# Apadaz™ (immediate-release benzhydrocodone with acetaminophen) for the Treatment of Acute Pain

**May 5, 2016**

KemPharm, Inc.

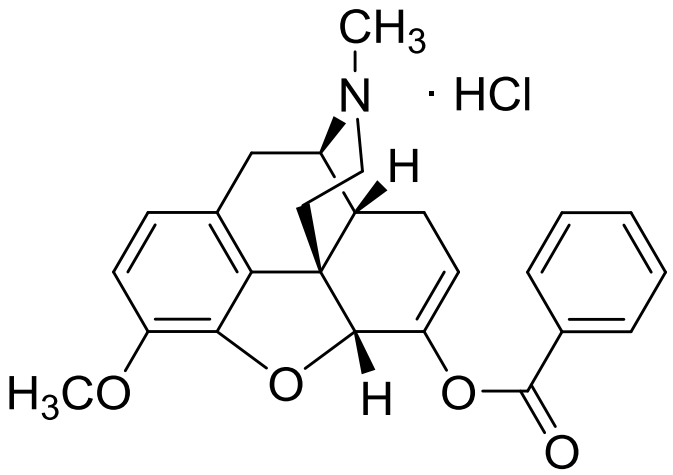
Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

# Introduction

**Travis Mickle, Ph.D.**
Co-Founder and Chief Executive Officer
KemPharm, Inc.

# Apadaz is a Fixed-Dose IR Hydrocodone Combination Product

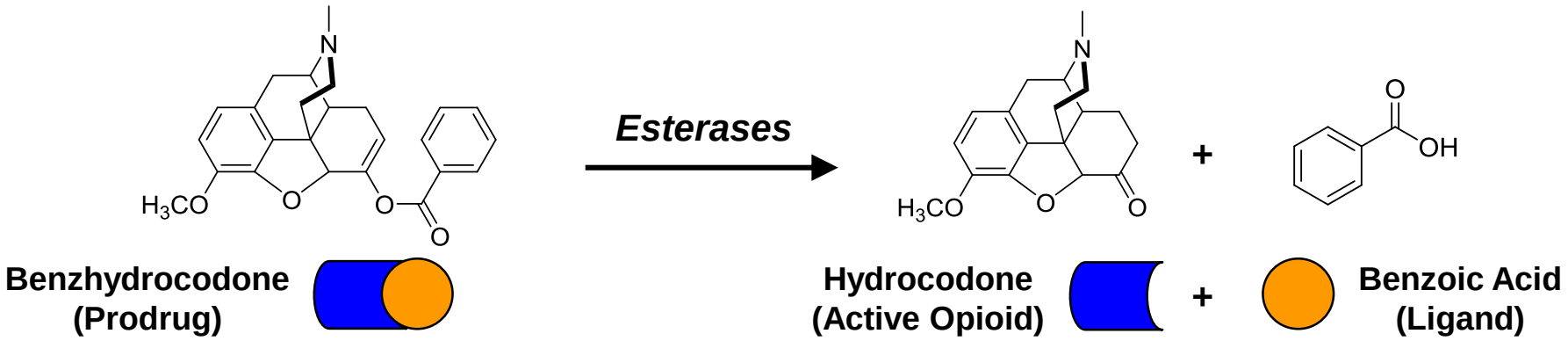
- Apadaz is composed of:
  - **Benzhydrocodone HCl [KP201]** (6.67 mg)
    - Prodrug: hydrocodone + benzoic acid
    - Equivalent to 7.5 mg hydrocodone bitartrate
  - **Acetaminophen [APAP]** (325 mg)
- Taken every 4-6 hours



# Abuse-Deterrent Features of Apadaz Imparted Using a Novel Approach

- Historical approaches to deter abuse:
  - Agonist/antagonist
  - Aversive agents
  - Physical/chemical barriers
- Apadaz is a prodrug that imparts abuse-deterrence at molecular level
  - No impact of crushing or grinding on release profile
  - Abuse-deterrence does not affect analgesia

# Apadaz Imparts Abuse-Deterrent Properties as Prodrug of Hydrocodone




- Intact prodrug is inert
- Ligand is naturally-occurring in berries

- Active hydrocodone cleaved from ligand through natural processes in GI tract

# Summary of Clinical Pharmacology

- Bioequivalent to reference drugs to meet requirement of 505(b)(2) pathway
- Bioequivalent to Norco
- No clinically significant food effect
- No systemic exposure to prodrug when taken orally

# Similar Incidence of AEs for Both Products

| | Apadaz (N=161) | Norco (N=141) |
|---|---|---|
| Nausea | 21% | 26% |
| Somnolence | 21% | 21% |
| Pruritus | 14% | 15% |
| Vomiting | 14% | 11% |
| Constipation | 12% | 14% |
| Dizziness | 8% | 6% |
| Headache | 3% | 3% |
| Hypotension | 3% | 0% |
| Flatulence | 1% | 1% |

AEs with incidence ≥1% (Pooled from Studies 102, 104, S01)

# Apadaz Offers Protections Against Non-Oral Routes of Abuse

| Route of Abuse | Summary of Findings with Apadaz |
|---|---|
| **Oral** | Drug Liking similar to Norco, as expected |
| **Intranasal** | Lower hydrocodone exposure and lower Drug Liking compared to Norco at early time points; increased nasal adverse effects |
| **Intravenous** | Cannot be efficiently extracted for IV injection; prodrug converts slowly to hydrocodone in blood |
| **Smoking / Vaporizing** | No release of hydrocodone |

# Agenda

| | |
|---|---|
| **Clinical Perspective** | **Jeffrey Gudin, M.D.**<br>Director<br>Pain Management and Palliative Care<br>Englewood Hospital and Medical Center |
| **Development Overview and Tampering Studies** | **Travis Mickle, Ph.D.**<br>Co-Founder and Chief Executive Officer<br>KemPharm, Inc. |
| **Clinical Abuse-Deterrence Studies** | **Lynn Webster, M.D.**<br>Vice President, Scientific Affairs<br>PRA Health Sciences |
| **Post-Market Surveillance**<br>**Future Studies** | **Travis Mickle, Ph.D.** |
| **Benefit-Risk Profile** | **Jeffrey Gudin, M.D.** |

# Additional Experts

| | |
|---|---|
| **Epidemiology** | **Simon Budman, Ph.D.**<br>**Founder and Chief Strategy Officer**<br>**Inflexxion, Inc.** |
| | **Theresa Cassidy, M.P.H.**<br>**Vice President, Health Analytics**<br>**Inflexxion, Inc.** |

# Clinical Perspective

**Jeffrey Gudin, M.D.**
Director, Pain Management and Palliative Care
Englewood Hospital and Medical Center

Clinical Instructor, Anesthesiology
Icahn School of Medicine, Mt. Sinai

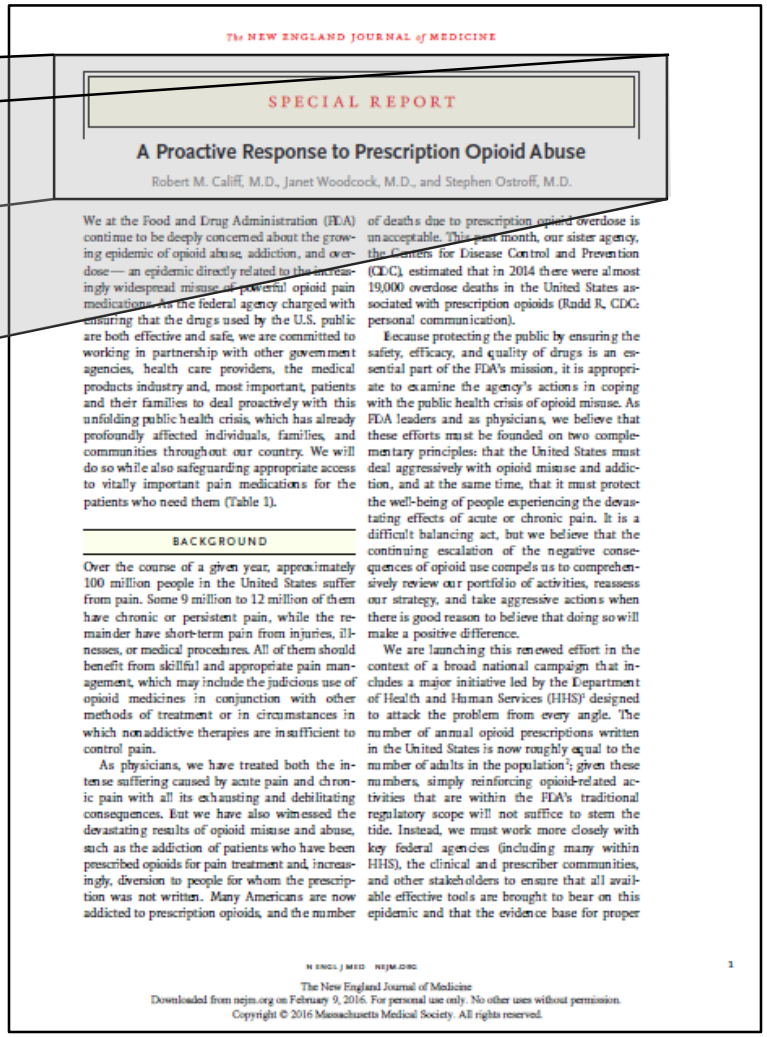
The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

## A Proactive Response to Prescription Opioid Abuse

Robert M. Califf, M.D., Janet Woodcock, M.D., and Stephen Ostroff, M.D.

We at the Food and Drug Administration (FDA) continue to be deeply concerned about the growing epidemic of opioid abuse, addiction, and overdose — an epidemic directly related to the increasingly widespread misuse of powerful opioid pain medications.



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A Proactive Response to Prescription Opioid Abuse

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We at the Food and Drug Administration (FDA) continue to be deeply concerned about the growing epidemic of opioid abuse, addiction, and overdose — an epidemic directly related to the increasingly widespread misuse of powerful opioid pain medications. As the federal agency charged with ensuring that the drugs used by the U.S. public are both effective and safe, we are committed to working in partnership with other government agencies, health care providers, the medical products industry and, most important, patients and their families to deal proactively with this unfolding public health crisis, which has already profoundly affected individuals, families, and communities throughout our country. We will do so while also safeguarding appropriate access to vitally important pain medications for the patients who need them (Table 1).

BACKGROUND

Over the course of a given year, approximately 100 million people in the United States suffer from pain. Some 9 million to 12 million of them have chronic or persistent pain, while the remainder have short-term pain from injuries, illnesses, or medical procedures. All of them should benefit from skillful and appropriate pain management, which may include the judicious use of opioid medicines in conjunction with other methods of treatment or in circumstances in which nonaddictive therapies are insufficient to control pain.

As physicians, we have treated both the intense suffering caused by acute pain and chronic pain with all its exhausting and debilitating consequences. But we have also witnessed the devastating results of opioid misuse and abuse, such as the addiction of patients who have been prescribed opioids for pain treatment and, increasingly, diversion to people for whom the prescription was not written. Many Americans are now addicted to prescription opioids, and the number of deaths due to prescription opioid overdose is unacceptable. This past month, our sister agency, the Centers for Disease Control and Prevention (CDC), estimated that in 2014 there were almost 19,000 overdose deaths in the United States associated with prescription opioids (Rudd R, CDC: personal communication).

Because protecting the public by ensuring the safety, efficacy, and quality of drugs is an essential part of the FDA's mission, it is appropriate to examine the agency's actions in coping with the public health crisis of opioid misuse. As FDA leaders and as physicians, we believe that these efforts must be founded on two complementary principles: that the United States must deal aggressively with opioid misuse and addiction, and at the same time, that it must protect the well-being of people experiencing the devastating effects of acute or chronic pain. It is a difficult balancing act, but we believe that the continuing escalation of the negative consequences of opioid use compels us to comprehensively review our portfolio of activities, reassess our strategy, and take aggressive actions when there is good reason to believe that doing so will make a positive difference.

We are launching this renewed effort in the context of a broad national campaign that includes a major initiative led by the Department of Health and Human Services (HHS)[1] designed to attack the problem from every angle. The number of annual opioid prescriptions written in the United States is now roughly equal to the number of adults in the population[2]; given these numbers, simply reinforcing opioid-related activities that are within the FDA's traditional regulatory scope will not suffice to stem the tide. Instead, we must work more closely with key federal agencies (including many within HHS), the clinical and prescriber communities, and other stakeholders to ensure that all available effective tools are brought to bear on this epidemic and that the evidence base for proper

# All Opioid Products with Abuse-Deterrent Labeling are Extended-Release/Long-Acting

- Six approved ER/LA opioids with abuse-deterrent labeling:
  - OxyContin (oxycodone)
  - Targiniq (oxycodone and naloxone)
  - Embeda (morphine sulfate and naloxone)
  - Hysingla ER (hydrocodone)
  - Morphabond (morphine sulfate)
  - Xtampza ER (oxycodone)
- Abuse-deterrent properties can lower, but not eliminate ability to abuse opioid

# Currently No Approved IR Opioid with Abuse-Deterrent Labeling

- No IR opioids labeled for abuse-deterrence
- Hydrocodone IR combination products:
  - 90 million dispensed prescriptions in 2015
  - Most commonly prescribed analgesic
  - Often the first opioid abused
- Unmet need to prevent escalation and progression of opioid abuse

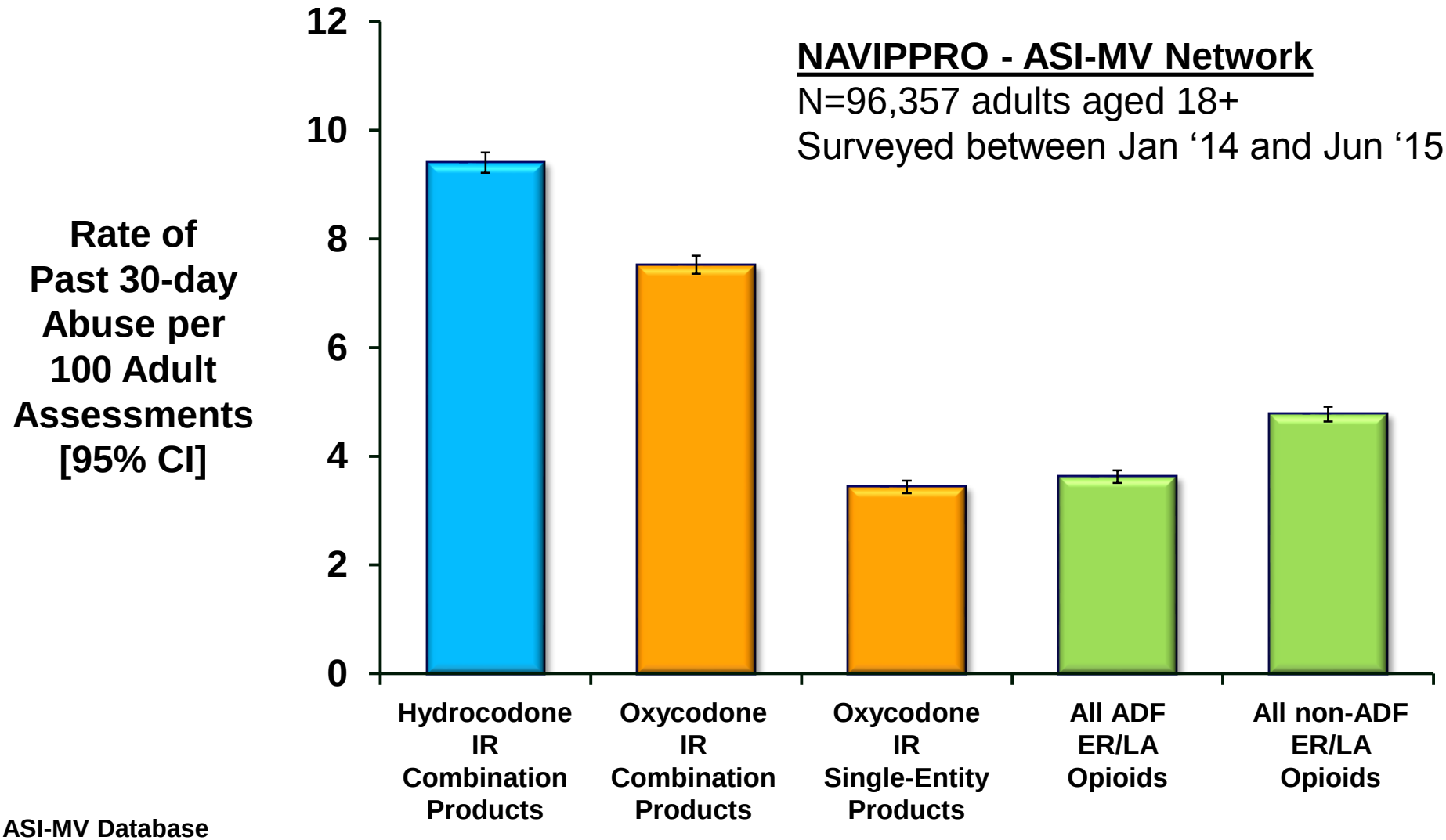
# Goal: Prevention of Progression from Oral Route to More Dangerous Routes of Administration


- Abusers progress to more dangerous routes as:
  - Opioid tolerance develops
  - Cost to maintain abuse patterns increases

