RoxyBond™ (oxycodone hydrochloride) Immediate-Release Tablets

April 5, 2017

Inspirion Delivery Sciences

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

Introduction

Stefan Aigner, MD

Co-Founder and Chief Executive Officer

Inspirion Delivery Sciences

Proposed RoxyBond Indication

RoxyBond is an opioid agonist indicated for management of pain severe enough to require the use of an opioid analgesic and for which alternative treatments are inadequate

RoxyBond: Abuse-Deterrent Immediate-Release Single-Entity Oxycodone Product

- Formulated with SentryBond™ Technology
  - Used in FDA approved MorphaBond ER™ (morphine ER), which has abuse-deterrent label claims
- Physical and chemical barriers to deter intranasal and IV abuse
  - Abuse-***deterrent***, not abuse-***proof***
  - Not expected to deter oral abuse
- Intended to replace easily abusable IR single-entity oxycodone products (e.g., Roxicodone)

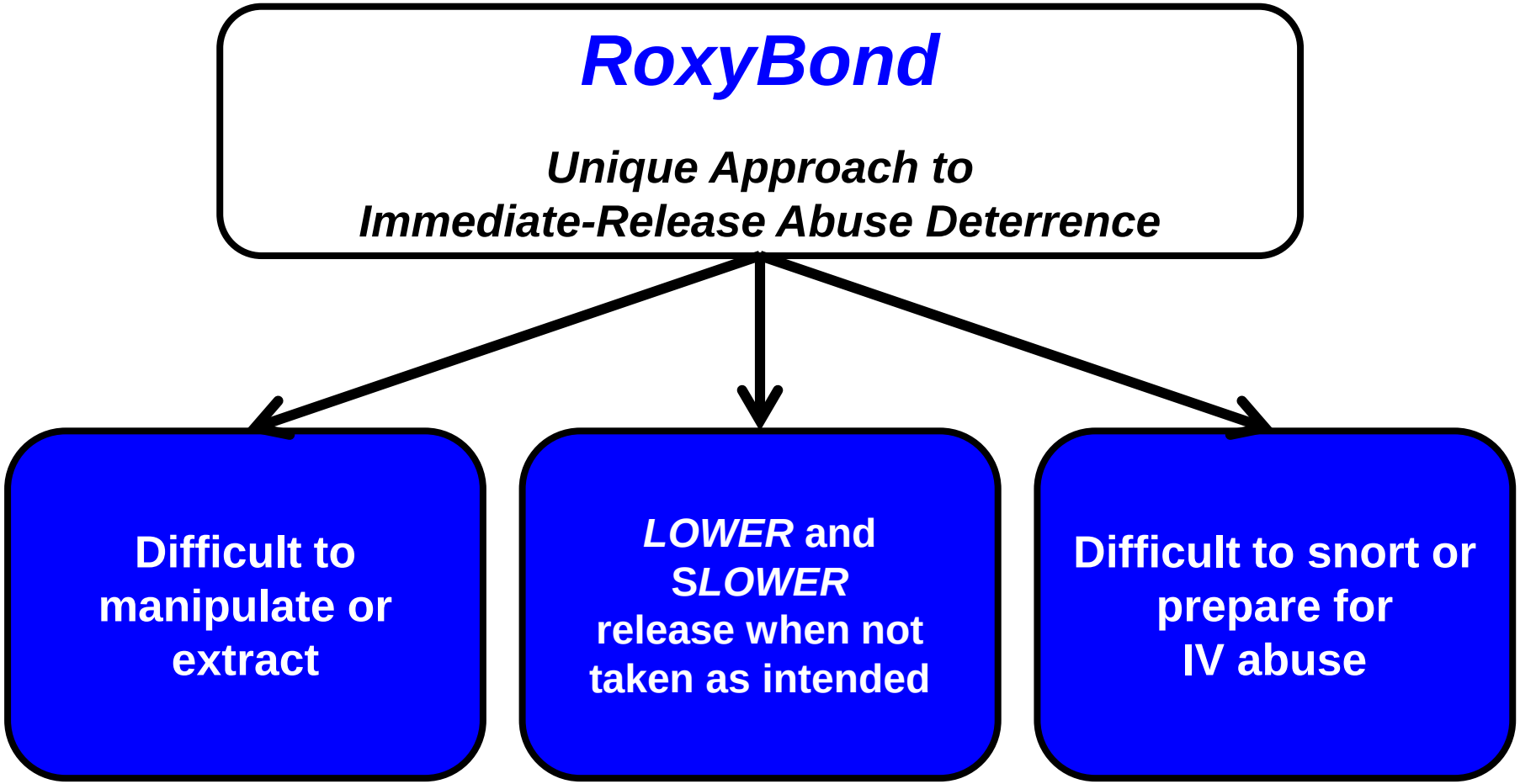
Current State of Abuse Deterrence for Opioid Products

- Opioid analgesics
  - Important treatment option for pain
  - At risk of diversion, misuse, and abuse
- FDA encourages development of abuse-deterrent opioids
  - 9 approved abuse-deterrent ER/LA opioids
  - No approved abuse-deterrent IR opioids
- IR profile poses challenge for abuse deterrence

Challenge of Abuse Deterrence for Immediate-Release Opioids

- ER opioids intended to release drug slowly
- Goals of manipulation/extraction with ER opioids:
  - Convert ER into IR
  - Transform into abusable form for snorting or injecting
- Most abuse-deterrent ER products resist manipulation and conversion into IR form
- IR products already have profile desired by abusers

RoxyBond Formulated with Physical and Chemical Barriers to Deter IN/IV Abuse



RoxyBond Regulatory Pathway and Dosage Strengths

- Used 505(b)(2) regulatory pathway
  - Roxicodone as reference listed drug (RLD)
- Dosage strengths same as Roxicodone: 5, 15, and 30 mg

RoxyBond Expected to Have Same Efficacy and Safety as Roxicodone

- RoxyBond demonstrated comparable bioavailability to Roxicodone
- RoxyBond strengths are dose proportional
- No clinically significant effect of food

Abuse-Deterrent Studies Designed in Accordance with FDA Guidance

- **Category 1** studies evaluated physical manipulation, chemical extraction, and syringeability
- **Category *2/3*** study evaluated intranasal human abuse potential

FDA. ***Abuse-Deterrent Opioids – Evaluation and Labeling: Guidance for Industry*. 2015.**

Inspirion Committed to Fulfilling Post-Approval Requirements

- RoxyBond expected to be incorporated into existing Opioid Analgesics REMS program
- **Category 4** studies to evaluate real-world impact
  - Monitor utilization of RoxyBond relative to comparators
  - Monitor abuse of RoxyBond including:
    - Route-specific abuse outcomes
    - Internet forums
    - Spontaneous adverse event reporting
  - Conduct formal observational studies

Agenda

Public Health Need for Abuse-Deterrent IR Opioid Analgesics	**Richard Dart, MD, PhD** Director, Rocky Mountain Poison & Drug Center Executive Director, RADARS® System
In Vitro Physical Manipulation and Chemical Extraction Studies	**Robert Bianchi** President and Chief of Scientific and Technical Affairs Prescription Drug Research Center
Intranasal Human Abuse Potential Study	**Lynn Webster, MD** Vice President PRA Health Sciences
Clinical Perspective	**Jeffrey Gudin, MD** Director, Pain Management Center Englewood Hospital and Medical Center

Public Health Need for Abuse-Deterrent IR Opioid Analgesics

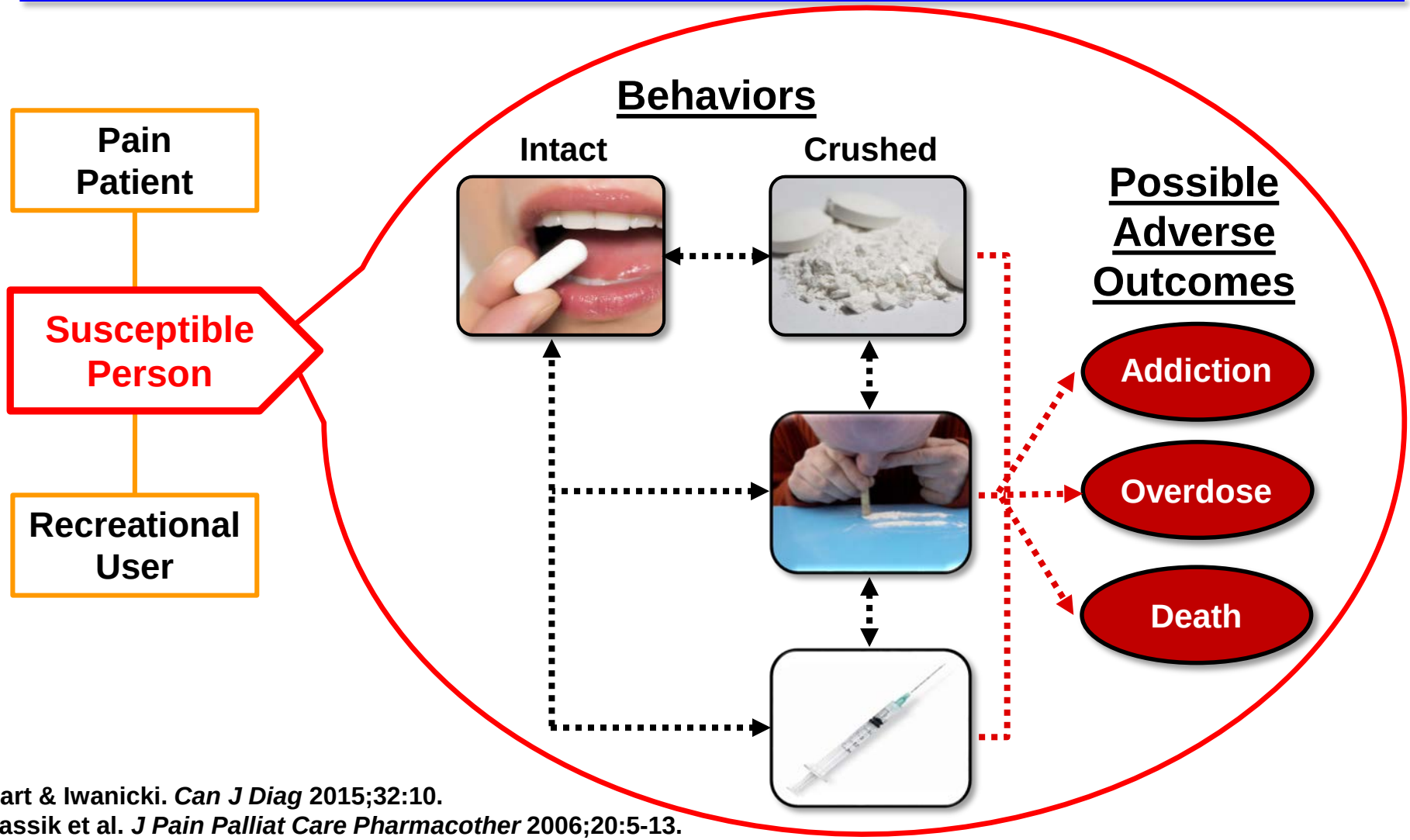
Richard C. Dart, MD, PhD

Director, Rocky Mountain Poison & Drug Center

Professor of Emergency Medicine,
University of Colorado School of Medicine

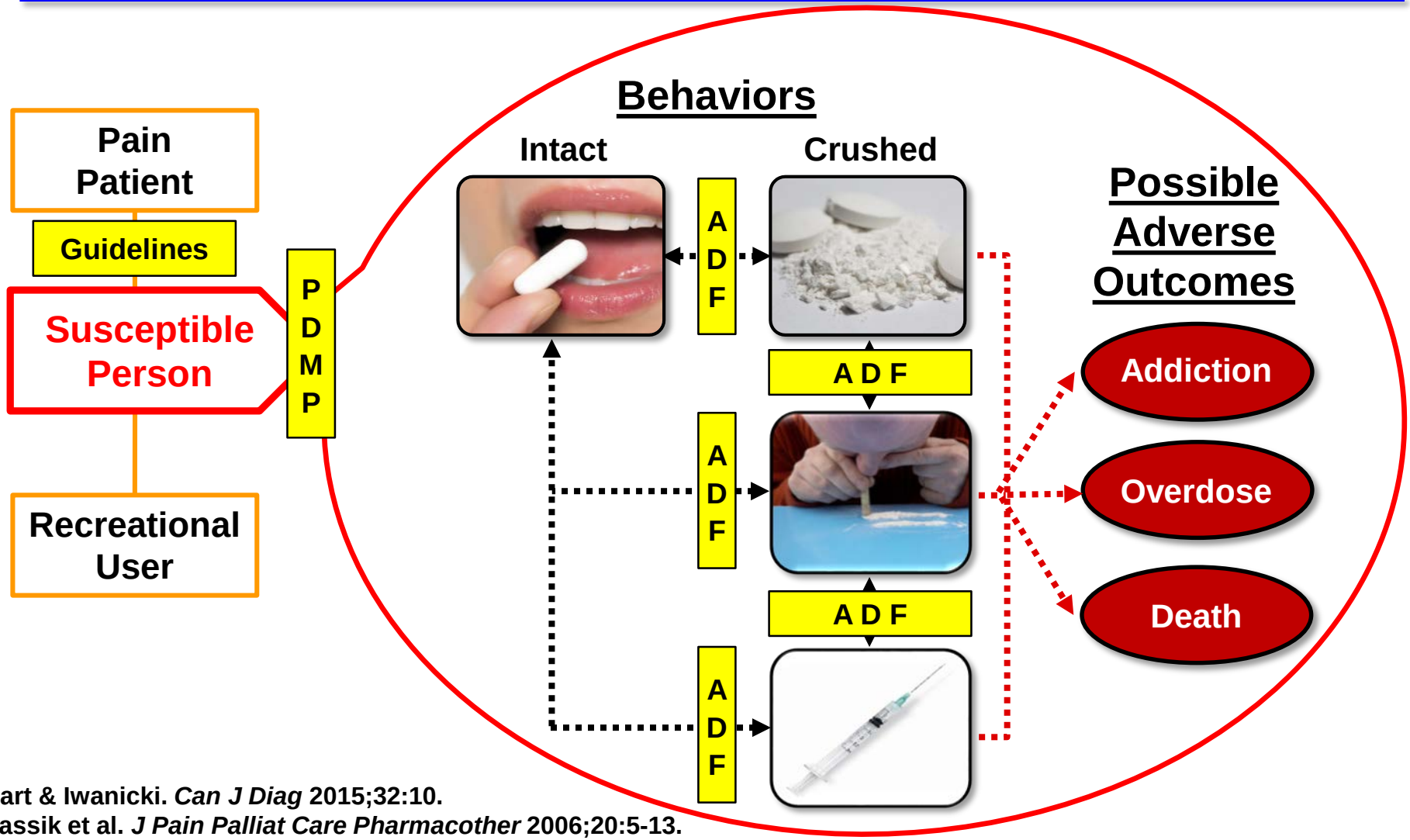
Executive Director, RADARS® System

Development of Prescription Opioid Abuse



Dart & Iwanicki. *Can J Diag* 2015;32:10.
Passik et al. *J Pain Palliat Care Pharmacother* 2006;20:5-13.
Vosburg et al. *J Child Adolesc Drug Abuse* 2016;25:105-12.

