In Vitro Abuse Deterrent Studies

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

KP201/APAP

May 5, 2016

Overview

- This presentation will focus on interpretation of **key data from a subset of in vitro studies** carried out to evaluate the abuse deterrence of KP201.

- The goal is to give the AC an understanding of **open questions or potential liabilities** associated with the proposed ADF features of this product.

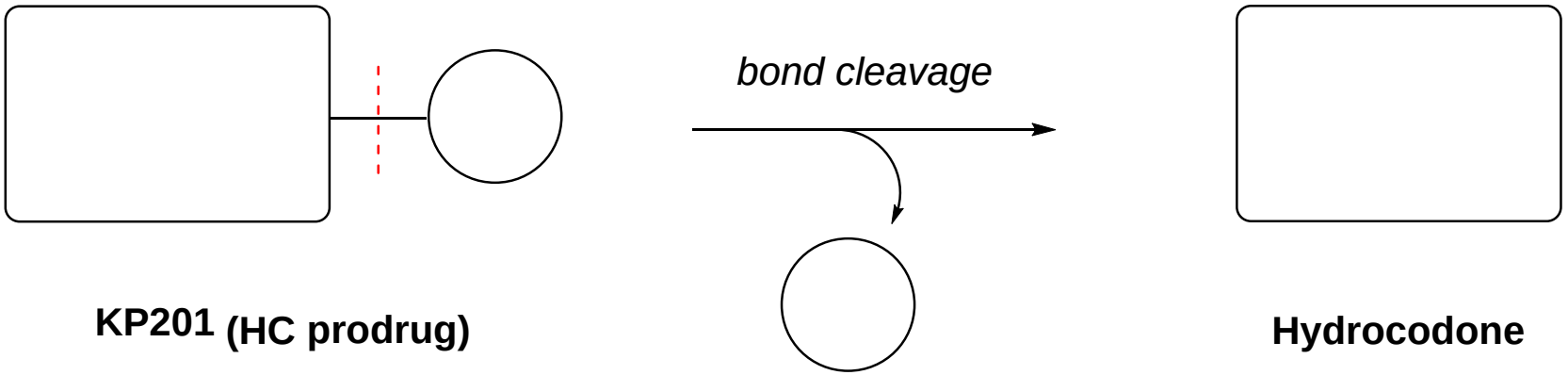
- Definitions:

  HB = hydrocodone bitartrate
  HC = hydrocodone
  KP201 = benzhydrocodone hydrochloride
  LV = large volume, ≥50 mL
  SV = small volume, ≥ 3 mL

Overview (cont.)

- Separation of APAP from KP201 during large volume (LV) extractions
- Hydrolysis of KP201 using simple, non-toxic conditions
- Solubility of KP201 vs. HB
- Similarity of extraction efficiency and low KP201/HC concentrations in solutions from small volume (SV) extractions of KP201/APAP and HB/APAP
- Similar volatility and low HC content from simulated smoking studies of KP201/APAP and HB/APAP

Proposed Mechanism of Abuse Deterrence



KP201 (HC prodrug)

- *Weak opioid receptor agonist*
- *Less soluble than hydrocodone*

Hydrocodone

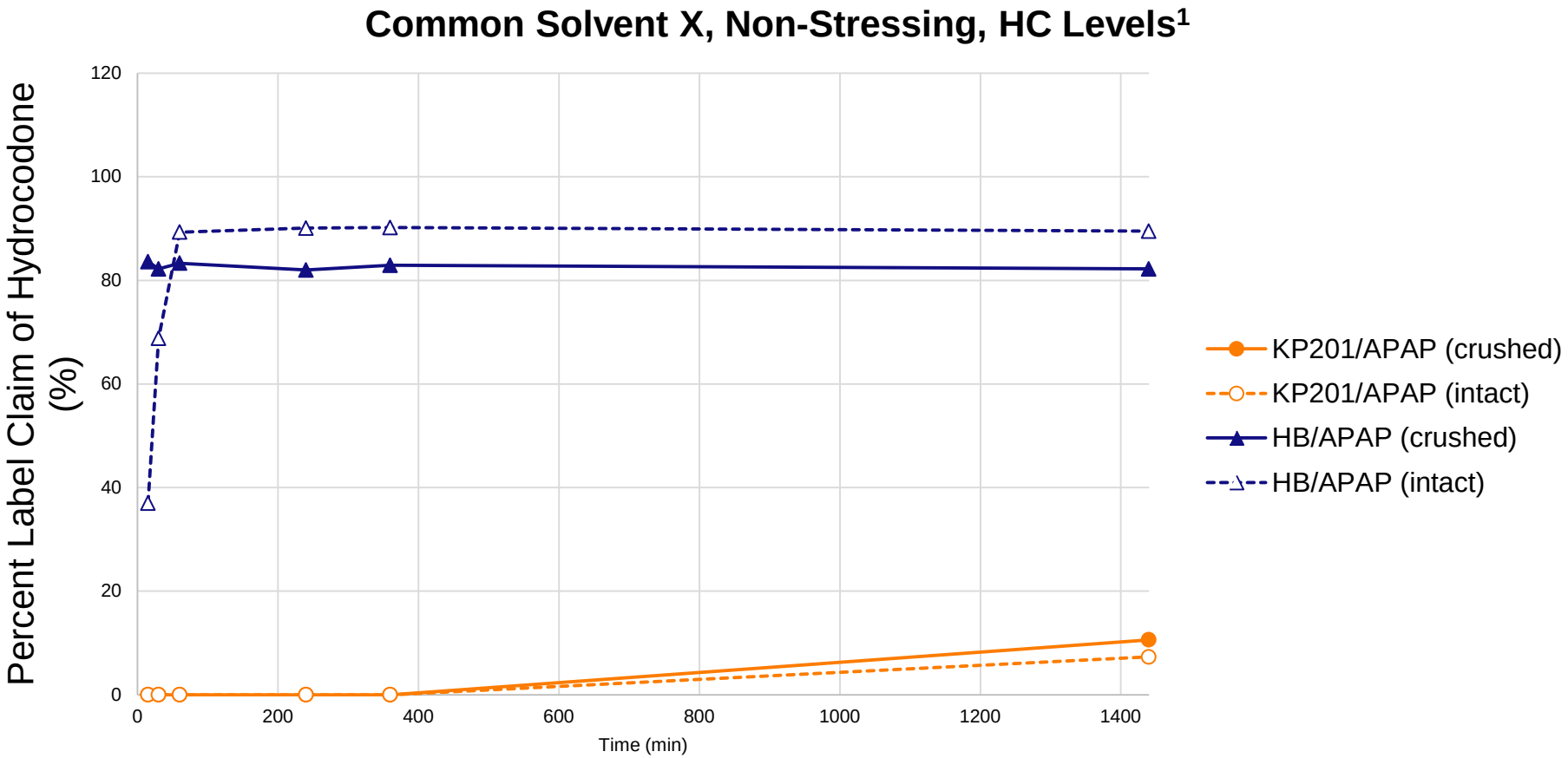
-Potent opioid receptor agonist
-Higher solubility than KP201

Physical Manipulation Studies

- No extensive crushing or grinding studies were carried out for this product since the formulation does not integrate abuse deterrent features.

- Particle size for crushed tablets used in extraction studies was determined and indicated that overall profiles are similar to the reference product.

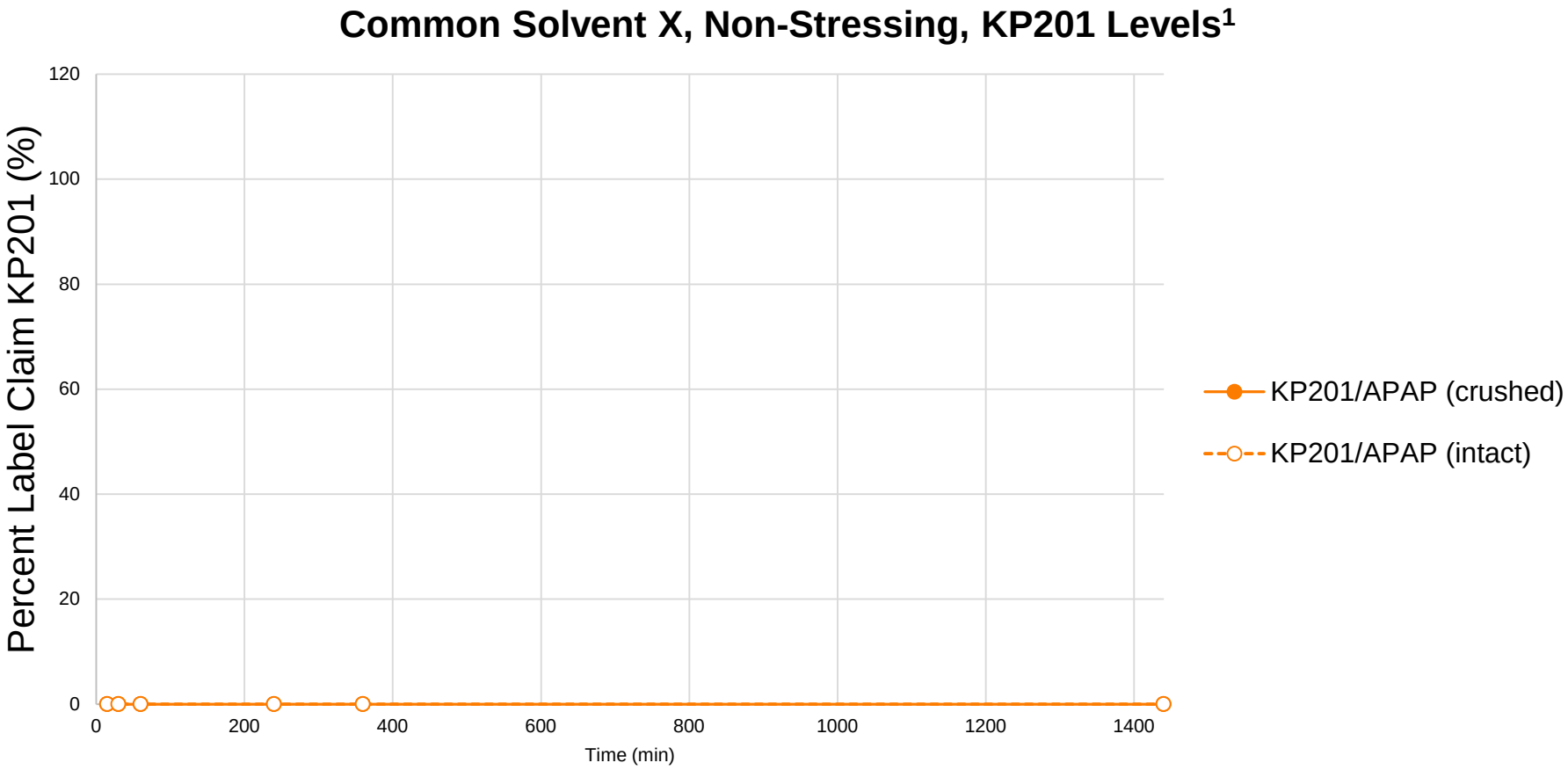
LV Study 1: APAP Can Be Extracted from KP201/APAP



- HC is rapidly extracted from HB/APAP tablets using common solvent X.
- Solvent X is safe, readily injectable/ingestible, and potentially highly relevant to IV use.

[1] Chart derived from material provided by Applicant in response to information request.

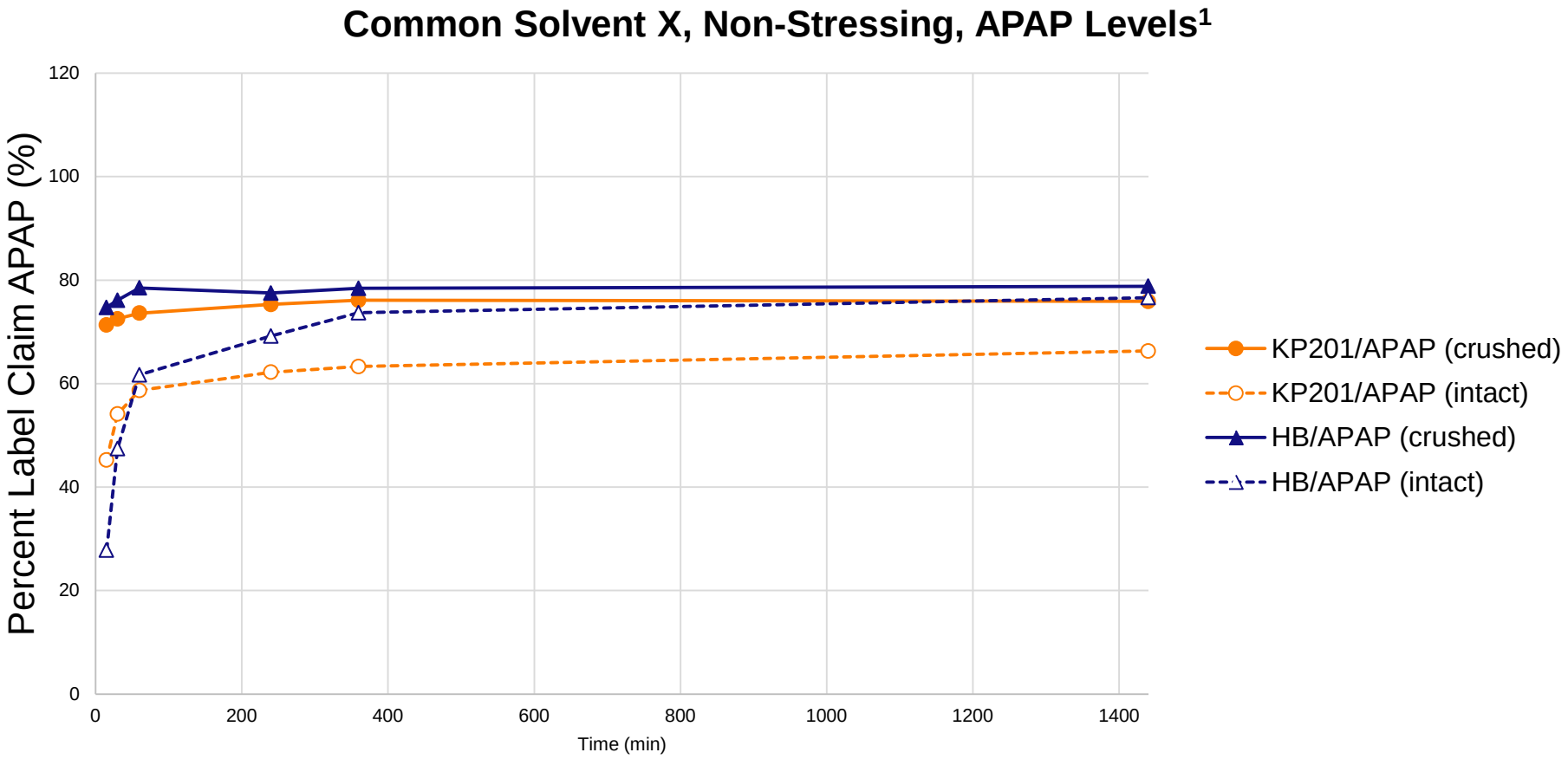
LV Study 1: APAP Can Be Extracted from KP201/APAP (cont.)



- KP201 is not extracted from KP201/APAP tablets using common solvent X.

[1] Chart derived from material provided by Applicant in response to information request.

