Oxycodone Extended-Release Tablets (IPC Oxy)

July 26, 2017

Intellipharmaceutics 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
Intellipharmaceutics 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 ≥ 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	✓	

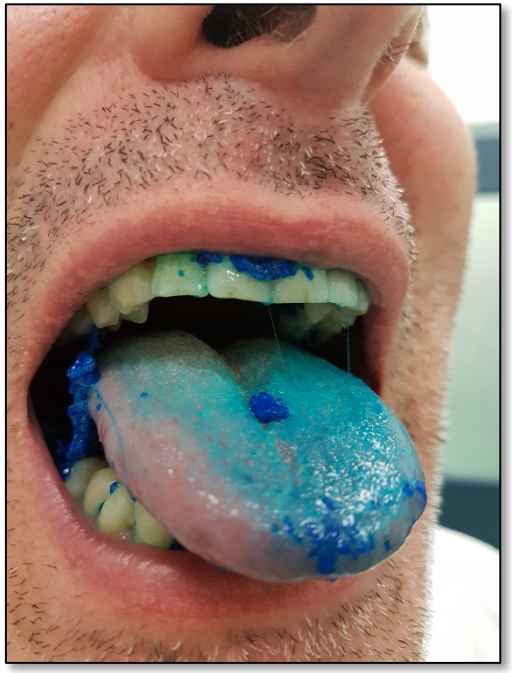
Results of Pre-Treatment with Internet Recipe Commonly Used to Defeat OxyContin

Tablet Form B, Pre-Treatment D, Volume 2, Solvent 1, Temperature A

Video will be available to the public on Intellipharmaceutics website and YouTube

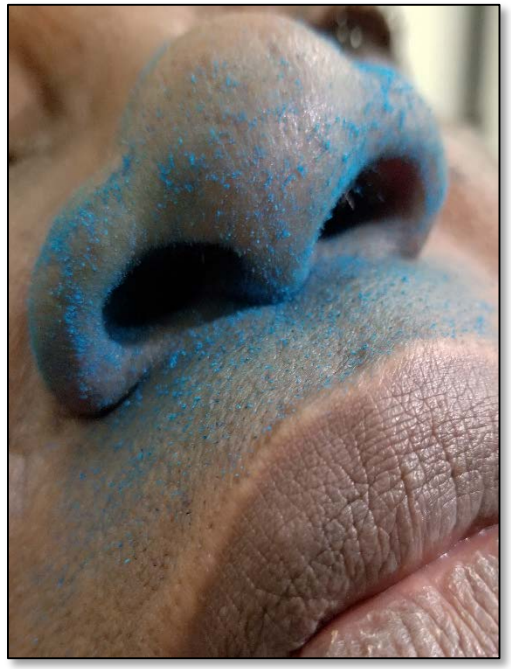
Staining Blue Dye: Innovative Feature of IPC Oxy

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[1,2]
- 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
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[1]	59	2
Prescriptions written	750,000	24,000,000
Rate per 100,000 prescriptions	7.9	< 0.01

1. FDA. Presentation on March 16-17, 2017. www.fda.gov

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

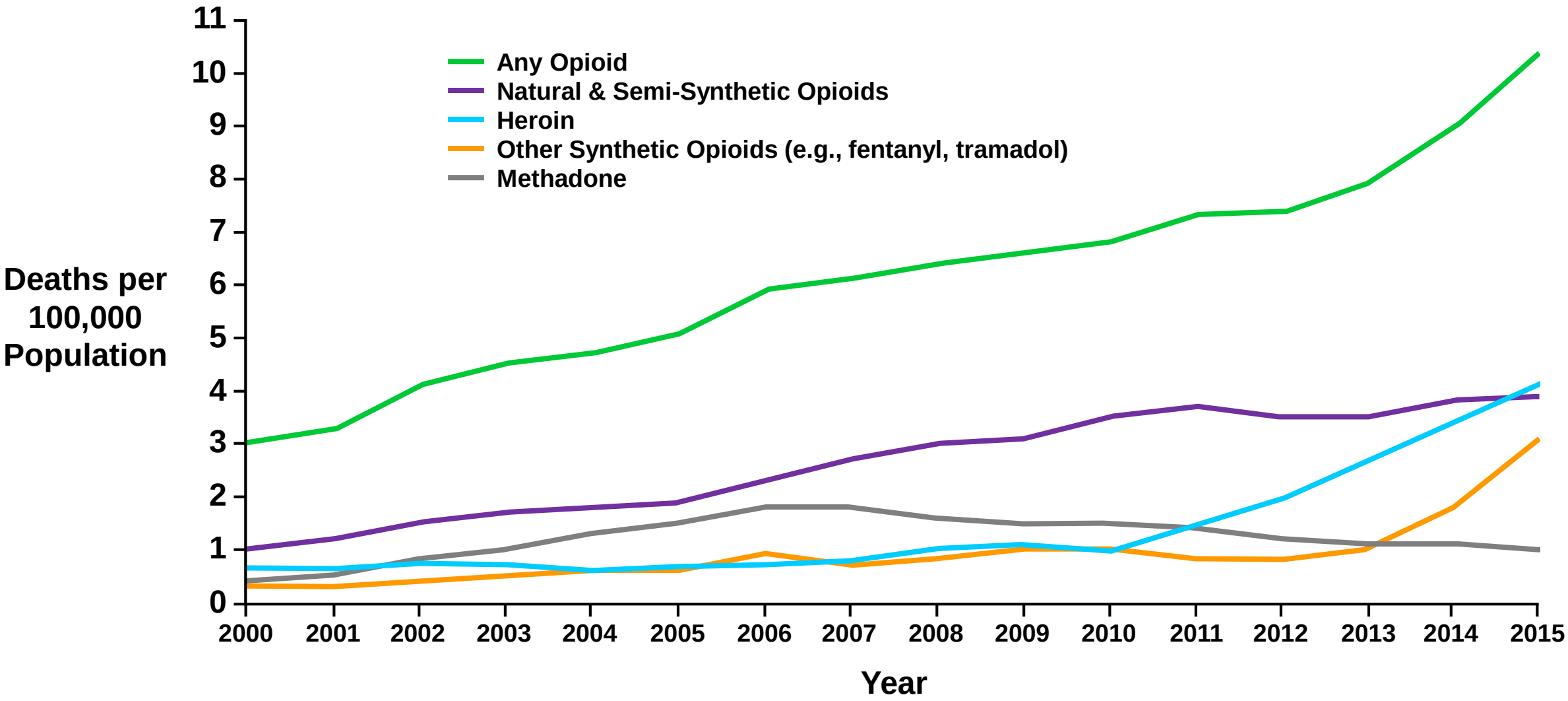
Richard C Dart, MD, PhD

Director, Rocky Mountain Poison & Drug Center

Professor of Emergency Medicine, University of Colorado School of Medicine

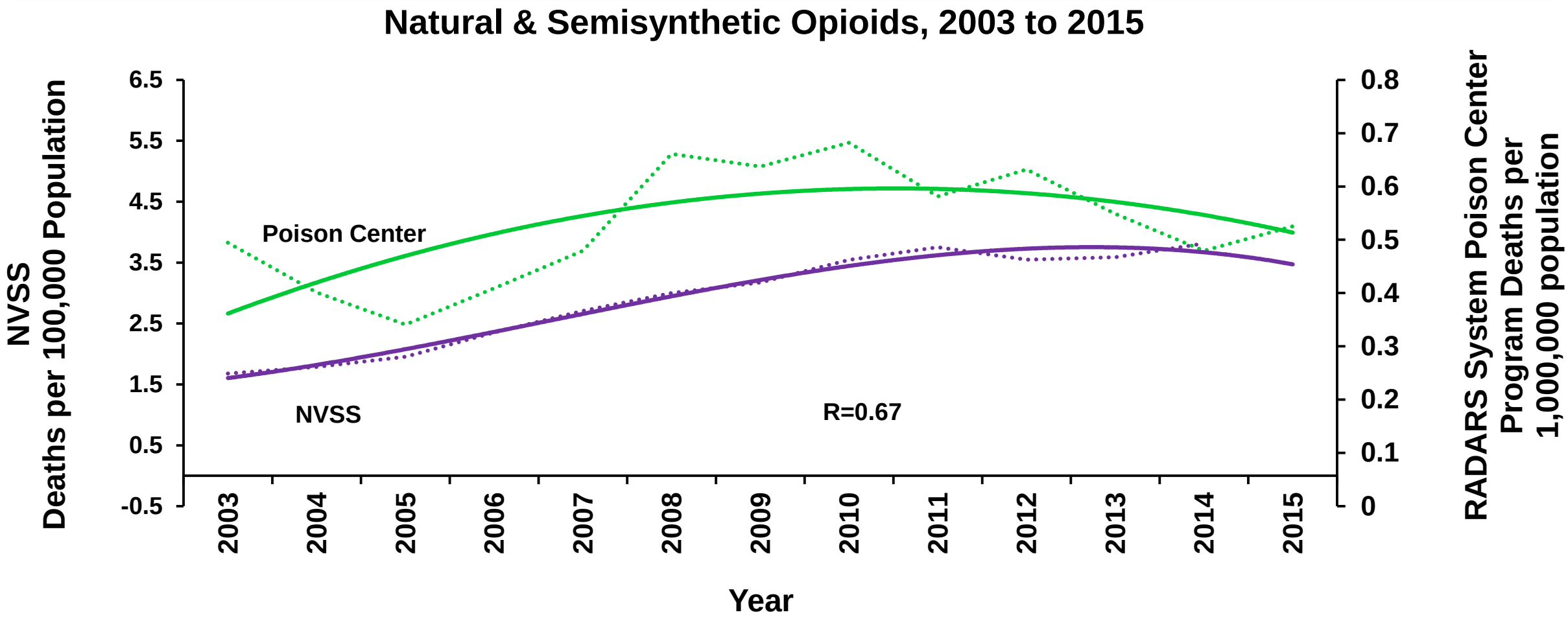
Executive Director, RADARS® System

Deaths from Prescription Opioids Remain at Historic High



CDC; 2016. https://wonder.cdc.gov

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



**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

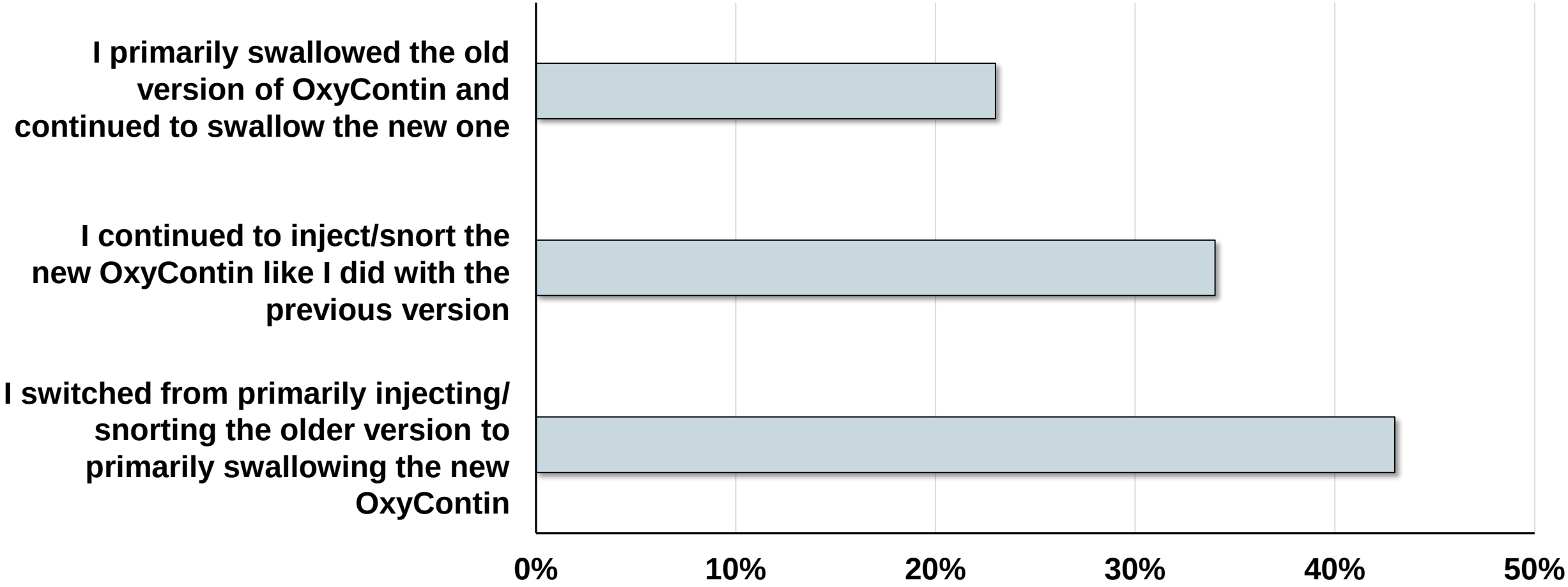
IV Route Increases Risk of Serious Health Consequences