# Surveillance Data Offer Window into Scope and Relevant Routes of Abuse

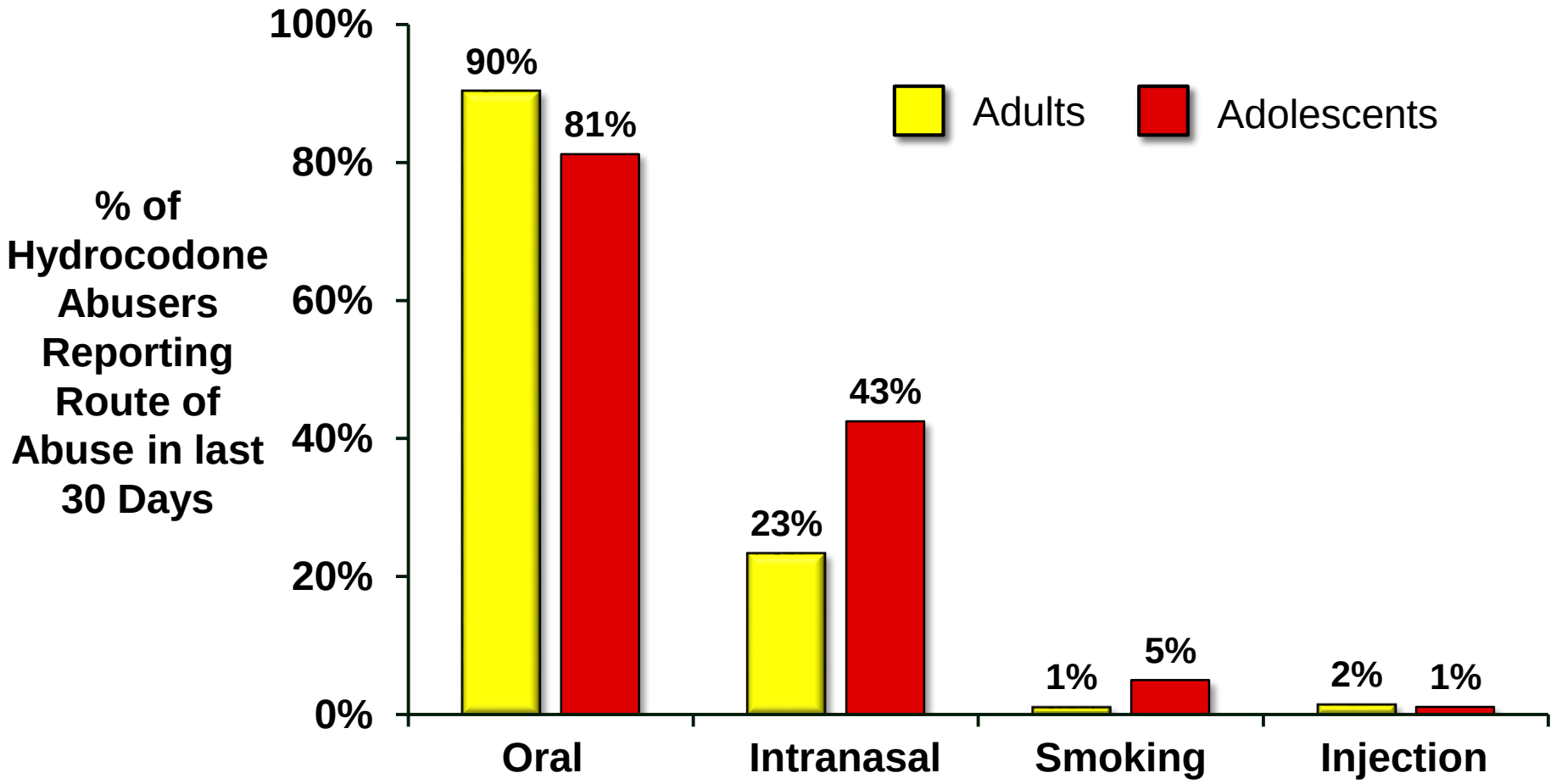
- Surveillance data are collected from drug abuse treatment centers
- Drug abuse surveillance is useful for understanding opioid abuse:
  - Extent of abuse
  - Routes of administration

# Hydrocodone IR Combination Products Are Commonly Abused



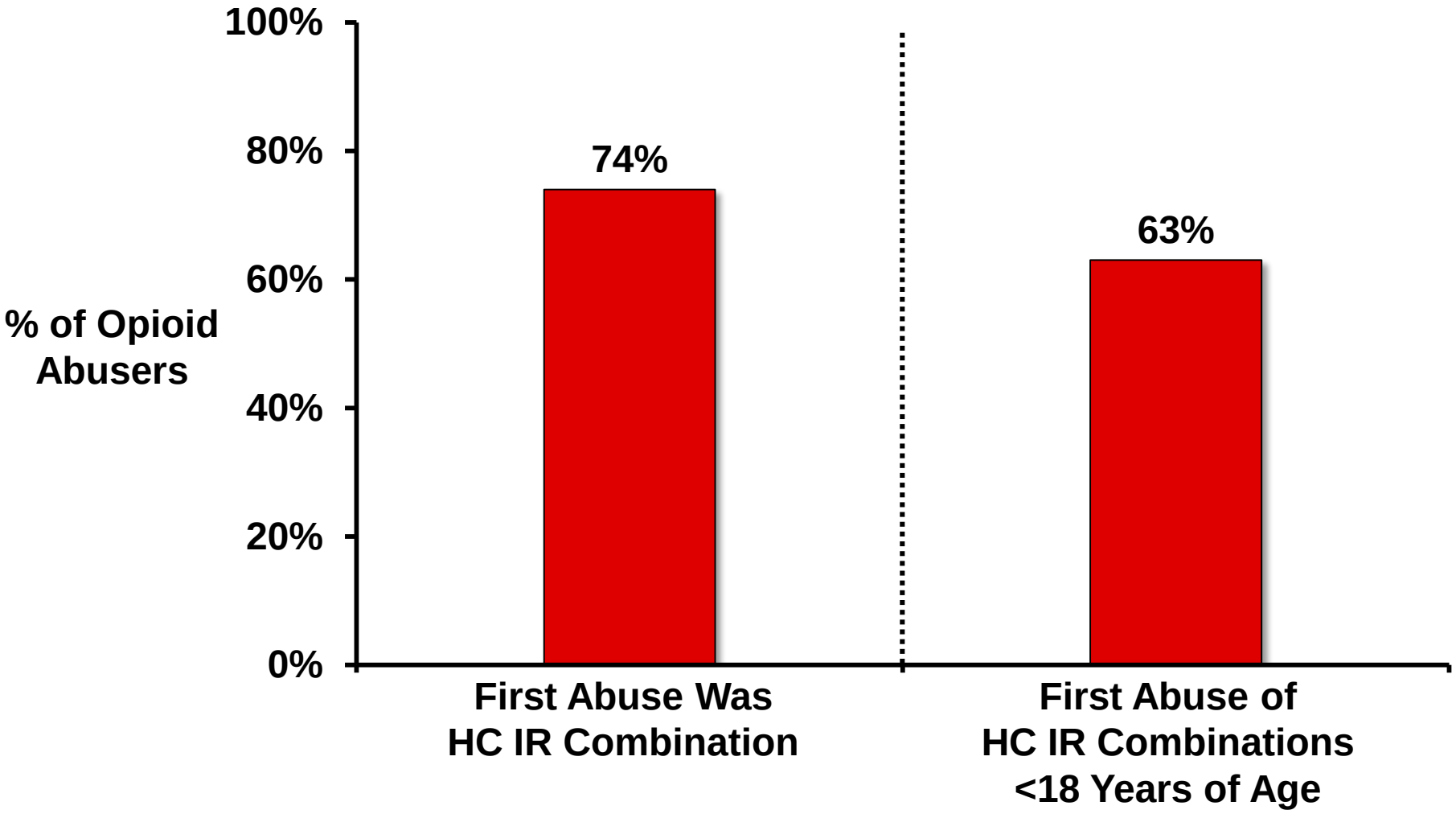

ASI-MV Database

# Prevalence of Abuse of Hydrocodone IR Combination Products by Route and Age

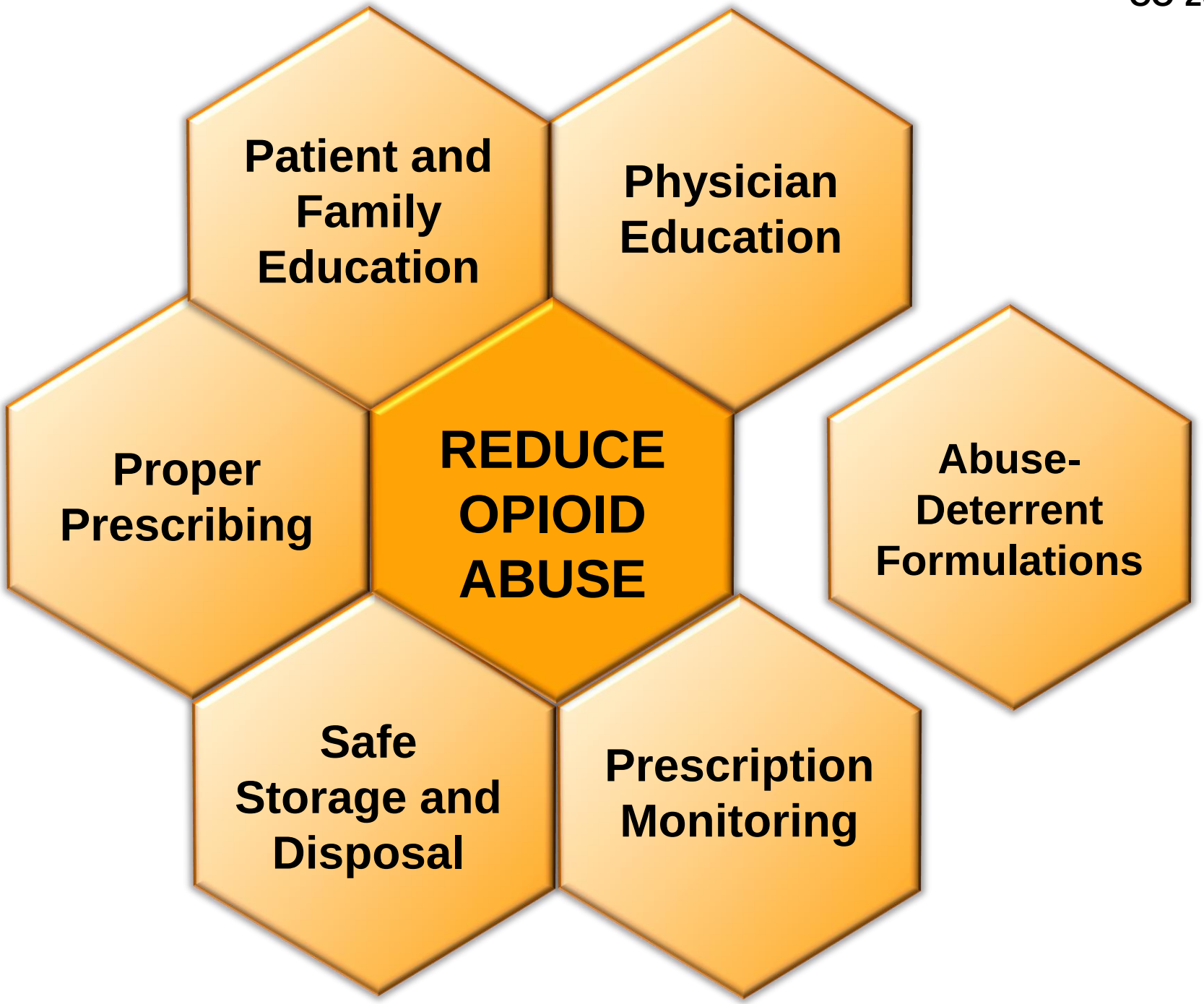



ASI-MV Database (Jan 12 – Jun 15; N=9,064)
CHAT Database (Jan 12 – Jun 15; N=468)

# Hydrocodone IR Combinations are Often the First Opioid Abused by Young People




2015 Inflexxion Internet Survey (N=472)


Patient and Family Education
Physician Education
Proper Prescribing
REDUCE OPIOID ABUSE
Abuse-Deterrent Formulations
Safe Storage and Disposal
Prescription Monitoring

# Development Overview

**Travis Mickle, Ph.D.**
Co-Founder and Chief Executive Officer
KemPharm, Inc.

# Apadaz Abuse-Deterrence Program Followed FDA Guidance

**Category 1**

**Lab-based *In Vitro* Manipulation and Extraction Studies**

Evaluates the difficulty with which AD properties can be defeated or compromised

**Category 2**

**Pharmacokinetic Clinical Trials**

Evaluates *in vivo* properties by measuring PK profiles of AD drug vs a comparator

**Category 3**

**Clinical Abuse Potential Studies**

Assessment of potential PD effects of AD drug vs a comparator

# Rationale for Tampering Studies

- As IR product, purpose of extraction is to remove acetaminophen and isolate hydrocodone to:
  - Reduce liver toxicity at high oral doses
  - Reduce insufflation volume
  - Prepare for injection
  - Prepare for freebasing/smoking

# Abuse-deterrent Products Increase Time and Effort It Takes To Extract Active Product

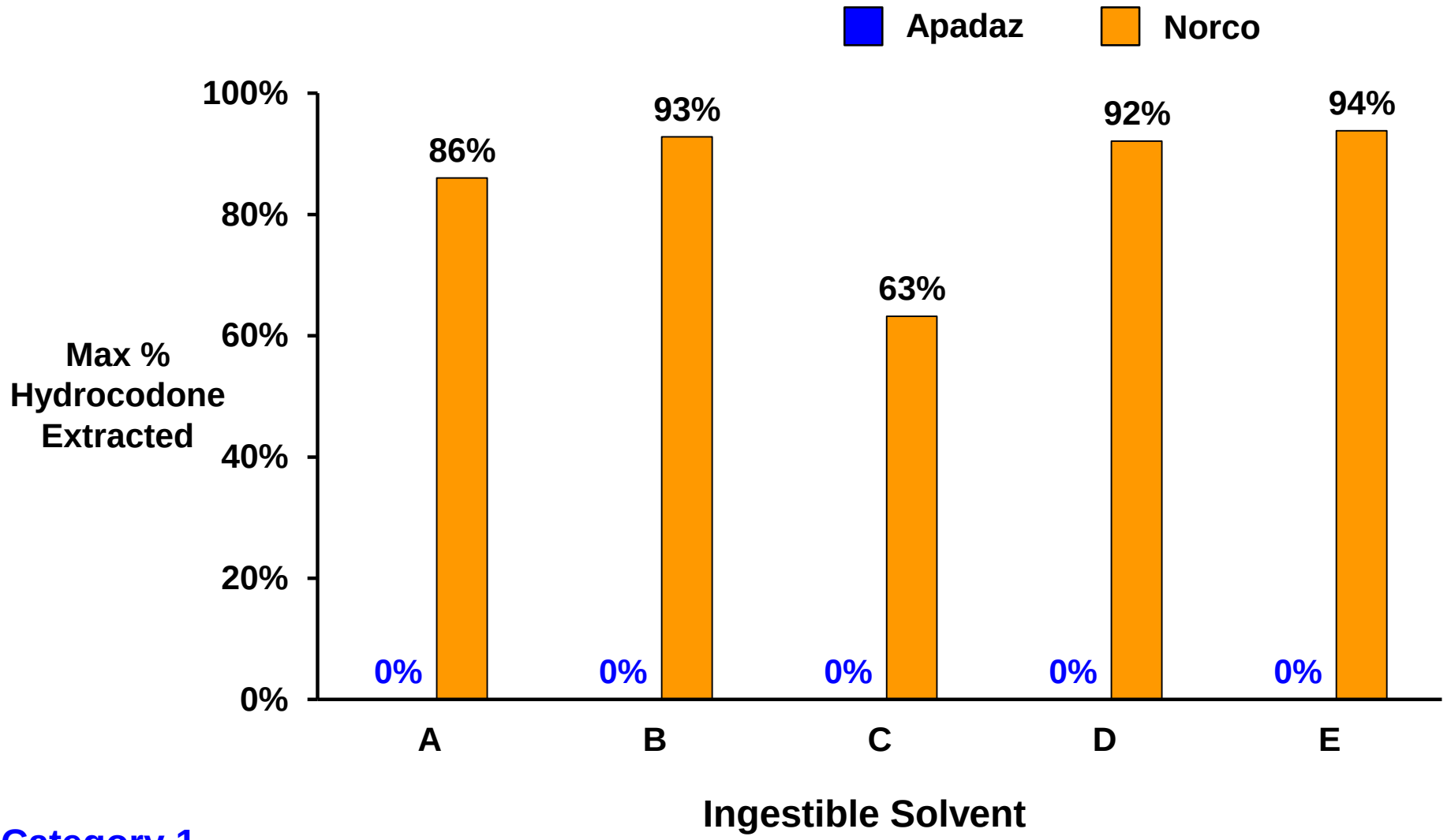
- Goal of abuse-deterrent formulation
  - Make manipulation more difficult and less attractive to abusers
    - Increase time
    - Increase effort

