Arymo™ ER (morphine sulfate) Extended-Release Tablets for the Treatment of Chronic Pain

August 4, 2016

Egalet Corporation

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

Introduction

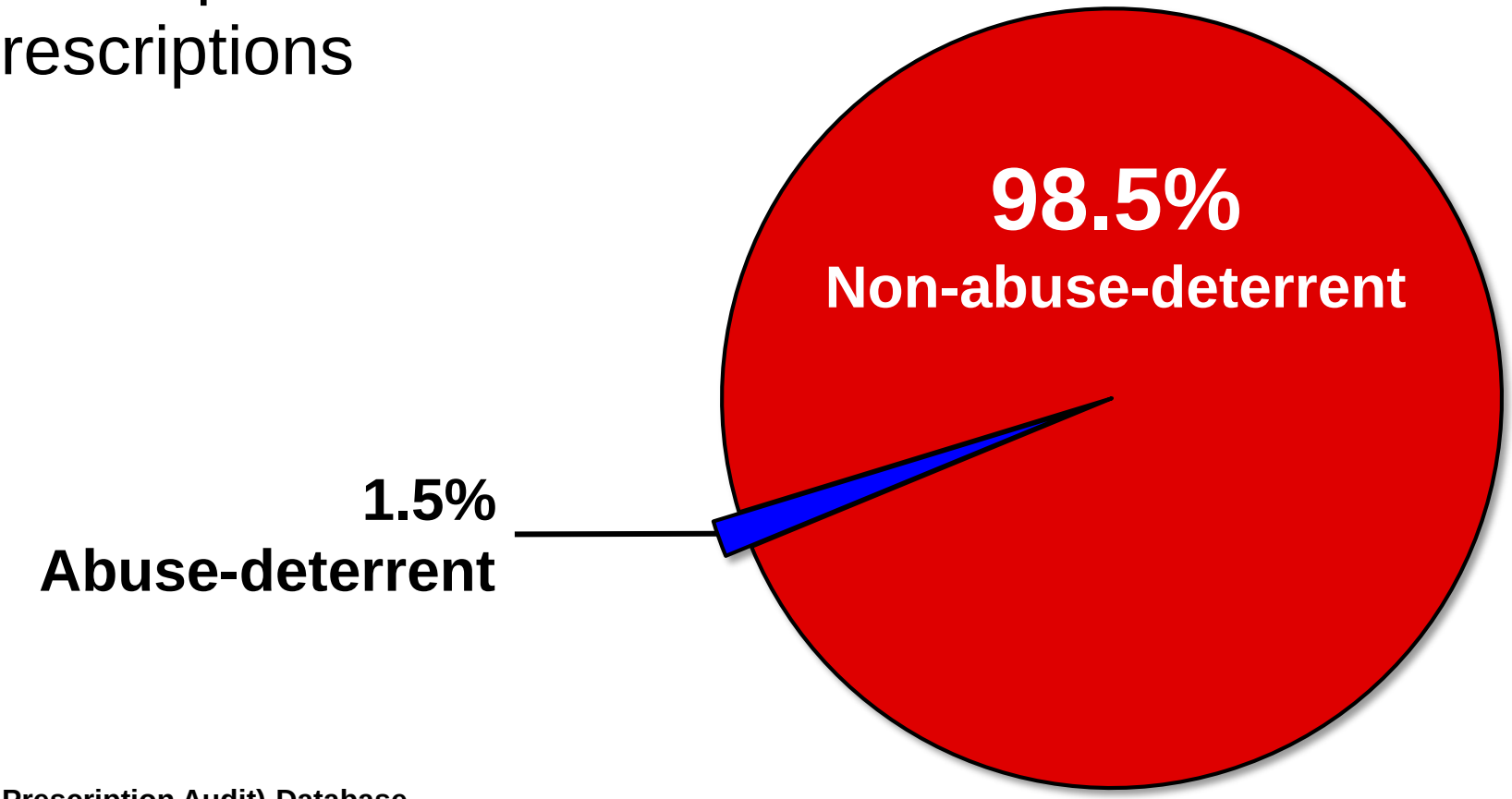
Robert Radie
President and Chief Executive Officer
Egalet Corporation

Morphine is the Most Commonly Prescribed ER Opioid in the U.S.

- 2015: 6.4 million ER morphine prescriptions

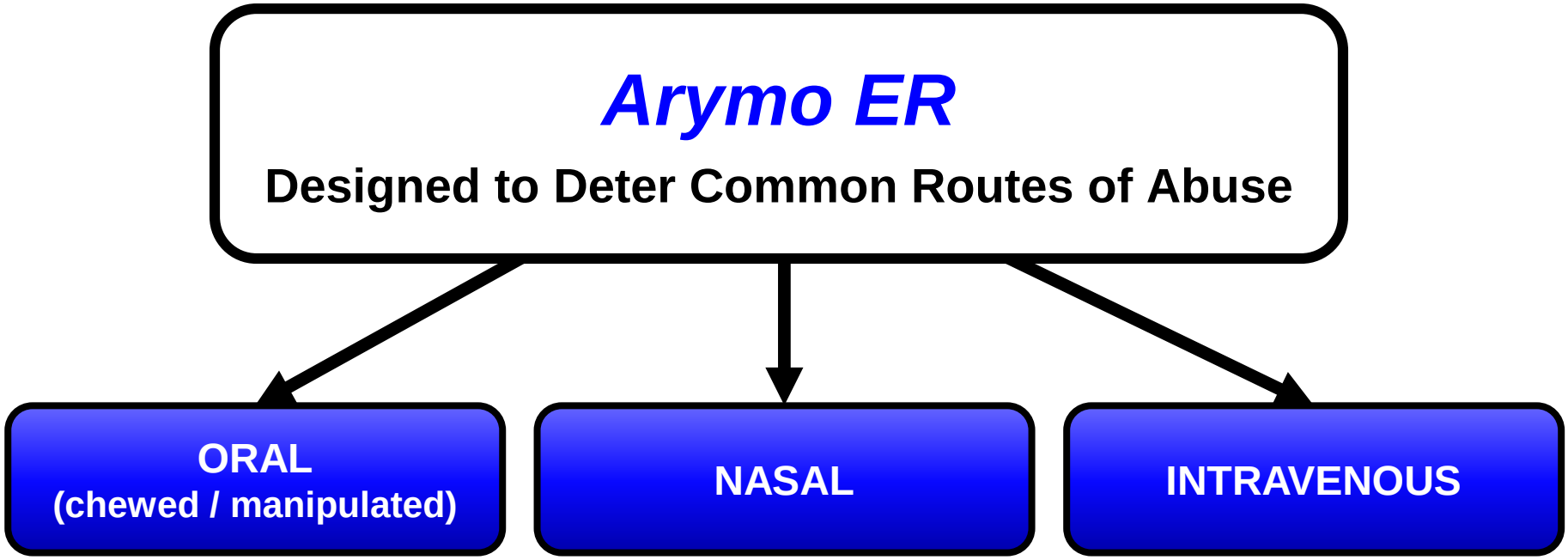
ER Morphine Prescriptions

January-April 2016



IMS (National Prescription Audit) Database

Arymo ER Provides a Broad Abuse-Deterrent Profile

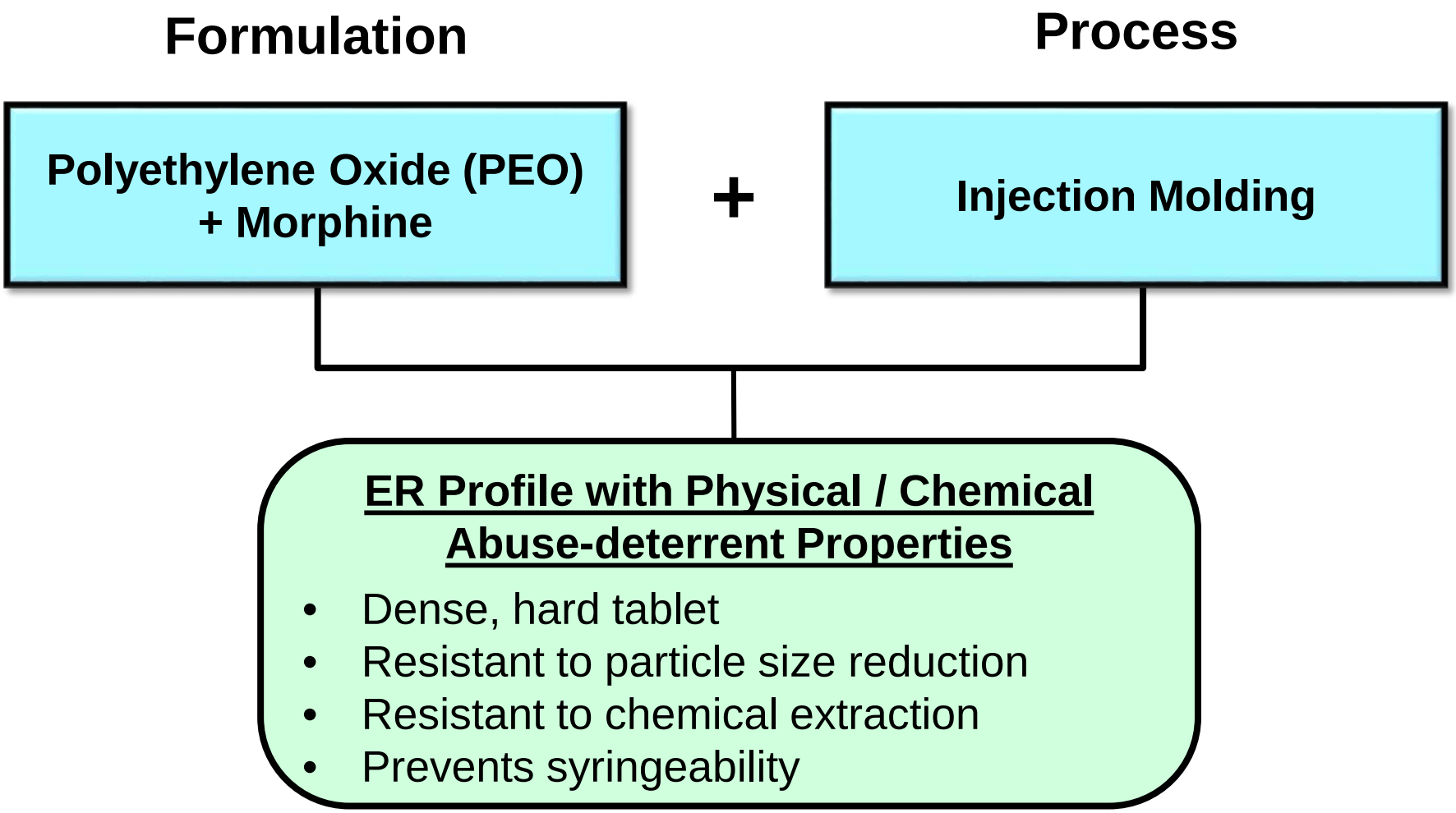


- Hard tablet
- Difficult to chew
- Resistant to particle size reduction and morphine extraction

- Difficult to reduce to a snortable powder

- Difficult to extract for injection
- Difficult to draw into syringe

Guardian™ Technology Confers Physical and Chemical Barriers to Abuse



Clinical Data Support Approval of Arymo ER

- Arymo ER was bioequivalent to MS Contin at all intended dosage strengths
- Bioequivalence scientific bridge to safety and efficacy
- No clinically significant food effect
- No evidence of alcohol dose dumping

15 mg **30 mg** **60 mg**

Comprehensive Abuse-Deterrent Development Program for Arymo ER

Category 1

In Vitro Testing

Resistance to Physical & Chemical Manipulation

Category 2

Clinical PK Studies

PK not converted to an immediate-release profile

C_{max} T_{max}

Category 3

Clinical Abuse-Deterrent Studies

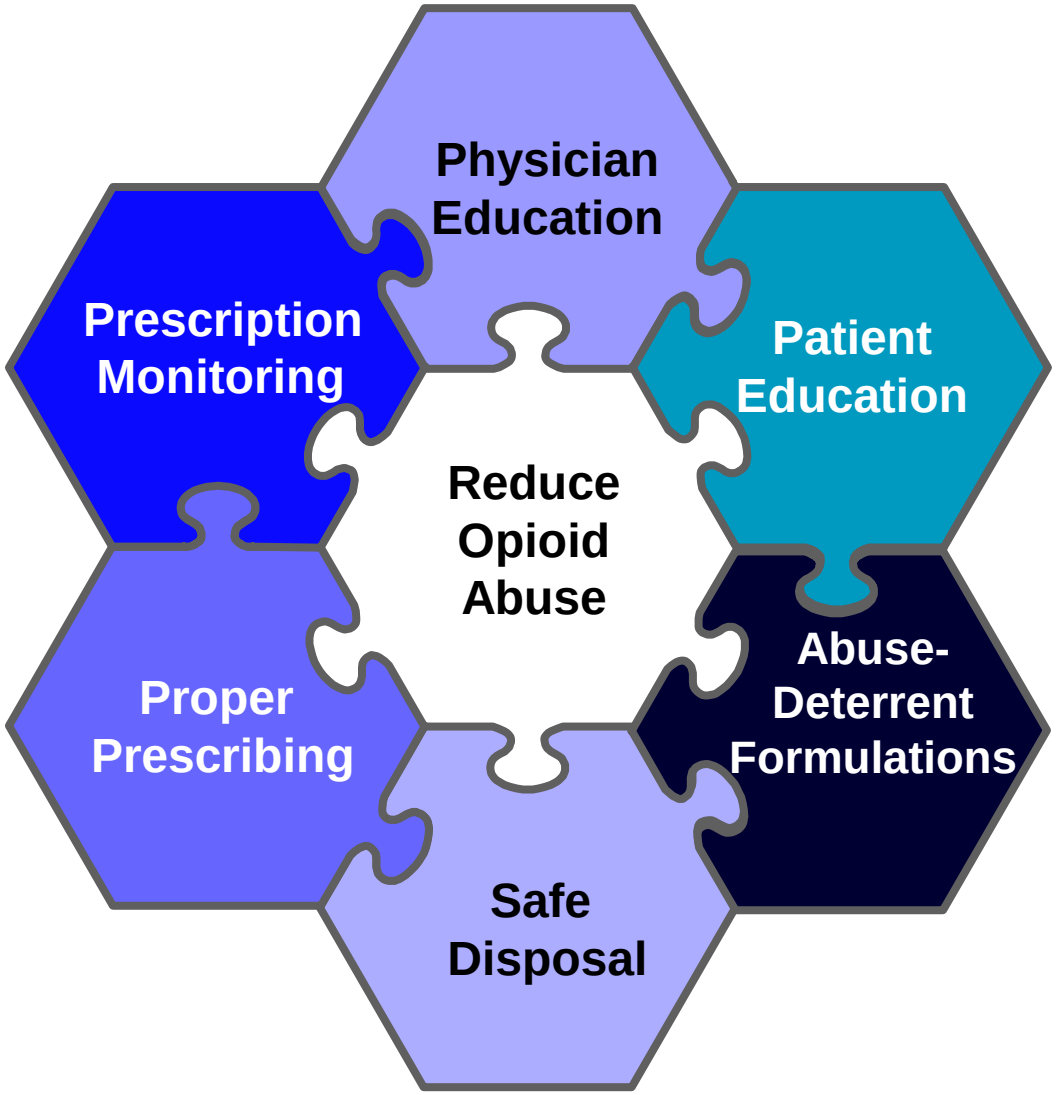
Drug Liking

Take Drug Again

Positive Drug Effects

- Committed to fulfilling post-approval requirements
- Category 4 study to assess real-world impact of Arymo ER on misuse and abuse

Abuse-Deterrent Formulations Are Part of the Solution



Agenda

Public Health Need	**Richard Dart, M.D., Ph.D.** Director Denver Health & Hospital Authority
Abuse-Deterrent Studies	**Jeffrey Dayno, M.D.** Chief Medical Officer Egalet Corporation
Clinical Relevance	**Nathaniel Katz, M.D., M.S.** President Analgesic Solutions

Additional Experts

Pain Management **Clinical Abuse Potential Studies**	**Lynn Webster, M.D.** **Vice President, Scientific Affairs** **PRA Health Sciences**
Category 1 Studies	**Edward Cone, Ph.D.** **Principal Scientist** **PinneyAssociates**
Clinical Pharmacology	**Mona Darwish, Ph.D.** **President** **Sci-Med Bridge, LLC**

Public Health Need for Abuse-Deterrent ER Morphine

Richard C. Dart, M.D., Ph.D.

Executive Director, RADARS® System

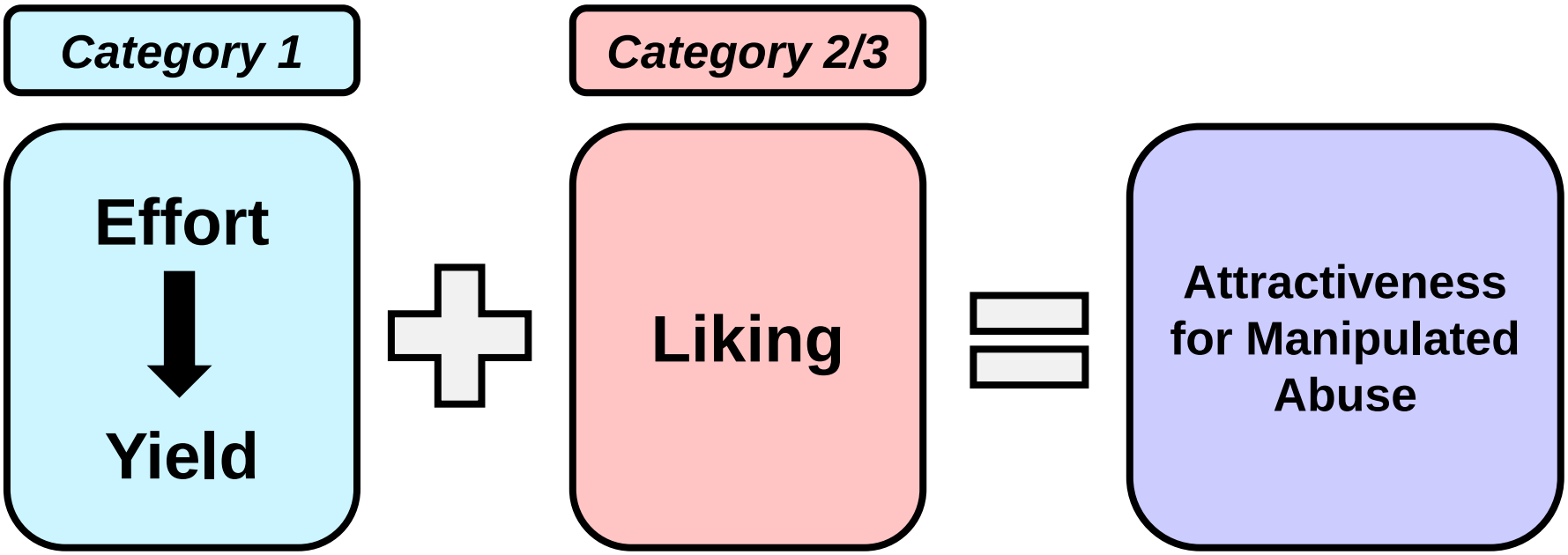
Director, Rocky Mountain Poison & Drug Center

Professor of Emergency Medicine,
University of Colorado School of Medicine

Abusers Chew or Manipulate ER Opioids for a Quick and Easy "High"

- Particle size reduction (PSR)
  - Defeats ER properties
  - Releases drug faster
  - Prepares drug for alternate routes of abuse (i.e., oral [chewed/manipulated], intranasal, intravenous)
- Smaller particle sizes = faster extraction

Attractiveness for Manipulated Abuse is Based on Effort, Yield, and Liking



How difficult is the product to manipulate?

How many small particles are produced?

How much drug is in abusable form?