- 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[1]
- Other health risks of injection
  - Hepatitis C[2]
  - Endocarditis[3,4]
  - Blood clots[5]

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

RADARS = Researched Abuse, Diversion and Addiction-Related Surveillance

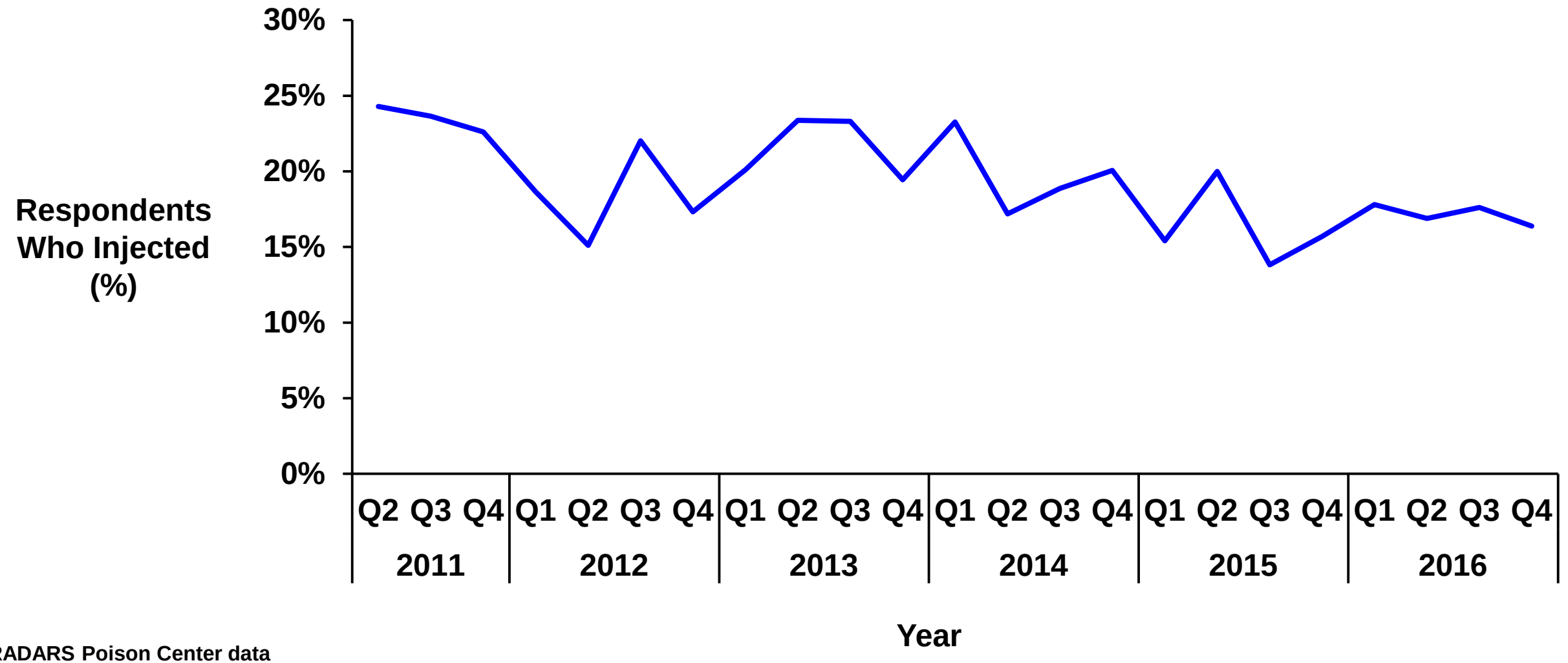
RAPID Data Show Some OxyContin Abusers Continued to Snort or Inject After Reformulation



Cicero & Ellis. *JAMA Psychiatry* 2015;72:424-30

RAPID = Researchers and Participants Interacting Directly; SKIP = Survey of Key Informants' Patients

Non-Oral Abuse Persists Despite OxyContin Reformulation



RADARS Poison Center data

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

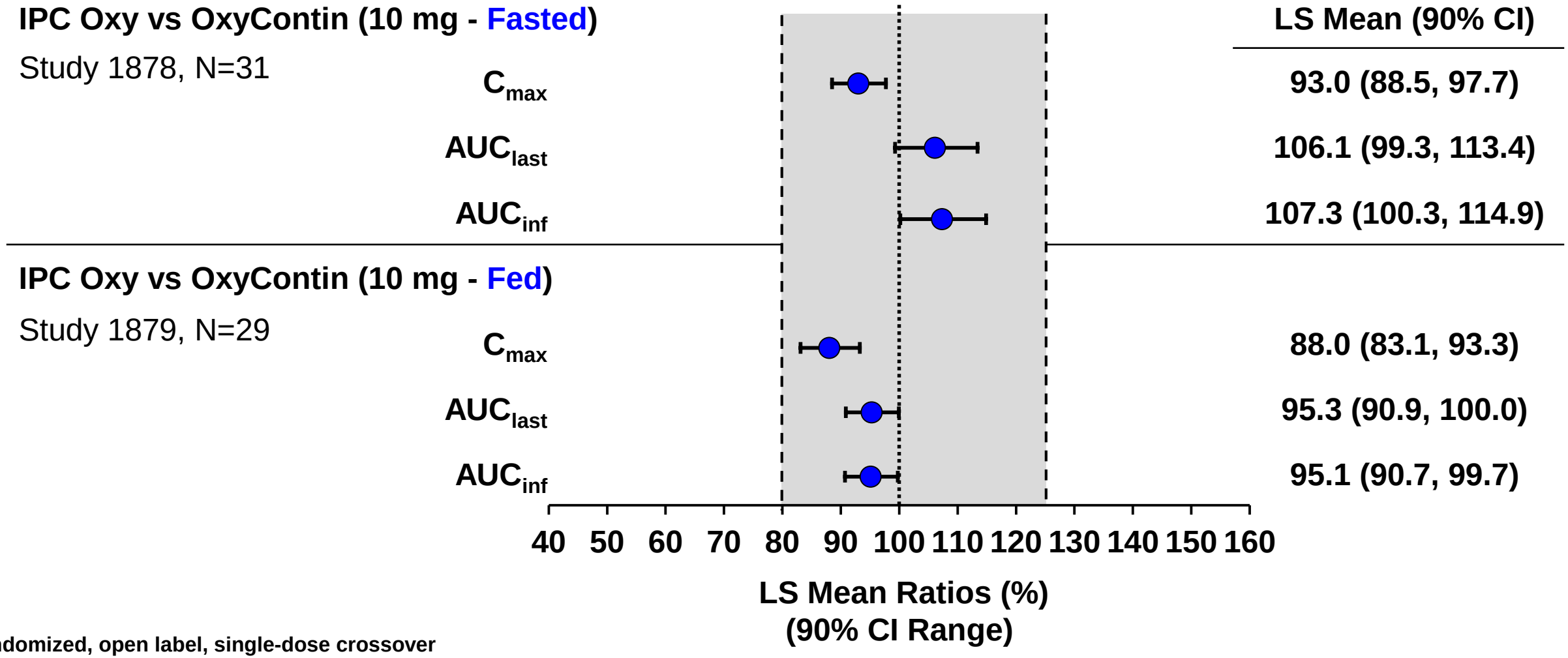
VP of Medical and Scientific Affairs for INC Research Early Phase

Adjunct Professor, Department of Pharmacology & Toxicology, University of Toronto

Clinical Pharmacology Overview

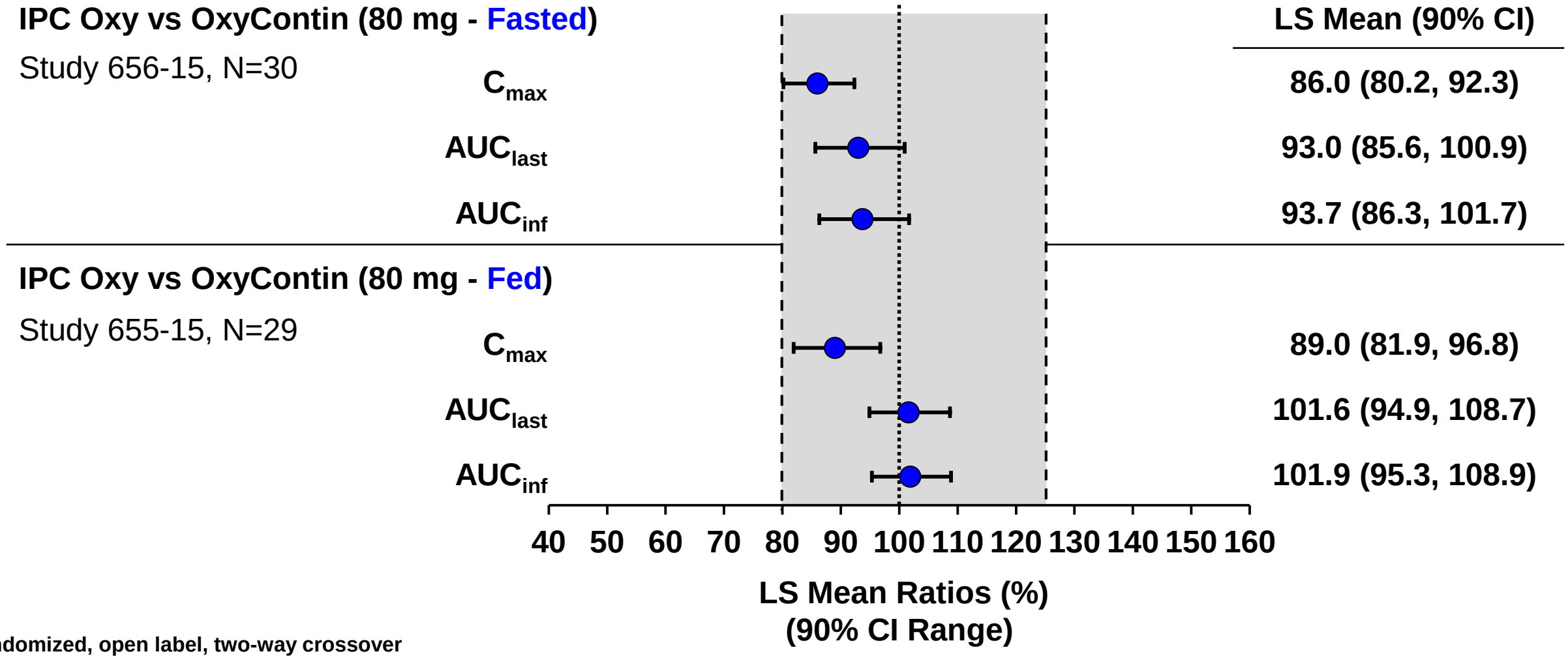
- Bioequivalence
- Dose proportionality
- Food effect