Theoretical Roles of Opioids with Abuse-Deterrent Properties



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Passik et al. *J Pain Palliat Care Pharmacother* 2006;20:5-13.
Vosburg et al. *J Child Adolesc Drug Abuse* 2016;25:105-12.

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

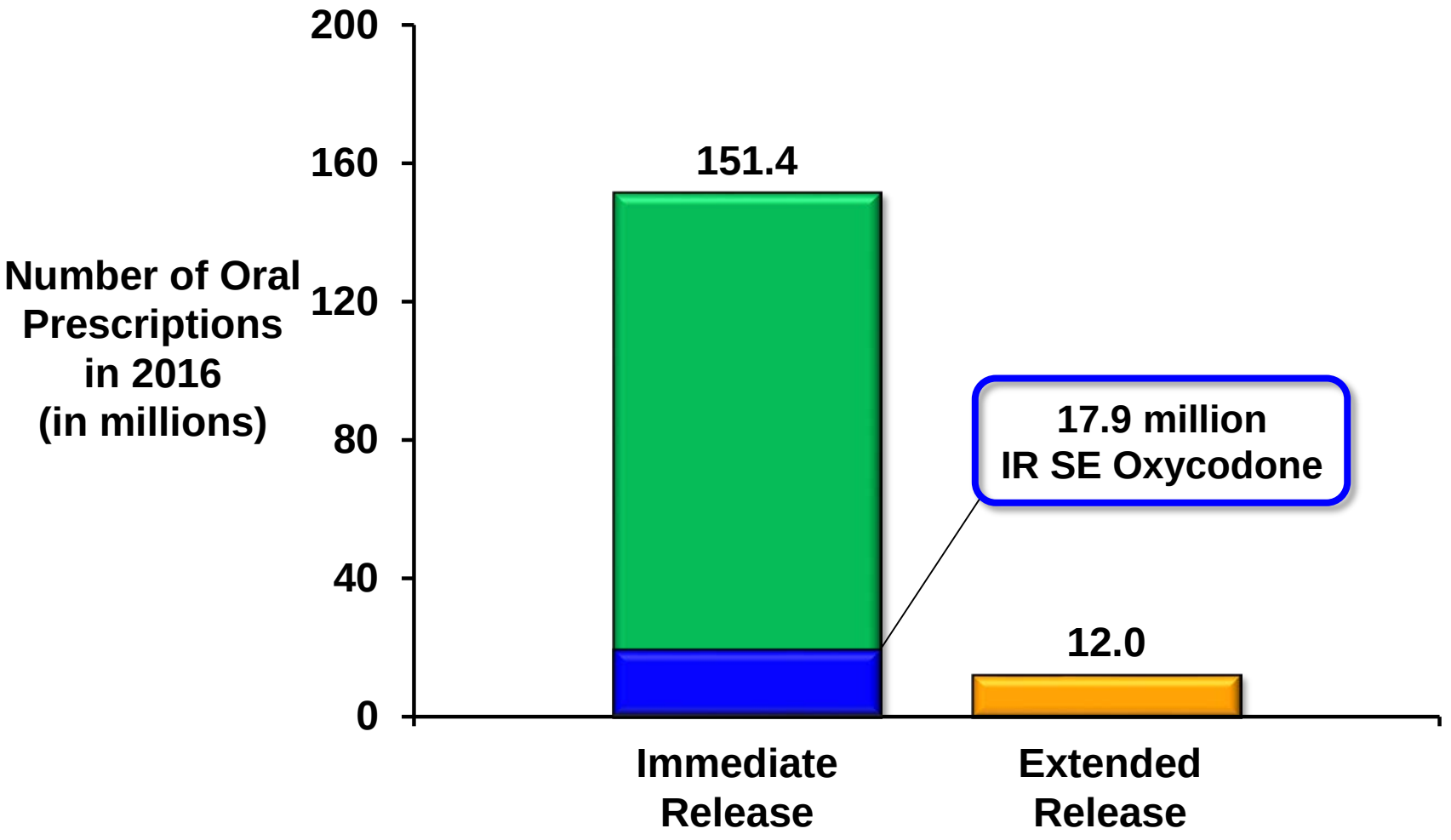
Novice / Recreational Abuser

- Deter dangerous routes of intranasal and IV abuse

Advanced Abuser

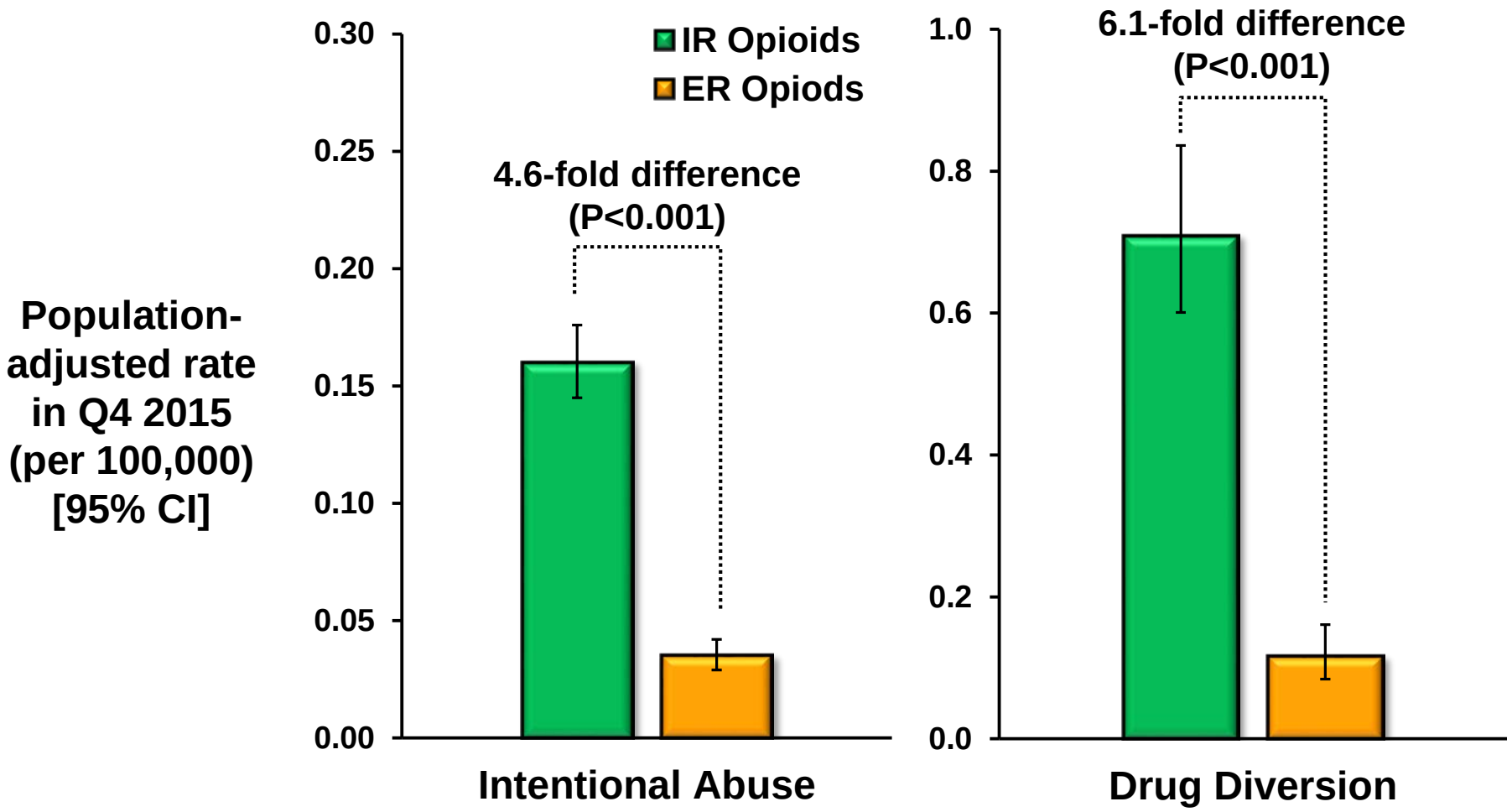
- Make dangerous routes of abuse more difficult with that ADF product

Most Oral Opioid Prescriptions Are Immediate Release; None Abuse Deterrent



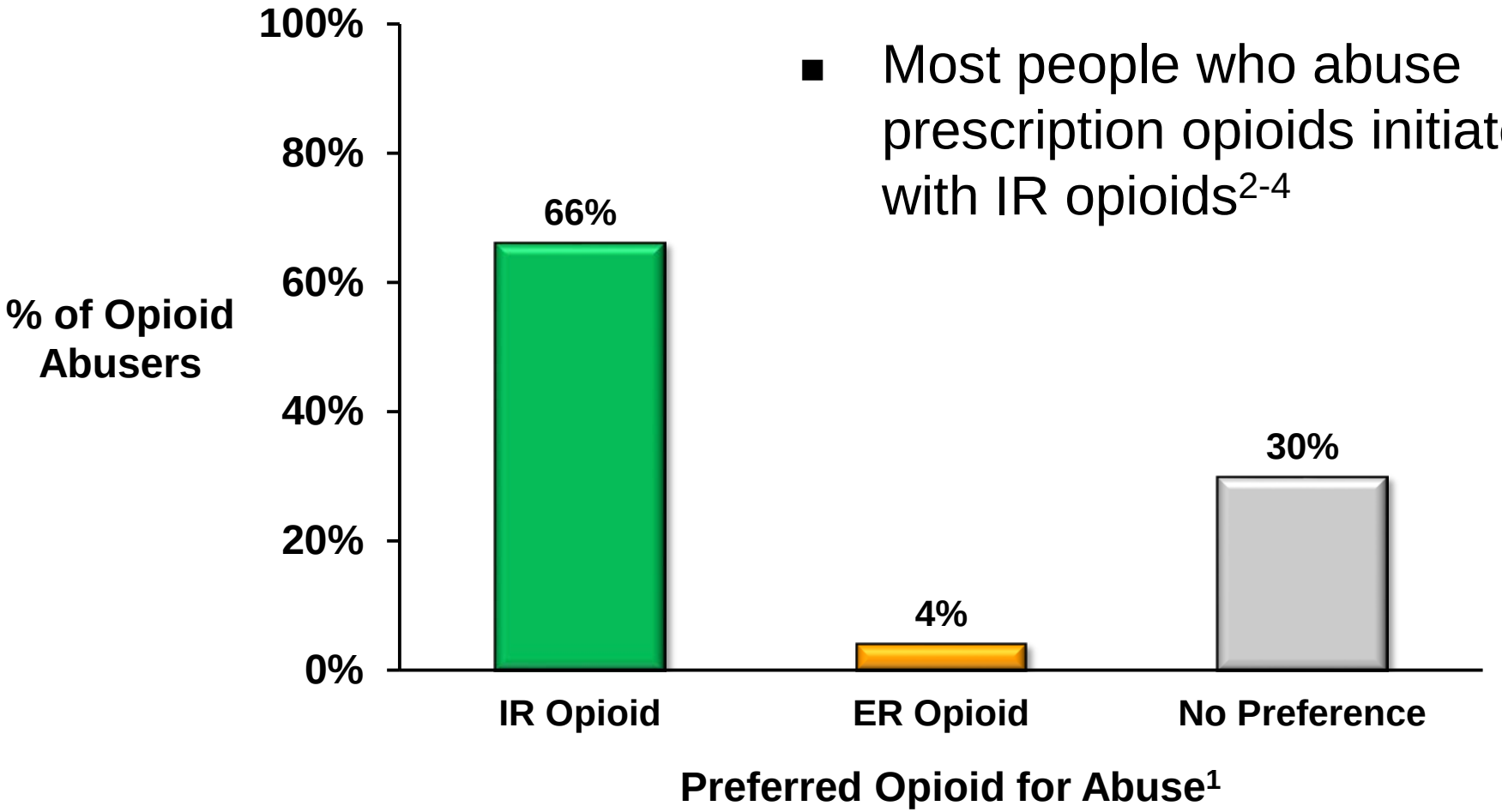
Symphony Health Solutions PHAST™ PRESCRIPTION Database.

Population-Adjusted Rates of Abuse and Diversion Higher with IR than ER Opioids



RADARS data published in Iwanicki et al. *PLoS One* 2016;11:e0167499.

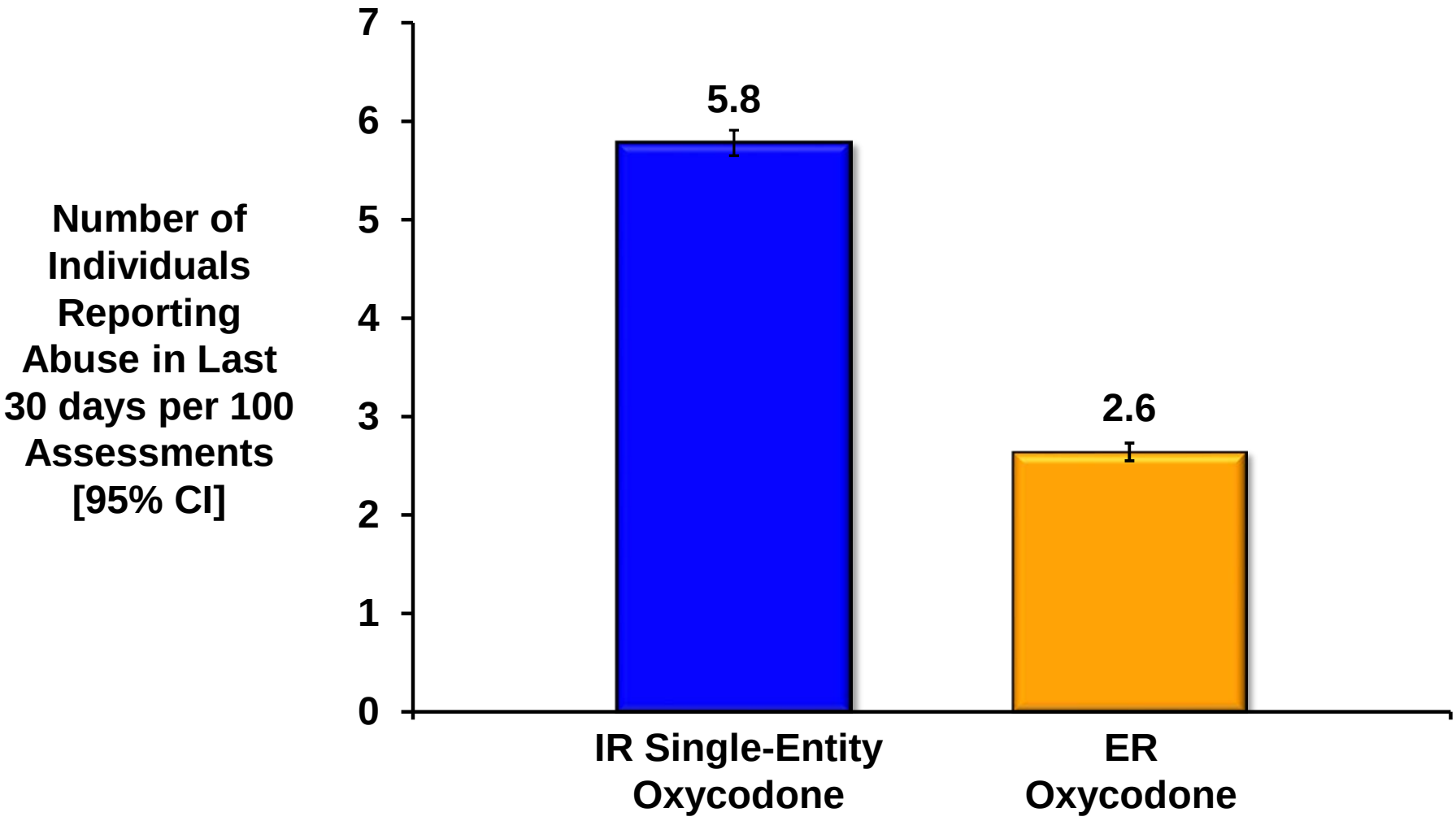
IR Opioids are Preferred Over ER Opioids for Abuse



