin
- No dose dumping with alcohol

# Public Health Perspective

---

**Edward M Sellers, MD, PhD, FRCPC, FACP**

Professor Emeritus, Pharmacology, Medicine and Psychiatry,  
University of Toronto

Principal, DL Global Partners Inc.



# Combination of Strategies Key to Solving Opiate Abuse Problem

---

- All ER opiates must be ADFs
- ADFs are one way to combat tampering and abuse
- Useful strategies
  - Combining new and established ADF approaches
  - Enhancing current technologies

# Potential Public Health Benefit

---

- ADFs approved based on
  - Formulation properties
  - Pre-market studies
- No product has received “deters abuse” labeling but some public health impact seen

# Reformulated OxyContin May Serve as a Model for Public Health Impact of an ADF

---

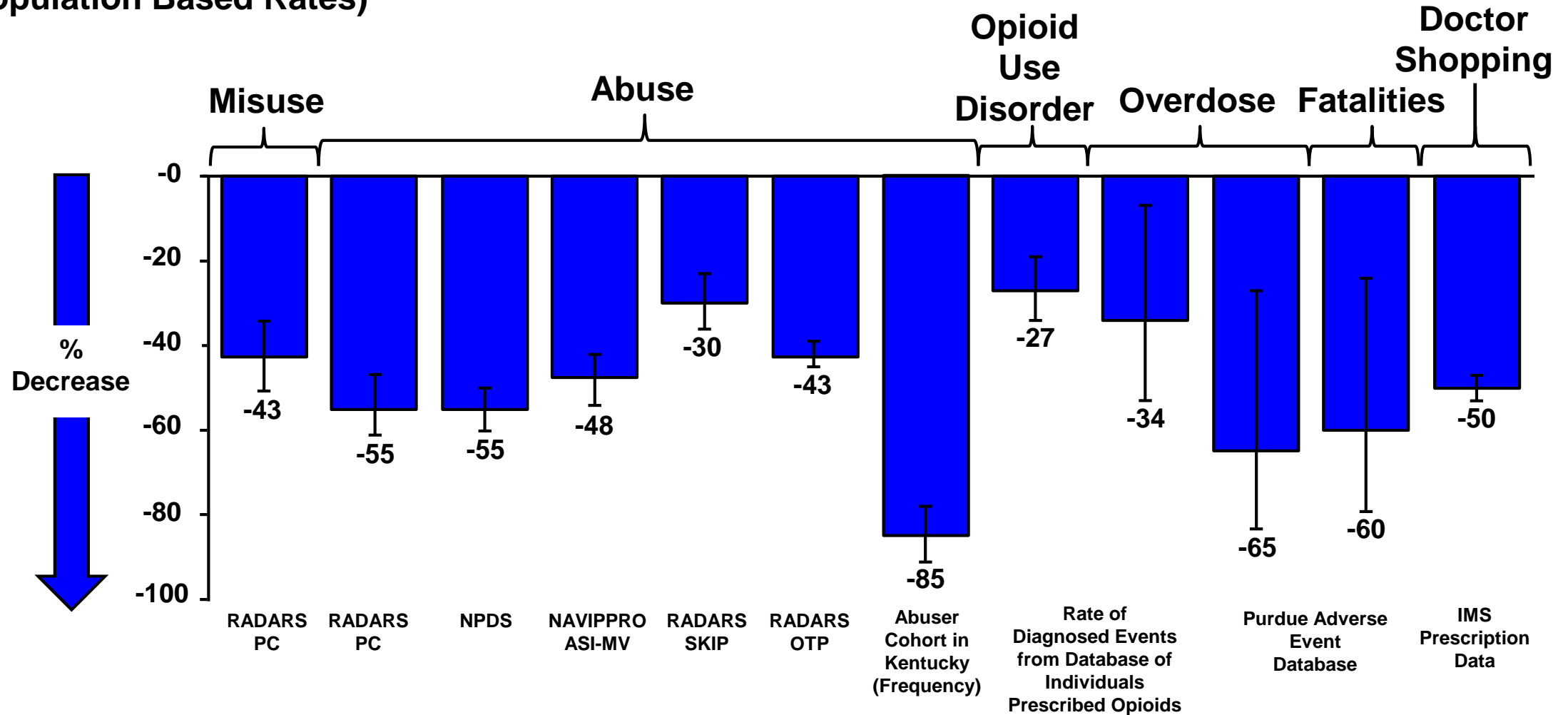
- Approved 2010 based on Category 1 studies only
- In vitro suggested ADF would impact abuse
- Category 1 studies proved predictive

