Quantitative Analysis of Opioid ADF PK/PD

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ASCPT Science at Sunrise Session: Opportunities in Evaluating Abuse Deterrence of Opioid Drug Products

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Disclaimer

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Outline

- Background
  - General Principles for Evaluating the Abuse Deterrence (AD) of Generic Solid Oral Opioid Drug Products –2017 FDA Guidance (https://www.fda.gov/downloads/Drugs/.../Guidances/UCM492172.pdf)
  - Product specific guidances (PSGs) for Hydrocodone, Oxycodone, and Morphine ER formulation with AD properties (https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm)
  - Consult Office of New Drugs at FDA for new drug applications
- PK/PD analysis to support PK metrics determination for comparative PK studies to evaluate AD
  - PK metrics to evaluate AD potential based on PK-PD relationship
- Conclusions

Approved AD Opioid Drug Products

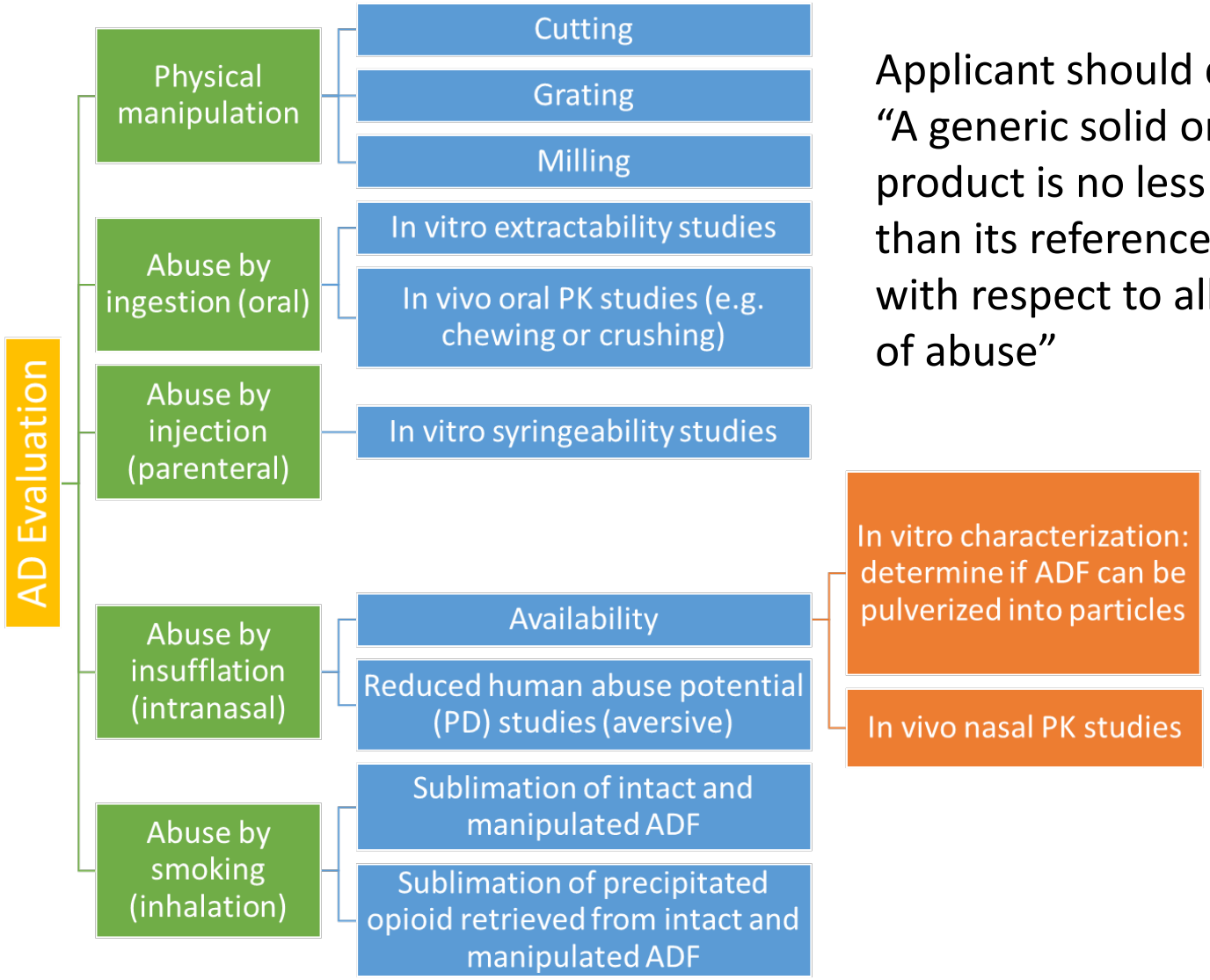
Product	Active Ingredient	AD Routes	Marketing Status
Hysingla ER Tablet	Hydrocodone bitartrate	Nasal, IV, oral	Available
Embeda ER Capsule	Morphine Sulfate /naltrexone	Nasal, Oral	Available
MorphaBond ER Tablet	Morphine sulfate	Nasal, IV	Available
OxyContin ER Tablet	Oxycodone HCl	Nasal, IV	Available
Xtampza ER Capsule	Oxycodone	Nasal, IV, Oral	Available
RoxyBond Tablet	Oxycodone	Nasal, IV	Available
Arymo ER Tablet	Morphine sulfate	Nasal, IV	Discontinued
Vantrela ER Tablet	Hydrocodone bitartrate	Nasal, IV, oral	Withdrawn
Troxyca ER Capsule	Oxycodone HCl /naltrexone HCl	Nasal, Oral	Withdrawn
Targiniq ER Tablet	Oxycodone HCl /naloxone HCl	Nasal, IV	Withdrawn

