Aximris XR (Oxycodone HCl Extended-Release) Tablets for Treatment of Chronic Pain

January 15, 2020

Intellipharmaceutics Corp.

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

Introduction

Isa Odidi, PhD, DSc., MBA
Chief Executive Officer, Co-Chief Scientific Officer and Co-founder
Intellipharmaceutics Corporation.

Proposed Aximris XR Indication

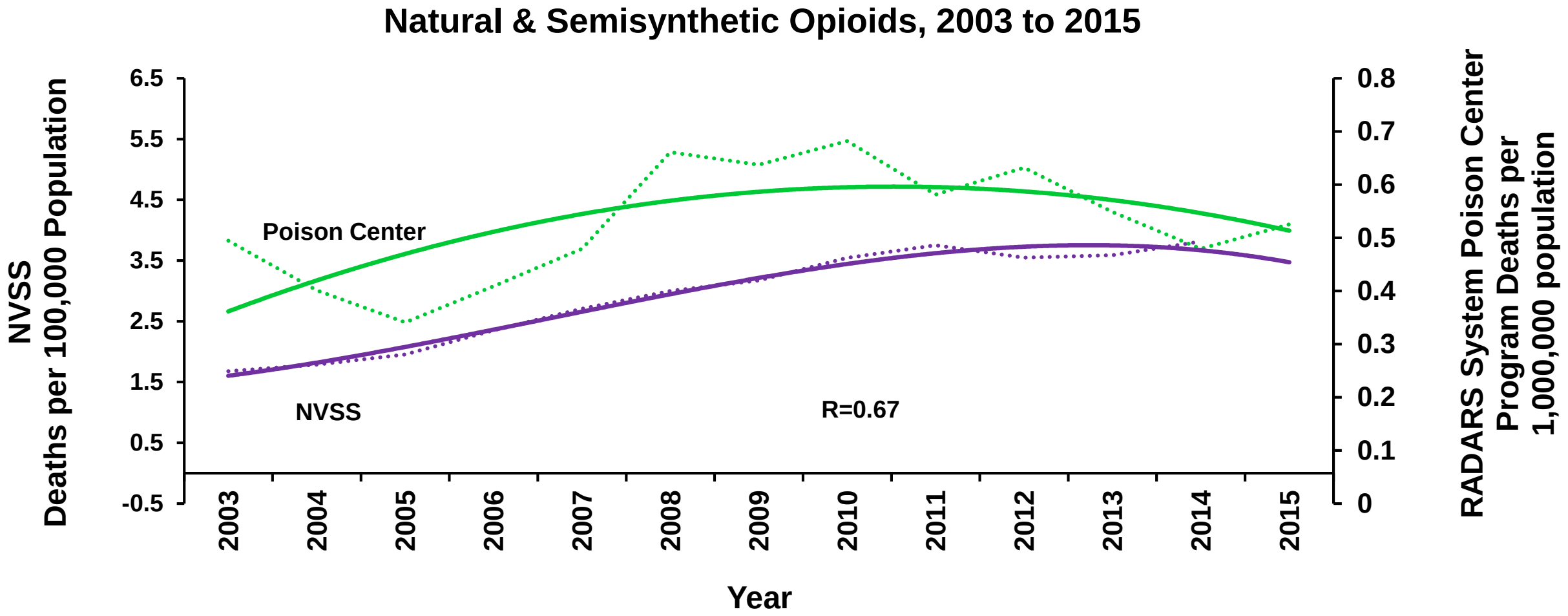
Aximris XR is an extended-release oxycodone product indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Why More Abuse-Deterrent Formulation (ADF) Options?

- Despite reformulation, IV abuse of oxycodone ER continues
- Risk of serious health consequences with IV drug use
  - Death or major adverse effect is 2.0-3.4 times greater[1]
  - 10% of HIV diagnoses and 13% of AIDS cases attributed to IV drug use[2,3]
  - Other health risks include: hepatitis C[4], endocarditis[5,6], blood clots[7]
- Improved ADF options needed to address vulnerabilities in easily abusable products and current ADFs
- FDA Guidance[8] anticipates innovation and incremental improvement of opioids with abuse deterrent properties

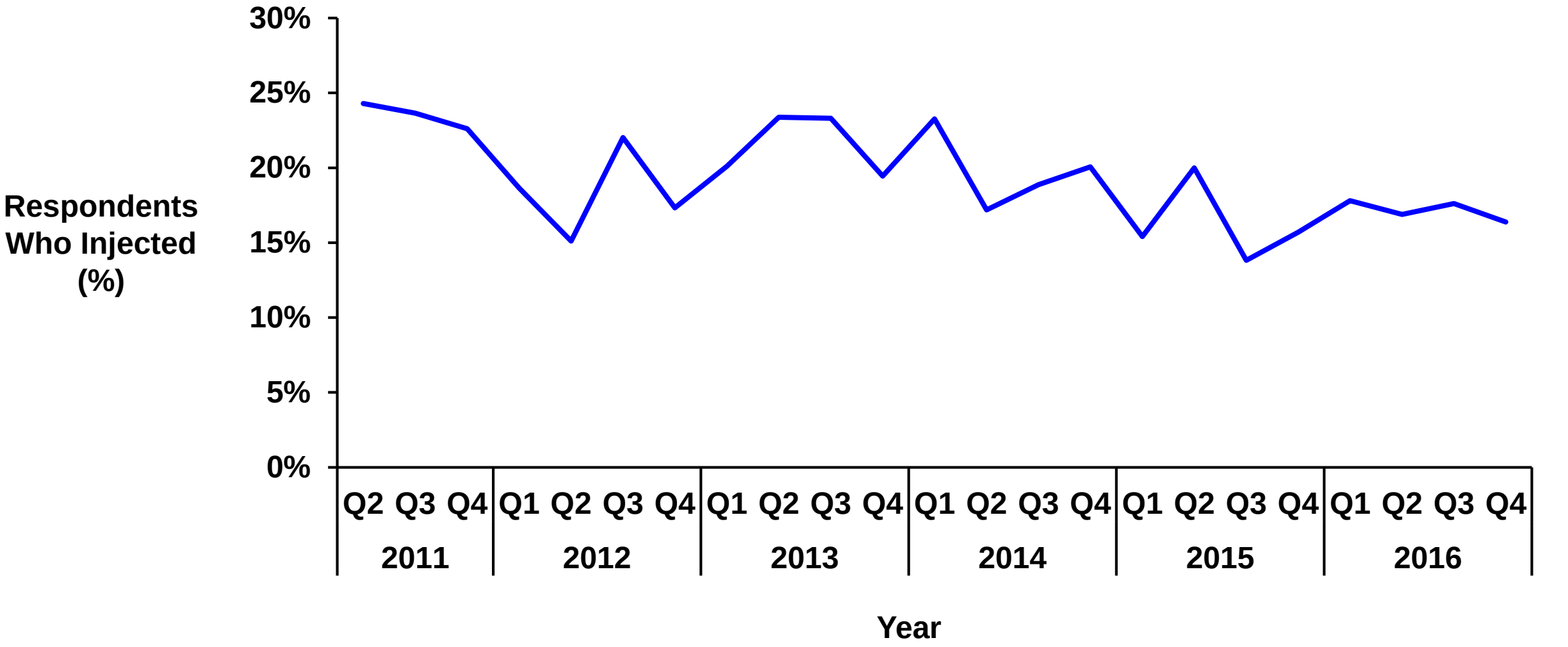
1. RADARS program 2.6
2. https://www.drugabuse.gov/publications/drugfacts/drug-use-viral-infections-hiv-hepatitis
3. CDC. HIV Surveillance Report, 2017;28
4. Bruneau et al. *Addiction* 2012;107:1318-27
5. Ronan & Herzig. *Health Affairs* 2016;35:832-7
6. Gordon & Lowy. *NEJM* 2005;353:1945-54
7. McLean et al. *Harm Reduct J* 2009;6:37
8. CDER. Abuse-Deterrent Opioids—Evaluation and Labeling. 2015.

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

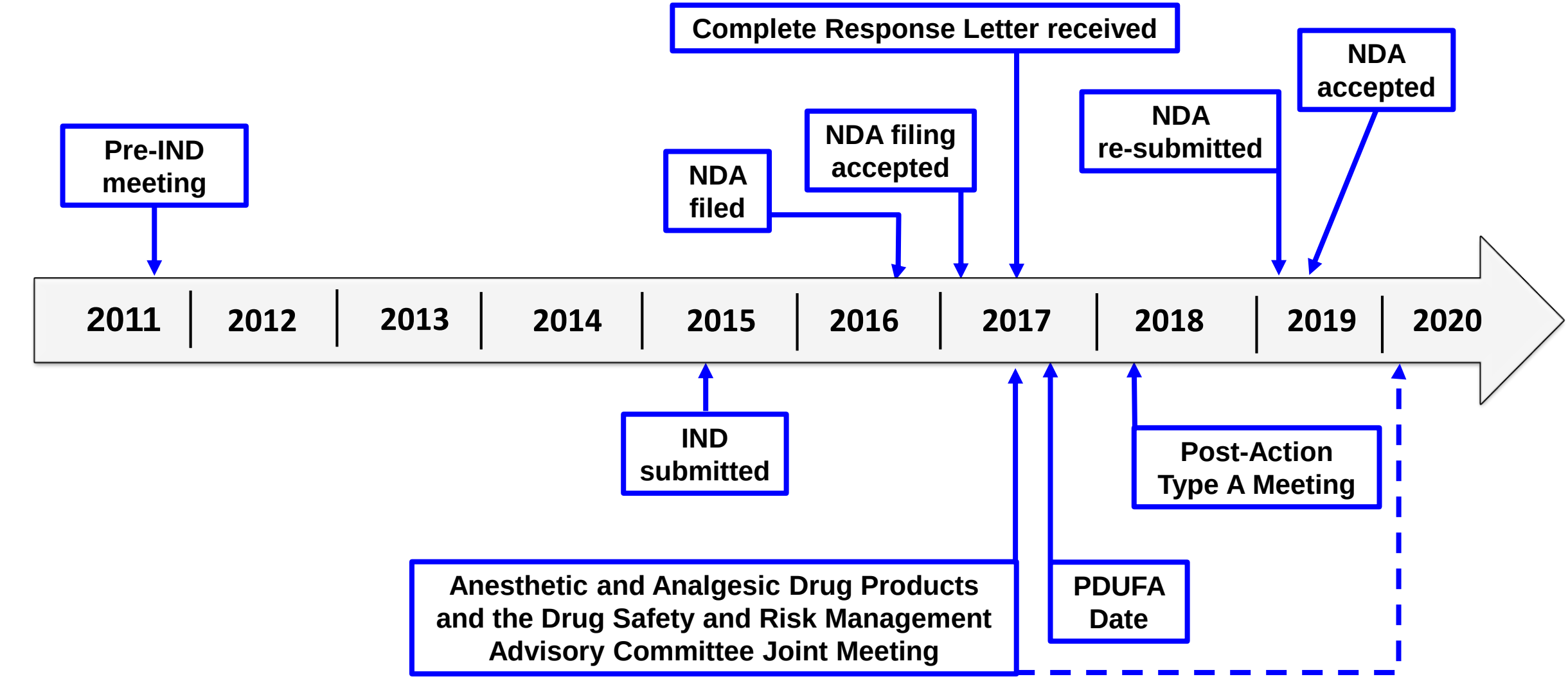


**T40.2 Natural and semisynthetic opioids: oxycodone, morphine, hydromorphone, oxymorphone, others
**RADARS System opioids: oxycodone, hydrocodone, morphine, hydromorphone, and oxymorphone. Deaths include cases followed to a known medical outcome whose death was related to the reported exposure

Non-Oral Abuse Persists Despite OxyContin Reformulation



Regulatory Pathway and Milestones



Aximris XR Development Program Followed FDA Guidance and Feedback

- Comprehensive set of in vitro abuse-deterrence studies (Category 1)
- 7 clinical PK studies
- 2 Clinical PK/PD studies (Category 2 and 3)
- Hemolytic and in vivo repeat dose IV toxicity studies

Aximris XR Formulated with Several Properties Intended to Make Abuse Difficult or Less Attractive

Properties	Aximris XR	OxyContin
Resistance to physical manipulation	✓✓	✓✓✓
Coagulate rapidly to form highly viscous material upon contact with small/large volumes of liquid	✓✓✓	✓✓
Resistance to extraction using standard methods abusers commonly use	✓✓✓	✓✓✓
Resistance to extraction using typical website/advanced “recipes”	✓✓✓	✓
Difficult to snort	✓✓	✓
Local irritating effects – Nasal congestion	✓✓	✓✓

✓✓✓= High ✓✓= Moderate ✓= Low

We are Very Committed to the Safe and Responsible Use of Aximris XR

- Participation in Opioid Analgesic REMS
- Aximris XR safe use program
- Responsible sales and marketing practices
- Pharmacovigilance studies and risk minimization measures
- Post-marketing studies under post market requirements (PMRs)

Agenda

Category 1 Abuse-Deterrence Studies and Nonclinical Excipient Safety Studies	**Olu Aloba Ph.D., RAC** Senior Director of CMC Services Camargo Pharmaceutical Services
Clinical Pharmacology and Abuse-Deterrence Human Abuse Potential Studies	**Ruth E. Stevens Ph.D., MBA** Chief Scientific Officer and Founder Camargo Pharmaceutical Services
Benefit/Risk Profile and Risk Mitigation Plans	**Isa Odidi Ph.D., D.Sc., MBA** Chief Executive Officer, Co-Chief Scientific Officer, Co-Founder Intellipharmaceutics Corporation

Additional Experts

REMS and Post-Marketing Surveillance	**Richard C. Dart, MD, PhD** Executive Director RADARS System Denver Health and Hospital Authority
Human Abuse Potential	**Stephanie Stanworth, M.S.** Independent Consultant

Category 1 Abuse-Deterrence Studies

Olu Aloba, RPh, PhD, RAC
Senior Director of CMC Services

Camargo Pharmaceutical Services

Aximris XR is Designed to Impede Transition to the Most Dangerous Route of Drug-Abuse

- **Design Approach**
  - Followed FDA Guidance and Feedback
  - Target established or anticipated manipulation practices or routes of abuse
  - Focus on known or expected behavioural tendencies
  - Use OxyContin as comparator
  - Make incremental improvements to deter abuse

Studies Supporting Category 1 Abuse-Deterrent Properties of Aximris XR

Category 1
Lab based in vitro manipulation and extraction studies

► Evaluated the difficulty with which AD properties of Aximris XR and OxyContin (comparator) can be compromised or defeated using typical abuser tactics and website/Advanced "recipes"

Category 2
Pharmacokinetic Clinical Trials

► Evaluated in vivo properties by measuring PK profiles of Aximris XR vs OxyContin and oxycodone IR as comparators.

► Two Clinical Trials (Oral and Intranasal) conducted

Category 3
Human Abuse Potential Clinical Trials

► Assessed potential PD effects of Aximris XR vs OxyContin and oxycodone IR as comparators.

► Two Clinical Trials (Oral and Intranasal) conducted

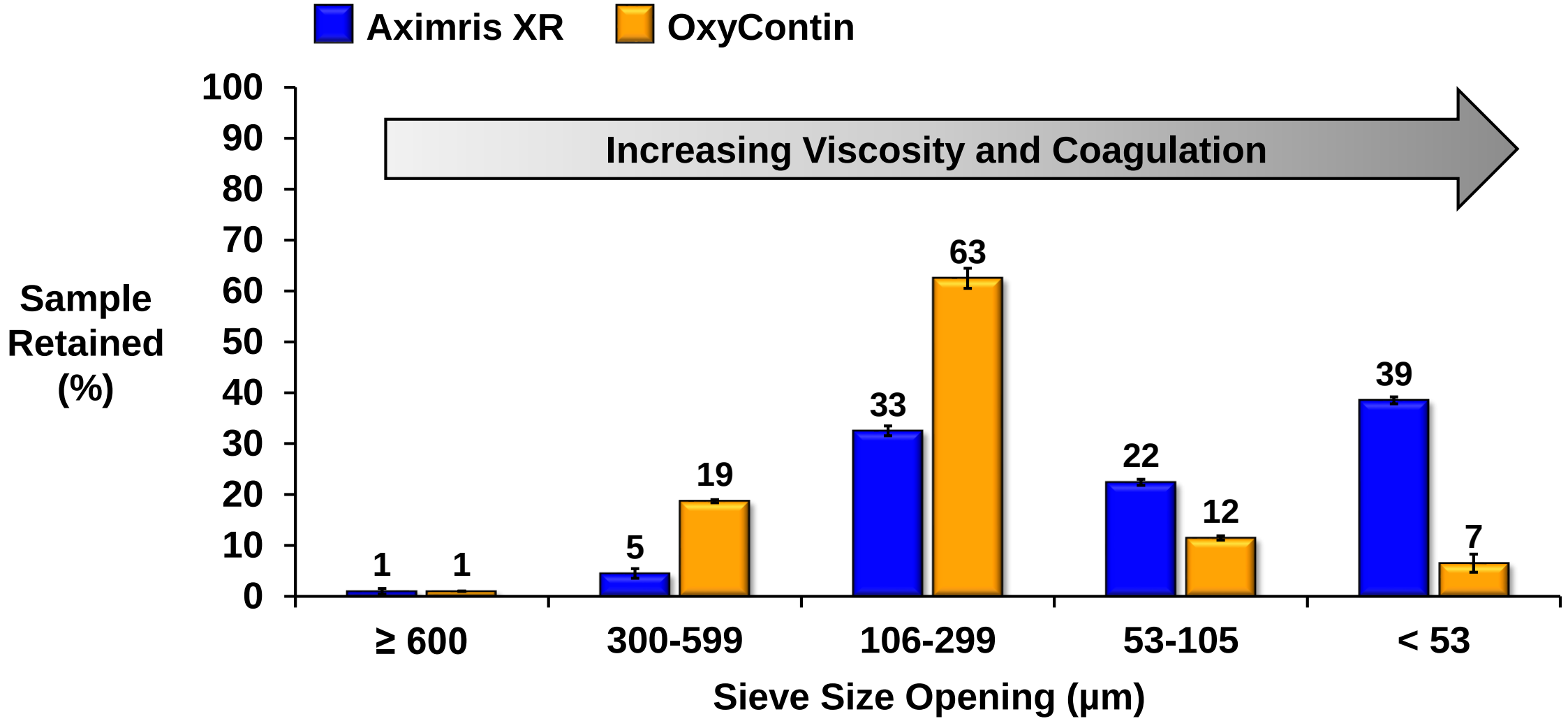
Overview of Category 1 Studies

- Particle size reduction/distribution
- Syringeability / Injectability and Small Volume Extraction
- Large Volume Extraction
- Alcohol Dose Dumping
- Manipulated Tablet Dissolution
- Simulated Smoking / Vaporization