# Extraction with Common Ingestible Solvents

5 Common Ingestible Solvents

Evaluated up to 24 hours

# Extraction of Hydrocodone from Apadaz Was Ineffective with Common Ingestible Solvents



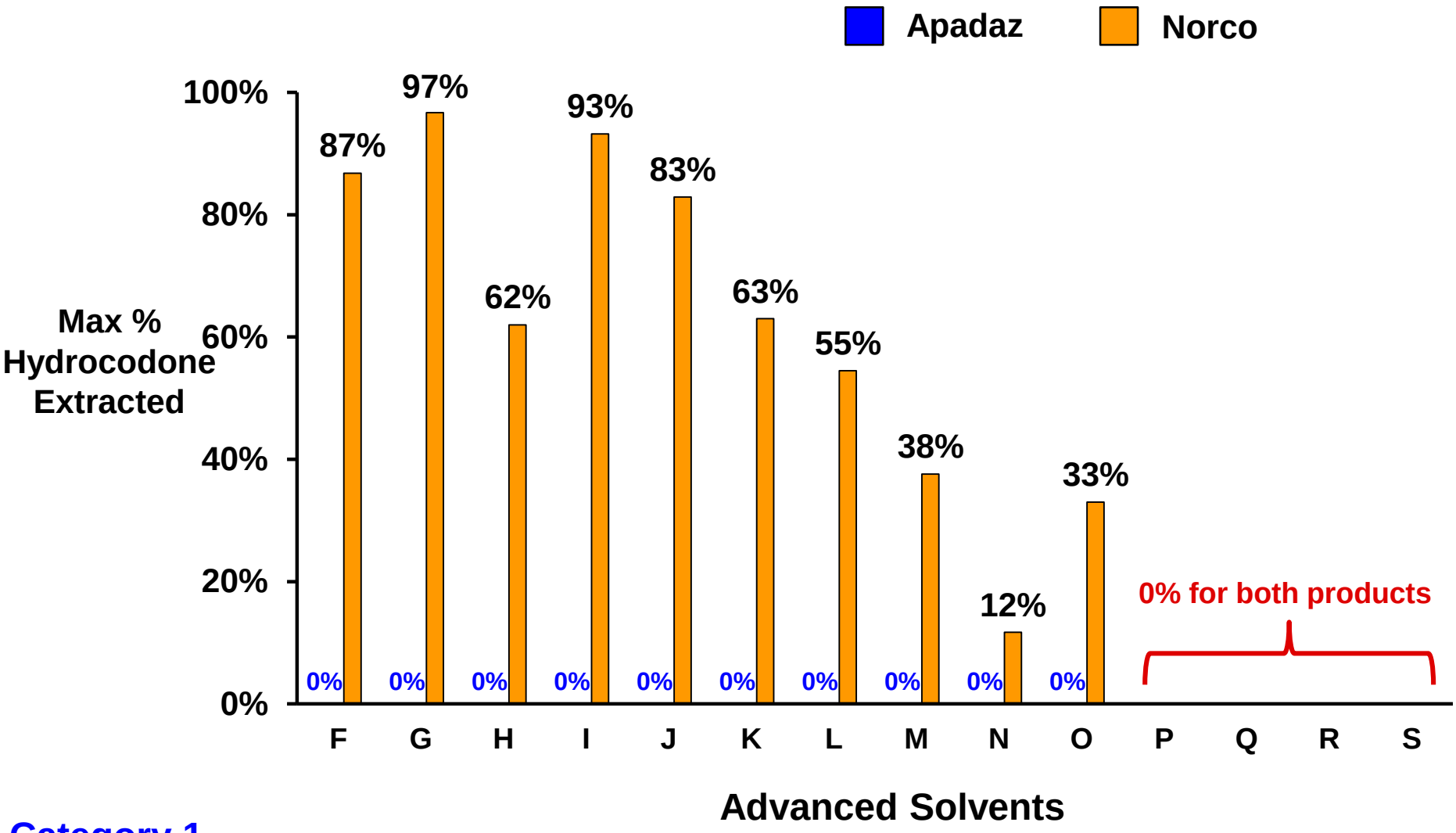

Category 1

# Extraction with Advanced Solvents

14 Advanced, Non-ingestible Solvents

Evaluated up to 24 hours

# Extraction of Hydrocodone from Apadaz Was Ineffective with Advanced Solvents



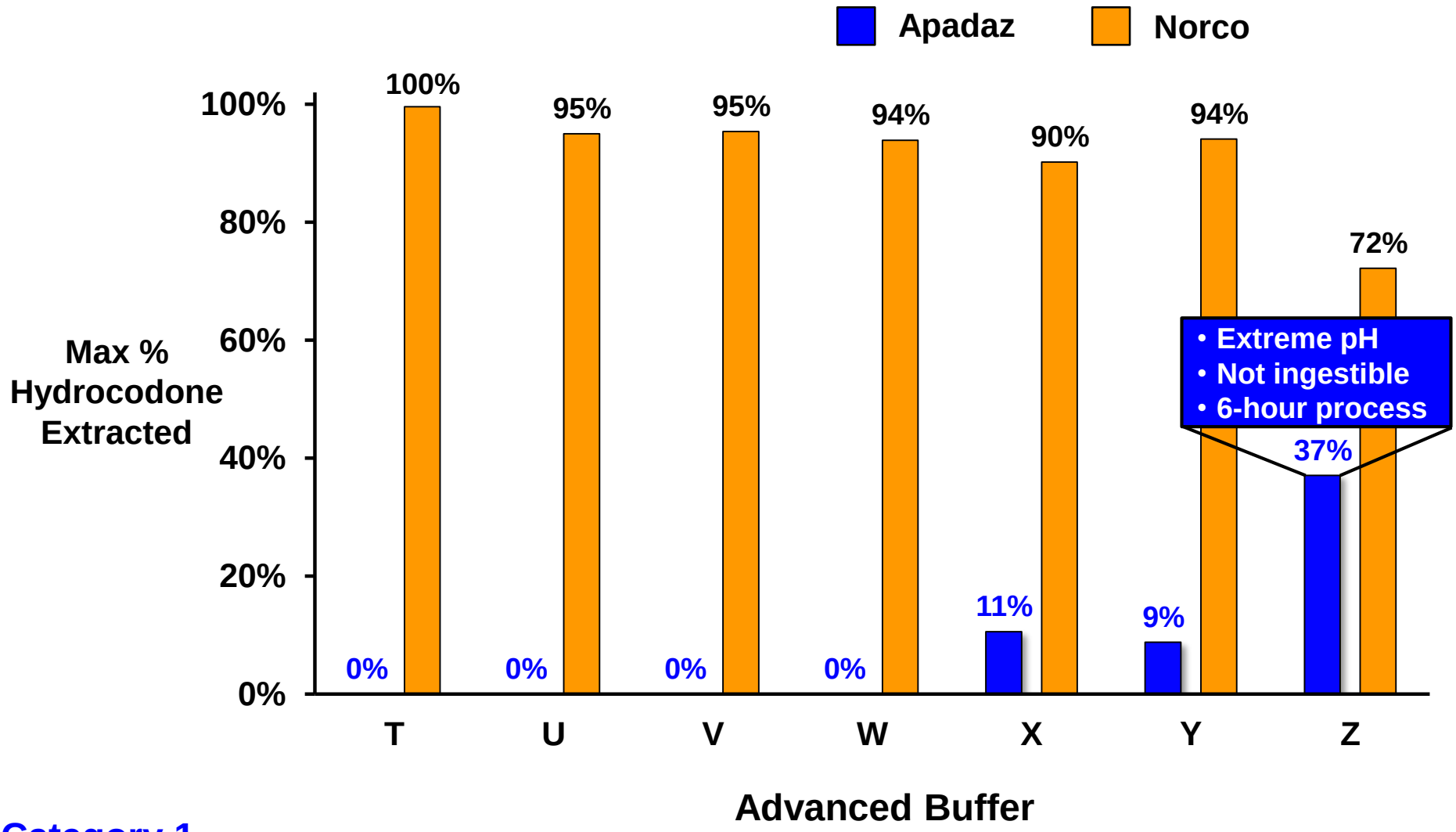

Category 1

# Extraction with Advanced Buffers

7 Advanced Buffers of varying pH

Evaluated up to 24 hours

# Extraction of Hydrocodone from Apadaz Was Inefficient with Advanced Buffers




Category 1

# Extraction of Hydrocodone with Heat and Continuous Agitation

20 solvents evaluated up to 24 hours

# Extraction at Various Temperatures and Continuous Agitation Did Not Yield Abusable Hydrocodone

| Solvent | Max % Hydro-codone Extracted | Time at Maximum Extraction | Solvent | Maximum % Hydro-codone Extracted | Time at Maximum Extraction |
|---|---|---|---|---|---|
| A | 0% | - | N* | 0% | - |
| B | 0% | - | O* | 0% | - |
| C | 0% | - | R* | 0% | - |
| D | 0% | - | T** | 0% | - |
| E | 0% | - | U** | 0% | - |
| F* | 0% | - | V** | 0% | - |
| G* | 0% | - | W** | 61% | 24 hours |
| J* | 0% | - | X** | 60% | 4 hours |
| K* | 0% | - | Y** | 63% | 6 hours |
| L* | 0% | - | Z** | 46% | 24 hours |

*Advanced non-ingestible solvents
**Advanced buffers

**Category 1**

# Hydrolysis

Covalent bond between benzoic acid and hydrocodone has to be broken to release hydrocodone from Apadaz prodrug

# Hydrolysis is Not a Feasible Way for Abusers to Tamper with Apadaz

- Fewer than 20% of samples tested released >50% of hydrocodone
  - Hydrolysis occurred only under specific conditions related to pH, with temperature modifications, over extended time
- Additional steps required to obtain abusable hydrocodone

# Route-Specific Manipulations

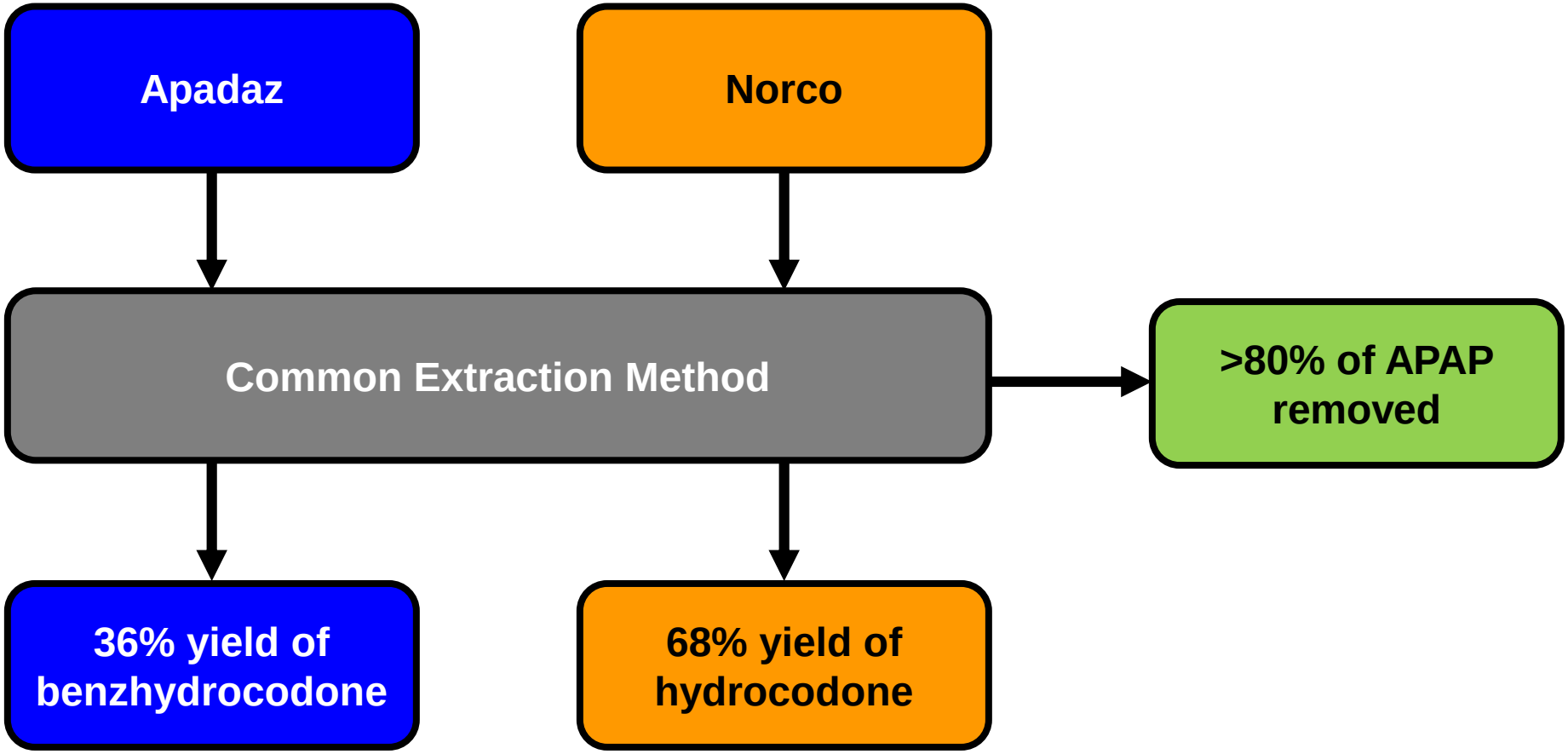
Injection

Smoking

# IV Preparation was Less Efficient for Apadaz Than Norco; Syringability is Feasible

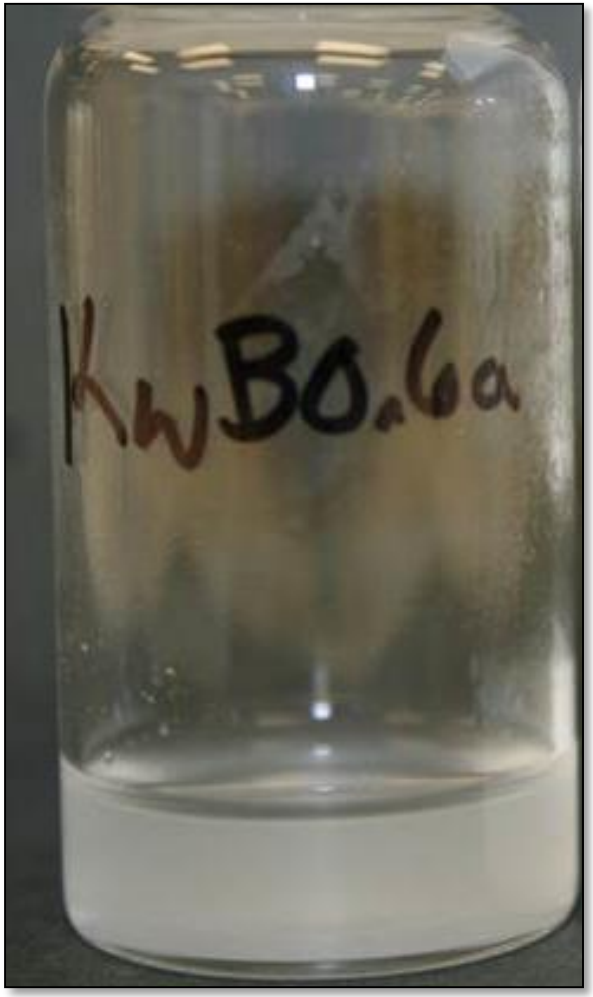
- Of 164 conditions tested:
  - 39 conditions yielded >70% hydrocodone from Norco
  - 1 condition yielded >70% benzhydrocodone from Apadaz
- Syringeability is feasible for both products
  - Only inactive prodrug can be extracted from Apadaz, and is less efficient than Norco