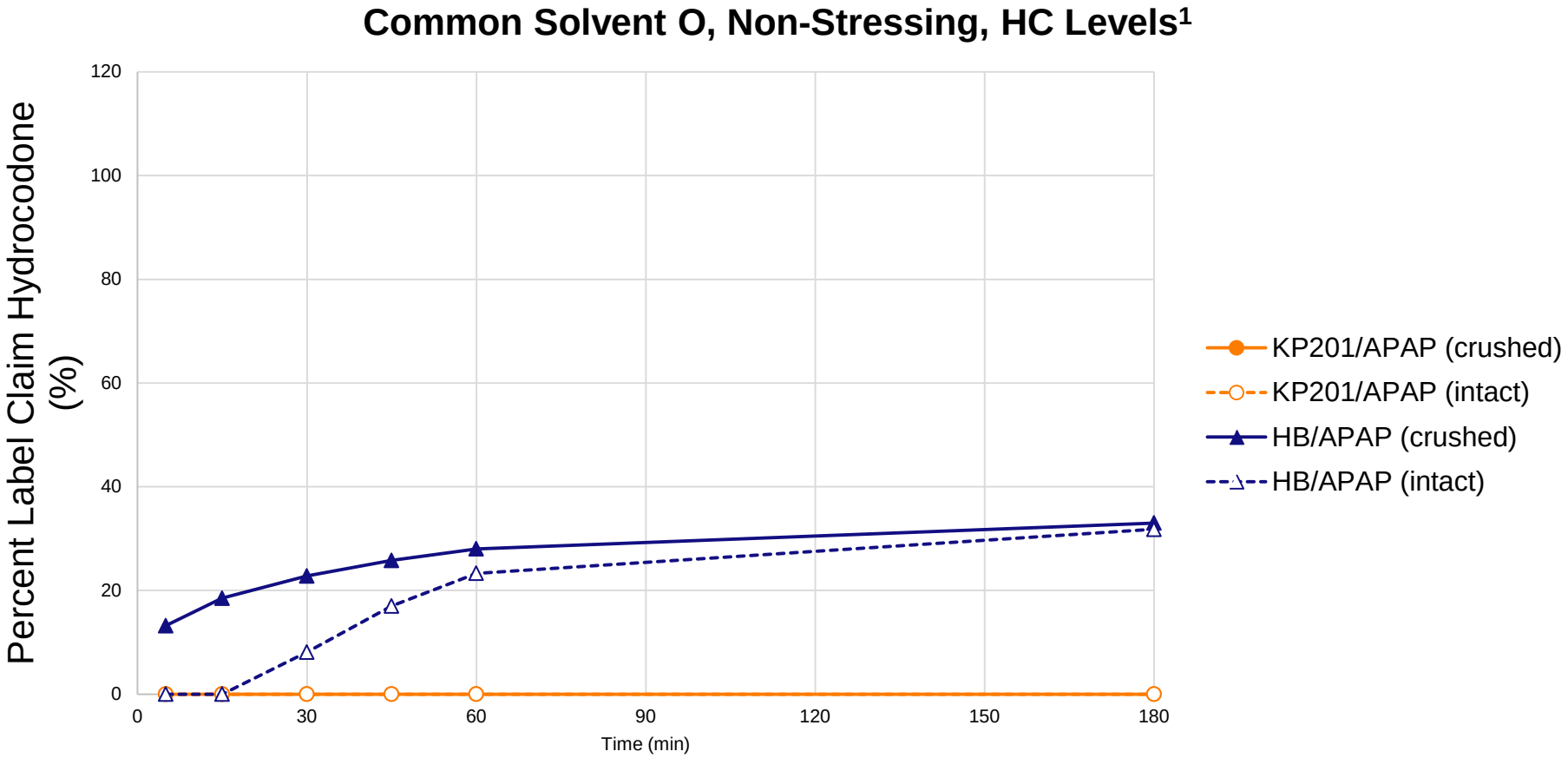
LV Study 1: APAP Can Be Extracted from KP201/APAP (cont.)



- APAP is extracted rapidly from both KP201/APAP and HB/APAP tablets using common solvent X.

[1] Chart derived from material provided by Applicant in response to information request.

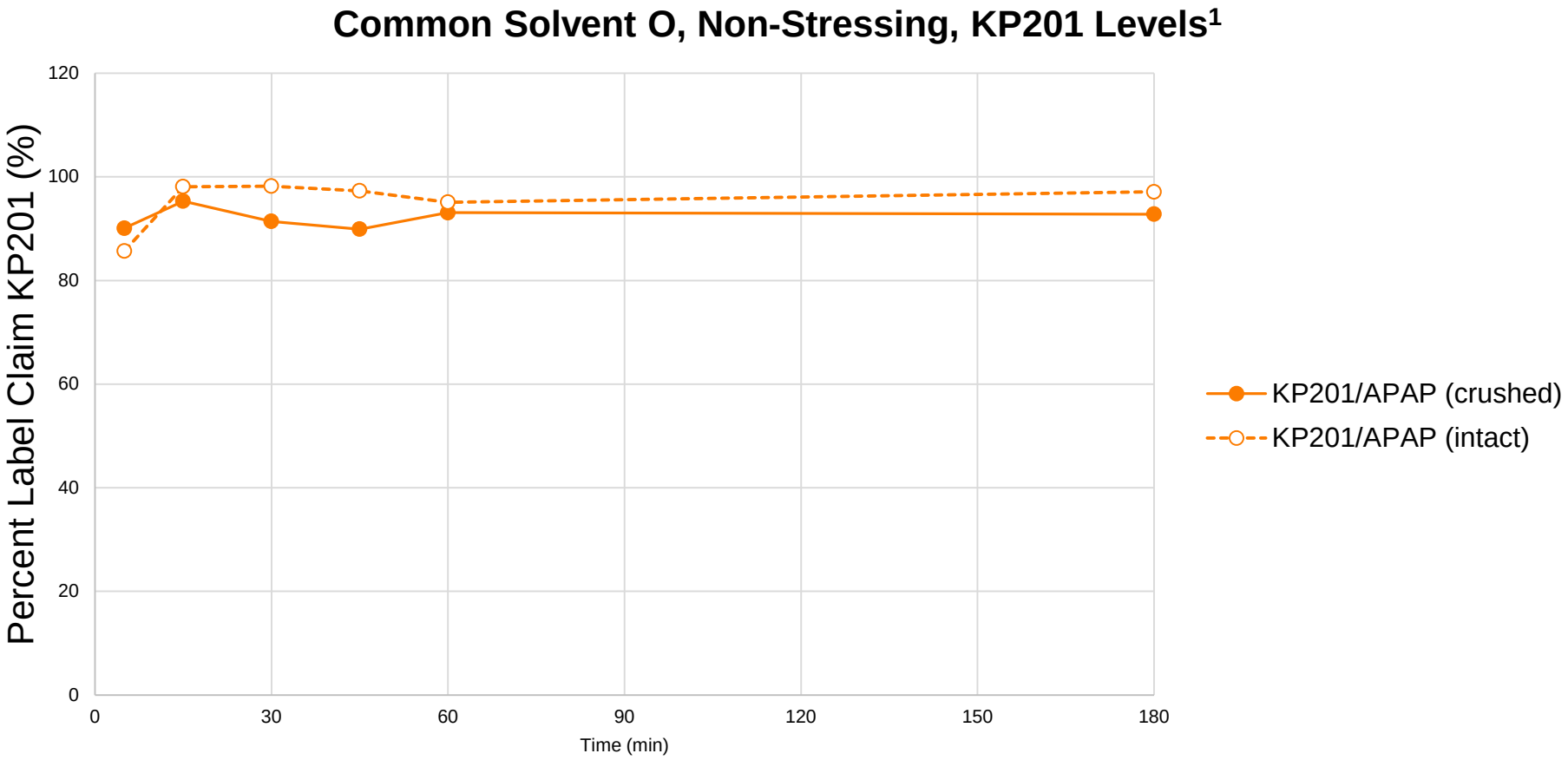
LV Study 2: KP201 Can Be Extracted from KP201/APAP



- HC is poorly extracted from HB/APAP tablets using common solvent O.
- Solvent O solutions must be evaporated and are not directly usable.

[1] Chart derived from material provided by Applicant in response to information request.

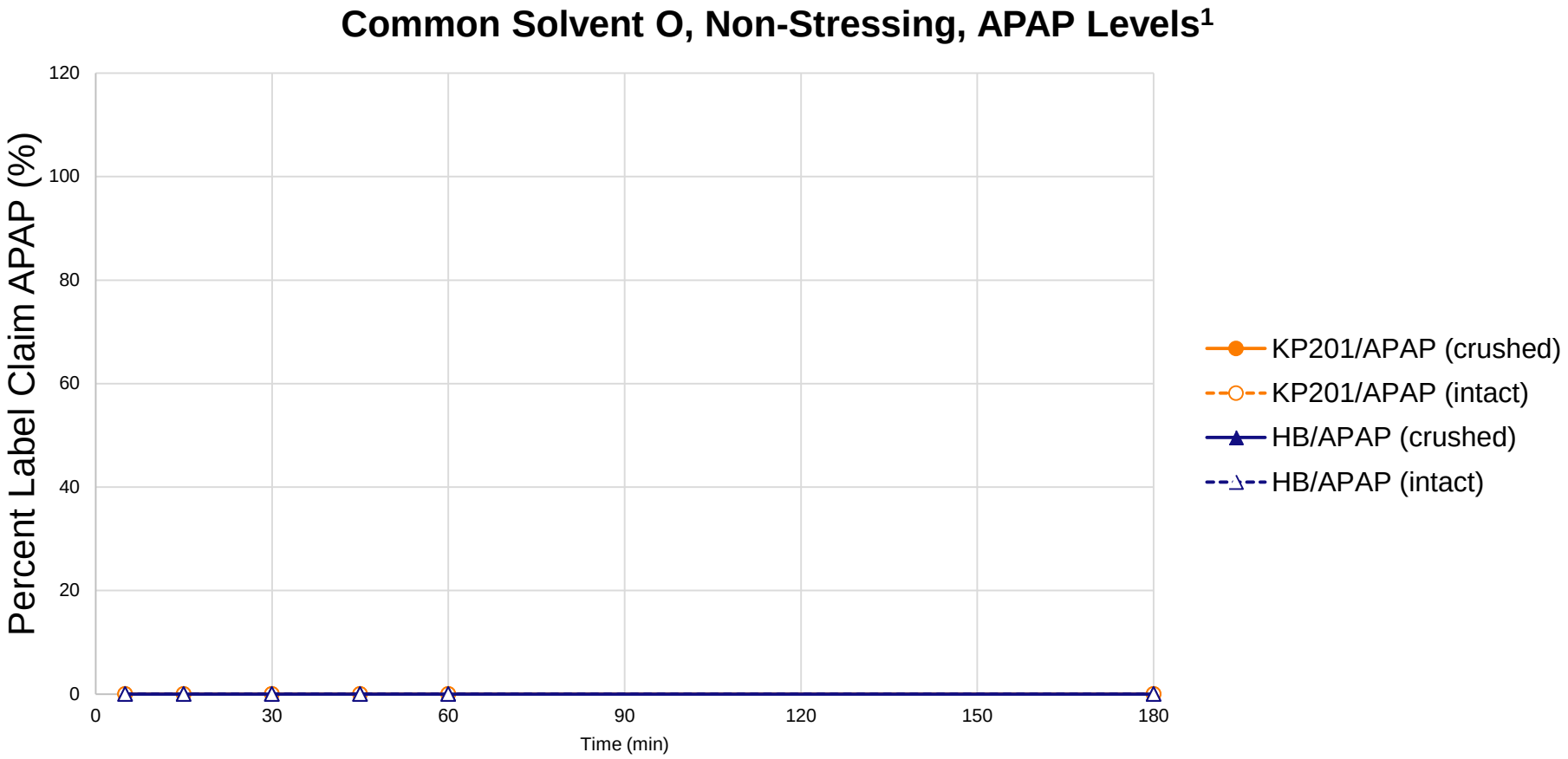
LV Study 2: KP201 Can Be Extracted from KP201/APAP (cont.)



- KP201 is rapidly extracted from KP201/APAP tablets using common solvent O.

[1] Chart derived from material provided by Applicant in response to information request.

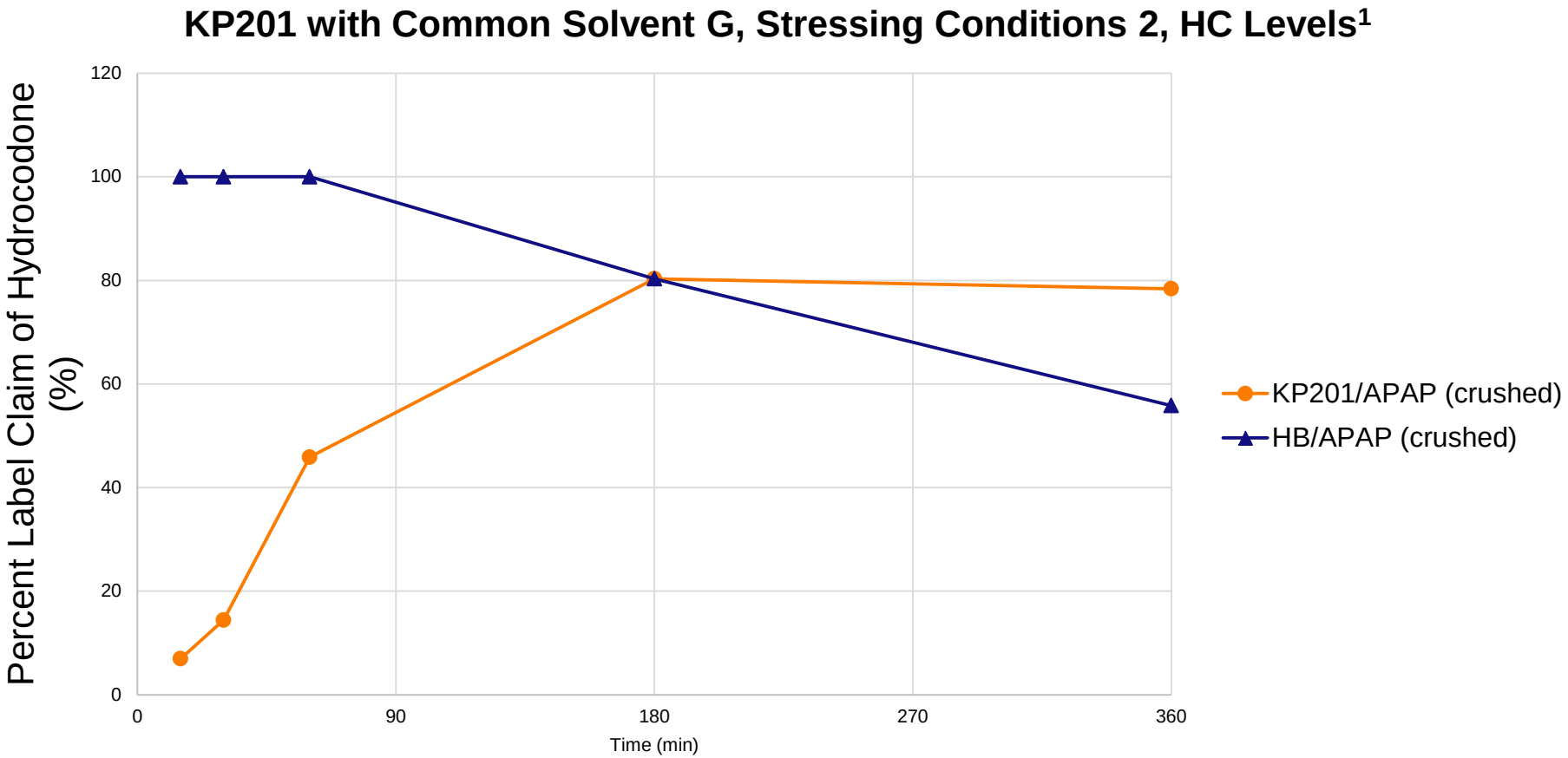
LV Study 2: KP201 Can Be Extracted from KP201/APAP (cont.)



- APAP is not extracted from KP201/APAP or HB/APAP tablets using common solvent O.

[1] Chart derived from material provided by Applicant in response to information request.