Didactic Assessment of Particle Size Reduction and Distribution

- Common methods and tools used to grind and defeat ER properties of ADF obtained from online literature and FDA guidance documents
- 10 household tools used by abusers chosen as representative of cutting, crushing, grating, and grinding by abusers
  - 7 tools reduced Aximris XR while 5 reduced OxyContin
- The optimized particle size reduction was achieved using an advanced kitchen appliance for grinding

Most Effective Tool Reduced 99% of Aximris XR and OxyContin to Particles <600 Microns after Grinding



Error Bars = SD; Experiment performed in triplicates

Overview of Category 1 Studies

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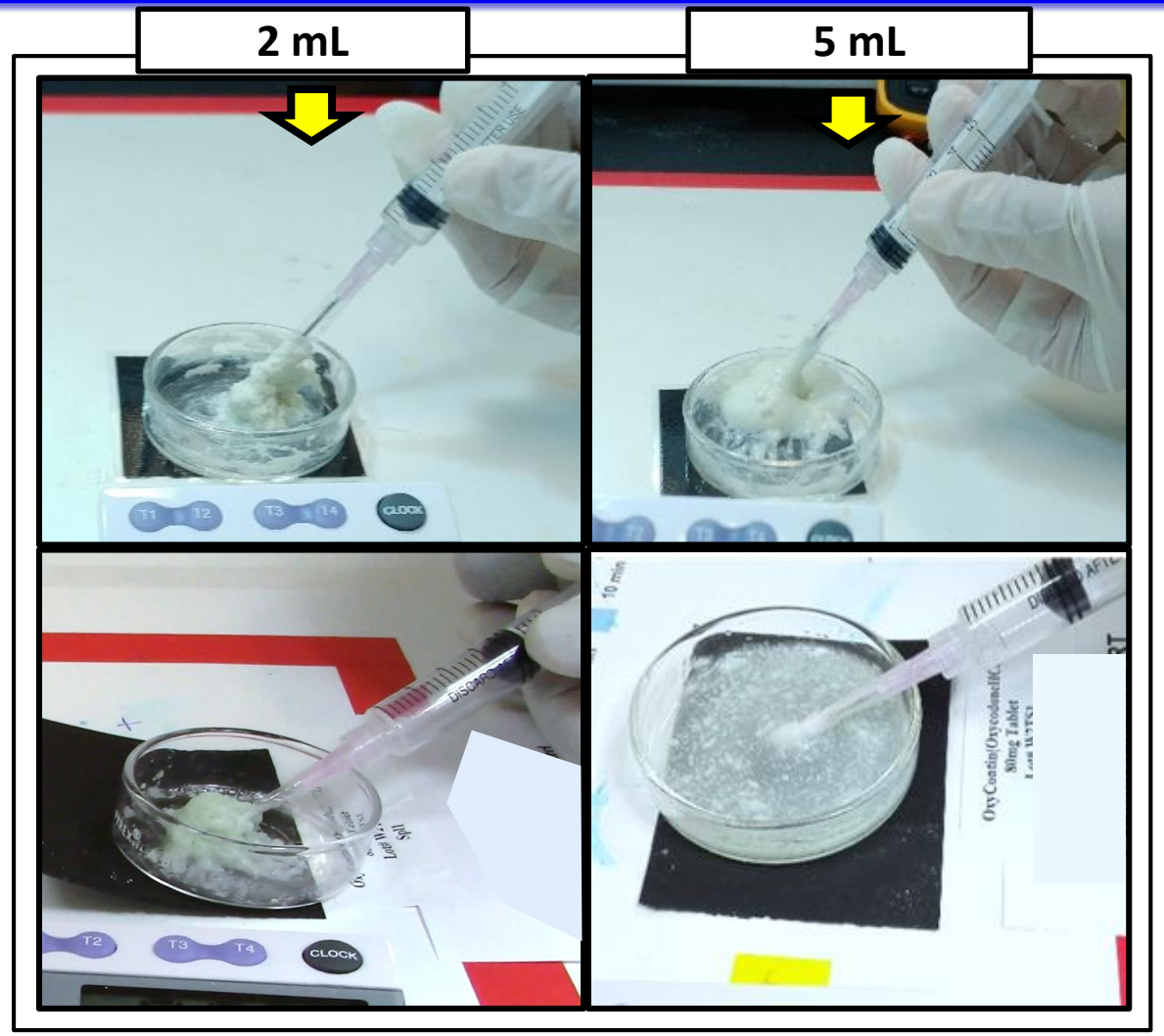
Common Methods for Preparing Solid Oral Dosage for IV Injection

- Grind tablet
- Extract the drug 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

Standard Syringeability / Injectability Studies Conducted to Simulate Common Abuser Practices

- Single dose of ground tablet tested with:
  - 5 different Volumes
  - 2 Solvents for extraction
  - Incubation up to 30 min
  - Agitation (two conditions)
  - Temperatures (two conditions)
- No conditions yielded suitable amounts of injectable oxycodone
- Both Aximris XR and OxyContin resist extraction for IV abuse using common abuser practices

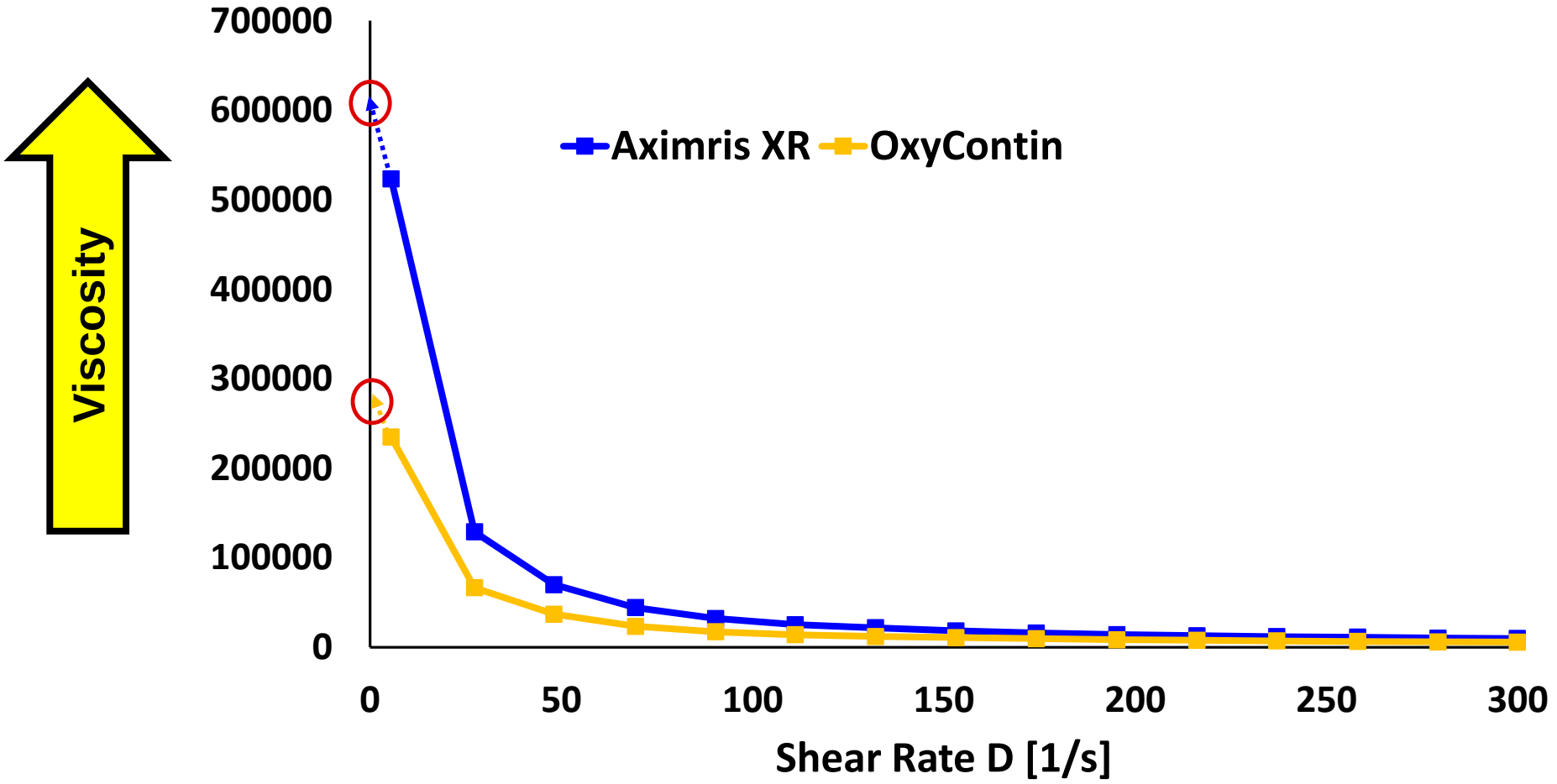
Drug Not Extractable from Aximris XR or OxyContin Using Common Abuser Methods

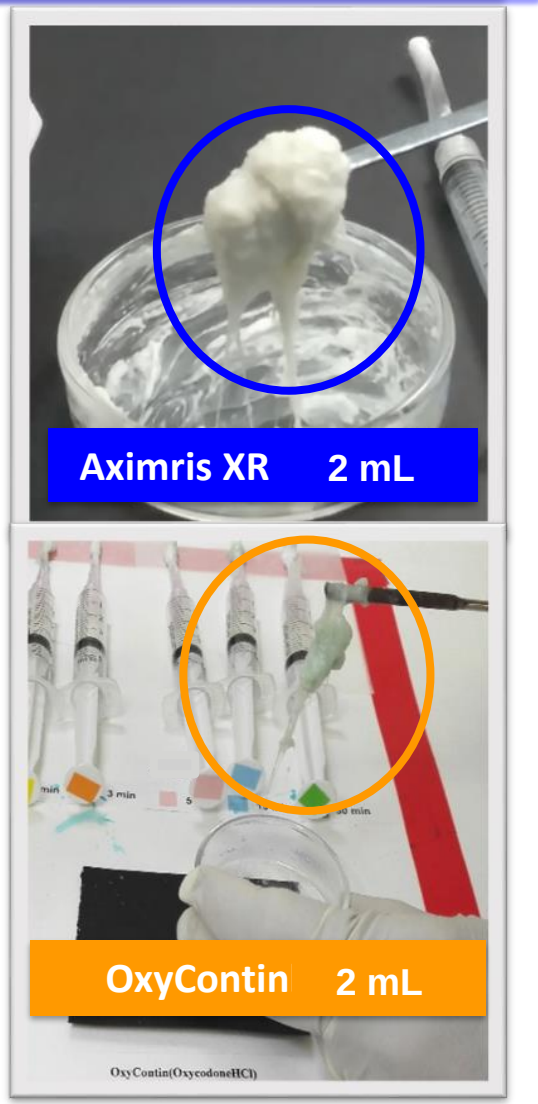


Standard/Common methods of drug extraction.

Ground, Untreated, Neutral Solution, No Agitation, Room Temperature

Aximris XR Ground is about 2x More Viscous than OxyContin in 2 mL Neutral Solution

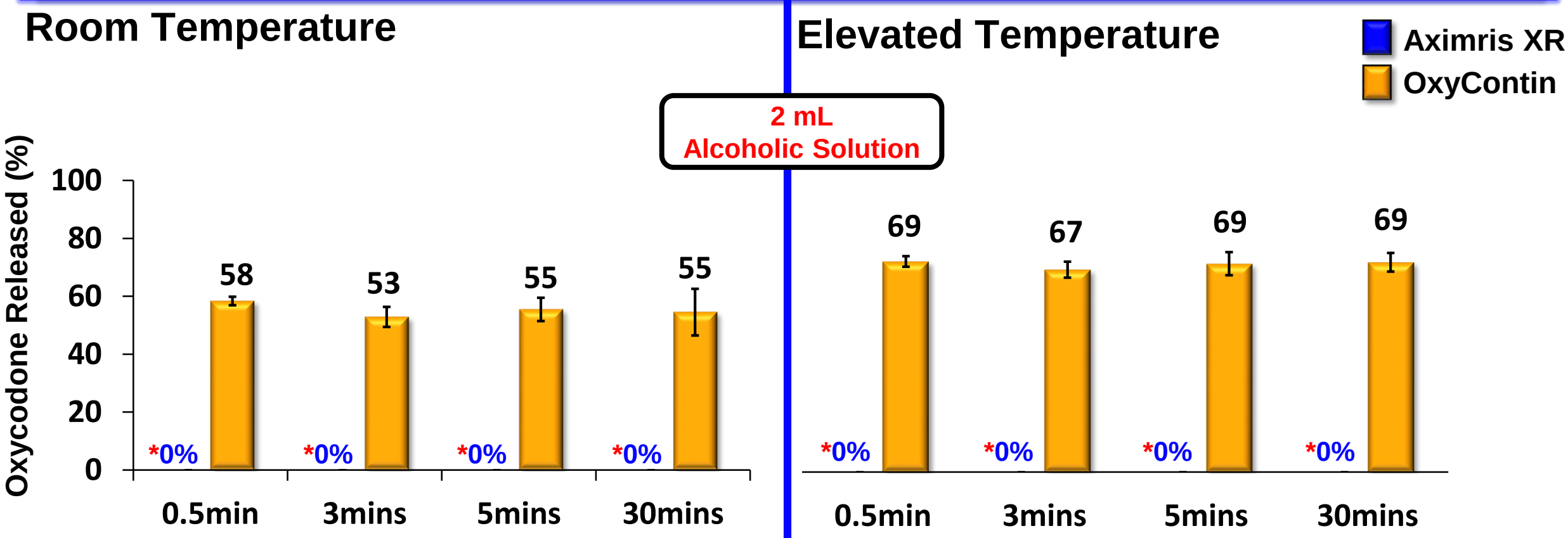




Studies Conducted Using Advanced "Recipe" Requested by the FDA

- Studies for Aximris XR and OxyContin evaluated:
  - Pre-treatment conditions (convection heat)
  - Tablet Form (Intact or Ground)
  - Volumes or Solvents
  - Agitation or Temperature conditions
  - Studies started with smallest needle, progressing to larger sizes

No Drug Extracted from Aximris XR Compared to OxyContin



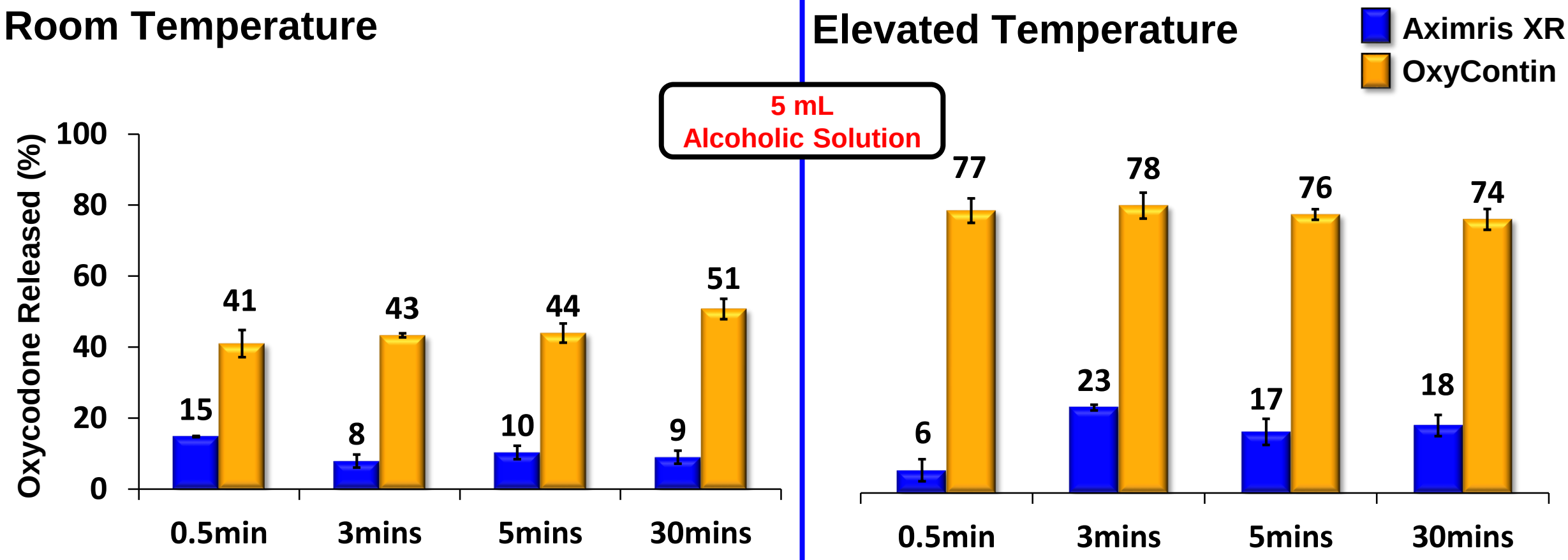
*Aximris XR Not Syringeable

Ground, Alcoholic Solution, 2 mL, No Agitation, Very Small Needle Gauge
Error bars = SD; Experiment performed in triplicates

Convection Heat pre-treatment

Advanced extraction method recommended by the FDA.

Less Drug Extracted from Aximris XR Compared to OxyContin

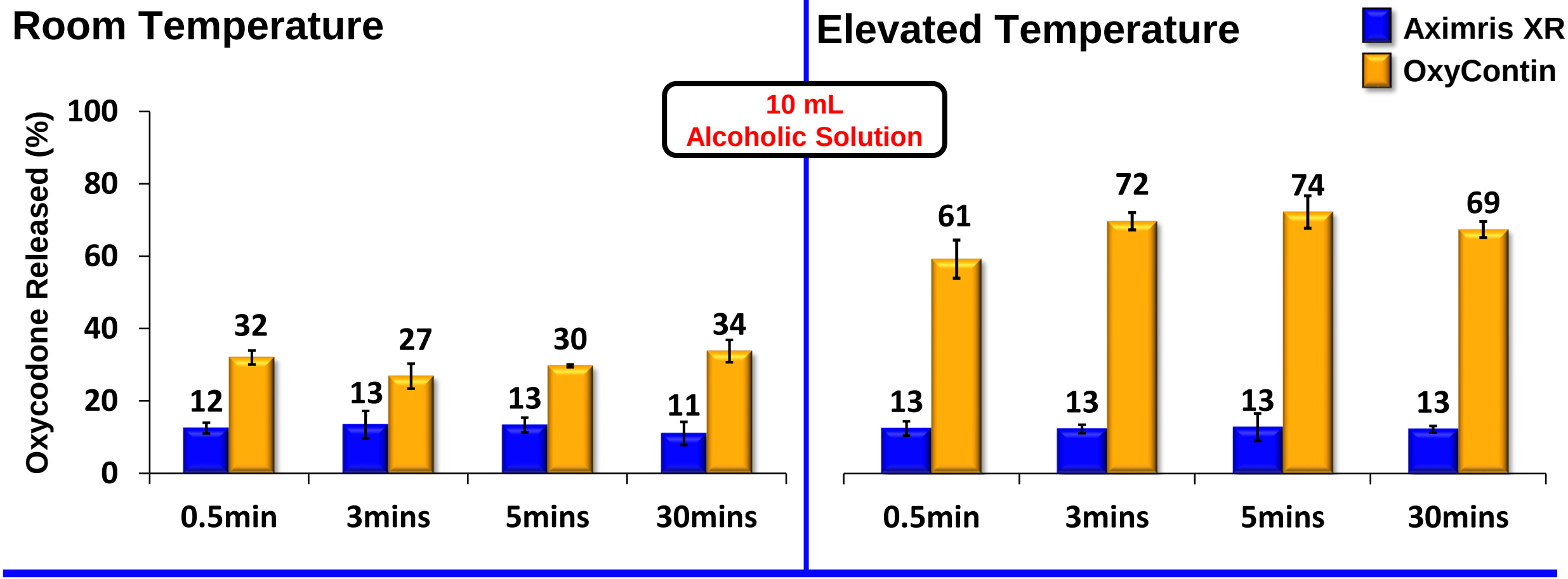


Ground, Alcoholic Solution, 5 mL, No Agitation, Very Small Needle Gauge
Error bars = SD; Experiment performed in triplicates

Convection Heat pre-treatment

Advanced extraction method recommended by the FDA.