# Common Extraction Method to Prepare IV Formulations is Inefficient for Apadaz

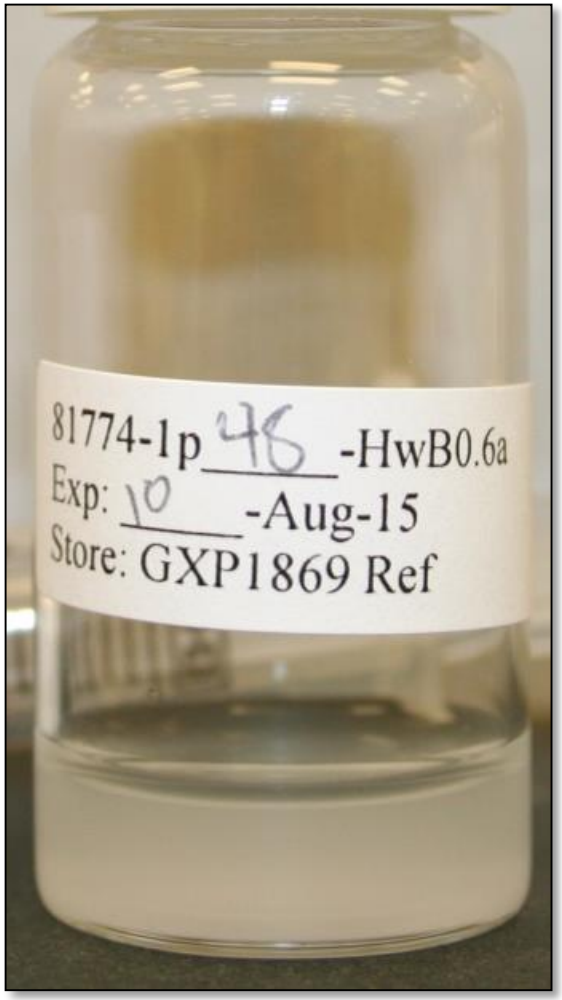


# Cloudy Mock IV Preparations Due to Undissolved Excipients and Acetaminophen

**Apadaz**



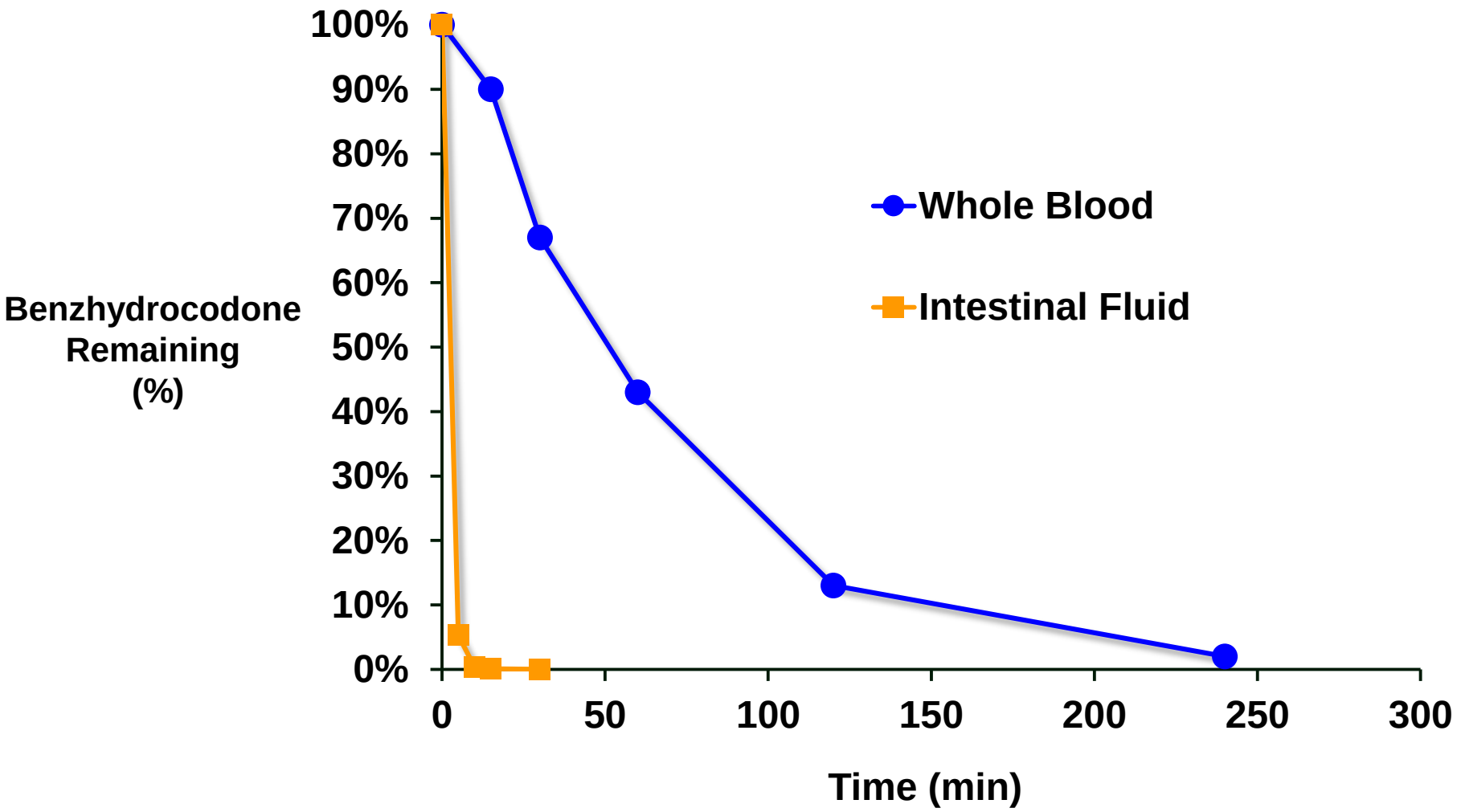

**Norco**



# Why Would an Abuser Inject?

- Bypass first-pass metabolism
  - Cocaine and heroin
- Injection gets opioid into brain more quickly
- Faster exposures, faster highs

# *In Vitro* Study: Stability of Apadaz in Whole Human Blood




Category 1

# Smoking Simulation Study

Category 1

# Apadaz Did Not Release Hydrocodone in Smoking Simulation Study

- Freebasing Apadaz was not possible
- Vaporizing or smoking Apadaz or benzhydrocodone at any temperature did not produce any hydrocodone

# Summary of Findings from Category 1 Evaluations of Apadaz

- Common ingestible solvents not effective in extracting Apadaz
- Harsh chemicals and heat typically required over 4-24 hours for moderate hydrocodone extraction
- Preparing Apadaz for IV injection was inefficient, and prodrug converts slowly in blood
- Smoking/freebasing Apadaz tablets not effective

# Clinical Abuse-Deterrence Studies

**Lynn Webster, M.D.**
Vice President, Scientific Affairs
PRA Health Sciences

# Apadaz Abuse-Deterrence Program Followed FDA Guidance

**Category 1**

Lab-based *In Vitro* Manipulation and Extraction Studies

Evaluates the difficulty with which AD properties can be defeated or compromised

**Category 2**

**Pharmacokinetic Clinical Trials**

**Category 3**

**Clinical Abuse Potential Studies**

Study A01: Oral abuse

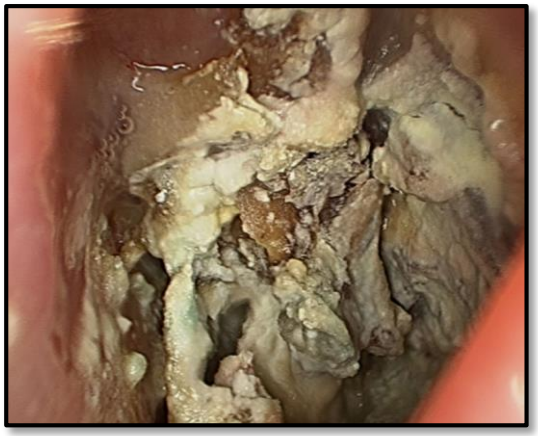
Study A02: IN abuse

Study A03: IN abuse with APIs

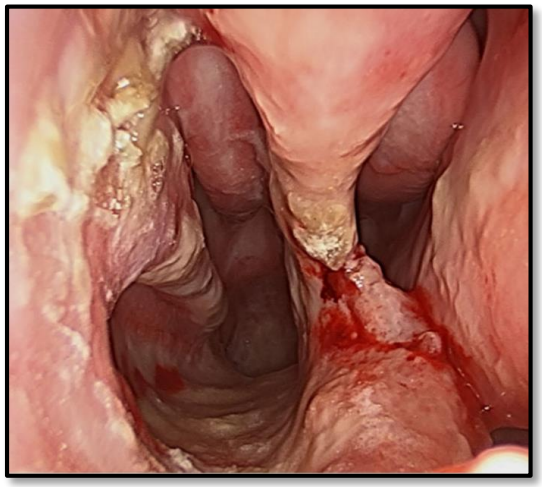
# Health Consequences of Intranasal Abuse of Hydrocodone Combination Products

- Nasal/facial pain
- Nasal obstruction
- Necrosis of nasal passages & soft palate
- Fungal rhinosinusitis
- Septal and palatal perforation

**Nasal Septal Injury from IN Hydrocodone-Acetaminophen Abuse**



**Pre-debridement**



**Post-debridement**

Yewell et al. *Ann Otol Rhinol Laryngol*
Volser et al. *Int Forum Allergy Rhinol* 2014;4:839-44.
Images: Alexander et al. *Laryngoscope* 2012;122:2378-81.

# Why Does an Abuser Snort Opioids?

- Snorting gets opioids into circulation faster
  - Circumvents first-pass metabolism
  - Provides greater exposures and faster highs

# How Do Abusers Snort Hydrocodone Combination Products?

1. Without manipulation (Study A02)
2. After removing APAP, using “Common Tampering Method” (Study A03)
   - Reduces snorting volume
   - Reduces potential for liver toxicity

# Drug Liking $E_{max}$ is a Relevant Primary Endpoint to Evaluate Abuse-Deterrent ER Opioids

- Primary endpoint: difference in maximum Drug Liking ($E_{max}$)[1]
  - Calculated as the average of every subject's maximum liking, regardless of time it occurred
- Evaluates manipulated AD ER vs. non-AD IR product at high dose
- Lower $E_{max}$ expected if AD ER product does not dose dump

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

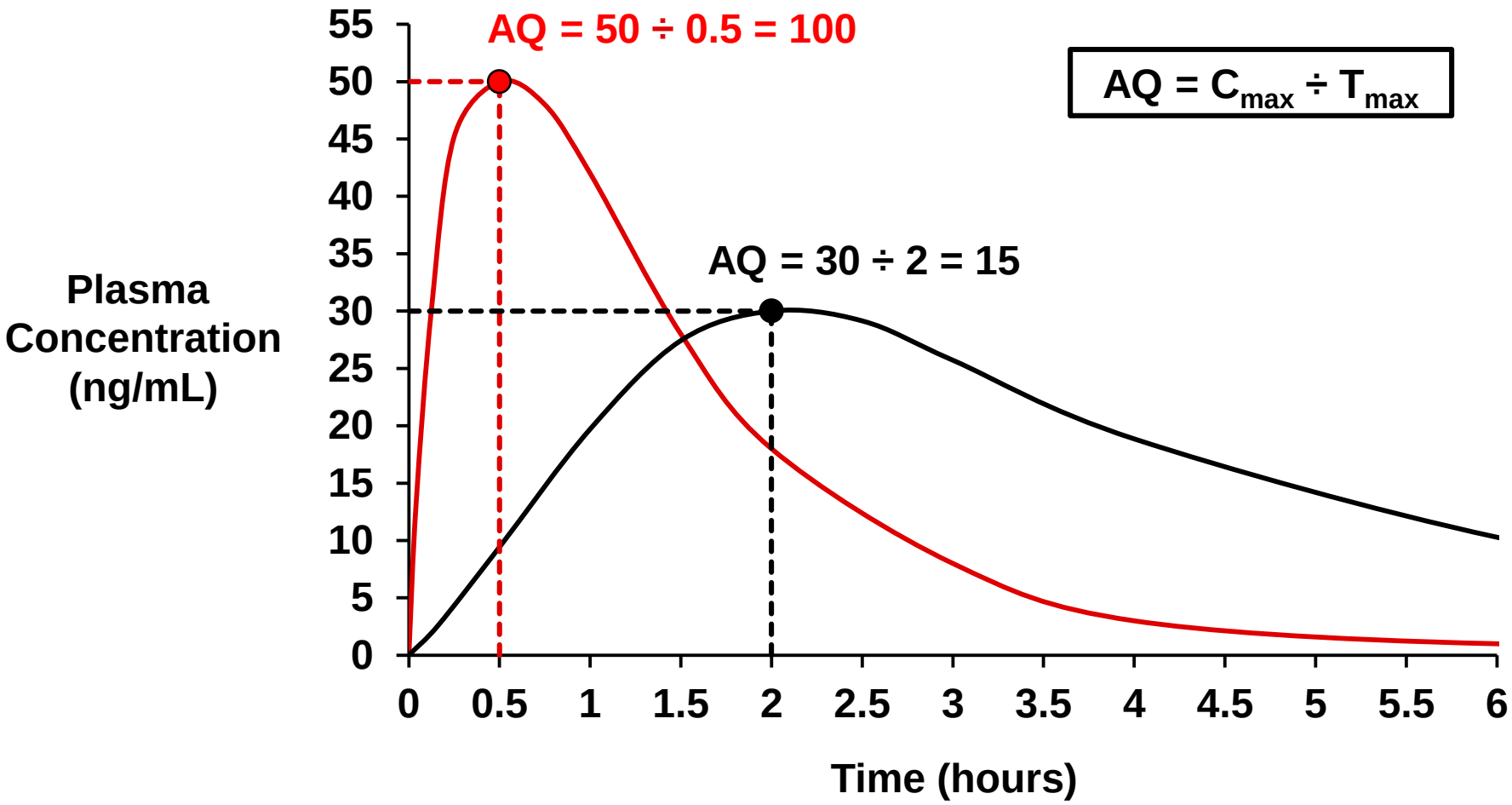
# Rationale of Drug Liking $E_{max}$ Harder to Apply to Abuse-Deterrent IR Opioids

- Differences between IR and ER in opioid quantity and timeframe of proper opioid delivery
  - ER products release more opioid *slowly*
  - IR products release less opioid *quickly*
- Time course of Drug Liking, particularly at early time points, may be more relevant than $E_{max}$
- Drug Liking $E_{max}$ does not account for time

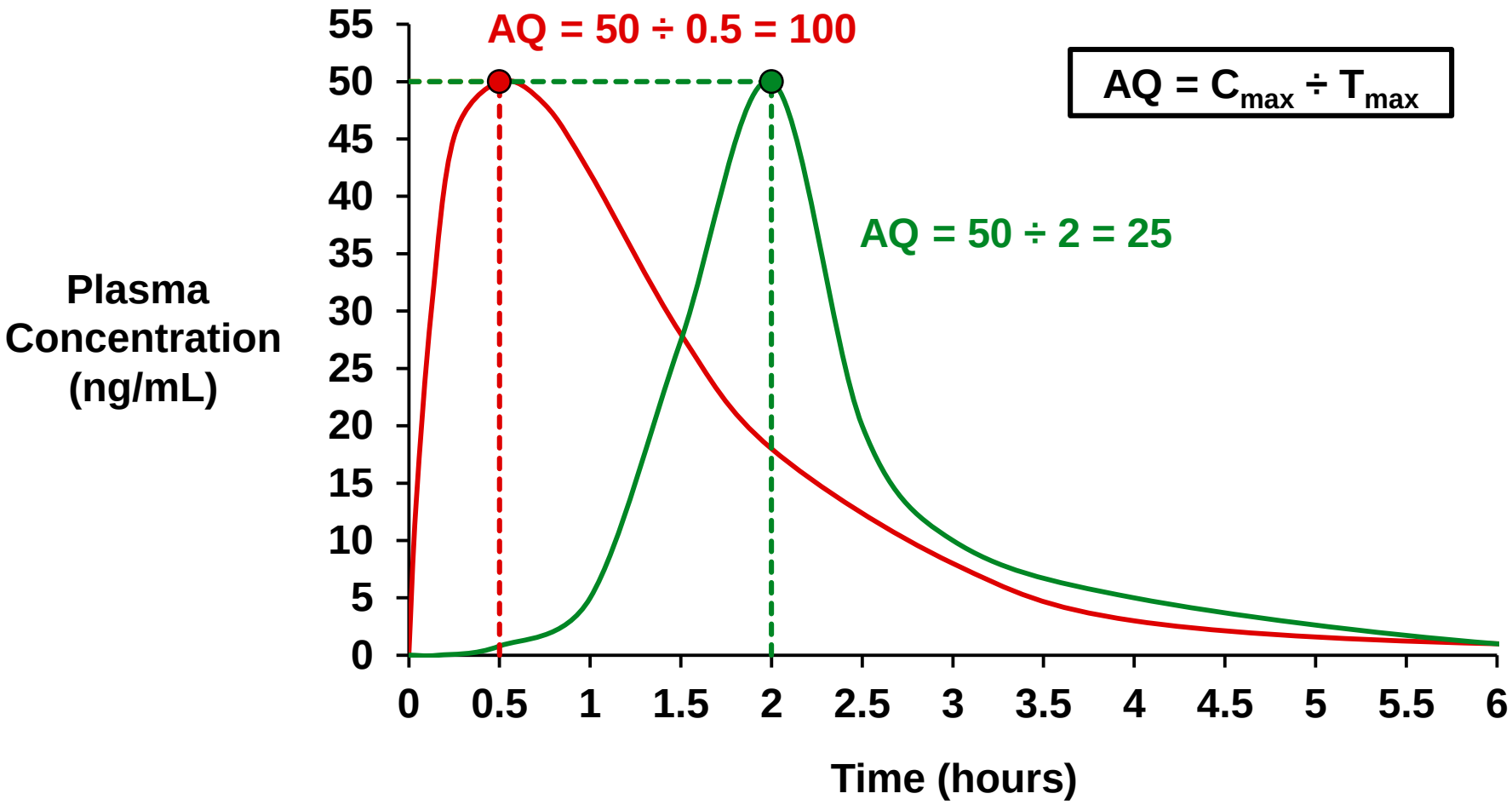
# Abuse Quotient

Moorman-Li et al. *P T* 2012;7:412-8.