General Principles for Evaluating Generic AD – 2017 FDA Guidance

- For product with AD labeling claim, a comparative evaluation of AD of T vs R for all potential routes of abuse
  - Tier-based approach to testing
  - Performance-based evaluation of abuse deterrence
  - Most effective manipulation
  - Sample selection after physical manipulation
  - Comparing T and R products in extraction studies
  - Statistical comparison of T and R products
- FDA intends to consider the totality of the evidence when evaluating the abuse deterrence of a generic solid oral opioid drug product.

www.fda.gov https://www.fda.gov/downloads/Drugs/.../Guidances/UCM492172.pdf

Overview of General Guidance for Generic AD Opioids



Applicant should demonstrate that: "A generic solid oral opioid drug product is no less abuse deterrent than its reference listed drug (RLD) with respect to all potential routes of abuse"

What PK Metrics Should Be Used to Compare Brand vs Generic AD?

Draft Guidance on Hydrocodone Bitartrate

Active Ingredient: Hydrocodone bitartrate

Dosage Form; Route: Tablet; extended release; oral

Recommended Studies: Two bioequivalence studies (1–2) and two in vivo comparative pharmacokinetic (PK) studies for abuse deterrence assessment (3–4)

3. Type of study: Fasting, comparative oral PK study of chewed drug products
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 60 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional Comments: See comments in Study 1. Patient-relevant chewing conditions that can discriminate between test and reference products' ability of deterring chewing should be identified. Determine relevant PK parameters including maximum concentration (C_{max}), area-under-the-curve (AUC_{0-t} and $AUC_{0-\infty}$), and time to maximum concentration (T_{max}). Applicants should submit partial AUCs (e.g., $AUC_{0\text{-}3\ hours}$ and $AUC_{0\text{-}4\ hours}$) as supportive data.

4. Type of study: Fasting, comparative nasal PK study with physically manipulated drug products, consistent with the recommendations in FDA's guidance, "*General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products,*" for tier 2 evaluation of abuse by insufflation as applicable
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 60 mg
Subjects: Non-dependent recreational opioid users, general population[1]
Additional Comments: See all comments in Study 1. Take scientifically appropriate and ethical steps to protect human subjects. This should include ensuring that each subject is not physically dependent on opioids (e.g., through a naloxone challenge test) and has not been seeking or undergoing treatment for abuse of controlled substances such that participating in the study could make them vulnerable to relapse.[2] Also see comments on PK parameters in Study 3. Pulverize test and reference products to a particle size range that is considered safe and tolerable for human insufflation studies. Characterize the formulation recovery, drug content, and particle size distribution of physically manipulated test and reference drug products used in the nasal PK study using validated analytical procedures.

Sample

PK metrics included in 7 PSGs for Morphine, Oxycodone, and Hydrocodone:

"Determine relevant PK parameters including maximum concentration (Cmax), area-under-the-curve (AUC0-t and AUC0-∞), and time to maximum concentration (Tmax). Applicants should submit partial AUCs (e.g., AUC0-3 hours and AUC0-4 hours) as supportive data"

What PK Metrics Should Be Used to Compare Brand vs Generic AD?

- Comparable C_{max} and AUC may not be sufficient in evaluating abuse deterrence
  - C_{max} and AUC are not significantly correlated with drug abuse potential endpoints (i.e., drug liking and take drug again)
- Additional BE metric can support generics to be no less AD than RLD
  - Literature reports suggest that the rate of rise of drug concentration contributes to differential abuse potential among drugs, formulations, and routes of administration
- Analysis only limited to data from non-combination product using antagonist or product with aversive agent

The Identification of Appropriate PK Metrics Related to Abuse Potential

PK Metrics

- Cmax: Maximum Drug Concentration
- Tmax: Time to reach to Cmax
- AUC: Area Under Curve
- AQ: Abuse quotient Cmax/Tmax
- PAUCx: Partial AUC for time 0 to x

Drug Abuse Potential

- VAS: Visual analogue scale
- TDA: VAS for take drug again
- DL: VAS for drug liking
- PAUECx: Partial AUC for DL from time 0 to x
- MAXTDA: maximum TDA
- MAXDL: maximum DL

What is VAS for TDA and DL?