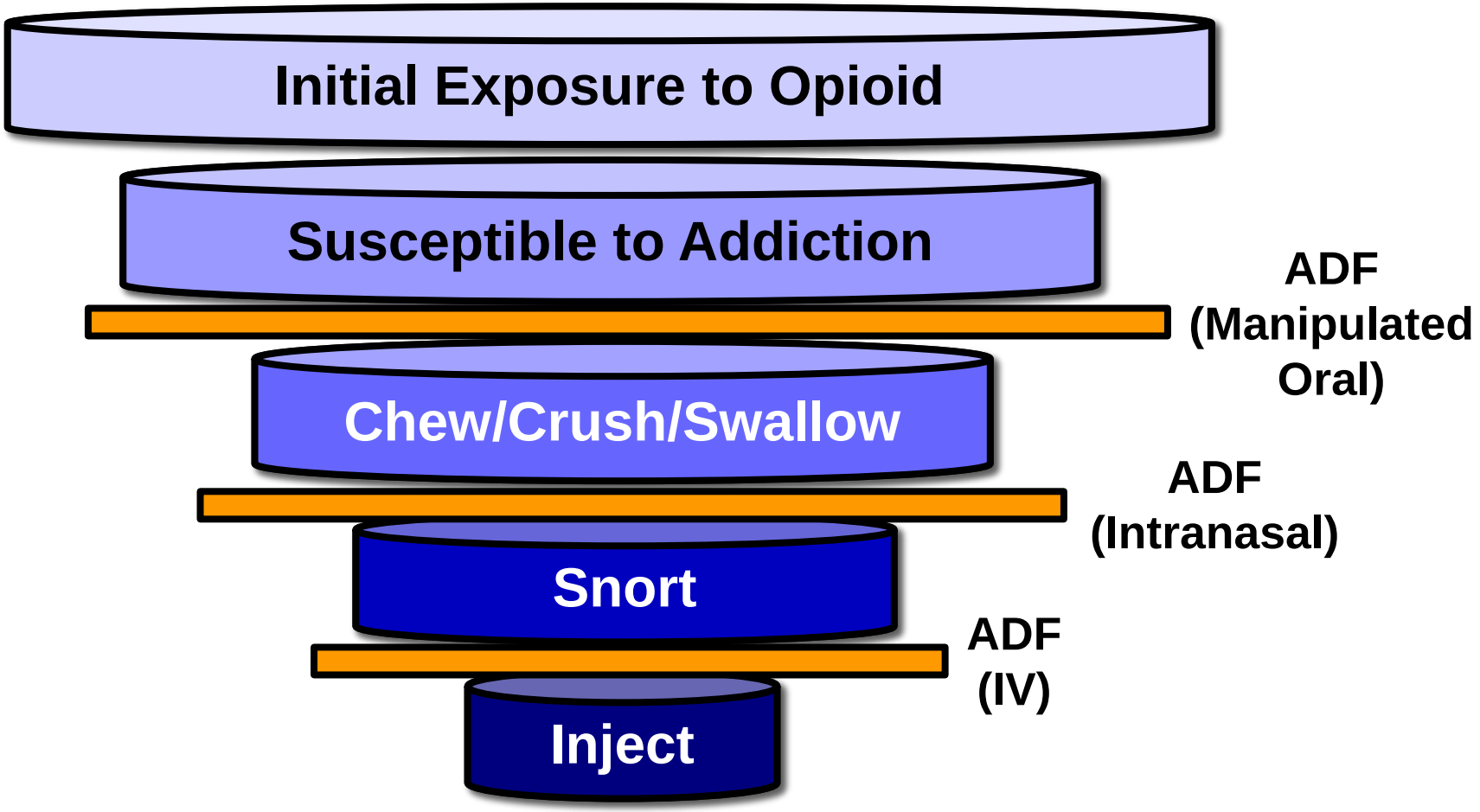
How much do abusers like the result?

Can the product be expected to lead to a reduction in abuse?

Two Primary Approaches to Abuse Deterrence

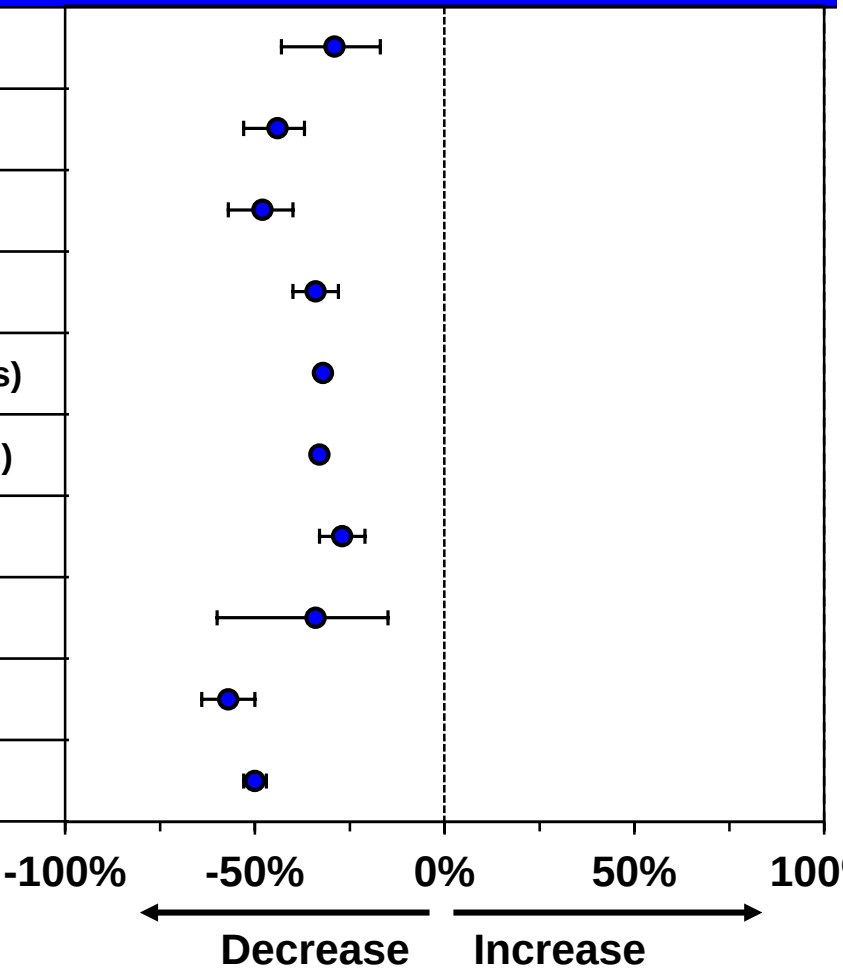
- Physical / chemical barriers (e.g., OxyContin)
  - Physical barriers against PSR
  - Chemical barriers against extraction
- Agonist / antagonist (e.g., Embeda)
  - More easily manipulated
  - Manipulation (e.g., chewing) releases antagonist (e.g., naltrexone)

ADFs May Intervene at Several Points in Progression of Substance Abuse



Abuse-Deterrent ER Oxycodone Has Been Effective in Deterring Abuse

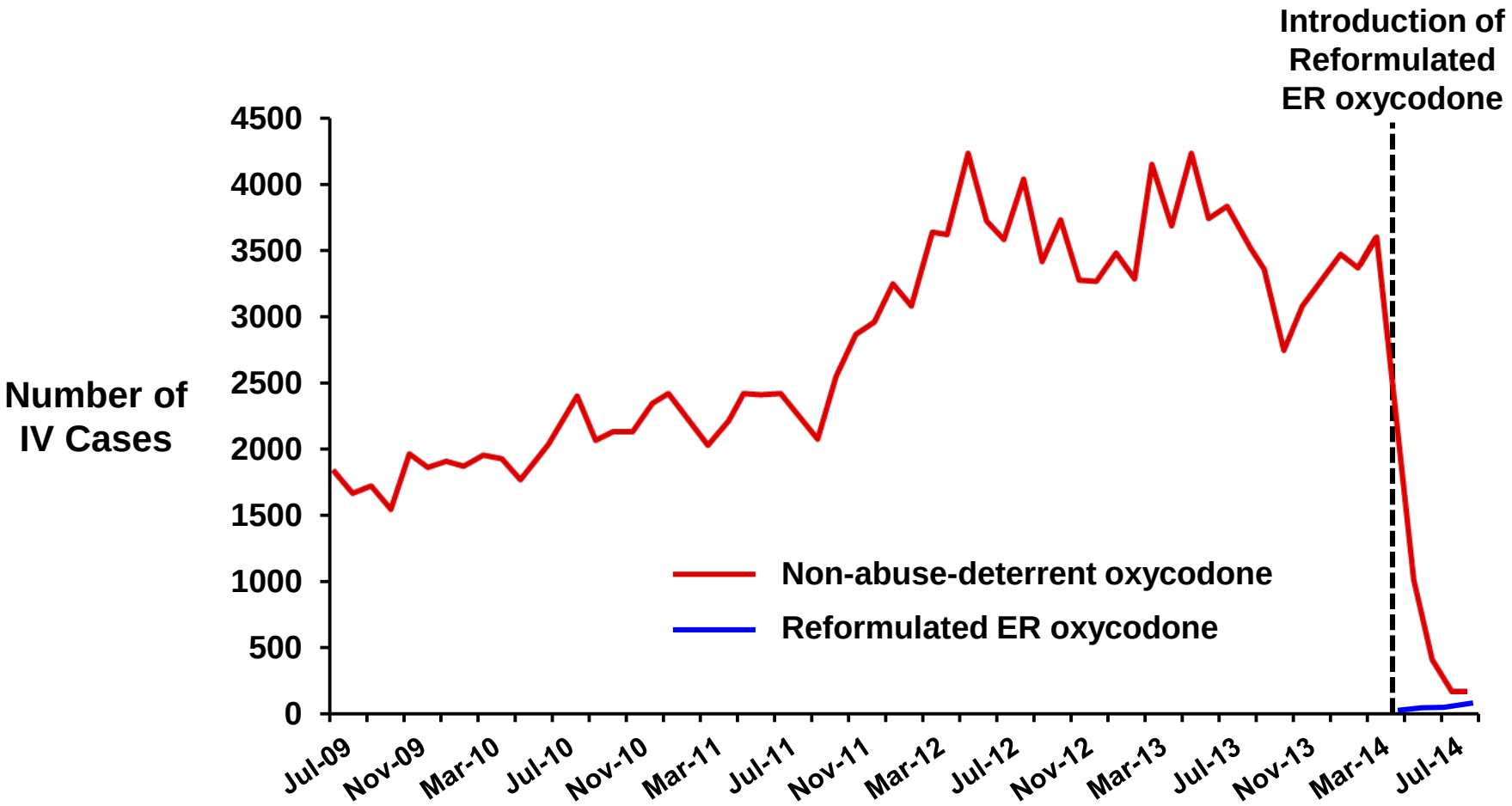
Outcome	Source	% Change [95% CI] Pre vs. Post Reformulation
Misuse	RADARS (Poison Centers)	
Abuse	RADARS (Poison Centers)	
	NPDS (Poison Centers)	
	NAVIPPRO (Treatment Centers)	
	RADARS SKIP (Treatment Centers)	
	RADARS OTP (Treatment Centers)	
Opioid Use Disorder	Marketscan - Opioid Users	
Overdose	Marketscan - Opioid Users	
Diversion	RADARS (Drug Diversion)	
Doctor Shopping	IMS Prescription Data	



Data adjusted for prescription volume

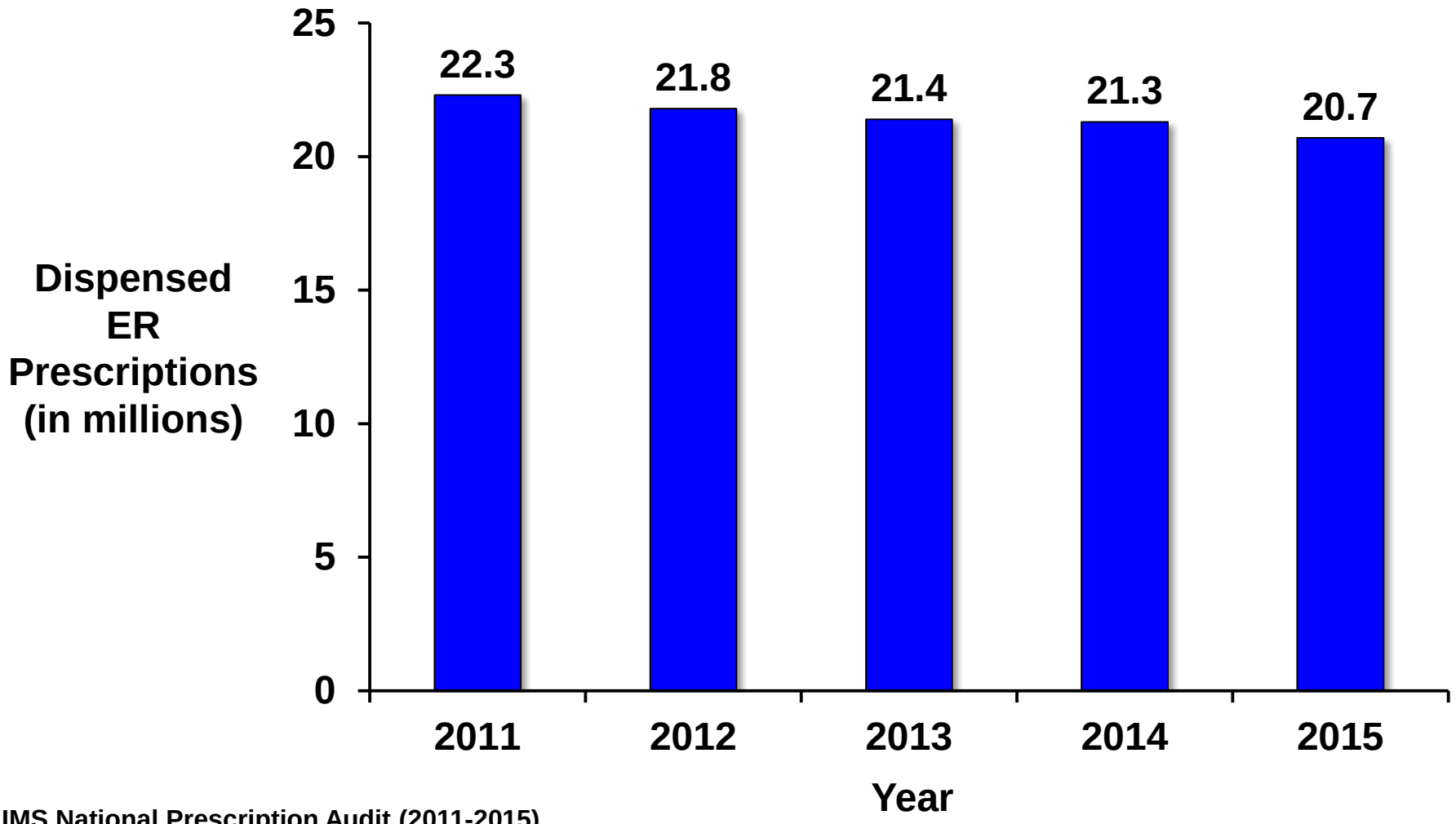
Coplan et al. *Clin Pharmacol Ther* 2016.

Abuse-Deterrent ER Oxycodone Reduces IV Abuse in Australia



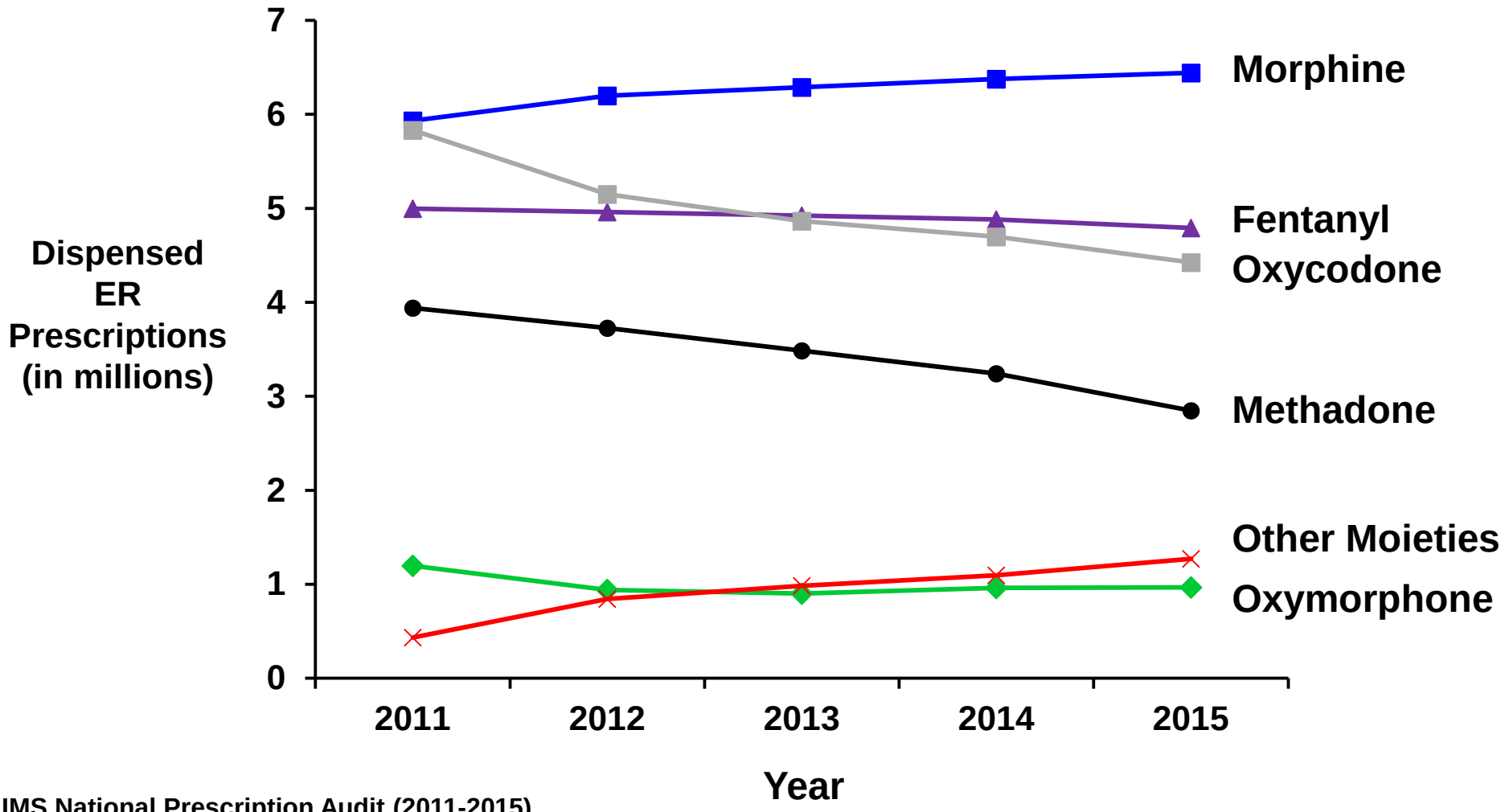
Degenhardt et al. *Drug Alc Dependence* 2015;151:56-57.