# Rate of Rise in Drug Levels Evaluated Using Abuse Quotient



# Abuse Quotient Simulation



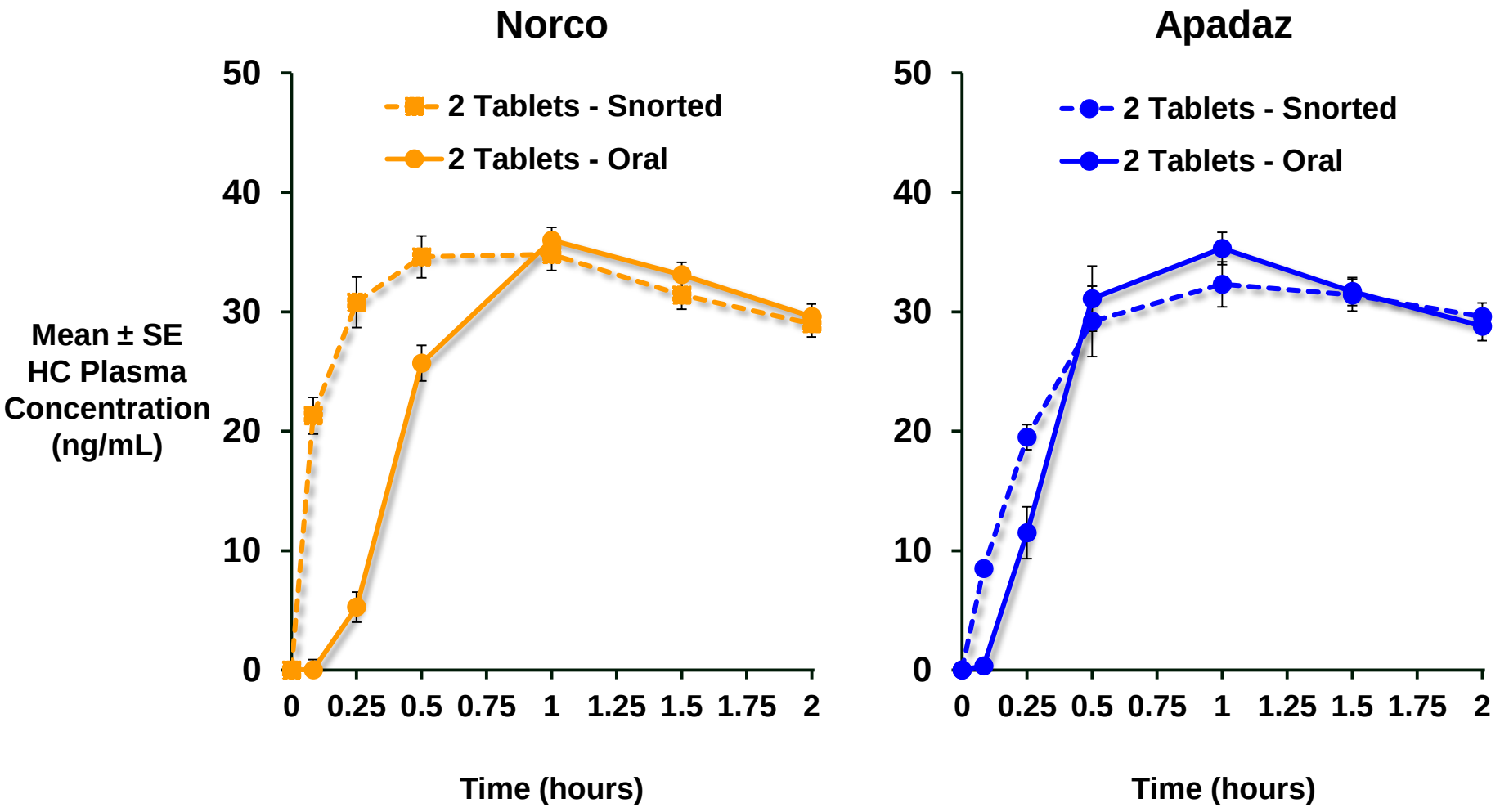
# Study A02:
# Intranasal Human Abuse Potential

**Apadaz vs. Norco**

Part A: Dose selection (2 tablets selected as largest volume that produced reliable Drug Liking scores)

Part B: Bioavailability and Drug Liking

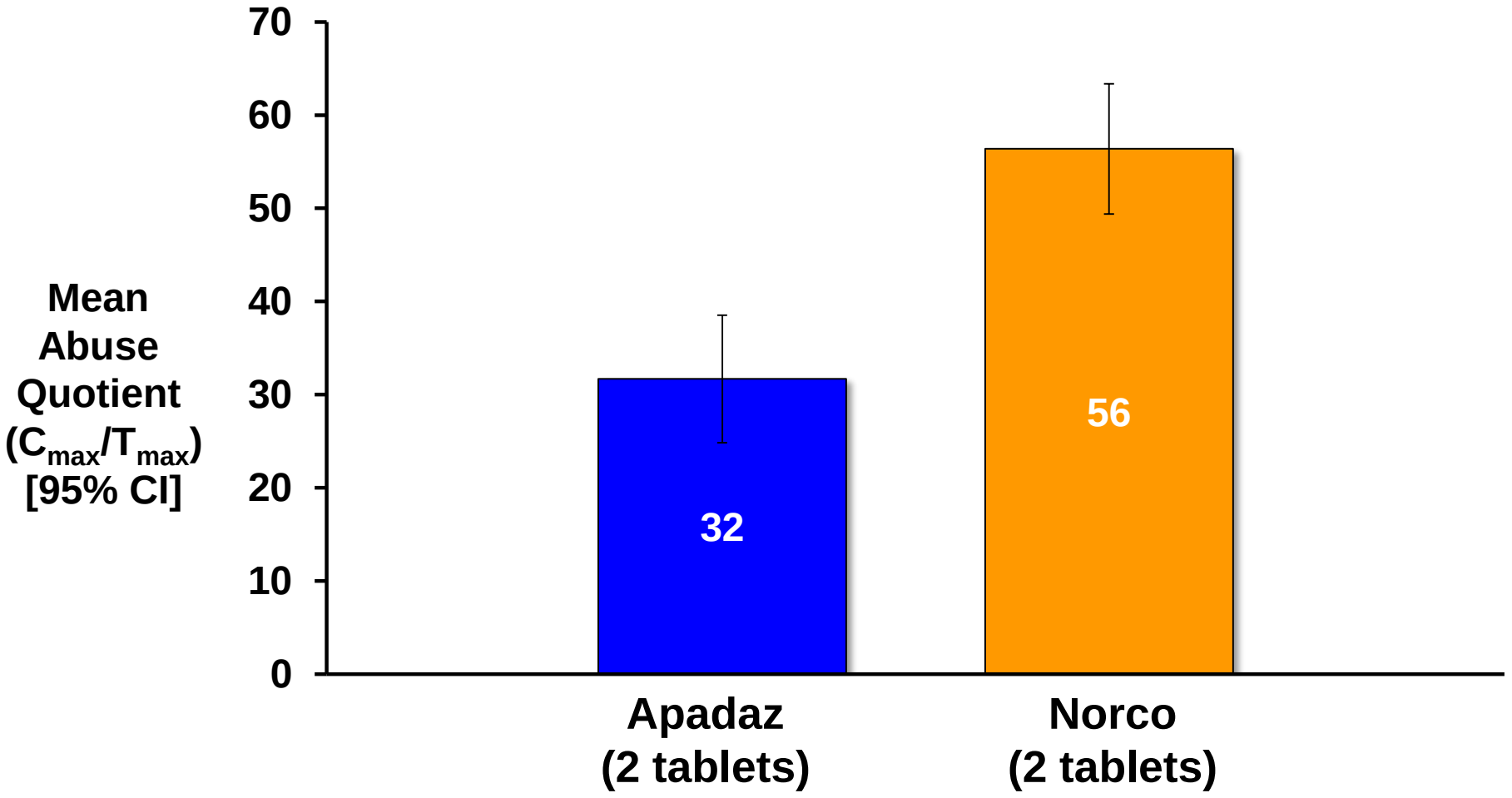
# Snorting Apadaz Does Not Accelerate Exposure to Hydrocodone




Category 2

Study A02: Intranasal HAP Study

# Apadaz Has Lower Abuse Quotient Than Norco When Snorted



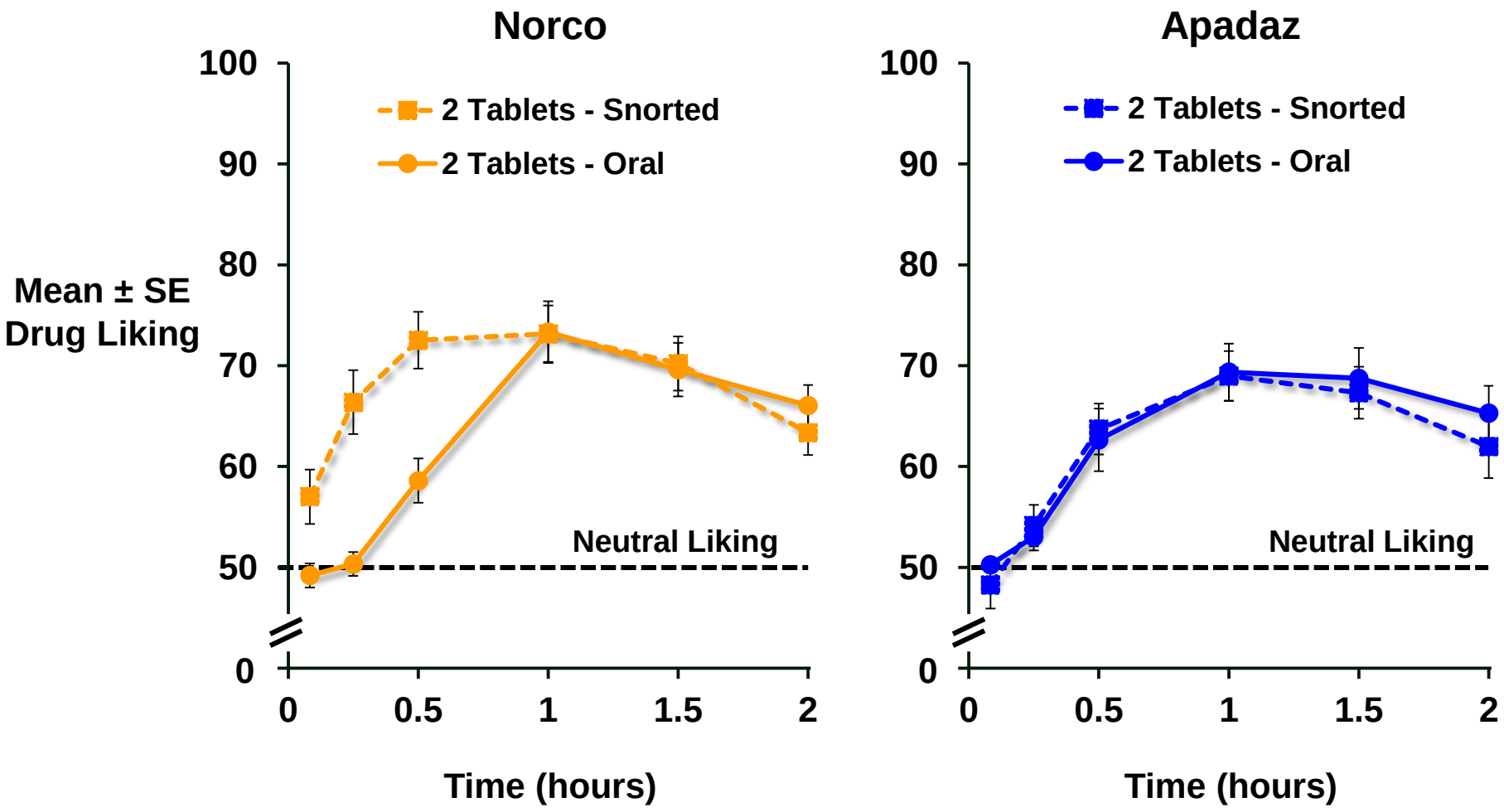



Study A02: Intranasal HAP Study (N=42)

# No Difference in Drug Liking $E_{max}$ in Study A02

| Drug Liking | Intranasal (2 Tablets) | |
|---|---|---|
| | Apadaz | Norco |
| $E_{max}$, mean | 75.9 | 79.0 |
| P-value | 0.28 | |

# Snorting Apadaz Does Not Increase Drug Liking at Early Time Points




Category 3

Study A02: Intranasal HAP Study (N=42)

# Apadaz Associated with Lower Ease of Insufflation

- Ease of Insufflation Score
  0=Very Easy  100 = Very Difficult

| Variable | Mean (SD) | | Difference (P-value) |
|---|---|---|---|
| | Apadaz | Norco | |
| **Ease of Insufflation (0-100 scale)** | 57 (36) | 43 (33) | 14 (p = 0.01) |

# Apadaz Associated with More Adverse Nasal Effects When Snorted

- Nasal Effect Assessment Score
  0=None 1=Mild 2=Moderate 3=Severe

| Variable | Mean (SD) | | Difference (P-value) |
|---|---|---|---|
| | Apadaz | Norco | |
| **Burning** | 1.6 (1.0) | 0.7 (0.7) | -1.0 (<0.001) |
| **Pain** | 1.0 (1.0) | 0.5 (0.8) | -0.5 (<0.001) |
| **Blow** | 1.5 (0.9) | 1.0 (0.9) | -0.5 (<0.001) |
| **Irritate** | 1.5 (1.0) | 0.7 (0.7) | -0.8 (<0.001) |
| **Congestion** | 1.5 (1.0) | 1.0 (0.8) | -0.5 (<0.001) |
| **Discharge** | 1.4 (1.0) | 0.8 (0.9) | -0.7 (<0.001) |

# Apadaz Associated with Higher Frequency of Nasal-Related Adverse Events

| Adverse Event | Apadaz Intranasal (N=44) | Norco Intranasal (N=43) |
|---|---|---|
| Respiratory, thoracic and mediastinal disorders | 66% | 21% |
| Nasal discomfort | 36% | 5% |
| Nasal congestion | 16% | 5% |
| Rhinorrhea | 16% | 9% |
| Throat irritation | 14% | 7% |
| Dry throat | 2% | 0% |
| Oropharyngeal pain | 2% | 2% |
| Upper-airway cough syndrome | 0% | 2% |



Study A02: Intranasal HAP Study (N=42)

# Study A03: Intranasal Bioavailability Study with Abuse Potential Assessments

**Benzhydrocodone vs. Hydrocodone Bitartrate**

- Subjects administered equivalent amounts of the API found in 2 tablets

# Study A03: Intranasal Bioavailability Study with Abuse Potential Assessments

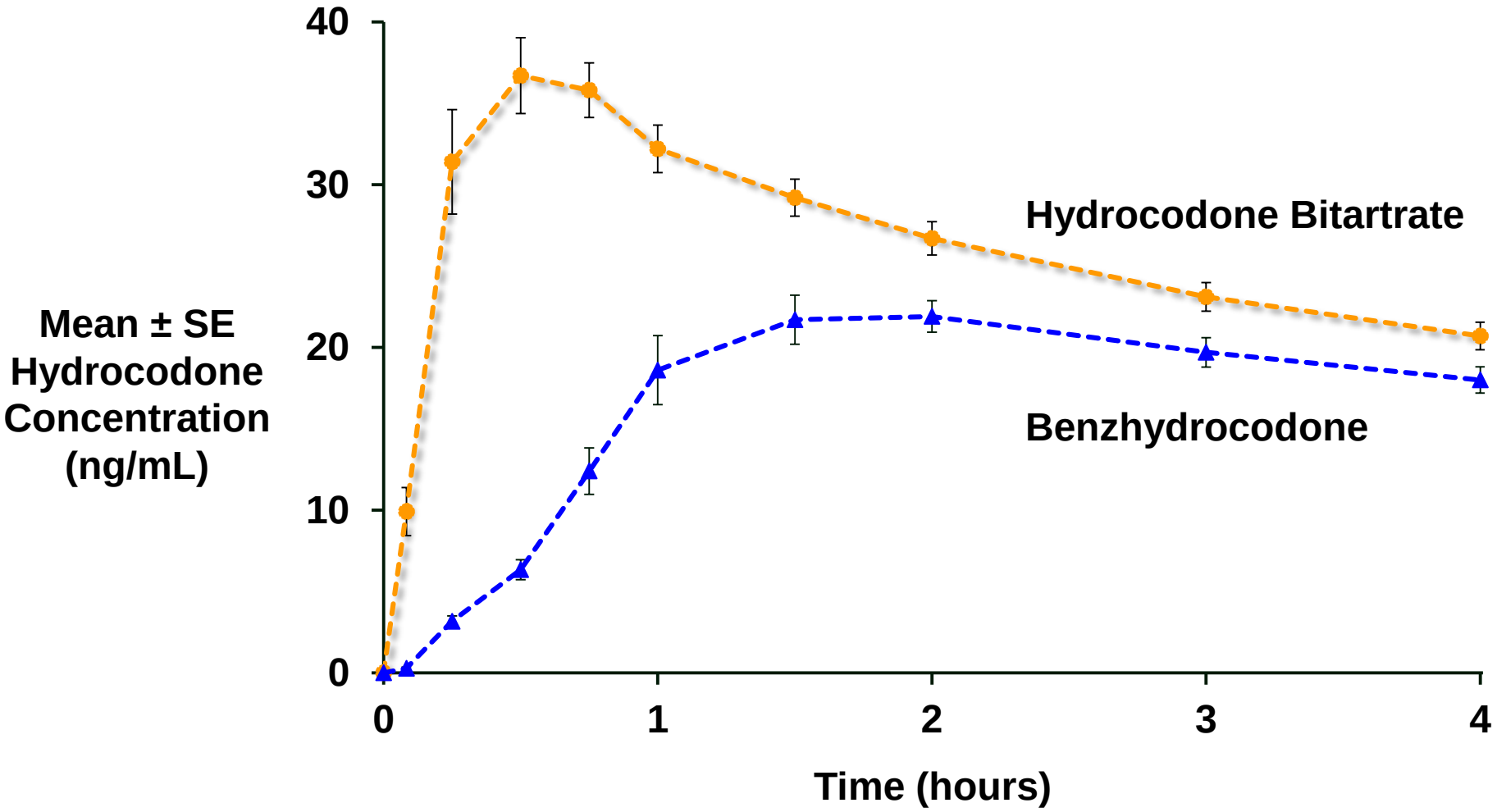
- No drug discrimination phase
- Lack of enrichment made it less likely to find differences in Drug Liking