- VAS scores assess subject's liking or disliking of the study drug either at a certain time point, or over a time period
  - Addiction Research Center Inventory (ARCI) questionnaire scales assess mood states and feelings associated with drug administration
- DL VAS assesses the subject's liking at the moment the question is asked. It is used for understanding the time course of drug effects
  - When evaluating the abuse potential of a substance or formulation, DL generally served as the primary endpoint
- TDA VAS assesses the subject's perception to take the drug again at least 8 hours after drug administration
- 2015 Guidance for Industry: Abuse-Deterrent Opioids Evaluation and Labeling
  - "The VAS should be the primary measure for drug liking because it appears to correlate most directly with potential for abuse".

How are VAS measures assessed?

- VAS measures can be assessed using either a unipolar or bipolar scale; and a rationale should be provided for the choice for a particular scale
- Bipolar scale:
  - 0-100 point
  - e.g., VAS for DL: “At this moment, my liking for this drug is”
  - 0 = “strong disliking”; 50 = “neither like or dislike”; 100 = “strong liking”
- Unipolar scale:
  - 0-100 point
  - e.g., VAS for TDA: “I would take this drug again”
  - 0 = “definitely not”; 100, “definitely so”

What is Partial AUC?

- Partial AUC (pAUC) is the metric OGD uses when the drug exposure within certain time period is clinically meaningful
  - For abuse deterrence, the initial drug exposure is important and pAUC can be used as a measure of rate of drug onset
- How to select pAUC
  - The relationship between PK variable and PD endpoints of clinical significance can be used to identify the most appropriate pAUC
  - Recommendations of pAUC can be API/product-specific
- Intent to identify pAUC as PK metric has motivated further research on PK-PD relationships based on data currently available

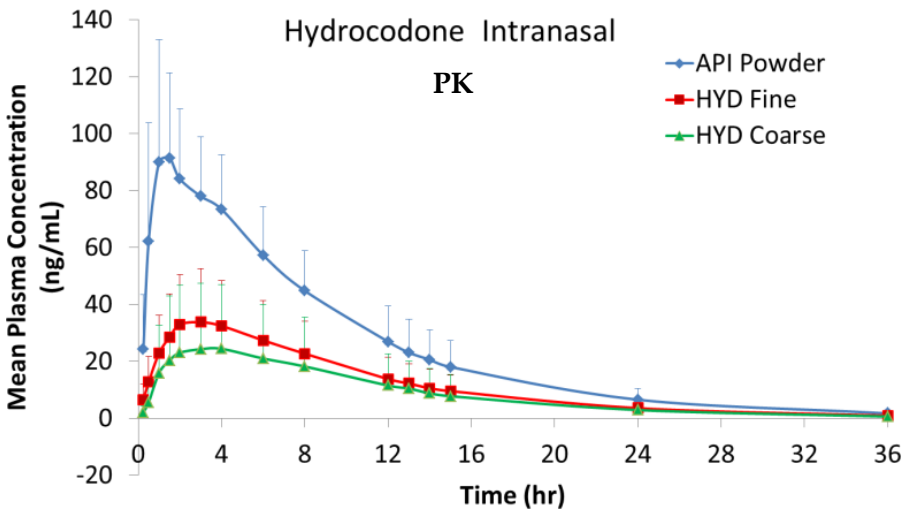
Research Goal

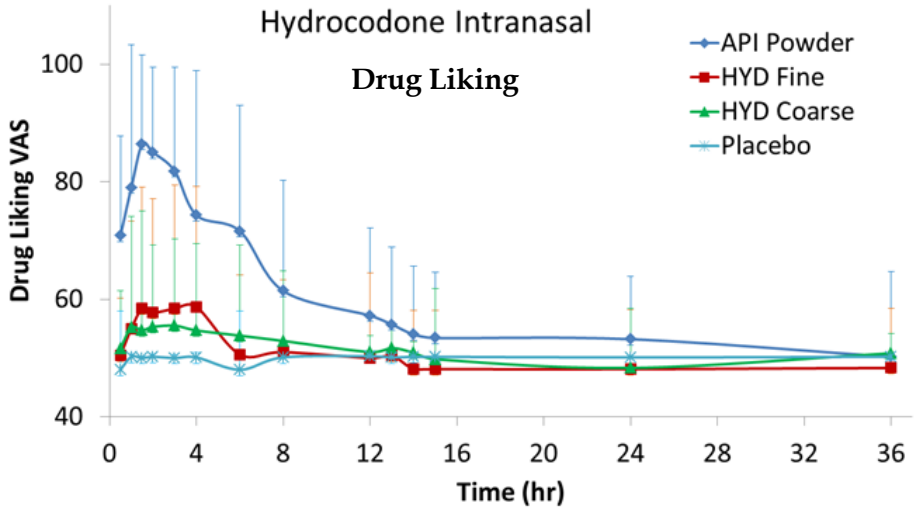
- Explore potential relationships between PK metrics, especially measures of the ascending part of the PK curve, and opioid abuse potential
- Implement the identified PK metrics in PSGs for AD evaluation