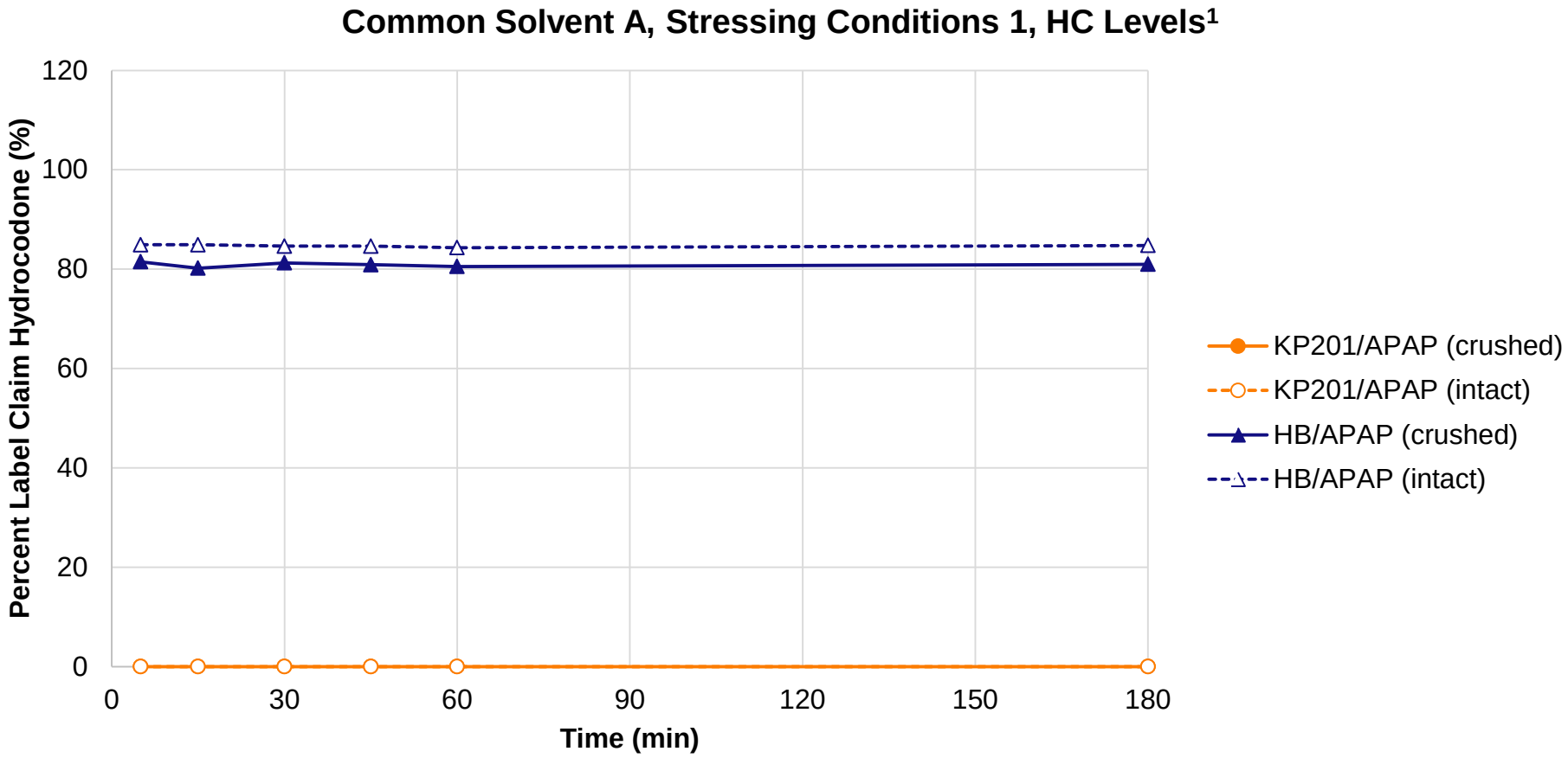
LV Extraction/Hydrolysis of KP201 Using Safe Conditions



- Solvent G and stressing conditions 2 (requested by FDA) are safe, readily injectable/ingestible, and potentially highly relevant to IV use.

[1] Chart derived from material provided by Applicant in response to information request.

Minor Condition Changes Can Lead to Hydrolysis During LV Extractions

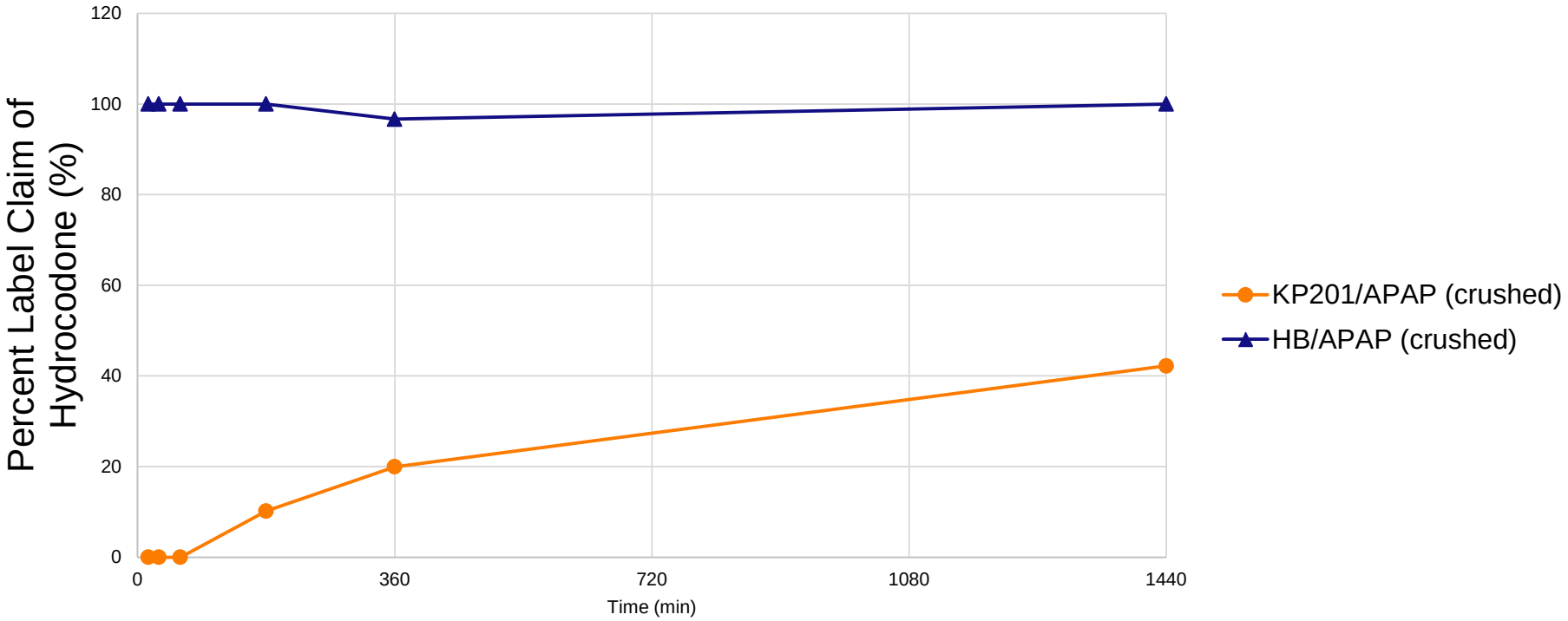


- Common solvent A and stressing conditions 1 do not cleave KP201 prodrug.

[1] Chart derived from material provided by Applicant in response to information request.

Minor Condition Changes Can Lead to Hydrolysis During LV Extractions

Common Solvent F, Stressing Conditions 2, HC Levels[1]



- Common solvent F (requested by FDA) is essentially identical to solvent A. Both solvents A&F are highly relevant, safe for ingestion/injection.
- Stressing conditions 2 (requested by FDA) and are slightly stronger than stressing conditions 1.

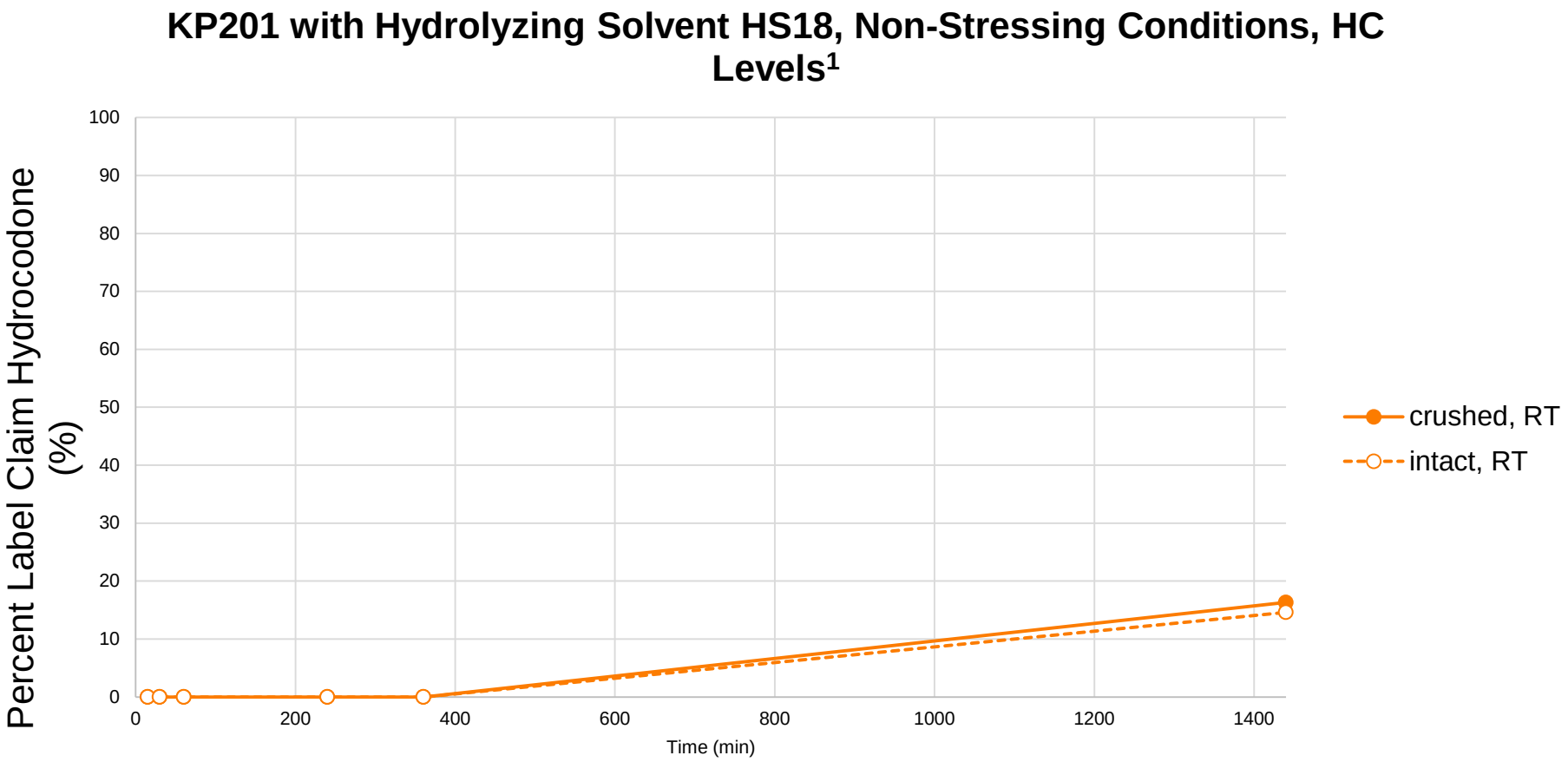
[1] Chart derived from material provided by Applicant in response to information request.

Reported Aq. Solubility of KP201

- ~140-270 mg/mL for HB vs. ~0.16-29 mg/mL for KP201 (higher solute concentrations).

- The solubility of KP201 is more variable than HB.

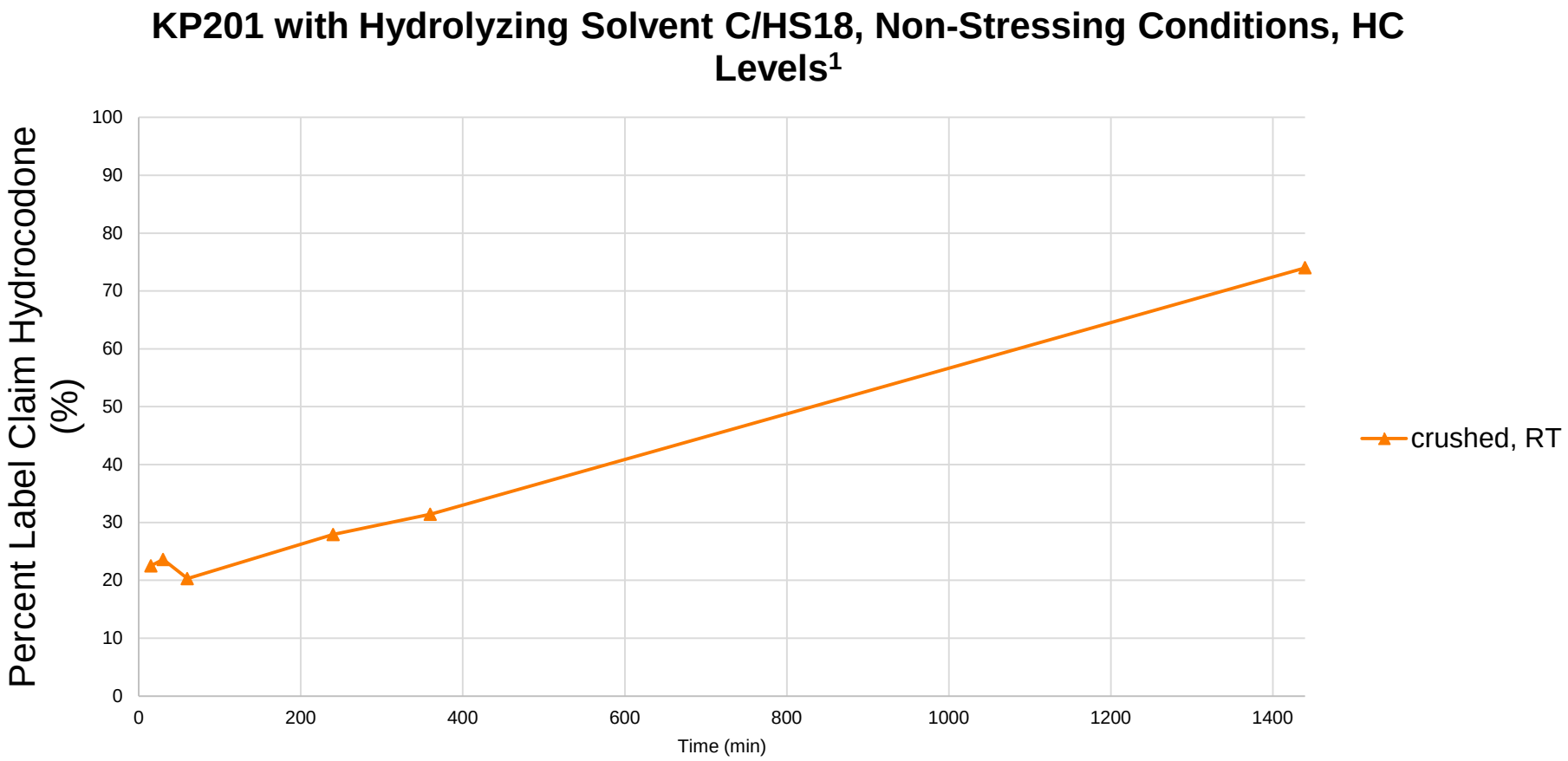
Solubility Effects on Hydrolysis



- HS18 only modestly effective for hydrolysis of KP201 under non-stressing conditions.

[1] Chart derived from material provided by Applicant in response to information request.

Solubility Effects on Hydrolysis



- In solvent C extracts, HS18 is far more effective for hydrolysis of KP201 – solubility?
- Both HS18 and solvent C are ingestible/injectable.

[1] Chart derived from material provided by Applicant in response to information request.

Similarity of Solutions Prepared by SV Extractions

- Several solvents/treatment conditions were grouped into two **classes** (1&2) based on a single common factor for the purposes of this analysis.