- Most people who abuse prescription opioids initiate with IR opioids[2-4]

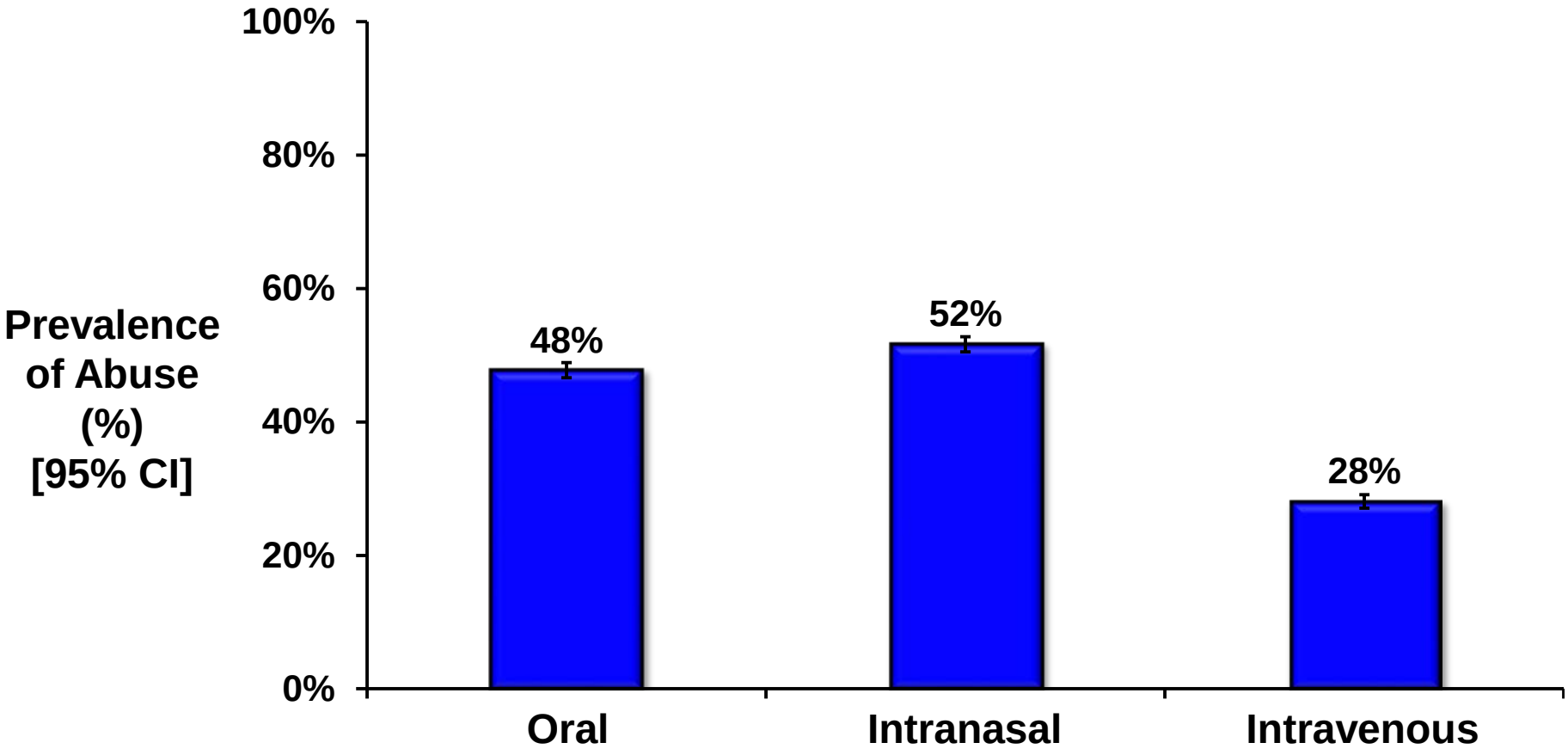
1. Cicero et al. *Pharmacoepidemiol Drug Saf* 2017;26:56-62.
2. Budman et al. *Harm Red J* 2009;6:8-14.
3. Cicero et al. *RADARS System Technical Report* 2015.
4. Lankenau et al. *Int J Drug Policy* 2012;23:37-44.

Rate of Abuse of IR SE Oxycodone Greater than ER Oxycodone



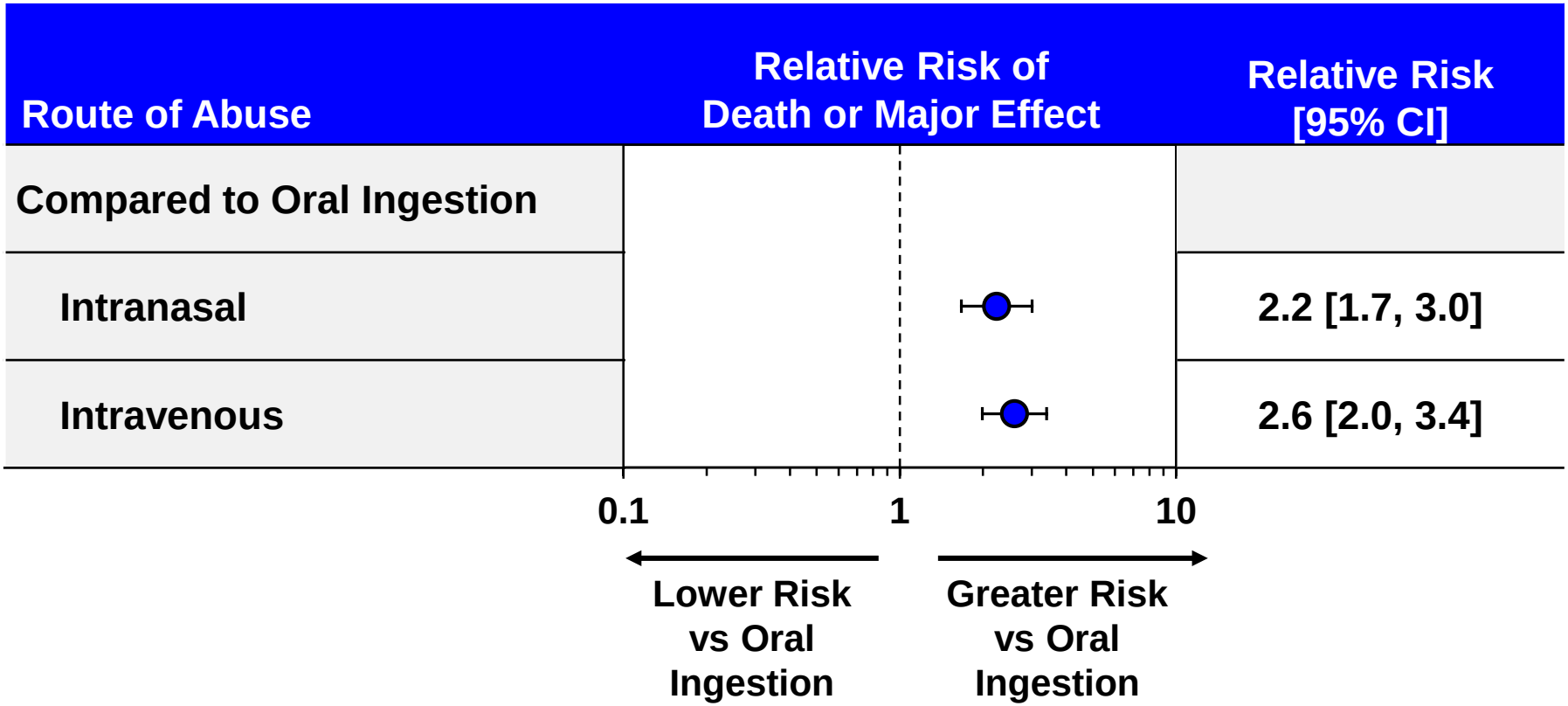
NAVIPPRO Addiction Severity Index-Multimedia Version (ASI-MV) [Q1 2015 - Q4 2016].

IR SE Oxycodone Widely Abused via Intranasal and IV Routes



NAVIPPRO Addiction Severity Index-Multimedia Version (ASI-MV) [Q1 2015 - Q4 2016].

IV and Intranasal Abuse of Prescription Opioids Associated With Serious Outcomes



RADARS System Poison Center Program, 2015 Data on File.

IV Route Poses Additional Risks for Serious Health Consequences

- 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.

Unmet Need For Abuse-Deterrent IR Opioid Analgesics

- IR opioids much more commonly prescribed, abused, and diverted than ER opioids
- IR SE oxycodone is commonly abused by high-risk intranasal and IV routes
  - Dangerous routes of abuse associated with serious health consequences
- Abuse-deterrent formulations designed to:
  - Complement other strategies
  - Replace easily abusable products

In Vitro Physical Manipulation and Chemical Extraction Studies

Robert Bianchi

President and Chief of Scientific and Technical Affairs

Prescription Drug Research Center

Comprehensive Category 1 Testing for Intranasal and IV Abuse

- Consistent with FDA's Guidance on Abuse-deterrent Opioids[1]
- Iterative testing approach with FDA
- Roxicodone used as non-abuse-deterrent comparator

1. FDA. *Abuse-Deterrent Opioids – Evaluation and Labeling: Guidance for Industry*. 2015.

Overview of Category 1 Studies

- Particle Size Reduction
  (with and without pre-treatment)
- Large Volume Extraction
- Small Volume Extraction
- Syringeability

Rationale for Reducing Particle Size of IR Opioids is to Get Drug in Abusable Form

Rationale for Particle Size Reduction	ER Opioids	IR Opioids
Convert ER into IR	✓	
Transform into abusable form for snorting or injection	✓	✓

- RoxyBond: Formulated for ***lower and slower*** release of oxycodone when manipulated for non-oral route compared to intact administration

Particle Size Reduction ≠ **Defeat of RoxyBond ADF Properties**

Category 1

Roxicodone Easily and Quickly Turned Into Abusable Form

- Roxicodone easily manipulated with Tool E
  - 100% of particles < 2000 microns
  - No further tools evaluated
  - Easily reduced to fine powder that could be snorted or prepared for IV abuse

RoxyBond Difficult to Get Into Abusable Form with Most Tools

Outcome	Tools						
	A	B	C	D	E	F	G
Time (sec)	300	300	300	60	118	300	31
Manipulation Difficulty (1-10)	10	9	7	6	7	8	1
Mean % Particles < 2000 Microns	0%	9%	25%	44%	64%	79%	92%

- Pre-treatments did not substantially increase yield of small particles
- Most effective tools used in subsequent studies
  - Roxicodone: Tool E
  - RoxyBond: Tool G

Category 1

Overview of Category 1 Studies

- Particle Size Reduction (with and without pre-treatment)
- Large Volume Extraction
- Small Volume Extraction
- Syringeability

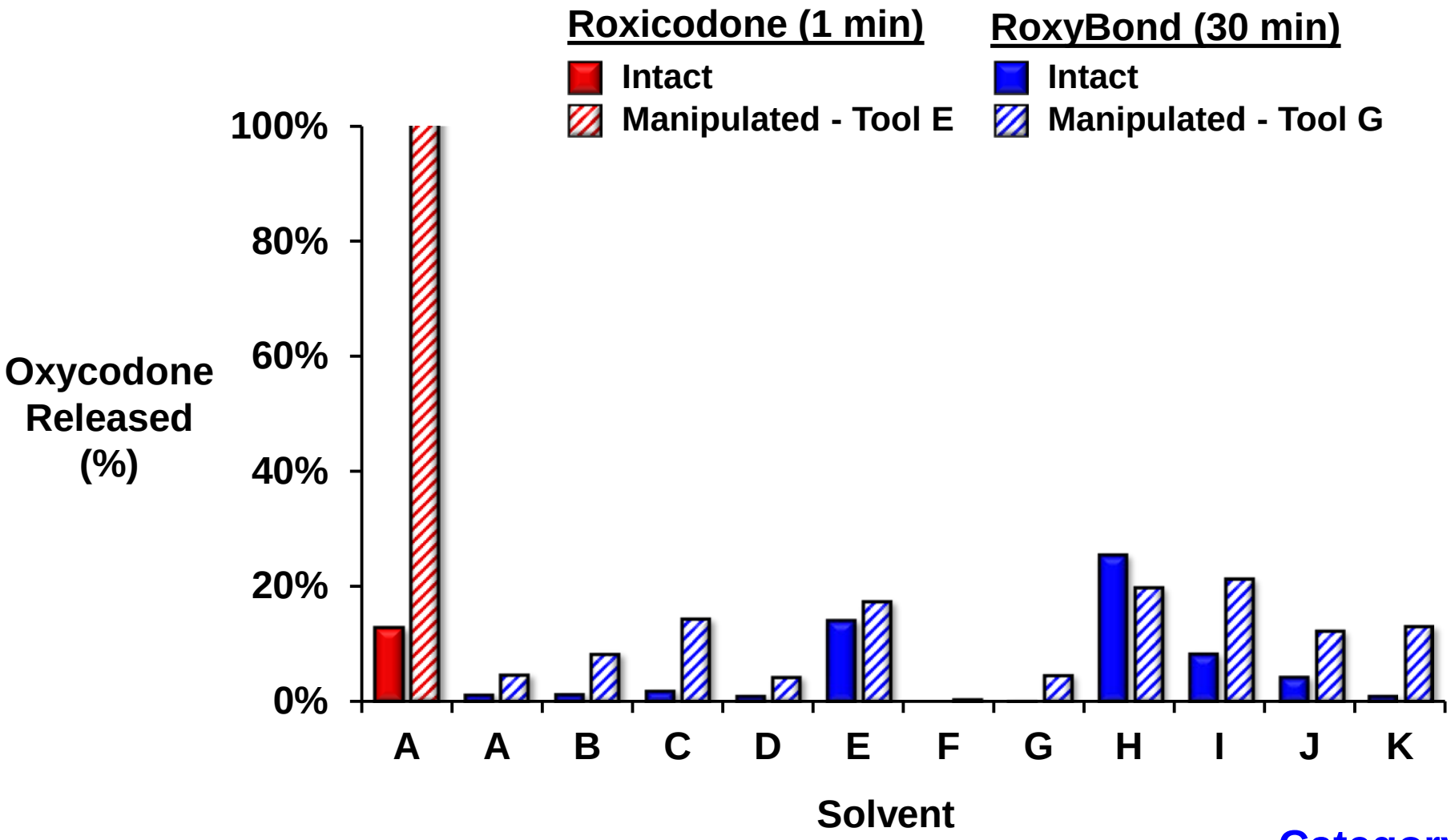
Large Volume Extraction Does Not Speed Oral Absorption for IR Oxycodone