PK/PD dataset for Analysis: Eleven Clinical Trials

Substance	BRAND	ROUTE
Oxycodone	OxyContin	IN
Oxycodone	Xtampza	IN (PO)
Oxycodone	Xtampza	PO
Oxycodone	RoxyBond	IN (PO)
Hydrocodone	Hysingla	PO
Hydrocodone	Hysingla	IN
Hydrocodone	Vantrela	IN (PO)
Hydrocodone	Vantrela	PO
Morphine	MorphaBond	IN (PO)
Morphine	Arymo	PO
Morphine	Arymo	IN (PO)

Hydrocodone PK-PD Profiles: Intranasal



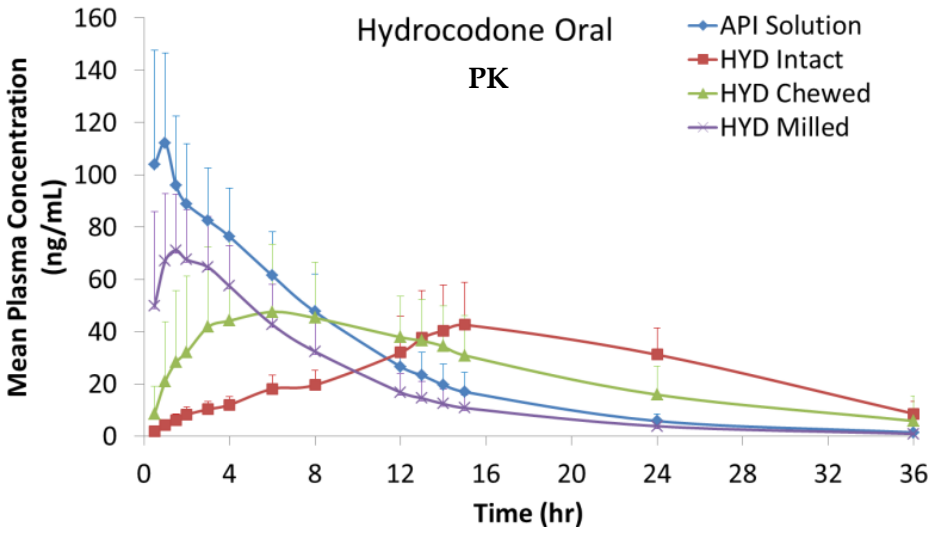


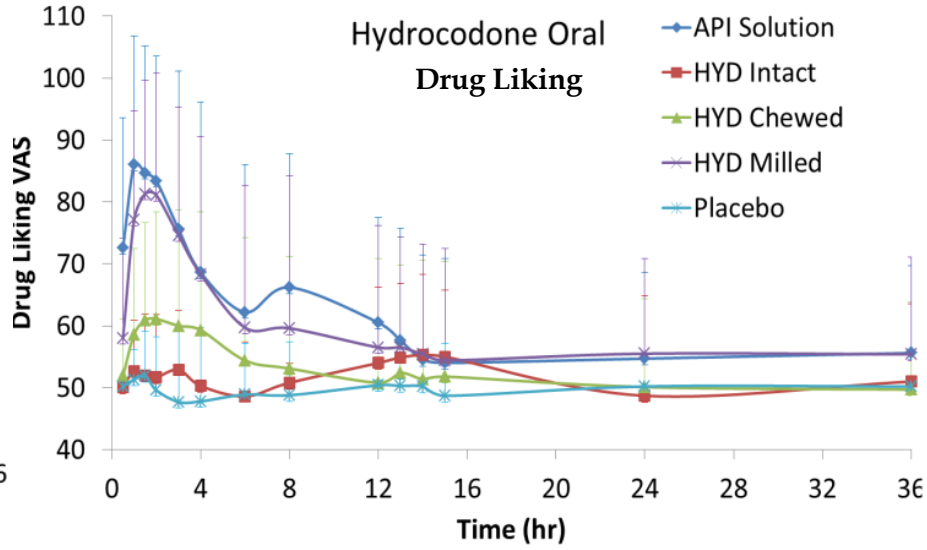
Maximum Take Drug Again VAS (Emax) from Intranasal Route