Demonstrated Bioequivalence to OxyContin (10 mg)



Randomized, open label, single-dose crossover

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

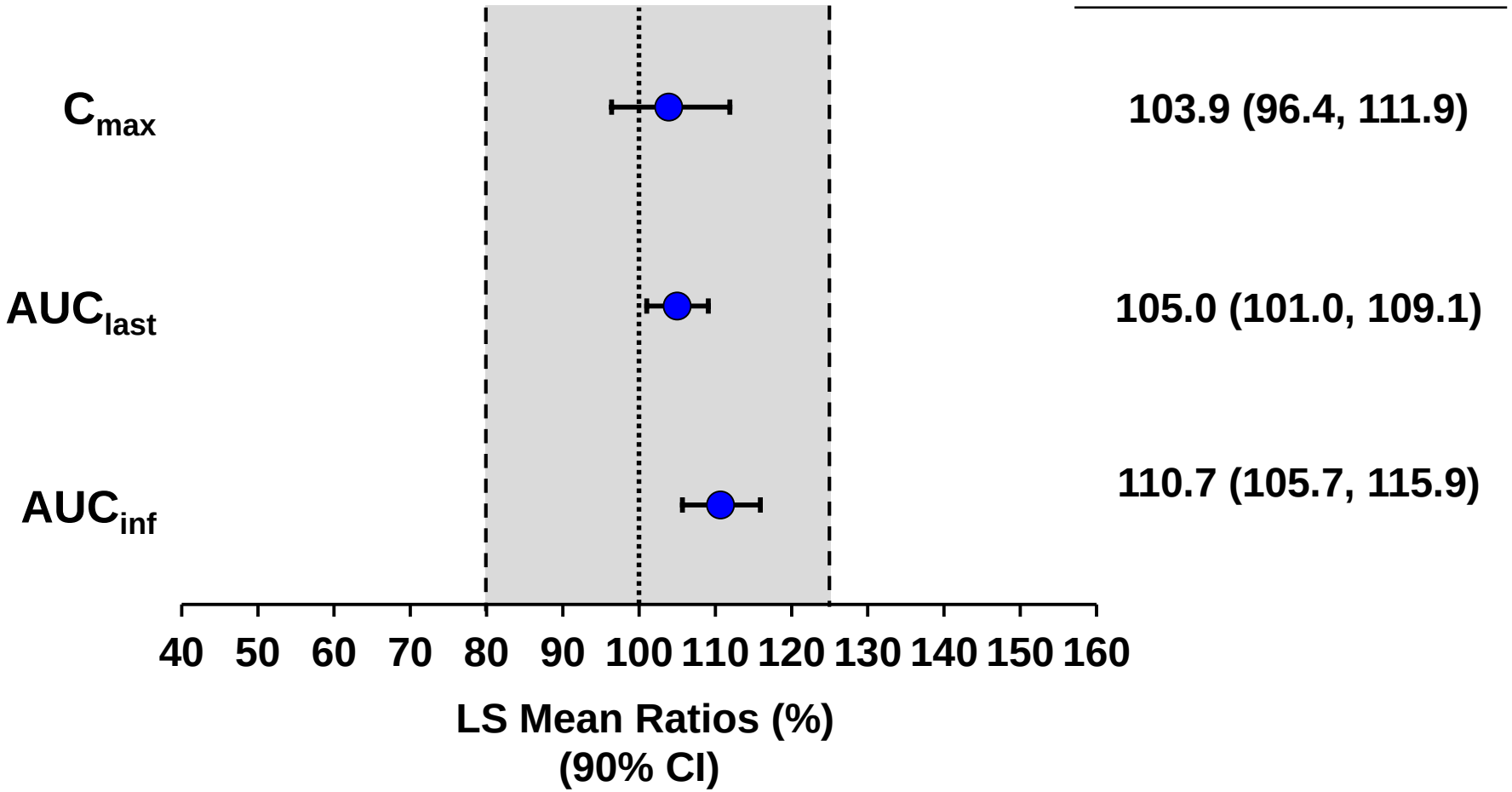


Randomized, open label, two-way crossover

Multiple Dose Study (80 mg)

IPC Oxy vs OxyContin (80 mg - Steady State)

Study 80-184, N=24



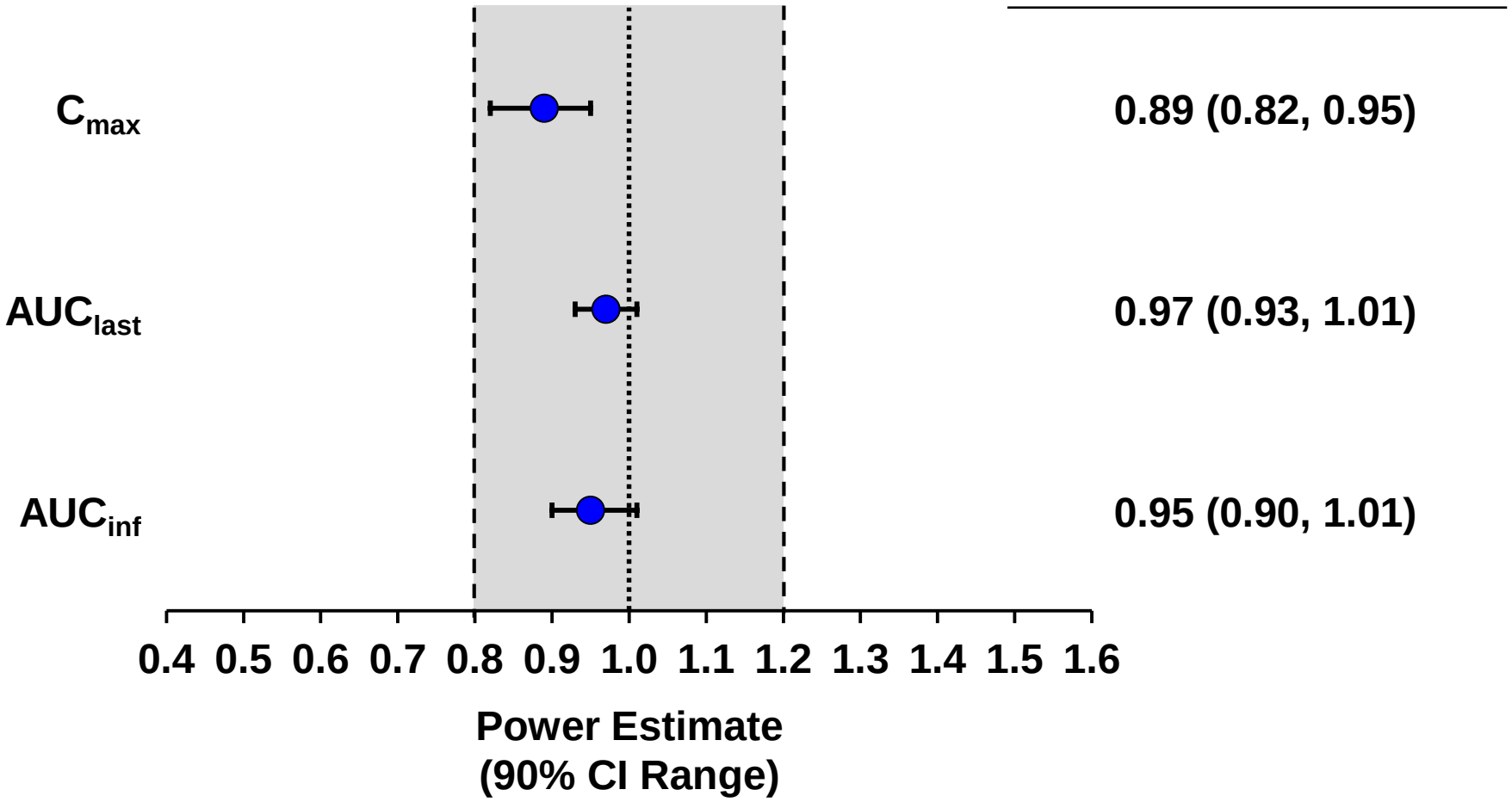
Dose Proportionality Design (Study 80-185)