ER Opioid Prescriptions Have Been Decreasing Over Last 5 Years



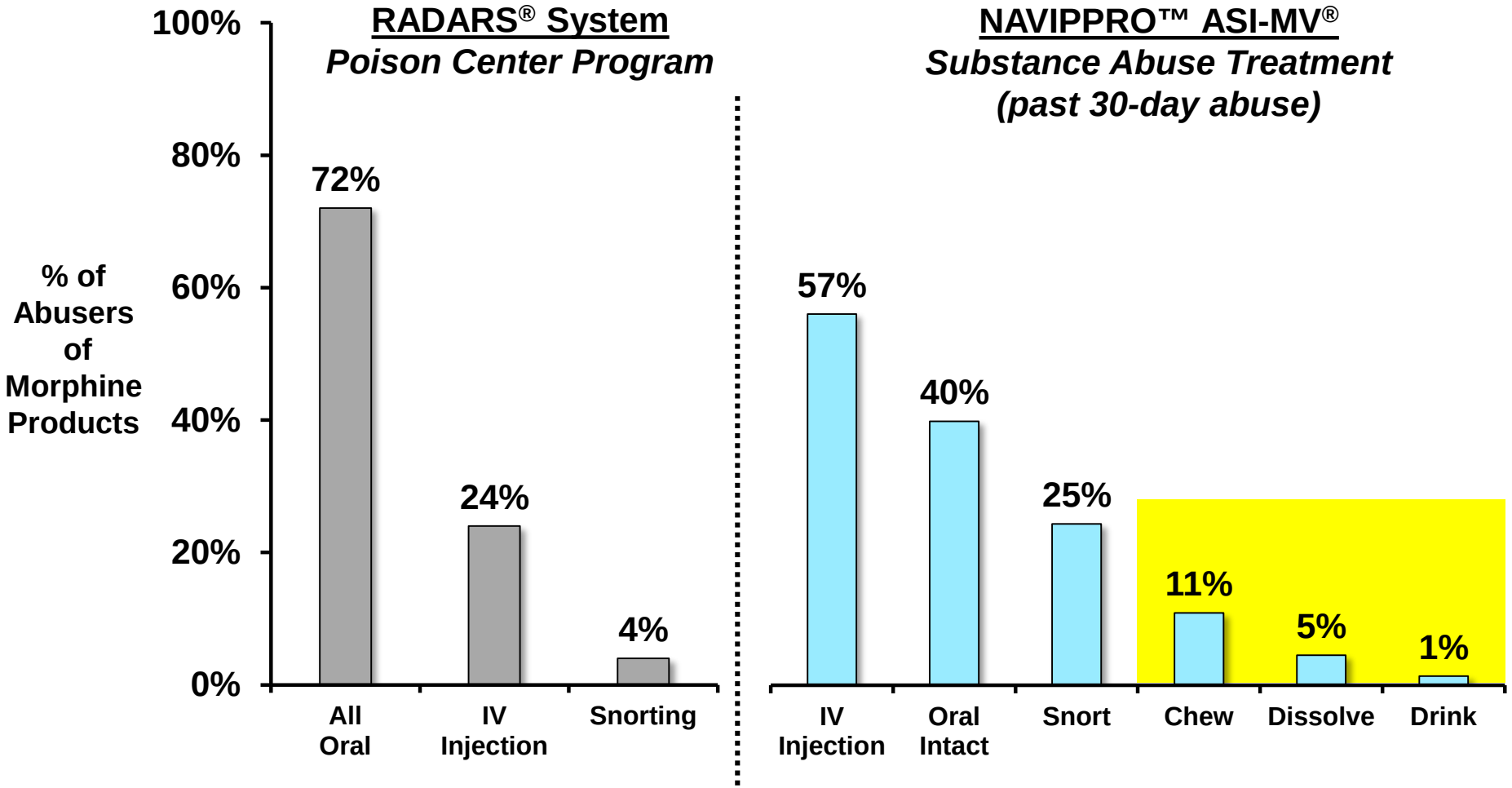
IMS National Prescription Audit (2011-2015)

Morphine Most Commonly Prescribed ER Opioid in the U.S.



IMS National Prescription Audit (2011-2015)

ER Morphine is Abused by Oral, Nasal, and IV Routes



RADARS Poison Control Center Program, 2015 data on file.
Inflexxion, 2015 data on file.

Public Health Need: ER Morphine Products with Physical / Chemical Barriers to Abuse

- ADFs with physical / chemical barriers should prevent chewing, hinder particle size reduction (PSR) and resist being turned into IR
- ADFs associated with significant reductions in misuse, abuse, and diversion
- ADFs have not led to more prescribing
- ER morphine is most commonly prescribed opioid and is abused through chewing, manipulated oral, snorting, and IV injection

Abuse-Deterrent Studies

Jeffrey M. Dayno, M.D.
Chief Medical Officer
Egalet Corporation

Development Program for Arymo ER Followed FDA Guidance

Category 1

In Vitro Testing

Resistance to Physical & Chemical Manipulation

Routes of Abuse

- Oral
- Intranasal
- Intravenous

Category 2

Clinical PK Studies

PK not converted to an immediate-release profile

C_{max} T_{max}

Two Clinical Trials

EG-008 – Oral PK and HAP Study

EG-009 – Intranasal PK and HAP Study

Category 3

Clinical Abuse-Deterrent Studies

Drug Liking

Take Drug Again

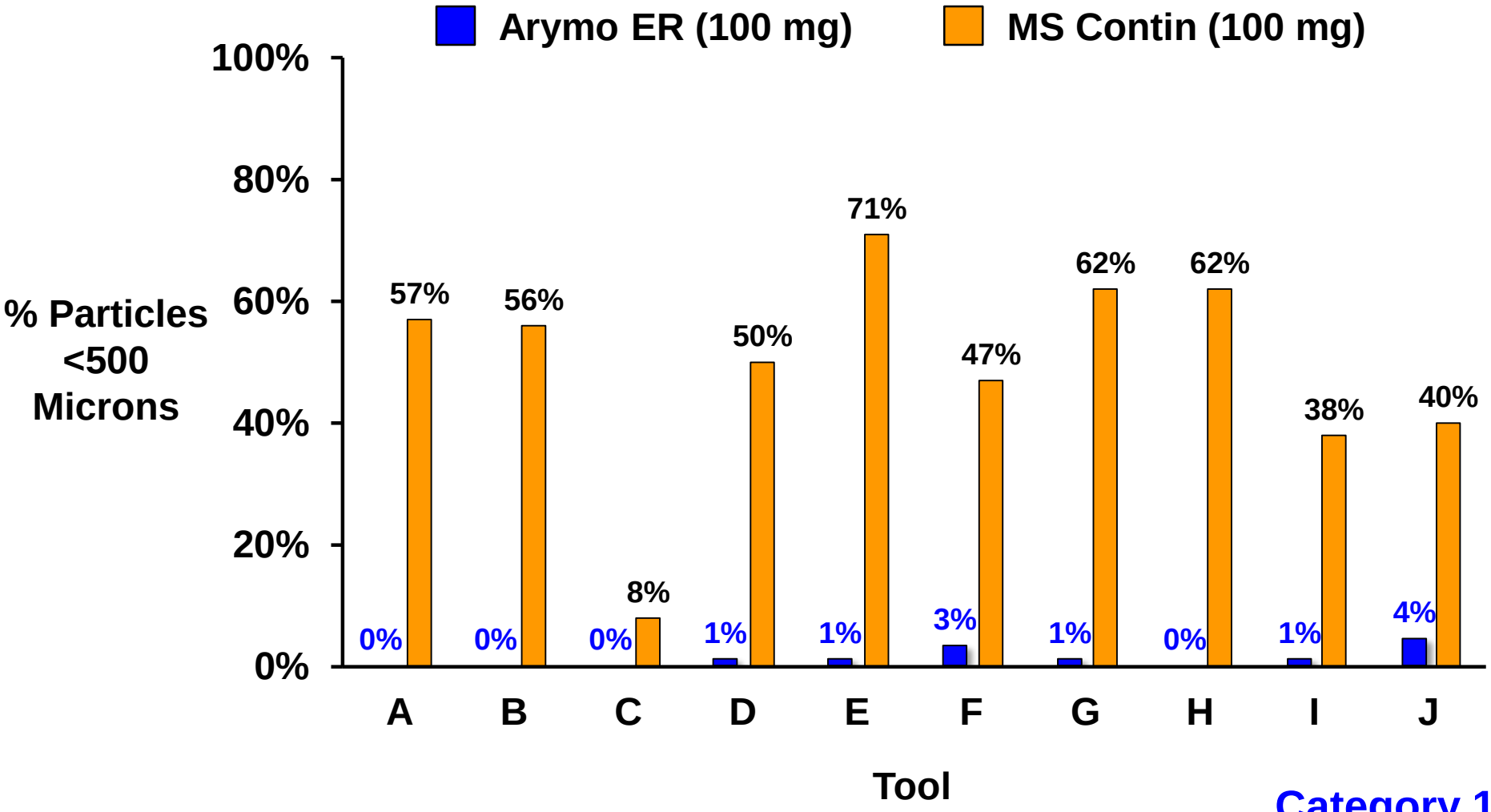
Positive Drug Effects

Category 1 Assessments to Evaluate Common Routes of Abuse

Assessments	Route of Abuse		
	Oral	IV	Intranasal
Single- and Multi-tool PSR	✓	✓	✓
Multi-tool PSR after Pre-treatment	✓	✓	✓
Tablet Hardness (Chewing)	✓		
Small Volume Extraction and Syringeability		✓	
Large Volume Extraction	✓	✓	✓
Alcohol Dissolution	✓		

PSR = particle size reduction

Arymo ER More Resistant to Particle Size Reduction than MS Contin



Category 1

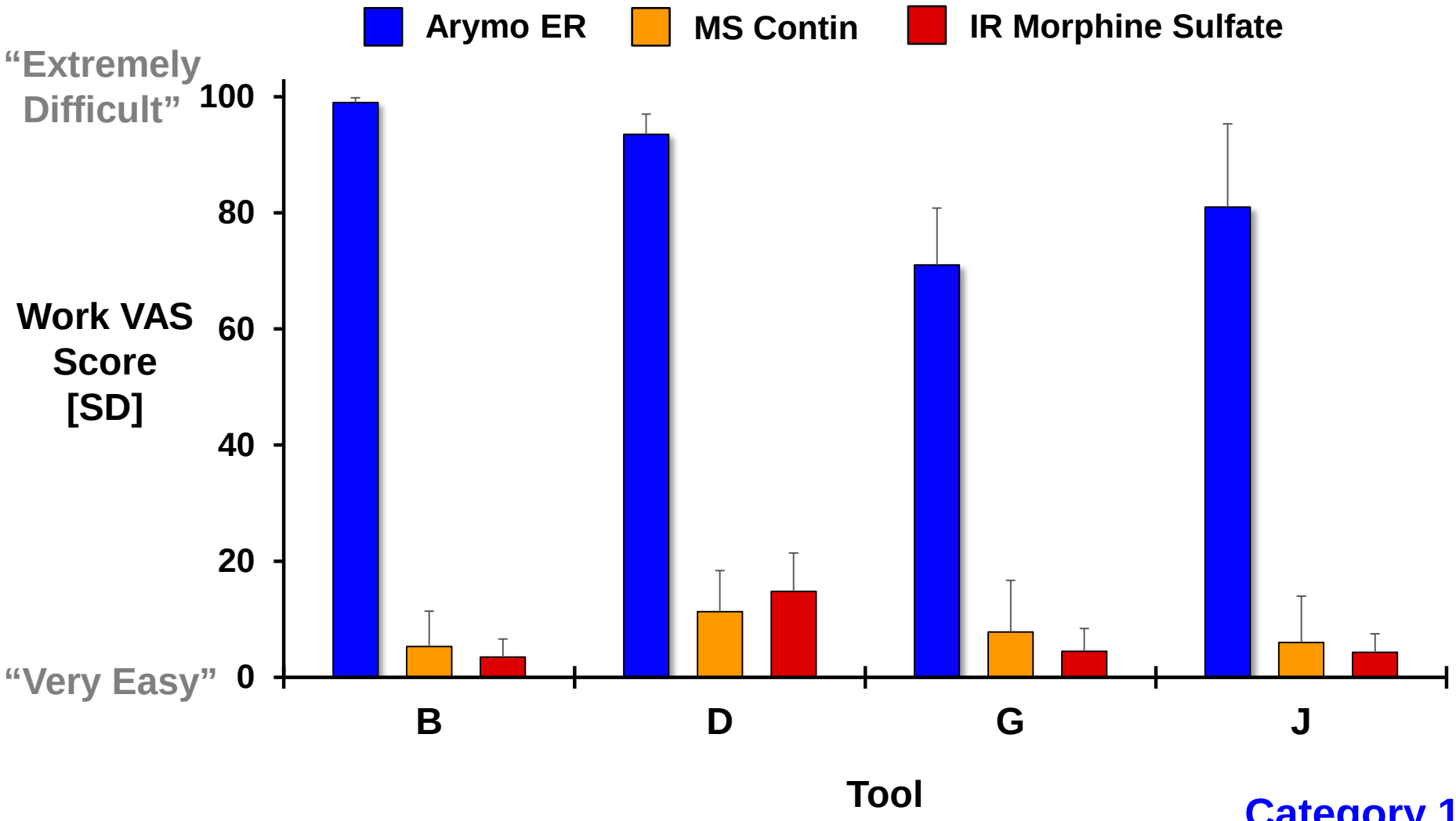
ALERRT™ Instrument

- Developed to measure “work” involved in physical manipulation of a formulation
- Assesses combination of time, effort, and resources
- Scores measured on VAS
  - 0 = “very easy” (uncoated aspirin)
  - 100 = “extremely difficult” (metal nut)

Methods for ALERRT™ Study

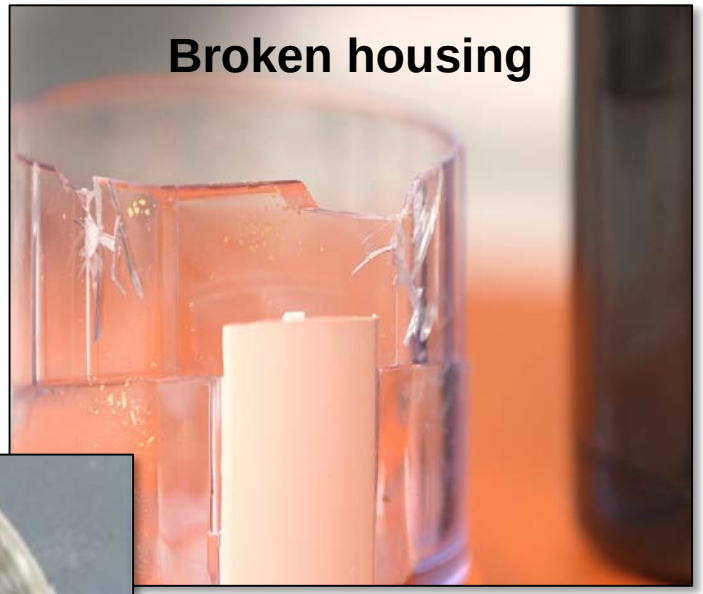
- Evaluated tools representative of instruments for cutting, crushing, grating, and grinding
- 4 trained laboratory technicians independently conducted physical manipulation on:
  - Arymo ER
  - MS Contin
  - IR morphine sulfate

ALERRT™: Arymo ER More Difficult to Manipulate than MS Contin and IR Morphine



Category 1

Many Tools Broke During Attempts to Manipulate Arymo ER



Category 1

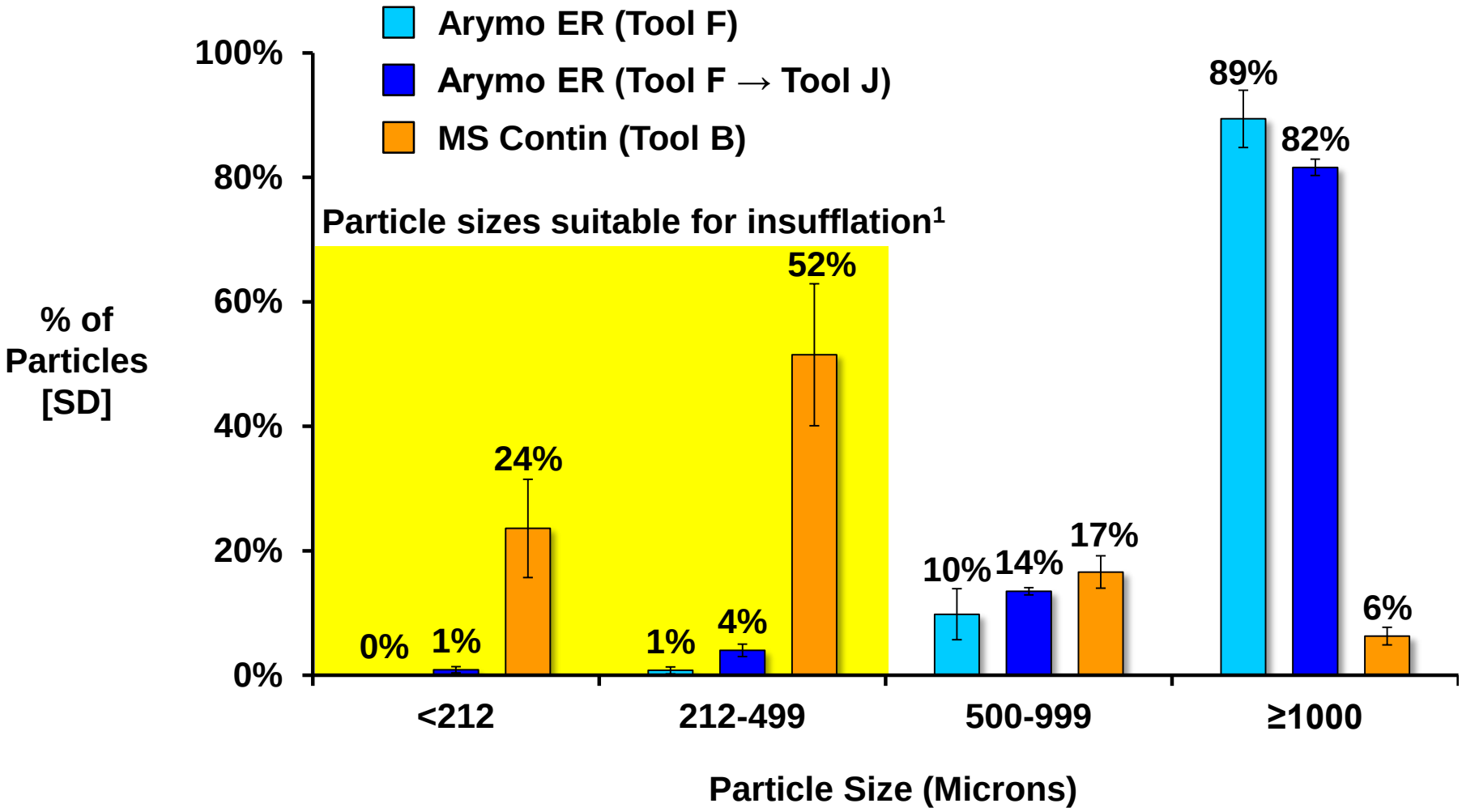
No Significant Increase in Particle Size Reduction with Multi-Tool Procedures

- Tool F → Tool B
  - No additional PSR achieved
- Tool F → Tool J
  - Minimal additional PSR achieved
- Tool F → Tool J → Tool B
  - No additional PSR achieved

Optimal Particle Size Reduction Methods

- Optimal PSR methods for Arymo ER
  - Single-tool: Tool F
  - Multi-tool: Tool F → Tool J
- Optimal PSR method for MS Contin
  - Single-tool: Tool B

Distribution of Particle Sizes Using Optimized PSR Methods



1. FDA. Guidance for Generic Solid Oral Opioid Drug Products, 2016.

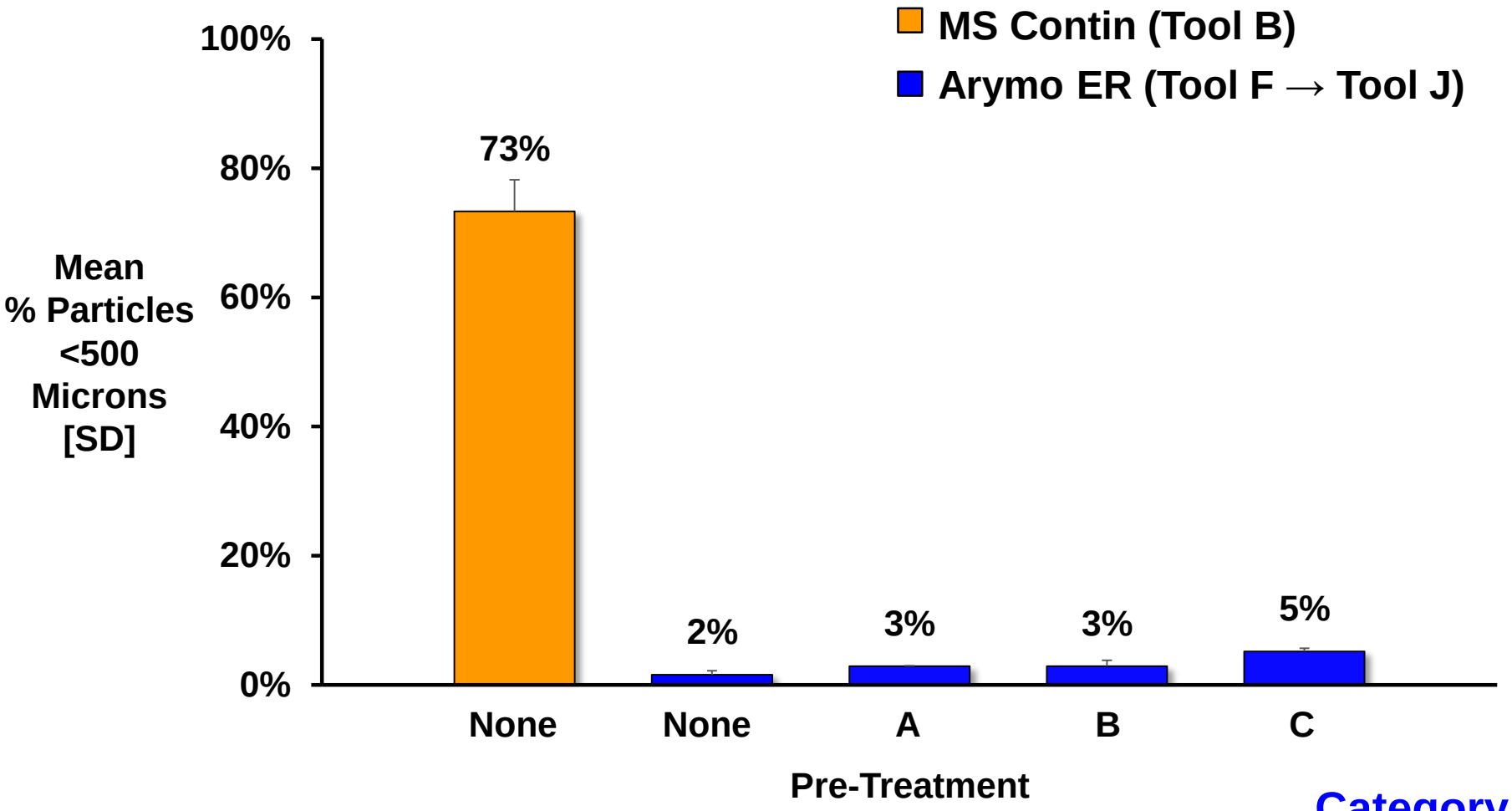
Category 1

Category 1 Assessments to Evaluate Common Routes of Abuse

Assessments	Route of Abuse		
	Oral	IV	Intranasal
Single- and Multi-tool PSR	✓	✓	✓
Multi-tool PSR after Pre-treatment	✓	✓	✓
Tablet Hardness (Chewing)	✓		
Small Volume Extraction and Syringeability		✓	
Large Volume Extraction	✓	✓	✓
Alcohol Dissolution	✓		

PSR = particle size reduction

Pre-Treatment Was Not Effective in Enhancing Particle Size Reduction of Arymo ER



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Tablet Hardness (Chewing)	✓		
Small Volume Extraction and Syringeability		✓	
Large Volume Extraction	✓	✓	✓
Alcohol Dissolution	✓		

PSR = particle size reduction

Hardness Testing Demonstrates that Arymo ER Would be Difficult to Chew

- Hardness of Arymo ER and MS Contin assessed using conventional hardness tester
  - Arymo ER: >400 newtons
  - MS Contin: 63 newtons
- Average maximum human bite force is ~300-350 newtons*
- Arymo ER would be difficult to chew, posing potential safety risk to human subjects

* Takaki et al. *Int Arch Otorhinolaryngol* 2014;18(3).