Oxycodone Parameter	Mean ± SD	
	Roxicodone 15 mg Intact Tablets	Roxicodone Liquid Concentrate 15 mg / 15 mL Oral Solution
C_{max} (ng/mL)	22 ± 8	21 ± 6
T_{max} (hr)	1.4 ± 0.7	1.9 ± 1.5

- Large volume extraction for IR oxycodone does not speed absorption over intact oral administration
- Resistance to physical manipulation and/or extraction not expected to deter oral abuse

Category 1

RoxyBond Difficult to Extract in Large Volumes of Ingestible and Non-ingestible Solvents



Volume C, Temperature A, Agitation B, Tablet Form A

Category 1

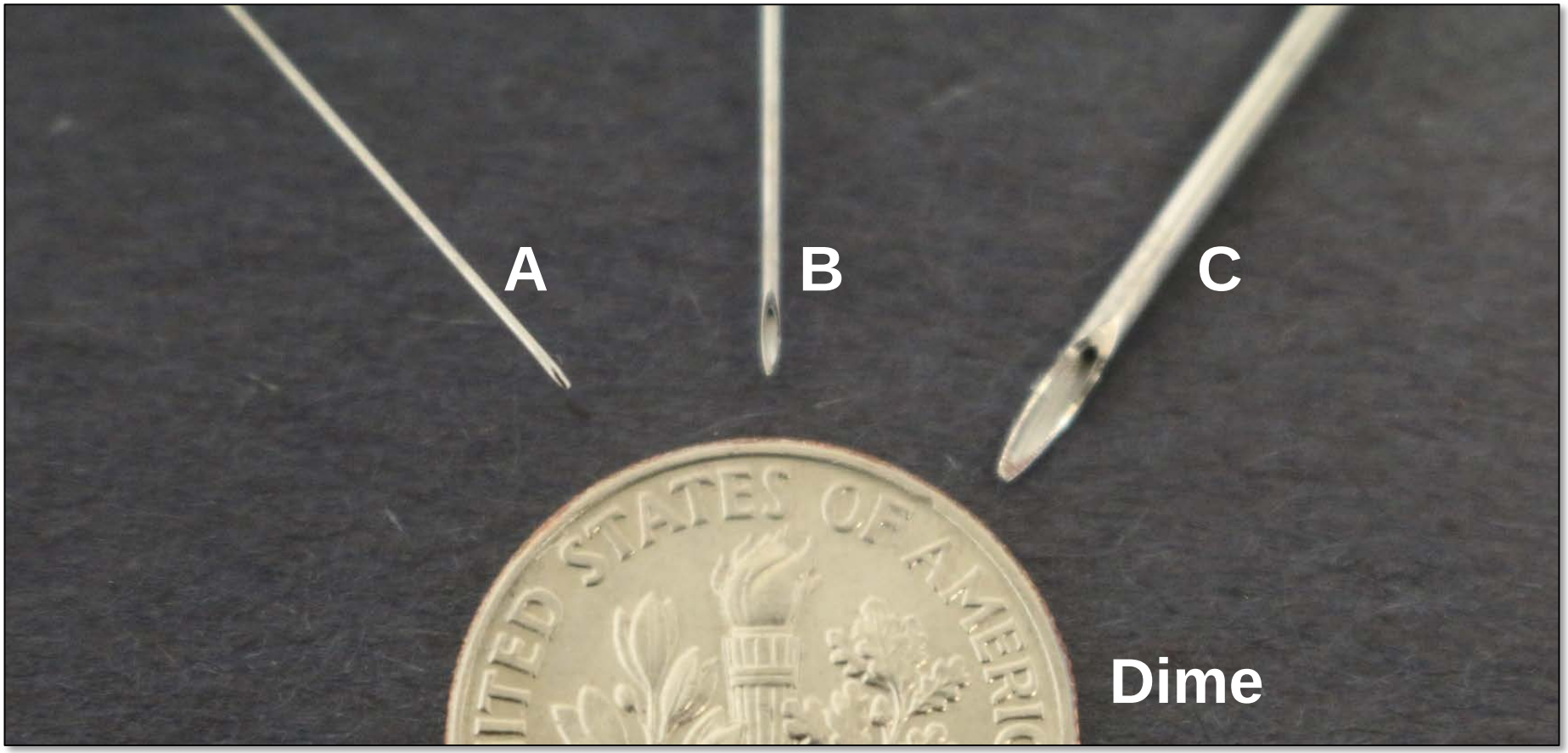
Overview of Category 1 Studies

- Particle Size Reduction
  (with and without pre-treatment)
- Large Volume Extraction
- Small Volume Extraction
- Syringeability

Small Volume Extraction and Syringeability Experiments

- Small volume extraction in injectable volumes of solvent
- Used smallest needle gauge able to syringe liquid
- Difficulty to syringe measured on 1-10 scale
  - 1 = “very easy to syringe”
  - 10 = “impossible”

Multiple Needle Gauges Used to Evaluate Syringeability



Category 1

RoxyBond Forms Viscous Material When Manipulated and Subjected to Liquid Environment

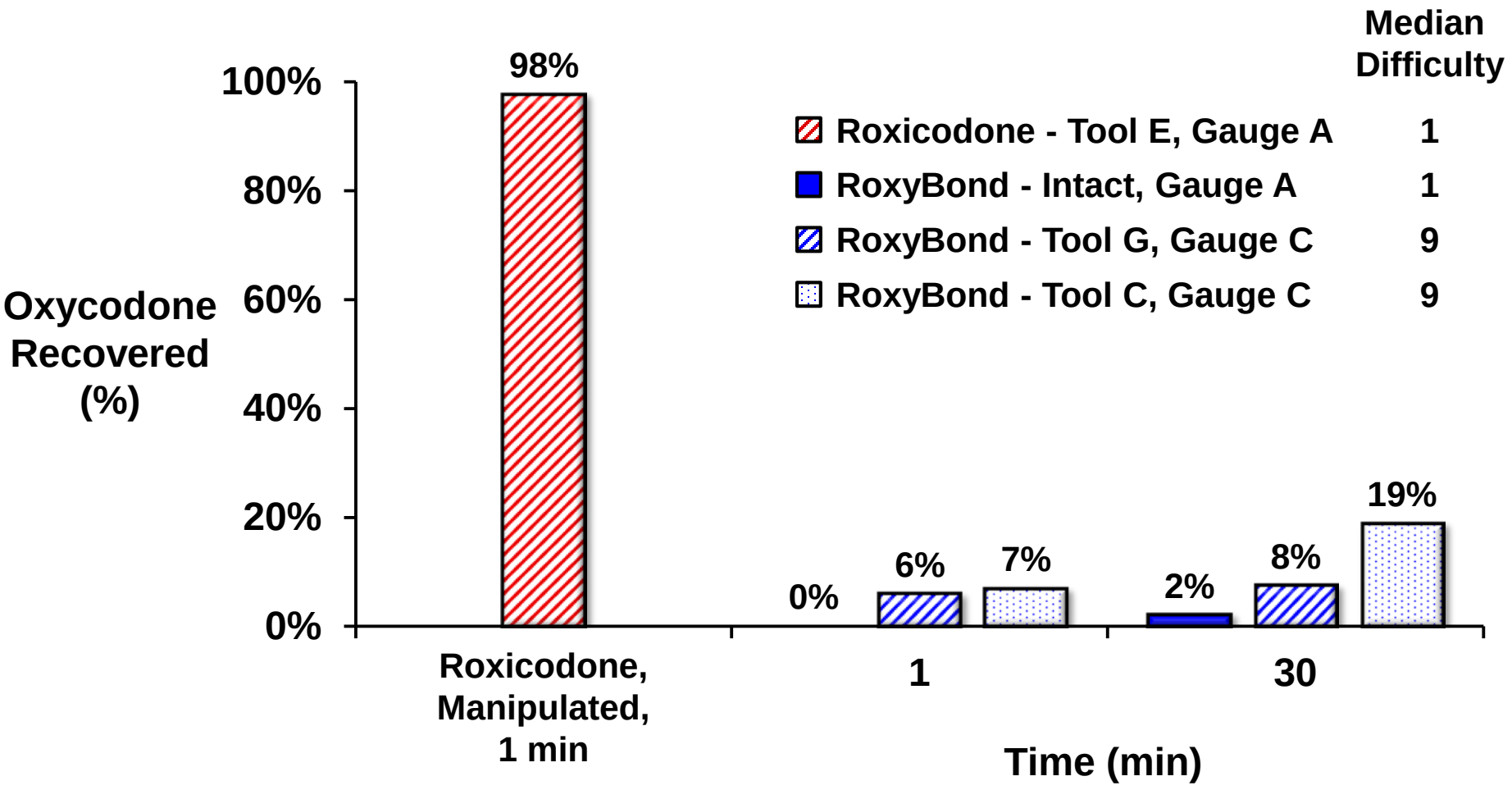
Roxicodone

RoxyBond

Volume A, Solvent A, Temperature A, Agitation B, Tablet Form A

Category 1

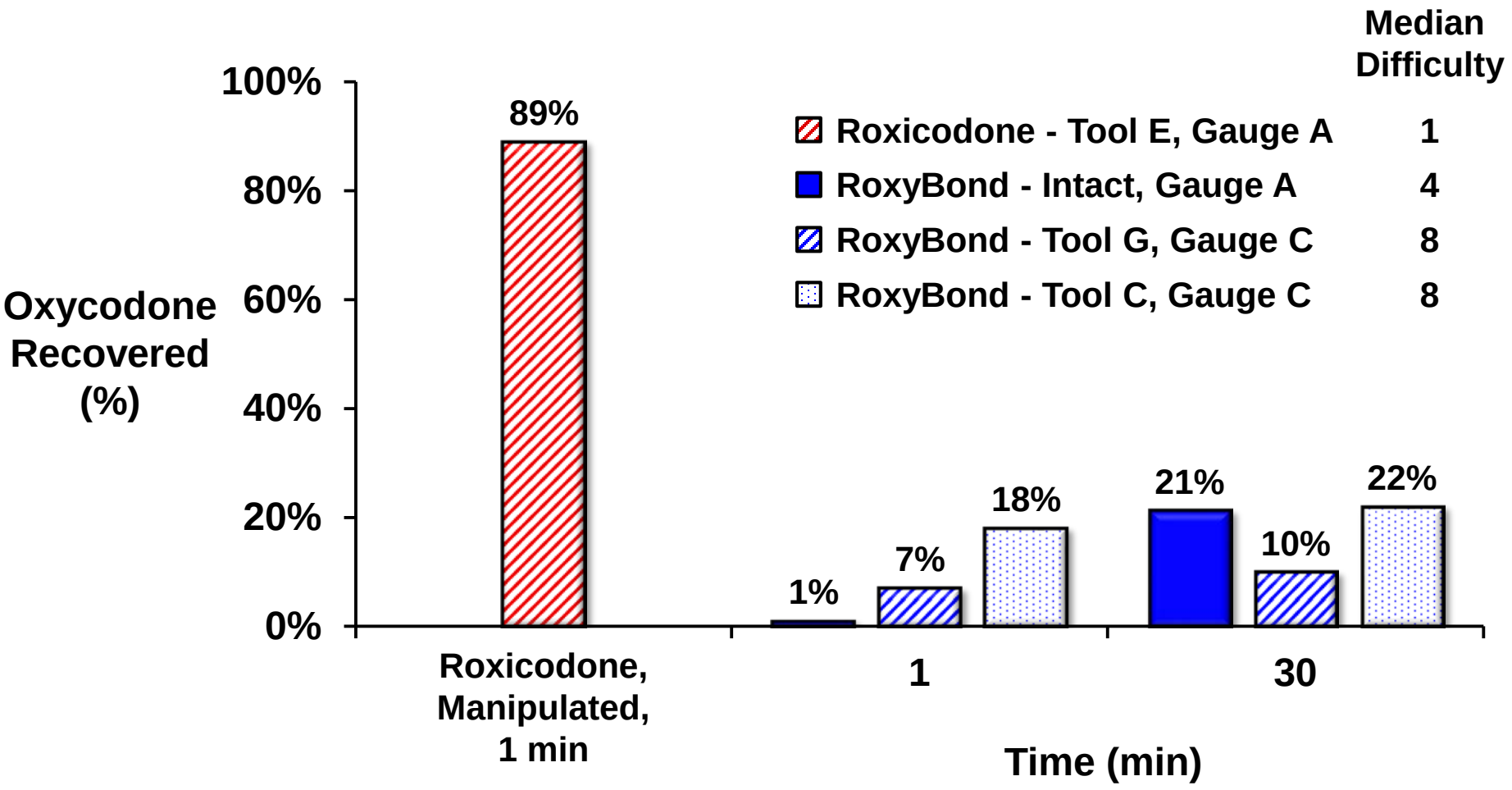
RoxyBond Resistant to Small Volume Extraction and Syringeability