Treatments	API Powder	HYD Fine	HYD Coarse	Placebo
Mean (SD)	85.2 (24.9)	40.7 (38.4)	36.4 (41.0)	2.0 (10.0)

Adapted from the presentation by Liang Zhao in 2016 FDA Public Meeting on Pre-market Evaluation of Abuse Deterrence Properties of Opioid Drug Products (https://www.fda.gov/Drugs/NewsEvents/ucm509853.htm)

Hydrocodone PK-PD Profiles: Oral

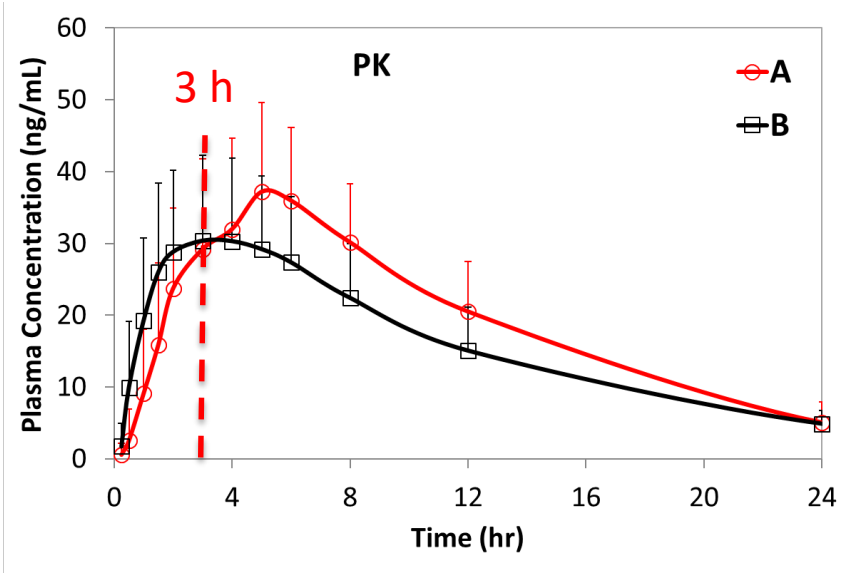


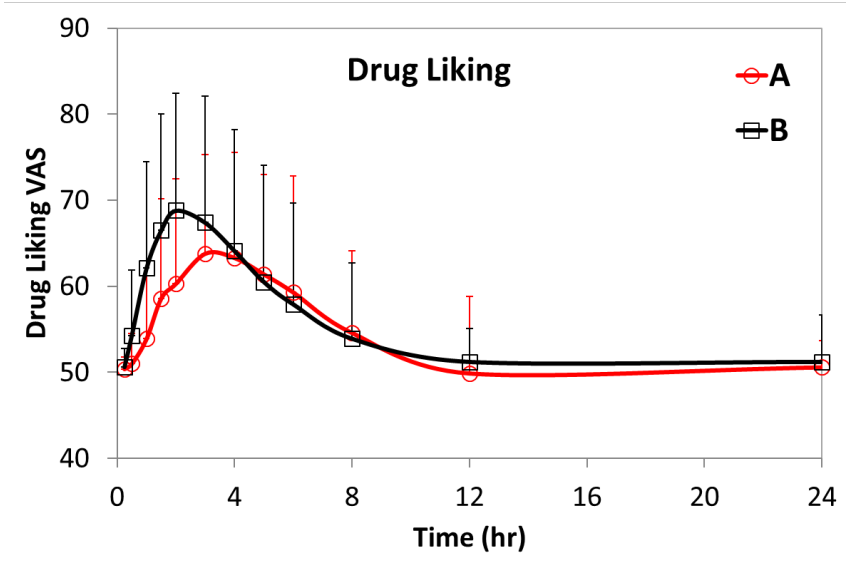


Maximum Take Drug Again VAS (Emax) from Oral Route					
Treatments	API Solution	HYD Intact	HYD Chewed	HYD Milled	Placebo
Mean (SD)	89.7 (21.2)	34.3 (36.0)	44.3 (40.8)	84.1 (28.1)	3.9 (15.9)

Adapted from the presentation by Liang Zhao in 2016 FDA Public Meeting on Pre-market Evaluation of Abuse Deterrence Properties of Opioid Drug Products (https://www.fda.gov/Drugs/NewsEvents/ucm509853.htm)