Less Drug Extracted from Aximris XR Compared to OxyContin

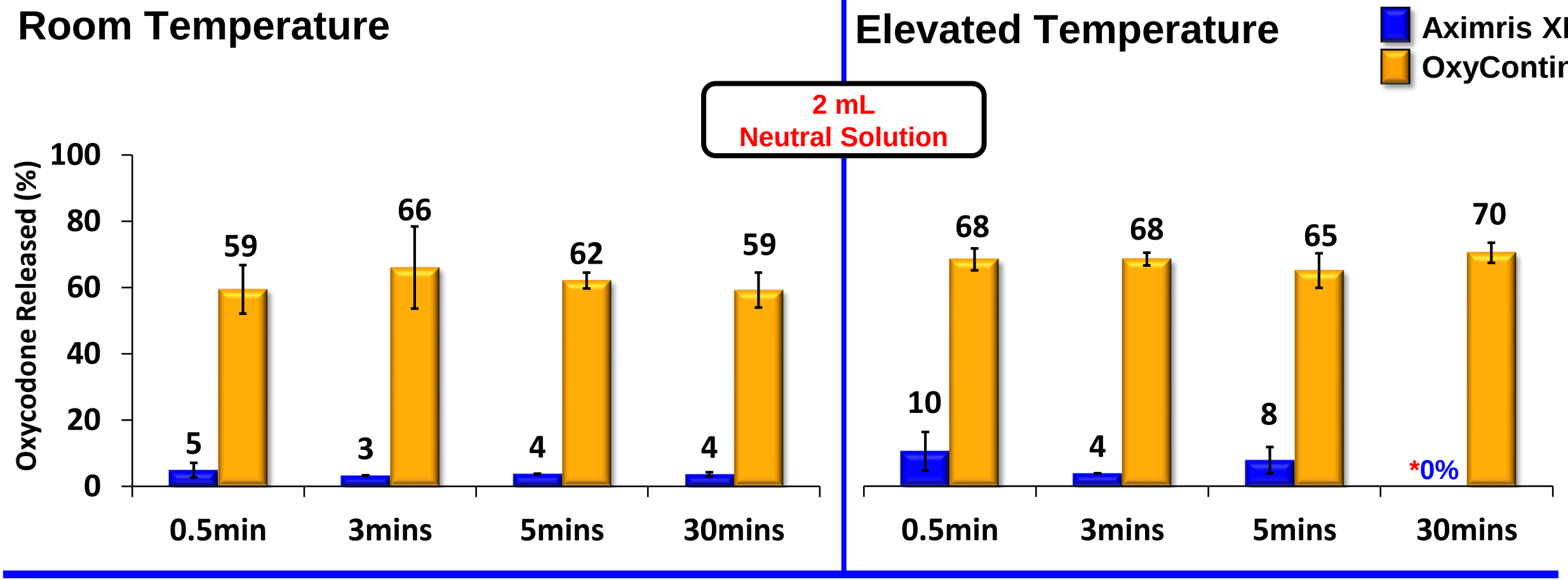


Convection Heat pre-treatment

Advanced extraction method recommended by the FDA.

Ground, Alcoholic Solution, 10 mL, No Agitation, Very Small Needle Gauge
Error bars = SD; Experiment performed in triplicates

Less Drug Extracted from Aximris XR Compared to OxyContin



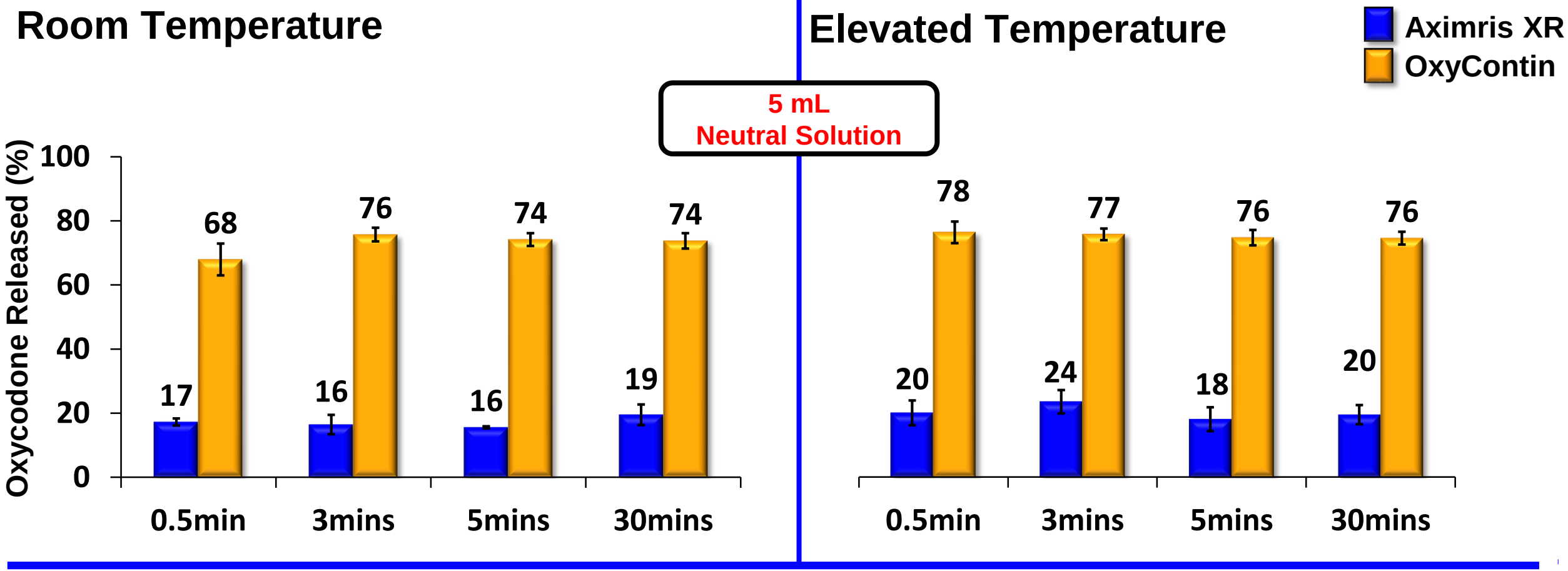
*Aximris XR Not Syringeable

Ground, Neutral Solution, 2 mL, No Agitation, Very small Needle gauge
Error bars = SD; Experiment performed in triplicates

Convection Heat pre-treatment

Advanced extraction method recommended by the FDA.

Less Drug Extracted from Aximris XR Compared to OxyContin

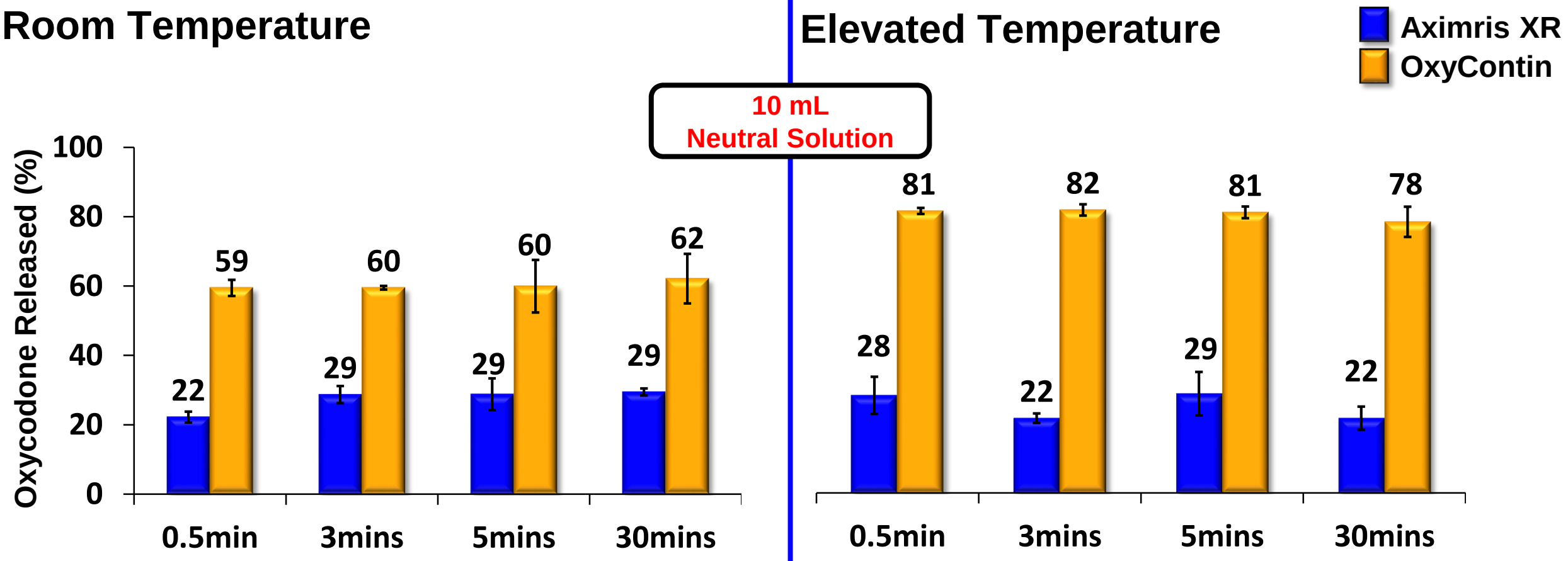


Convection Heat pre-treatment

Advanced extraction method recommended by the FDA.

Ground, Neutral Solution, 5 mL, No Agitation, Very small Needle gauge
Error bars = SD; Experiment performed in triplicates

Less Drug Extracted from Aximris XR Compared to OxyContin

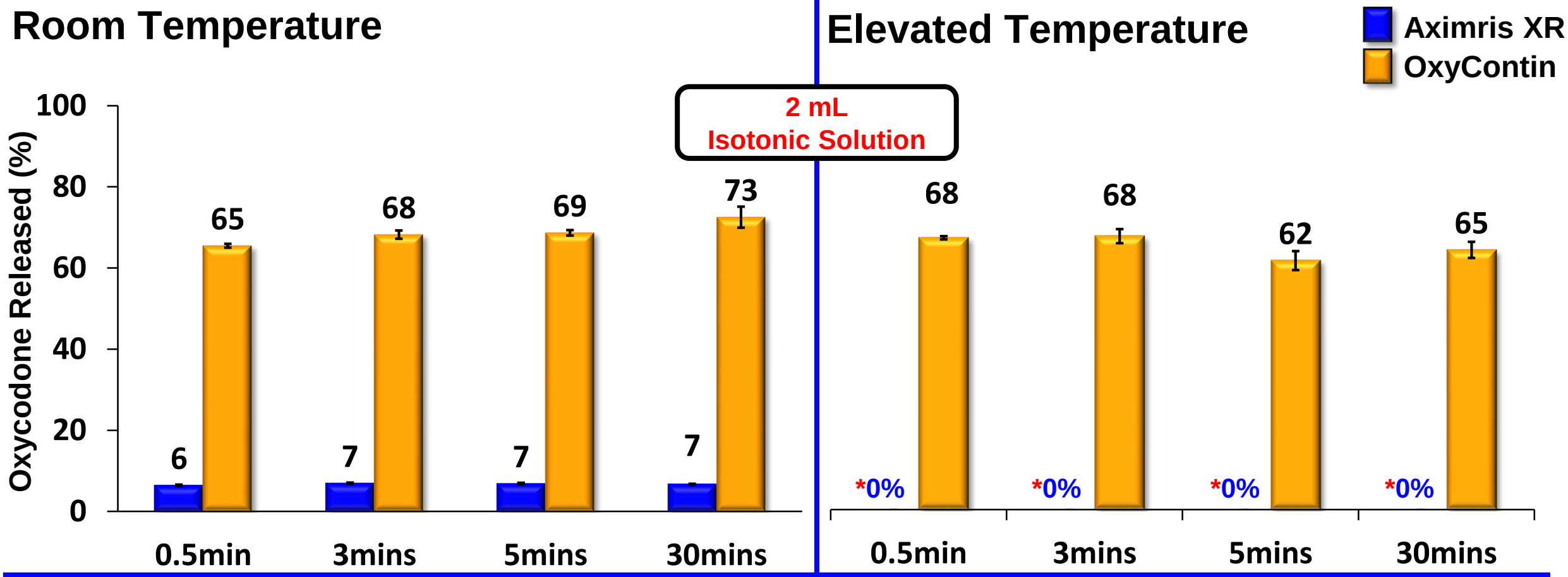


Ground, Neutral Solution, 10 mL, No Agitation, Very small Needle gauge
Error bars = SD; Experiment performed in triplicates

Convection Heat pre-treatment

Advanced extraction method recommended by the FDA.

Difficult to Extract Drug from Aximris XR Compared to OxyContin



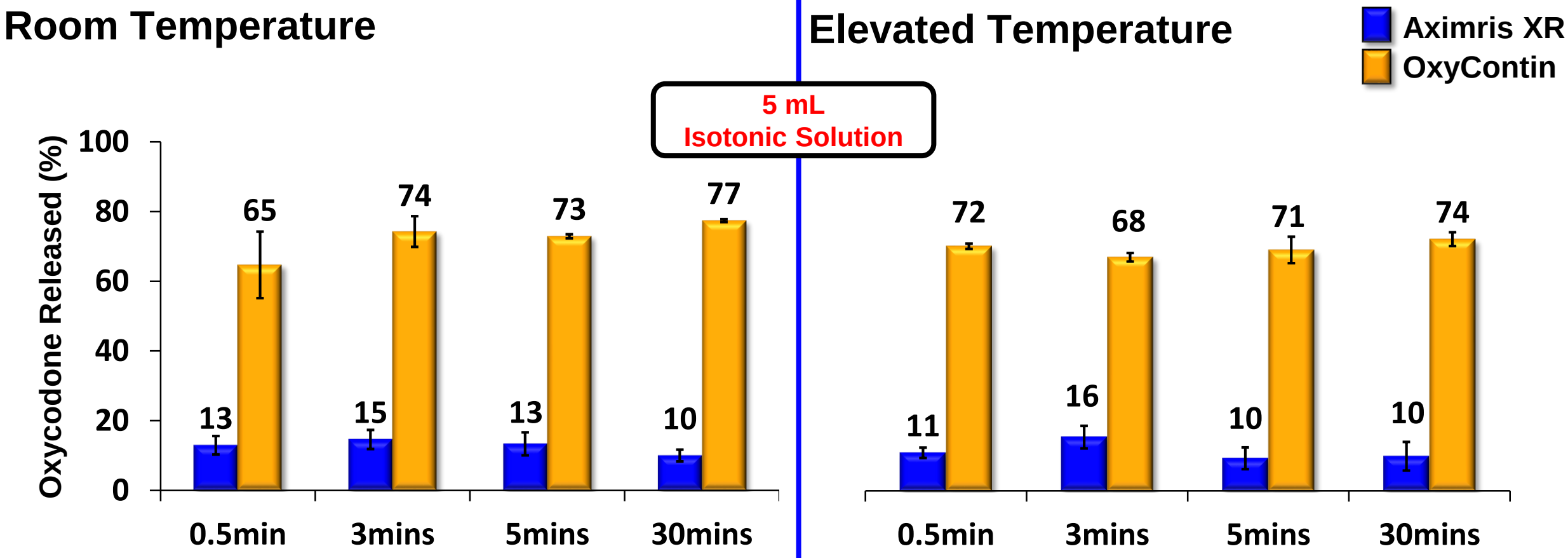
*Aximris XR Not Syringeable

Ground, Isotonic Solution, 2 mL, No Agitation, Very small Needle gauge
Error bars = SD; Experiment performed in triplicates

Convection Heat pre-treatment

Advanced extraction method recommended by the FDA.

Less Drug Extracted from Aximris XR Compared to OxyContin

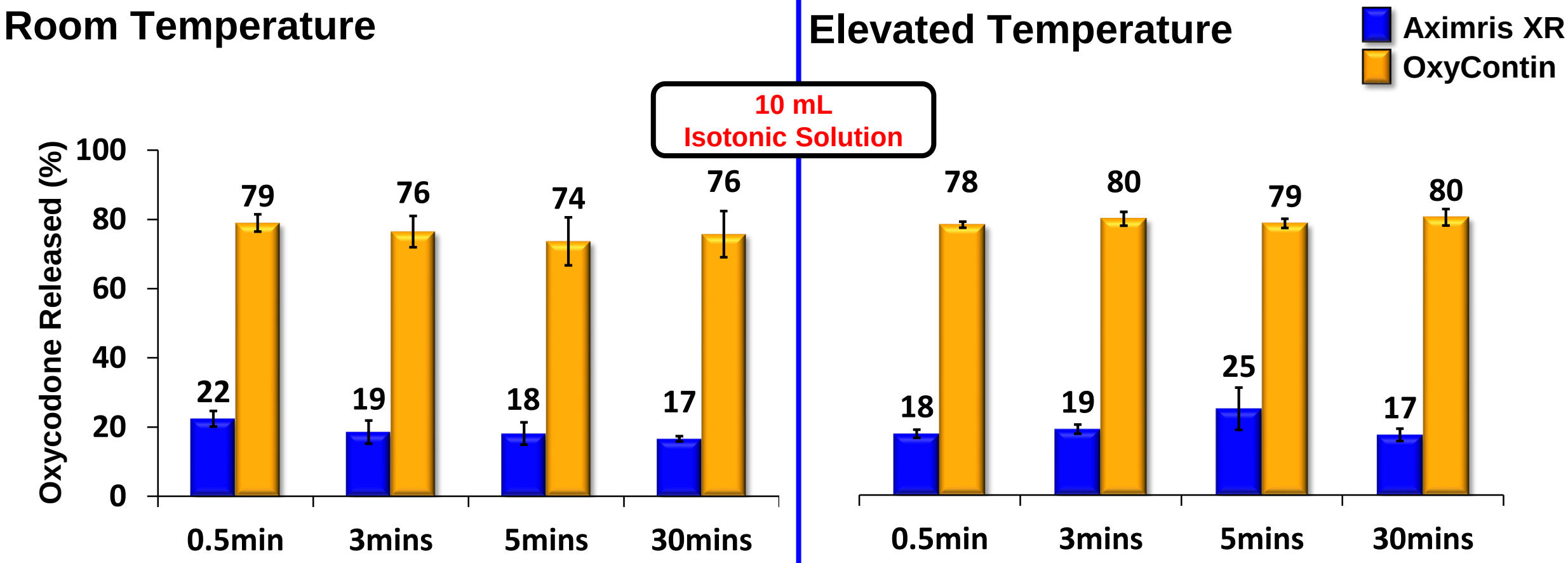


Ground, Isotonic Solution, 5 mL, No Agitation, Very small Needle gauge
Error bars = SD; Experiment performed in triplicates

Convection Heat pre-treatment

Advanced extraction method recommended by the FDA.