Volume A, Solvent A, Temperature A, Agitation A, Tablet Form A

Category 1

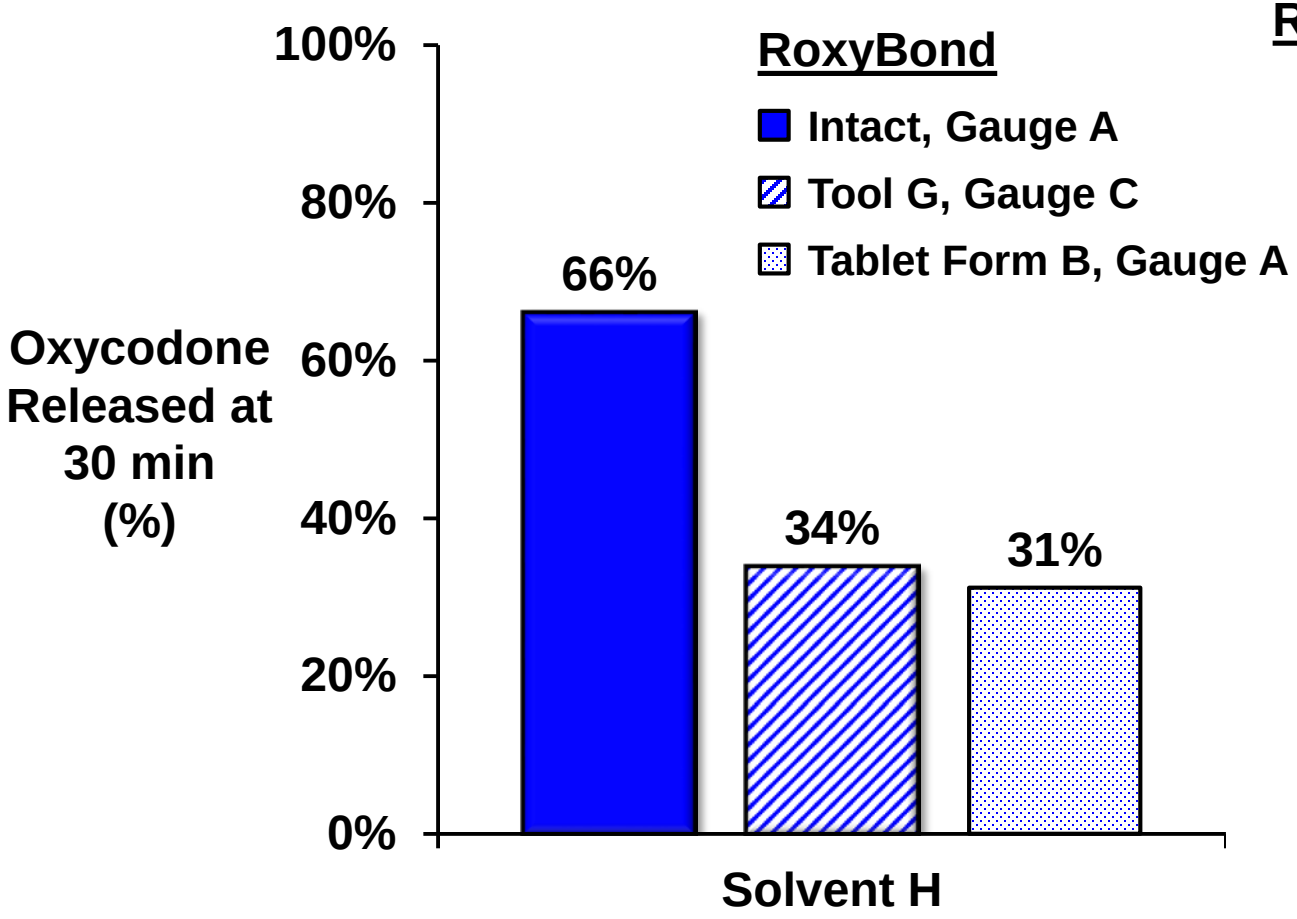
Extreme Temperature Modification Did Not Appreciably Increase Yield of Oxycodone from RoxyBond



Volume A, Solvent A, Temperature B, Agitation A, Tablet Form A

Category 1

Complex, Multi-Step Process Required to Prepare RoxyBond Solution for IV Abuse



Required Steps for Abuse

Pre-Treatment D

↓

Large IV Volume B

↓

Extreme Solvent H

↓

Agitation B

↓

Extended Time Point

↓

Neutralize Solvent

Volume B, Temperature A, Agitation B, Tablet Form A (unless specified), Pre-Treatment D

Category 1

RoxyBond Demonstrated Physical and Chemical Abuse-Deterrent Properties

- Difficult to convert into abusable form for intranasal or IV abuse
- Particle size reduction did not defeat abuse-deterrent properties
- All extraction experiments produced considerably lower and slower oxycodone release compared to Roxicodone
- Manipulated RoxyBond was difficult to syringe

Intranasal Human Abuse Potential Study

Lynn Webster, MD
Vice President, Scientific Affairs
PRA Health Sciences

Study 002: Intranasal HAP Study

- Randomized, double-blind, double-dummy, placebo-controlled, 4-period crossover study
- Enrolled recreational, nondependent opioid users experienced in nasal insufflation
- 31 subjects entered treatment phase
- 29 subjects completed study

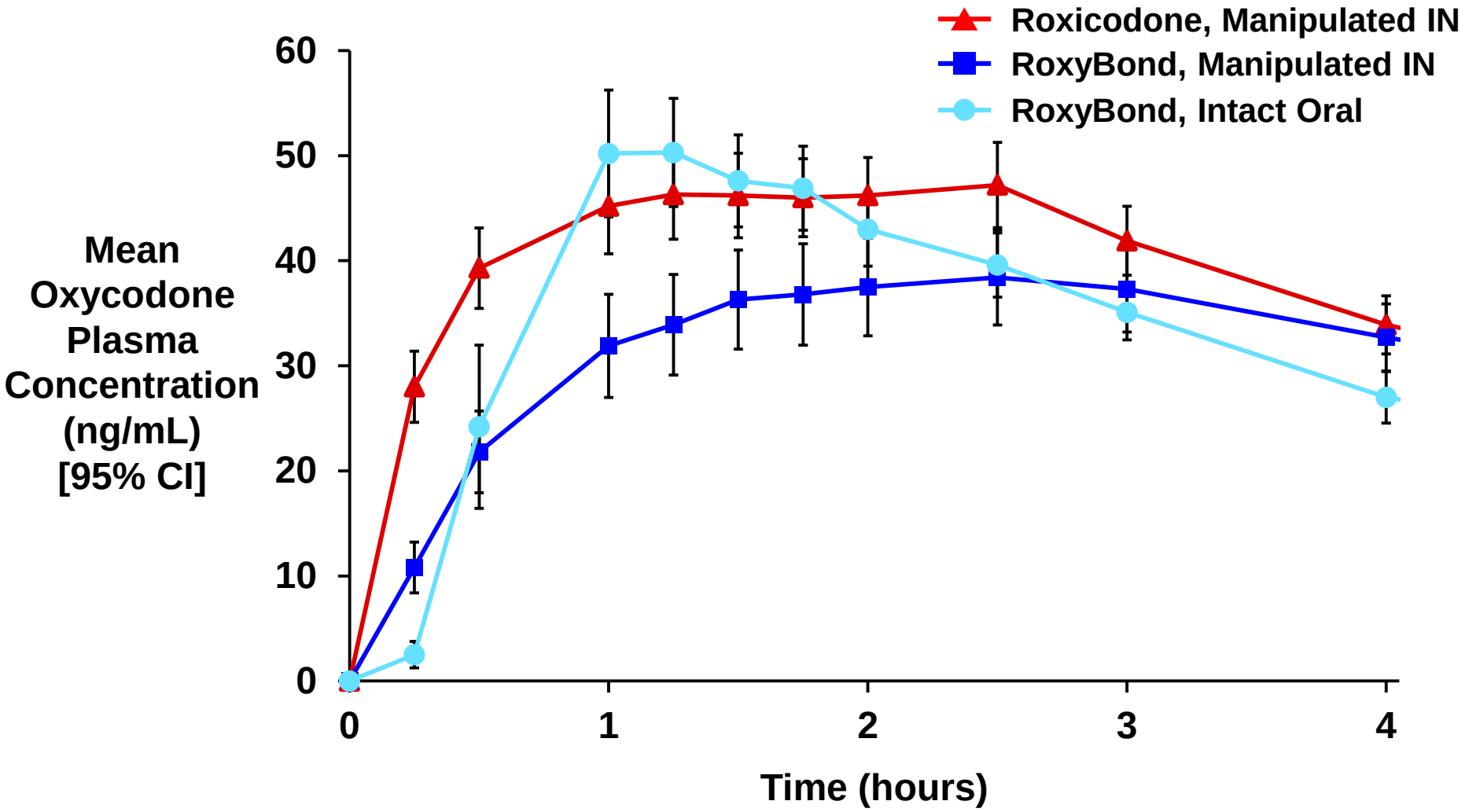
Treatments in Intranasal HAP Study

- 4 treatment arms
  - Roxicodone, manipulated [Tool E] (IN)
  - RoxyBond, manipulated [Tool G] (IN)
  - RoxyBond, intact (oral)
  - Placebo
- Active treatments used 30 mg dosage strength

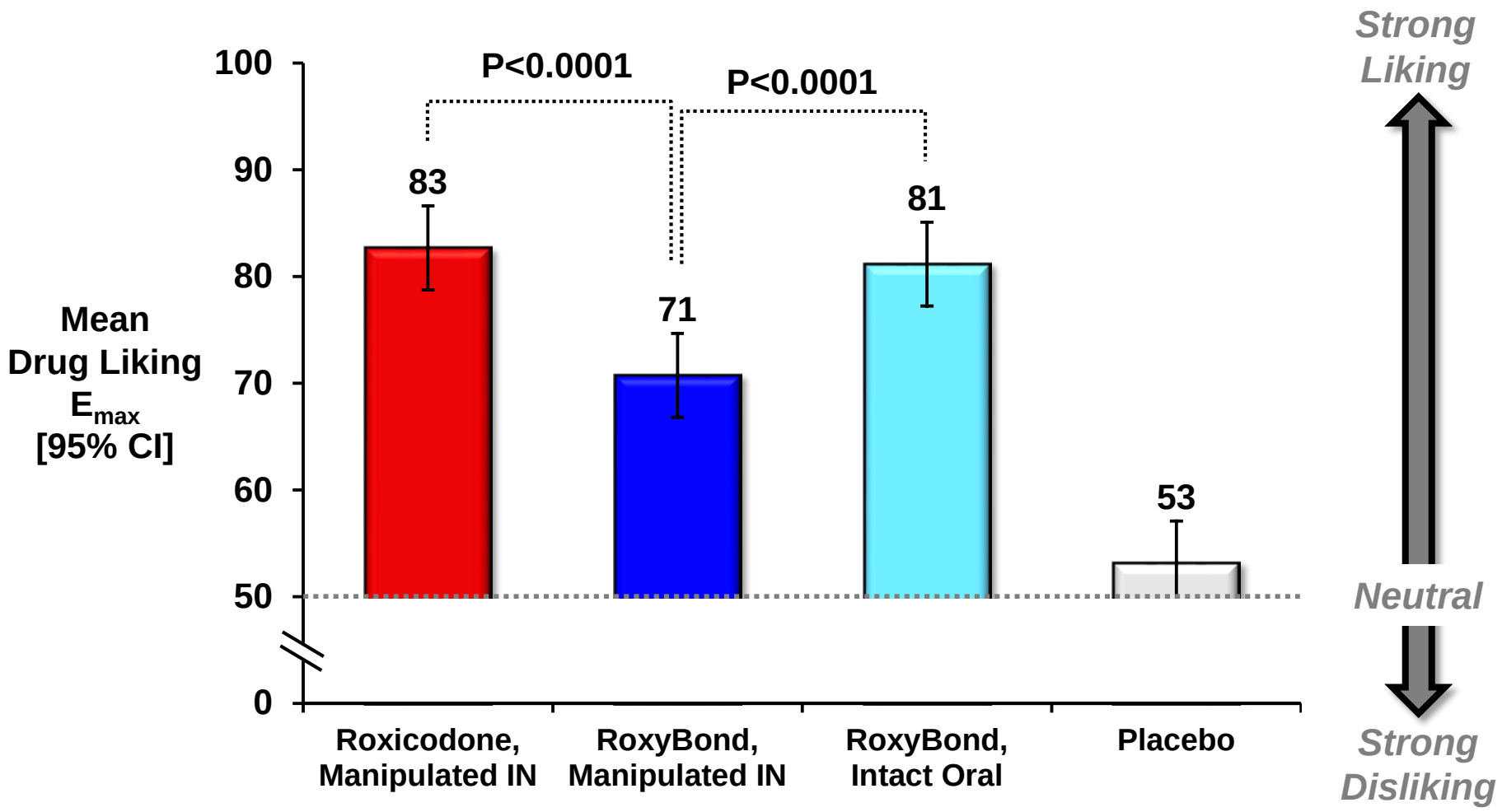
Endpoints Intranasal HAP Study

- Primary Endpoint
  - Drug Liking E_{max}
- Key Secondary Endpoints
  - Take Drug Again E_{max}
  - Overall Drug Liking E_{max}
  - Drug Effects Questionnaire
  - Ease of Snorting Assessment

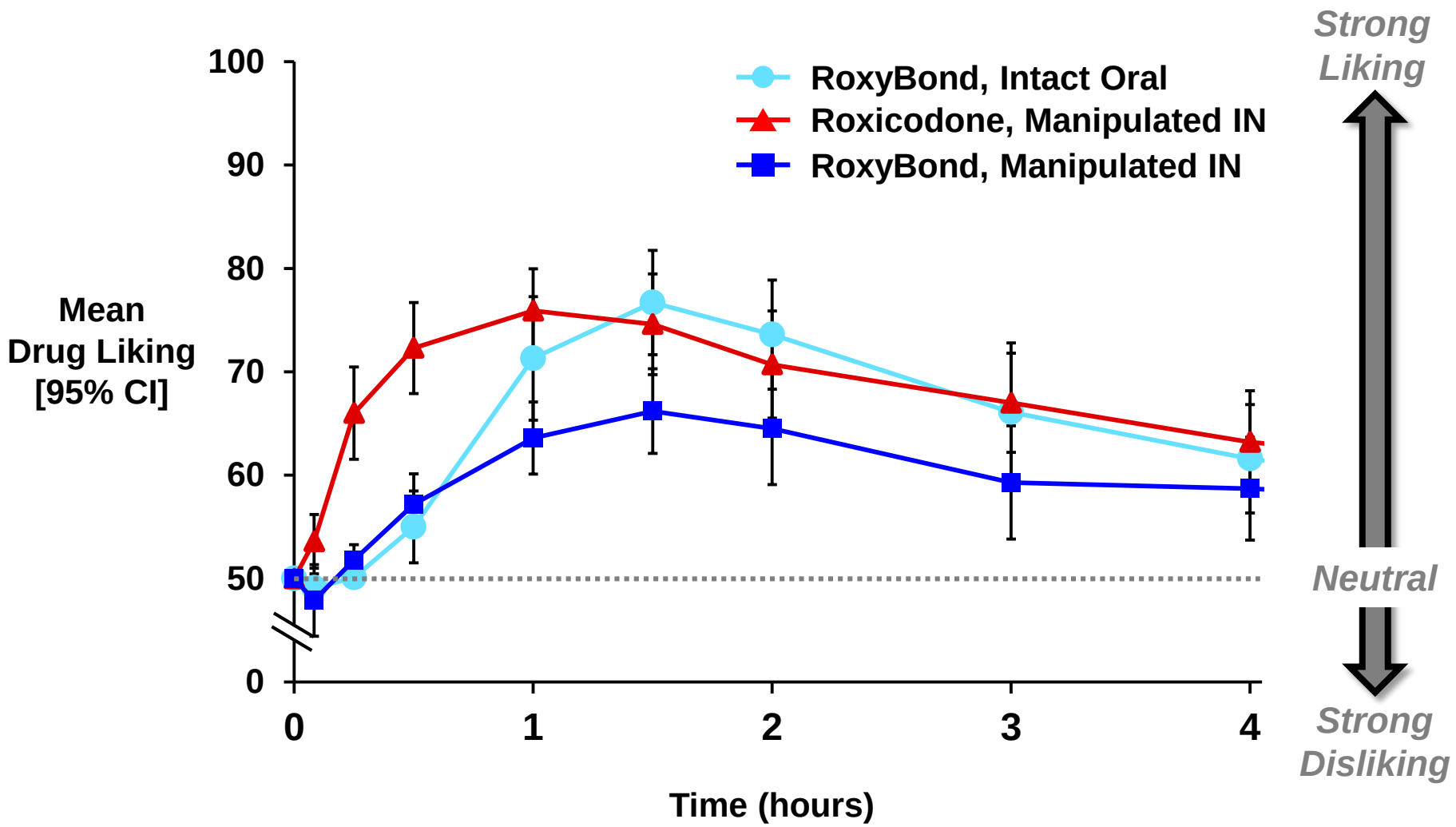
Lower Oxycodone Concentrations for Manipulated IN RoxyBond