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Tablet Hardness (Chewing)	✓		
Small Volume Extraction and Syringeability		✓	
Large Volume Extraction	✓	✓	✓
Alcohol Dissolution	✓		

PSR = particle size reduction

Arymo ER Gelling Properties Impart Abuse Deterrence

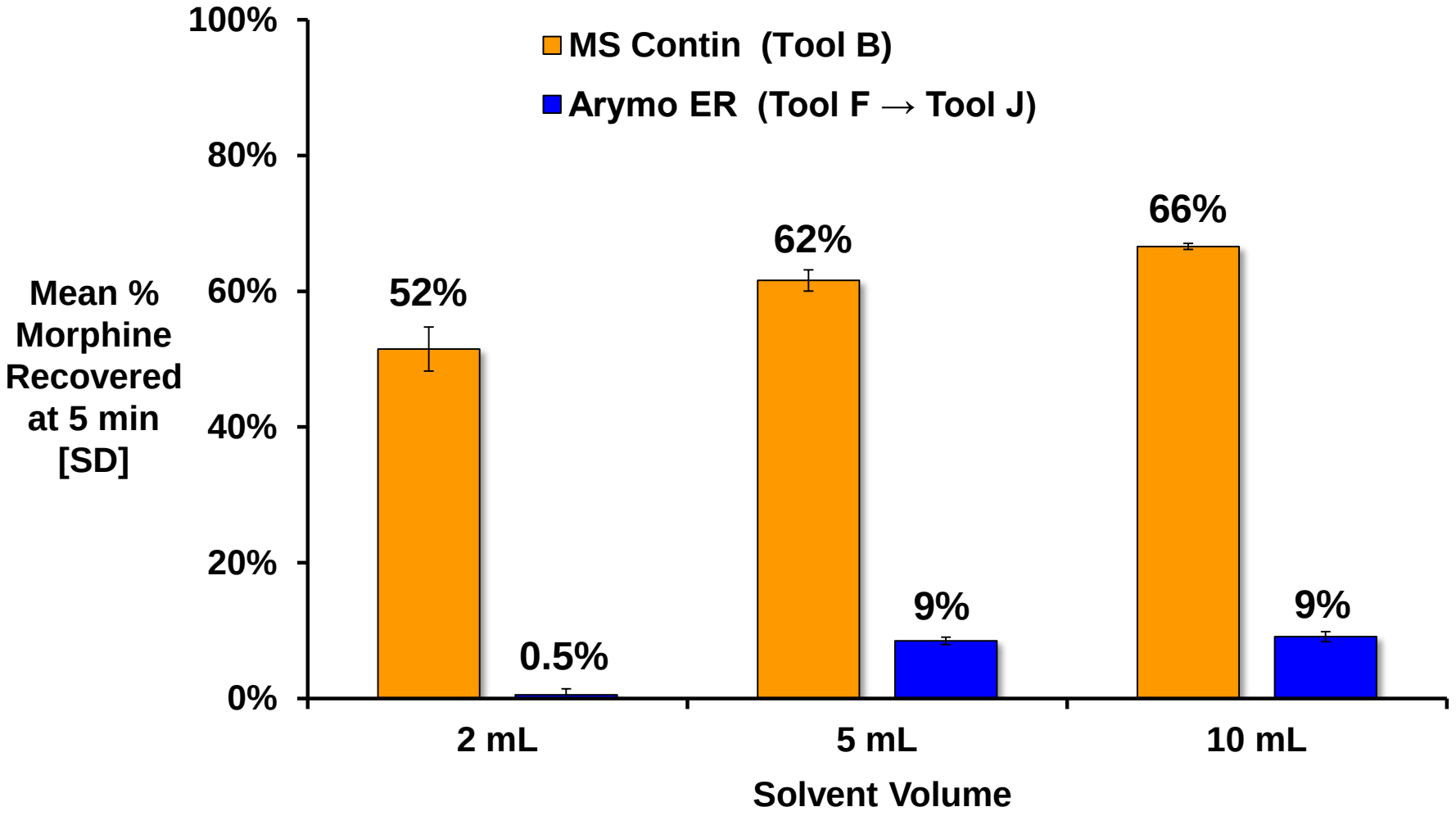
Arymo ER

MS Contin

3 mL of IV Solvent A, Temperature A

Category 1

Less Morphine Recovered from Arymo ER in Small Volume IV Extraction



N=3
Temperature B, Agitation A

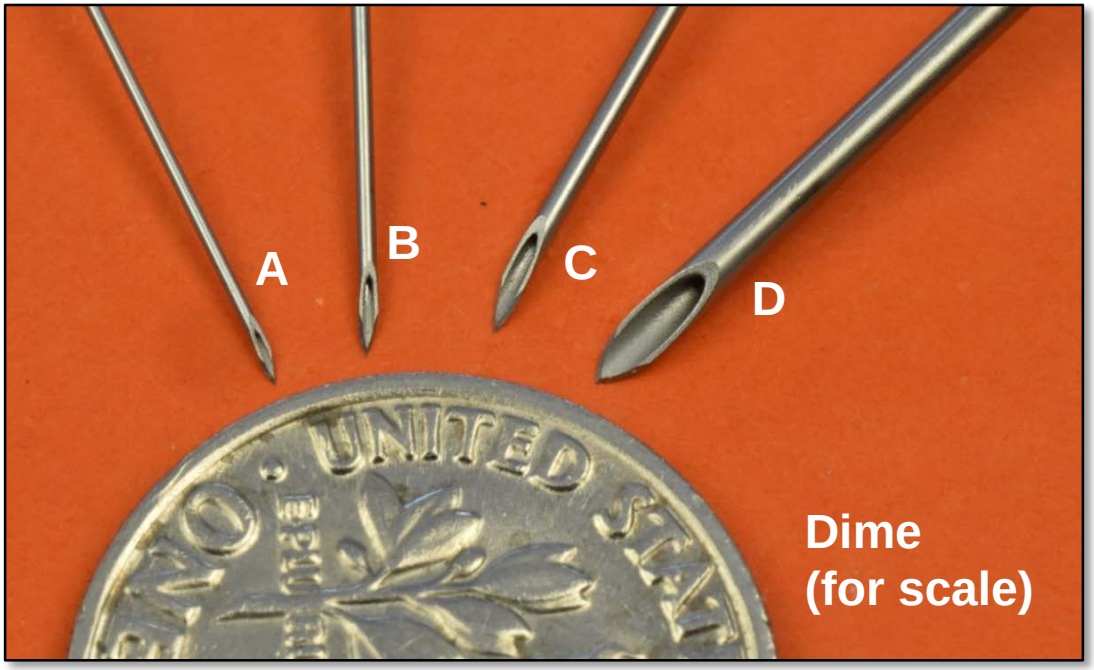
Category 1

"Gel Blob" Syringability Study with Long Extraction Times

- 12 extraction conditions evaluated
  - 4 and 24 hours of extraction
  - Injection solvents 1 and 2
  - 3 forms of Arymo ER
    - Intact
    - Tool F
    - Tool F → Tool J

"Gel Blob" Study: Limited Amounts of Morphine Were Recovered From Arymo ER

- 9 of 12 extractions conditions recovered <10% morphine
- 3 remaining conditions recovered 16-18% morphine
  - Required largest needle evaluated (Gauge D)
  - Extreme case, larger than those commonly used



Category 1

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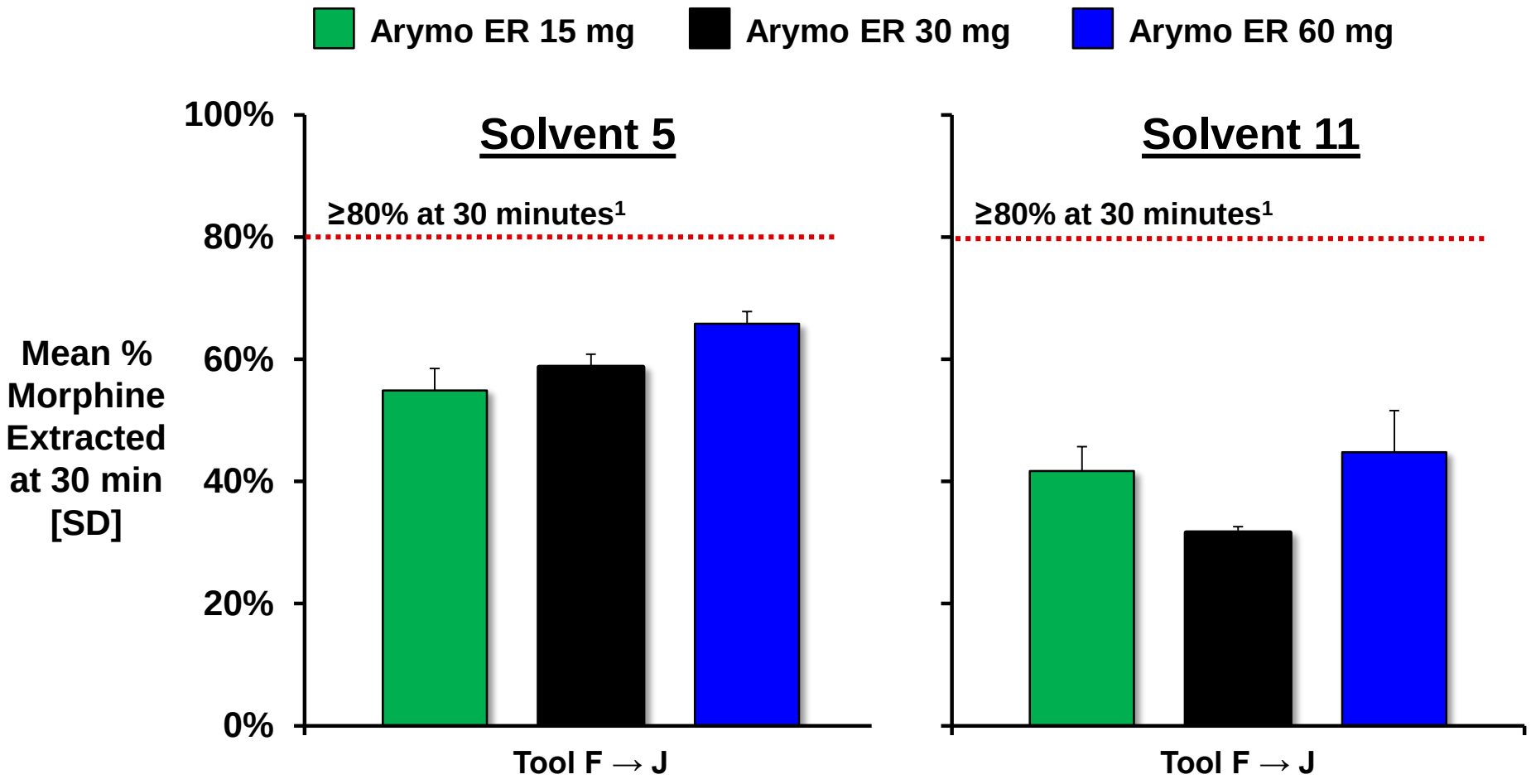
Single- and Multi-tool PSR	✓	✓	✓
Multi-tool PSR after Pre-treatment	✓	✓	✓
Tablet Hardness (Chewing)	✓		
Small Volume Extraction and Syringeability		✓	
Large Volume Extraction	✓	✓	✓
Alcohol Dissolution	✓		

PSR = particle size reduction

Arymo ER Resists Extraction in Large Volumes of Solvents



Temperature A, Agitation B

1. FDA. Guidance for Generic Solid Oral Opioid Drug Products, 2016.

Category 1

Category 1 Assessments to Evaluate Common Routes of Abuse

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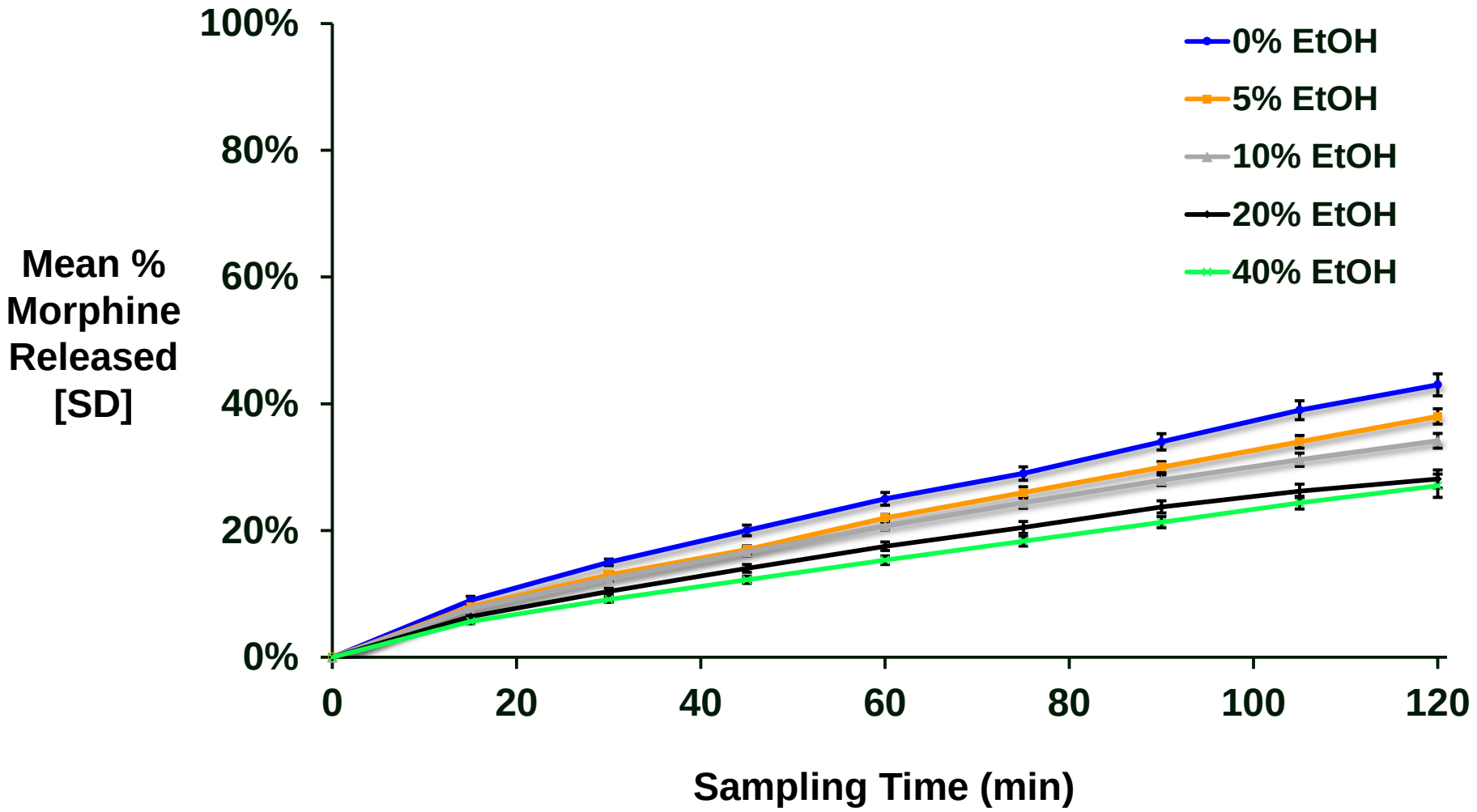
Single- and Multi-tool PSR	✓	✓	✓
Multi-tool PSR after Pre-treatment	✓	✓	✓
Tablet Hardness (Chewing)	✓		
Small Volume Extraction and Syringeability		✓	
Large Volume Extraction	✓	✓	✓
Alcohol Dissolution	✓		

PSR = particle size reduction

No Evidence of Alcohol Dose Dumping



Dissolution media: 0.1N HCl, replicates=12

Category 1

Abuse-Deterrent Studies for Arymo ER in Accordance with FDA Guidance

Category 1

In Vitro Testing

Resistance to Physical & Chemical Manipulation

Routes of Abuse

- Oral
- Intranasal
- Intravenous

Category 2

Clinical PK Studies

PK not converted to an immediate-release profile

C_{max} T_{max}

Two Clinical Trials

EG-008 – Oral PK and HAP Study

EG-009 – Intranasal PK and HAP Study

Category 3

Clinical Abuse-Deterrent Studies

Drug Liking

Take Drug Again

Positive Drug Effects

EG-009: Intranasal HAP Study

- Randomized, double-blind, double-dummy, 5-period crossover study
- Enrolled adult nondependent recreational opioid users experienced in nasal insufflation