# Common Extraction Method Applied to Reduce Bulk for Snorting Is Inefficient for Apadaz

- Practical Extraction results:
  - >80% of APAP removed for both products
  - 68% yield of hydrocodone from Norco
  - 36% yield of benzhydrocodone from Apadaz

- Study A03 assumptions (assumes best case):
  - 100% of APAP removed
  - 100% yield of hydrocodone and benzhydrocodone

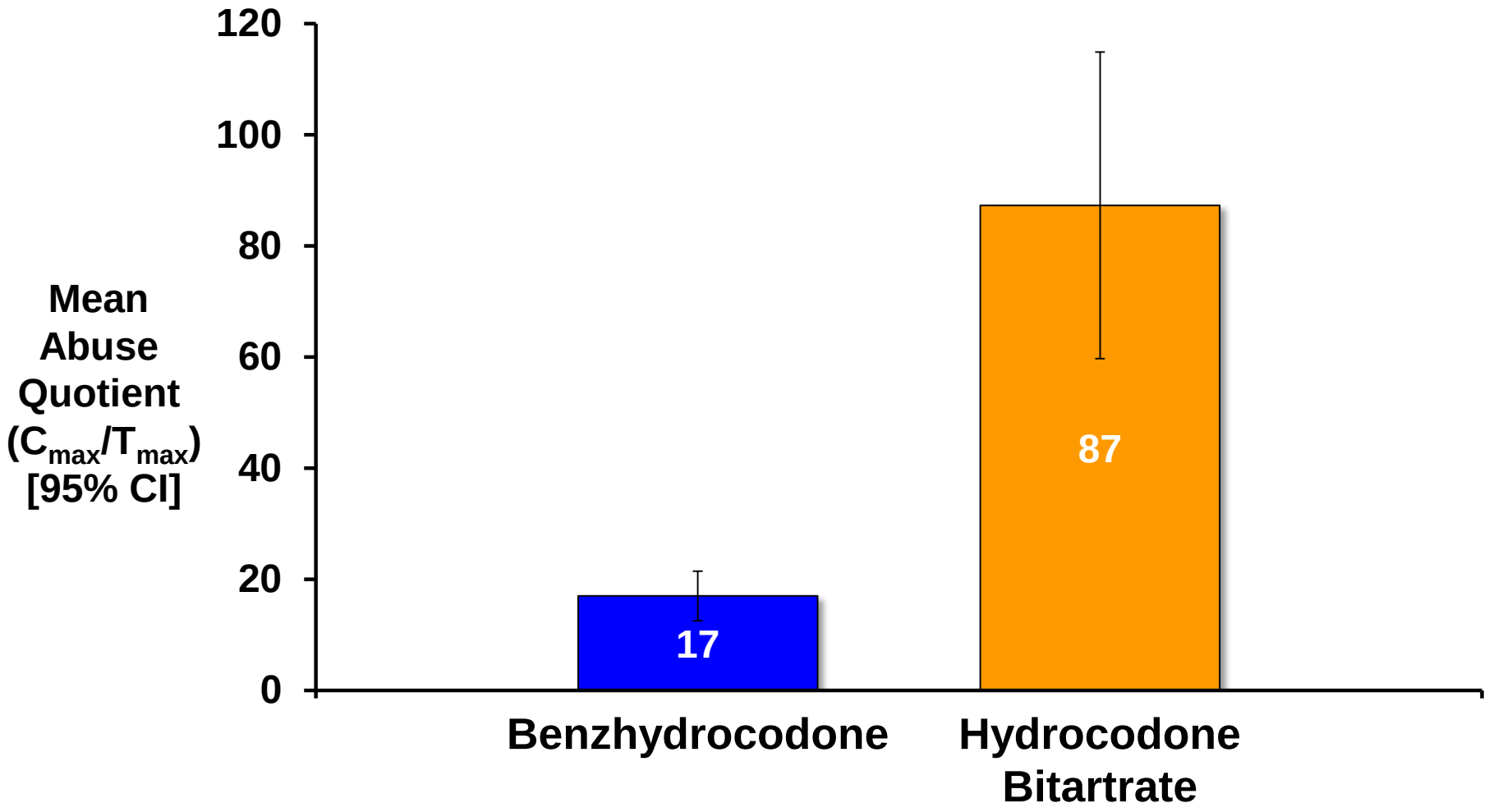
# Intranasal Administration of Apadaz Prodrug Leads to Lower HC Release




Category 2

Study A03: Intranasal Study of APIs (N=24)

# 5-Fold Lower Abuse Quotient With Snorted Apadaz Prodrug



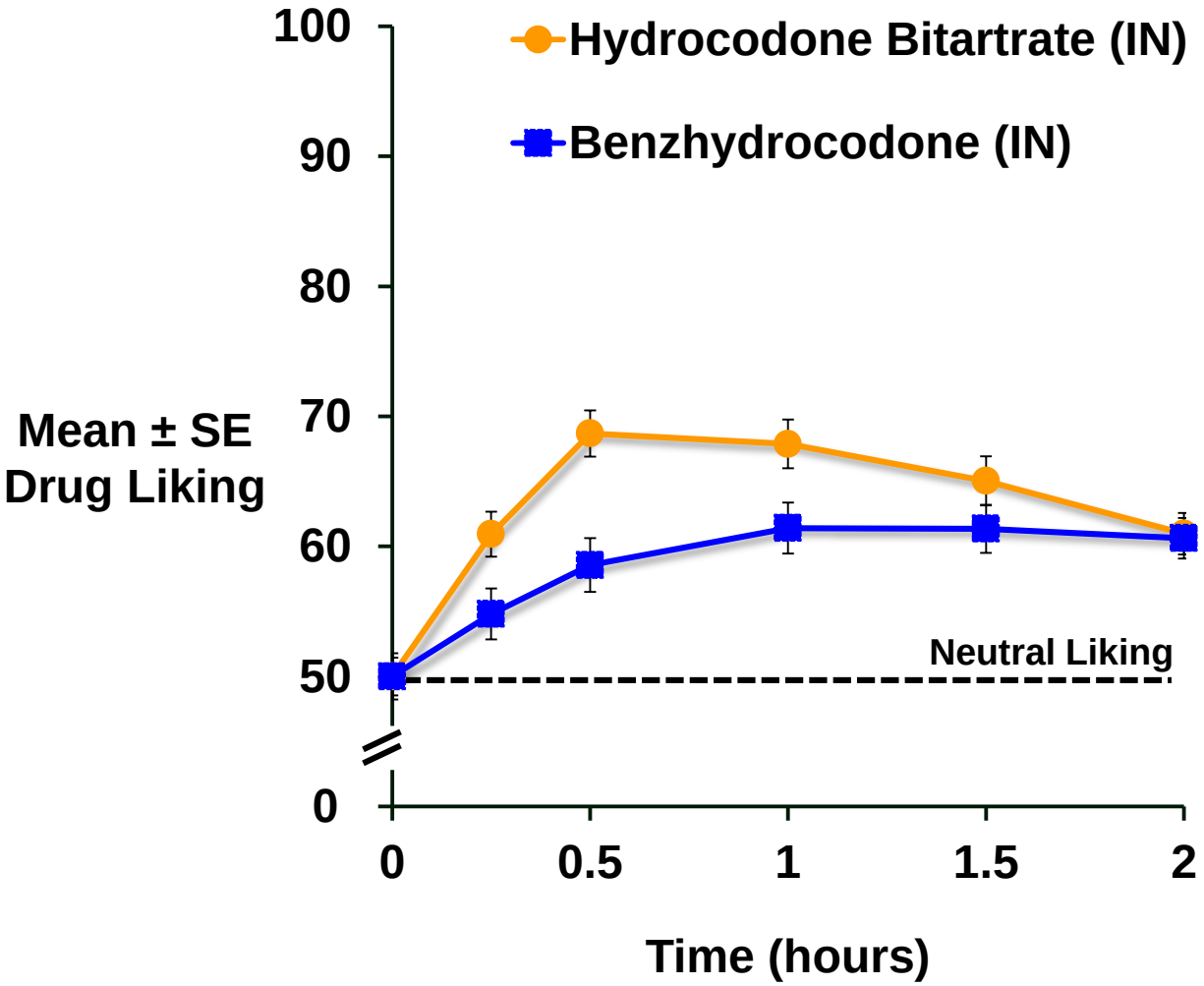



Study A03: Intranasal Study of APIs (N=24)

# Differences Observed in Drug Liking $E_{max}$ with APIs

| Drug Liking | Intranasal | |
|---|---|---|
| | Benzhydrocodone | Hydrocodone Bitartrate |
| $E_{max}$, mean | 67.4 | 73.2 |
| P-value | 0.004 | |

# Differences in Drug Liking with APIs Over Time Mirrored PK Findings in Study A03




Category 3

Study A03: Intranasal HAP Study of APIs (N=51)

# Snorting Apadaz Prodrug Associated with Lower Ease of Insufflation than Hydrocodone API

| Variable | Mean (SD) | | Difference (P-value) |
|---|---|---|---|
| | Benzhydrocodone | Hydrocodone Bitartrate | |
| Ease of Insufflation | 79 (20) | 66 (26) | 13 (p = 0.004) |

# Summary of Findings from Intranasal Clinical Abuse Potential Studies of Apadaz

- **With Apadaz, abusers do not achieve the rapid highs they seek from snorting**
- Snorting with APAP (A02)
  - Unlike Norco, Apadaz produced nearly identical profiles for PK and Drug Liking compared to oral
- Snorting without APAP (A03)
  - Most common tampering method to remove APAP is half as efficient with Apadaz
  - Even at equimolar doses, benzhydrocodone produced lower hydrocodone exposure and Drug Liking
- Apadaz was harder to snort than Norco, with or without APAP

# Post-Market Surveillance Future Studies

**Travis Mickle, Ph.D.**
Co-Founder and Chief Executive Officer
KemPharm, Inc.

# Epidemiologic Approach to Post-Market Surveillance and Evaluation of Abuse Profile

- Epidemiologic program evaluating abuse and routes of abuse
- Continued market surveillance
  - Specific for Apadaz
  - Generally related to entire opioid market

# Several Sources of Post-Marketing Data

- Continuation of current market surveillance similar to pre-approval approach
- NAVIPPRO database
  - **ASI-MV® Network** (adults)
  - **CHAT®** (adolescents)
  - **WIS®: Internet Monitoring**
- Additional sources as needed for support

# Surveillance Monitoring and Epidemiological Studies to Monitor Use and Abuse of Apadaz

- Surveillance monitoring for abuse
  - Initial abuse expected to be low
  - Monitoring tools to provide early assessment of abuse potential
- Post-market epidemiological studies
  - Primary study assessing rates and routes of abuse
  - Supportive study to monitor and assess discussion among recreational drug abusers

# Benefit-Risk Profile

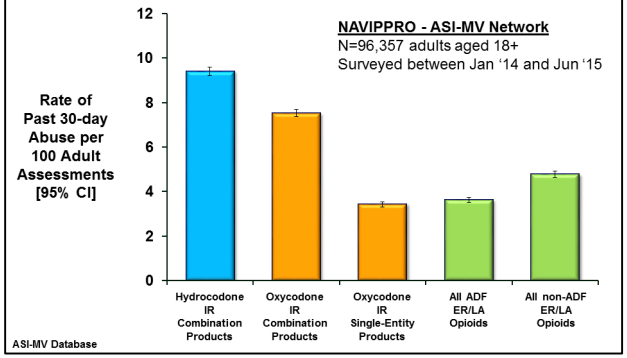
**Jeffrey Gudin, M.D.**
Director, Pain Management and Palliative Care
Englewood Hospital and Medical Center

Clinical Instructor, Anesthesiology
Icahn School of Medicine, Mt. Sinai

# Epidemiologic Data Illustrate the Need for Abuse-Deterrent Hydrocodone IR Combination

CO-17

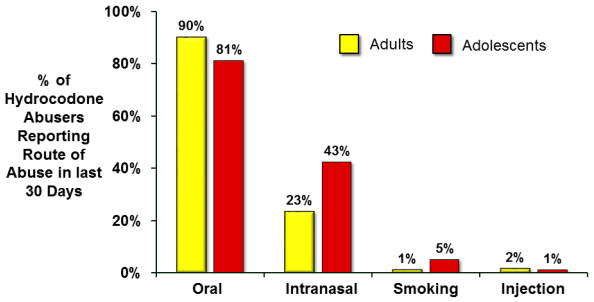
## Hydrocodone IR Combination Products Are Commonly Abused




ASI-MV Database

CO-18

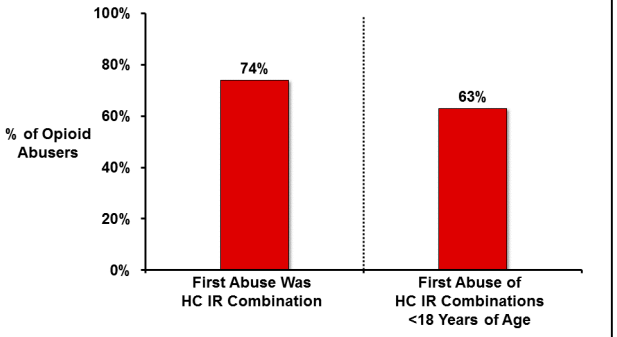
## Prevalence of Abuse of Hydrocodone IR Combination Products by Route and Age




ASI-MV Database (Jan 12 – Jun 15; N=9,064)
CHAT Database (Jan 12 – Jun 15; N=468)

CO-19

## Hydrocodone IR Combinations are Often the First Opioid Abused by Young People




2015 Inflexxion Internet Survey (N=472)

CO-15

## Goal: Prevention of Progression from Oral Route to More Dangerous Routes of Administration

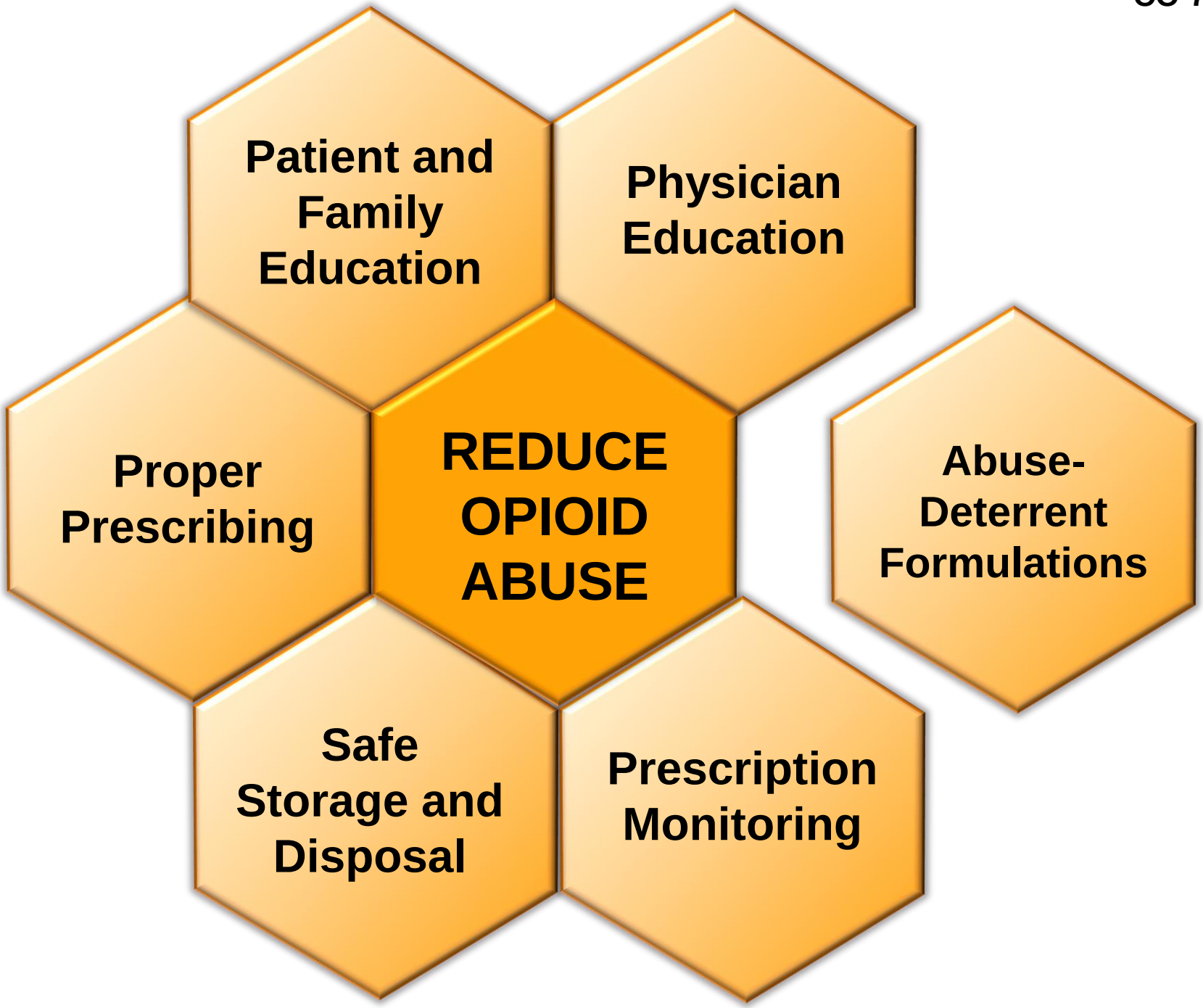

- Abusers progress to more dangerous routes as:
  - Opioid tolerance develops
  - Cost to maintain abuse patterns increases

# Apadaz: First Abuse-Deterrent Hydrocodone IR Combination Product

| | |
|---|---|
| **Physical/ Chemical Manipulations** | • **Prodrug: No impact of physical tampering on release**<br>• **Prodrug is very difficult to chemically manipulate** |
| **Smoking** | • **Apadaz cannot be smoked/vaporized to release HC** |
| **IV injection** | • **Extraction for injection is inefficient and expensive**<br>• **Slow conversion of inactive prodrug to HC in blood** |
| **Intranasal** | **<u>When Crushed and Snorted:</u>**<br>• **Abusers don't get more rapid exposure or faster highs**<br>• **No advantage over oral administration**<br>• **More nasal AEs, harder to snort**<br>**<u>When Crushed, APAP Extracted, and Snorted:</u>**<br>• **Extraction yields ½ as much API compared to Norco**<br>• **Lower exposures and Drug Liking vs. Norco API**<br>• **Harder to snort** |

# Apadaz Bioequivalent to Hydrocodone IR Combination Products; No Additional Risk

- Similar hydrocodone, hydromorphone and acetaminophen exposures to currently marketed products when taken as intended
- No clinically significant effect of food
- Safety of Apadaz in patients would be similar to existing products
  - No systemic exposure to prodrug
  - Ligand (benzoic acid) is naturally-occurring in berries


Patient and Family Education
Physician Education
Proper Prescribing
REDUCE OPIOID ABUSE
Abuse-Deterrent Formulations
Safe Storage and Disposal
Prescription Monitoring

# Apadaz™ (immediate-release benzhydrocodone with acetaminophen) for the Treatment of Acute Pain

**May 5, 2016**

KemPharm, Inc.