Use of Early pAUC in Addressing Comments from Branded Industry Working Group

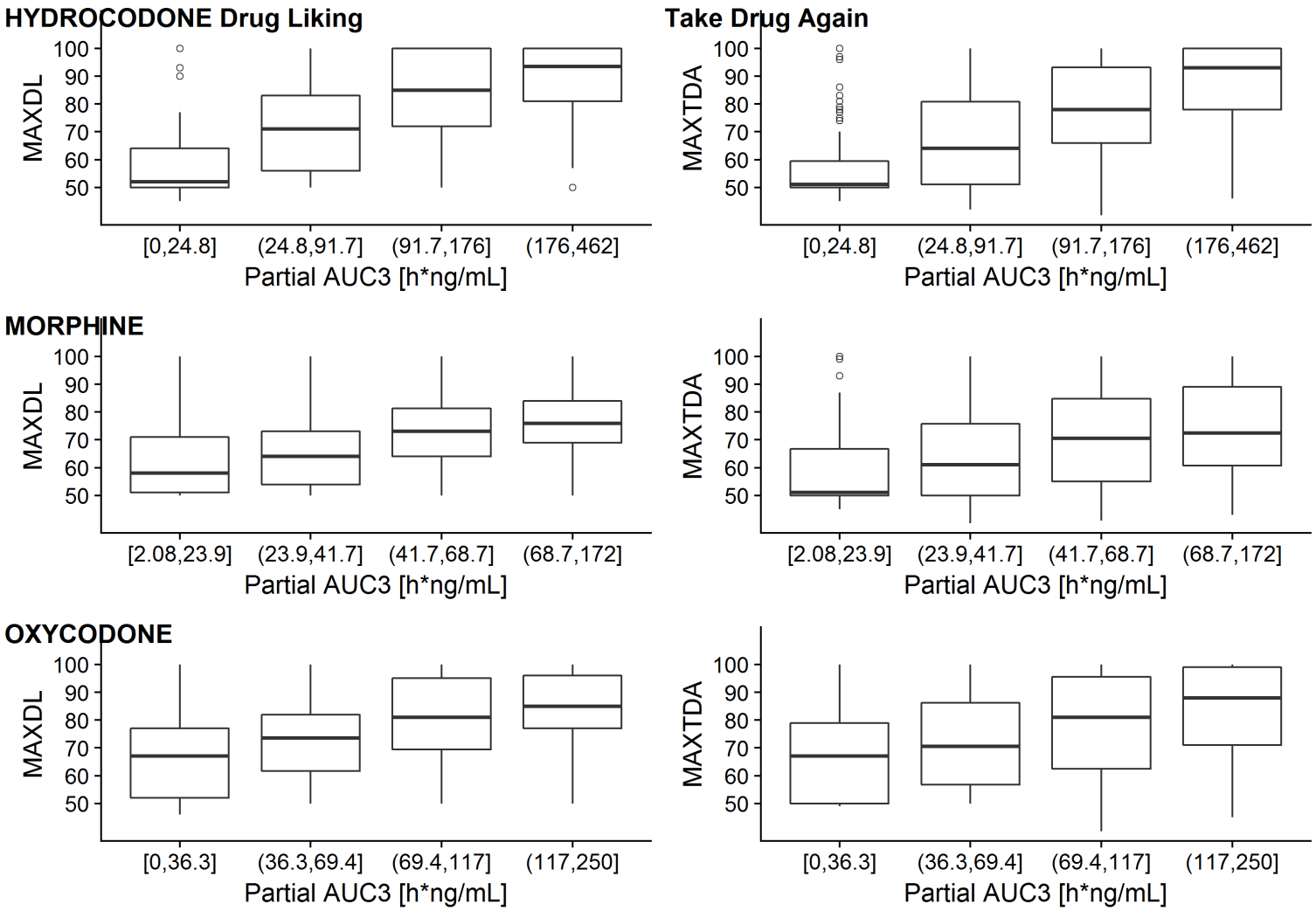




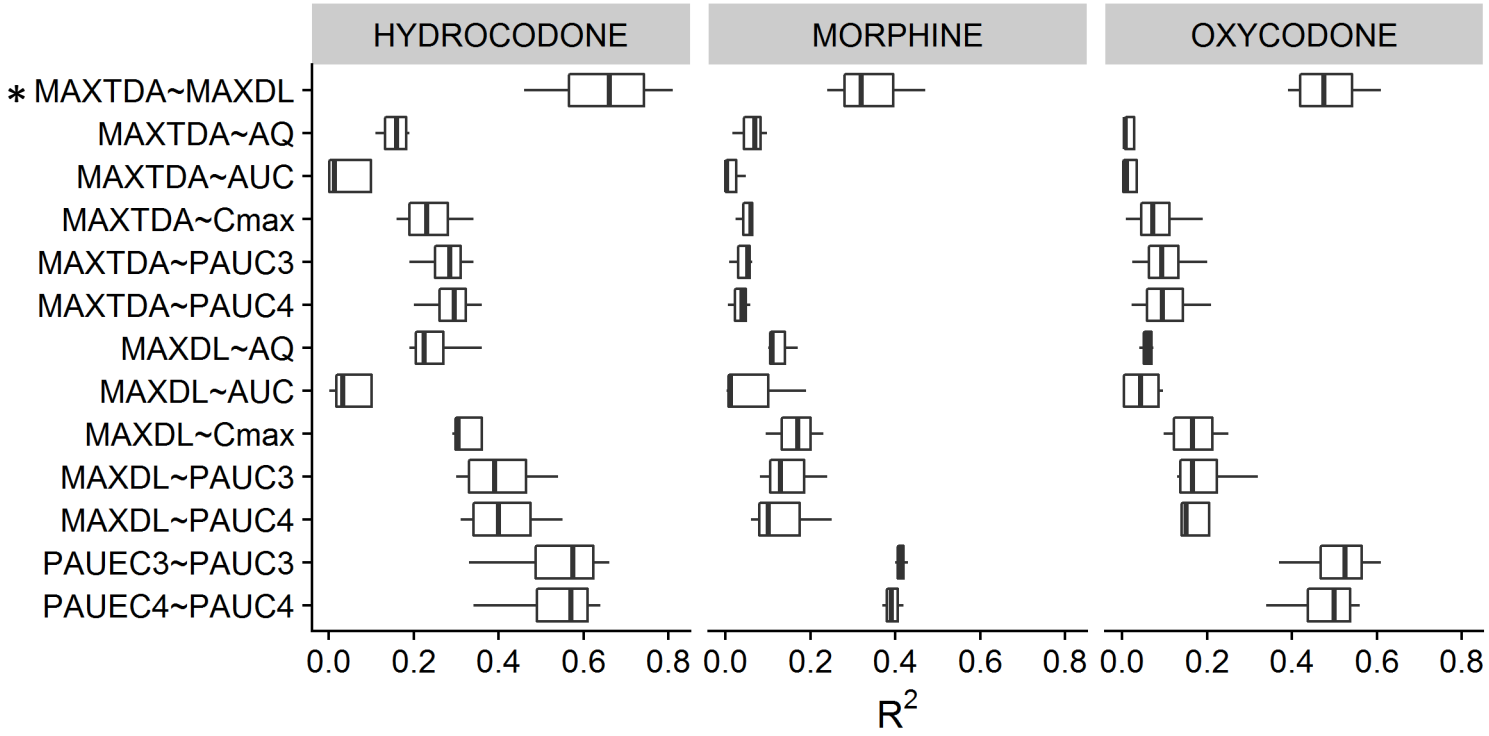
- BIWG commented that compared to A, B had lower Cmax, but produced greater MAXDL
- Geometric mean ratio (A/B)
  - pAUC3: 0.66 (90% CI: 56.49-76.48%)
  - pAUC4: 0.76 (90% CI: 66.71-87.50%)

PK/PD Curves Adapted from the presentation by Jeffrey M. Dayno in 2016 FDA Public Meeting on Pre-Market Evaluation of Abuse-Deterrent Properties of Opioid Drug Products. (https://www.fda.gov/Drugs/NewsEvents/ucm509853.htm)

Correlation between VAS and Categorized PAUC3 for Each API



Highest Correlation between Early PAUEC and Early PAUC among PK/PD Metrics



- PK metrics: Cmax, AUC, AQ, PAUC3, PAUC4
- PD metrics: MAXDL, MAXTDA, PAUEC3, PAUEC4
- R^2: variation in a PD metric that can be explained by a PK metric using a linear regression model

On-going Research: Nasal PK/PD studies of oral combination products containing opioid agonists and antagonists

- Contract #HHSF223201610004I
- Awarded to BioPharma Services USA Inc. in Sep 2018
- Objective: to investigate factors that affect PK and PD effects of opioid agonists and antagonists
- Specific Aims:
  - In vitro characterization of milled products containing morphine sulfate and naltrexone hydrochloride
  - Nasal PK and PD (abuse potential) study of milled products
- Impact: may help determine critical study design parameters when comparing abuse deterrence of a combination product in the nasal route between a generic product and its RLD

Future Research: PK Study of Opioid Drug Products following Oral Ingestion of Chewed Products

- Contract – future plan
- Objective: to investigate factors that affect bioavailability (i.e., PK) of opioid drug products following oral ingestion of chewed products and develop in vitro in vivo correlation/relationship.
- Specific Aims:
  - In vitro evaluation of oral abuse deterrence via chewing
  - Oral chewing PK study of opioid drug products
  - Develop in vitro in vivo correlation/relationship
- Impact: expected to help determine critical study design parameters when comparing abuse deterrence of an opioid product in the oral route between a generic product and its RLD when chewed. The results from this study will also help validate in-house developed in vitro chewing study methods and can aid in product development.