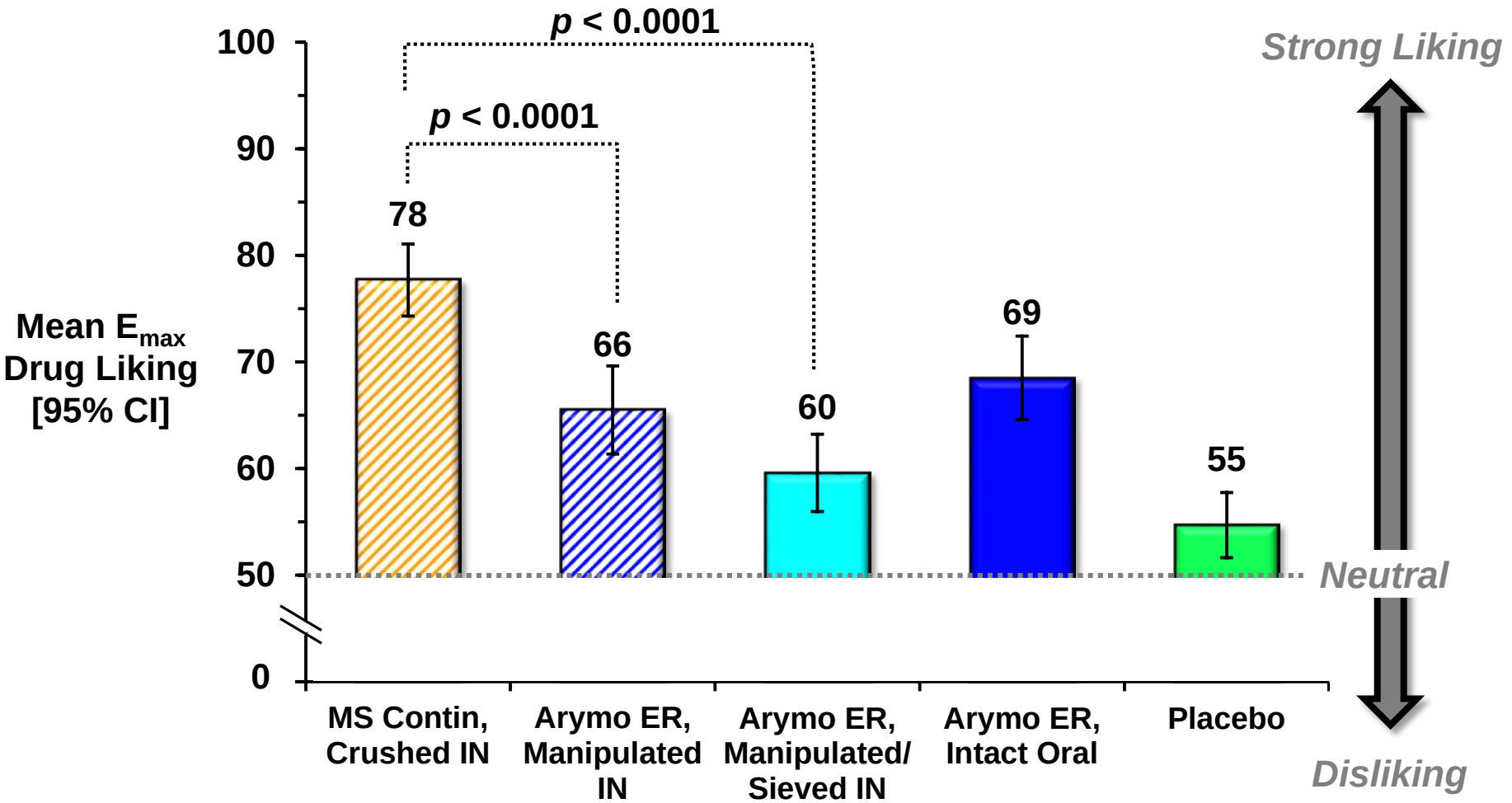
Treatment Arms in Intranasal HAP Study Prepared by Site Pharmacy

- MS Contin, crushed IN (60 mg)
  - Tool B
- Arymo ER, manipulated IN (60 mg)
  - Tool F → Tool J
- Arymo ER, manipulated/sieved IN (60 mg)
  - Tool F → Tool J, then sieved
- Arymo ER, intact oral (60 mg)
- Placebo

Endpoints in Intranasal HAP Study

- Primary: Maximum (E_{max}) Drug Liking
- Secondary
  - Overall Drug Liking
  - Take Drug Again
  - Drug Effects Questionnaire
- Pharmacokinetics (PK)
  - C_{max}
  - T_{max}
  - AUC

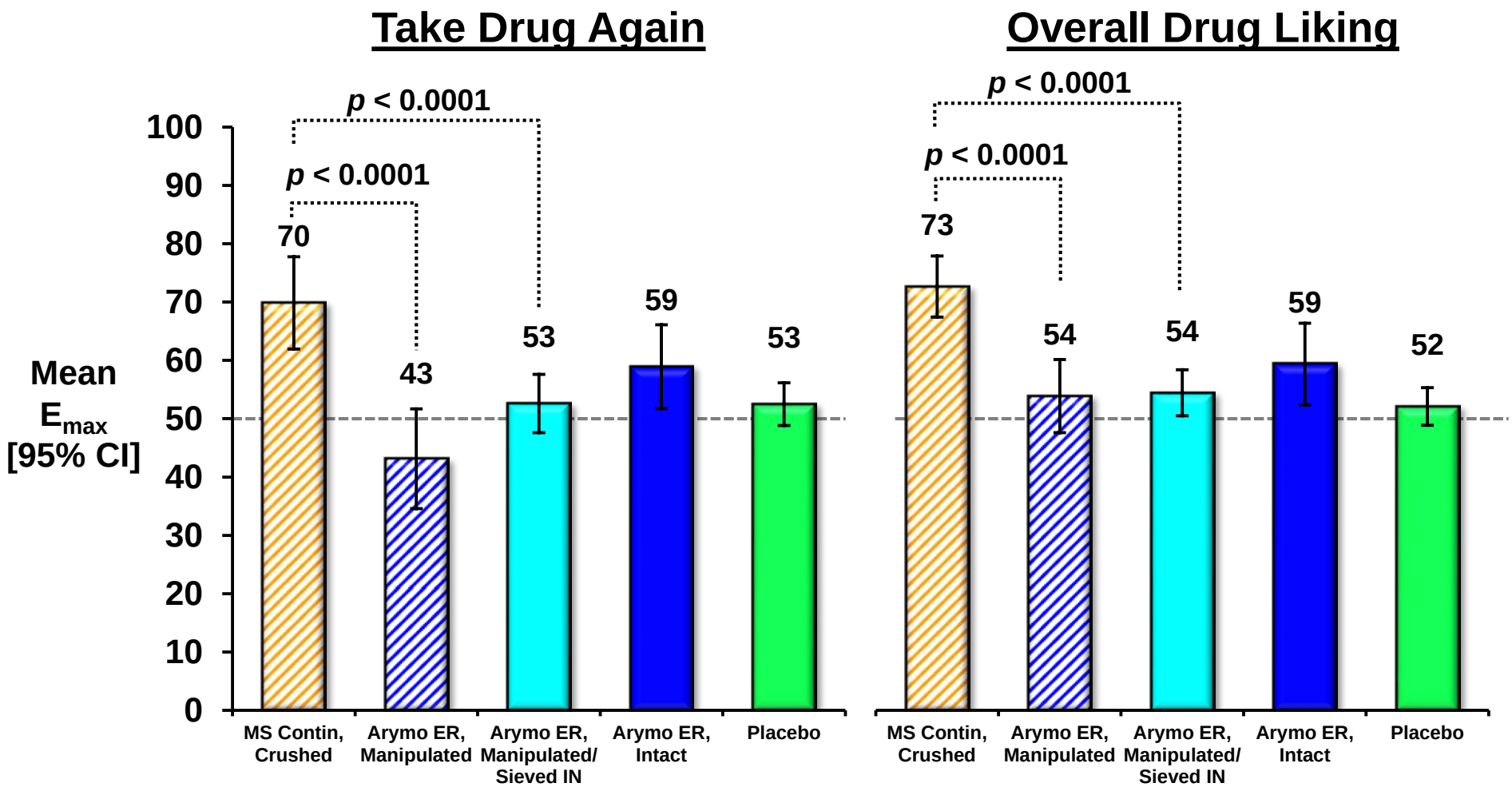
Significantly Lower Maximum Drug Liking for Arymo ER Compared to MS Contin after Snorting



Study EG-009: Intranasal HAP Study (N=46)

Category 3

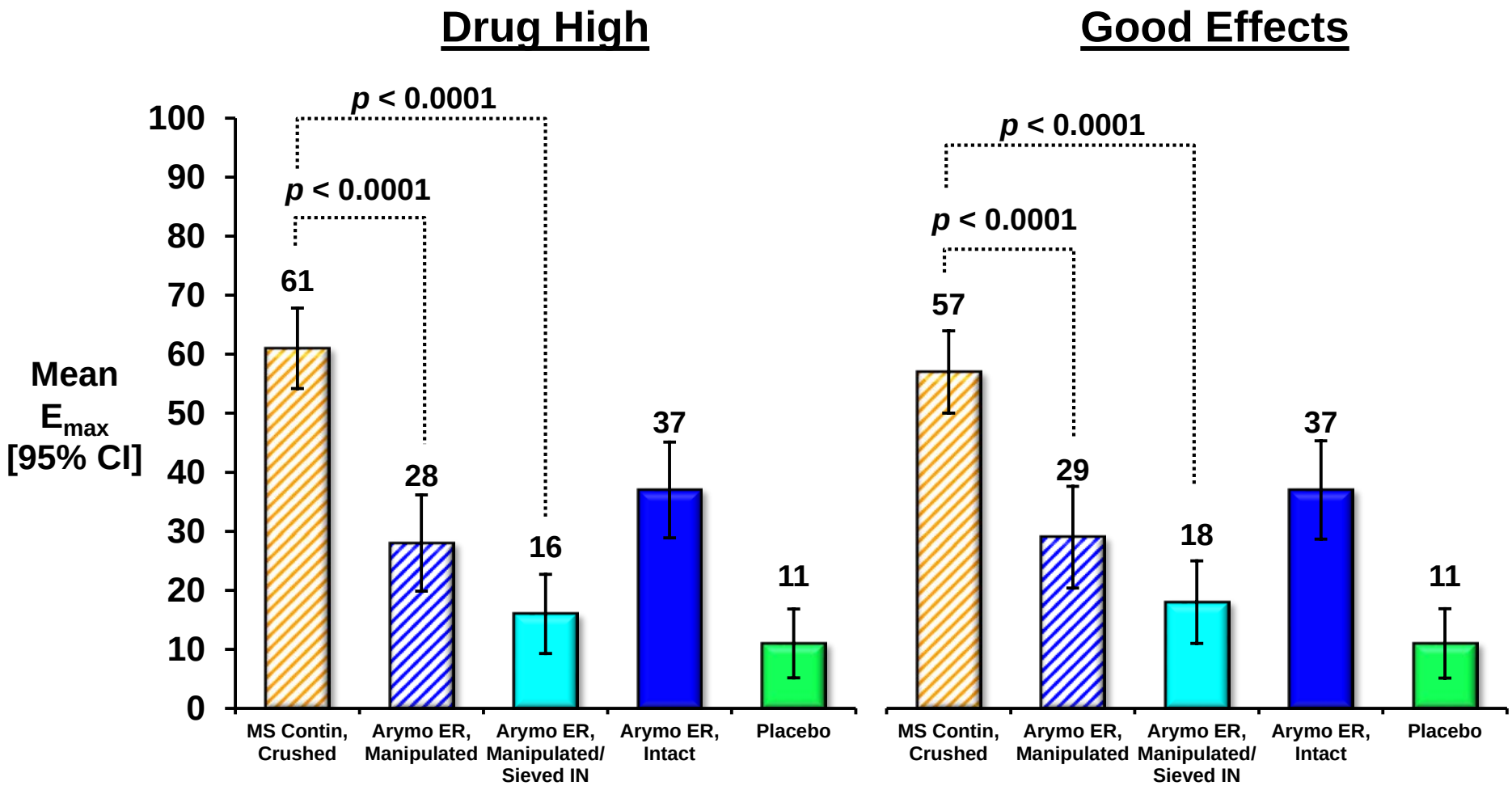
Take Drug Again and Overall Drug Liking for Arymo ER Similar to Placebo



Study EG-009: Intranasal HAP Study (N=46)

Category 3

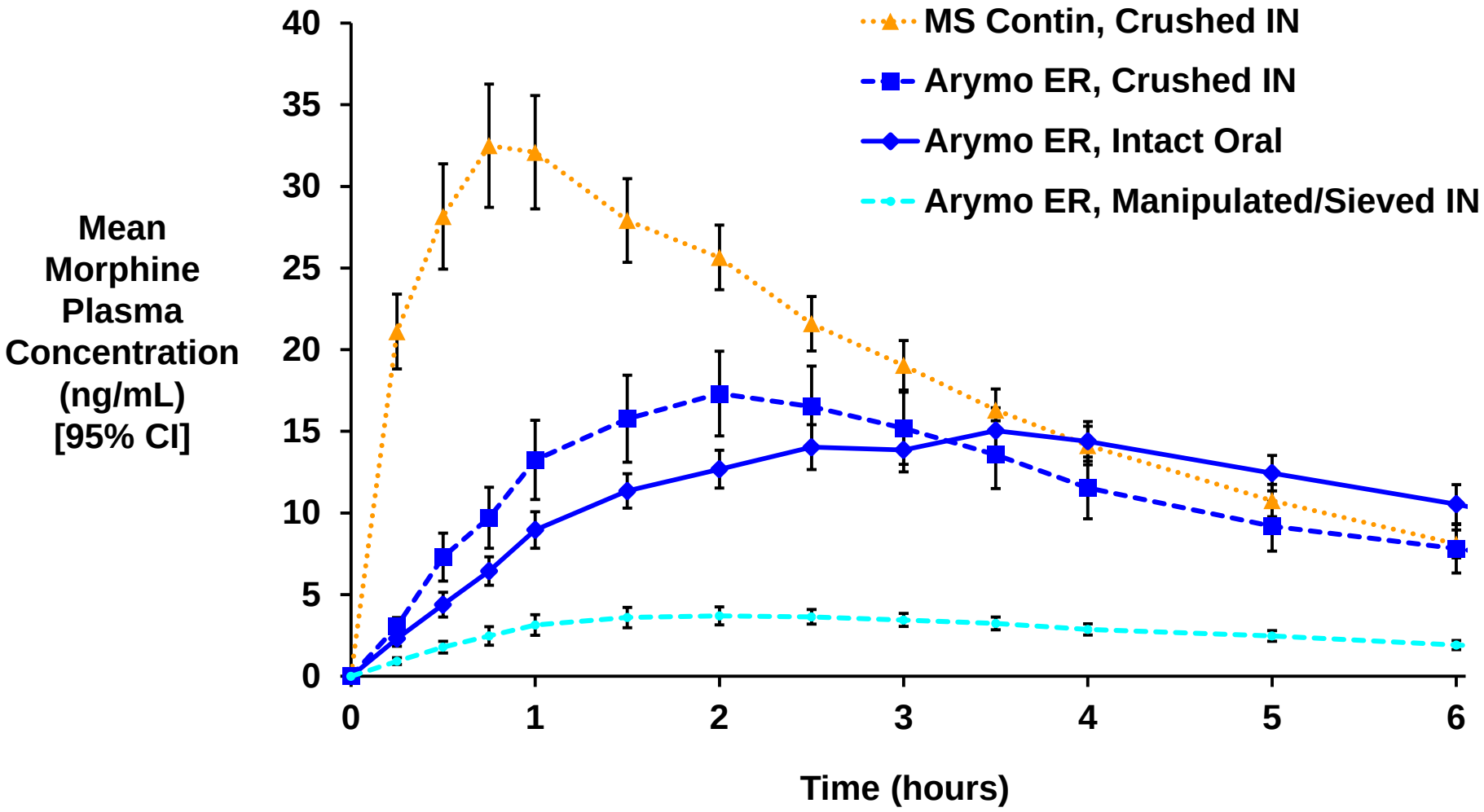
Arymo ER Associated with Lower VAS Scores on Drug High and Good Effects



Study EG-009: Intranasal HAP Study (N=46)

Category 3

Lower Morphine Concentrations after Snorting Arymo ER Compared to MS Contin



Study EG-009: Intranasal HAP Study (N=46)

Category 2

EG-008: Oral HAP Study

- Randomized, double-blind, triple-dummy, 4-period crossover study
- Enrolled adult nondependent recreational opioid users
- Chewing has been most common manipulation in oral HAP studies
- Chewing Arymo ER would not provide effective PSR and poses potential safety risk

Study EG-008: Oral HAP Study (N=38)

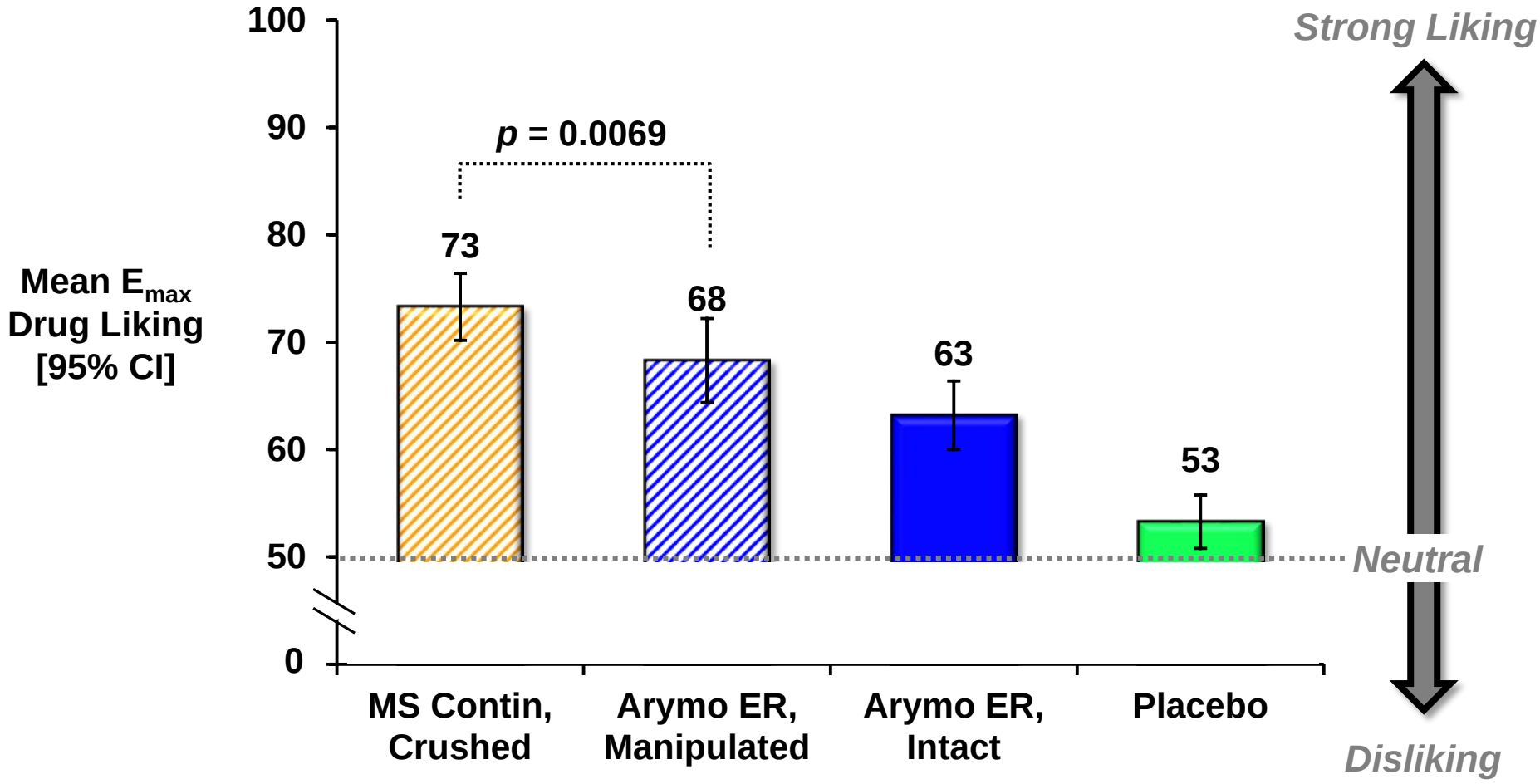
Treatment Arms in Oral HAP Study Prepared by Site Pharmacy

- Crushed MS Contin (60 mg)
  - Tool B
- Manipulated Arymo ER (60 mg)
  - Tool F
- Intact Arymo ER (60 mg)
- Placebo

Endpoints in Oral HAP Study

- Primary: Maximum (E_{max}) Drug Liking
- Secondary
  - Overall Drug Liking
  - Take Drug Again
  - Drug Effects Questionnaire
- Pharmacokinetics (PK)
  - C_{max}
  - T_{max}
  - AUC