KP201/APAP[1]

Conditions	Label Claim of KP201 Extracted from KP201/APAP in 5 mL
1	71.6
1	69.8
1	66.2
1	64.6
1	59.4
1	59.4
1	58.2
1	57.9
1	54.9
2	24.2
2	16.5
2	12.6

HB/APAP[1]

Conditions	Label Claim of HC Extracted from HB/APAP in 5 mL
2	78.9
1	78.8
1	77.6
2	75.1
1	74.2
1	73.8
1	73.5
1	73.3
1	72
2	71.4
1	70
1	67.1

- Difference in % extraction between KP201/APAP and HB/APAP are not substantial.
- Differences appear mainly to be a solvent class effect (low KP201 solubility under 2).
- No HC was released from KP201; stressing conditions were mild in this case.

[1] Table derived from material provided by Applicant in NDA.

Injectability and Low Drug Concentrations of SV Extracts

- Syringeability of KP201/APAP or HB/APAP IV extracts were comparable (by glide force analysis).
- Optimized injectable solutions prepared by the Applicant required multiple steps and resulted in solutions with low KP201 (0.22-2.6 mg/mL) or HC (2.9-3.6 mg/mL) concentrations. The extent to which drug abusers might use such procedures or inject multiple milliliters (3 – 4 or more) of solution are unknown.
- Injectable extracts of KP201/APAP did not exhibit any significant difference in precipitation risk when compared to HB/APAP when simulated in vitro IV delivery studies (blood, plasma) were performed.

Comparability of and Low Drug Concentrations Resulting From Simulated Smoking Studies

Sample[1]	KP201 (% Label Claim)	HC (% Label Claim)	APAP (% Label Claim)
HC base	ND	26.3	ND
HB	ND	9.4	ND
HB/APAP tablet	ND	4.7	ALQ (>27.4%)
KP201 base	24.6	BLQ (<0.8%)	ND
KP 201 HCl	4.5	BLQ (<0.9%)	ND
KP201/APAP tablet	2.4	BLQ (<1.4%)	10.2

ND = none detected

- KP201 and HC appear to have similar volatility (24.6% vs 26.3% for free bases).
- No HC observed from KP201/APAP vaporization but LOQ only 1.4%.
- Very low levels of HC observed from RLD (4.7% or about 0.22 mg).

[1] Table derived from material provided by Applicant in NDA.

Conclusions

- KP201 **may be more efficiently separated from APAP** using some common conditions when compared to HB/APAP.

- **Mild, safe, and relevant conditions exist for hydrolysis KP201 to HC.** Optimization of these conditions may require abuser experimentation or longer processing times.

- The low solubility of KP201 may help to reduce the rate of hydrolysis under certain conditions. **This advantage may be limited** based on use of certain safe and highly relevant solvents.

Conclusions (cont.)

- In general, prepared IV injectable solutions of KP201 and HC have **comparable concentrations.** Extraction efficiency for KP201 may be reduced with certain classes of solvents. The KP201 (from KP201/APAP) or HC (from HB/APAP reference product) **concentrations in such solutions are low even when using optimized procedures.**

- HC was not recovered from smoking experiments with KP201/APAP; however, **KP201 and HC appear to have similar volatility.** Low HC levels (4.7%/0.22 mg) released during smoking studies with the HB/APAP suggest that **smoking may not be a reasonable route of abuse for the reference product.**

Results of Human Abuse Potential Studies

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Controlled Substance Staff (CSS)

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CDER, Office of Biostatistics

May 5, 2016
FDA Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

Silver Spring, Maryland

Clinical Studies Under NDA 208-653

- Oral Human Abuse Potential Study KP201.A01
- Intranasal Human Abuse Potential Study KP201.A02
- Clinical PK/PD Study KP201.A03

In this presentation:

- "KP201" will be used to refer to "benzhydrocodone HCl"
- "APAP" will be used to refer to acetaminophen
- "KP201/APAP", not APADAZ, will be used to refer to the product under development

Pharmacodynamic Measures

Drug Liking Visual Analog Scale (VAS) – 0-100-point Bipolar Scale (Primary Measure)

- Question: "Do you like the drug effect you are feeling now?"
- 0 = "Strong disliking" ; 50 = "Neither like nor dislike"; 100 = "Strong liking"

High VAS – 0–100-point Unipolar Scale (Secondary Measure)

- Question: "How high are you now?"
- 0 = "None"; 100 = "Extremely"

Take Drug Again VAS - 0–100-point Bipolar Scale (Secondary Measure)

- Question: "Would you want to take the drug you just received again, if given the opportunity?"
- 0 = "Definitely would not"; 50 = "Do not care"; 100 = "Definitely would"

Relevant Pharmacodynamic Parameters:

- Emax – Maximum (Peak) Effect
- TEmax – Time of Peak Effect
- AUE0-x – Area Under the Effect Curve from 0 to x hours post-dosing, where x = 0.5, 1, or 2 hours

Primary Endpoint and Statistical Model

- The primary endpoint for studies KP201.A01 and KP201.A02 is the Emax of Drug Liking VAS over the 24 hour collection interval.
- Statistical analyses of pharmacodynamic measures of Drug Liking VAS, High VAS and Take Drug Again VAS were conducted by the FDA CDER Office of Biostatistics
- The statistical model used was a mixed-effects model with period, sequence and treatment as fixed effects as well as subjects as a random effect.
- The hypotheses of the statistical tests were:

  $H_0 : \mu_{Norco} - \mu_{KP201/APAP} \leq 0$ versus $H_a : \mu_{Norco} - \mu_{KP201/APAP} > 0$

  $H_0 : \mu_{Norco} - \mu_P \leq 15$ (or 30 for High) versus $H_a : \mu_{Norco} - \mu_P > 15$ (or 30 for High)
- All tests were one-sided with α=0.025.

Pharmacokinetics

- For purposes of assessing pharmacokinetic/pharmacodynamic relationships (PK/PD), focus will be on pharmacokinetics of hydrocodone in plasma

- Will not be discussing plasma levels of KP201 or of hydromorphone, a metabolite of hydrocodone

- Statistical analysis will be that generated by the Sponsor using least square geometric mean ratio (test/control) along with the corresponding 90% confidence intervals.

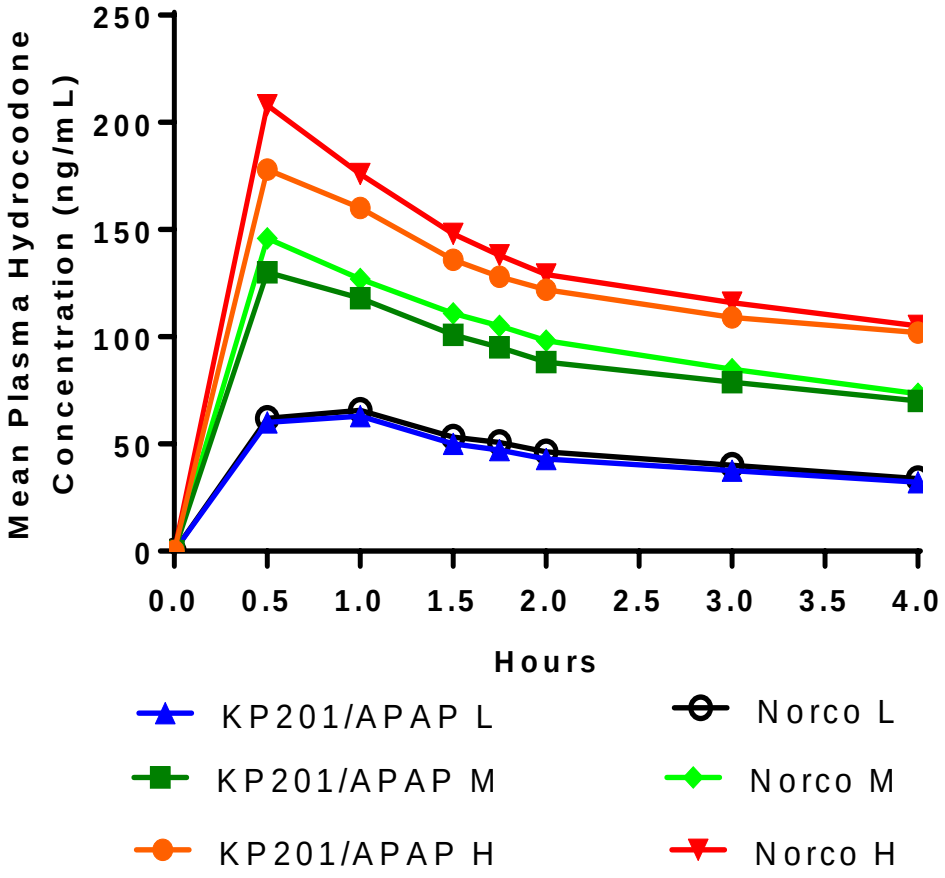
Relevant Pharmacokinetic Parameters:

- Cmax – Maximum observed plasma concentration of hydrocodone
- Tmax – Time to which Cmax occurs
- AUC0-xhr – Area under the hydrocodone plasma concentration vs time curve over the first 0.5, 1, or 2 hours post-dosing

Oral Study KP201.A01

- Randomized, double-blind, placebo-controlled, single-dose, seven-way crossover study
- Primary objective : determine the abuse potential of KP201/Acetaminophen (APAP) 6.67mg/325 mg Tablets relative to Hydrocodone Bitartrate (HB)/APAP (7.5 mg/325 mg) (Norco) Tablets when administered orally to nondependent, recreational opioid users.
- 62 subjects completed the study.
- Treatments:
  - KP201/APAP Low (L) – 4 Tablets – 26.68 mg/1,300 mg
  - KP201/APAP Medium (M) – 8 Tablets – 56.36 mg/2,600 mg
  - KP201/APAP High (H) – 12 Tablets – 80.04 mg/3,900 mg
  - Norco Low (L) – 4 Tablets – 30 mg/1,300 mg
  - Norco Medium (M) – 8 Tablets – 60 mg/2,600 mg
  - Norco High (H) – 12 Tablets – 90 mg/3,900 mg
  - Placebo

Oral Study KP201.A01
Pharmacokinetics of Plasma Hydrocodone

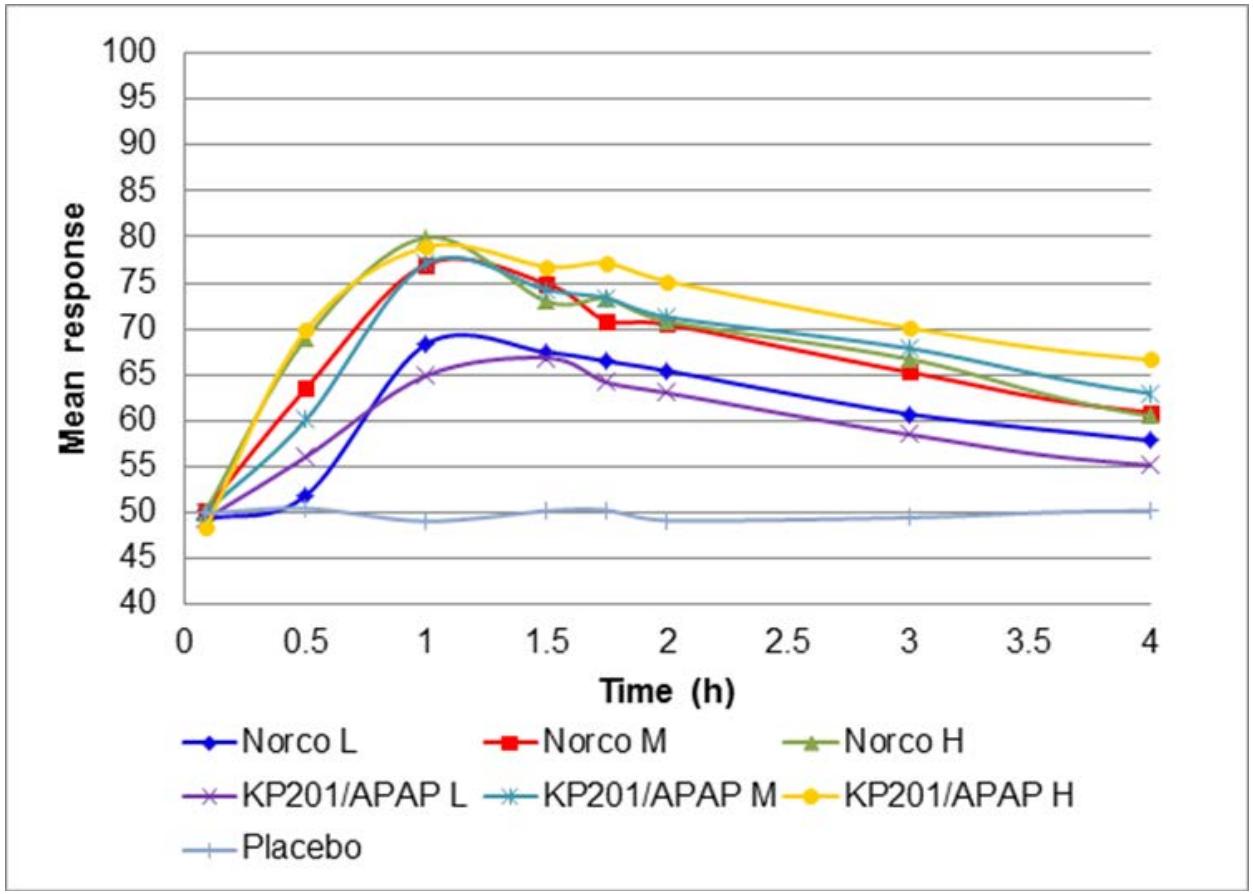


Dose dependent increases were observed in the plasma hydrocodone concentration.

Median Tmax for all treatments was about 1 hour. Most of the rise in mean concentration was within the first 30 minutes.

For medium (8 tablets) and high (12 tablets) doses, but not low dose (4 tablets), Cmax and AUC0-1hr were statistically significantly lower for KP201/APAP compared to Norco. (Cmax Medium, p=0.0333, Cmax High, p=0.0134)

Oral Study KP201.A01
Mean Drug Liking Time Course Profile

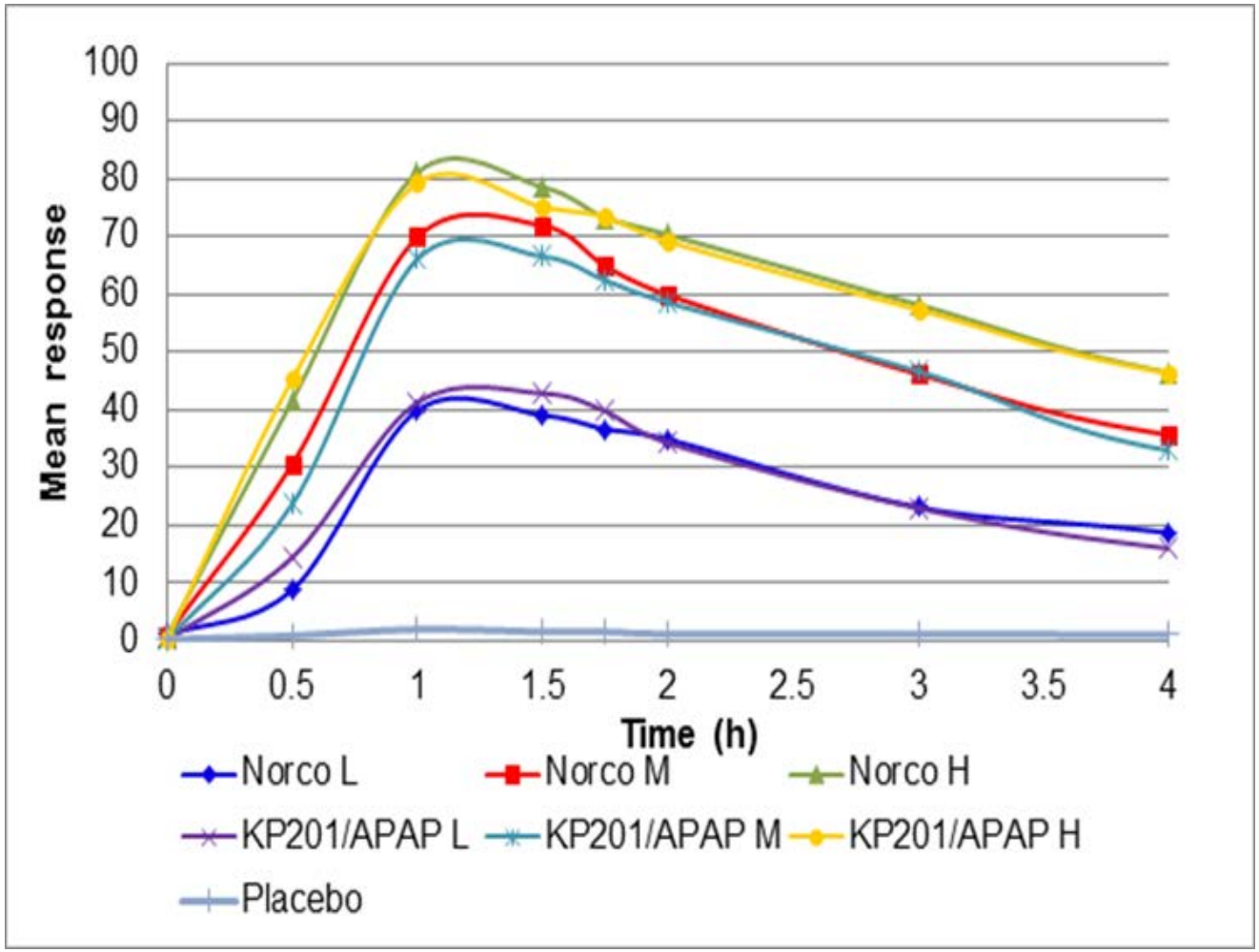


Much of the rise was within the first hour post-dosing.