- 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

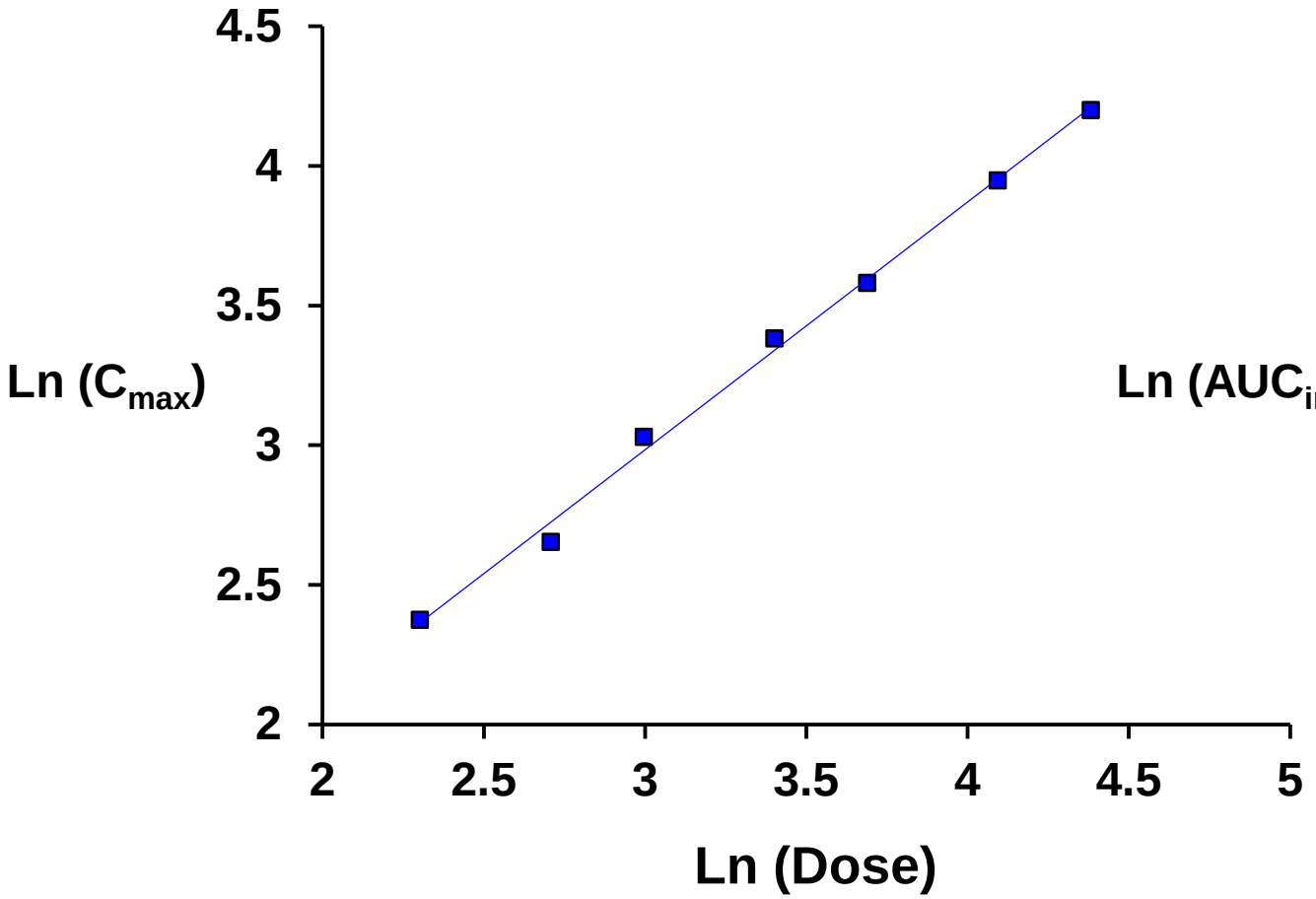
Dose Proportional Between All 7 Doses

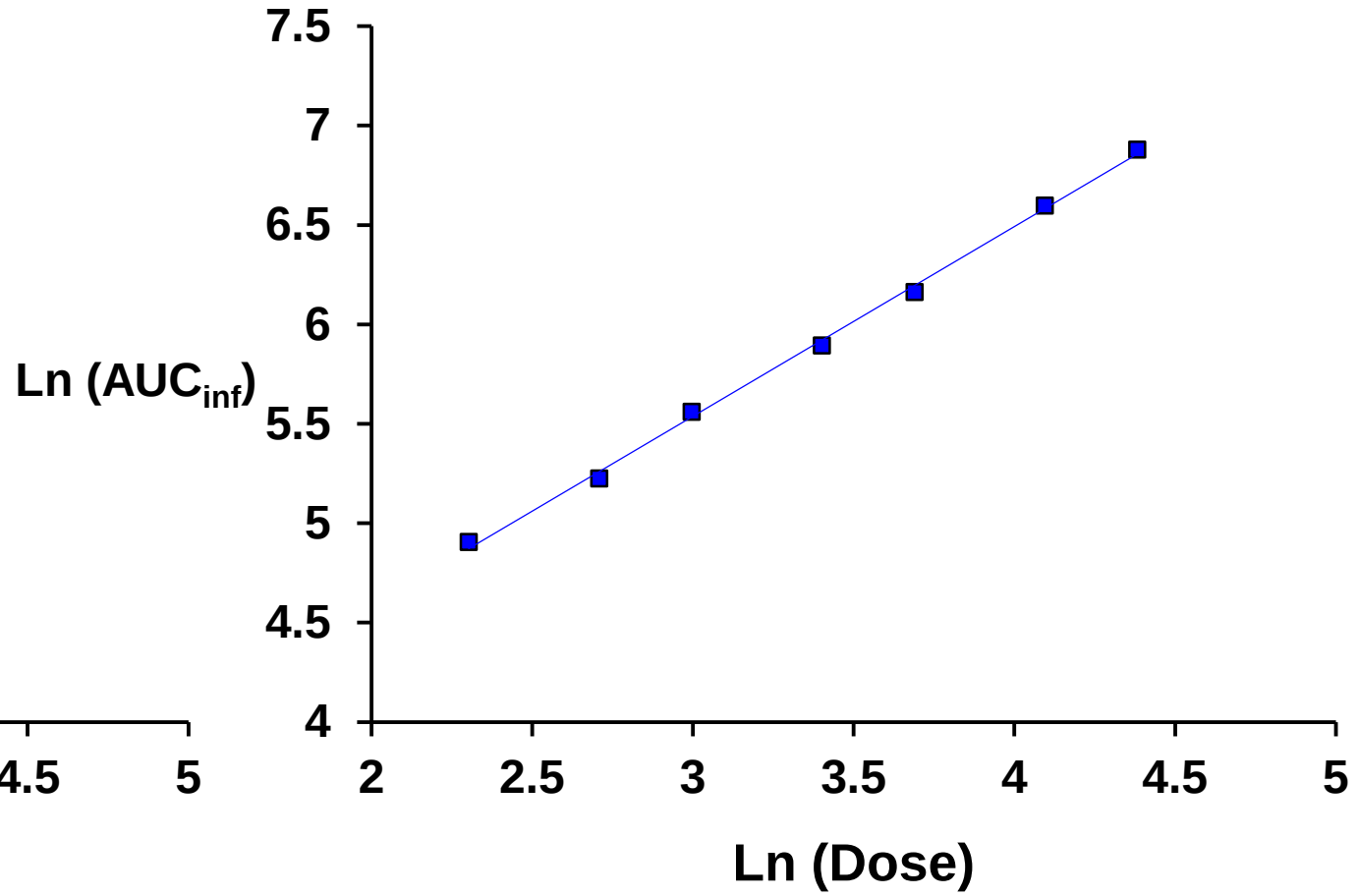
Dose Proportionality of IPC Oxy

Study 80-185, N=22



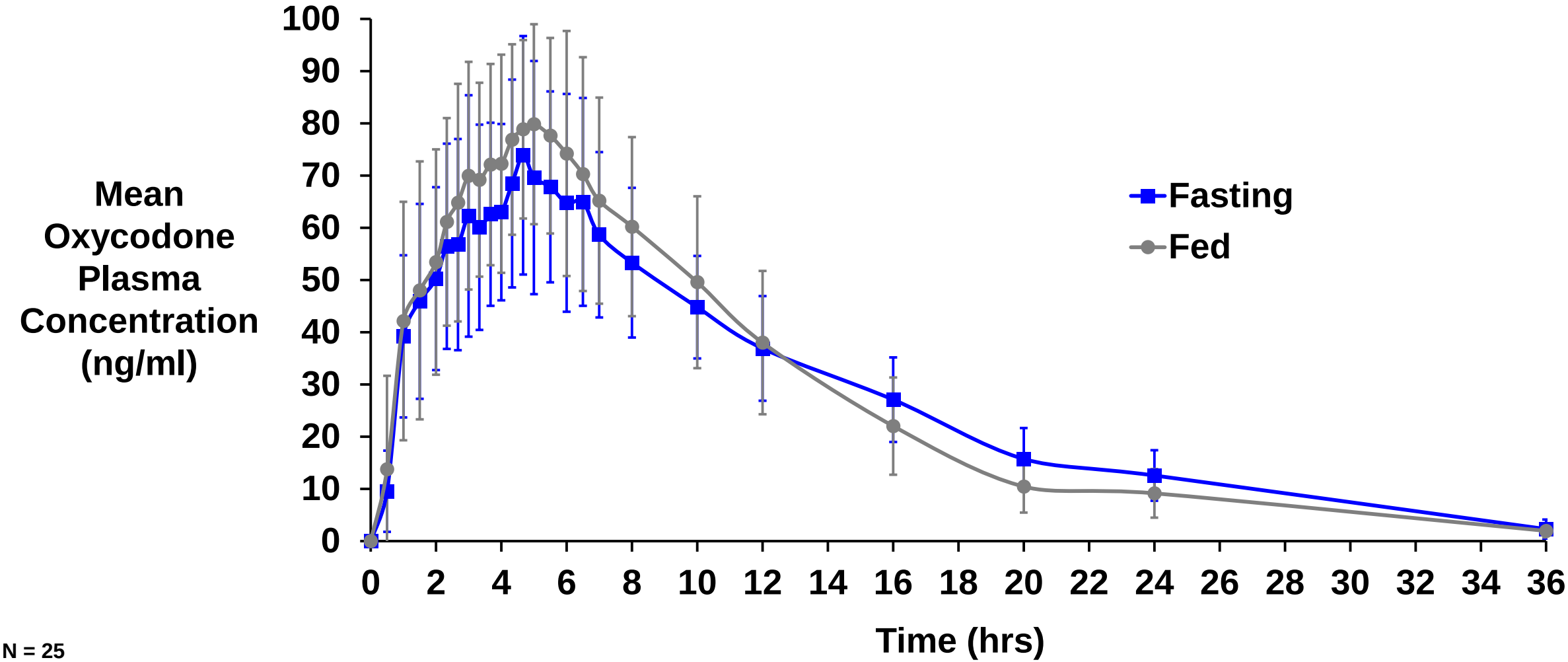
Least Square Means (Study 80-185)





N = 22

No Clinically Significant Food Effect (Study 80-186)