Significantly Lower Maximum Drug Liking for Manipulated RoxyBond



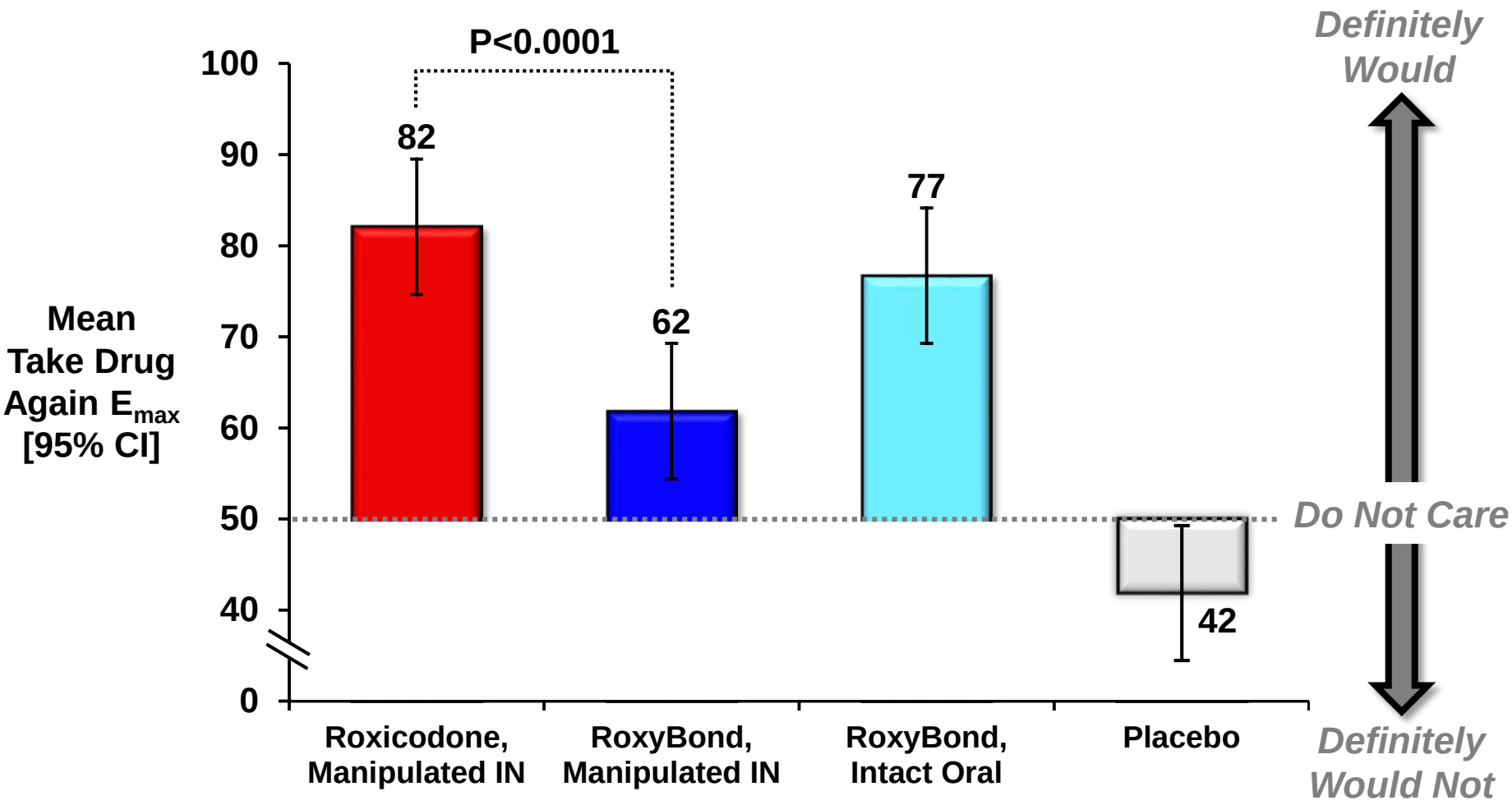
Lower Drug Liking for Manipulated RoxyBond At Early Time Points



Study 002: Intranasal HAP Study

Category 3

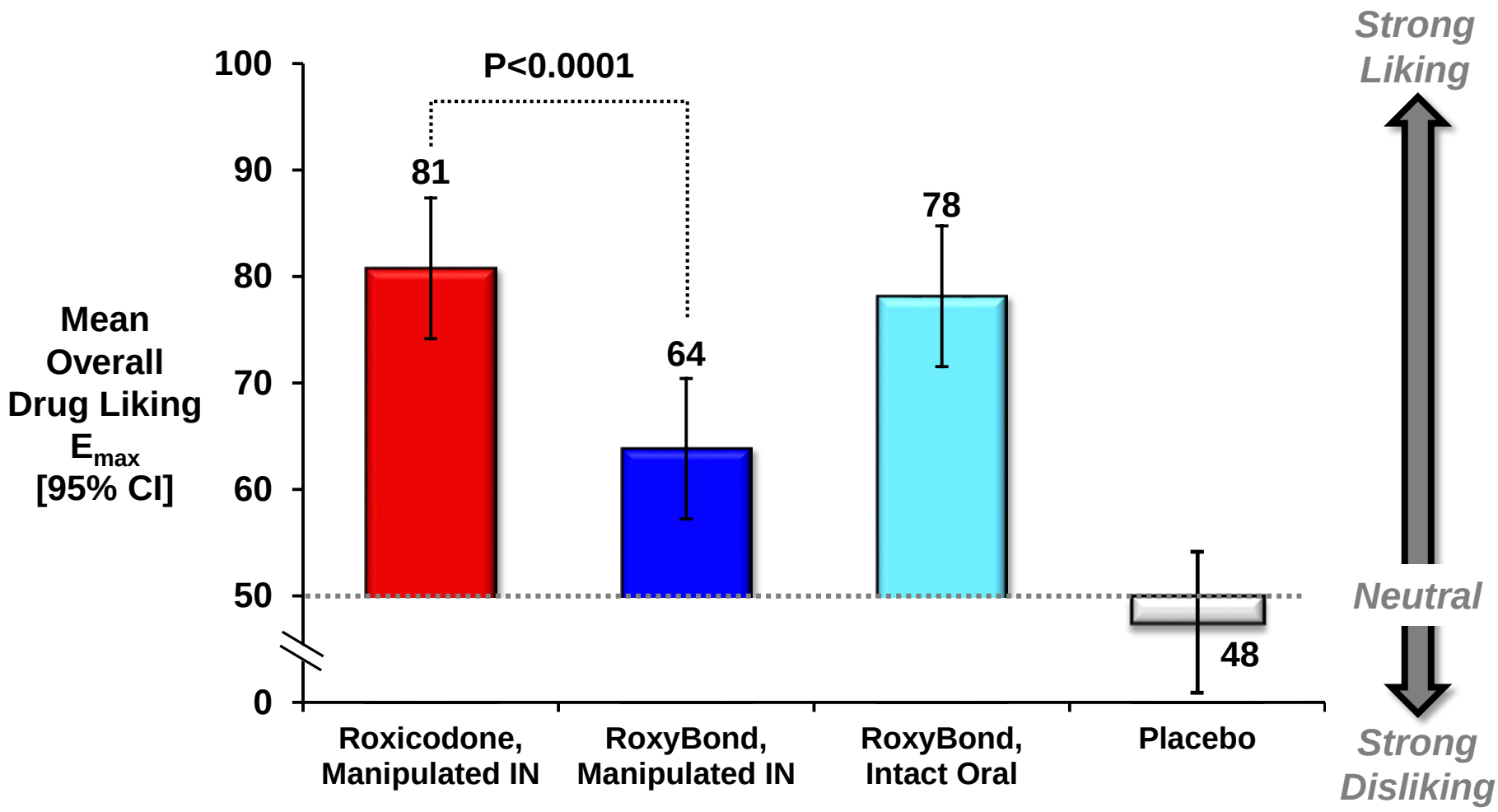
Significantly Lower Take Drug Again for Manipulated RoxyBond



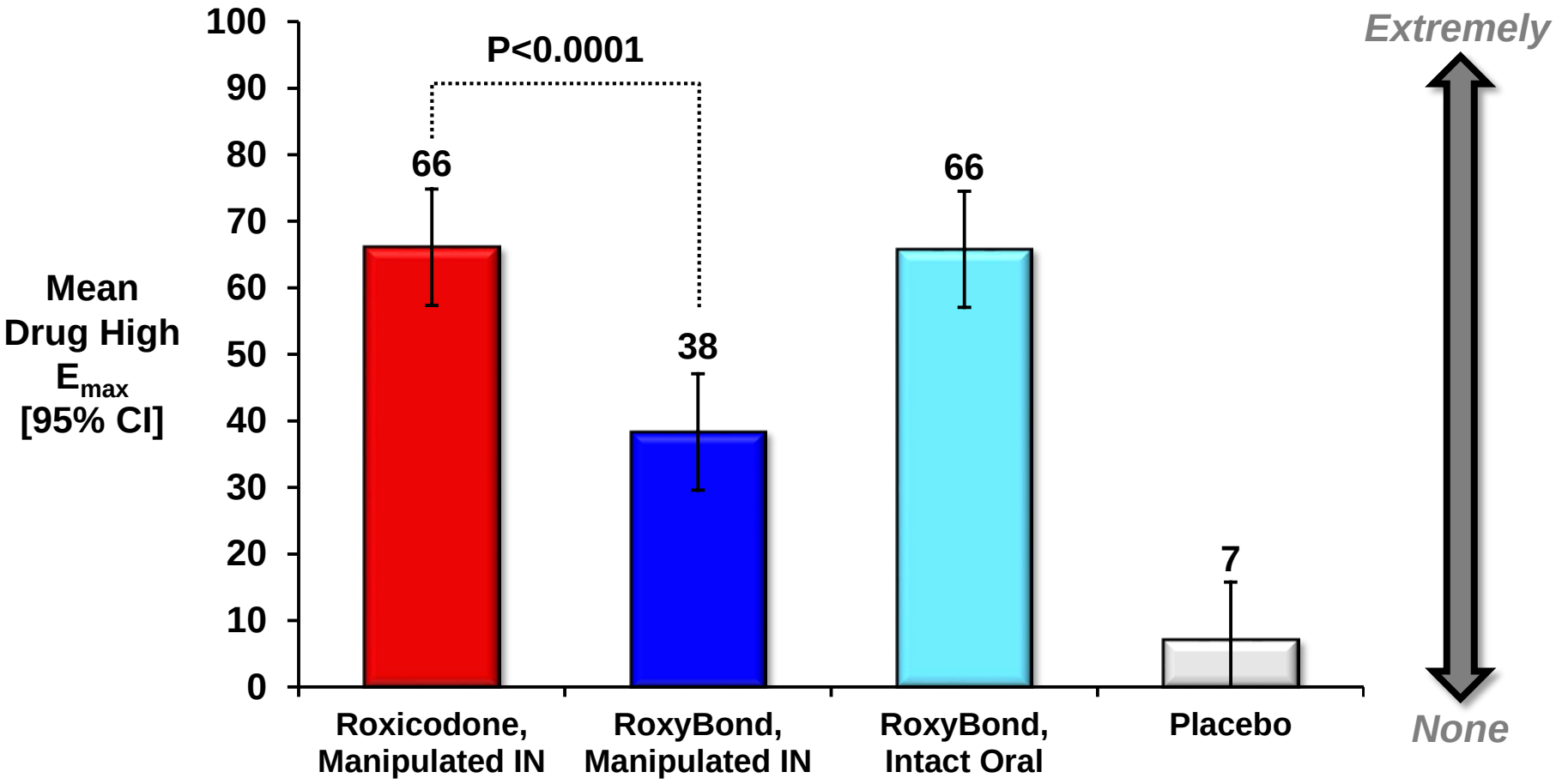
Study 002: Intranasal HAP Study

Category 3

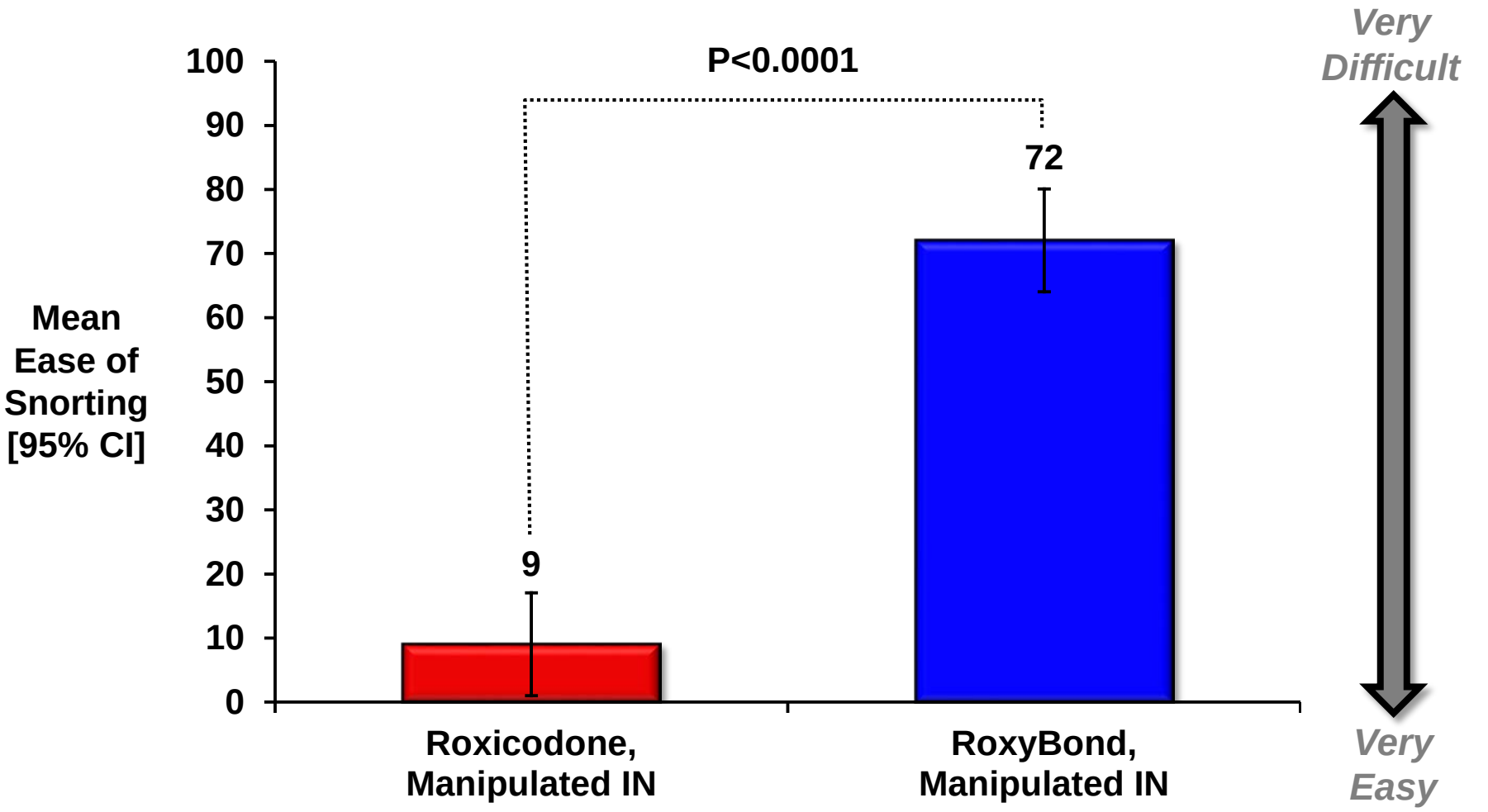
Significantly Lower Overall Drug Liking for Manipulated RoxyBond