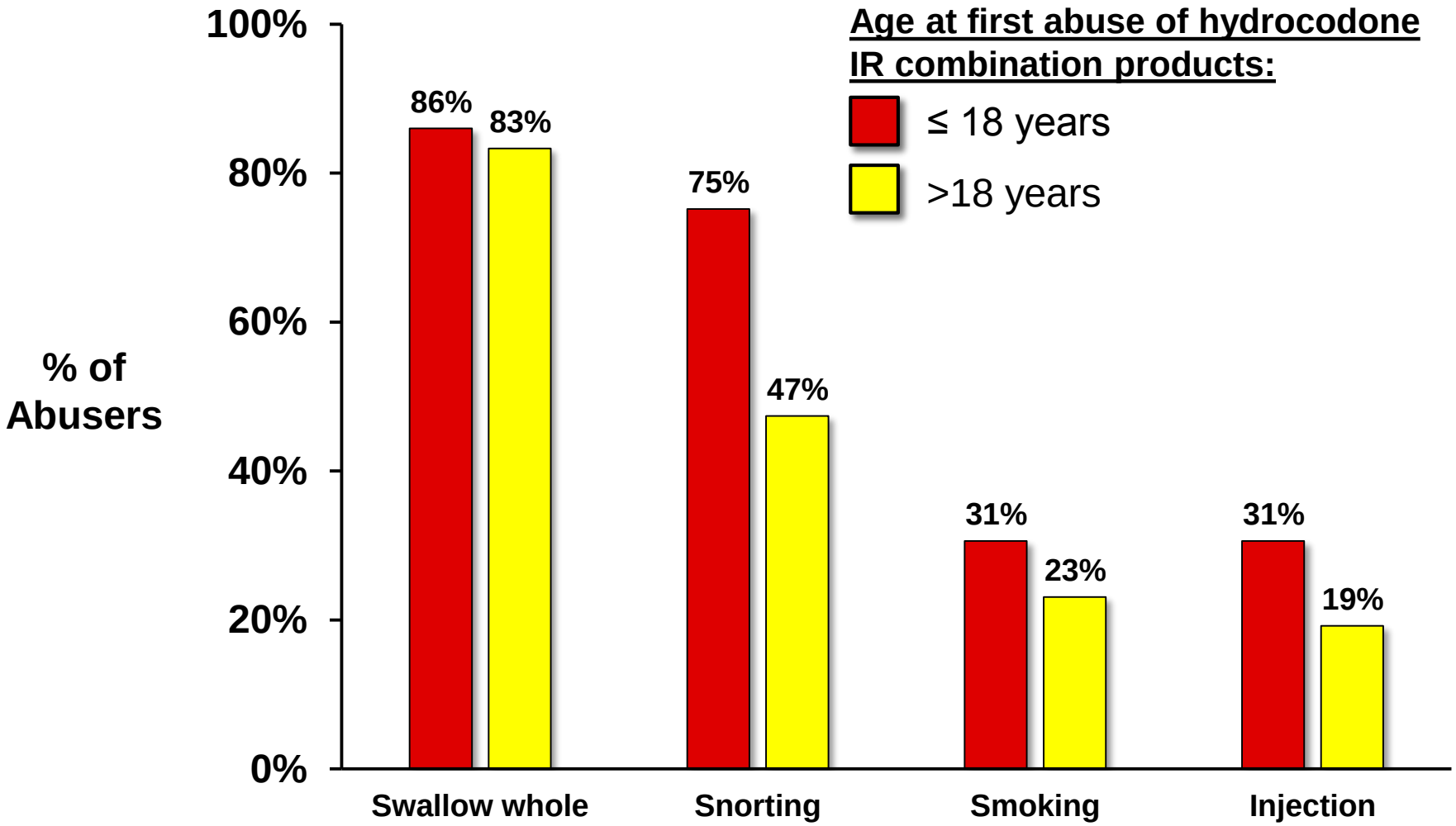
Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

# Backup Slides Shown

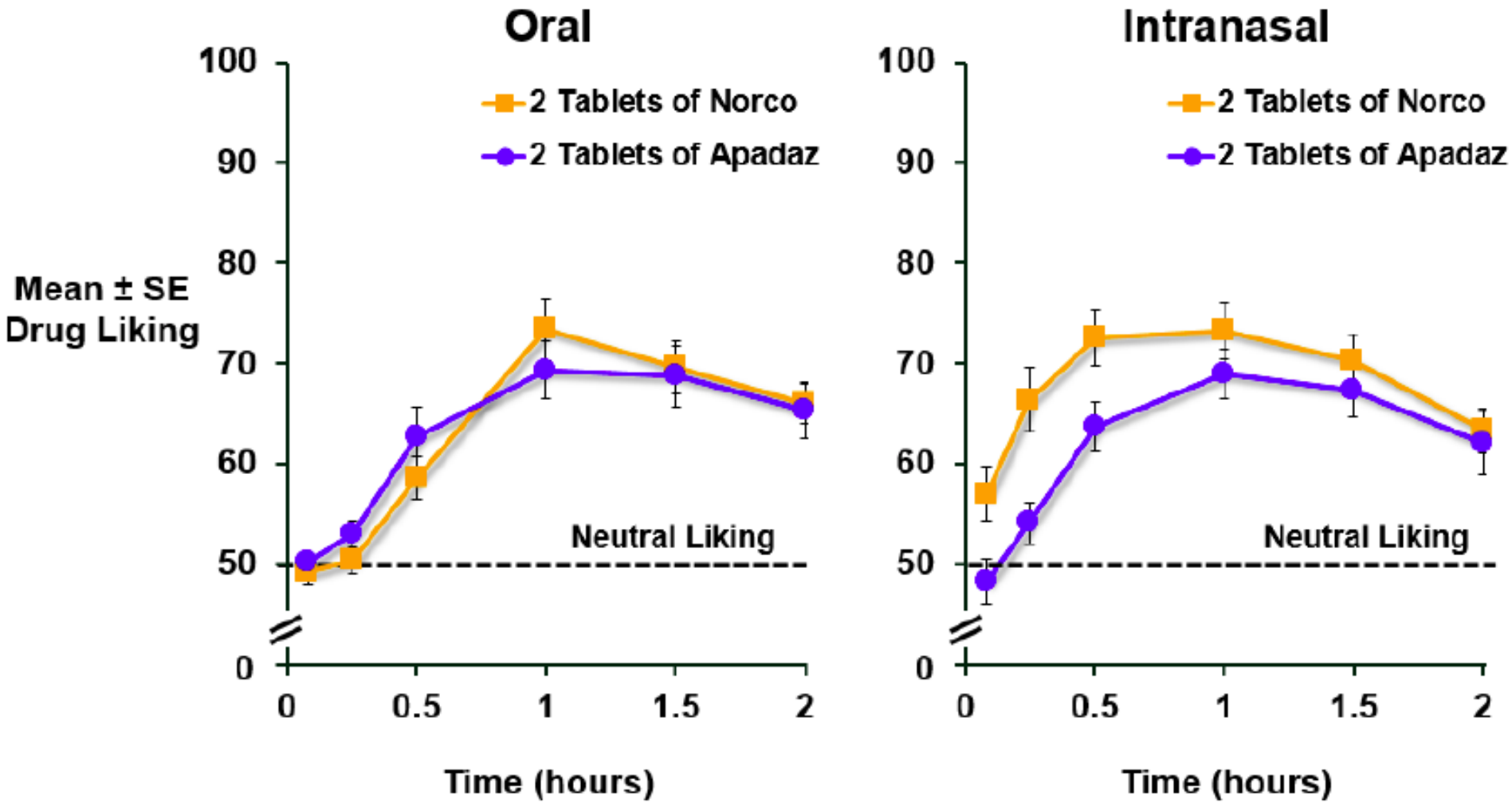
# Drug Liking
# Study A02

| | Intranasal | | | | Oral | | | |
|---|---|---|---|---|---|---|---|---|
| | Apadaz | | Norco | | Apadaz | | Norco | |
| Parameter | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| $AUE_{0-0.5}$ | 30.2 | 6.3 | 36.1 | 8.9 | 30.8 | 3.9 | 28.2 | 4.6 |
| P-value | <0.0001 | | | | 0.1244 | | | |
| $AUE_{0-1}$ | 63.5 | 12.6 | 72.6 | 16.4 | 63.7 | 11.7 | 62.3 | 11.6 |
| P-value | <0.0001 | | | | 0.4689 | | | |
| $AUE_{0-2}$ | 129.8 | 26.6 | 141.8 | 30.3 | 131.7 | 26.3 | 131.9 | 25.1 |
| P-value | 0.0079 | | | | 0.9896 | | | |
| $AUE_{0-4}$ | 249.6 | 53.3 | 262.3 | 51.8 | 249.5 | 47.5 | 251.5 | 41.2 |
| P-value | 0.1219 | | | | 0.8270 | | | |
| $AUE_{0-8}$ | 467.0 | 83.2 | 477.0 | 77.6 | 456.2 | 70.2 | 459.6 | 71.9 |
| P-value | 0.4112 | | | | 0.7991 | | | |
| $AUE_{0-24}$ | 1294 | 187.0 | 1281 | 198.6 | 1264 | 83.1 | 1263 | 127.2 |
| P-value | 0.5847 | | | | 0.9610 | | | |

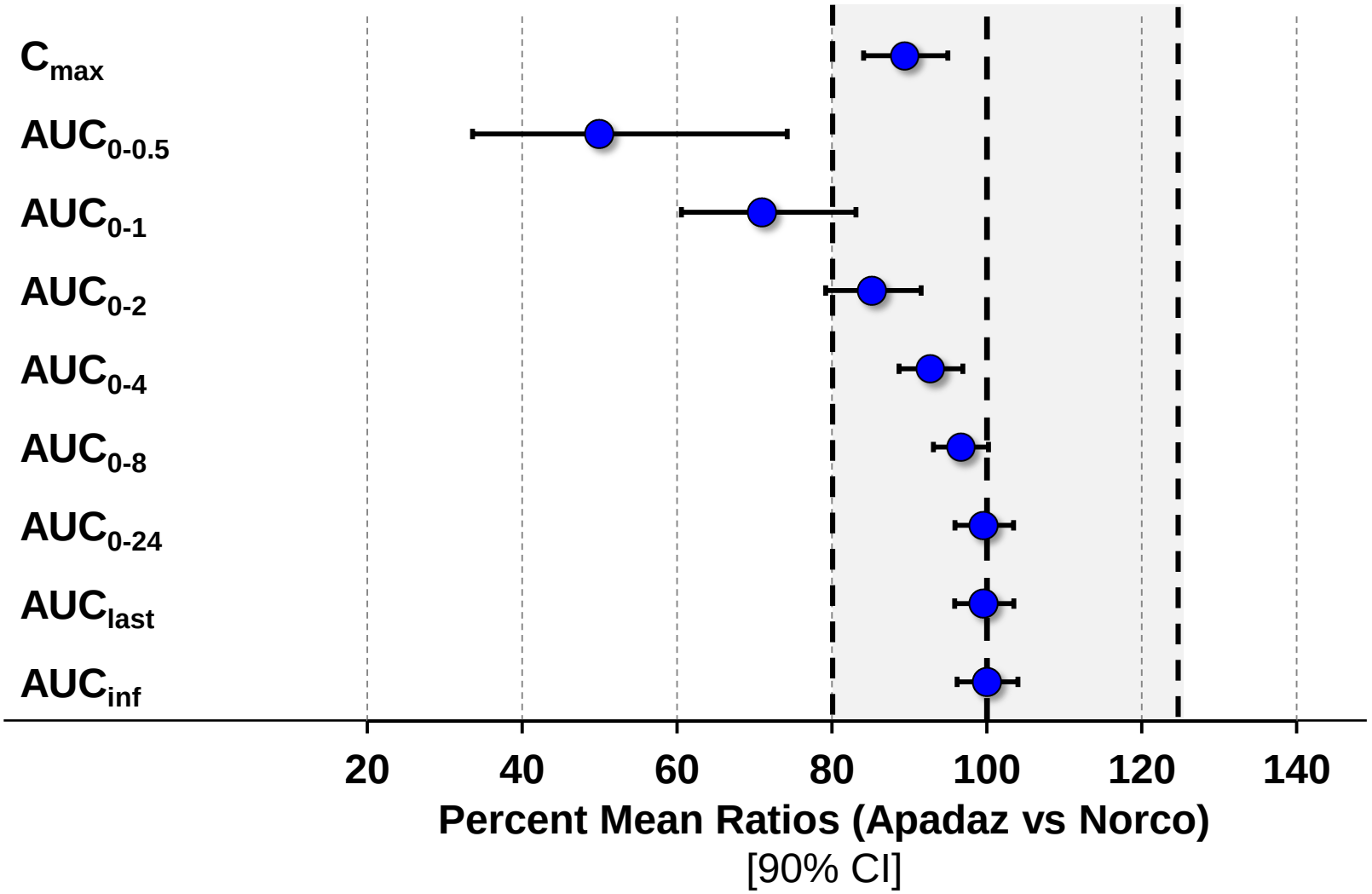
# Earlier Exposure to Abuse of Hydrocodone IR Combination Products Associated with Non-Oral Routes of Abuse