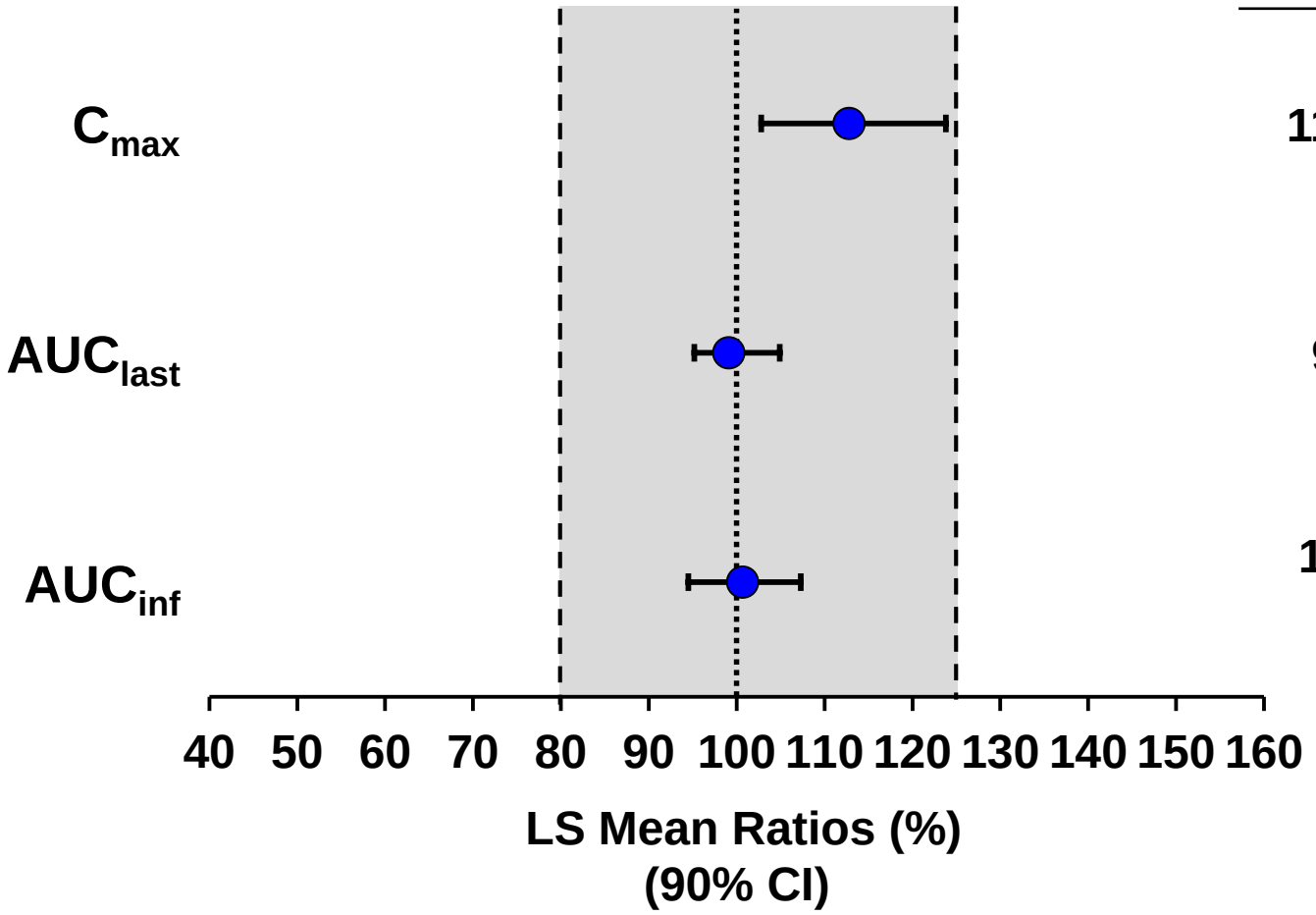


N = 25
Error bars = SD

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

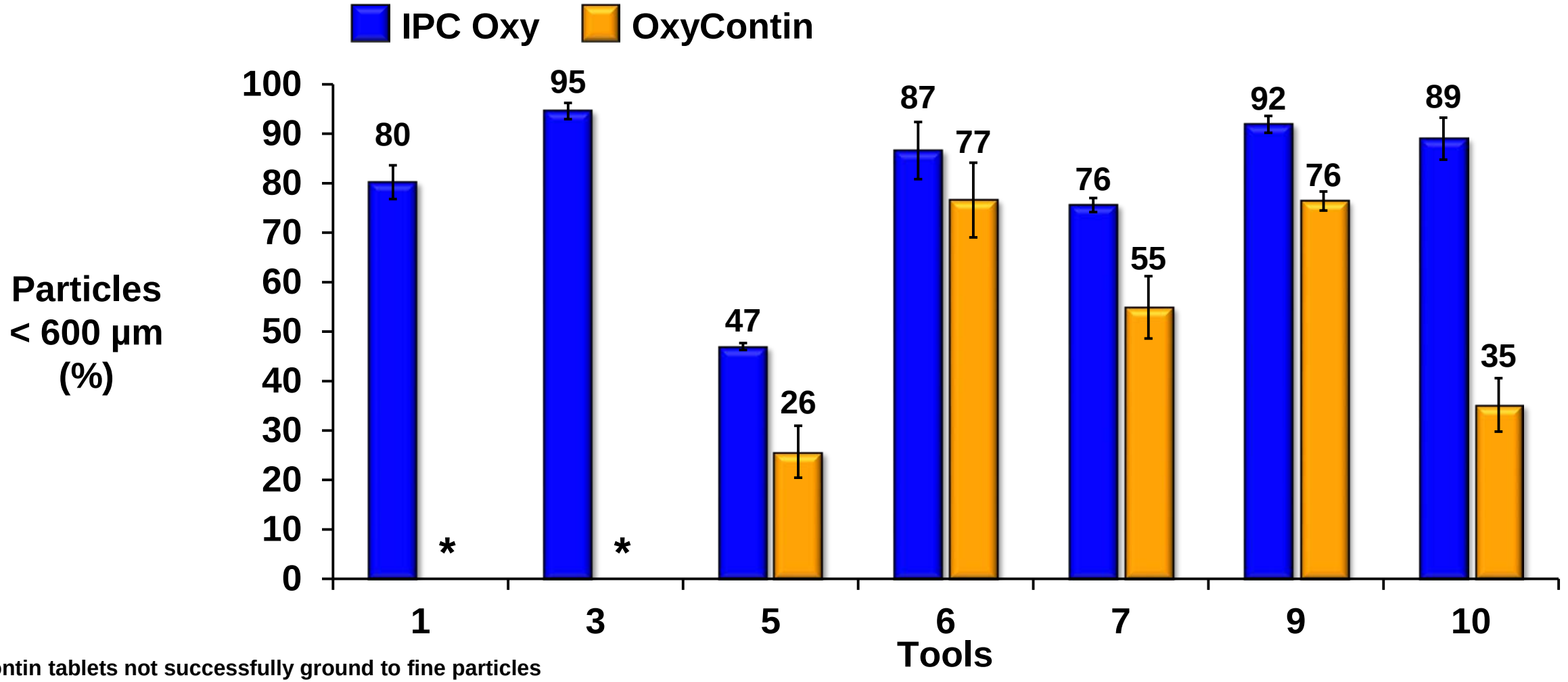
- Particle Size Reduction
- Syringeability / Injectability and Small Volume Extraction
- Large Volume Extraction
- Alcohol Dose Dumping
- Manipulated Tablet Dissolution
- Dye Elimination
- Simulated Smoking / Vaporization

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

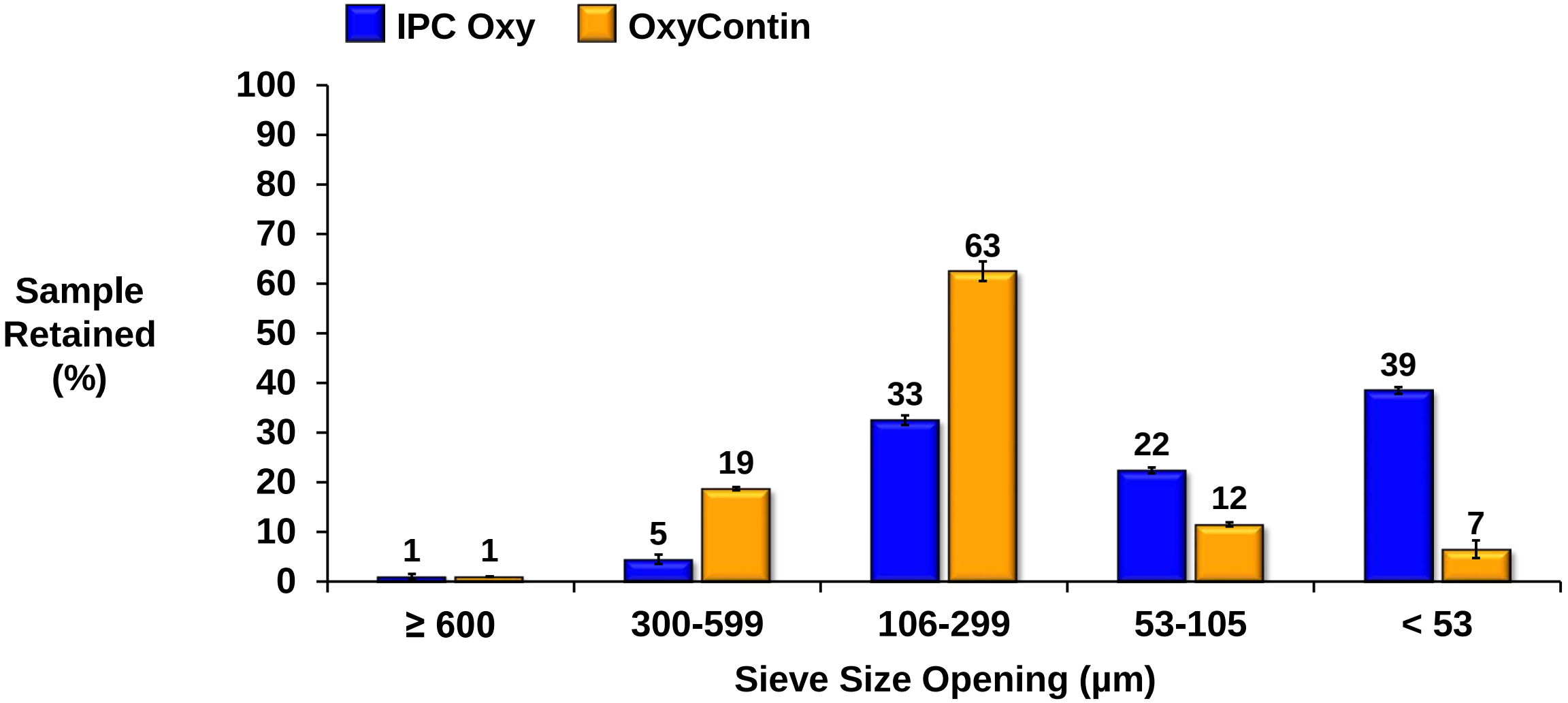
API = active pharmaceutical ingredient

IPC Oxy Yielded More Particles < 600 µm 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



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

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

Picture from bluelight.org

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

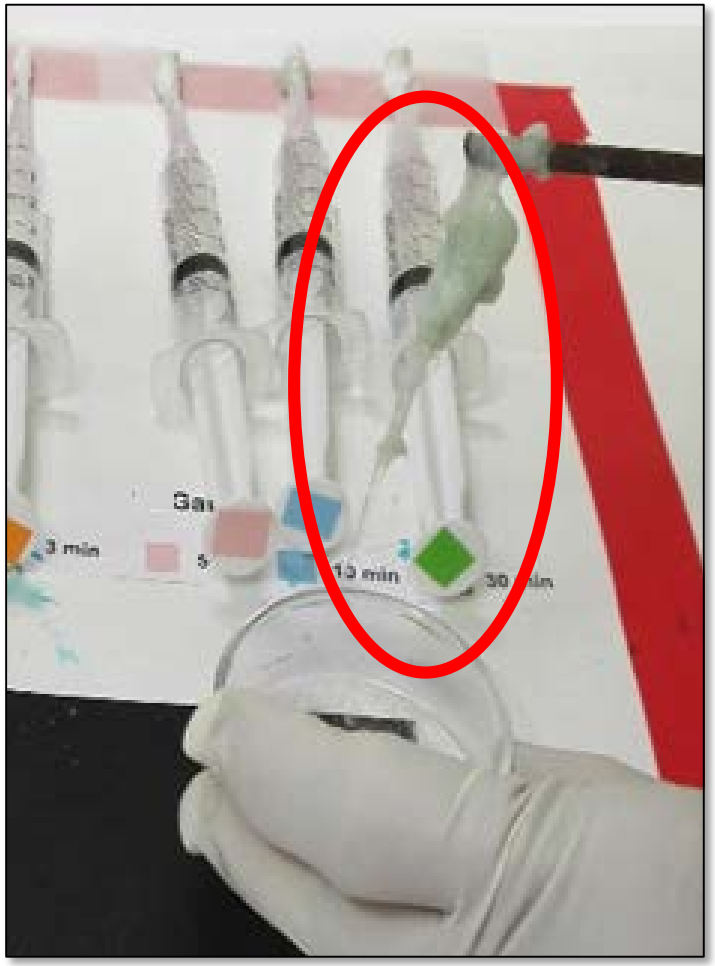
Standard Syringeability / Injectability Studies Conducted to Simulate Common Abuser Practices

- 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 (≥ 20%)
  - Supports IPC Oxy and OxyContin IV abuse-deterrent properties

Pictures of Abuse-Deterrence with Standard Methods

IPC Oxy

OxyContin

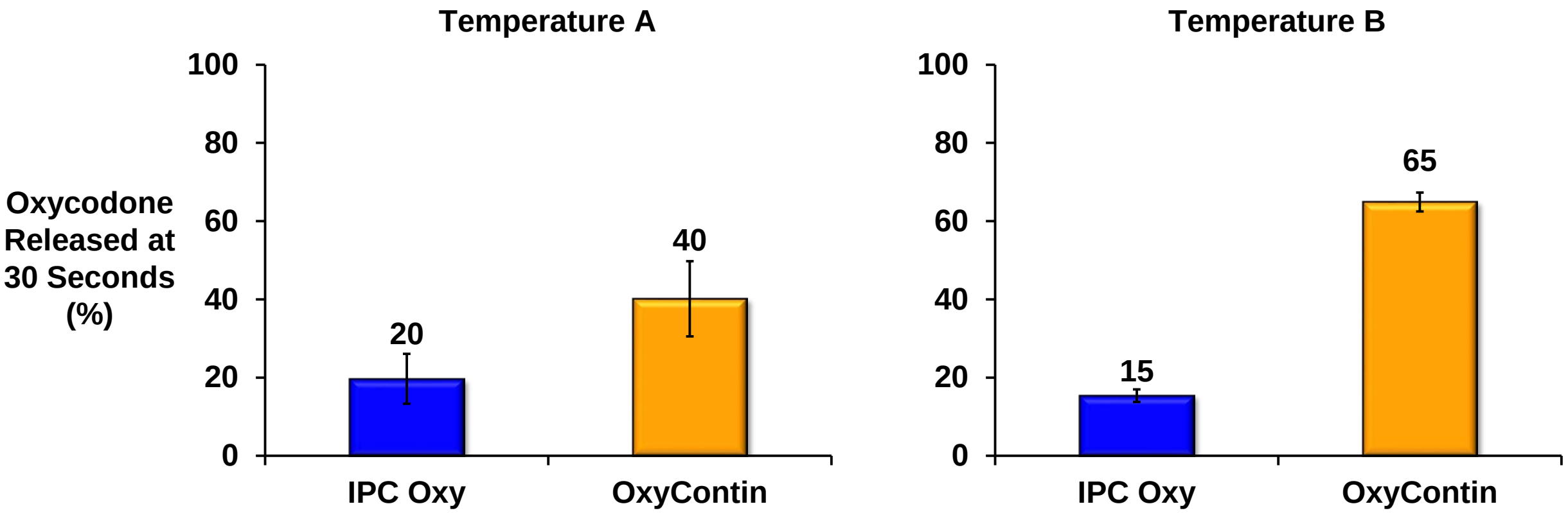


Tablet Form B, Pre-Treatment A, Volume 1, Solvent 1, Agitation A, Temperature A, 30 Minutes