Significantly Lower Drug High for Manipulated RoxyBond



RoxyBond Significantly More Difficult to Snort than Roxicodone



Study 002: Intranasal HAP Study

Category 3

Clinical Relevance of HAP Results

Meta-Analysis: Reduction in Overall Drug Liking Associated with Decrease in Non-Medical Use

ORIGINAL ARTICLE

Positive subjective measures in abuse liability studies and real-world nonmedical use: Potential impact of abuse-deterrent opioids on rates of nonmedical use and associated healthcare costs

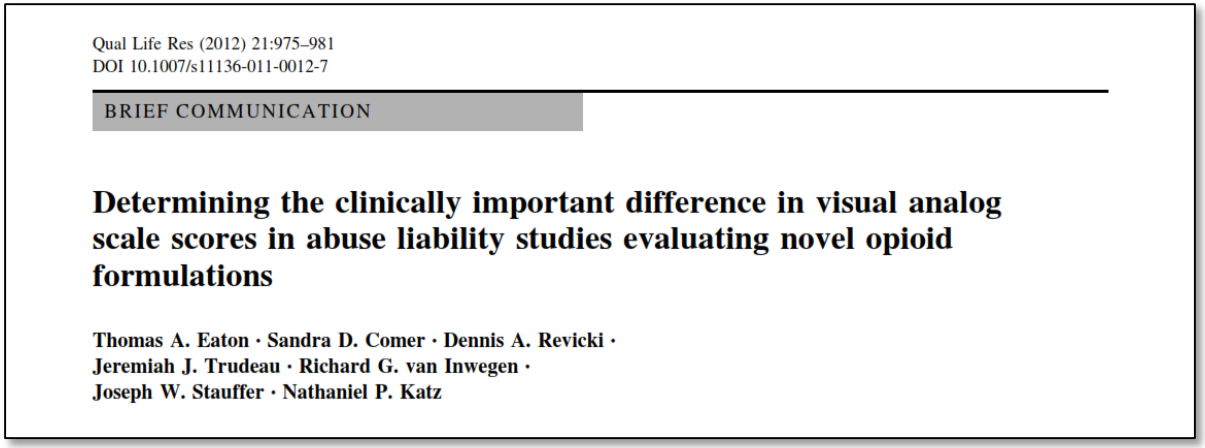
Alan G. White, PhD; Joseph LeCates, PhD; Howard G. Birnbaum, PhD; Wendy Cheng, MPH, MPhil; Carl L. Roland, PharmD, MS; Jack Mardekian, PhD

5 mm reduction in Overall Drug Liking E_{max} for ADF ER oxycodone → ~10.1% reduction in non-medical use

- 17 mm reduction in Overall Drug Liking E_{max} for RoxyBond likely to lead to reductions in abuse

White et al. *J Opioid Manag* 2015;11:199-210.

Literature Provides Support for Clinical Significance of RoxyBond HAP Study



Qual Life Res (2012) 21:975–981
DOI 10.1007/s11136-011-0012-7

BRIEF COMMUNICATION

Determining the clinically important difference in visual analog scale scores in abuse liability studies evaluating novel opioid formulations

Thomas A. Eaton · Sandra D. Comer · Dennis A. Revicki · Jeremiah J. Trudeau · Richard G. van Inwegen · Joseph W. Stauffer · Nathaniel P. Katz

- Determined clinically important difference in Drug High E_{max} in treatment setting[1]
- 8-10 mm differences in Drug High E_{max} led to clinically significant changes in drug-taking behavior
- 28 mm lower Drug High E_{max} for RoxyBond supports lower IN abuse potential

1. Eaton et al. *Qual Life Res* 2012;21:975-81.

RoxyBond Can Be Expected to Deter Intranasal Abuse

- Met primary endpoint with statistically significantly lower Drug Liking E_{max}
- Met secondary endpoints
  - Less likely to Take Drug Again
  - Lower Overall Drug Liking
  - Lower Drug High
  - More difficult to snort
- PK consistent with PD
- Results consistent with clinical significance in literature

Clinical Perspective

Jeffrey Gudin, MD

Director

Pain Management and Palliative Care

Englewood Hospital and Medical Center

Questions for Joint Advisory Committee

- Should RoxyBond be approved for the proposed indication, management of pain severe enough to require an opioid analgesic?
- Whether there are sufficient data to support a finding that RoxyBond has properties that can be expected to deter:
  - Intranasal route of abuse
  - Intravenous route of abuse

RoxyBond Expected to Have Same Efficacy and Safety as Roxicodone

- Comparable bioavailability
  - Equivalent efficacy and safety expected
- Available in commonly prescribed oxycodone strengths and dosing schedule
- Can be taken without regard to food
- No new risks compared to existing products

Questions for Joint Advisory Committee

- Should RoxyBond be approved for the proposed indication, management of pain severe enough to require an opioid analgesic?
- Whether there are sufficient data to support a finding that RoxyBond has properties that can be expected to deter:
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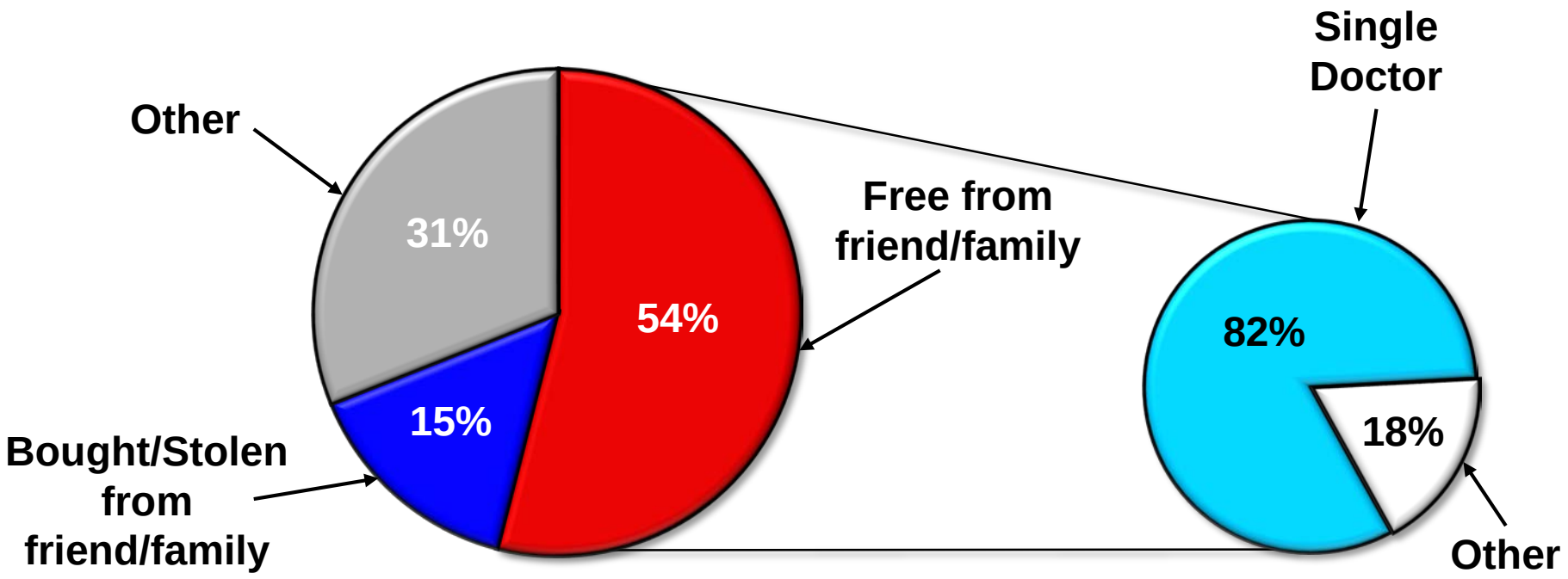
  - Intravenous route of abuse

Most Nonmedical Opioid Users Obtain Drug from Friend or Family



- Difficult to ascertain risk of diversion
- ADFs benefit patients and individuals with access to their medicine cabinet

National Survey on Drug Use and Health. SAMSHA 2011-2012.

Important Real-World Considerations for Abuse Deterrence

- Most abusers start with IR products[1-3]
  - RoxyBond is opportunity to intervene earlier, deter progression to more dangerous routes
- ADFs are abuse deterrent, not abuse proof
  - Can be defeated with enough knowledge, time, and effort
- Clinically relevant questions for ADFs:
  - *Does it make abuse more difficult?*
  - *Does it make the experience less rewarding?*

1. Budman et al. *Harm Red J* 2009;6:8-14.
2. Cicero et al. *RADARS System Technical Report* 2015.
3. Lankenau et al. *Int J Drug Policy* 2012;23:37-44.

RoxyBond Can Be Expected to Deter Intranasal and IV Abuse

Slows release and resists extraction of oxycodone when manipulated compared to intact oral administration

Intranasal Abuse Deterrence

- Difficult to get into abusable form
- More difficult to snort than Roxicodone
- Lower and slower absorption
- Significantly lower Drug Liking and Take Drug Again

IV Abuse Deterrence

- Resistant to particle size reduction
- Difficult to extract
- Forms viscous material when manipulated
- Resists syringeability

Significant improvement over non-abuse-deterrent products

ADFs One Component to Address Prescription Opioid Epidemic

- Full impact cannot be realized until all opioids are abuse-deterrent
- FDA's goal: ADFs for all major opioids

RoxyBond™ (oxycodone hydrochloride) Immediate-Release Tablets

April 5, 2017

Inspirion Delivery Sciences

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

Back-up Slides

Gastric pH When Taking PPI Similar to Gastric pH After a Meal

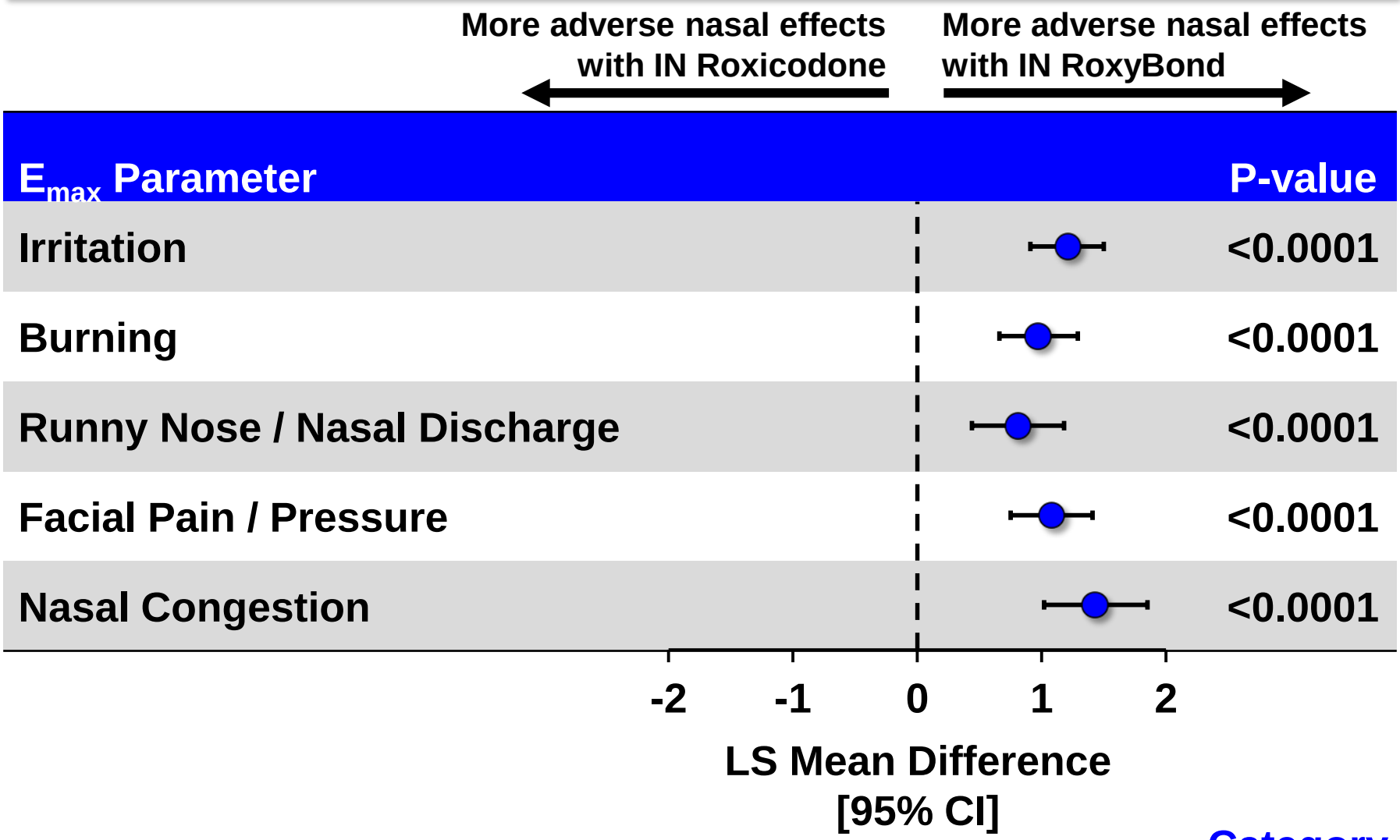
- PPI pH at steady state, median (min, max)[1]
  - Esomeprazole – 4.8 (2.5, 5.8)
  - Tenatoprazole – 5.0 (2.3, 5.8)
- Effect of food on pH, median (interquartile range)[2]
  - Fasted – 1.7 (1.4, 2.1)
  - Fed – 5.0 (4.3, 5.4)
- No clinically significant effect of food on oxycodone bioavailability with RoxyBond

1. Hunt et al. *Am J Gastroenterology* 2005;100:1949-1956.
2. Dressman et al. *Pharm Res* 1990;7:756-61.

Similar Food Effects with RoxyBond and Roxicodone

- RoxyBond (fed vs. fasted)
  - 23% increase in AUC
  - 18% increase in C_{max}
  - T_{max} delay from 1.8 to 2 hrs
- Roxicodone (fed vs. fasted)
  - 27% increase in AUC
  - T_{max} delay from 1.25 to 2.54 hrs
- Inspirion agrees with FDA conclusion that “a food restriction should not be recommended for RoxyBond (FDA briefing book; p. 55)”