Less Drug Extracted from Aximris XR Compared to OxyContin

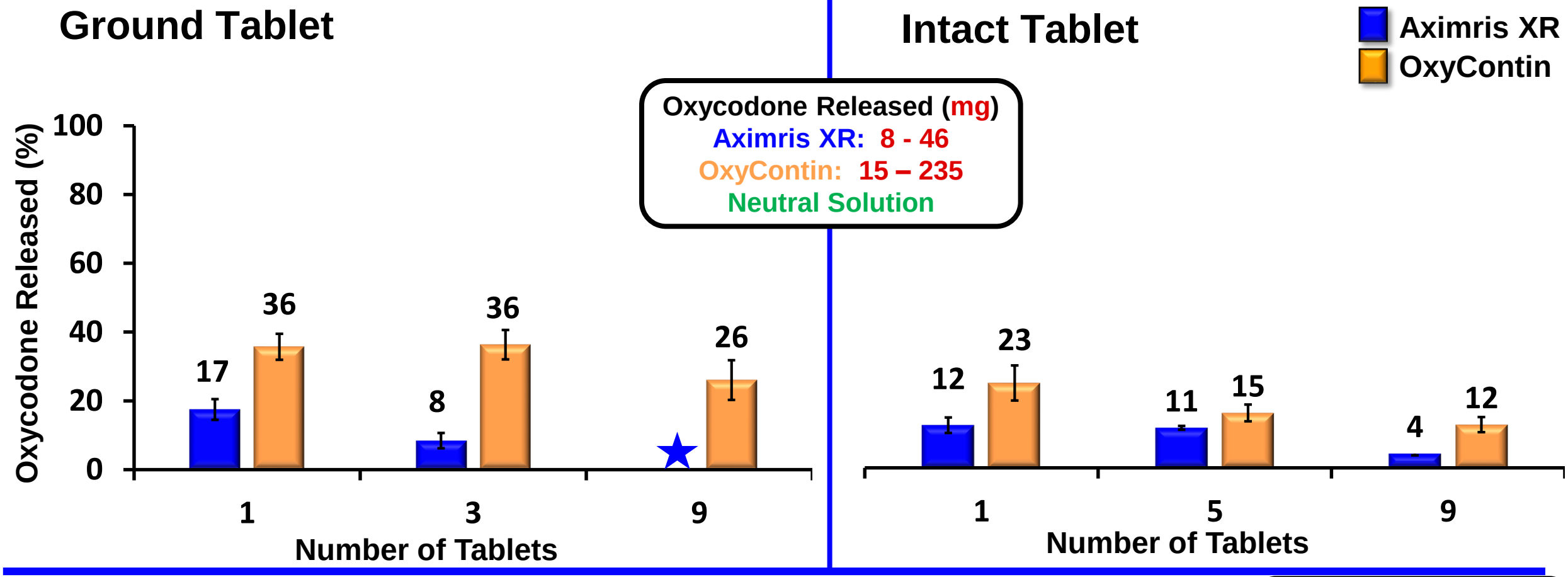


Ground, Isotonic Solution, 10 mL, No Agitation, Small Needle gauge
Error bars = SD; Experiment performed in triplicates

Convection Heat pre-treatment

Advanced extraction method recommended by the FDA.

Less Drug is Extracted from Aximris XR Compared to OxyContin as the Number of Manipulated Tablets Increases using Neutral Solution



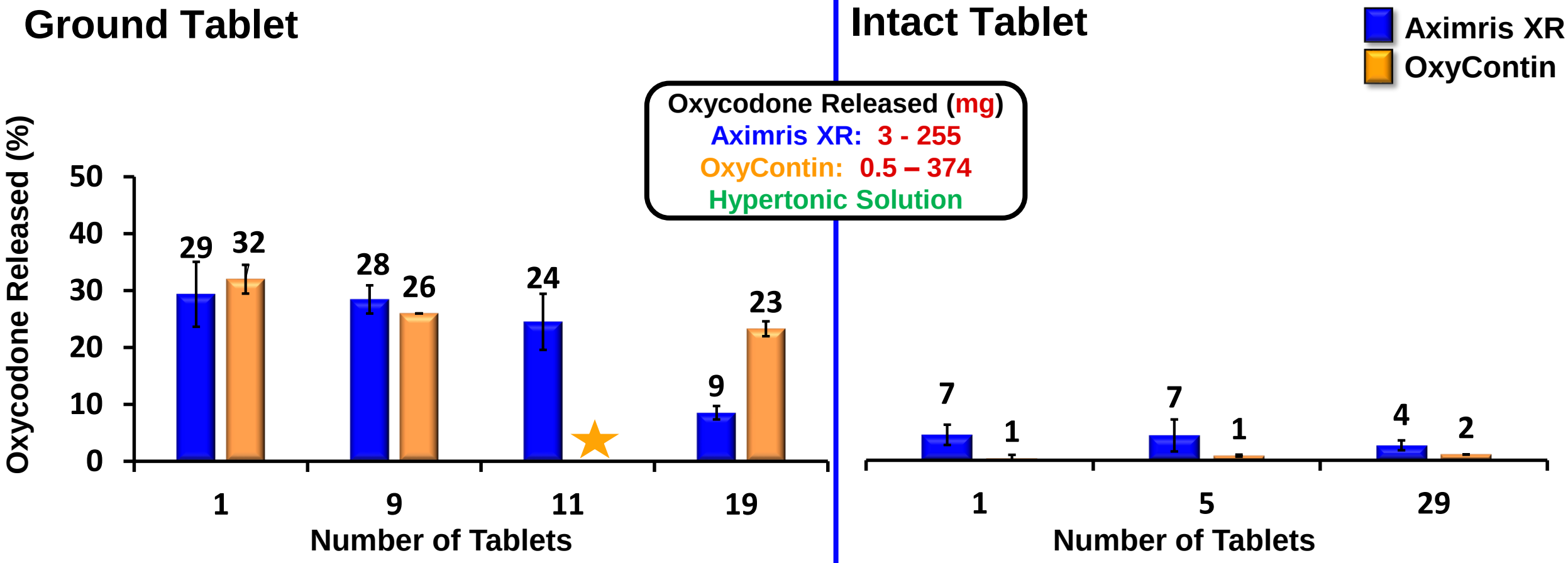
★ Aximris XR not Syringeable if ≥ 3 tablets

Neutral Solution, 30 mL, Elevated Temperature, High Agitation
Error bars = SD; Experiment performed in triplicates

Convection Heat pre-treatment

Advanced extraction method recommended by the FDA.

Less or Similar Drug is Extracted from Aximris XR Compared to OxyContin as the Number of Manipulated Tablets Increases in Hypertonic Solution



★ OxyContin samples not tested

Hypertonic Solution, 30 mL, Elevated Temperature, High Agitation
Error bars = SD; Experiment performed in triplicates

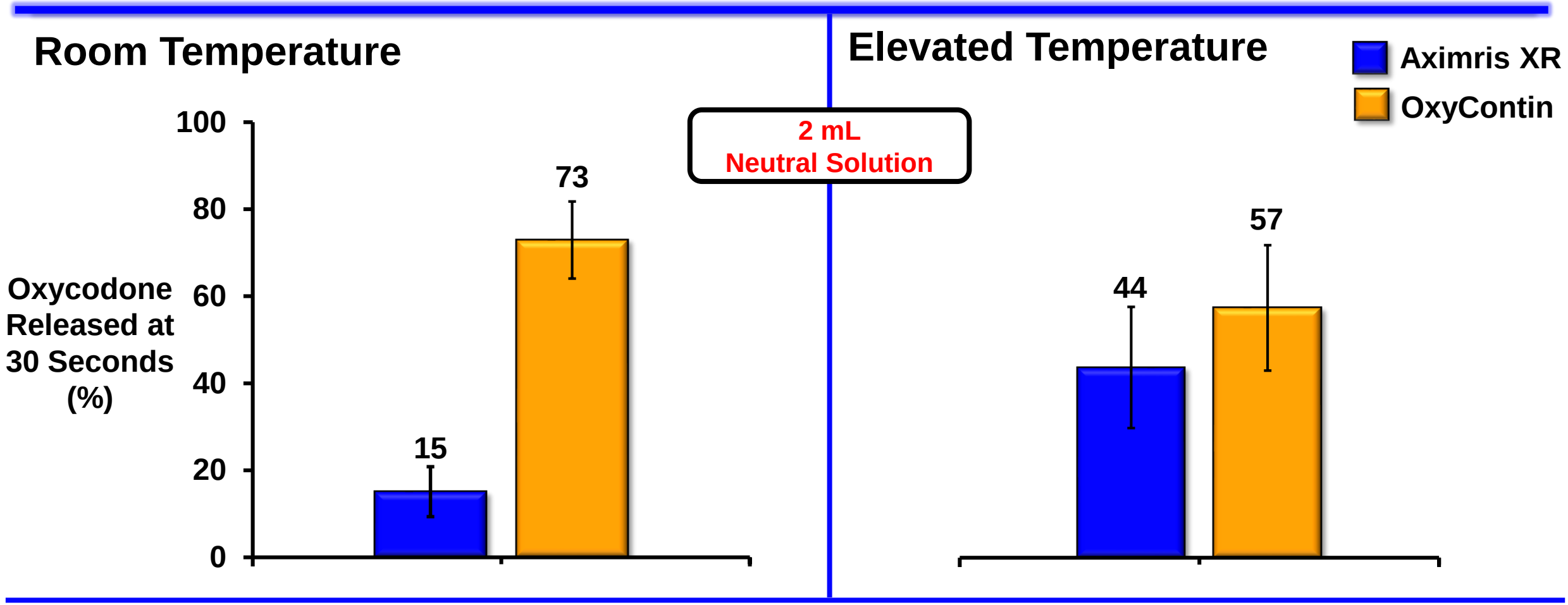
Convection Heat pre-treatment

Advanced extraction method recommended by the FDA.

Studies Conducted Using Internet/Advanced "recipes"

- Most common method cited on drug abuse websites (e.g., bluelight.org) to defeat the IV abuse deterrence property of ADFs is radiant heat pre-treatment
- Aximris XR and OxyContin subjected to radiant heat pre-treatment prior to drug extraction
- Extraction Conditions:
  - Tablet Form (Intact or Ground)
  - Volumes or Solvents
  - Agitation or Temperature conditions
  - Studies started with smallest needle, progressing to larger sizes

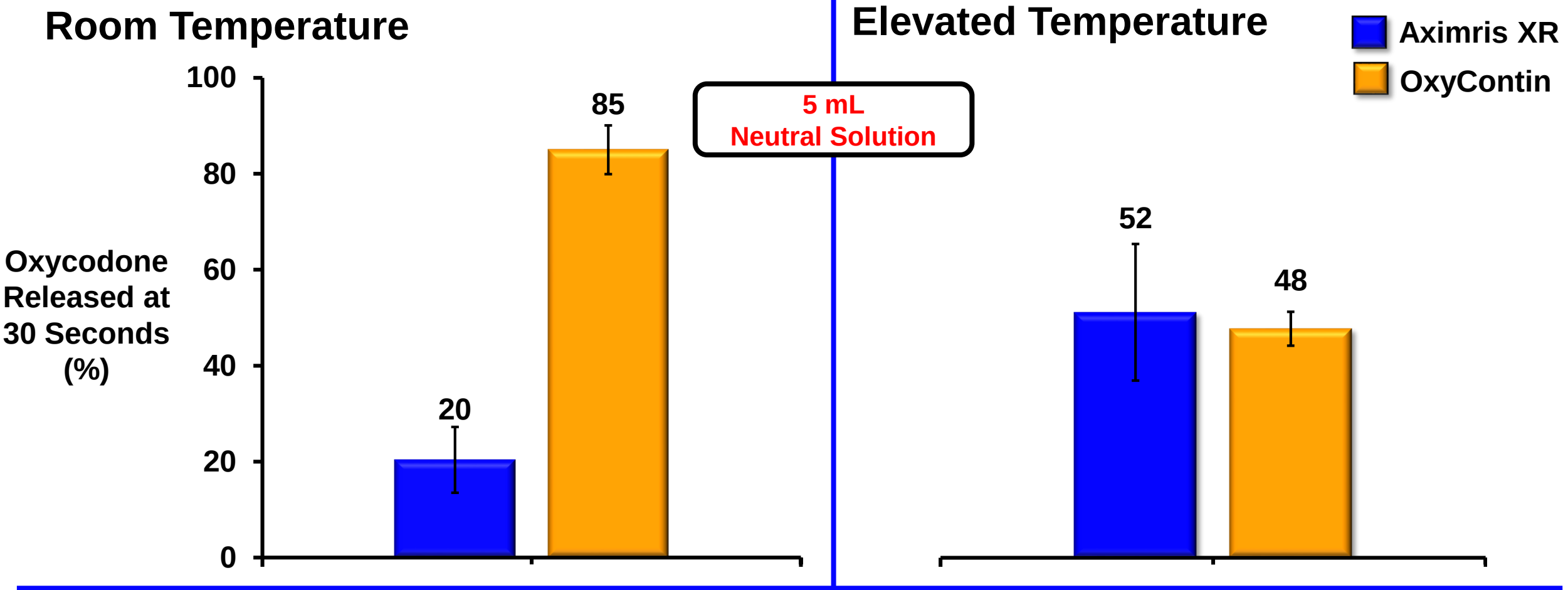
Less Drug Extracted from Aximris XR Compared to OxyContin Using Internet/Advanced "recipes"



Ground Tablets, Neutral Solution, No Agitation, Radiant Heat Pre-treatment, Large Needle Gauge, 2mL
Error bars = SD; Experiment performed in triplicates

Advanced extraction method from drug abuse website.

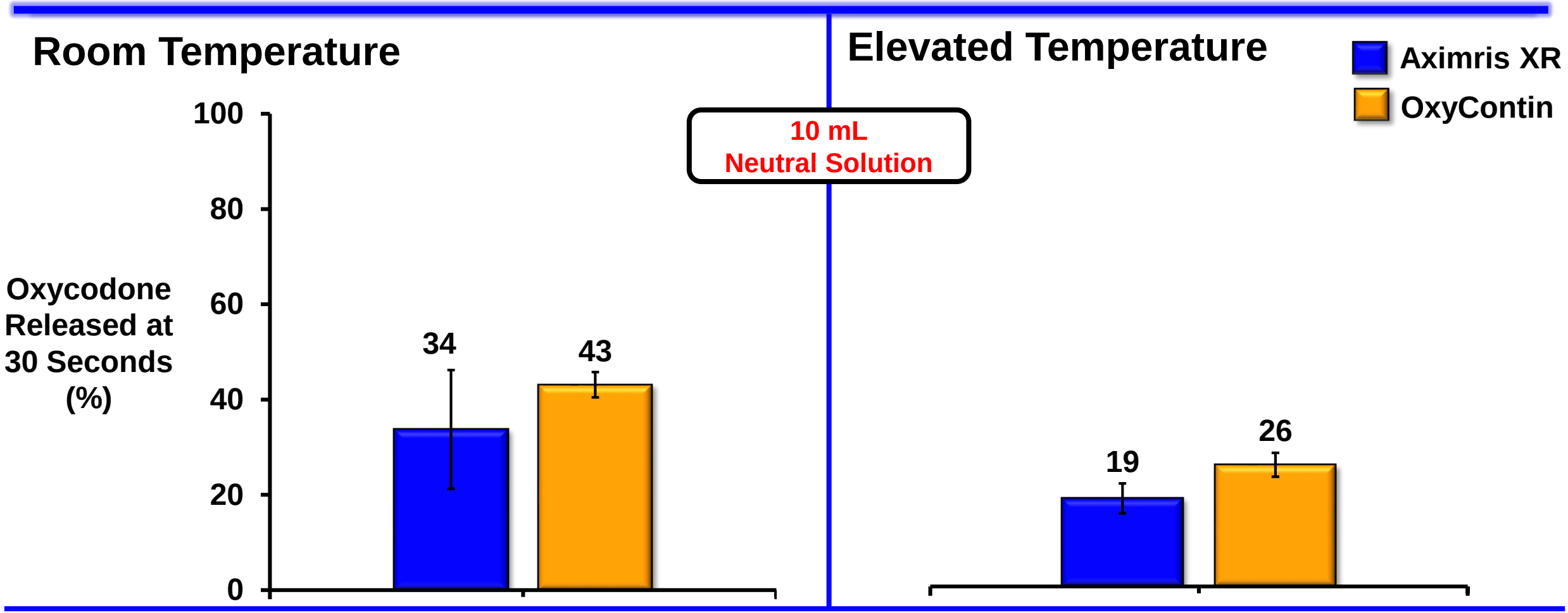
Overall Less or Similar Drug Extracted from Aximris XR Compared to OxyContin Using Internet/Advanced "recipes"



Ground Tablets, Neutral Solution, No Agitation, Radiant Heat Pre-treatment, Large Needle Gauge, 5mL
Error bars = SD; Experiment performed in triplicates

Advanced extraction method from drug abuse website.

Overall Similar Amount of Drug Extracted from Aximris XR Compared to OxyContin Using Internet/Advanced "recipes"



Advanced extraction method from drug abuse website.

Ground Tablets, Neutral Solution, No Agitation, Radiant Heat Pre-treatment, Large Needle Gauge, 10mL
Error bars = SD; Experiment performed in triplicates

Overview of Category 1 Studies

- Particle size reduction/distribution
- Syringeability / Injectability and Small Volume Extraction
- Large Volume Extraction
- Alcohol Dose Dumping
- Manipulated Tablet Dissolution
- Simulated Smoking / Vaporization

Large Volume Extraction Methods

- Studies investigated the effect of temperature, agitation and time on drug extraction from ground and intact tablet using 100 or 200mL ingestible and non-ingestible solvents.
- Results
  - Intact Tablet - Aximris XR had similar or lower extraction efficiency than OxyContin except for one of the solvents
  - Ground Tablet - No apparent difference between both products.