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

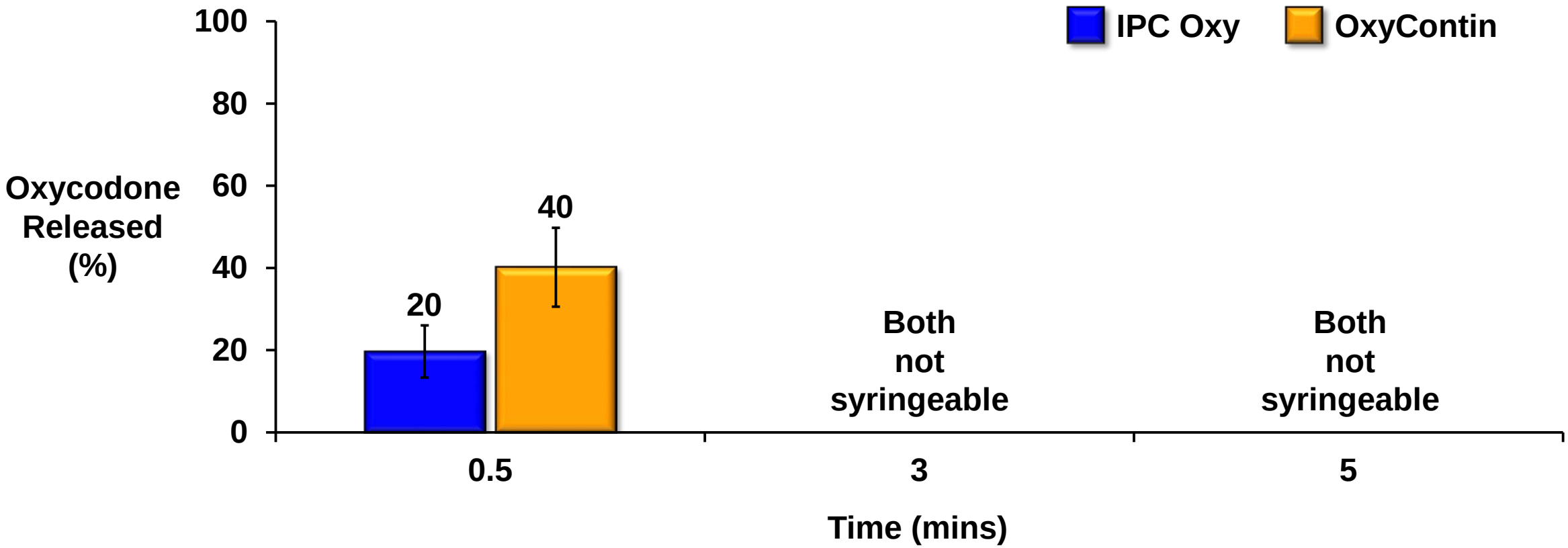
- Drug abuse websites offer instructions for how to defeat gelling properties of ADFs
- Most typical manipulation involves Pre-treatment D
- Studies for IPC Oxy and OxyContin evaluated:
  - Pre-treatment D
  - Tablet Form B
  - Volumes 1, 2 or 3
  - Solvent 1
  - Agitation A
  - Temperature A or B

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



Tablet Form B, Pre-Treatment D, Volume 1, Solvent 1, Agitation A, Needle Gauge A, 30 seconds
Error Bars = SD; Experiment performed in triplicates

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

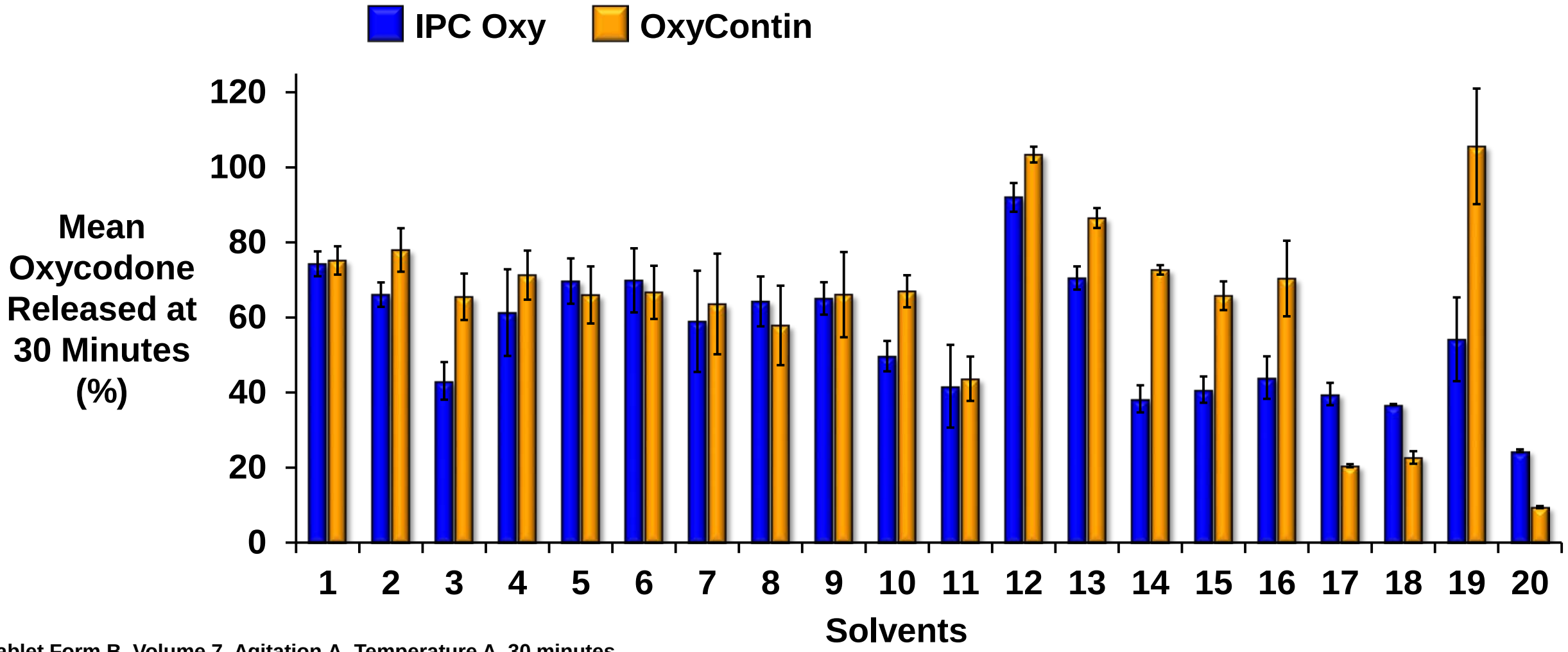
Overview of Category 1 Studies

- 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

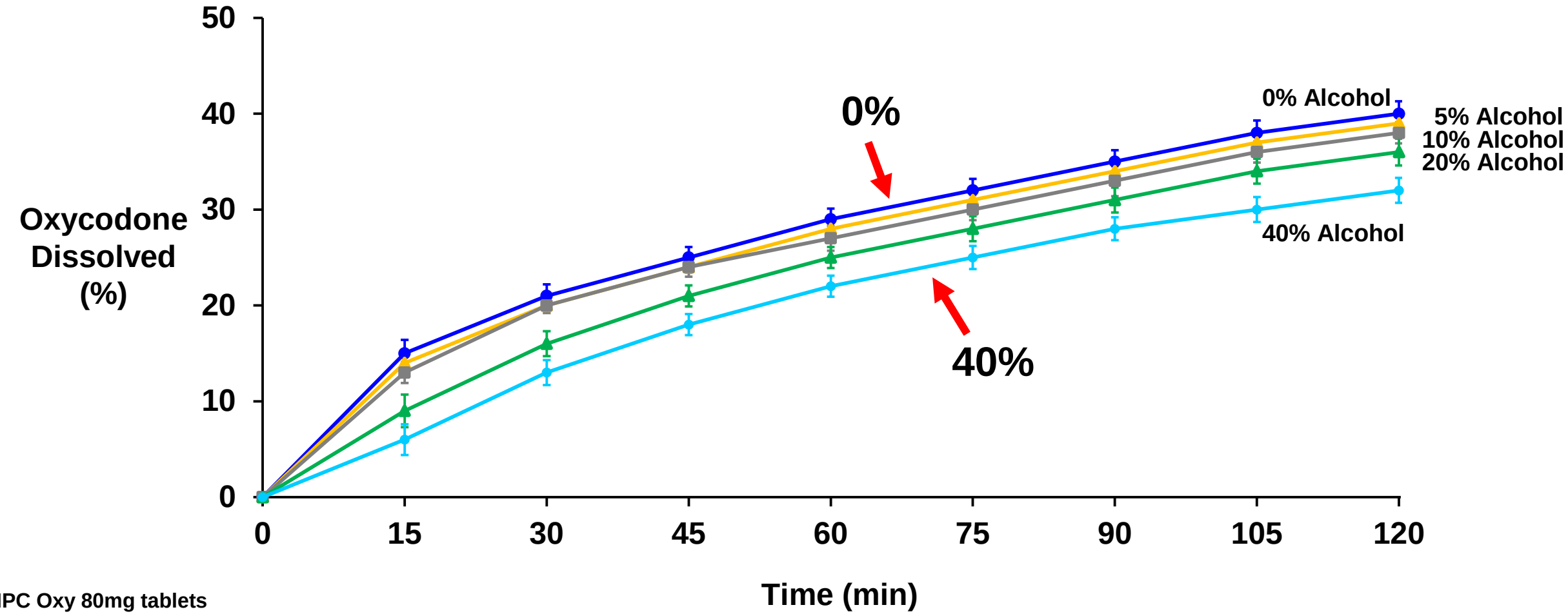


Tablet Form B, Volume 7, Agitation A, Temperature A, 30 minutes
Error Bars = SD; Experiment performed in triplicates