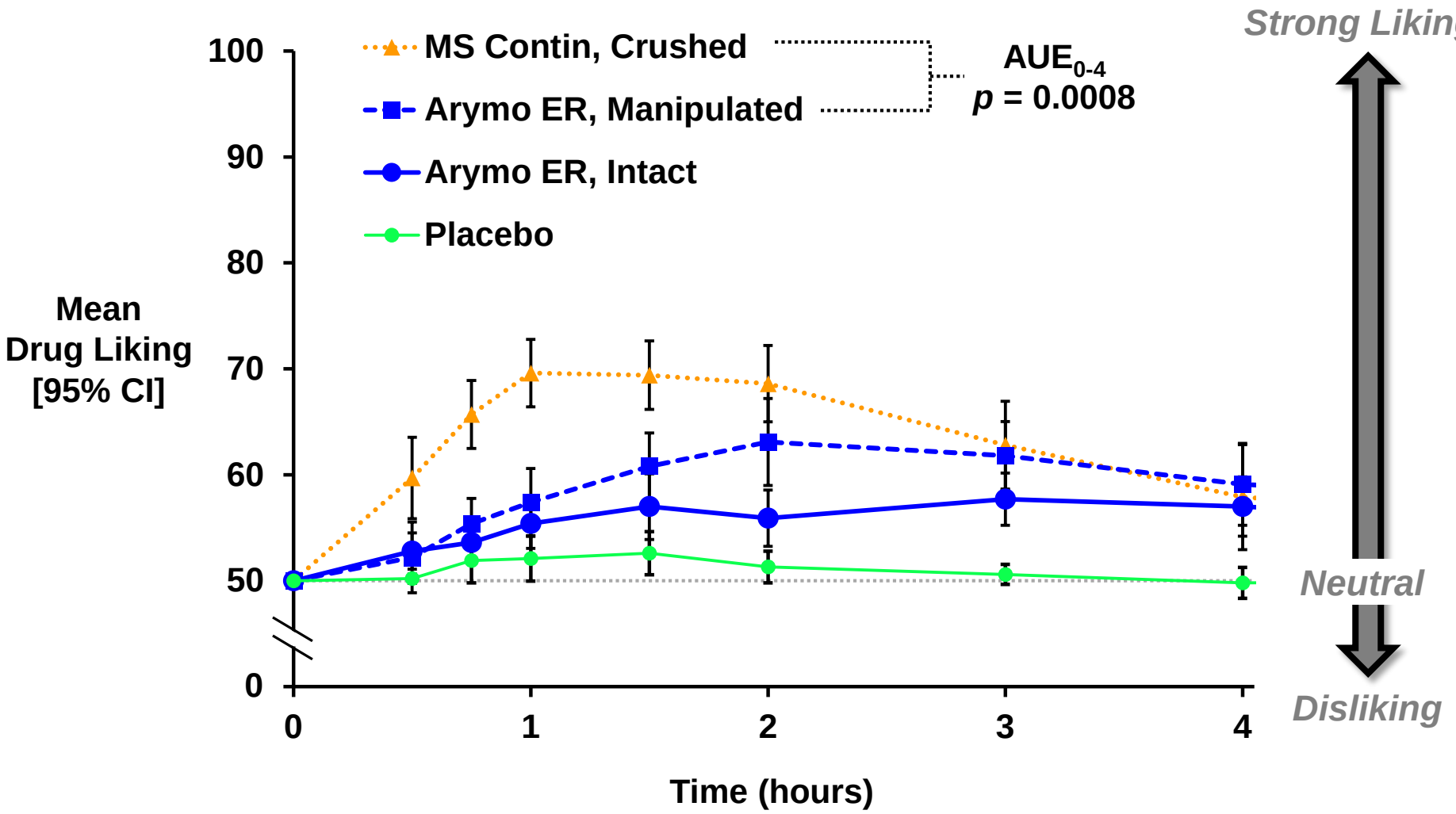
Significantly Lower Maximum Drug Liking with Manipulated Oral Arymo ER



Study EG-008: Oral HAP Study (N=38)

Category 3

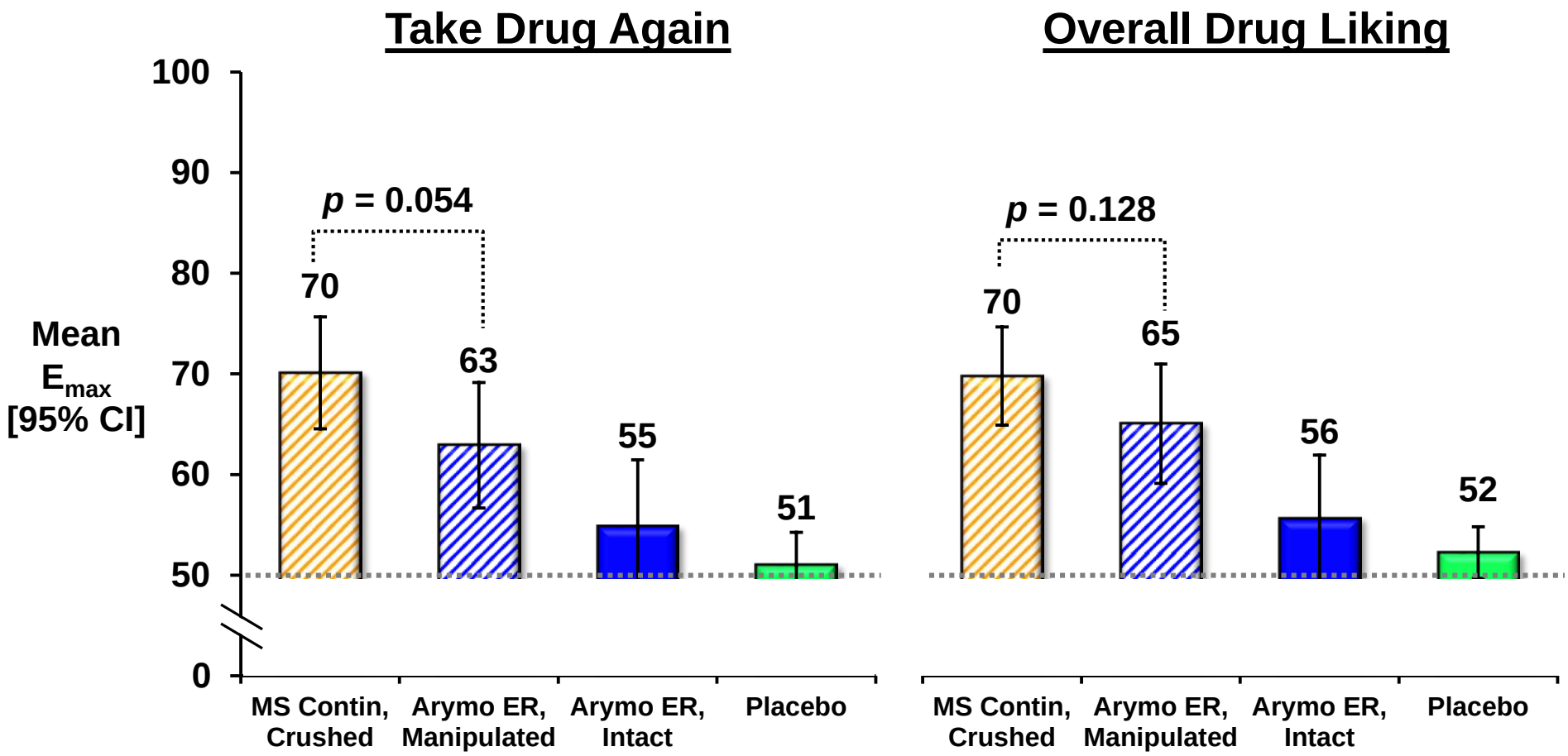
Lower Mean Drug Liking for Manipulated Arymo ER at Early Time Points



Study EG-008: Oral HAP Study (N=38)

Category 3

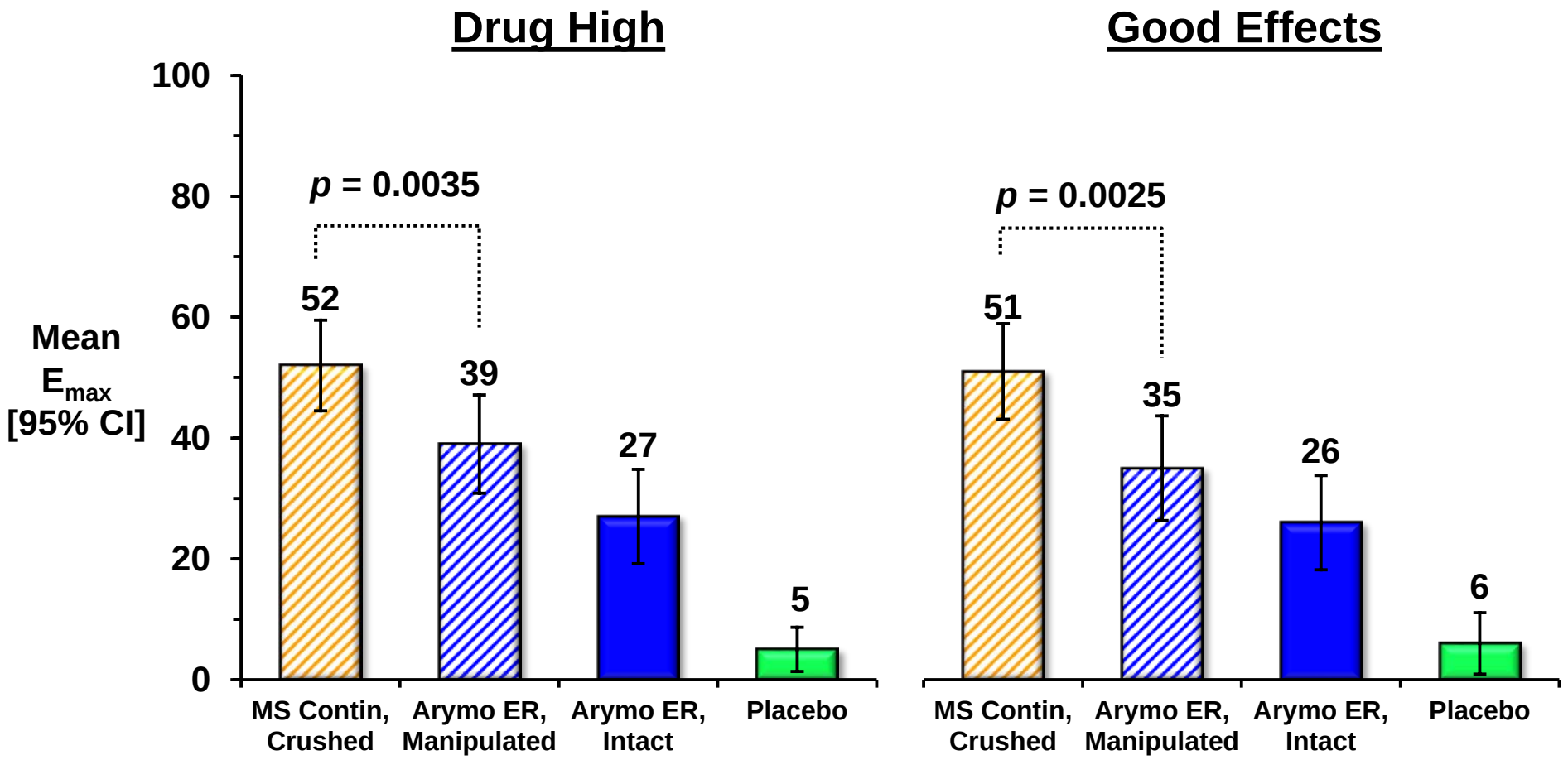
Key Secondary Endpoints in Oral HAP Study



Study EG-008: Oral HAP Study (N=38)

Category 3

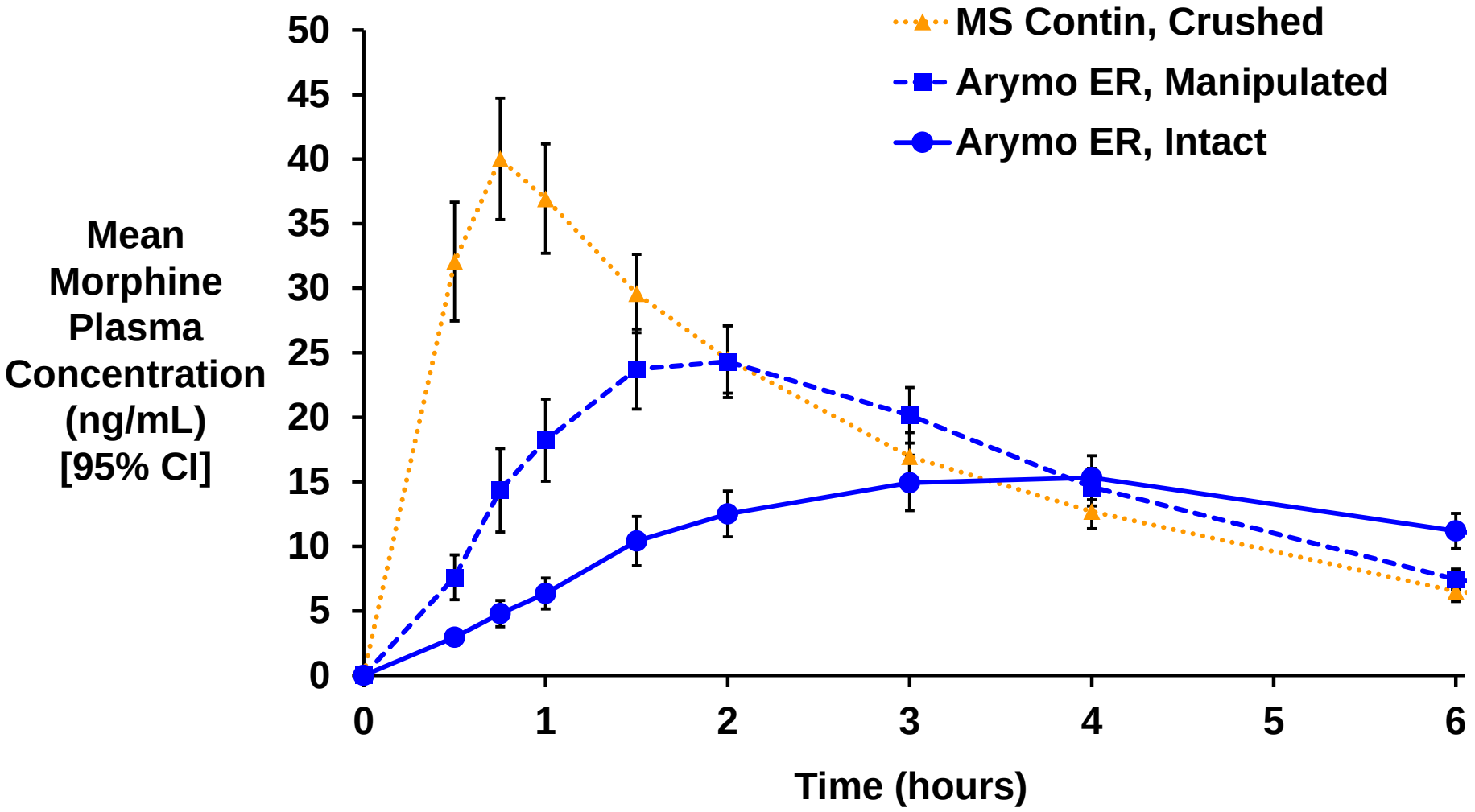
Significant Differences Observed in Drug High VAS and Good Effects VAS



Study EG-008: Oral HAP Study (N=38)

Category 3

Arymo ER Does Not Exhibit IR Profile after Manipulation for Oral Abuse



Study EG-008: Oral HAP Study (N=38)

Category 2

Category 1 and 2/3 Development Program Support Abuse Deterrence

Resistant to Particle Size Reduction

INTRAVENOUS

- Gels in solution
- Difficult to extract
- Difficult to draw into syringe

NASAL

- Difficult to reduce to snortable powder
- Met primary endpoint for Category 2/3
- Statistically significant for all secondary PD measures
- PK consistent with PD results

ORAL (chewed / manipulated)

- Difficult to chew
- Met primary endpoint for Category 2/3
- All secondary PD measures supportive
- PK consistent with PD results

Clinical Relevance of Arymo ER Abuse-Potential Data

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CEO, Analgesic Solutions
Adjunct Associate Professor
Tufts University School of Medicine

Two Primary Questions for Today's Advisory Committee Meeting

- Should Arymo ER be approved for the treatment of chronic pain?
- Should Arymo ER be labeled as an abuse-deterrent product?
  - IV route
  - Nasal route
  - Oral route (chewed / manipulated)

Arymo ER Has Met Regulatory Standard for Approval

- Arymo ER is bioequivalent to MS Contin
- No clinically significant effect of food
- No acceleration of release with alcohol (i.e., no alcohol dose-dumping)

Two Ways to Assess Clinical Relevance of Pre-Marketing Abuse-Deterrent Studies

- Compare route-specific laboratory results to real-world outcomes
- Determine *Clinically Important Difference* associated with change in drug-taking behavior

In Vitro Syringeability Findings Predict Real-World IV Abuse Deterrence

In Vitro Findings

OxyContin OP

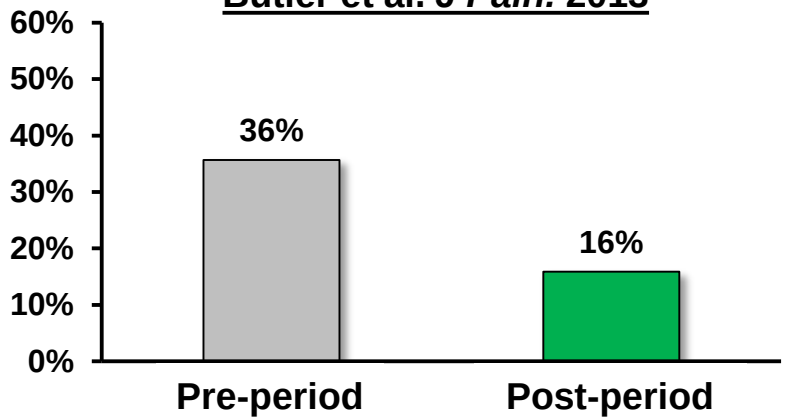
"When subjected to an aqueous environment, OXYCONTIN gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a needle."

OxyContin® Label

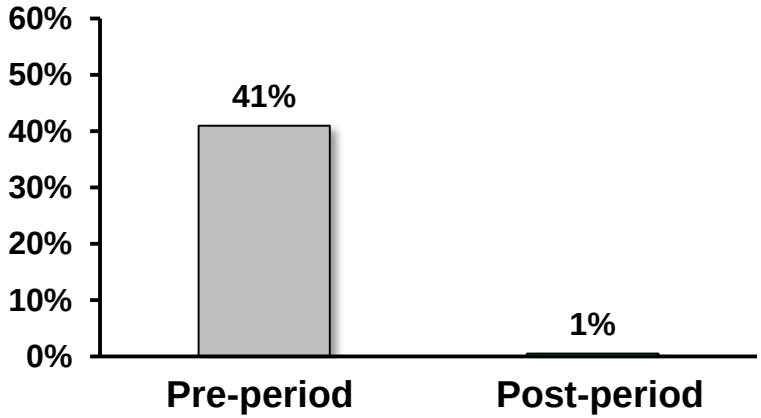
Arymo ER

Real-world Evidence from Epidemiologic Studies

Butler et al. *J Pain.* 2013



Havens et al. *Drug Alcohol Depend.* 2014



Intranasal Human Abuse Potential Findings Predict Real-World Nasal Abuse Deterrence

Intranasal HAP Studies

OxyContin OP

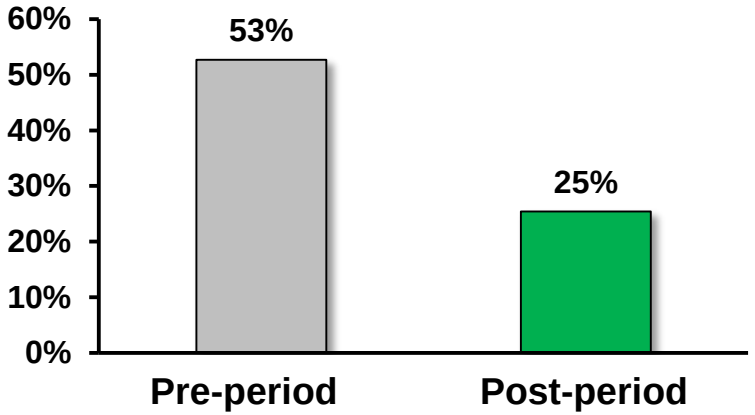
Mean E_{max} Drug Liking		
Crushed OxyContin (original)	Crushed OxyContin OP	Difference
94.0	80.4	13.6

Arymo ER

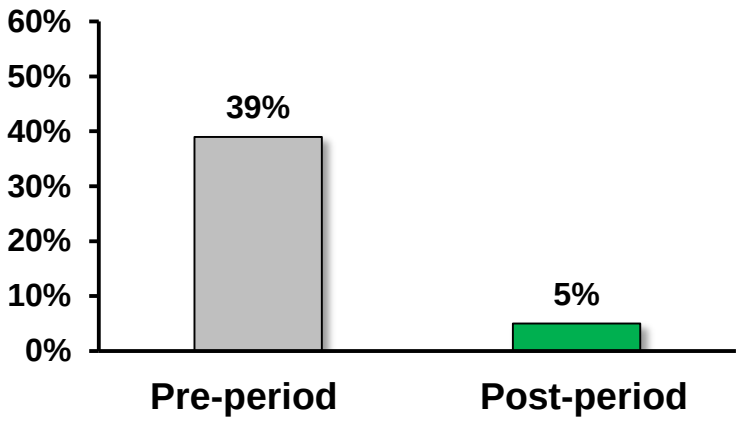
Mean E_{max} Drug Liking		
Crushed MS Contin	Manipulated Arymo ER	Difference
77.7	65.5 (not sieved)	12.2
77.7	59.6 (sieved)	18.1

Real-world Evidence from Epidemiologic Studies

Butler et al. *J Pain.* 2013

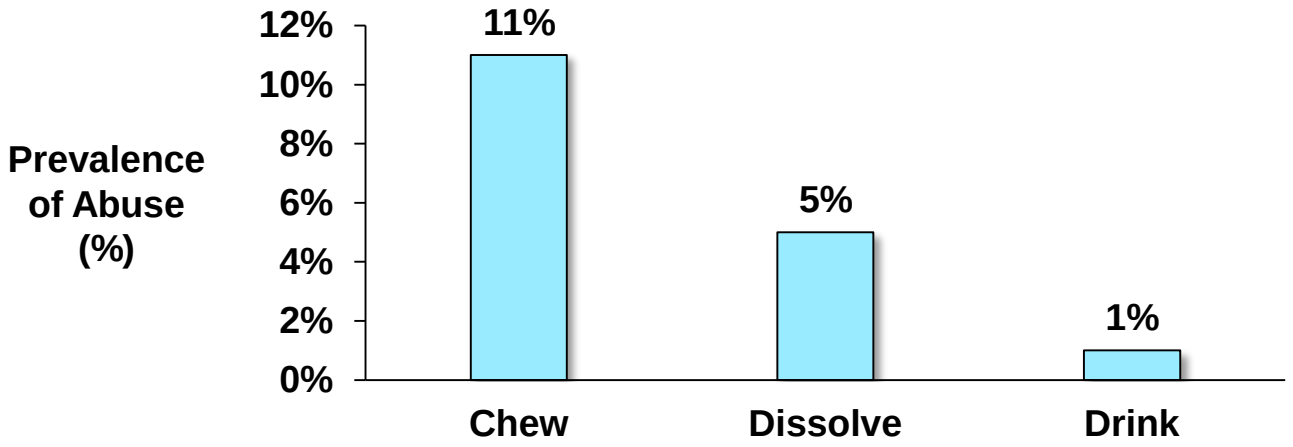


Havens et al. *Drug Alcohol Depend.* 2014



Arymo ER Would be Difficult or Impossible to Chew

- Chewing is most common form of manipulated oral abuse for ER morphine*



- Arymo ER hardness > 400 N
- Average maximum human bite force in literature is ~300-350 N†

*** Inflexxion, 2015 data on file.**

† Takaki et al. *Int Arch Otorhinolaryngol* 2014;18(3).