Overview of Category 1 Studies

- Particle size reduction/distribution
- Syringeability / Injectability and Small Volume Extraction
- Large Volume Extraction
- Alcohol Dose Dumping
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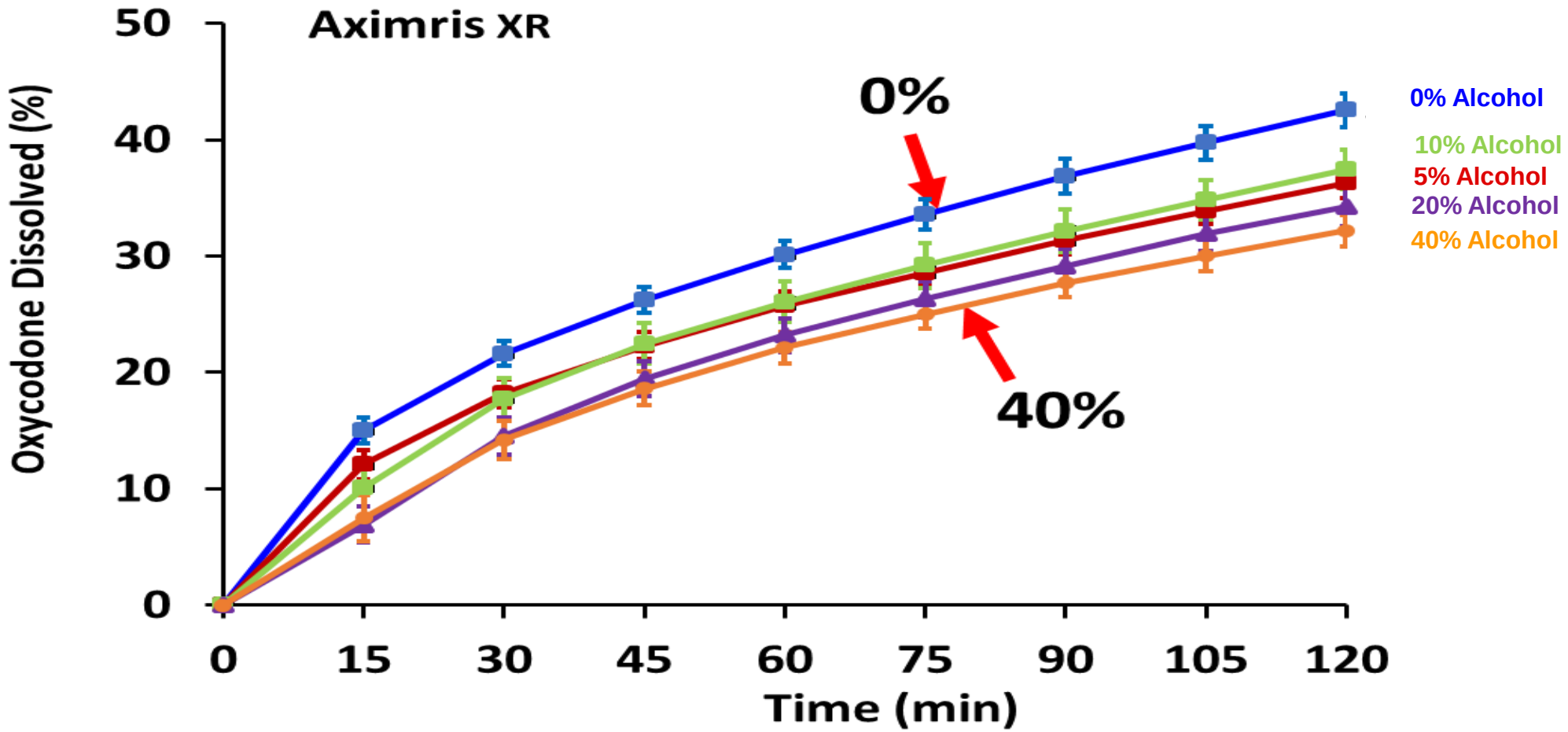
- Simulated Smoking / Vaporization

Aximris XR shows NO dose dumping with alcohol



Intact Aximris XR 80mg tablets, Acidic Dissolution Media
Error Bars = SD; Experiment performed with 12 replicates

Overview of Category 1 Studies

- Particle size reduction/distribution
- Syringeability / Injectability and Small Volume Extraction
- Large Volume Extraction
- Alcohol Dose Dumping
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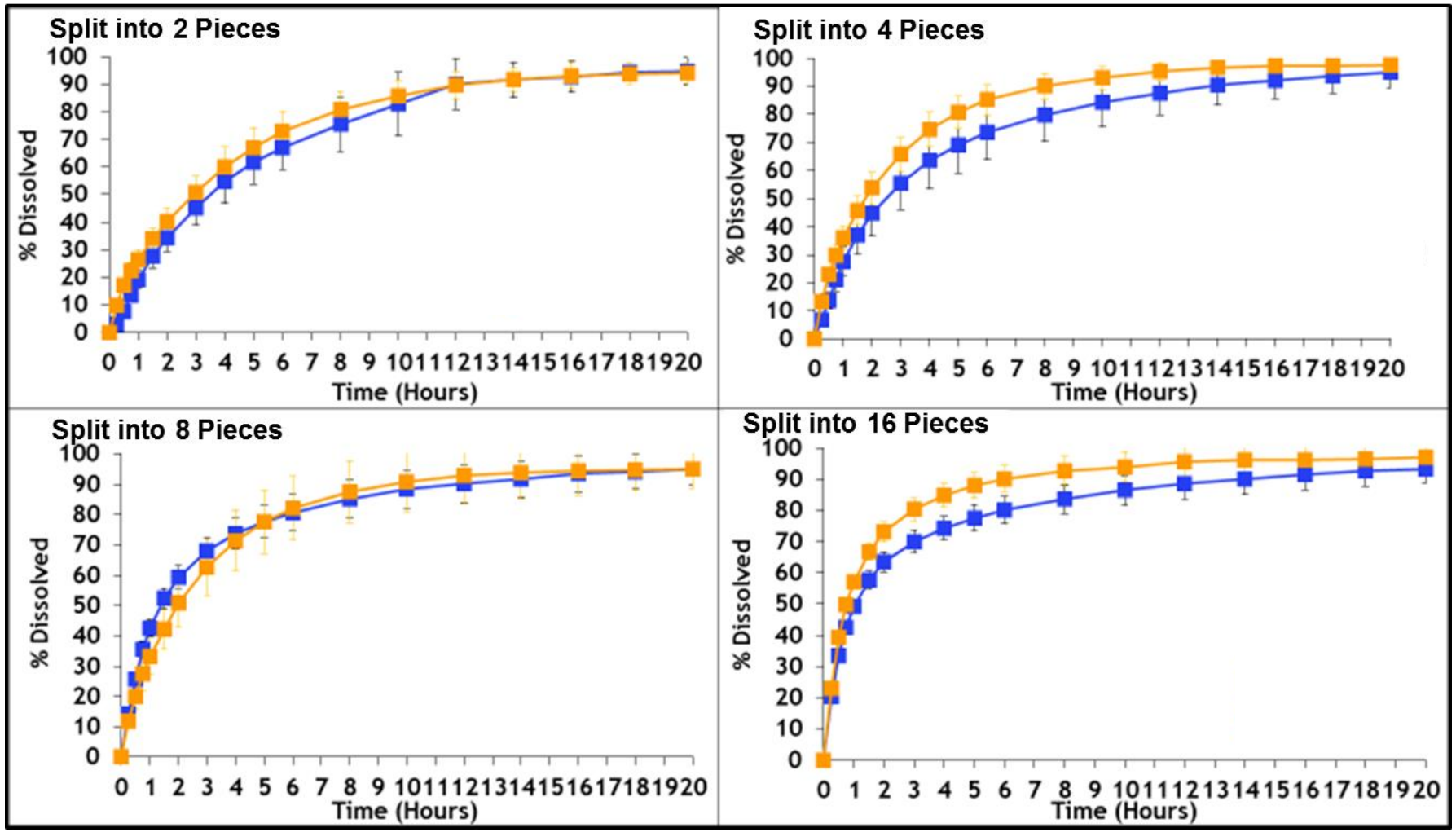
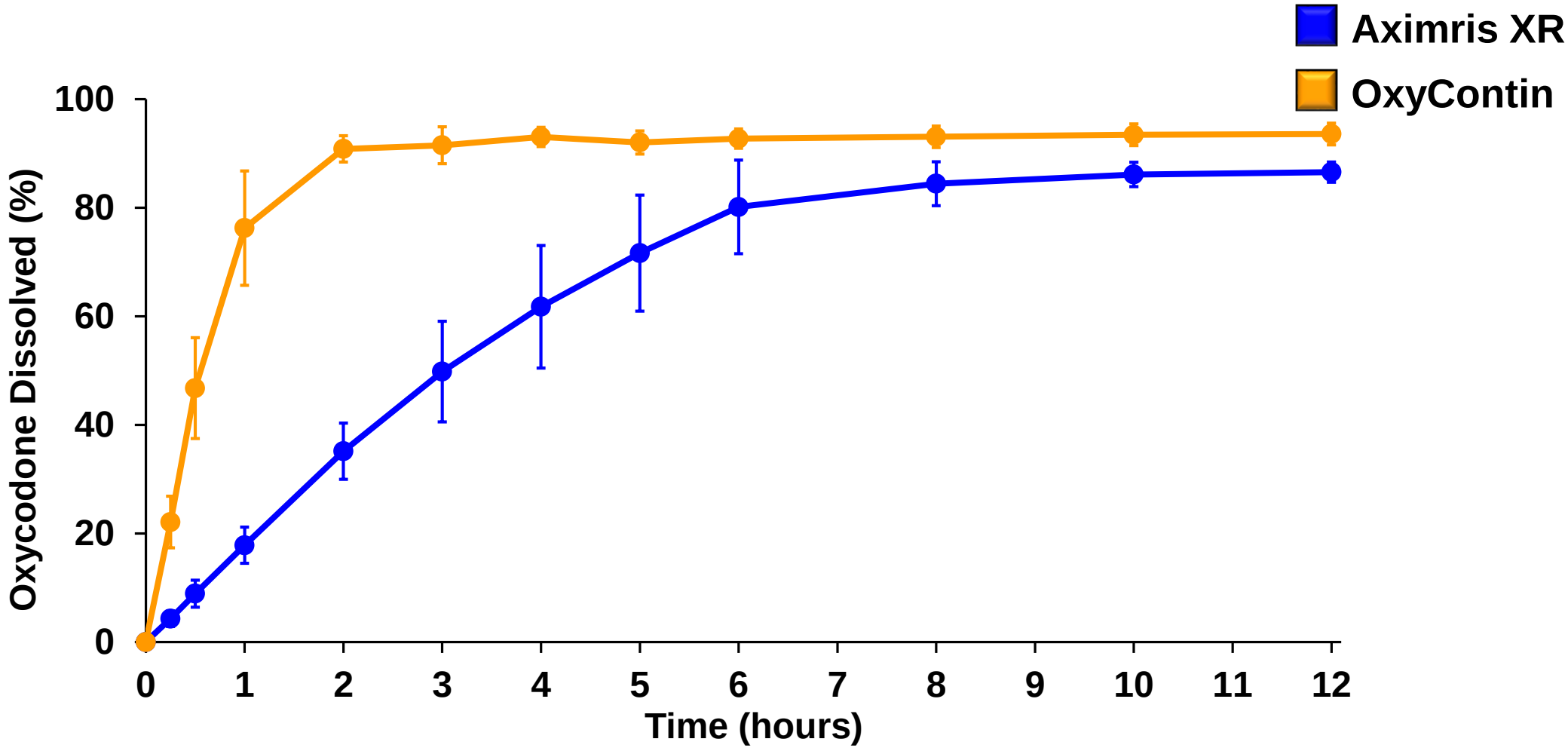
- Simulated Smoking / Vaporization

Aximris XR and OxyContin Maintain ER Properties in Tablet Forms



Basic Dissolution Media
Error Bars = SD; Experiment performed with 6 replicates

Aximris XR has Greater Resistance against Radiant Heat Pre-treatment Known to Defeat OxyContin



Intact, Radiant heat pre-treatment with rotation, Neutral Dissolution Media
Error Bars = SD; Experiment performed with 6 replicates

Overview of Category 1 Studies

- Particle size reduction/distribution
- Syringeability / Injectability and Small Volume Extraction
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- Alcohol Dose Dumping
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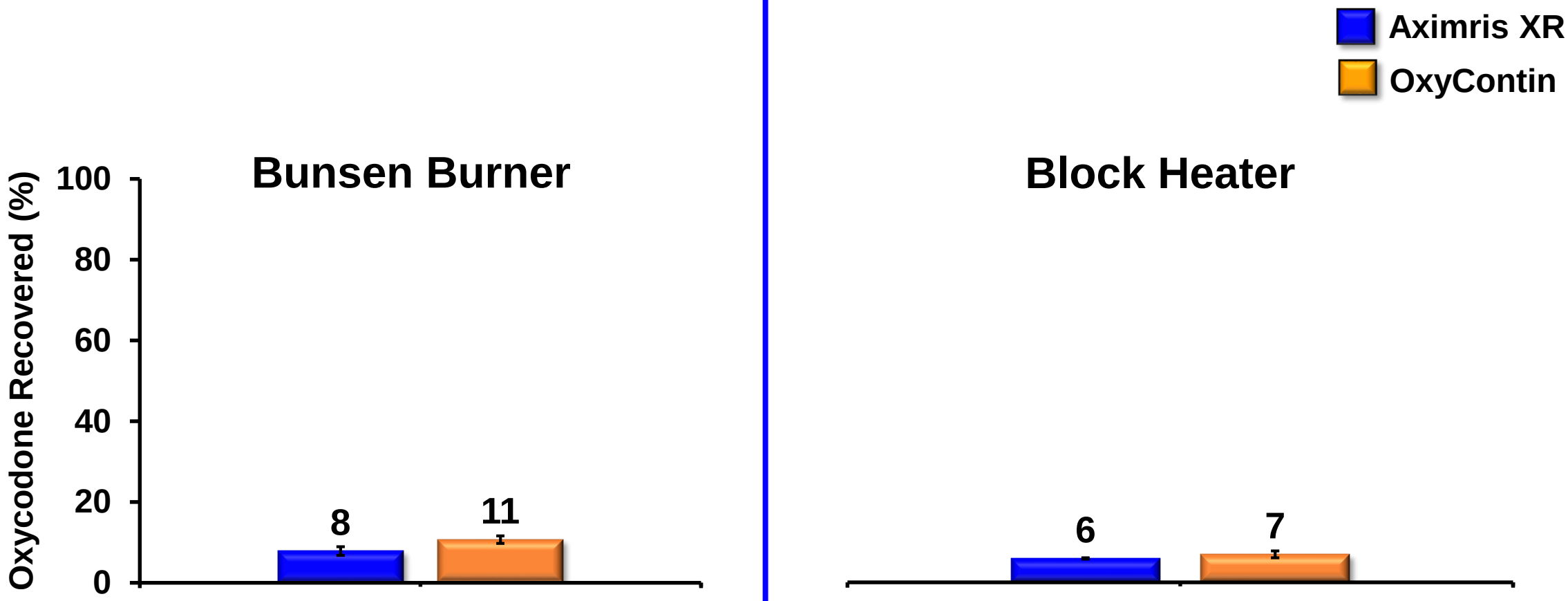
- Simulated Smoking / Vaporization

Release of Oxycodone through Smoking is Similar for Aximris XR and OxyContin



Error bars = SD; Experiment performed in triplicates

Summary and Findings from Category 1 Evaluations of Aximris XR

- Grinding to small particles intensifies Aximris XR viscosity and coagulation features making it much more resistant to drug extraction than OxyContin
- Aximris XR is highly resistant to common/standard methods of IV abuse
- Aximris XR provides superior resistance to preparing IV injection compared to OxyContin
- Aximris XR does NOT dose dump in alcohol
- Smoking is NOT an efficient route of administration for Aximris XR

Nonclinical Excipient Safety Studies

Olu Aloba, RPh, PhD, RAC
Senior Director of CMC Services

Camargo Pharmaceutical Services

Rationale for Performing Excipient Safety Studies

- FDA request for assessment of potential (IV) exposure risk of toxicity of syringeable material from manipulated Aximris XR following microwaving or heating

- Assessment of the safety of Aximris XR excipients if abused by the oral, intranasal and vaping route

Oral, Intranasal and Vaping Excipient Exposure Risk Assessments

- Oral route
  - Exposure to excipients in Aximris XR by the oral route at the maximum tolerable daily dose (MTDD) of oxycodone is anticipated to have low risk of toxicity
- Intranasal and Smoking/vaping route
  - Based on the limited information available for the excipients, potential for irritation and respiratory tract toxicity were identified, although a quantitative prediction of risk was not possible.

Maximum Tolerable Daily Dose = MTDD; FDA Inactive Ingredient Database = IID

Intravenous Excipient Exposure Risk Assessments of Syringeable Material

- Characterization of volatile and semi-volatile organic components
- In vitro hemocompatibility study
- Repeated dose IV toxicity in rabbits

Characterization of Volatile and Semi-Volatile Organic Components

- Volatile and semi-volatile organic components of syringeable material were characterized and identified
- Compounds assessed for general toxicity and cancer risk
- Conclusion
  - Lifetime exposure would not pose any significant toxicity or cancer risk
- Caution
  - This does not mean that parenteral administration of abused Aximris XR can not lead to adverse effects
  - Cases of thrombotic microangiopathy associated with parenteral abuse have been associated with another ER oxycodone product

Hemolytic Potential & In Vitro Blood Compatibility Studies of Syringeable Solution of Aximris XR

- Determined using human plasma, serum, and whole blood
- Determined the potential to form flocculent material
- Test Items
  - Extract using Isotonic Solution (Test Item 1)
  - Extract using Tap water (Test Item 2)
  - Tap water (vehicle)
  - Sterile normal saline (Negative control)
  - 2% Saponin [w/v] in water (Positive control)

In vitro Hemocompatibility Studies Support that Aximris XR is Non-Hemolytic

Sample	Mean Hemoglobin (mg/mL)	% Hemolysis (Relative to Total Hemoglobin)	% Hemolysis (Corrected for Negative Ctrl)	Hemolytic Grade
Test Item 1	1.513	0.684	0.24%	Non-Hemolytic
Test Item 1 (OD Corrected) *	< 0	N/A	0% †	Non-Hemolytic
Test Item 1 (10-fold Dilution)	0.952	0.431	0%	Non-Hemolytic
Test Item 2	17.614	7.965	7.3%	Non-Hemolytic
Test Item 2 (OD Corrected) *	15.931	7.204	6.6%	Non-Hemolytic
Test Item 2 (10-fold Dilution)	0.970	0.439	0%	Non-Hemolytic
Vehicle (Tap water)	> 53.76 ‡	N/A	> 25% ‡	Hemolytic
Vehicle (Tap water 10-fold Dilution)	0.977	0.442	0%	Non-Hemolytic
0.9% Sodium Chloride for Injection USP (Negative Control)	0.977	0.442	0%	Non-Hemolytic

Values < 10% are considered to be non-hemolytic.
* OD Corrected Samples account for Test item 1 and 2 Drabkin's Blank OD interference as the test items are colored
† Hemoglobin concentration below detection limit of standard curve. ‡ Hemoglobin concentration exceeded standard curve.