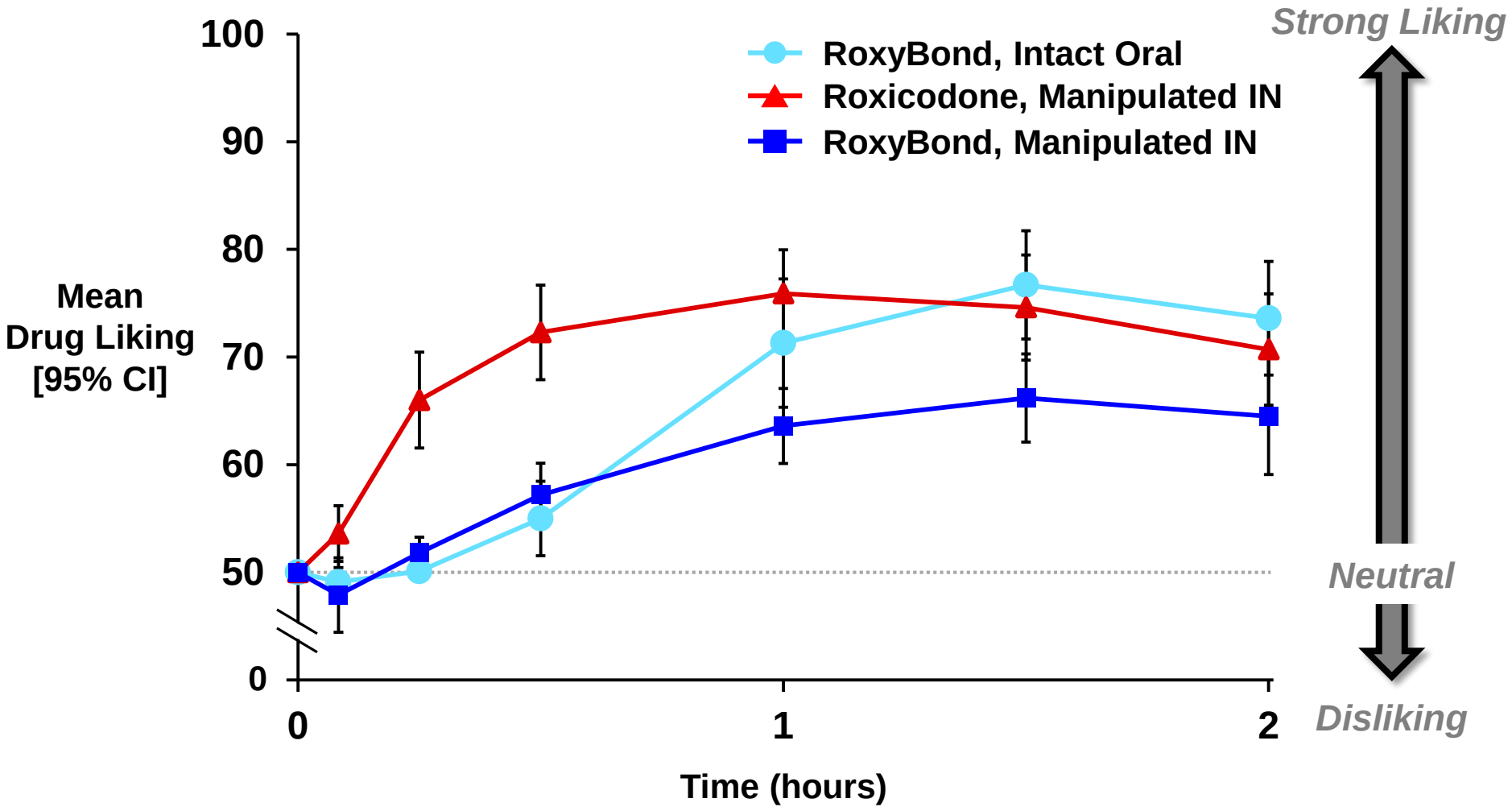
RoxyBond Produced Significantly More Adverse Nasal Effects



Study 002: Intranasal HAP Study

Category 3

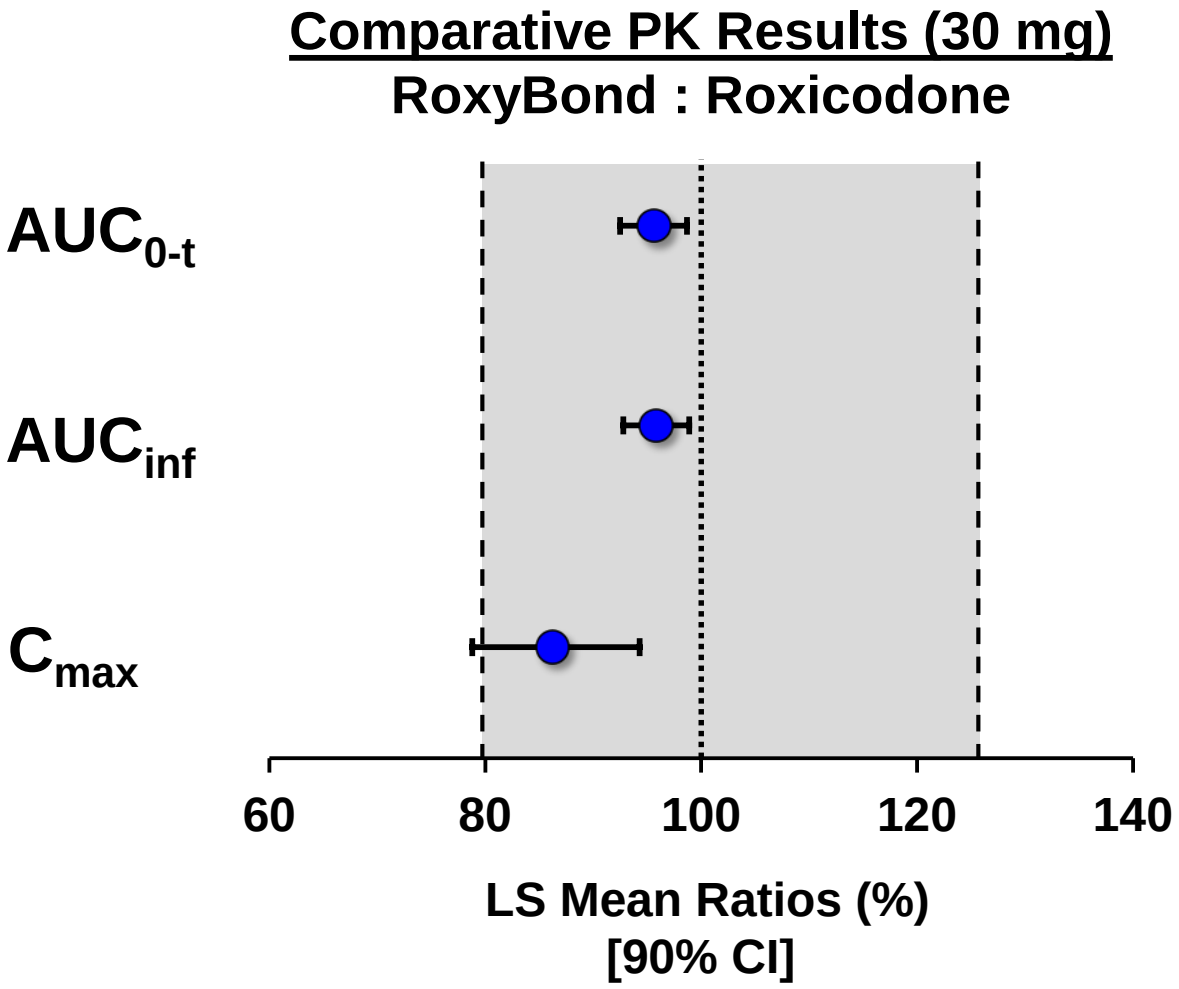
Lower Drug Liking for Manipulated RoxyBond At Early Time Points



Study 002: Intranasal HAP Study (N=29)

Category 3

RoxyBond Expected to Have Same Efficacy and Safety as Roxicodone



- Strengths are dose proportional
- No clinically significant effect of food

Note: Gray shaded area reflects bioequivalence range of 80% to 125%

Electric Tool G Produced the Largest Percentage of Small Particles

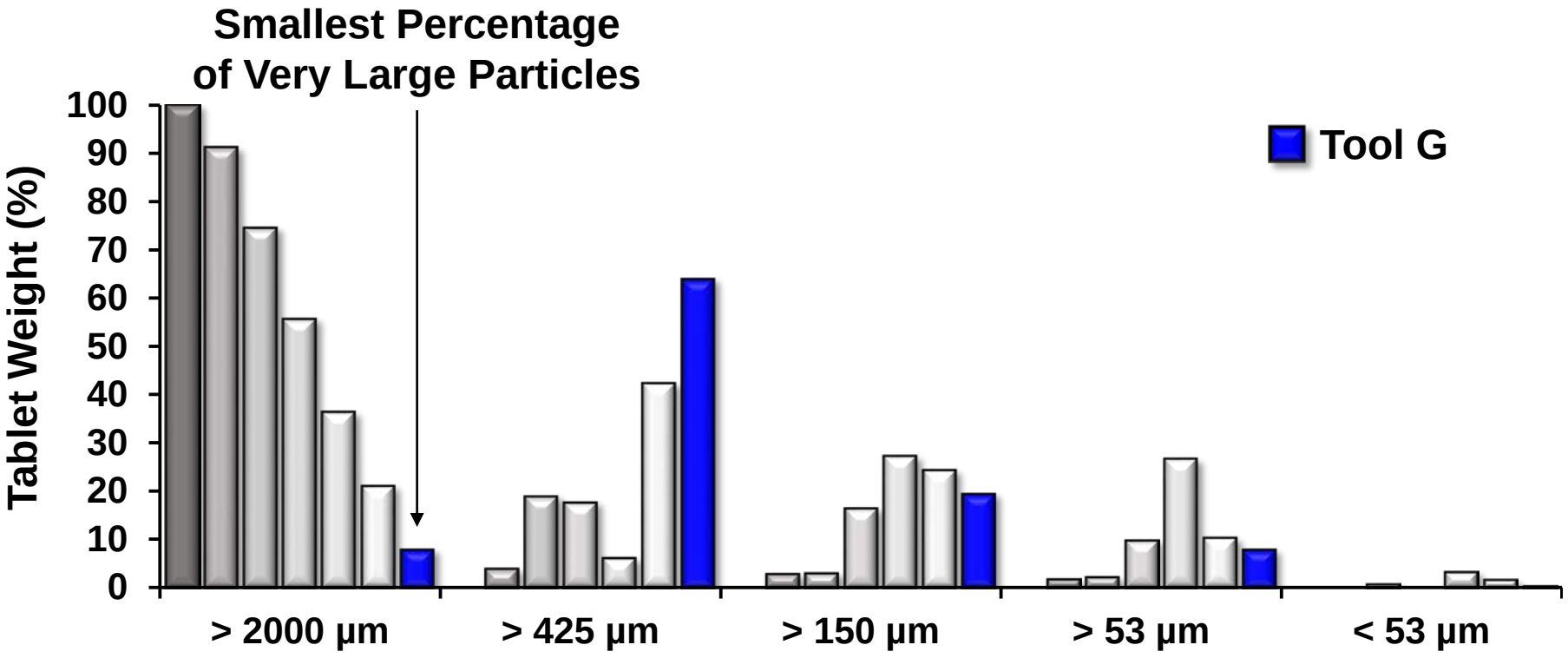
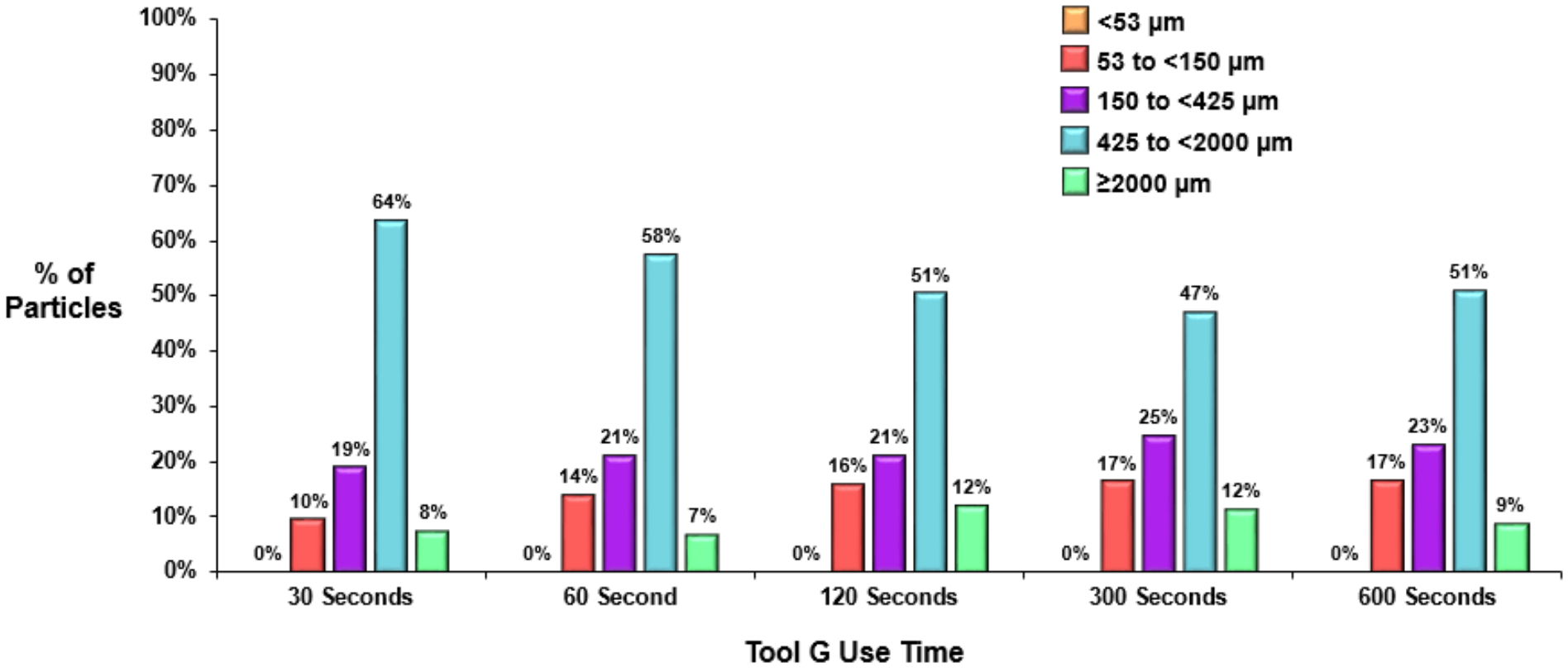


Table 11: Treatment Emergent Adverse Events - Intranasal HAP Study O-ARIR-002

Adverse Event	Manipulated Roxicodone Intranasal (N = 30)	RoxyBond Manipulated Intranasal (N = 30)	RoxyBond Intact Oral (N = 31)	Placebo (N = 29)
Generalized Pruritus	23.3%	6.7%	12.9%	0.0%
Nausea	13.3%	13.3%	6.5%	0.0%
Vomiting	6.7%	10.0%	6.5%	0.0%
Pruritus	0.0%	0.0%	12.9%	0.0%

HAP = human abuse potential; N = number of subjects.

Figure 7: Particle Size Distribution Results for Varying Use Times with Tool G



RoxyBond Manipulated with Tool G

Individual PK Curves