# Figure 25: Mean Drug Liking in First Two Hours of Study A02



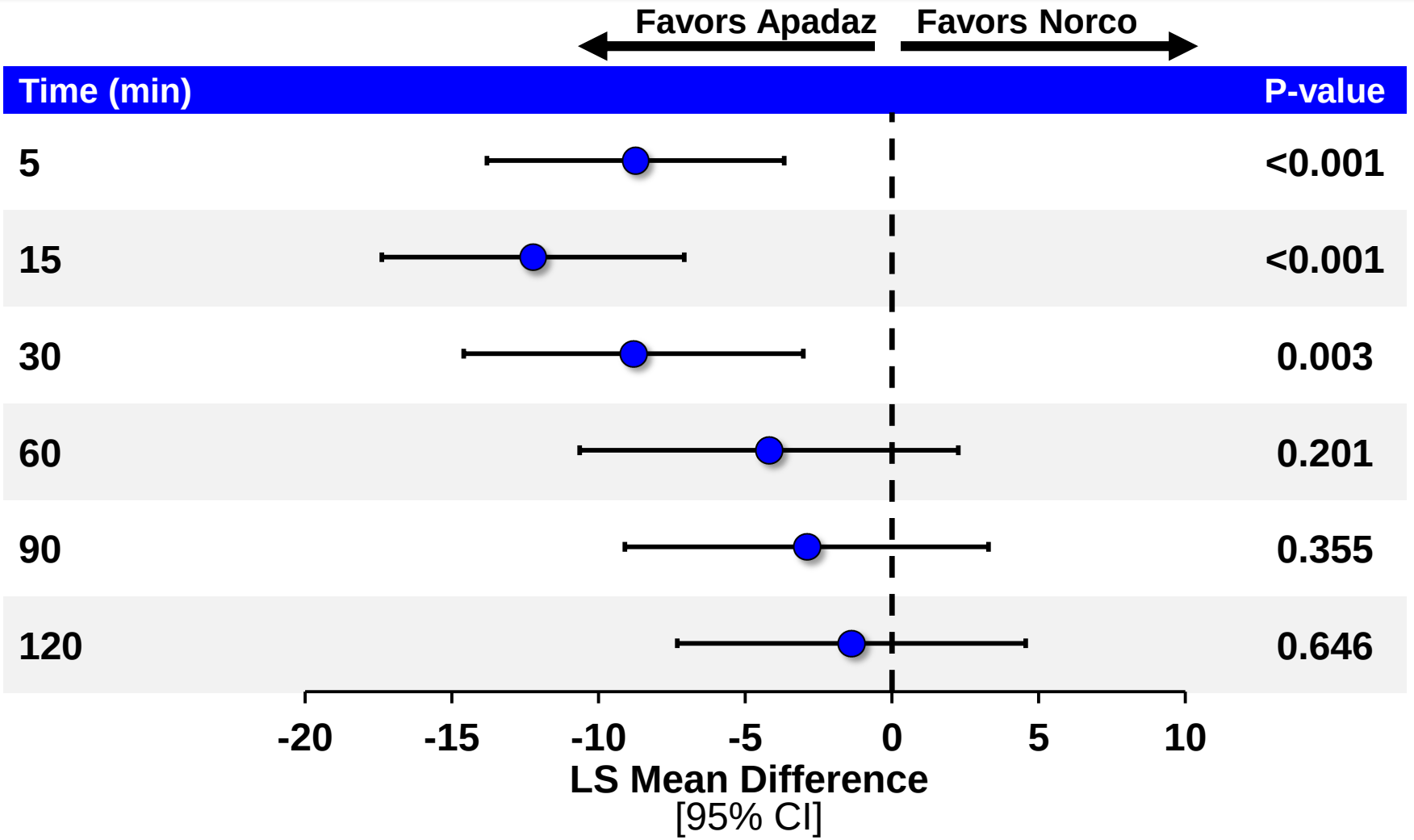
# Lower Early HC Exposure with Apadaz with Intranasal Administration




Category 2

Study A02: Intranasal HAP Study (N=42)

# Significantly Lower Drug Liking for Intranasal Administration of Apadaz vs. Norco at Early Time Points




Study A02: Intranasal HAP Study (N=42)

# Enzyme Hydrolysis Study of Benzhydrocodone

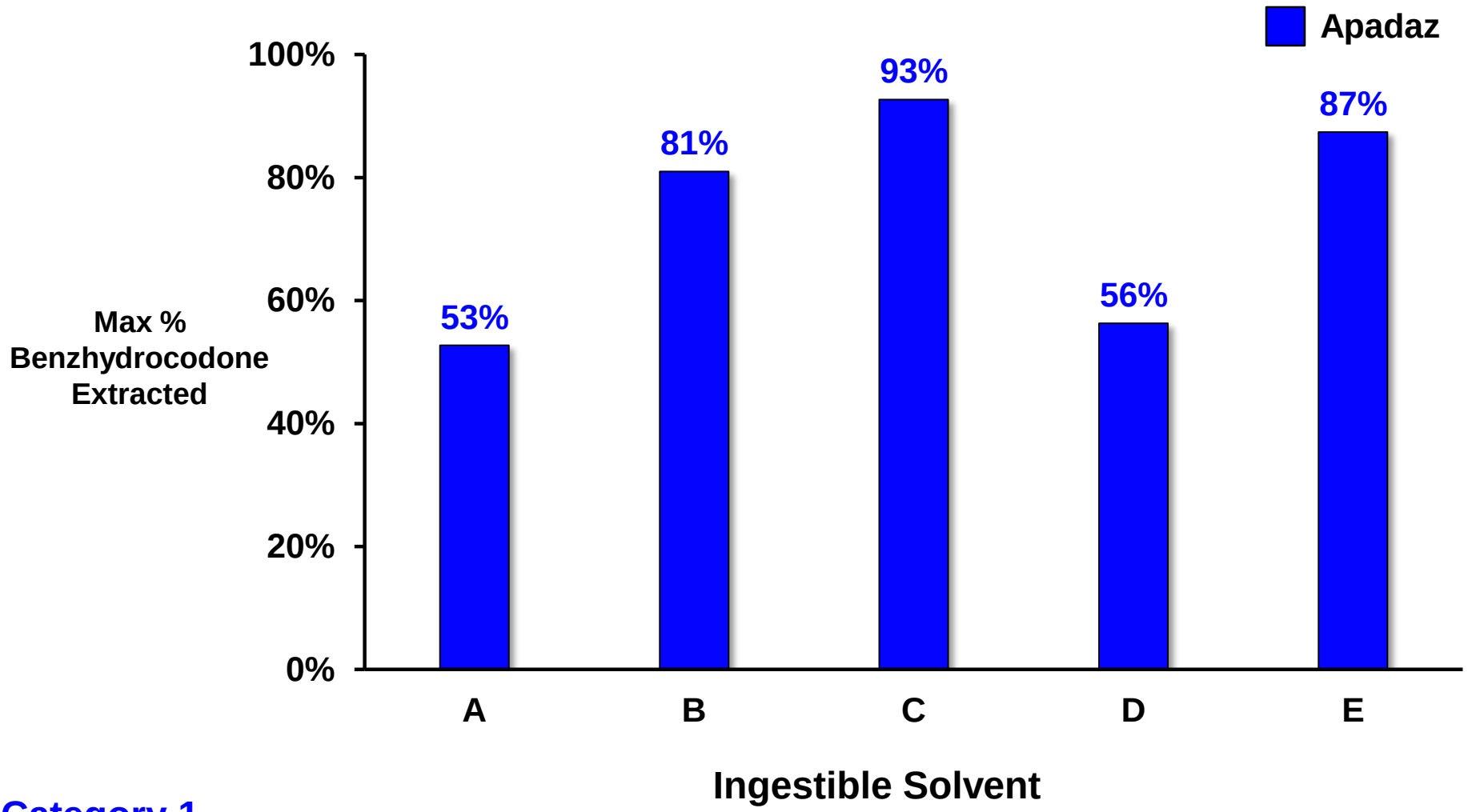
| Enzyme | %-Release of Hydrocodone After 2 Hours |
|---|---|
| α-Chymotrypsin | 0% |
| Amylase | 0% |
| Bromelain | 0% |
| Esterases | 100% |
| Papain | 0% |
| Pepsin | 0% |
| Protease | 0% |
| Trypsin | 0% |
| Commercial Digestive Enzyme Cocktail | 0% |

Data Not Reviewed by FDA

# Coefficient of Variation for PK Parameters for All PK Studies with Therapeutic Doses

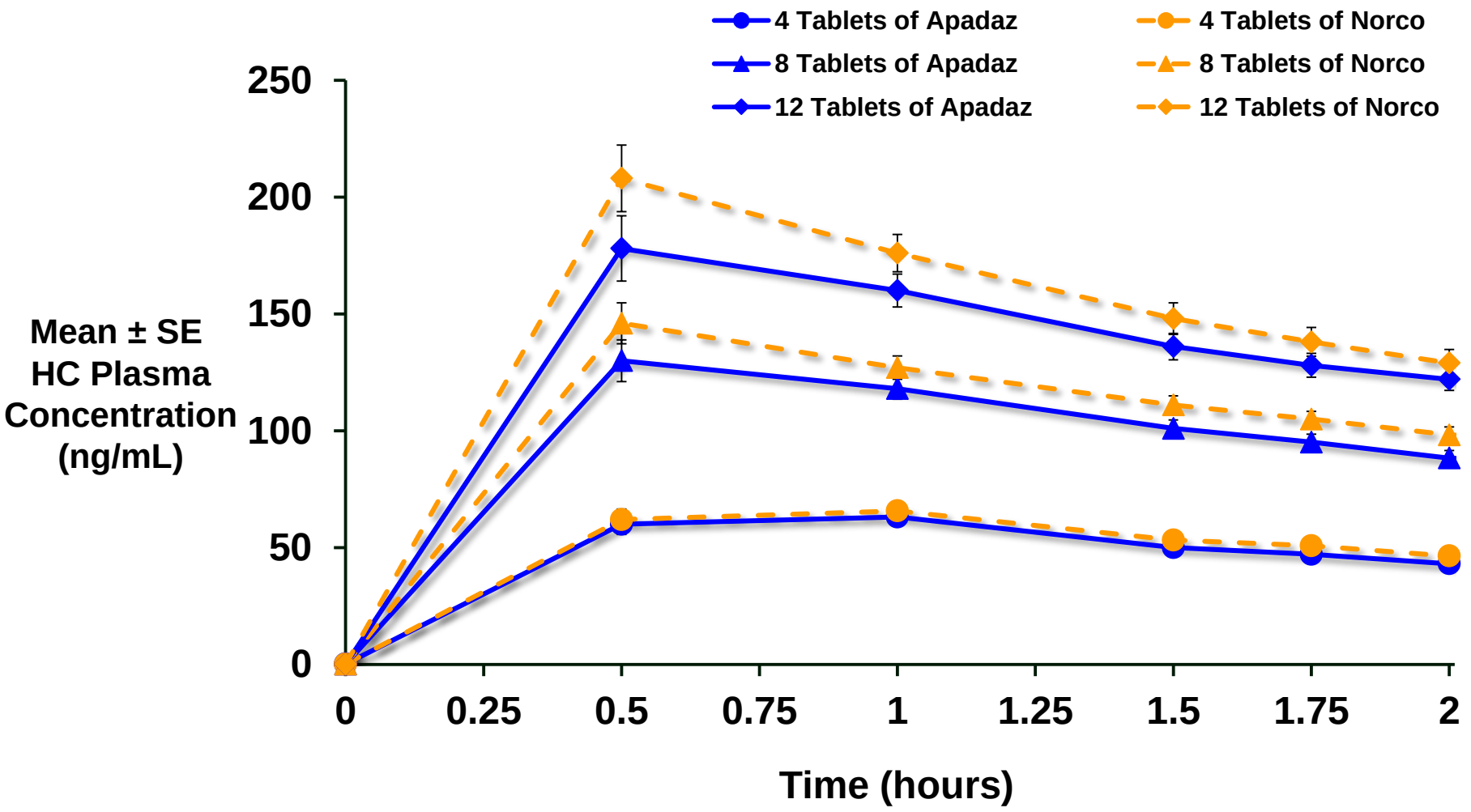
| Study | Drug | $C_{max}$ | $AUC_{last}$ |
|---|---|---|---|
| 101 | KP201 (1x5 mg) | 29.97 | 24.6 |
| 101 | KP201 (2x5 mg) | 26.04 | 25.6 |
| 101 | Norco (10 mg) | 31.55 | 26.43 |
| 102 | Apadaz | 24.63 | 25.67 |
| 102 | Norco | 25.24 | 26.36 |
| 103 | Apadaz (Day 1) | 24.77 | 24.8 |
| 103 | Apadaz (Day 4) | 23.49 | 27.42 |
| 104 | Apadaz (fasted) | 25.24 | 28.98 |
| 104 | Apadaz (fed) | 22.49 | 21.38 |
| 104 | Norco (fed) | 36.49 | 22.38 |
| 105 | Apadaz | 21.02 | 25.79 |
| 105 | Vicoprofen | 18.11 | 20.02 |
| 106 | Apadaz | 28.33 | 24.61 |

# Extraction of Hydrocodone from Apadaz Was Ineffective with Ingestible Solvents




Category 1

# Hydrocodone Exposures at Supratherapeutic Doses Similar Between Products




Category 2

Study A01: Oral HAP Study (N=62)

# Benzoic Acid Is Safe for Injection

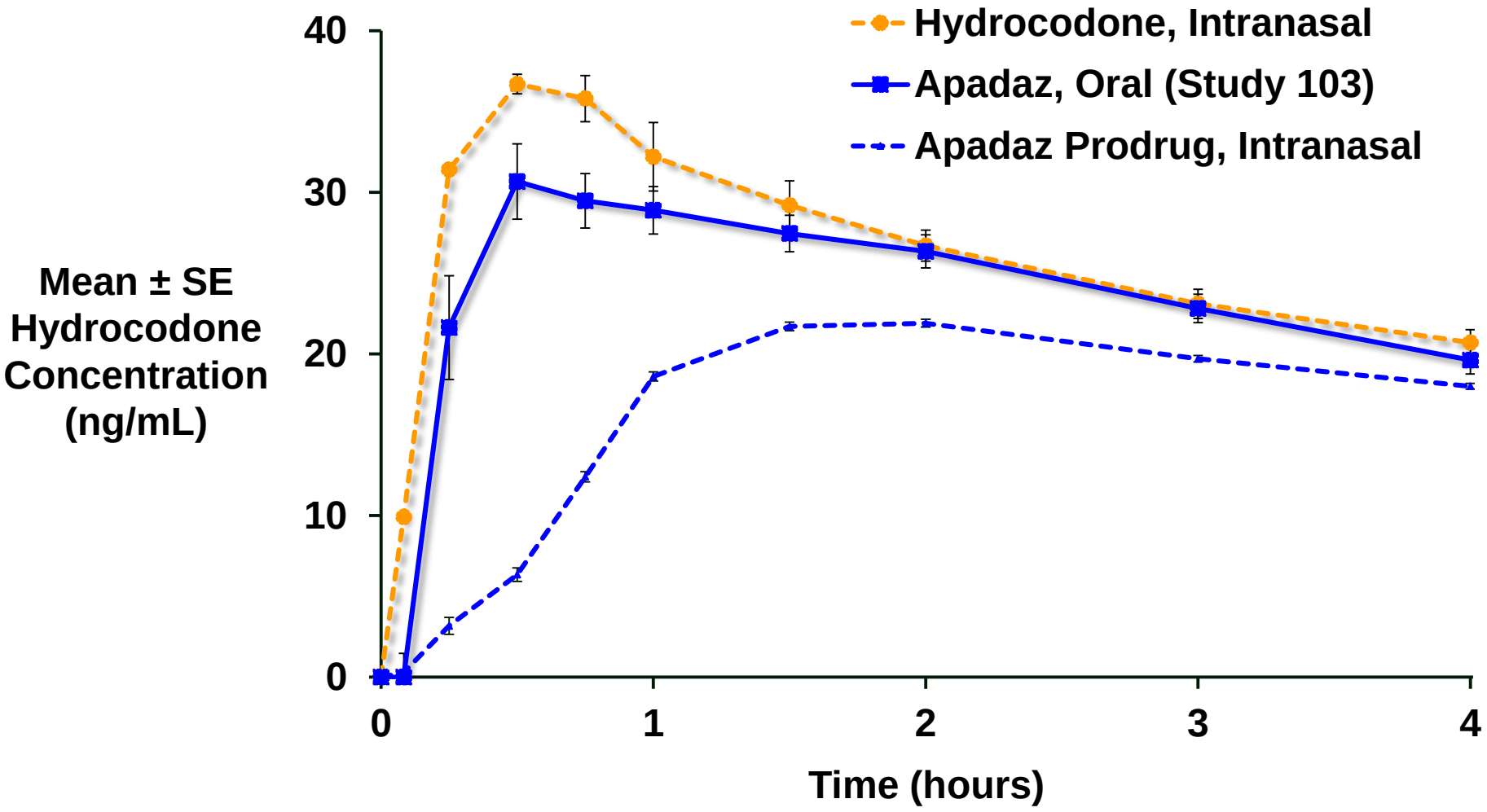
- Ammonul® (sodium phenylacetate and sodium benzoate [BzONa]) for acute hyperammonemia in adult and pediatric patients (250 mg/kg of BzONa in loading phase)
- Used as preservative in some drug injections (e.g., Diazepam Injection, USP)

# Benzoic Acid in Benzhydrocodone

- 27.7% of benzhydrocodone mass is benzoic acid
- 1.85 mg of benzoic acid per tablet
- Naturally occurs in berries and some fruits
- 1 cup of cranberries contains about 50 mg benzoic acid[1]
- Used as preservative in fruit juice, soda, salad dressing, etc.
- 75–100% of oral doses up to 160 mg/kg excreted as hippuric acid within 6 hours(2)
- Estimated intake of benzoic acid in U.S.[2]
  - Average consumer: 161 mg/day/day
  - High consumers: 511 mg

**1. Clague JA, Fellers CR. Relation of Benzoic Acid Content and Other Constituents of Cranberries to Keeping Quality. Plant Physiol. 1934;9(3):631-636.**
**2. Concise International Chemical Assessment Document (CICADS 26, 2000): Benzoic Acid and Sodium Benzoate**

# Intranasal Administration of Apadaz Prodrug Leads to Lower HC Release




Category 2

Study A03: Intranasal Study of APIs (N=24)

# Clarification of Sponsor Solvent X and FDA Solvent G

**Sponsor Solvent X**

- Advanced buffer
- 4 hours under stress conditions to extract 60% hydrocodone
- Stress +/- 4 hours reduced percent extracted
- Turned black in color
- FDA banned as food additive

**FDA Solvent G**

- Advanced laboratory equipment required to maintain stress temperature
- 3 hours under stress condition #2 required for effective hydrolysis