Two Ways to Assess Clinical Relevance of Pre-Marketing Abuse-Deterrent Studies

- Compare route-specific laboratory results to real-world outcomes
- Determine *Clinically Important Difference* leading to change in drug-taking behavior

8- to 10-Point Reduction in E_{max} Drug High is Clinically Important

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

- Estimated clinically important difference (CID) for E_{max} Drug High is 8-10 mm

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

5-Point Reduction in E_{max} Drug Liking is Clinically Important

- Meta-analysis of multiple human abuse potential studies across molecules
- Compared to “non-medical use” (NMU) rates in NSDUH and DAWN using multiple regression
- For ER morphine ADF, 5-point reduction in E_{max} Drug Liking predicted 20% reduction in lifetime NMU

White et al. *J Opioid Manage* 2015;11(3):199-210.
NSDUH = National Survey of Drug Use and Health
DAWN = Drug Abuse Warning Network

Arymo ER Reductions in Drug High and Drug Liking are Clinically Important

Arymo ER Condition	E_{max} Drug High		E_{max} Drug Liking	
	Treatment Difference	Clinically important? (8-10 mm*)	Treatment Difference	Clinically important? (5 mm†)
Nasal Manipulated	**33.5**	**Yes**	**12.2**	**Yes**
Nasal Manipulated/sieved	**45.2**	**Yes**	**18.1**	**Yes**
Manipulated Oral	**13.1**	**Yes**	**5.0**	**Yes**

Treatment differences in HAP studies do not reflect the fact that Arymo ER was more difficult to manipulate than MS Contin

***** Eaton et al. *Qual Life Res* 2012;21:975-81.
† White et al. *J Opioid Manage* 2015;11(3):199-210.

Totality of Data Support Broad Abuse-Deterrent Profile of Arymo ER

Intravenous

- Resists small volume extraction to 24 hours
- Difficult to draw into a needle

Nasal

- Low yield of particles amenable for snorting
- Less liking than non-ADF comparator

Oral

- Difficult or impossible to chew
- Less liking than non-ADF comparator after optimal manipulation

Arymo™ ER (morphine sulfate) Extended-Release Tablets for the Treatment of Chronic Pain

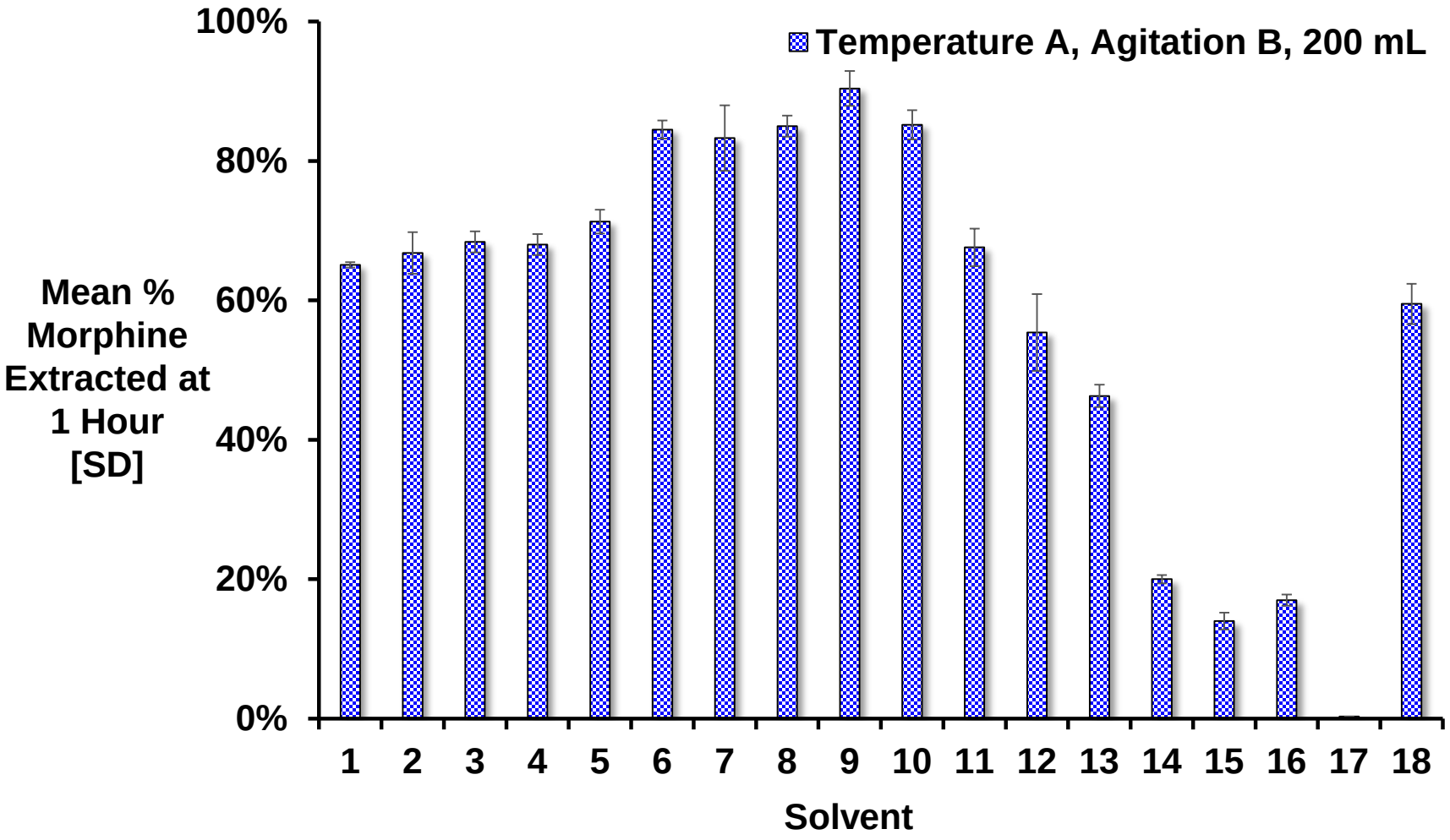
August 4, 2016

Egalet Corporation

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

Backup Slides Shown

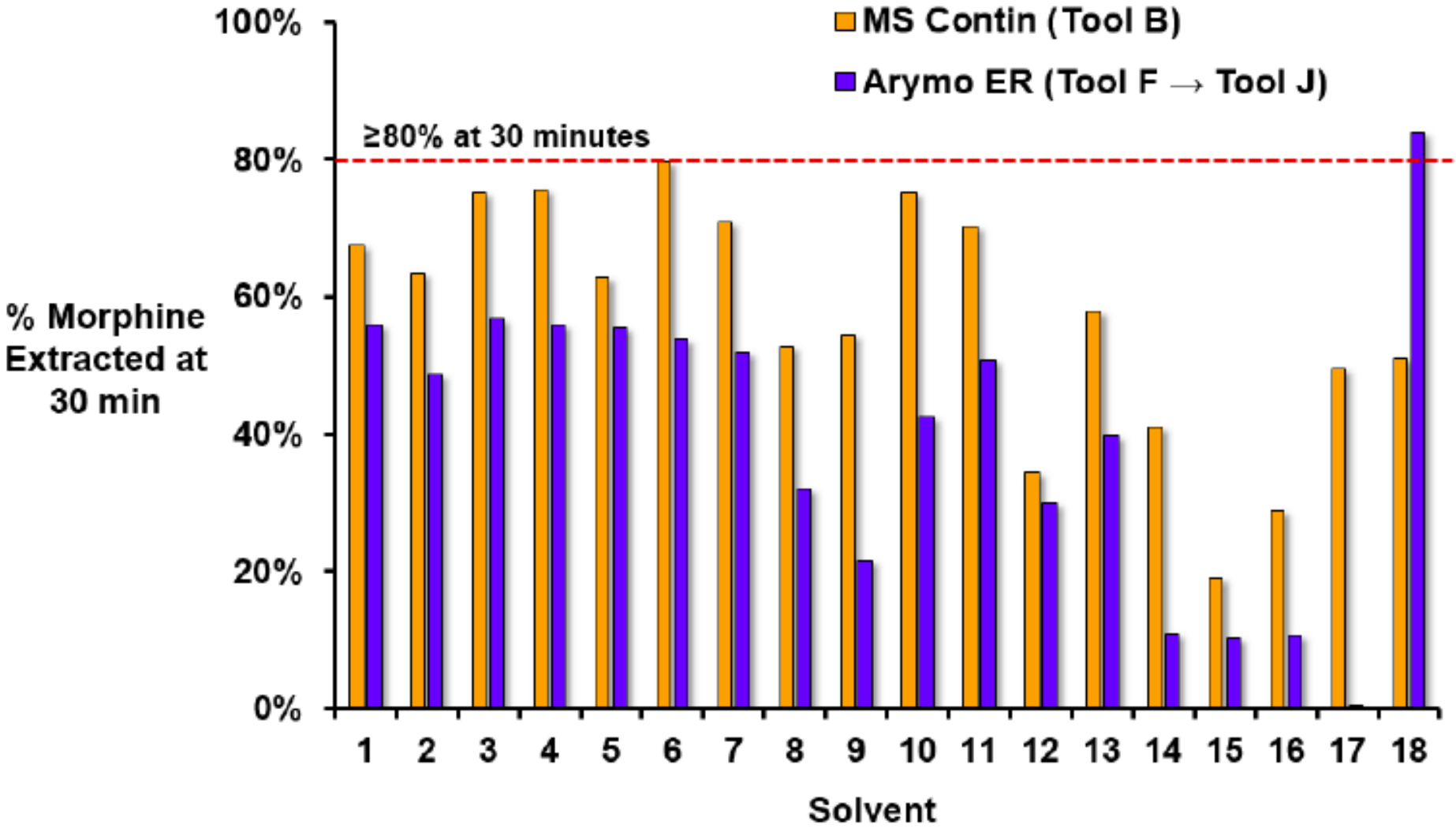
Large Volume Extraction – Arymo ER 60mg at 1 Hour



Category 1

Manipulated Arymo ER (Tool F -> Tool J); N=3

Figure 20: Morphine Extraction in Large Volumes of Ingestible and Non-Ingestible Solvents at Temperature A and Agitation B with Maximal Manipulation at 30 Minutes



Development Process to Identify Optimal PSR for Arymo ER

Exploratory Phase

- 25 tools
- Representative of cutting, crushing, grating, grinding

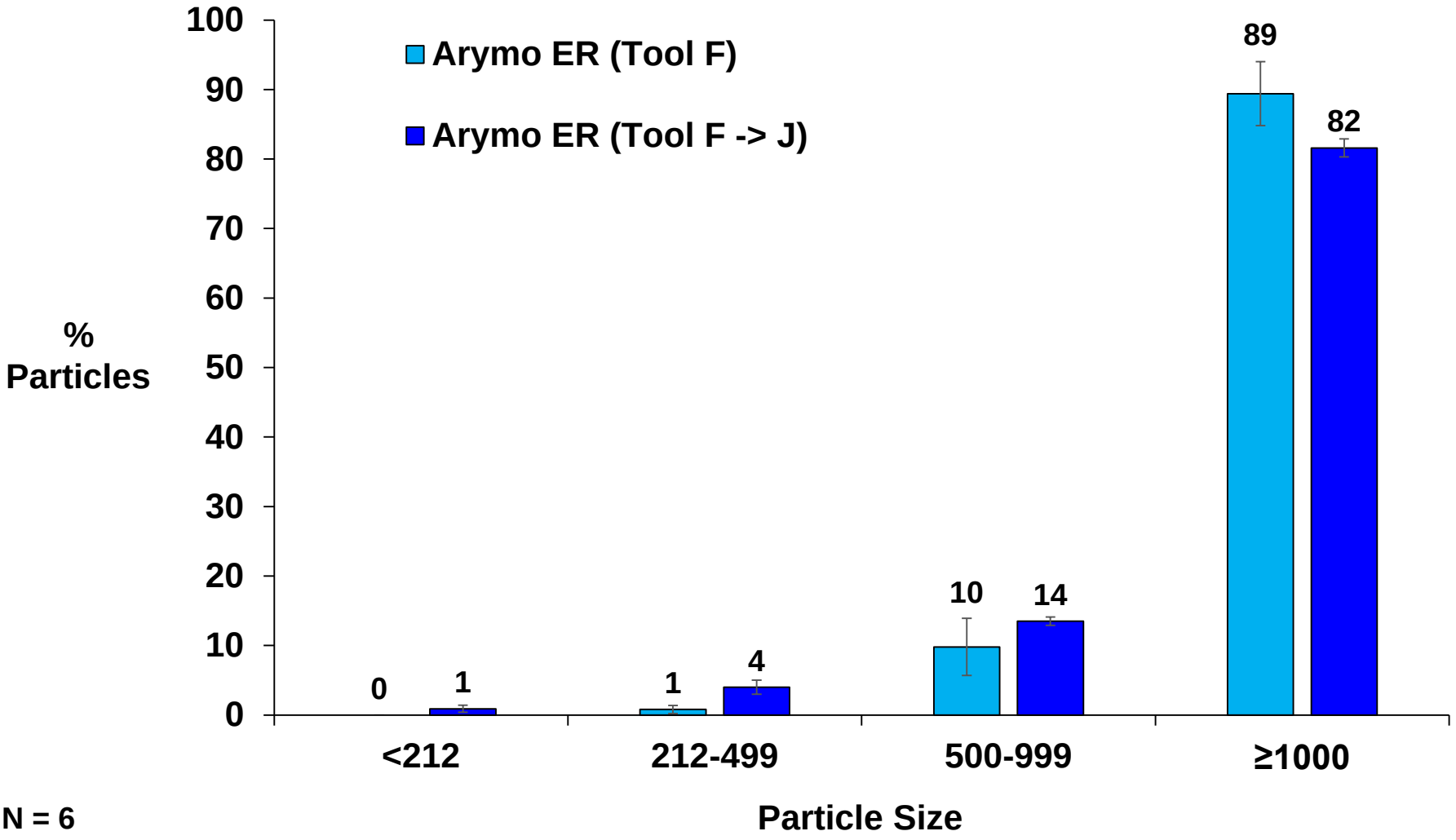
Screening Phase

- 10 tools (mechanical and electrical)
- MS Contin crushed to fine powder
- Arymo ER tested 5 x longer to identify tools effective for Arymo ER

Single- and Multi-Tool PSR

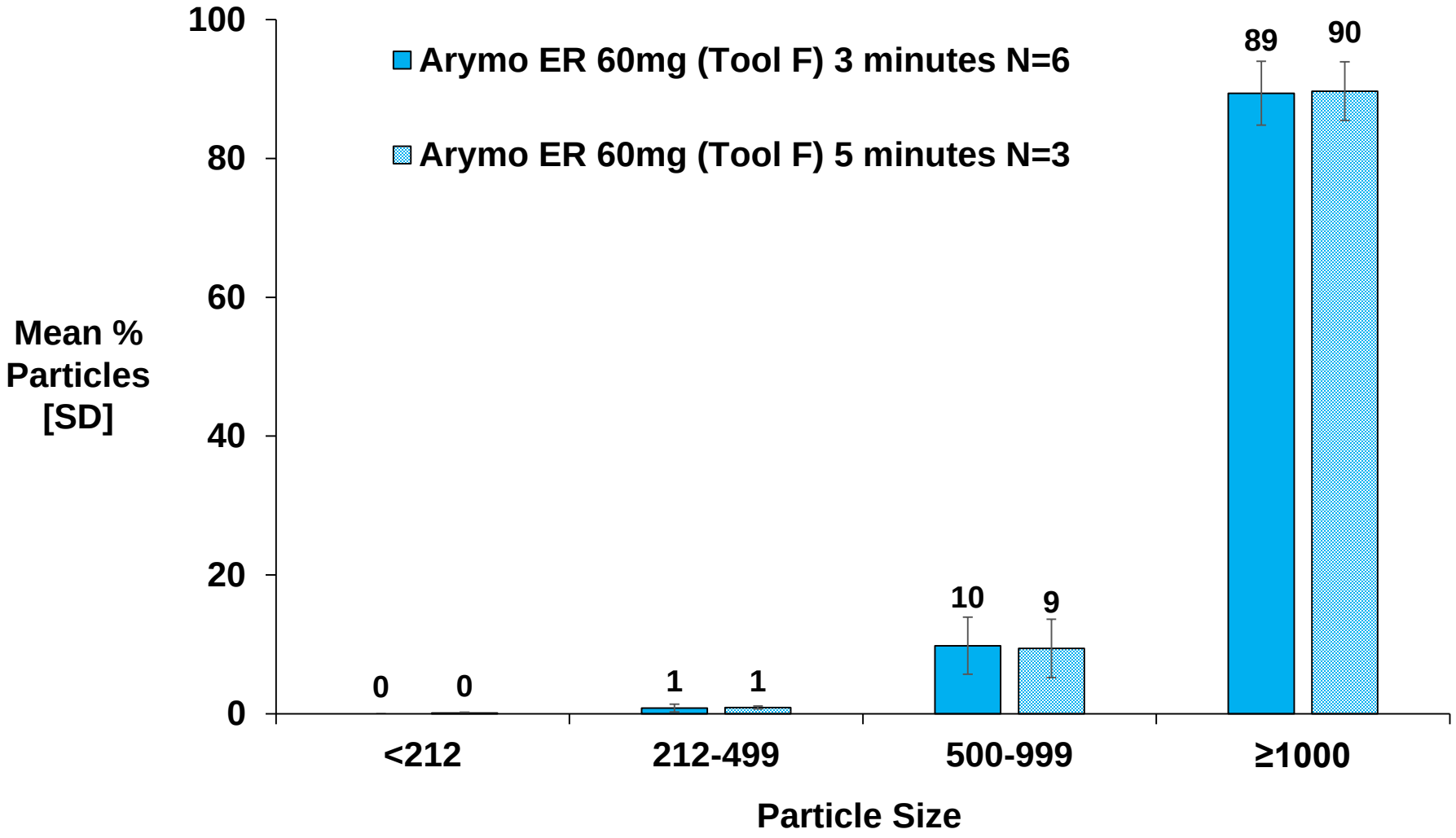
- MS Contin crushed to fine powder with Tool B
  - Does not require multi-tool process
- Arymo ER single tool result: Tool F & Tool J (< 5% particles < 500 microns)
- Arymo ER challenged with sequential multi-tool procedure (F → J)
  - No significant changes in PSR
  - Increasing time resulted in plateau effect on PSR