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

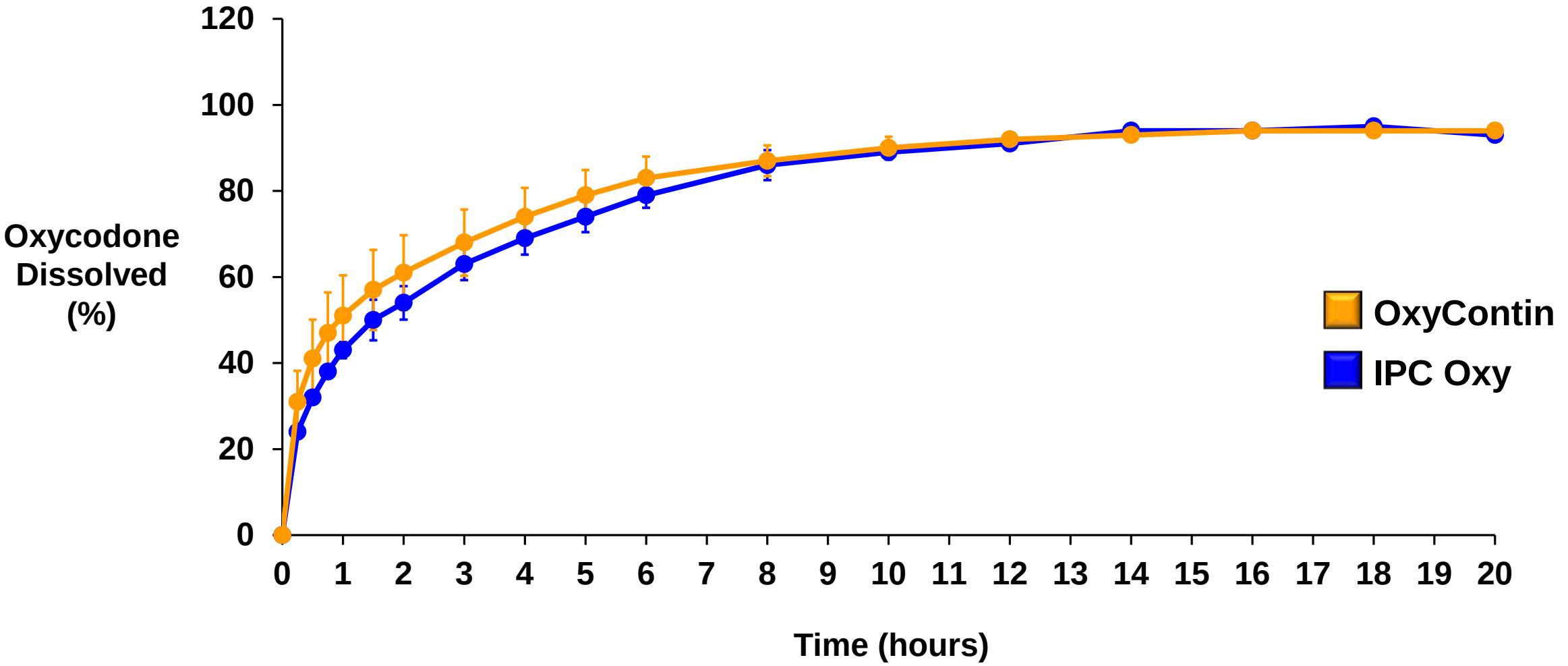


IPC Oxy 80mg tablets
Error Bars = SD; Experiment performed with 12 replicates

Overview of Category 1 Studies

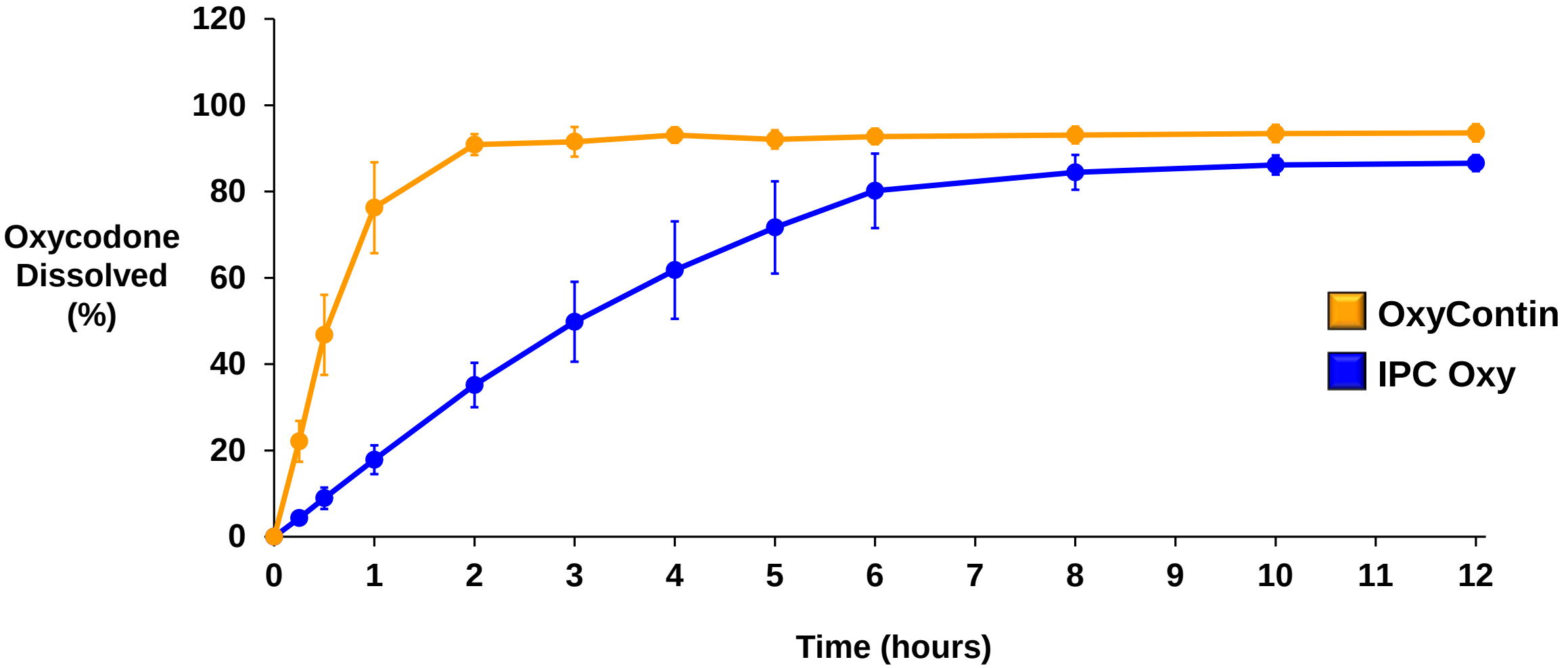
- Particle Size Reduction
- Syringeability / Injectability and Small Volume Extraction
- Large Volume Extraction
- Alcohol Dose Dumping
- Manipulated Tablet Dissolution
- Dye Elimination
- Simulated Smoking / Vaporization

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
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- 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

Experiment performed in triplicates

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

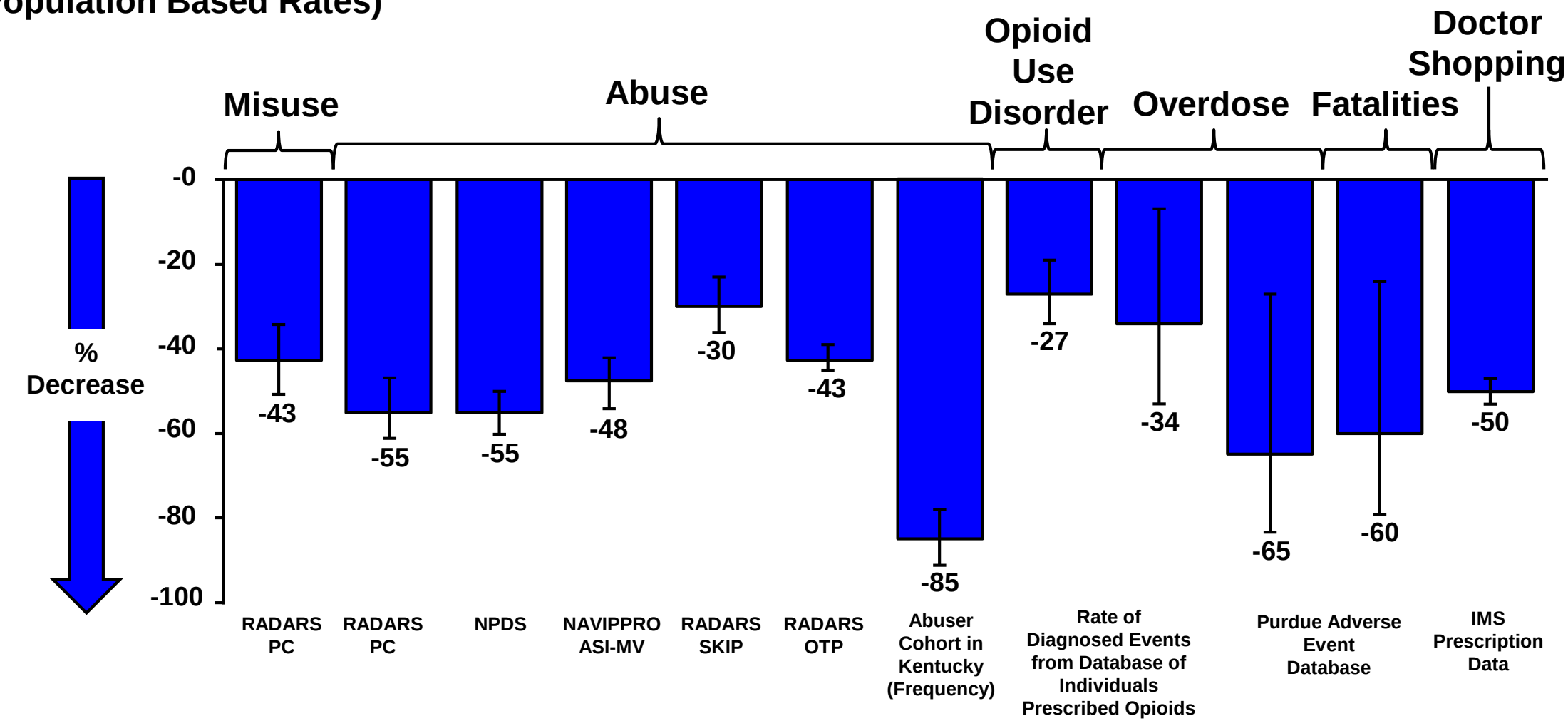
Post-Marketing Epidemiologic Studies of Reformulated OxyContin