Repeat-Dose In Vivo IV Toxicity Study Methods

- Study in rabbits randomized into 3 groups of 4 animals each
- Test items and dosing plan
  - Group 1 (G1) (negative control), N=4, sterile 0.9% Normal Saline
  - Group 2 (G2), N=4, extract in Tap Water
  - Group 3 (G3) N=4, extract in 0.9% Normal Saline
- Each received once daily bolus injections (1 mL/kg) for 3 days
- Study conducted in full compliance with ICH and GLP guidelines
- Evaluations of local effects, hematological effects, thrombotic microangiopathy, overt toxicity, tissue damage

Conclusion from Repeat-Dose In Vivo IV Toxicity Study in Rabbits

- Solutions were well tolerated
- No local (injections site) or systemic effects in any organ/system
- The rabbits study showed that there is no evidence of overt toxicity or tissue damage that would be associated with thrombotic microangiopathy, retinal damage, or acute kidney injury from this study

Overall Conclusion from Nonclinical Excipient Safety Studies

- Safety of the excipients for intranasal and intravenous use is indeterminate.
- Excipients were shown to be hemocompatible
- Excipients have a low potential for thrombotic microangiopathy and other blood vessel adverse effects

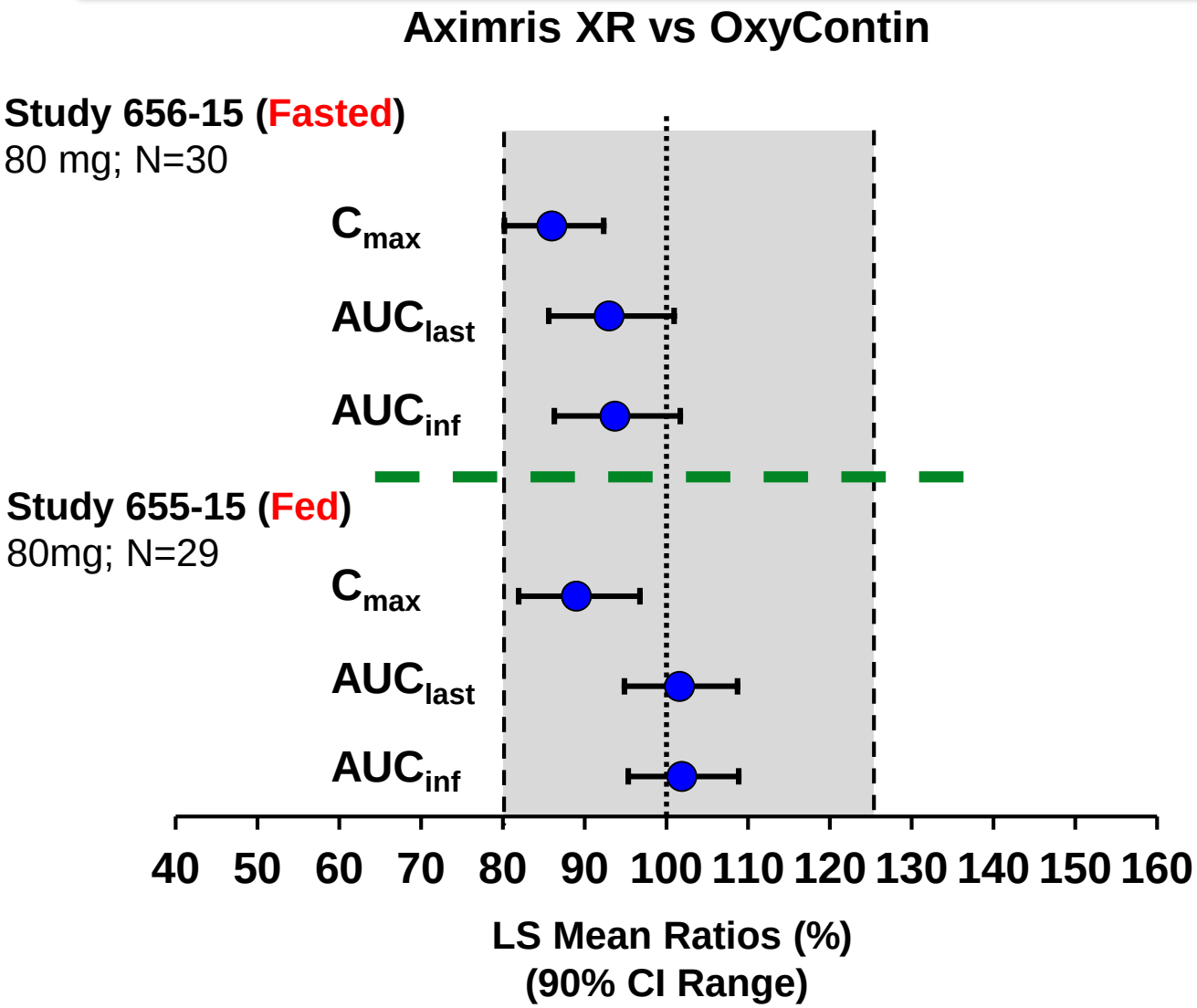
Clinical Pharmacology

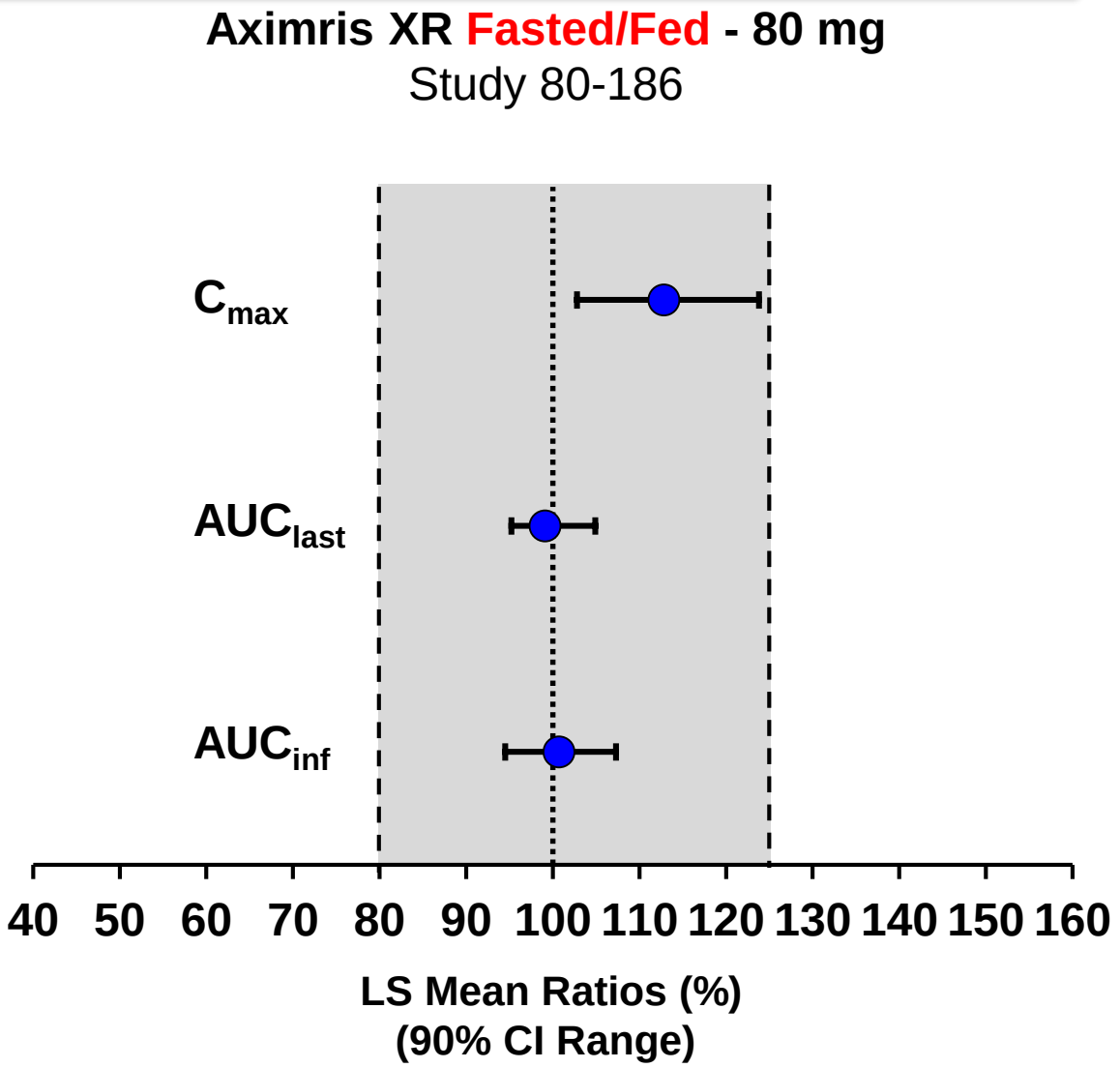
Ruth Stevens, PhD, MBA
CSO, Exec VP
Camargo Pharmaceutical Services

Clinical Pharmacokinetic (PK) Program Followed FDA Guidance and Feedback

Study	Purpose	Subjects Analyzed	Treatment Arms (Food Condition)
1878	Fasted bioequivalence study at 10 mg dose	31	10 mg Aximris XR (fasted) 10 mg OxyContin (fasted)
1879	Fed bioequivalence study at 10 mg dose	29	10 mg Aximris XR (fed) 10 mg OxyContin (fed)
656-15	Fasted bioequivalence study at 80 mg dose	30	80 mg Aximris XR (fasted) 80 mg OxyContin (fasted)
655-15	Fed bioequivalence study at 80 mg dose	29	80 mg Aximris XR (fed) 80 mg OxyContin (fed)
80-184	Steady state study at 80 mg dose (6 consecutive doses every 12 hours)	24	80 mg Aximris XR 80 mg OxyContin
80-185	Dose proportionality study	22	10 mg, 15 mg, 20 mg, 30 mg, 40 mg, 60 mg, and 80 mg Aximris XR (fasted)
80-186	Food effect study at 80 mg dose	25	80 mg Aximris XR (fasted and fed)

Aximris XR Demonstrated Bioequivalence to OxyContin at 80 mg – Fasted & Fed – No Food Effect

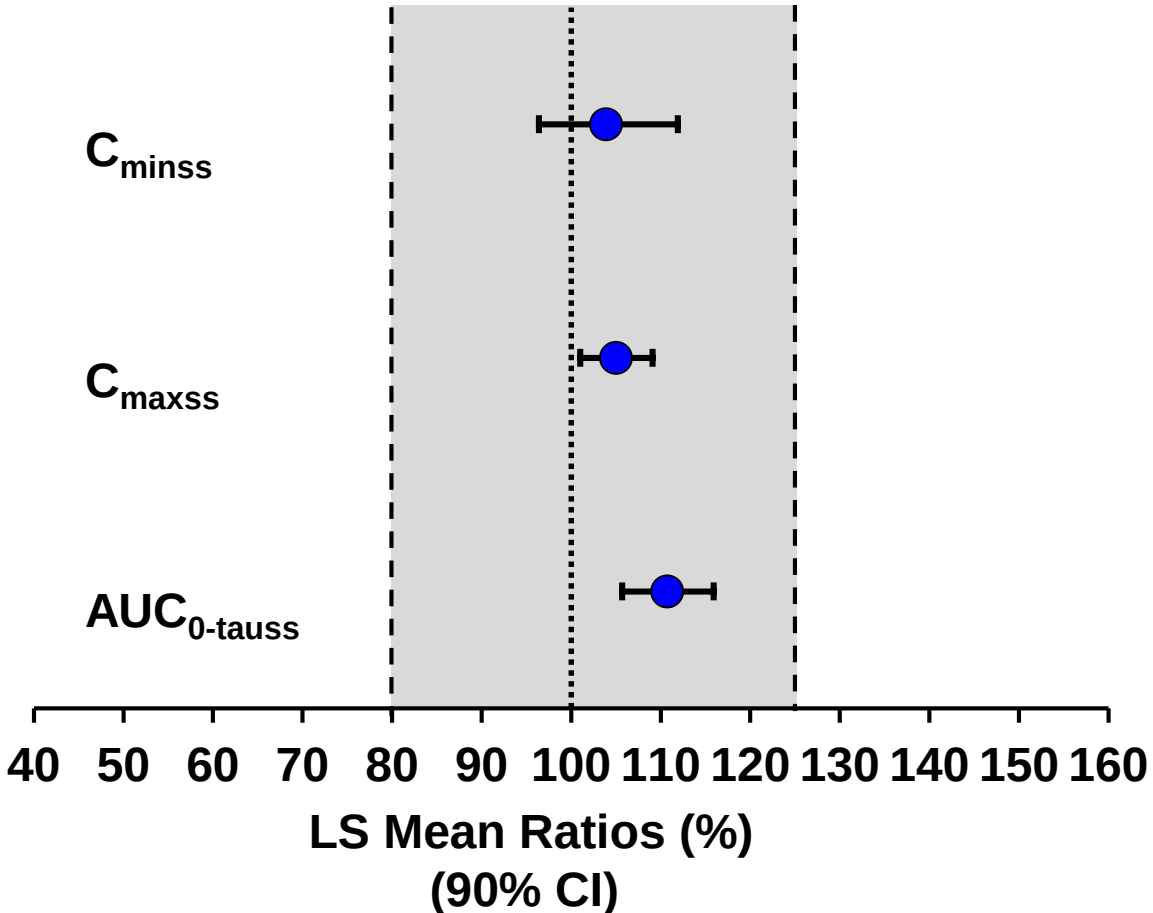




Aximris XR Bioequivalent to OxyContin at Steady State & All 7 Strengths of Aximris XR are Dose Proportional

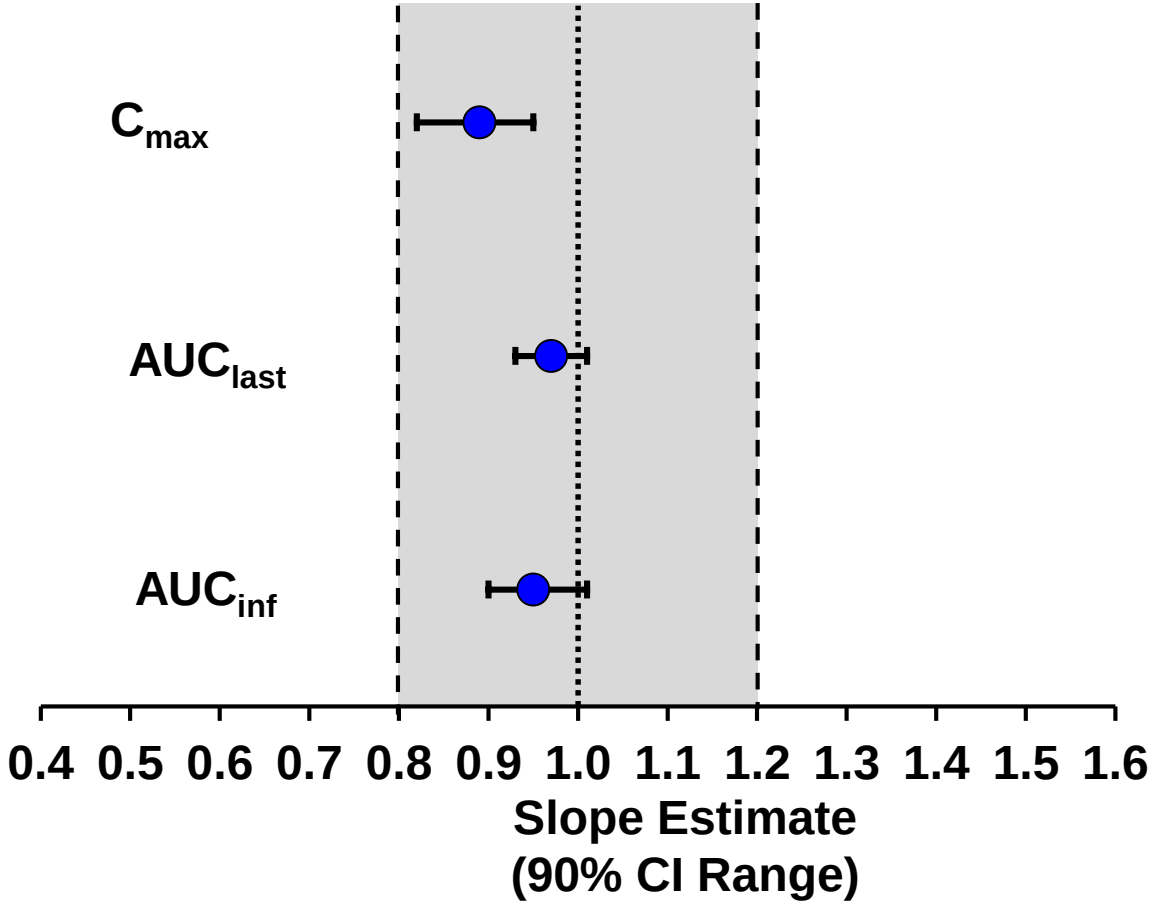
Aximris XR vs OxyContin, 80 mg Steady State

Multiple Dose Study 80-184, N=24



Aximris XR Dose Proportionality Study 80-185, N=22

Aximris XR: 10mg, 15mg, 20mg, 30mg, 40mg, 60mg, 80mg



Clinical Pharmacology Summary

- Aximris XR is bioequivalent to OxyContin
  - Supports approval of 505(b)(2) application
  - Well-established safety and efficacy profile
- No food effect; patients can take Aximris XR medication without regard to meals
- At steady-state, $AUC_{o\text{-}tau_{ss}}$, $C_{max_{ss}}$, C_{avg} and T_{max} after multiple dosing are comparable between Aximris XR and OxyContin
- Aximris XR demonstrated dose proportionality among all doses

Abuse-Deterrence Studies [Human Abuse Potential]

Category 1
Lab based in vitro manipulation and extraction studies

►Evaluated the difficulty with which AD properties of Aximris XR and OxyContin (comparator) can be compromised or defeated using typical abuser tactics and website/Advanced "recipes"

Category 2
Pharmacokinetic Clinical Trials

► Evaluated in vivo properties by measuring PK profiles of Aximris XR vs OxyContin and oxycodone IR as comparators.

Category 3
Human Abuse Potential Clinical Trials

► Assessed potential PD effects of Aximris XR vs OxyContin and oxycodone IR as comparators.