Median TEmax is around 1 hour for all active treatments.

At each dose level, the mean AUE0-1hr of Drug Liking for KP201/APAP was found not to be statistically significantly smaller than that produced by Norco ($p \geq 0.1999$).

Oral Study KP201.A01
Mean High Time Course Profile



Much of the rise in mean High is within the first hour following dosing with Norco and KP201/APAP

Median TEmax was around 1 hour for all active treatments

At each dose level, the mean AUE0-1hr of High for KP201/APAP was not statistically significantly smaller than that produced by Norco ($p \geq 0.1259$)

Oral Study KP201.A01
Mean Emax (N=62)

Oral Treatment	Mean (SE) Emax (mm)		
	Bipolar Drug Liking VAS (Primary)	Unipolar High VAS (Secondary)	Bipolar Take Drug Again VAS (Secondary)
Norco L	72.5 (2.1)	48.2 (3.9)	66.3 (2.6)
KP201/APAP L	72.6 (2.2)	49.6 (4.2)	69.3 (2.9)
Norco M	83.4 (2.1)	76.6 (3.3)	66.0 (3.6)
KP201/APAP M	82.4 (2.1)	72.6 (3.2)	71.5 (3.0)
Norco H	87.4 (2.0)	85.1 (3.2)	66.6 (3.2)
KP201/APAP	87.8 (1.9)	85.5 (2.5)	72.4 (3.1)
Placebo	51.5 (0.4)	2.6 (1.2)	49.6 (1.3)

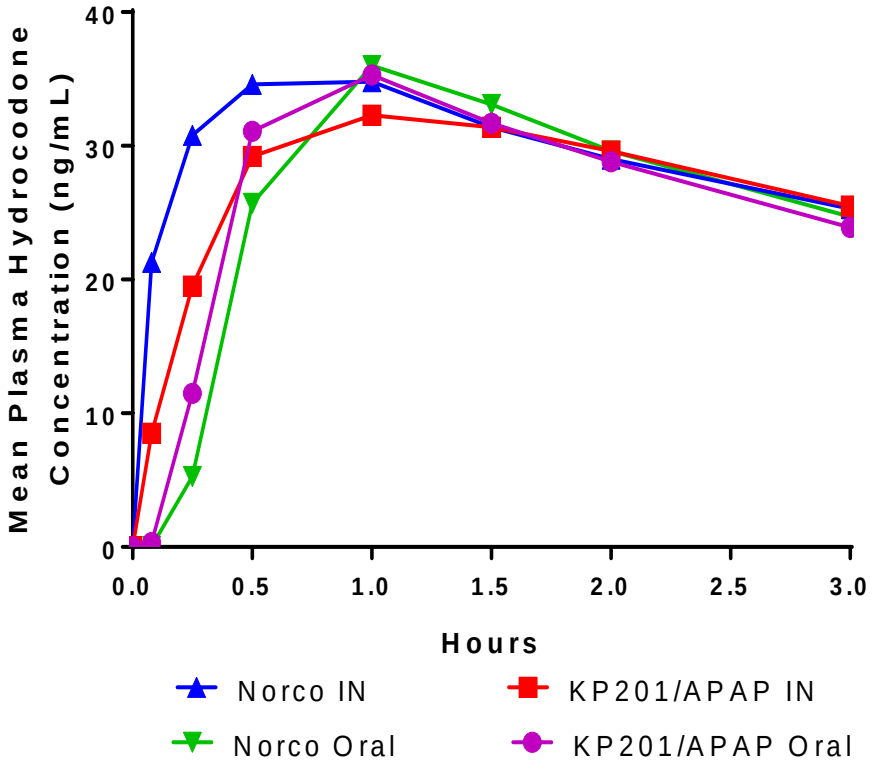
The primary analysis failed to demonstrate that the mean of KP201/APAP is statistically significantly smaller than that of Norco for all doses for all three measures (all p-values $\geq$0.1401, some p-values >0.5000). The test for the mean difference in Emax between each dose of Norco and placebo was statistically significant (p-value <0.025).

Intranasal Study KP201.A02

- Randomized, double-blind, double-dummy, placebo-controlled, single-dose, two-part, five-way crossover study by the intranasal (IN)route
- Primary objective of the Main Study (**Part B**) was to determine the abuse potential of crushed KP201/APAP relative to crushed Norco at the dose (2 tablets) determined in the Dose Selection Phase (**Part A**) when administered intranasally to non-dependent, recreational opioid users.
- Part B Treatments to 42 completers – 2 Tablets
  - Norco (15mg/650 mg) IN (850 mg powder)
  - Norco (15 mg/650) Intact Oral
  - KP201/APAP (13.34 mg/650 mg) IN (1,100 mg powder)
  - KP201/APAP (13.34 mg/650 mg) Intact Oral
  - Placebo [oral and IN (975 mg powder)]

All subjects insufflated 100% of dose of Norco. Thirty-eight (38) of 44 subjects insufflated 100% of KP201/APAP dose with remaining subjects insufflating between 91.5% and 99.4% of dose. Thirty seven (37) of 42 subjects insufflated full placebo powder. Remainders insufflated between 61.1% and 99.4% of placebo powder.

Intranasal (IN) Study KP201.A02
Mean Hydrocodone (HC) Plasma Concentration



For all treatments most of the rise in mean plasma HC occurs within the first 30 minutes.

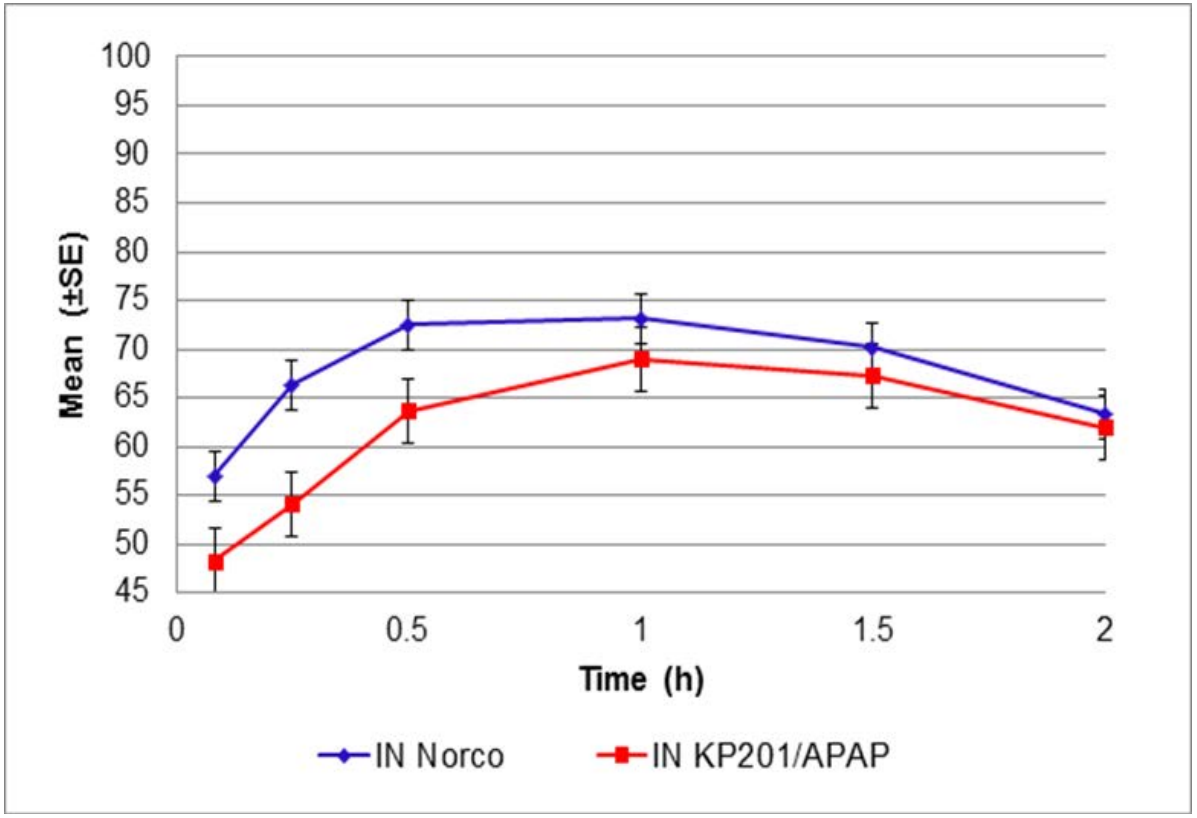
No difference in HC AUC the first hour after oral and IN KP201/APAP. Cmax higher after oral compared to IN KP201/APAP ($p=0.0004$).

HC Cmax was statistically significantly lower following IN KP201/APAP compared to IN Norco ($p=0.0027$)

AUC for HC at 0.5, 1, and 2 hours post-dosing was statistically significantly lower ($p \leq 0.0044$) following IN KP201/APAP compared to IN Norco.

Study KP201.A02
Mean Time Course Profiles by Intranasal Treatment

Bipolar Drug Liking VAS

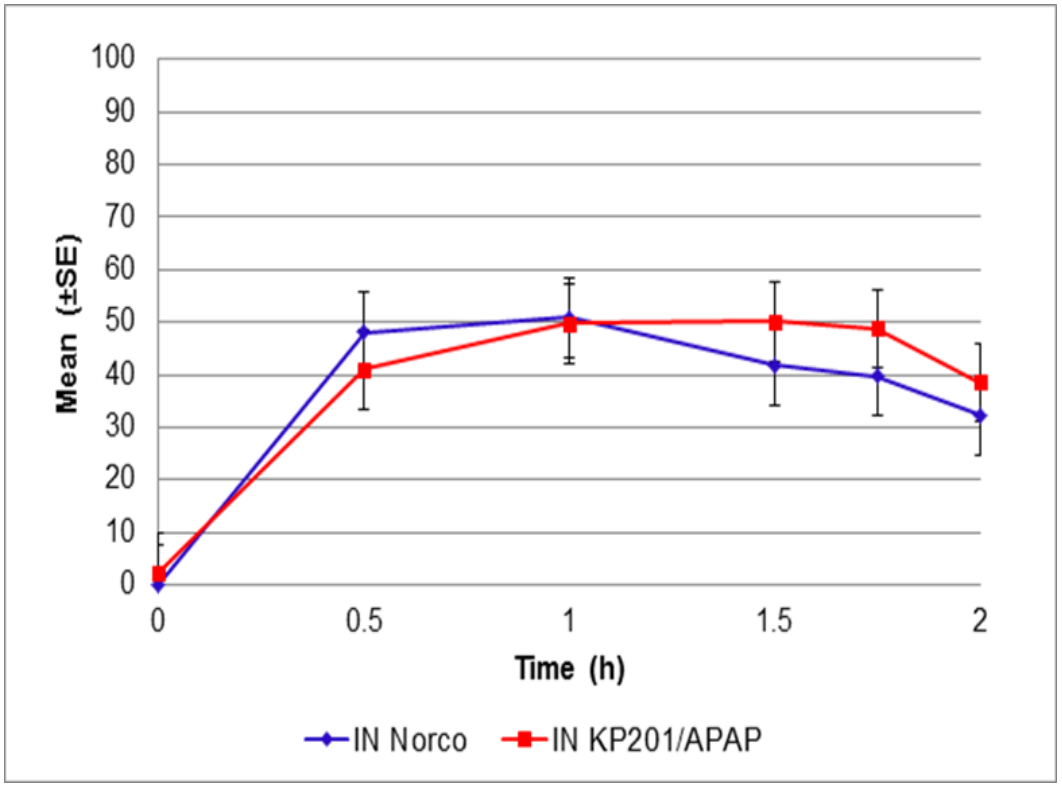


Mean AUEs at 0.5 and 1 hour post-dosing with KP201/APAP were statistically significantly($p<0.0001$) smaller than those following IN Norco for Drug Liking VAS.

Median TEmax for Drug Liking:
0.6 hrs IN Norco
1.1 hrs IN KP201/APAP

Study KP201.A02
Mean Time Course of High by Intranasal Treatments

Unipolar High VAS



Most of the rise in mean High was achieved within the first 0.5 hours.

Median TEmax:
1.2 hrs Norco IN,
1.4 hrs KP201/APAP IN

With IN KP201/APAP the mean AUEs for High over the first 0.5 hour and 1 hour were not statistically significantly lower than those produced by IN Norco ($p \geq 0.0807$).

Intranasal Study KP201.A02 Emax (N=42)

Treatment	Mean (SE) Emax (mm)		
	Drug Liking VAS (Primary)	High VAS (Secondary)	Take Drug Again VAS (Secondary)
Norco Intranasal	79.0 (2.7)	59.1 (5.1)	74.5 (3.9)
KP201/APAP Intranasal	75.9 (2.3)	61.8 (4.6)	69.5 (3.9)
Norco Oral	77.9 (2.6)	60.3 (4.9)	75.6 (3.6)
KP201/APAP Oral	76.9 (2.7)	61.2 (5.1)	73.3 (4.1)
Placebo	53.0 (1.2)	8.8 (3.8)	48.2 (2.2)

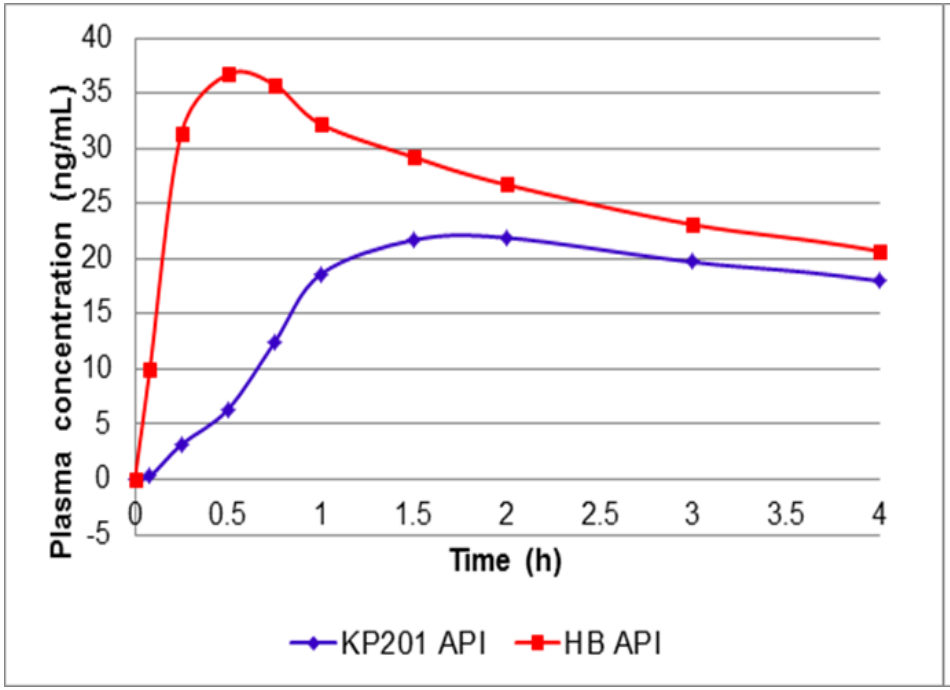
The primary analysis failed to demonstrate that the mean of KP201/APAP IN is statistically significantly smaller than that of Norco IN for all doses for all three measures (all p values $\geq$0.1569, some p values >0.5000). The test for the mean difference in Emax between Norco IN and placebo IN was statistically significant ($p<0.025$).