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					

Coplan et al. Clin Pharmacol Ther 100(3):275-86;2016

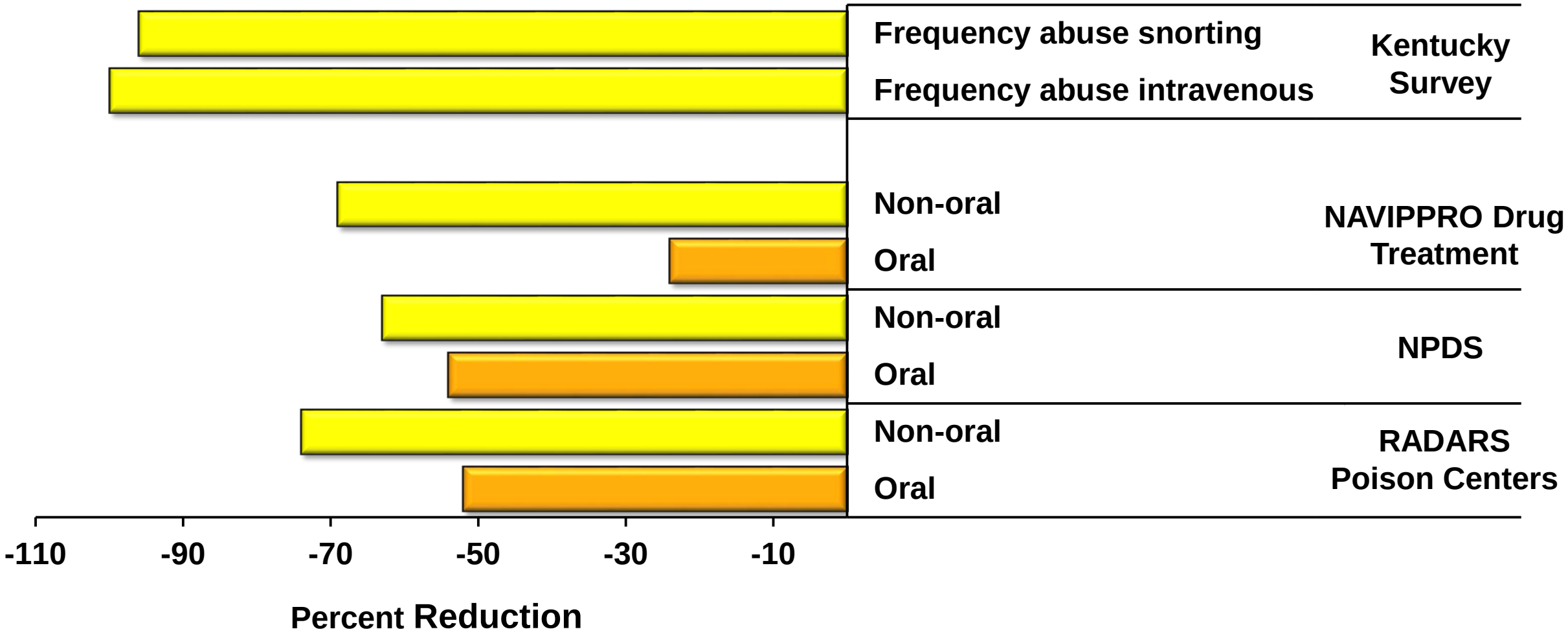
Significant Reductions in Measures of OxyContin Abuse

(Population Based Rates)



Modified from Coplan et al. Clin Pharmacol Ther 100(3):275-86;2016

Greater Impact of OxyContin ADF on Non-Oral Abuse



Modified from Coplan et al. Clin Pharmacol Ther 100(3):275-86;2016

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

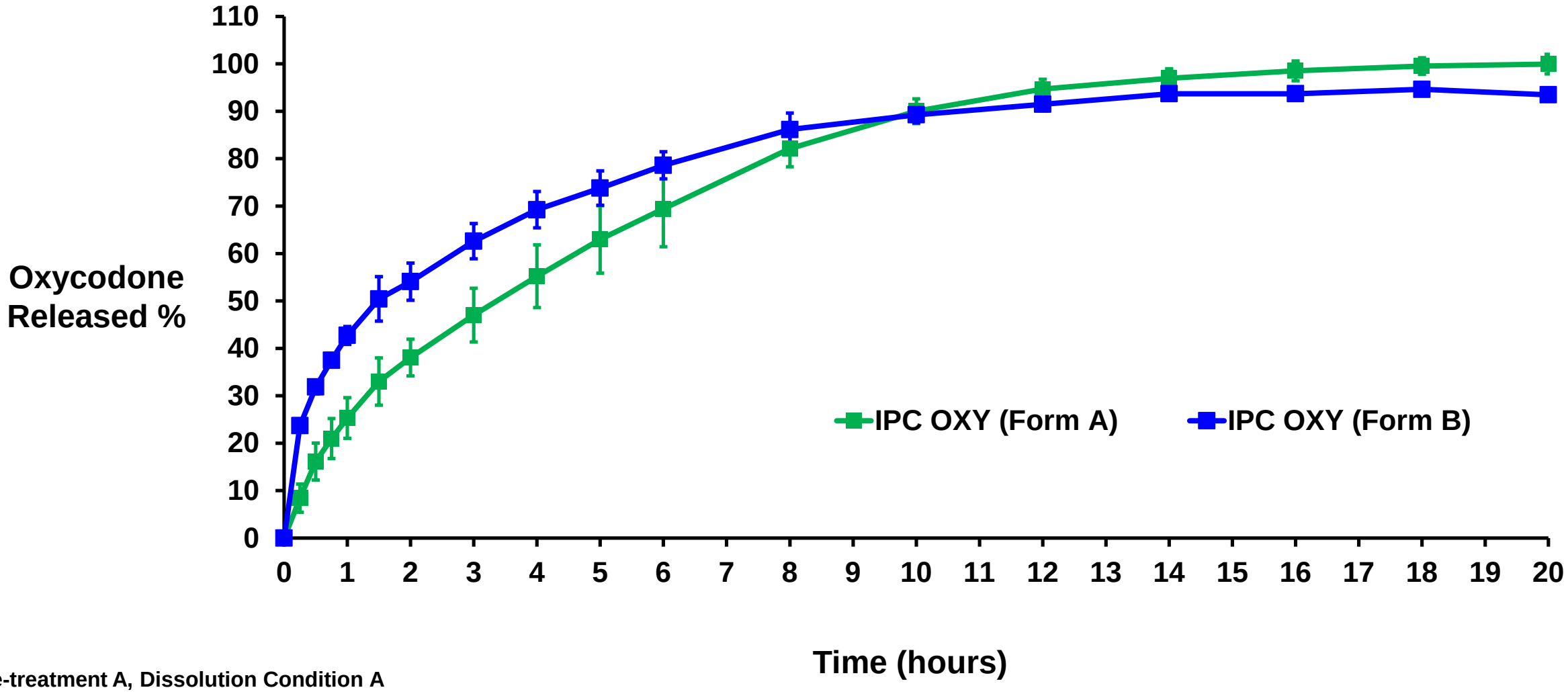
Oxycodone Extended-Release Tablets (IPC Oxy)

July 26, 2017

Intellipharmaceutics Corp.

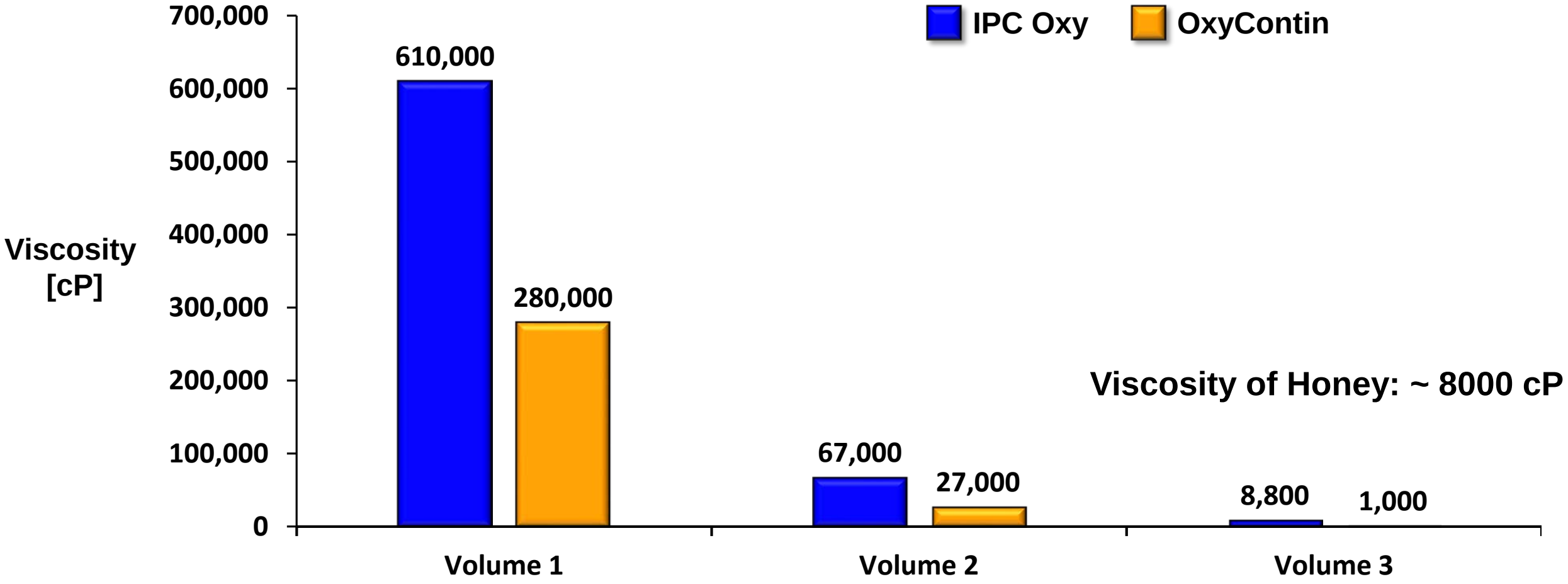
Joint Meeting of the Anesthetic & Analgesic Drug Products Advisory Committee & Drug Safety & Risk Management Advisory Committee

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



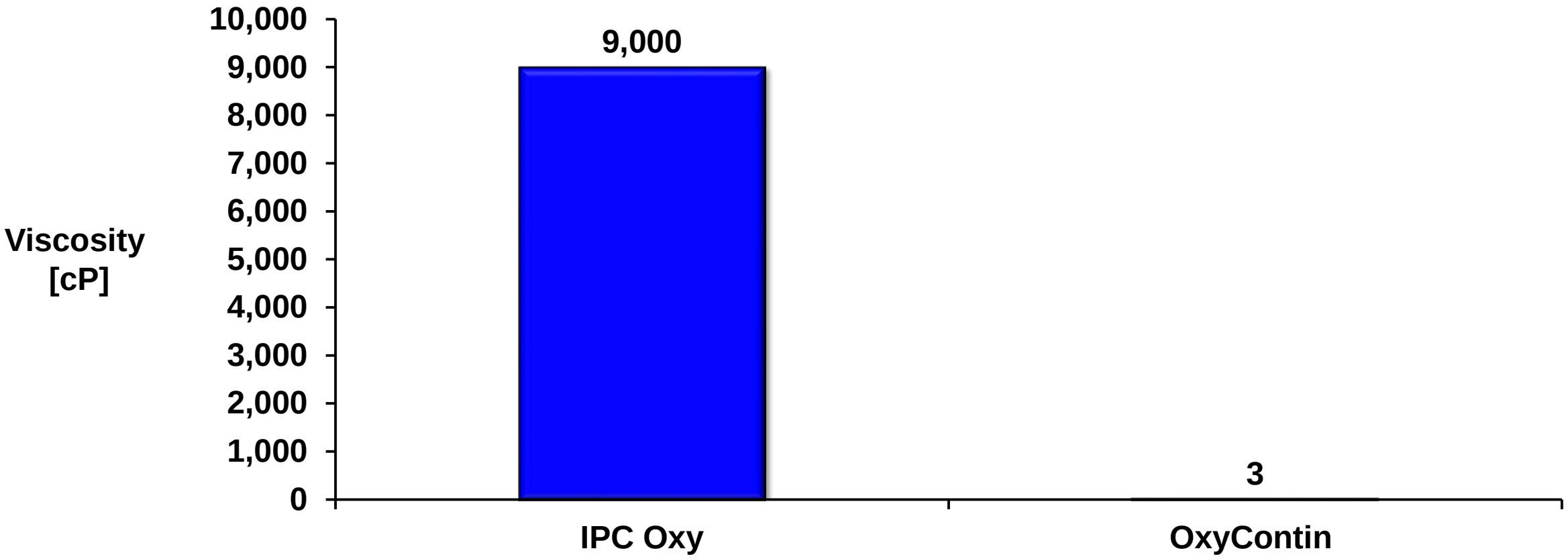
Pre-treatment A, Dissolution Condition A
Error Bars = SD; Experiment performed with 6 replicates

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



Tablet Form B, Solvent 1, Pre-treatment A, Volume 1, 2, 3 , ~ Temperature A

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



Tablet Form B, Solvent 1, Pre-treatment D, Volume 1 , ~ Temperature A