# Post-Marketing Epidemiologic Studies of Reformulated OxyContin

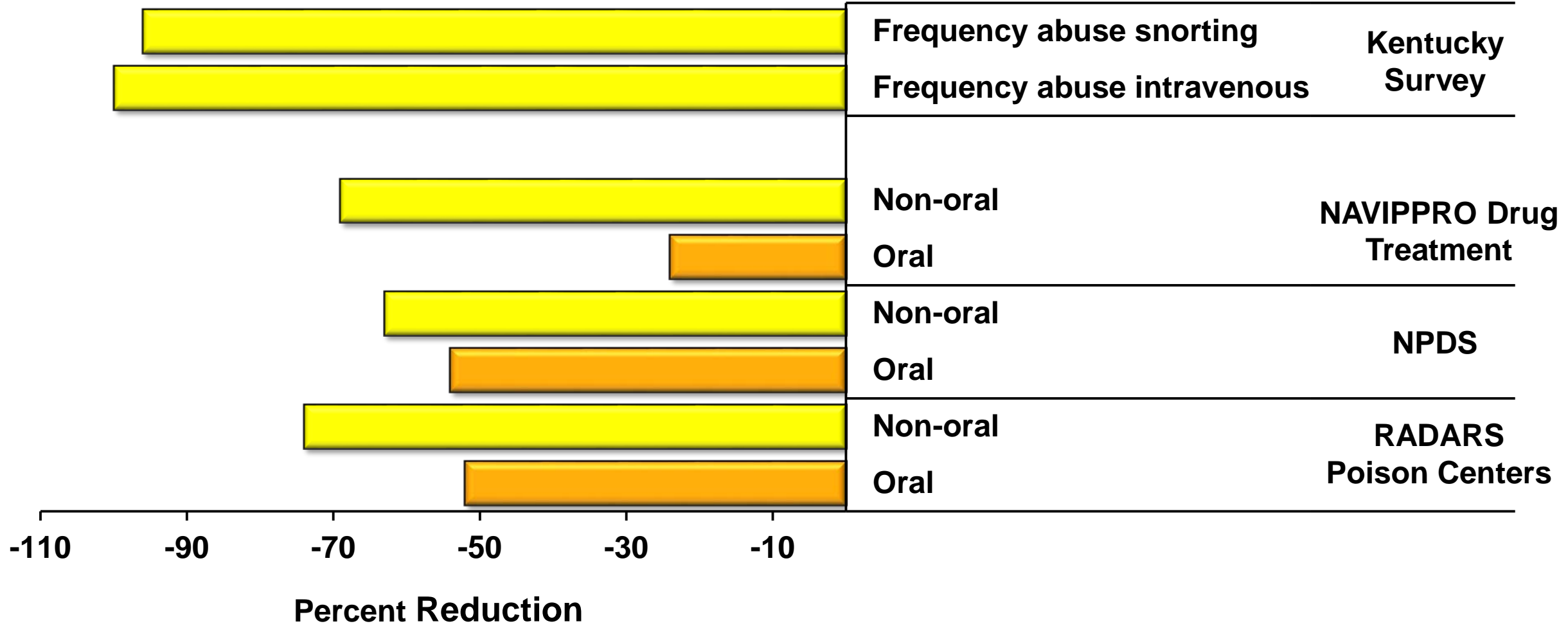
Study	Abuse	Misuse	Addiction	Overdose	Death	Diversion
National Poison Data System	✓	✓				
RADARS System Poison Center	✓	✓				
NAVIPRO ASI-MV	✓					
RADARS Drug Treatment: OTP and SKIP	✓					
Abuser Cohort in Kentucky	✓					
Retrospective Cohort in MarketScan Claims Database	✓		✓	✓		
Fatalities reported to pharmacovigilance system				✓	✓	
RADARS: Drug Diversion/ Street Diversion						✓
Doctor / Pharmacy-Shopping Patients						✓
Drug Utilization Study	Contextual					