► Two Clinical Trials (Oral and Intranasal) conducted

Overview of Category 2 and 3 Studies

- Intranasal Human Abuse Potential Study
- Oral Human Abuse Potential Study

Aximris XR Has Higher C_{max} and partial AUCs But Similar Overall Exposure (AUC_{inf}) to Other Active Treatments

	Arithmetic Mean Parameters (SD)						
	C_{max} (ng/mL)	T_{max} (hr)*	$AUC_{0\text{-}1h}$ (ng*hr/mL)	$AUC_{0\text{-}2h}$ (ng*hr/mL)	$AUC_{0\text{-}last}$ (ng*hr/mL)	$AUC_{0\text{-}inf}$ (ng*hr/mL)	$t_{1/2}$ (hr)
Aximris XR Tablets 30 mg, Ground (N=31)	92.01 (21.80)	0.5 (0.25 – 2.00)	70.52 (16.52)	147.73 (32.17)	579.57 (136.93)	589.37 (140.17)	4.00 (0.48)
OxyContin 30 mg, Ground (N=32)	55.55 (14.42)	1 (0.25 - 3.00)	39.81 (12.47)	91.38 (25.29)	520.97 (100.11)	549.02 (101.73)	5.30 (1.46)
Oxycodone IR 30 mg, Crushed (N=32)	55.42 (11.38)	2 (0.25 – 6.00)	31.91 (9.91)	74.67 (21.78)	453.55 (88.62)	465.73 (93.17)	4.25 (0.59)

Aximris XR and OxyContin Appear To Have Similar Drug Liking VAS E_{max} and Take Drug Again VAS E_{max}

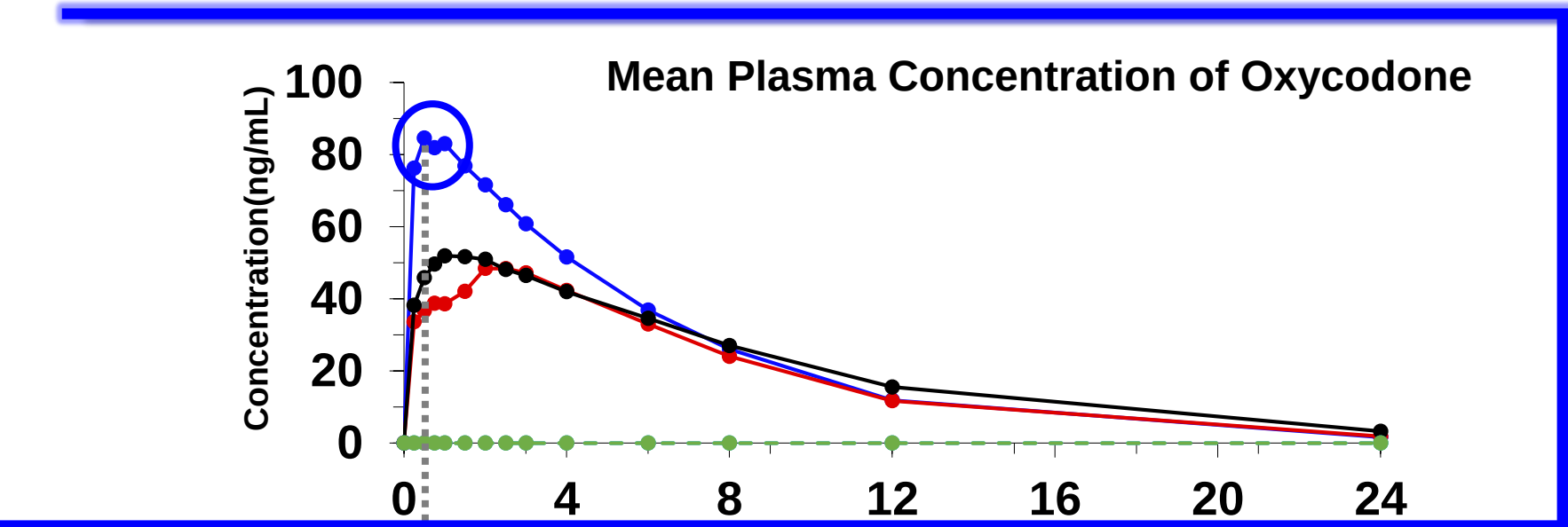
Statistic	AXIMRIS XR 30 mg, Ground (N=30)	OxyContin 30 mg, Ground (N=30)	Oxycodone IR 30 mg, Crushed (N=30)	Placebo (Aximris XR) (N=30)	Placebo (Oxycodone IR/Aximris XR) (N=30)
Drug Liking VAS E_{max}					
Mean (SD)	87 (13)	86 (14)	86	51 (4)	53 (7)
Median	88.0	89.0	87.5	50.0	50.0
Range	50 – 100	50 – 100	50 - 100	50 – 69	50 – 81
Take Drug Again VAS E_{max}					
Mean (SD)	78 (24)	81 (24)	85 (18)	49 (8)	51 (6)
Median	89.5	90.5	92	50.0	50.0
Range	0 – 100	1 – 100	41 - 100	8 – 63	50 – 83

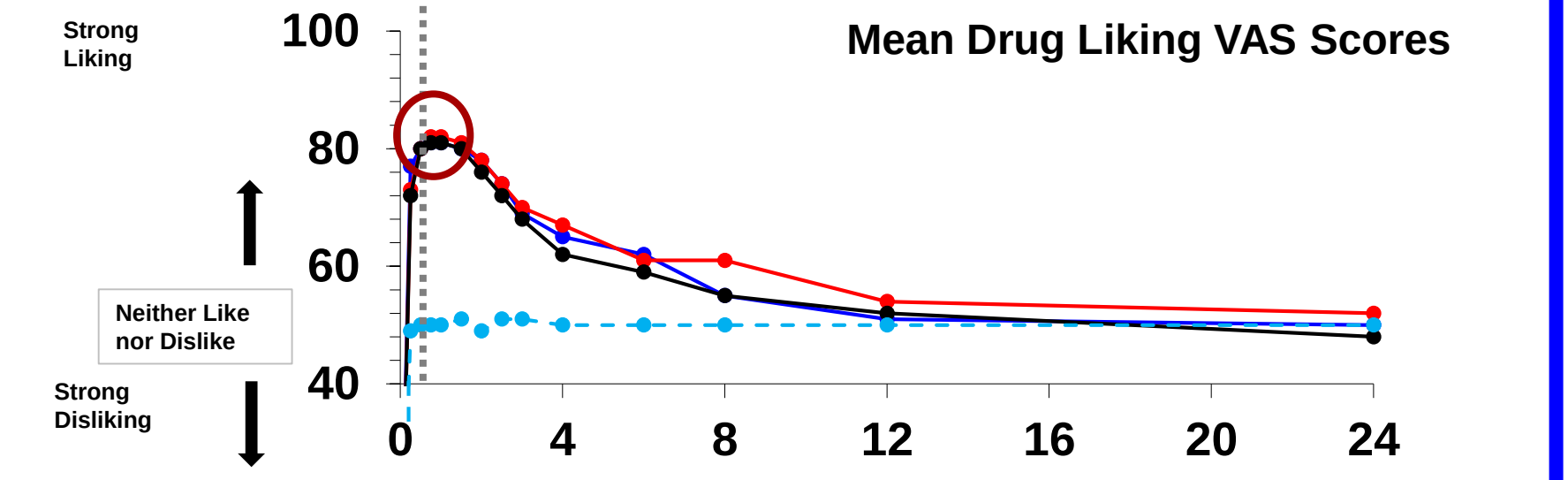
Intranasal Study

Completers population

E_{max}=maximum effect; range=minimum – maximum; SD=standard deviation; IR=immediate-release; VAS=visual analog scale

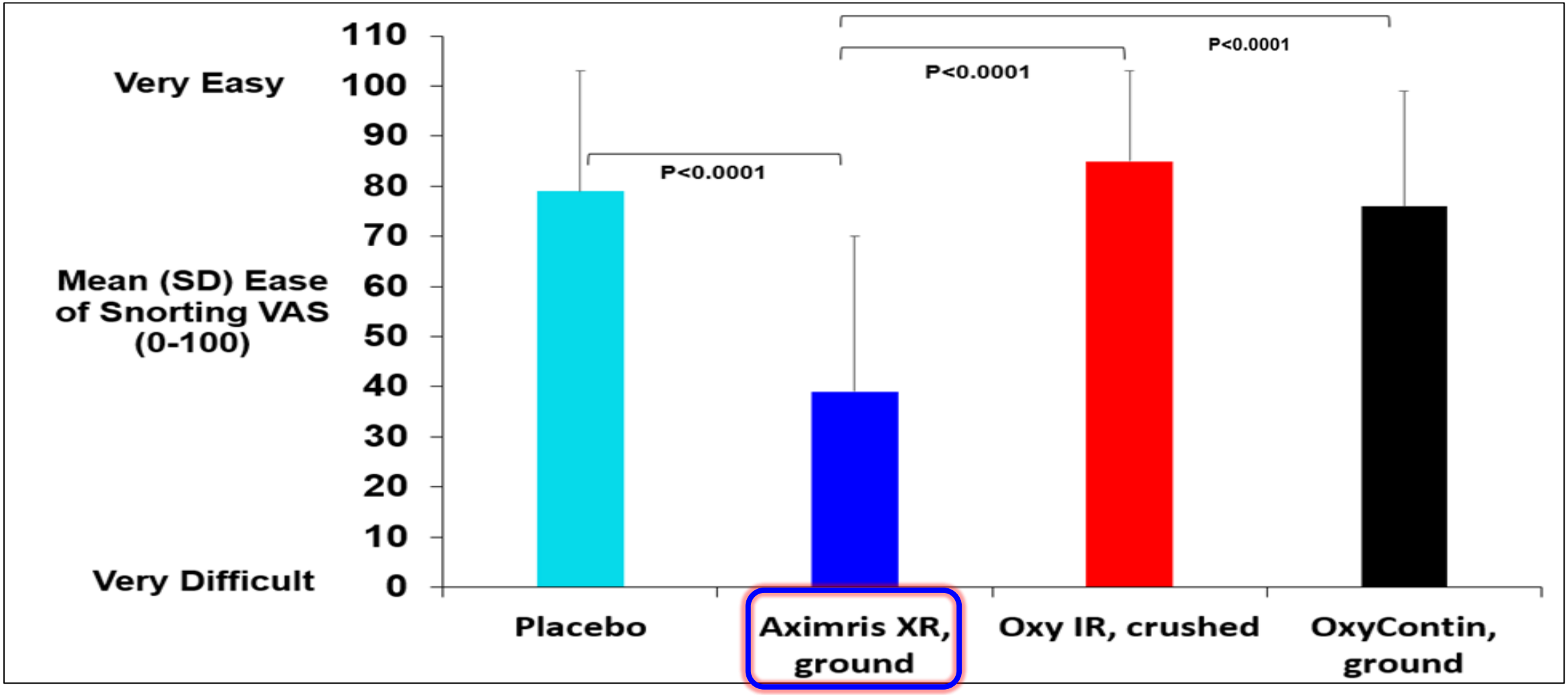
Pharmacokinetics Vs Pharmacodynamics: Aximris XR vs OxyContin vs oxycodone IR





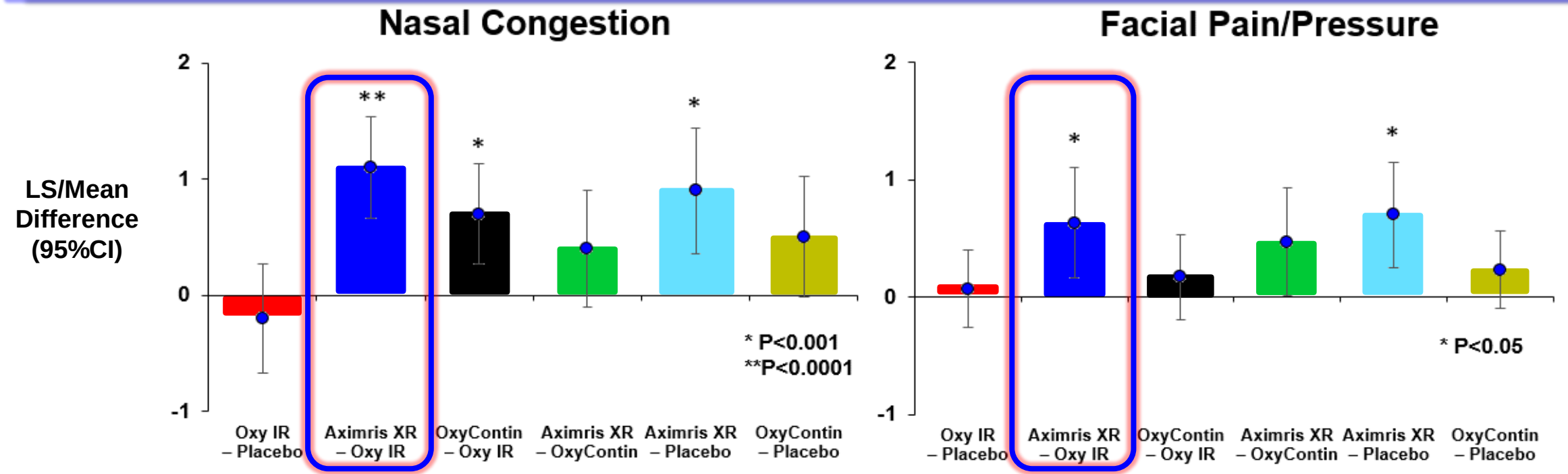
- Aximris XR, ground
- Oxycodone IR, crushed
- OxyContin, ground
- Placebo (Aximris XR, ground)
- Placebo (Oxycodone IR, crushed/OxyContin, ground)

Aximris XR is More Difficult to Snort



Study OXC3/2/0816: Intranasal HAP Study

Aximris XR Cause More Local Irritation Effects By Intranasal Route



TEAEs

MedDRA Preferred Term	Aximris XR 30 mg, Ground (N=32)	Oxycodone IR 30 mg, Crushed (N=32)	OxyContin 30 mg, Ground (N=32)	Placebo (IPC Oxycodone ER) (N=32)	Placebo (Oxycodone IR/ OxyContin) (N=32)
Nasal congestion	5 (15.6)	0	4 (12.5)	7 (21.9)	1 (3.1)
Throat irritation	4 (12.5)	1 (3.1)	4 (12.5)	4 (12.5)	0
Dry throat	1 (3.1)	0	0	2 (6.3)	0
Increased viscosity of upper respiratory secretion	2 (6.3)	0	0	0	0

Overview of Category 2 and 3 Studies

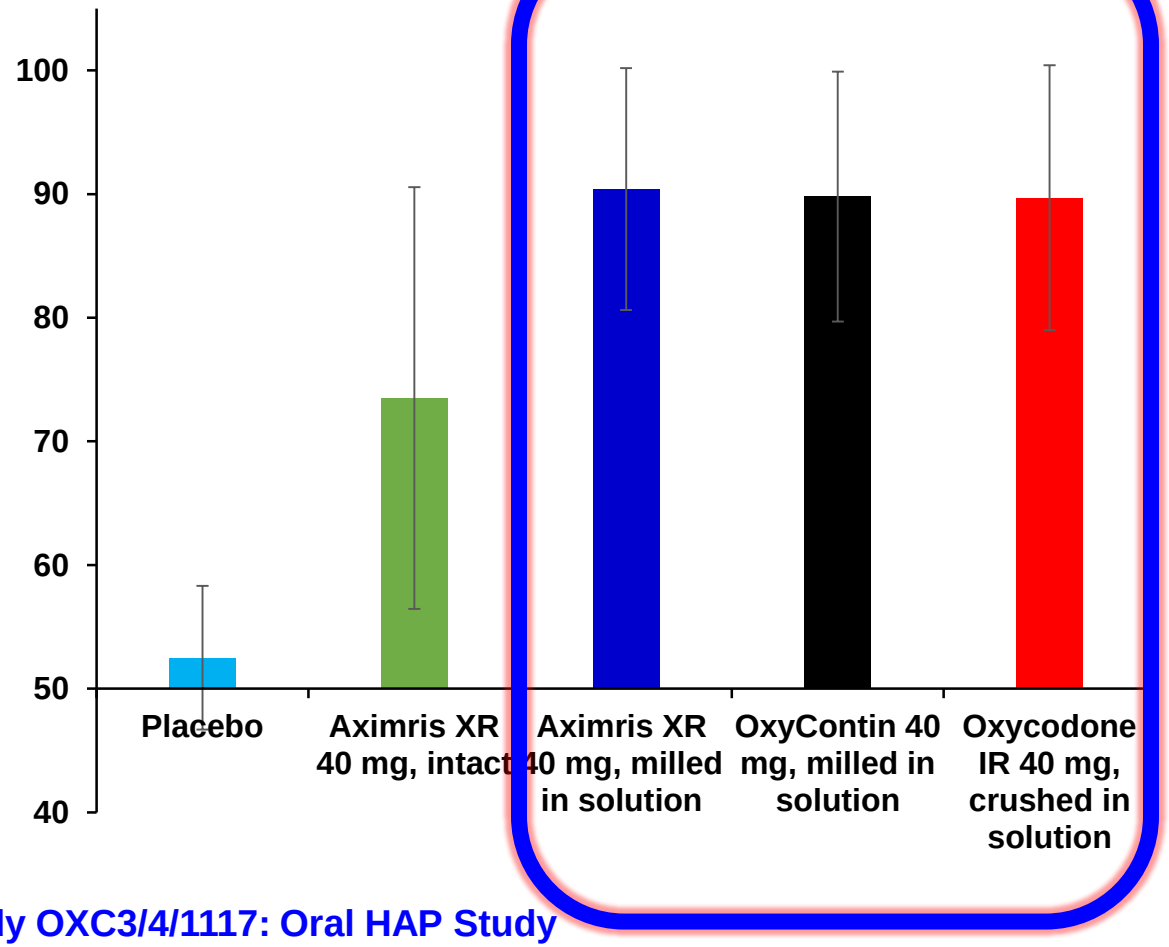
- Intranasal Human Abuse Potential Study
- Oral Human Abuse Potential Study

Aximris XR has Similar Rate and Extent of Exposure to other active treatments – Oral Manipulation