Arymo ER Particle Size Reduction: Tool F vs Tool F → J

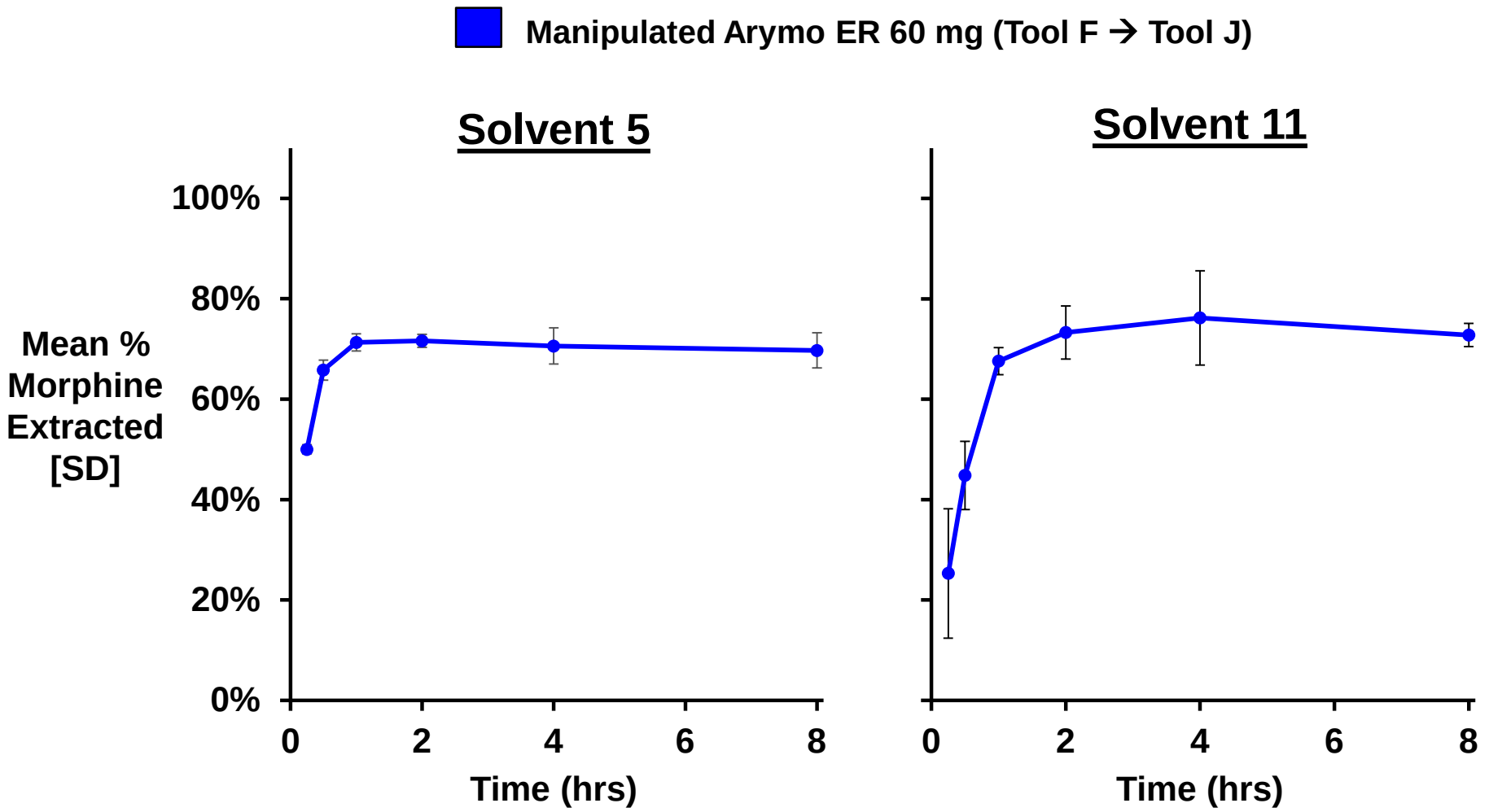


N = 6

Arymo ER Particle Size Reduction: Tool F at 3 and 5 Minutes



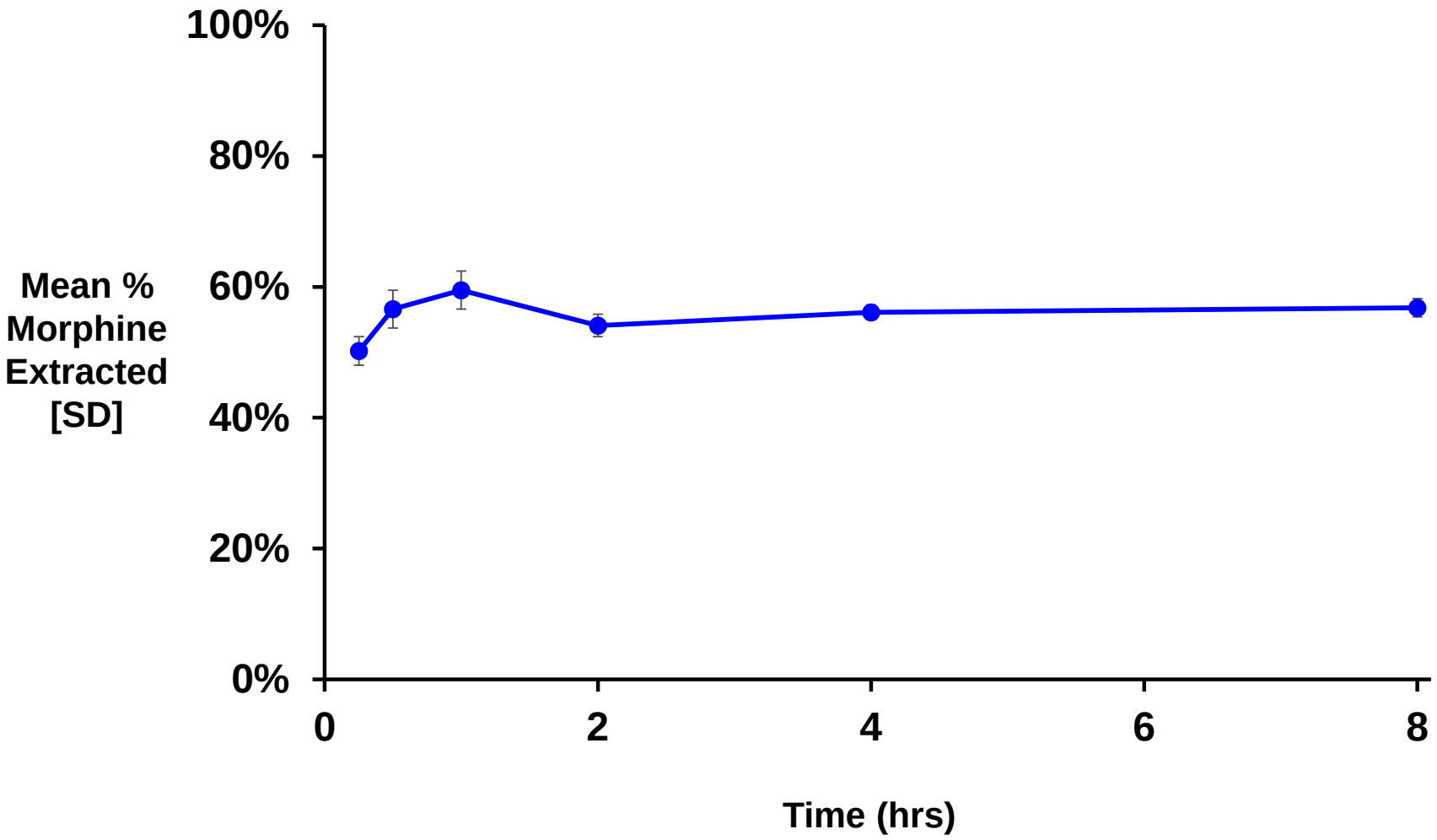
Morphine Extraction from Arymo ER Over Time



Category 1

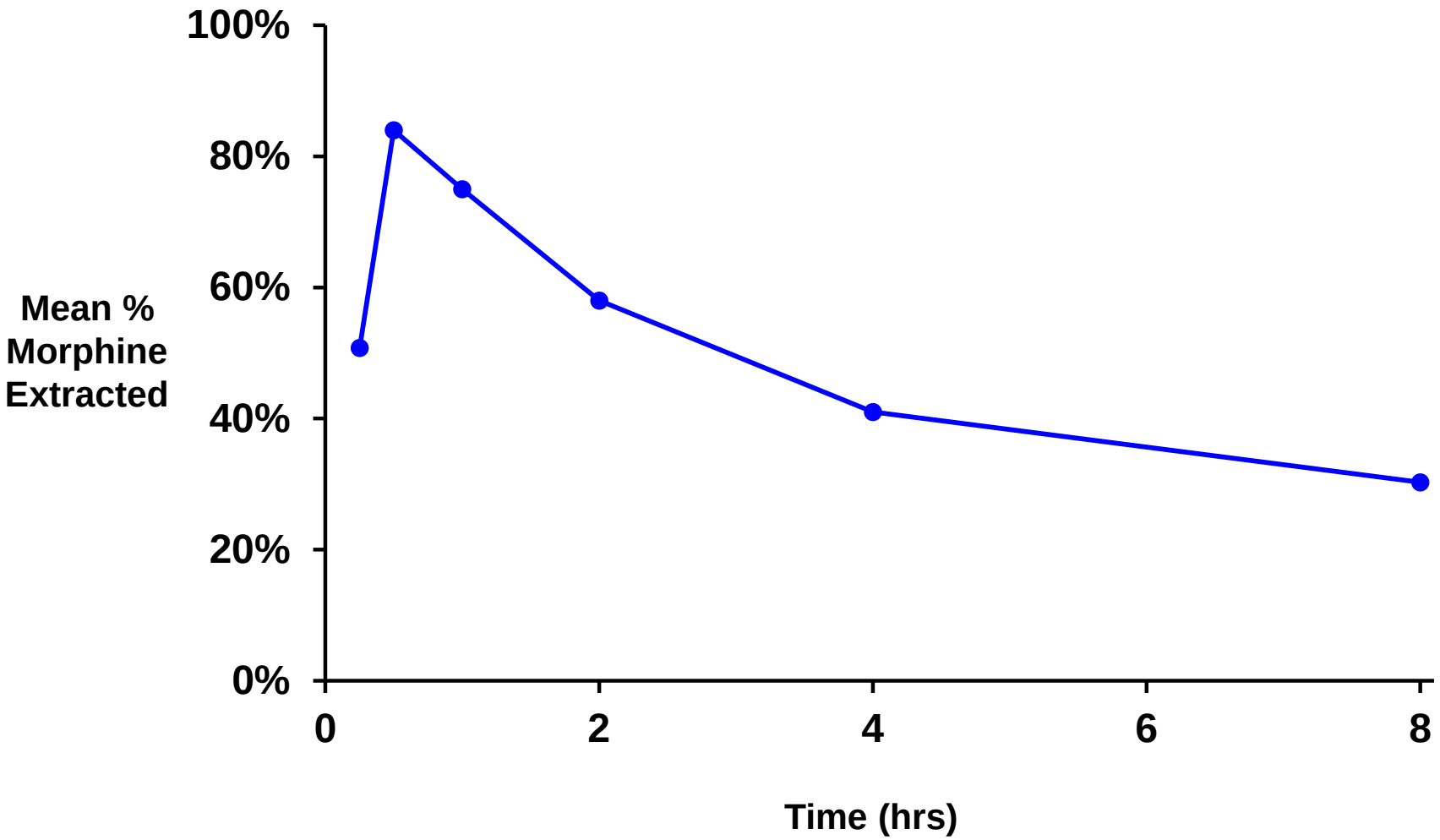
Temperature A, Agitation B, 200 ml, N=3

Arymo ER 60 mg
Solvent 18



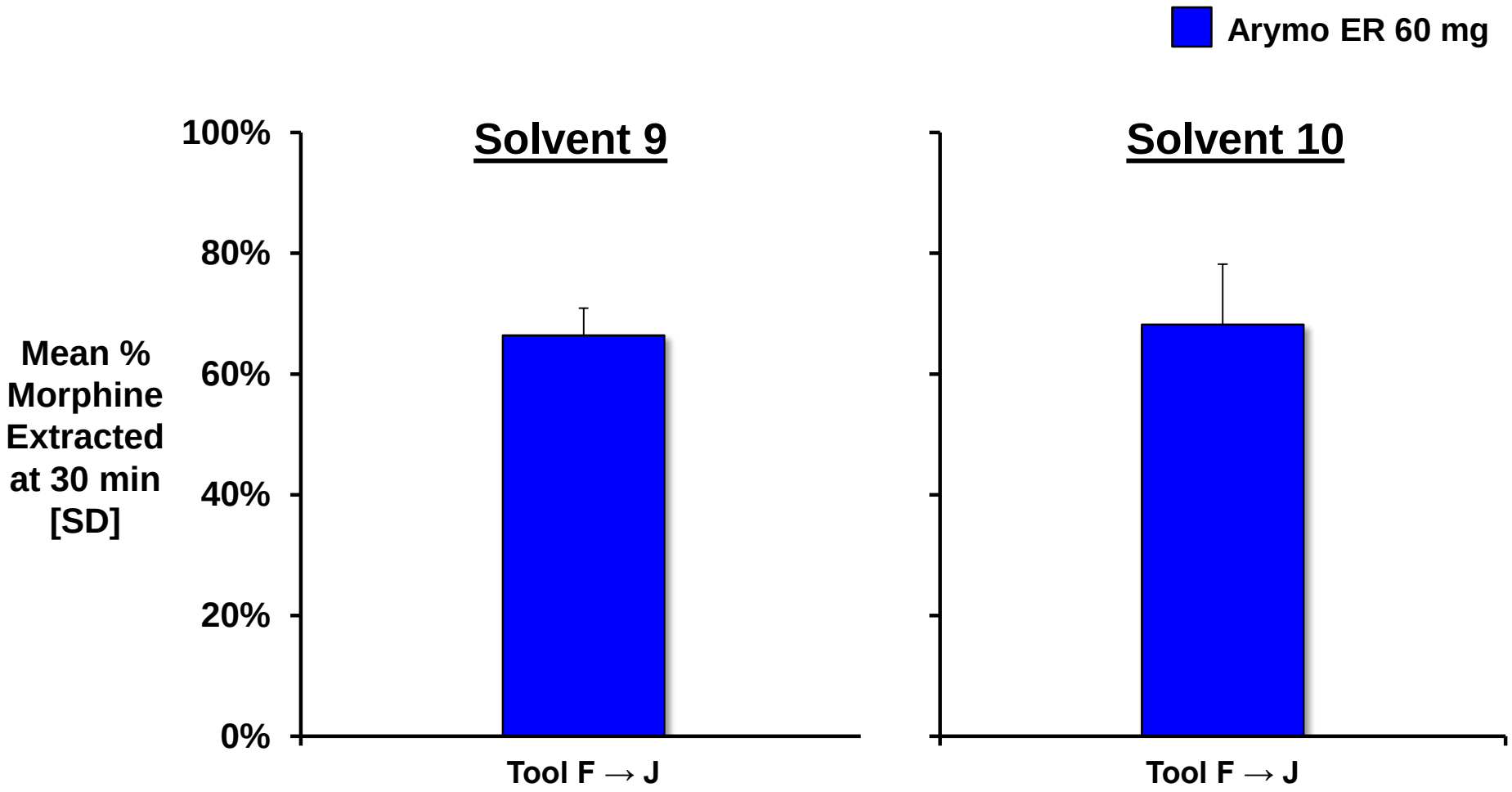
Temperature A, Agitation B, 200 ml, N=3

Arymo ER 100 mg
Solvent 18



Temperature A, Agitation B, 50 ml, N=1

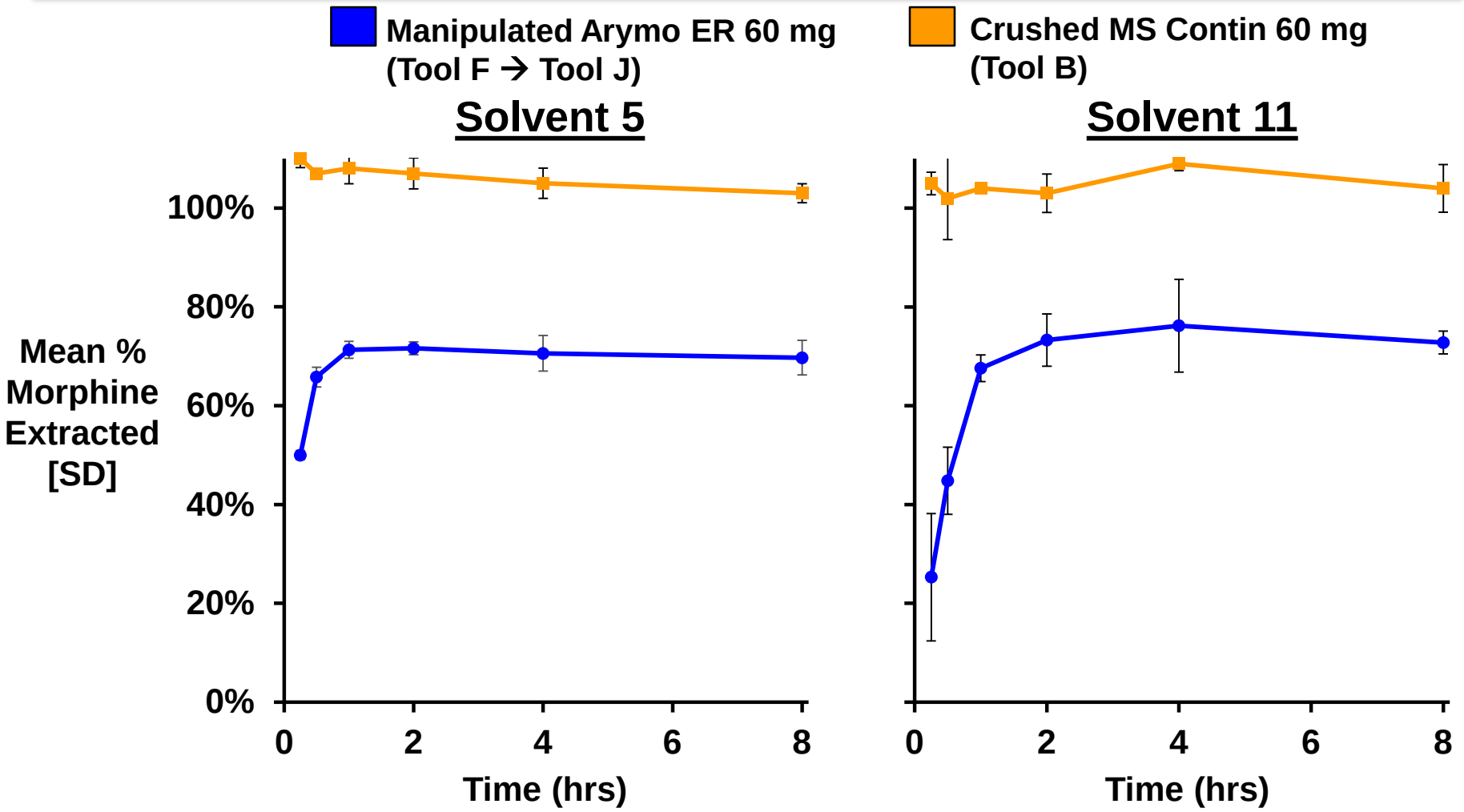
Arymo ER Resists Extraction in Large Volumes of Solvents 9 and 10



Temperature B, Agitation B

Category 1

Morphine Extraction from Arymo ER and MS Contin Over Time



Category 1

Temperature A, Agitation B, 200 ml, N=3
*FDA has not reviewed MS Contin data

Figure 31: Ease of Snorting VAS Scores in Intranasal HAP Study EG-009