# Significant Reductions in Measures of OxyContin Abuse

(Population Based Rates)



# Greater Impact of OxyContin ADF on Non-Oral Abuse



# IPC Oxy has Features Expected to Discourage Abuse

---

- Modest resistance to crushing
- Intravenous abuse
  - Produces a very viscous gel on contact with water
  - Impossible to syringe and inject using typical tactics
  - Not defeated by typical website “recipes”
- Intranasal abuse – crushed product
  - Particle size not the only deterrent
  - IPC Oxy gel limits absorption, causing leakage and drug loss
  - Nasal irritation from sodium lauryl sulfate
- Blue dye may deter oral and intranasal abuse

# Summary

---

- Multiple ADF features desirable in one product
- IPC Oxy shown increased gelling properties
- Post-market data for OxyContin ER consistent with Category 1 data
- IPC Oxy demonstrated IV abuse deterrence and may also deter other types of abuse



# Oxycodone Extended-Release Tablets (IPC Oxy)

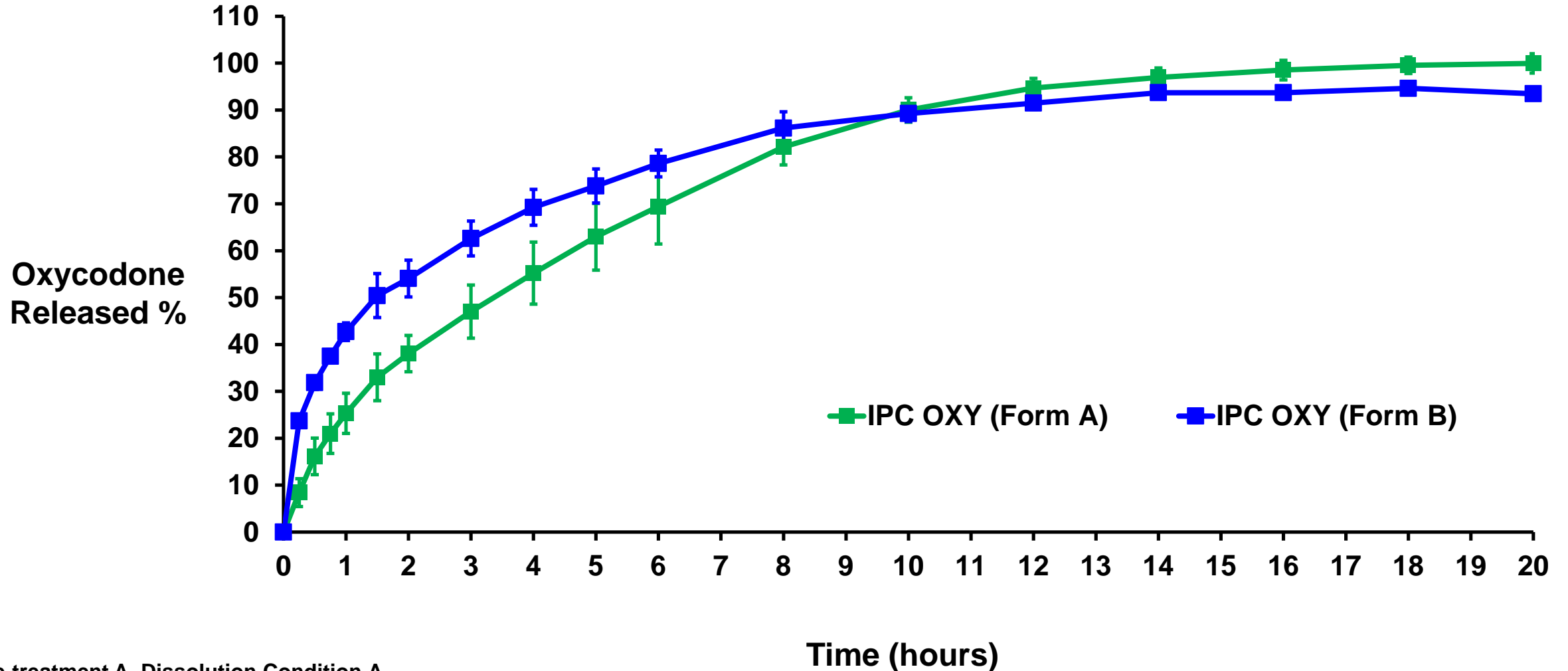
---

**July 26, 2017**

**Intellipharmaceuticals Corp.**

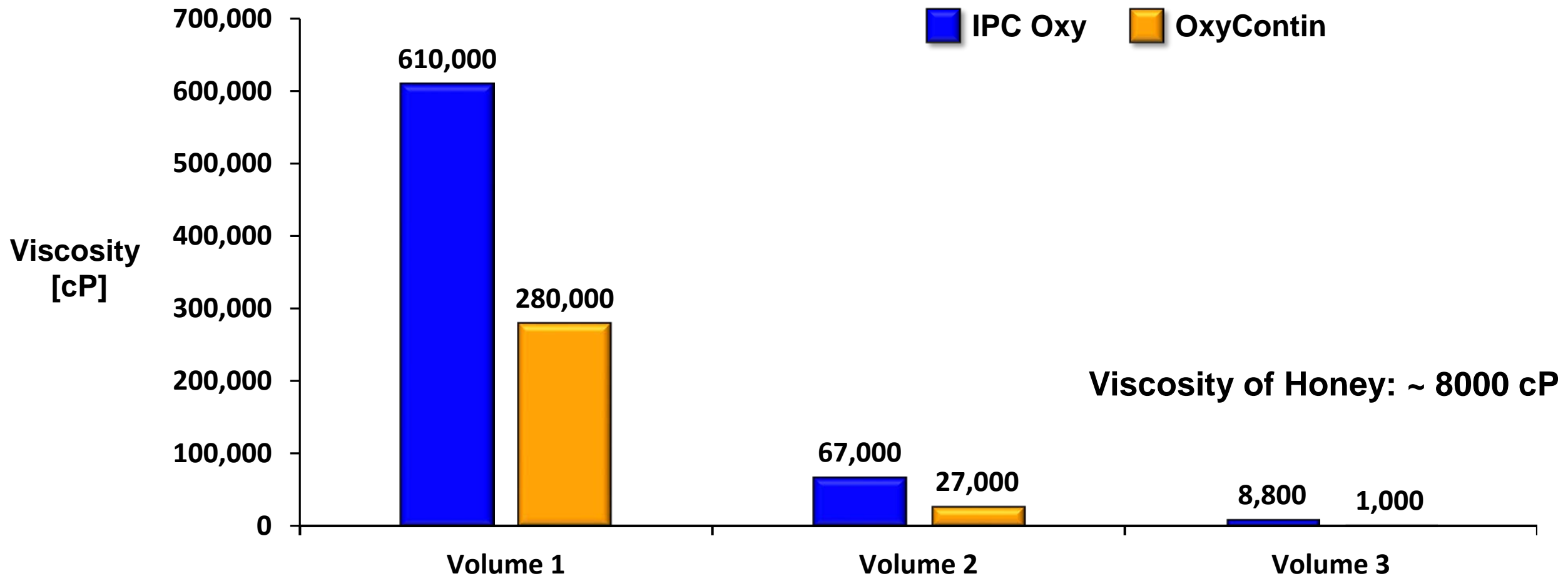
Joint Meeting of the Anesthetic & Analgesic Drug Products Advisory  
Committee & Drug Safety & Risk Management Advisory Committee

# In-vitro Drug Release of IPC Oxy Tablet Form A and Tablet Form B –Dissolution Condition A



Pre-treatment A, Dissolution Condition A  
Error Bars = SD; Experiment performed with 6 replicates

# Viscosity is Higher with IPC Oxy than OxyContin in Tablet Form B, Pre-treatment A, Volume 1, 2 and 3



# Viscosity is Higher with IPC Oxy Than Household Products in Tablet Form B, Pre-treatment D, Volume 1

---