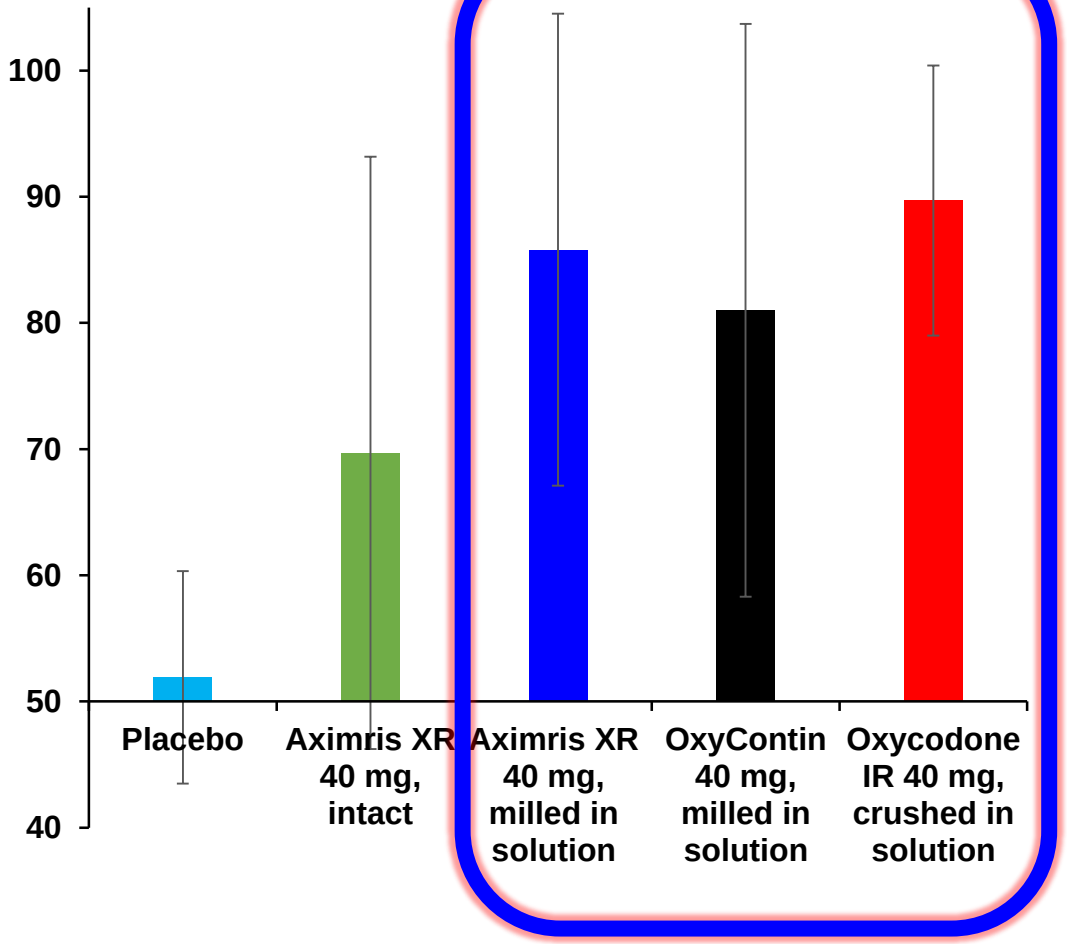
	Arithmetic Mean Parameters (SD)							
	C_{max} (ng/mL)	T_{max} (hr)*	AUC_{0-1h} (ng*hr/mL)	AUC_{0-2h} (ng*hr/mL)	AUC_{0-4h} (ng*hr/mL)	AUC_{0-t} (ng*hr/mL)	AUC_{0-inf} (ng*hr/mL)	$t_{1/2}$ (hr)
Aximris XR 40 mg, Milled in Solution (N=40)	67.20 (20.32)	1.30 (0.53 – 5.03)	31.57 (12.83)	90.55 (30.60)	184.80 (51.81)	503.11 (144.16)	509.50 (146.96)	4.76 (0.84)
OxyContin 40 mg, Milled in Solution (N=40)	69.64 (20.63)	1.03 (0.53 – 5.03)	34.28 (14.93)	92.59 (29.82)	183.08 (45.51)	491.31 (137.03)	497.36 (139.62)	4.70 (0.75)
Oxycodone IR 40 mg, Crushed in Solution (N=40)	74.05 (23.55)	1.03 (0.28 – 5.07)	41.63 (16.59)	102.02 (34.34)	197.53 (56.80)	533.71 (147.47)	539.98 (150.81)	4.69 (0.82)
Aximris XR 40 mg, Intact (N=40)	36.15 (9.33)	5.02 (1.05 – 12.05)	5.01 (4.15)	24.55 (12.36)	80.15 (29.28)	553.77 (143.83)	568.20 (149.19)	6.30 (1.90)

Aximris XR and OxyContin Have Similar Drug Liking VAS E_{max} and Take Drug Again VAS E_{max}

Drug Liking VAS E_{max} (Completers Population)



Take Drug Again VAS E_{max} (Completers Population)



Study OXC3/4/1117: Oral HAP Study

Summary of Findings from Category 2 and 3 Evaluations of Aximris XR

Route of Abuse	Summary of Abuse Potential Findings
Intranasal PK	● C_{max} and partial AUCs significantly higher for Aximris XR, but overall exposure similar for all the active test products ● Both Aximris XR and OxyContin are NOT differentiated from oxycodone IR
Intranasal PD	● Aximris XR and OxyContin are NOT statistically different from oxycodone IR ● Aximris XR and OxyContin Drug Liking VAS E_{max} and Take Drug Again VAS E_{max} are NOT statistically different ● Aximris XR is rated more difficult to snort ● Aximris XR is more irritating (nasal congestion, dry throat, upper respiratory secretions)
Oral PK/PD	● Aximris XR and OxyContin have similar systemic exposure ● Aximris XR and OxyContin Drug Liking VAS E_{max} and Take Drug Again VAS E_{max} are NOT statistically different ● Both Aximris XR and OxyContin are NOT statistically different from oxycodone IR

Benefit/Risk Profile and Risk Mitigation Plans

Isa Odidi, PhD, DSc., MBA
Chief Executive Officer and Co-Chief Scientific Officer
Intellipharmaceutics Corporation.

Aximris XR is Bioequivalent to Oxycontin; Beneficial to Patients, No Additional Risk

- Aximris XR is bioequivalent to OxyContin
  - Supports approval of 505(b)(2) application
  - Supports reliance on well-established safety and efficacy profile for the intended patient population
- Aximris XR demonstrated dose proportionality among all doses
- Aximris XR has no clinically significant food effect. Patients can take Aximris XR medication without regards to meals

Aximris XR has Features Intended to Impede IV Route of Abuse; No Additional Risk

Physical Manipulations	Results in hyperviscosity and hypercoagulability
IV Injection (Common Methods)	It is difficult to syringe and inject Aximris XR using common methods of IV abuse
IV Injection (Internet/ Advanced “recipes”)	Aximris XR not easily defeated by typical website “recipes”

Aximris XR and OxyContin Appear to Have Similar Intranasal Human Abuse Potential

- Aximris XR has higher C_{max} and partial AUCs but similar overall exposure to all the active treatments
- Aximris XR and OxyContin mean E_{max} values not statistically significantly different with respect to;
  - Drug Liking VAS
  - Take Drug Again VAS
  - High VAS
  - Overall Drug Liking VAS
- Aximris XR was rated more difficult to snort
- Aximris XR caused slightly higher incidence of nasal congestion compared to OxyContin and displayed local irritating effects which may make it less attractive to abuse

No New Safety Signals Beyond What is Already Known for Oxycodone Products. No Deaths or Serious Adverse Events

Clinical Program	Clinical Safety
Seven Phase 1 Pharmacokinetic Studies	No new safety signal beyond what is already known for OxyContin
Intranasal Human Abuse Potential Study	No deaths or serious adverse events
Oral Human Abuse Potential Study	No deaths or serious adverse events or discontinuations due to adverse events

Benefit and Risk Evaluation of Using Aximris XR As Labeled

- If used as labeled Aximris XR carries similar benefits and risks as OxyContin and other approved extended release oxycodone products
- Use of opioid analgesic products carries the risk of serious safety concerns that must be taken into account when prescribing opioids
- All patients treated with opioids such as Aximris XR require careful monitoring

Benefit and Risk Evaluation of Using Aximris XR Not As Labeled

- Aximris XR is for oral use only
- Manipulation or abuse of Aximris XR poses a risk of overdose and death
- Excipients in Aximris XR designed for oral use only
  - Parenteral administration of excipients not intended for IV injection can be expected to result in adverse effects and severe health consequences

Benefits and Risk to Public Health

- Aximris XR demonstrated superior IV abuse-deterrent properties
- Approval and addition of an IV abuse–deterrent formulation such as Aximris XR is expected to add to already available abuse-deterrent products
- Public health concerns of approving another opioid and adding a new opioid into the marketplace however;
  - Studies[1] show that approval of new branded opioid products alone does not appear to be a primary driver of increased opioid prescribing
  - Number of opioid analgesic prescriptions dispensed has declined since 2012 despite increasing number of opioid analgesic approvals[1]
- No unique features of Aximris XR has been identified that would result in new unintended consequences following its use nevertheless, Intellipharmaceutics will closely monitor these risks post approval

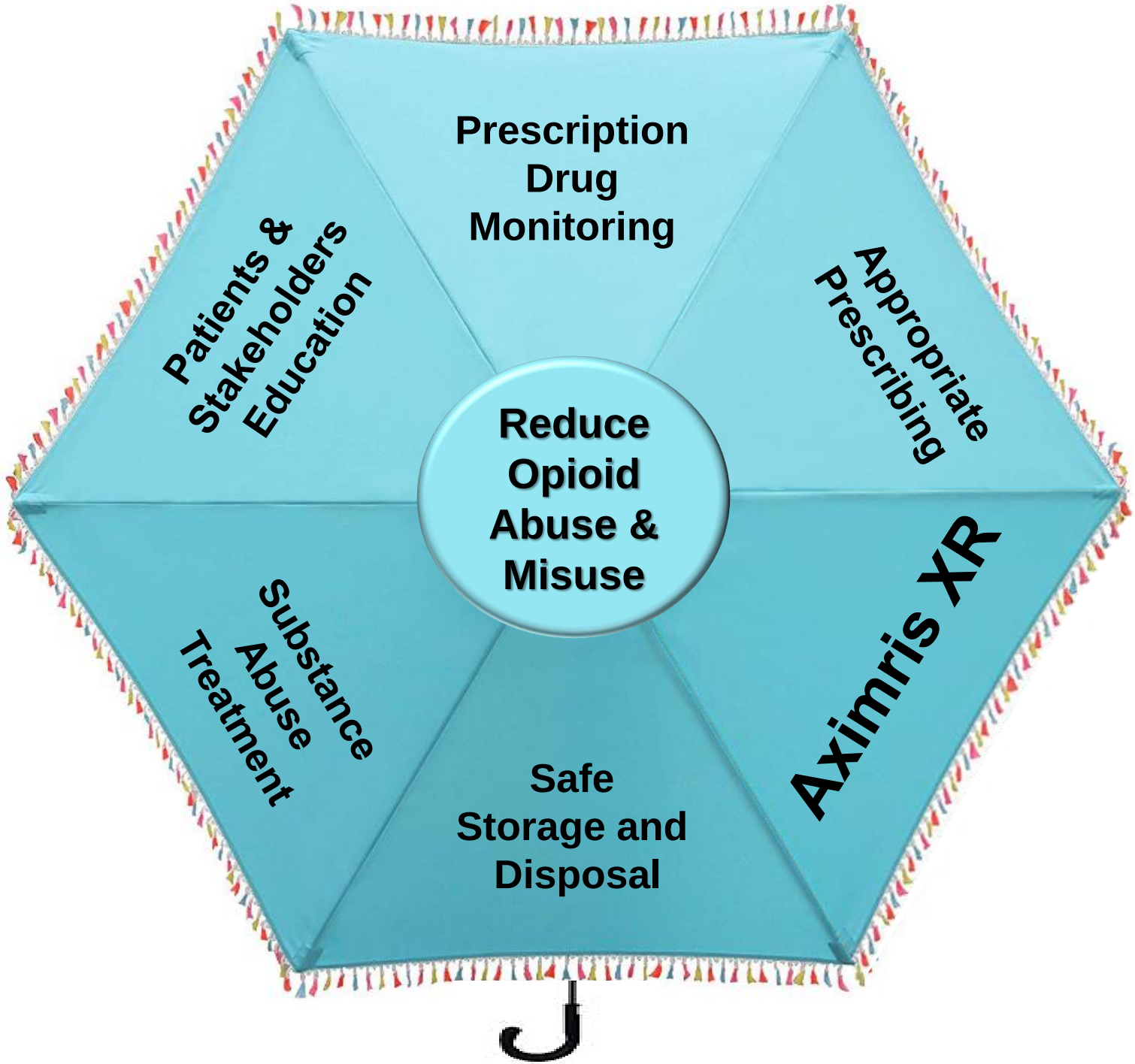
[1]Chai G, et al, Anesthesiology, Volume 128, No 5, May 2018, pages 953-966

Commitment to the Safe and Responsible Use of Aximris XR

- Participation in “The Opioid Analgesic REMS”
- Aximris XR safe use program
  - Education for all health care providers (AHCPs)
  - Safe use initiative program to influence practices
- Secure supply chain and responsible sales and marketing practices
- Pharmacovigilance studies and risk minimization measures
- Work with FDA and RADARS® for a comprehensive post-marketing surveillance solution and Development of formal epidemiologic studies per FDA guidance
  - Acute health events, drug transactions, illicit market price, web monitoring and entering treatment

Conclusion

- Aximris XR demonstrates abuse-deterrence to the most dangerous route of abuse
- Bioequivalent to OxyContin
- Similar Drug Liking and Take Drug Again to OxyContin
- Similar risks and benefits to other approved ADFs
- No clinically significant effect of food
- Approval of an IV abuse-deterrent formulation such as Aximris XR is expected to add to already available abuse-deterrent products


Prescription Drug Monitoring
Appropriate Prescribing
Aximris XR
Safe Storage and Disposal
Substance Abuse Treatment
Patients & Stakeholders Education
Reduce Opioid Abuse & Misuse

Aximris XR (Oxycodone HCl Extended-Release) Tablets for Treatment of Chronic Pain

January 15, 2020

Intellipharmaceutics Corp.

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

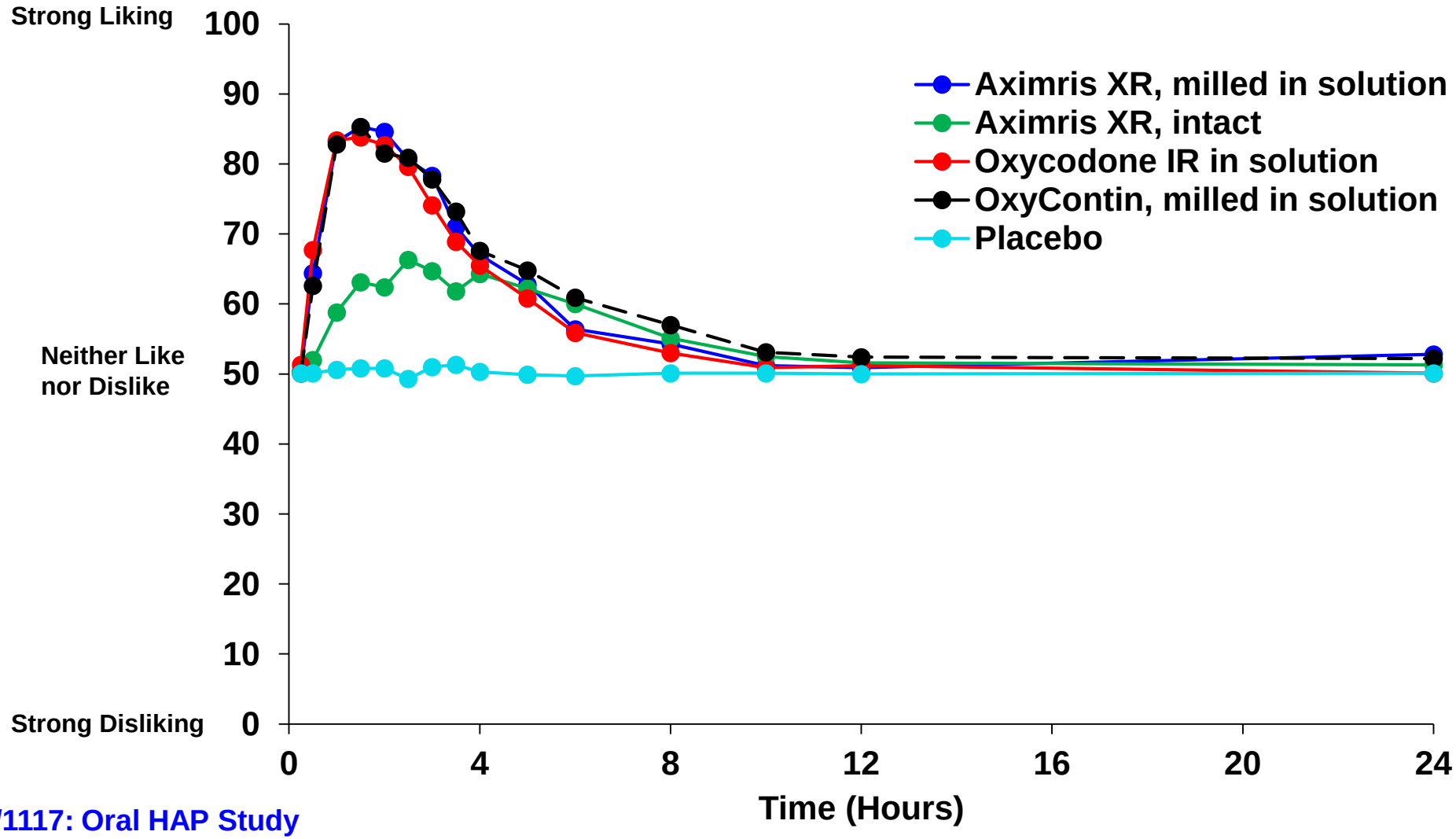
Backup Slides

Treatment Emergent Adverse Events Occurring in at Least 10% Any Treatment Group – Intranasal Study

System Organ Class Preferred Term	IPC Oxycodone ER 30 mg Ground N=32	Oxycodone IR 30 mg Crushed N=32	OxyContin 30 mg Ground N=32	Placebo IPC Oxycodone ER N=32	Placebo Oxycodone IR/ OxyContin N=32
	n (%)	n (%)	n (%)	n (%)	n (%)
Psychiatric disorders					
Euphoric mood	13 (41)	13 (41)	15 (47)	0	0
Respiratory, thoracic and mediastinal disorders					
Nasal congestion	5 (16)	0	4 (12)	7 (22)	1 (3)
Throat irritation	4 (12)	1 (3)	4 (12)	4 (12)	0
Nervous system disorders					
Somnolence	5 (16)	7 (22)	5 (16)	0	2 (6)
Headache	6 (19)	3 (9)	3 (9)	2 (6)	0
Dizziness	7 (22)	1 (3)	2 (6)	0	0
Skin and subcutaneous tissue disorders					
Generalized pruritus	6 (19)	3 (9)	3 (9)	0	0
Pruritus	1 (3)	5 (16)	4 (12)	0	0
Gastrointestinal disorders					
Nausea	8 (25)	2 (6)	3 (9)	0	0

Source: FDA Backgrounder Table 3, page. 26; IR=immediate release; ER=extended-release; percentages rounded

Aximris XR and OxyContin Have Similar Mean Drug Liking VAS Scores over Time



Study OXC3/4/1117: Oral HAP Study