Intranasal Study KP201.A03

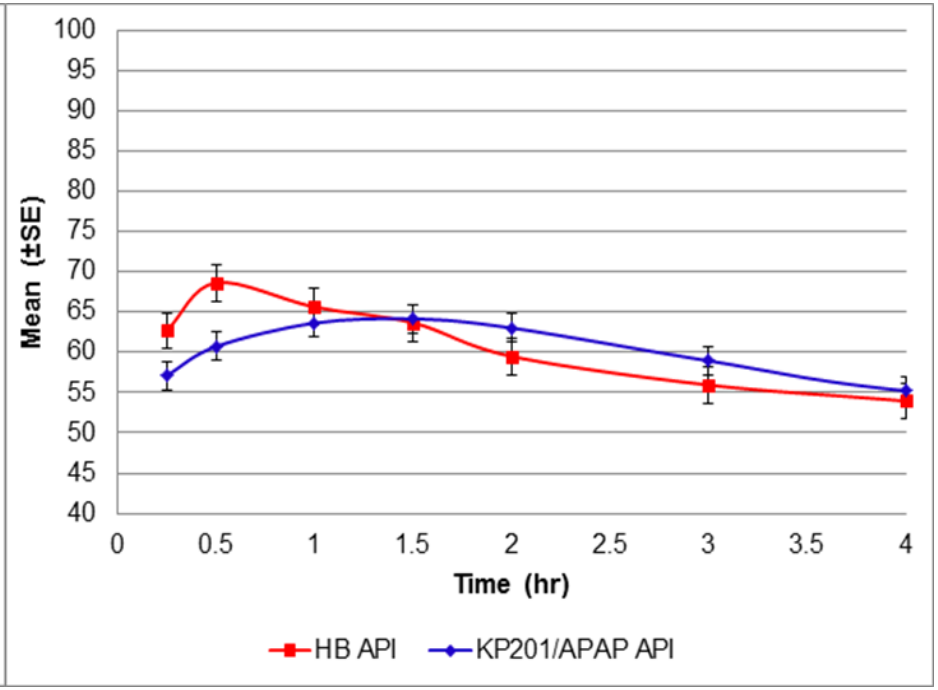
- Randomized, double-blinded, single dose two-way crossover study with primary objective to compare the rate and extent of absorption of hydrocodone and hydromorphone from the active pharmaceutical ingredients (APIs), KP201 and hydrocodone bitartarte (HB), when administered intranasally to non-dependent, recreational opioid users.
- Drug Liking VAS was conducted.
- Treatments included
  - KP201 API 13.34 mg IN
  - Hydrocodone Bitartrate (HB) API 15.00 mg IN
- Two cohorts were used.
  - Cohort 1 – No Hydrocodone PK Data, Drug Liking Data Obtained
  - Cohort 2 – Hydrocodone PK Data and Drug Liking Data Obtained – 24 Subjects and 25 subjects, respectively
- Study has deficiencies that limit use to assess abuse deterrent properties of KP201/APAP Tables.

Intranasal Study KP201.A03
PK and PD time course profiles

Mean plasma hydrocodone concentration time course (Cohort 2 – 24 Subjects)



Mean time course profiles for bipolar Drug Liking VAS (Cohort 2 - 25 Subjects)



Cmax and AUC at all intervals were statistically significantly greater for HB compared to KP201.
Median Tmax – 0.5 hr HB, 1.75 hrs KP201

No statistically significant reduction in mean of Emax of Drug Liking by IN KP201 API compared to IN HB API (p=0.0615).
Median TEmax – 0.5hr HB, 1.0 hr KP201

Intranasal Study KP201.A03 Significant Deficiencies

- Study involved insufflation of KP201 API and hydrocodone bitartrate API, and not the products KP201/APAP and hydrocodone bitartrate/APAP. As such, this study does not take into account possible effects of either mass of powder (13-15 mg versus 850 to 1,100 mg) to be insufflated or the effects of APAP on the insufflation experience as would occur following insufflation of the products.
- There was no Drug Discrimination (Qualification) Phase intended to select subjects having an appropriate placebo and active comparator response using the Drug Liking VAS.
- There was no placebo treatment in the Treatment Phase of the study. It is not known how subjects might have responded on the Drug Liking VAS when administering placebo intranasally. It also was not possible to validate assessment of the Drug Liking VAS.
- There were no additional subjective reinforcing measures (i.e., High VAS or Take Drug Again VAS) conducted which could be used to support observed effects on the Drug Liking VAS.

Summary

1. In oral human abuse potential study KP201.A01, at similar dosage levels of low, medium, or high, oral KP201/APAP and Norco produced similar levels of Drug Liking, High, and Take Drug Again, all of which were greater than that produced by placebo. This study failed the primary endpoint of maximum effect (Emax) for Drug Liking. The greater early exposure to plasma hydrocodone following medium and high oral doses of Norco compared to that following oral doses of KP201/APAP did not translate to higher levels of Drug Liking, High, or Take Drug Again.

2. In study KP201.A02, insufflation of Norco and KP201/APAP produced similar maximum Drug Liking, High or Take Drug Again that was higher than that produced by insufflation of placebo. There was a failure of the primary endpoint of maximum effect (Emax) of Drug Liking. Results of the Take Drug Again VAS demonstrate that subjects were willing again, if given the opportunity, to insufflate either Norco or KP201/APAP. The extent of Drug Liking, but not of High, experienced over the first hour was lower following KP201/APAP compared to Norco; the clinical relevance of this difference is not known, particularly in lieu of the absence of differences with respect to High VAS and to Take Drug Again VAS.

Summary (continued)

3. For a variety of reasons noted in this presentation, study KP201.A03 cannot be used to assess either the abuse potential or abuse deterrent effects of KP201/APAP Tablets against Norco via the intranasal route of administration.

Drug Utilization Patterns for Combination Hydrocodone/Acetaminophen and Selected Opioid Analgesics, Years 2011-2015

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FDA/CDER
Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) &
Drug Safety and Risk Management Advisory Committee (DSaRM)
May 5, 2016

Outline

- Sales Distribution
- Patient and Prescription Utilization
- Prescriber Specialty
- Diagnoses Associated with Use
- Limitations
- Conclusion

Selected Opioid Analgesics

- **Oral Immediate-Release (IR) Combination products :**
  - Hydrocodone/acetaminophen
  - Oxycodone/acetaminophen
- **Oral Immediate-Release (IR) Single-Entity (SE) products :**
  - Oxycodone IR
  - Oxymorphone IR
  - Morphine IR
  - Hydromorphone IR
  - Tapentadol IR
- **Oral Extended-Release (ER) product :**
  - Hydrocodone ER

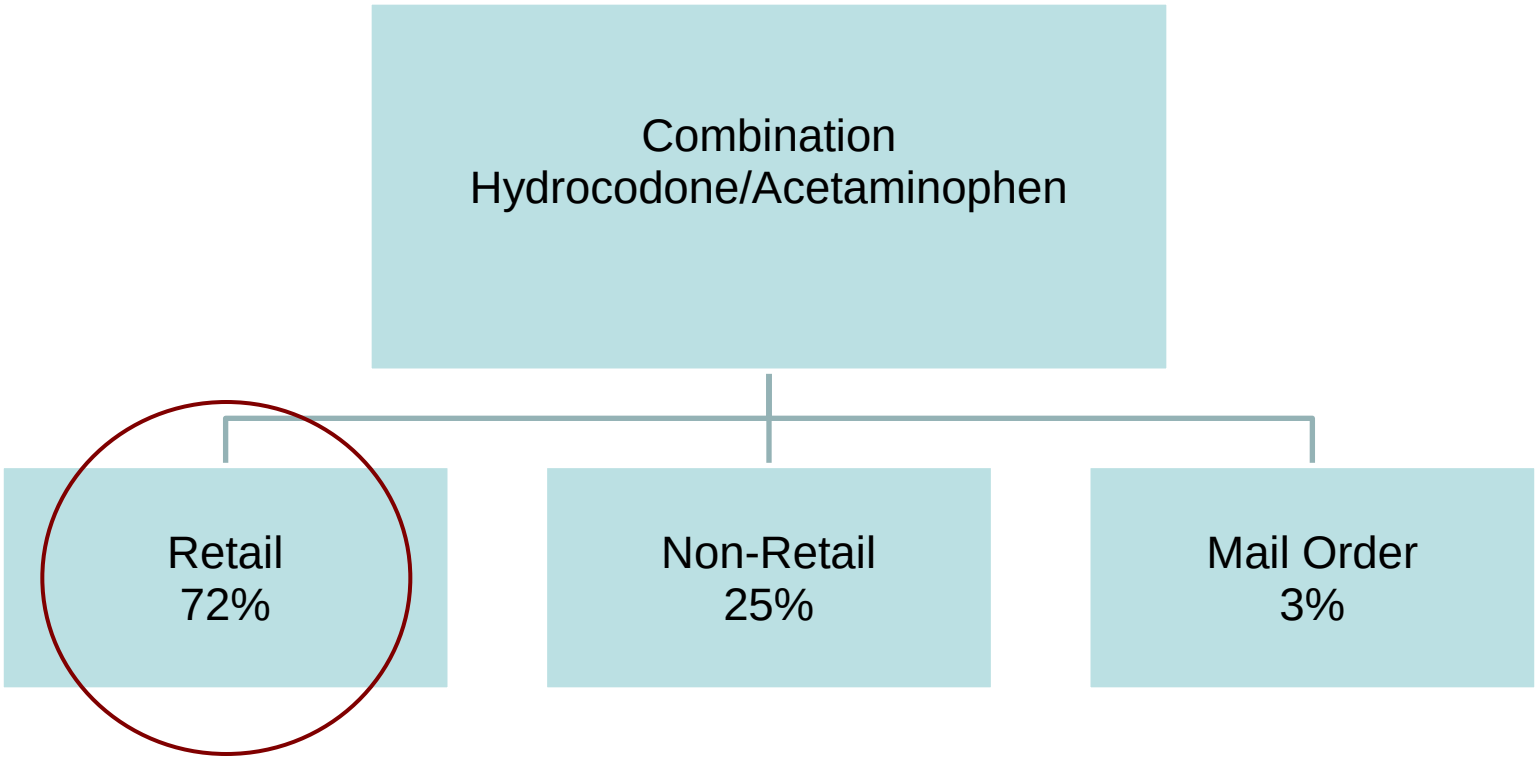
Sales Distribution Data

- IMS National Sales Perspectives Database™
- Captures sales of drug products from manufacturers to all retail and non-retail settings
  - Retail chain pharmacies, mail-order pharmacies, hospitals, etc.
- Data are nationally projected
- Does not represent actual patient use

Sales Distribution Data

Year 2011-2015

IMS Health, IMS National Sales Perspective™, Extracted March 2016



Database Descriptions

Patient Utilization :

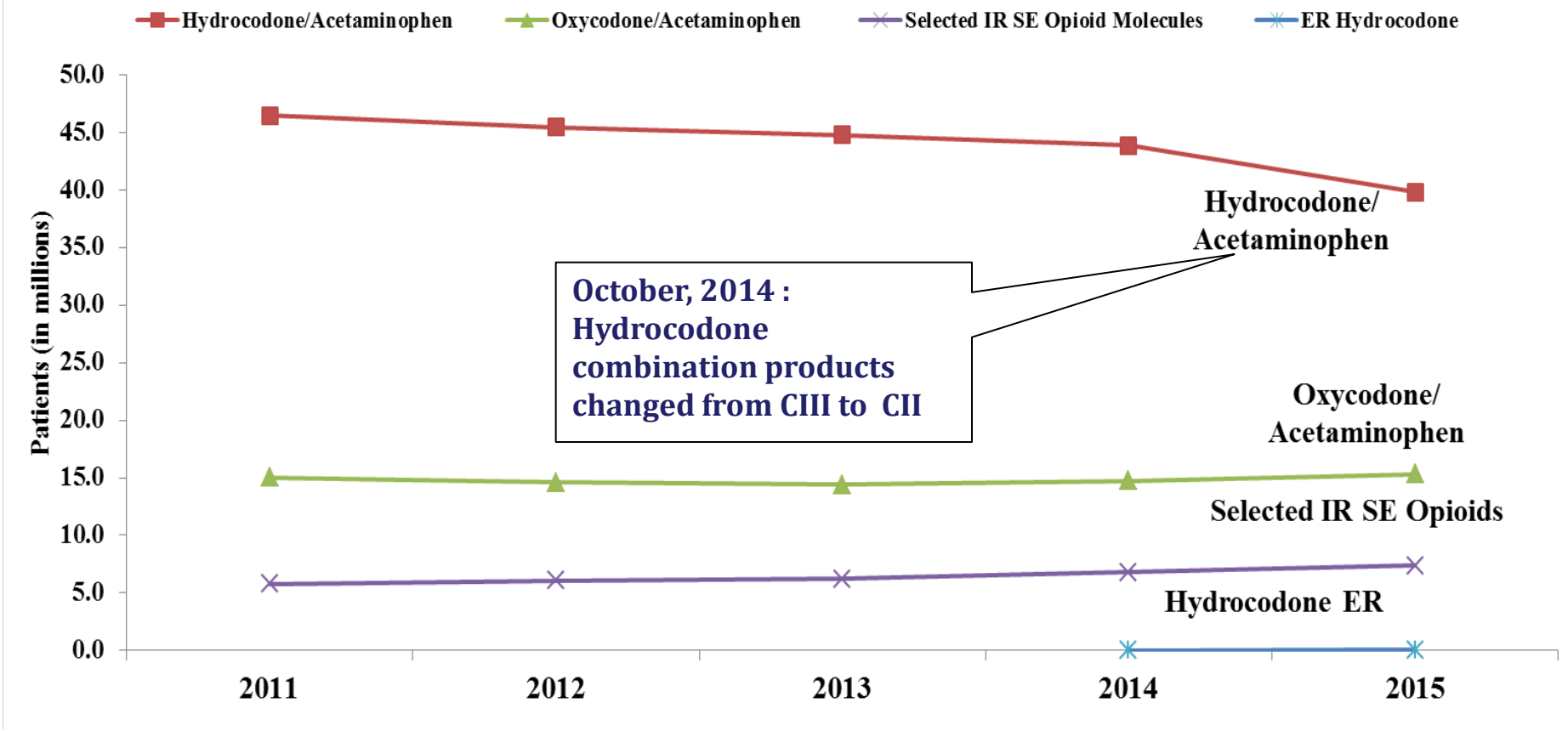
- IMS Health, Total Patient Tracker (TPT) Database
- Estimate the total number of patients across all drug and therapeutic classes
- Data are nationally projected to the outpatient pharmacy retail setting
  - Database captures over 2.1 billion prescriptions claims per year

Prescription Utilization and Prescriber Specialty Data :

- IMS Health, National Prescription Audit™(NPA) Database
- Measures dispensing of prescriptions out of retail pharmacies into the hands of consumers
- Data can be stratified by prescriber specialty

Patient Drug Utilization:

Nationally estimated number of patients who received a dispensed prescription for combination hydrocodone/acetaminophen and other selected* opioid analgesics from U.S. outpatient retail pharmacies

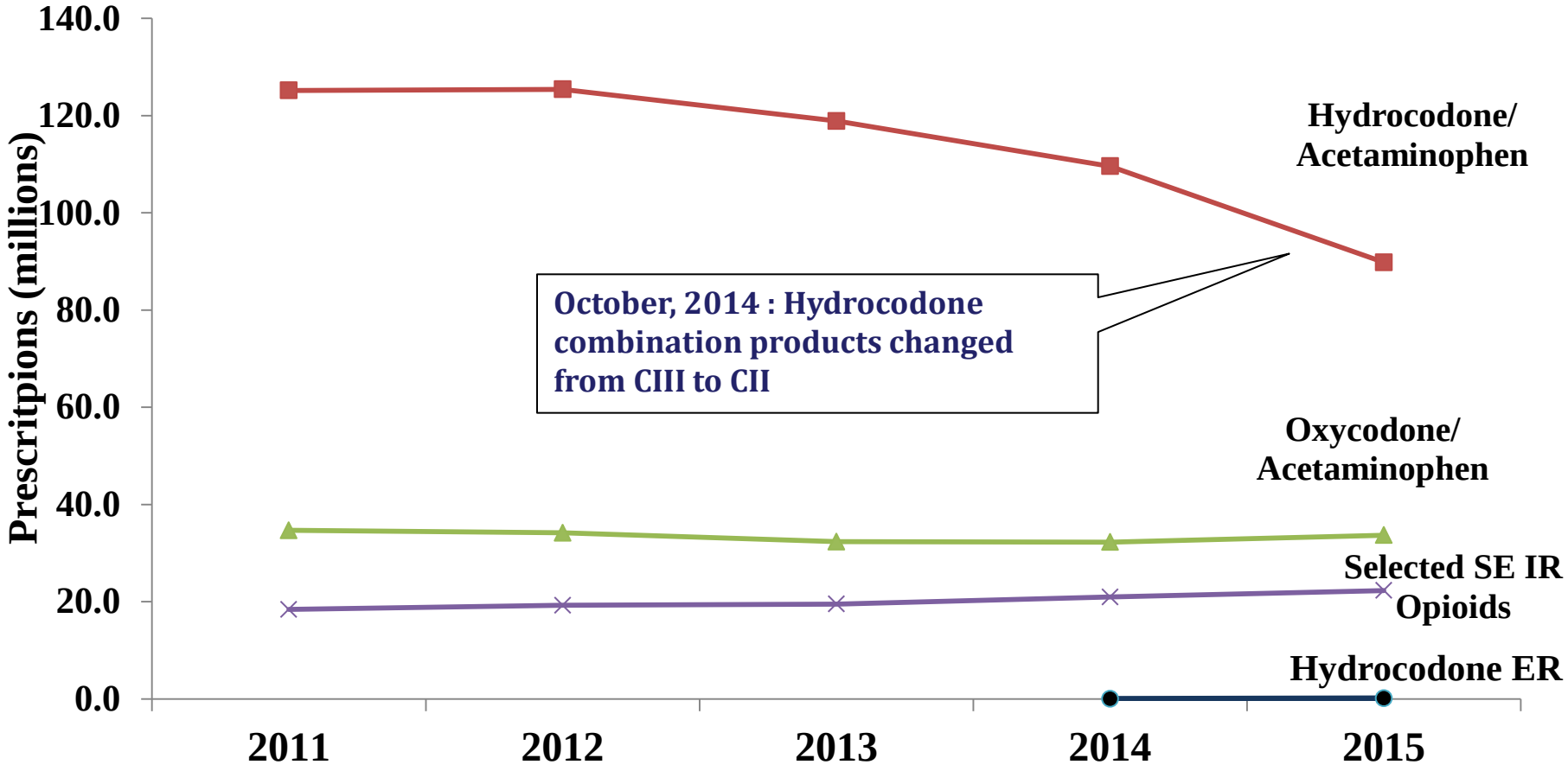


*** Selected IR SE Opioid Molecules include: Oxycodone, Hydromorphone, Morphine, Tapentadol, and Oxymorphone**

Source: IMS, National Prescription Audit™ (NPA). Data Extracted February 2016.

Prescription Drug Utilization:

Nationally estimated number of prescriptions dispensed for combination hydrocodone/ acetaminophen and other selected* opioid analgesics from U.S. outpatient retail pharmacies

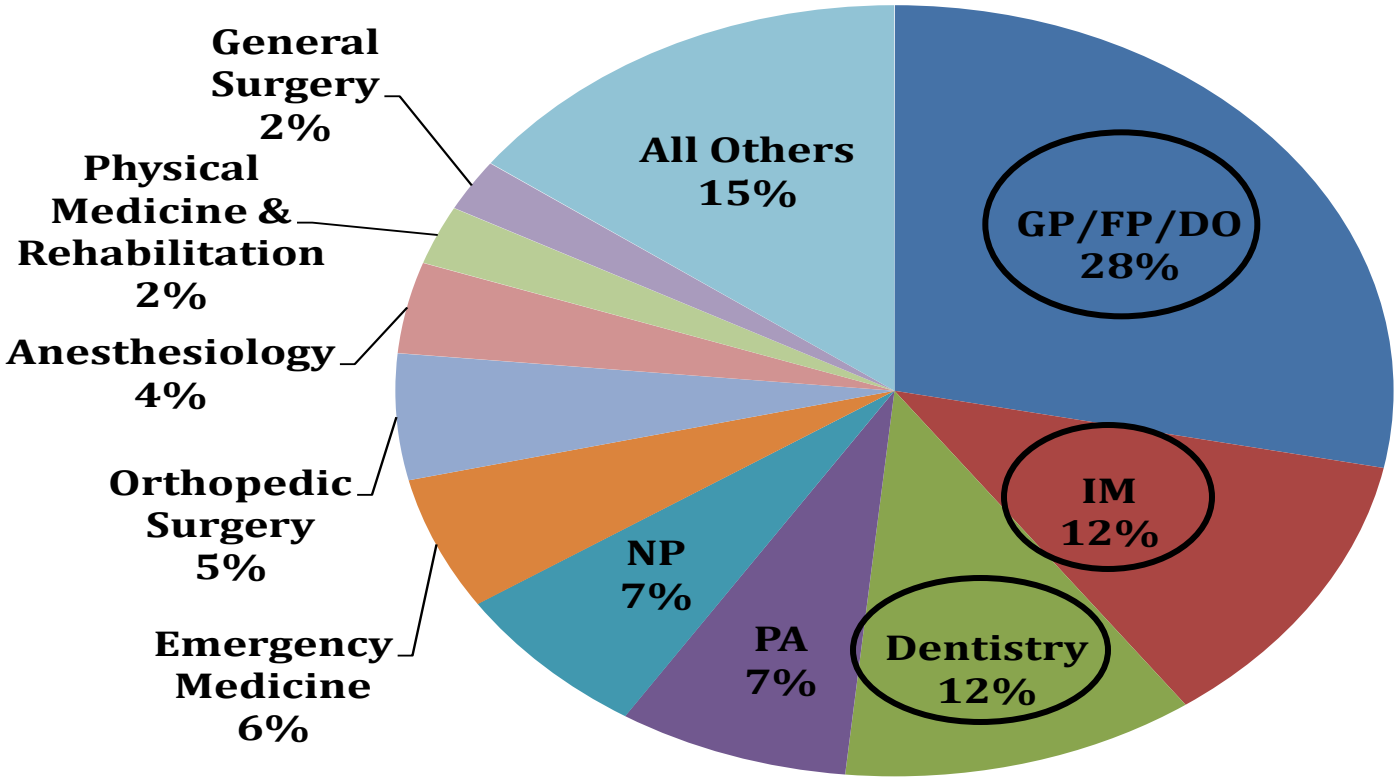


*** Selected IR SE Opioid Molecules include: Oxycodone, Hydromorphone, Morphine, Tapentadol, and Oxymorphone**

Source: IMS, National Prescription Audit™ (NPA). Data Extracted February 2016.

Top Prescriber Specialty: 2015

Top 10 prescriber specialties by the nationally estimated number of prescriptions dispensed for hydrocodone/acetaminophen from U.S. outpatient retail pharmacies, 2015



GP/FP/DO: General Practice/Family Practice/Osteopathic Medicine; NP: Nurse Practitioner; PA: Physician Assistant; IM: Internal Medicine

Source: IMS Health, National Prescription Audit (NPA). June 2013 - February 2015. Extracted February 2016.

U.S. Office-Based Physician Survey Data:

- Encuity Research, LLC, TreatmentAnswers™ and Treatment Answers™ with Pain Panel Database
- Monthly survey of 3,200 office-based physicians representing 30 specialties across the United States
  - Primarily office-based physicians, does not include dentists
- Data nationally projected to reflect national prescribing patterns
- Help characterize use of drug products in clinical practice

Diagnoses for Hydrocodone/Acetaminophen: 2015

- **Reported as "Acute"**
  - Injury and Poisoning (ICD-9, 800-999), 42% of drug use mentions for acute conditions
  - Disease of the Musculoskeletal System and Connective Tissue (ICD-9, 710-739), 17% of drug use mentions for acute conditions
- **Reported as "Chronic"**
  - Disease of the Musculoskeletal System and Connective Tissue (ICD-9, 710-739), 54% of drug use mentions for chronic conditions
  - Follow Up Visits (ICD-9, V01-V91), 14% of drug use mentions for chronic conditions

Source: Encuity Research Treatment Answers™ Audit LLC. Extracted March 2016.

Limitations

- Only outpatient retail pharmacy use was assessed
- Diagnoses information are not linked to dispensed prescriptions
- Diagnoses obtained from physician survey database does not include prescribers such as dentists

Summary of Findings:

- Decreased utilization of hydrocodone/acetaminophen from 2011- 2015
- Prescribed primarily by primary care prescribers followed by dentists
- Used widely for both acute and chronic conditions based on office-based physician survey data
  - Dentists were not included in the survey population

Is Snorting a Relevant Route of Abuse for Hydrocodone Combination Products?

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Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and Drug Safety and Risk Management Advisory Committee (DSaRM) Joint Meeting
May 5, 2016

Overview

- Background
- Sponsor-submitted studies and other available data
  - Key findings
  - Limitations
- Overall interpretation of the data

Background

Hydrocodone Combination Products (HCPs)

- Contain up to 10 mg immediate-release (IR) hydrocodone in fixed combination with a non-opioid active pharmaceutical ingredient, most commonly acetaminophen
- IR hydrocodone available only as HCPs
- HCPs comprise vast majority of all hydrocodone prescribed
- Most widely prescribed opioid analgesics

Misuse and Abuse of Hydrocodone

- In 2011, there were an estimated 82,480 emergency department visits related to nonmedical use of hydrocodone[1]
- An estimated 24.3 million people in the U.S. have used hydrocodone for nonmedical purposes in their lifetime[2]
- Reduction in misuse/abuse following 2014 rescheduling??
  - Decrease in calls to Texas poison control centers involving hydrocodone misuse and abuse[3]

1. Drug Abuse Warning Network, 2011: Selected Tables of National Estimates of Drug-Related Emergency Department Visits: Center for Behavioral Health Statistics and Quality, SAMHSA, 2013.
2. Results from the 2014 National Survey on Drug Use and Health: Detailed Tables; Includes non-institutionalized U.S. residents aged 12 years and older
3. Haynes et al., *Clinical Toxicology* 2016

Abuse-Deterrent Opioids: Relevant Routes of Abuse

- According to FDA guidance,[1]

  "Abuse-deterrent technologies should target known or expected routes of abuse relevant to the proposed product."

- **How can we determine relevance?**

1. *Abuse-deterrent Opioids—Evaluation and Labeling: Guidance for Industry*, April 2015

Considering Relevance: Epidemiologic Questions

- **Scope -- How widespread is nasal abuse of hydrocodone combination products (HCPs)?**
  - What proportion of HCP abusers snort it?
  - Vary across HCP abuser populations?
  - It snorting a preferred/exclusive route?
  - Do those who try snorting HCPs continue to do so?
  - How do these estimates translate to absolute numbers?
- **Adverse Outcomes -- What is the risk of harm associated with nasal HCP abuse?**

Studies Reviewed

1. NAVIPPRO®[1] studies submitted by Sponsor

Study	Description
ASI-MV®[2] (adults)	Information on recent drug abuse obtained from individuals being assessed for substance abuse disorders in treatment centers and other settings
CHAT®[3] (13-18 years)	
Internet Surveys	Anonymous survey of Bluelight.org visitors
2014	Use and abuse of HCPs
2015	Progression of HCP Use

2. Published literature

1. National Addictions Vigilance Intervention and Prevention Program
2. Addiction Severity Index—Multimedia Version
3. Comprehensive Health Assessment for Teens

Key Findings

1. Scope
2. Adverse outcomes

Prevalence of Nasal Abuse in Selected Samples of HCP Abusers

	Study Setting	Findings
ASI-MV	Adults assessed for substance abuse in treatment programs/other settings	23.3% of past 30-day HCP abusers reported snorting it
CHAT	Adolescents assessed for substance abuse in treatment programs/other settings	42.7% of past 30-day HCP abusers reported snorting it
Cicero, 2013[1]	Adults entering non-methadone treatment for Rx opioid addiction	26.6% of those indicating hydrocodone as primary drug reported snorting it

Cicero et al., *Pain* 2013

Varying Prevalence of Snorting in HCP Abuser Subgroups

ASI-MV Subgroup	Past 30-day HCP abusers (n)	% of HCP abusers who report snorting it
Treatment/assessment setting		
Corrections	2,877	**11%**
Residential/inpatient treatment	9,968	**29%**
Concomitant abuse of other prescription opioids in past 30 days		
Abused only HCPs	9,262	**10%**
Abused ≥1 additional opioid	12,534	**33%**

Table created by reviewer, based on data provided in NAVIPPRO® ASI-MV study reports and Sponsor's response to FDA information request

- 85% of nasal HCP abusers have a "considerable" or "extreme" drug problem
- 82% of nasal HCP abusers reported abusing ≥ 1 other opioid product, compared to 56% of oral HCP abusers

Varying Prevalence of Snorting in HCP Abuser Subgroups

Self-reported lifetime nonmedical drug use in a rural (n=101) and an urban (n=111) sample of prescription drug nonmedical users in Kentucky[1]

	Rural (%)	Urban (%)
Hydrocodone	**90.1**	**91.9**
Swallowing	68.3	91.9
Snorting	74.3	6.3
Injecting	0	0
OxyContin	**86.1**	**23.6**
Swallowing	25.7	22.5
Snorting	68.3	3.6
Injecting	44.6	0
Methadone	**77.2**	**3.6**
Swallowing	27.7	3.6
Snorting	64.4	0
Injecting	1.0	0
Morphine	**53.5**	**4.6**
Swallowing	14.9	3.6
Snorting	17.8	0.9
Injecting	33.7	0

1. Table adapted from Young et al., *Harm Reduction Journal* 2010

Snorting as the Preferred or Exclusive Route for HCPs

	Study Setting	Findings
2014 NAVIPPRO® Internet Survey	Visitors to Bluelight.org	Of those ever using HCPs nonmedically, **6.7% reported snorting is preferred route** for HCPs
2015 NAVIPPRO® Internet Survey	Visitors to Bluelight.org	Of those continuing non-medical HCP use, **6.3% reported snorting it during most recent use**
Butler, 2011[1]	Adults assessed for substance abuse in treatment programs/ other settings	Of those reporting past 30-day HCP abuse, **5.5-7.5% only reported snorting it**

1. Butler et al., *Harm Reduction Journal* 2011; additional NAVIPPRO ASI-MV 2010-2013 data provided to FDA by and presented with permission from study authors

Frequency of Nasal HCP Abuse in Continuing Users

2015 NAVIPPRO® Internet Survey

Frequency of nasal HCP abuse, as a percent of continuing HCP non-medical users (n=394)

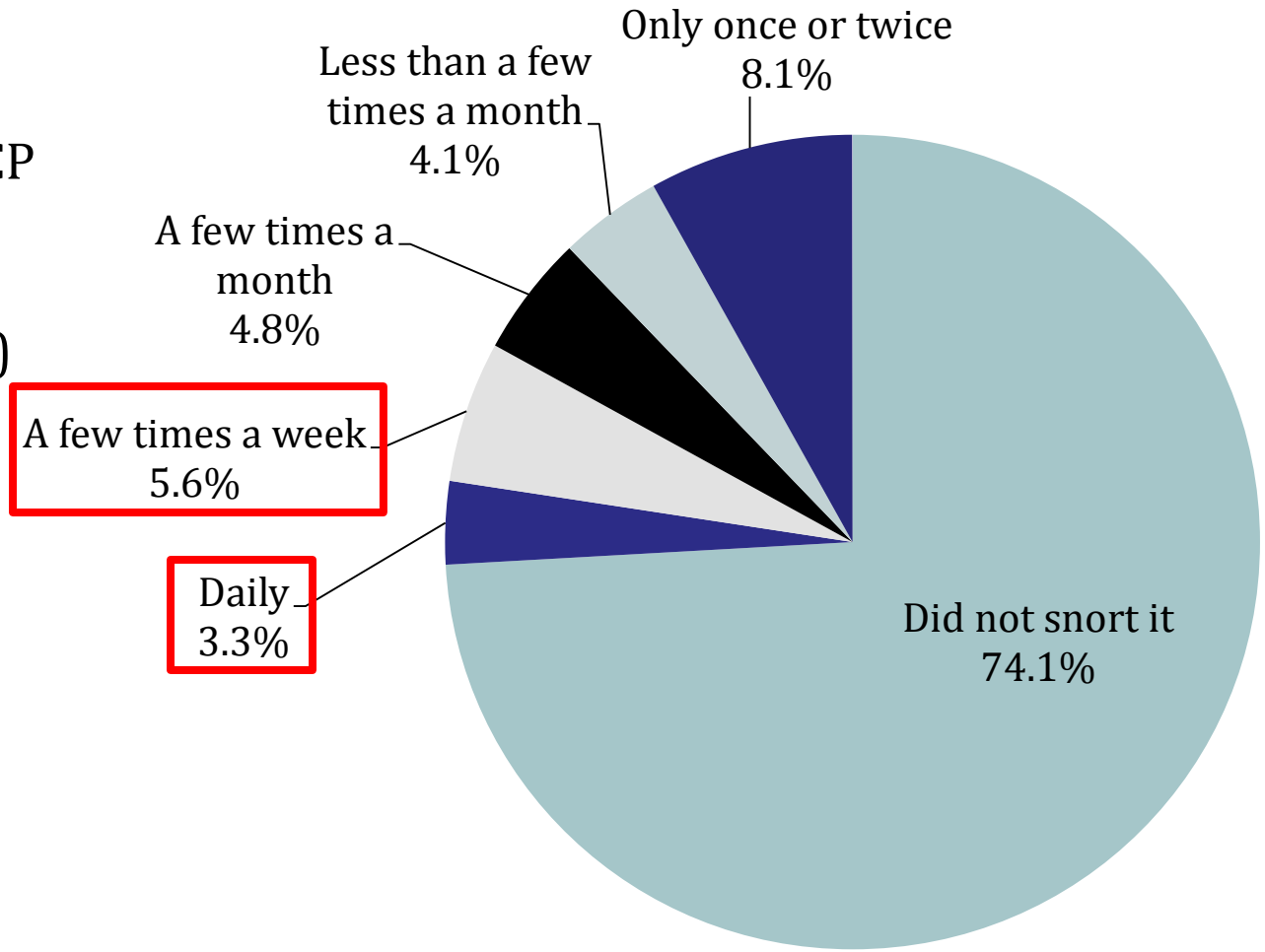
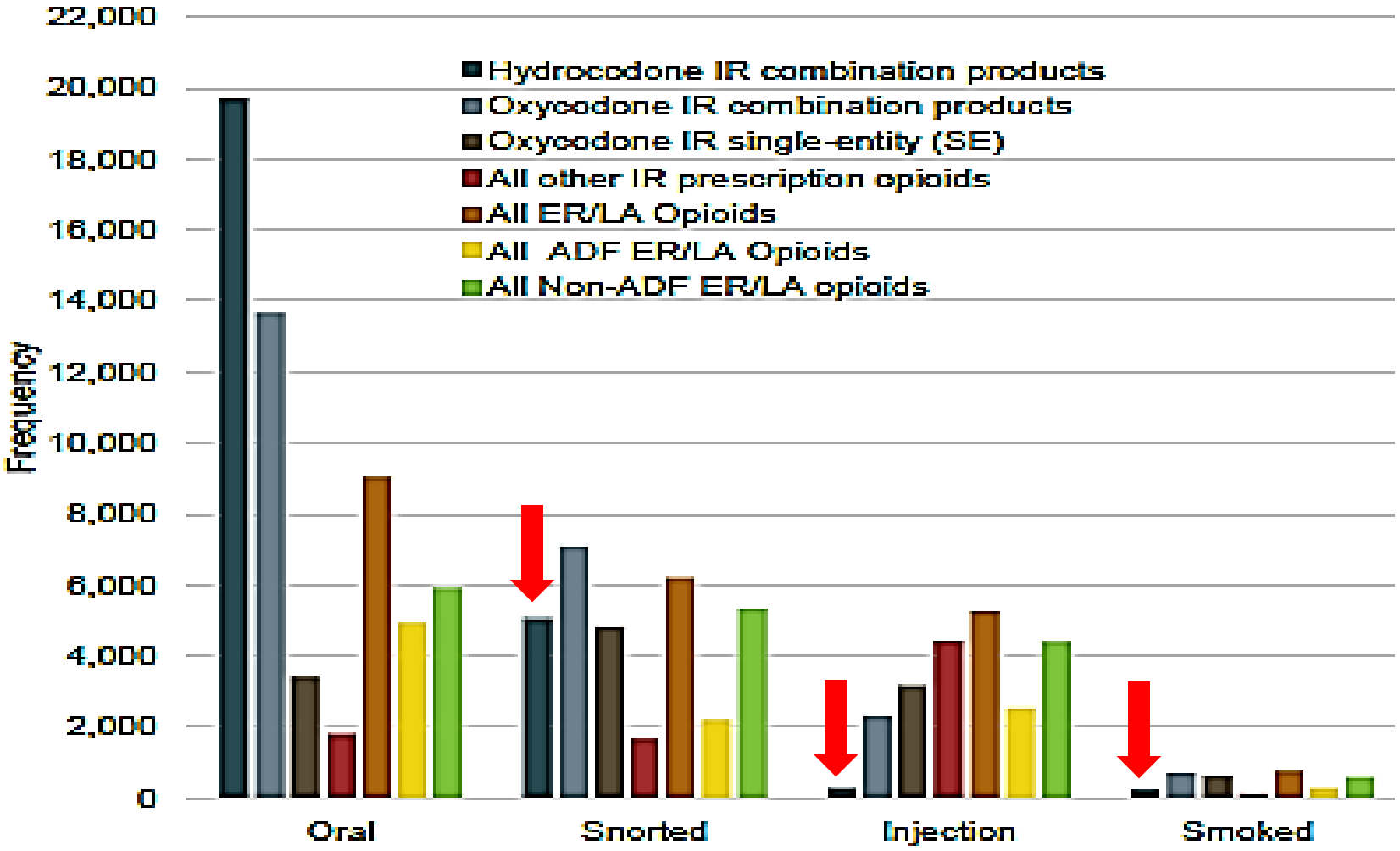


Figure created based on data provided in NAVIPPRO® 2015 Internet Survey Report

Nasal HCP Abuse: Absolute Numbers

Frequency of abuse, by route, for HCPs and comparator opioids within the NAVIPPRO® ASI-MV network (1/2012 - 6/2015)



Study Limitations

- **Poorly defined outcome measures**
  - Intent and referent timeframe of questions unclear
  - Example: "*How have you usually used [DRUG]? Please select all that apply*."
- **May not reflect HCP abuse patterns in broader population**
  - Not nationally representative
    - For example, >70% CHAT sites in Missouri
  - Non-oral abusers may be over-represented
    - High proportion of ASI-MV and CHAT participants have advanced substance use disorders
    - Internet surveys may select for non-oral abusers, as non-oral routes of abuse are frequent topics in online drug discussion forums

Summary: Scope of Nasal HCP Abuse

- Prevalence of snorting among HCP abusers varies widely
- Not uncommon in certain populations
  - Adolescents being assessed for treatment
  - Those with more advanced substance use disorders
  - Those abusing multiple opioids
- Snorting infrequently the preferred or exclusive route
- Ongoing frequent HCP snorting may be uncommon
- Unknown prevalence in general population
- HCP misuse/abuse is widespread, so even a small proportion of HCP abusers snorting may translate to large absolute numbers

Adverse Outcomes: Nasal Tissue Damage

- Case reports and case series:[1-5]
  - Tissue necrosis, perforated septum/palate, fungal rhinosinusitis
  - Some cases with documented nasal HCP abuse
  - Drug use histories unclear
  - Nasal abuse of other opioids, cocaine
- True incidence of nasal tissue damage due to snorting HCPs is unknown

1. Yewell et al., *Ann Otol Rhinol Laryngol* 2002
2. Alexander et al., *Laryngoscope* 2012
3. Sloan and Klimkina, *J Opioid Manag* 2009
4. Birchenough et al., *J Craniofac Surg* 2007
5. Volser et al., *Int Forum Allergy Rhinol* 2014

Adverse Outcomes: Addiction

- Alternate routes associated with more advanced substance use disorder[1]
- But, snorting may be more a *result* than a *cause* of worsening substance use disorder
- Unknown whether an HCP formulation that deterred nasal abuse would decrease the risk of addiction

1. Katz et al., *Am J Drug and Alcohol Abuse* 2011

Adverse Outcomes: Overdose

- **Epidemiologic data extremely limited**
  - Neither national overdose death data[1] nor coded administrated claims data indicate specific prescription opioids or route
  - Data sources relying on medical records (e.g., emergency department case reviews)[2] do not capture route of abuse consistently

1. CDC National Vital Statistics System Multiple Cause of Death database
2. Drug Abuse Warning Network

Adverse Outcomes: Overdose

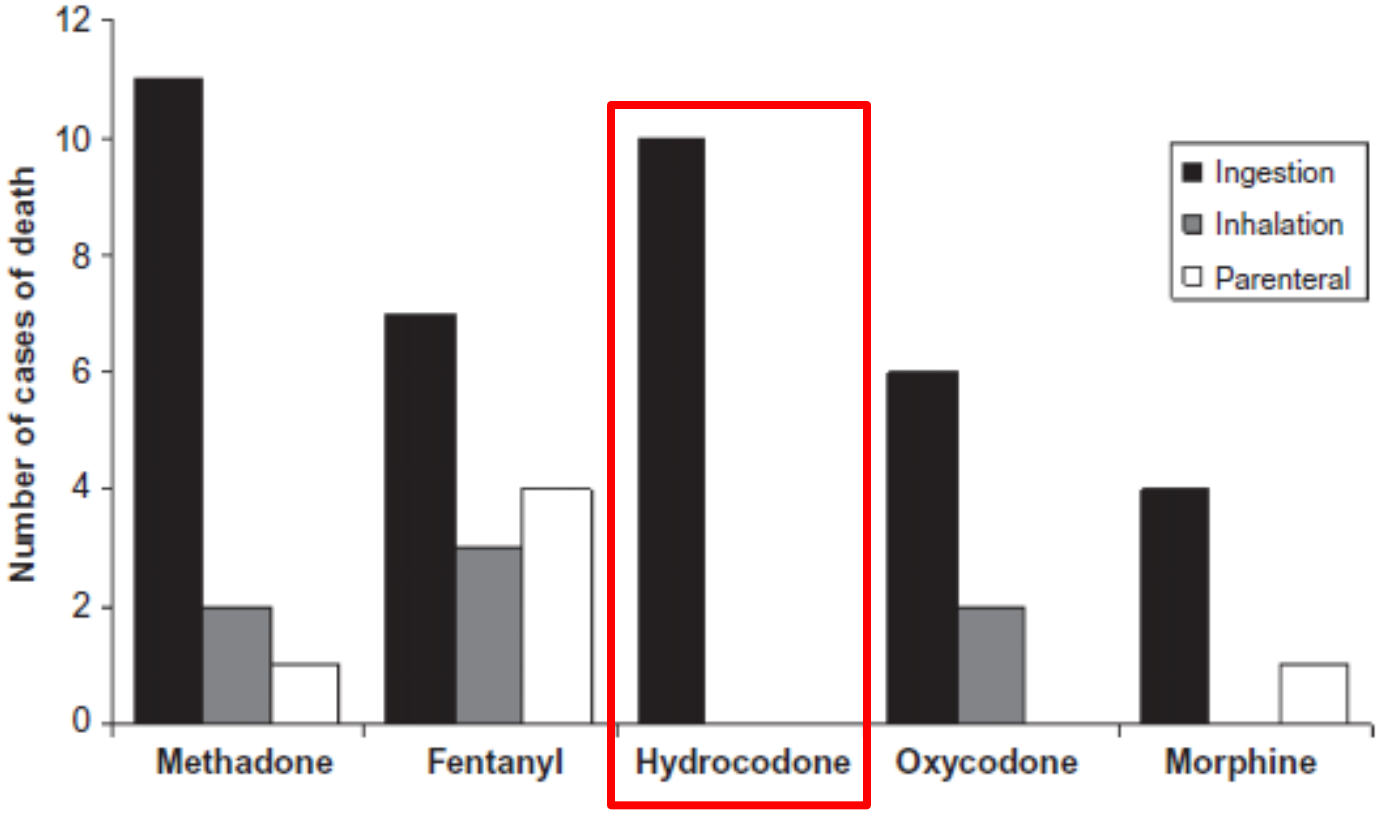
- **West Virginia medical examiner study (2008):**
  - 22.4% of unintentional prescription opioid overdose deaths involved a nonmedical route of administration[1]
- **U.S. poison center call study (2007-2008):**
  - Nasal and parenteral opioid exposures associated with more severe outcomes[2]
  - Did not examine calls for HCPs specifically

1. Hall et al., *JAMA* 2008
2. Katz et al., *Am J Drug and Alcohol Abuse* 2011

Adverse Outcomes: Overdose

- **U.S. poison control center call data (2006)**

Deaths due to the intentional misuse or abuse of prescription opioids, by product suspected to have caused death and route of administration



Katz et al., *Am J Drug and Alcohol Abuse* 2011

Adverse Outcomes: Overdose

- **Limitations of poison center data for assessing route of abuse and overdose deaths**
  - Caller may not recognize or report non-oral routes of exposure
  - Unattended/pre-hospital fatalities not captured
  - Very small number of fatal events captured, relative to actual number of prescription opioid overdose deaths

Adverse Outcomes: Overdose

- **HCP clinical and pharmacologic considerations**
  - Relatively low dose ceiling for hydrocodone (10 mg)
  - Limited amount of material can be administered nasally and absorbed at one time
  - Snorting does not have same infectious risks as injection (e.g., HIV, hepatitis C, skin abscesses)
  - Substantial potential harm from supratherapeutic oral ingestion

Summary: Adverse Outcomes

- Incidence of adverse outcomes associated with HCP nasal abuse is unknown
- Case reports of nasal tissue damage and infection, but other drugs may have contributed
- Clinical and pharmacologic factors suggest lower risk of overdose from snorting HCPs than from single-ingredient, higher dose opioids
- Very limited data suggest most hydrocodone-related deaths involve oral ingestion

Overall Interpretation

- The epidemiologic data, interpreted in the context of clinical and pharmacologic factors, suggest that large numbers of individuals may have snorted HCPs but that nasal abuse may make a relatively small contribution to the overall harms associated with misuse and abuse of HCPs.

Thank you

Acknowledgements

Kunthel By

Alex Secora

Cyndy Kornegay

Stephine Keeton