Conclusions

- In vivo PK studies are part of generic ADF recommendations for bioequivalence assessment

- Based on the identified PK-PD relationship for opioid abuse potential, current PSGs recommend using partial AUCs as supportive measures of AD

- Ongoing internal assessment to further understand the relationships among formulation parameters, PK metrics, and PD endpoints as measures of abuse potential

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- **The CDER Opioids Task Force**


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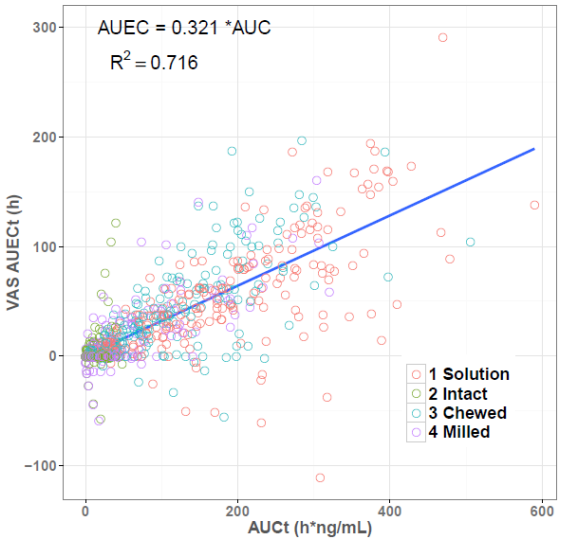
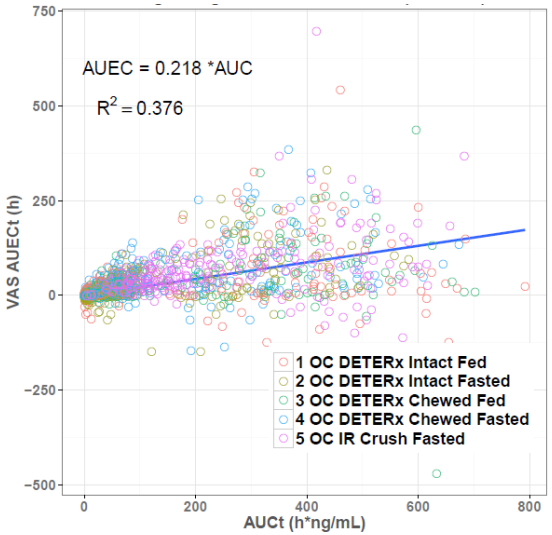
VAS PAUEC$_{0-4}$ and PAUC$_{0-4}$

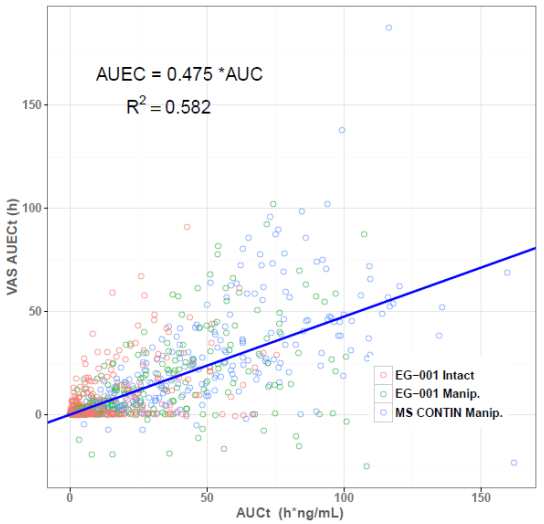
Hydrocodone Oral



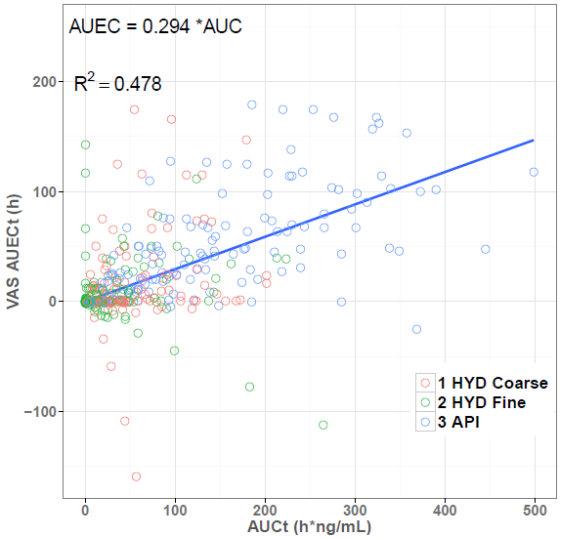
Oxycodone Capsule Oral



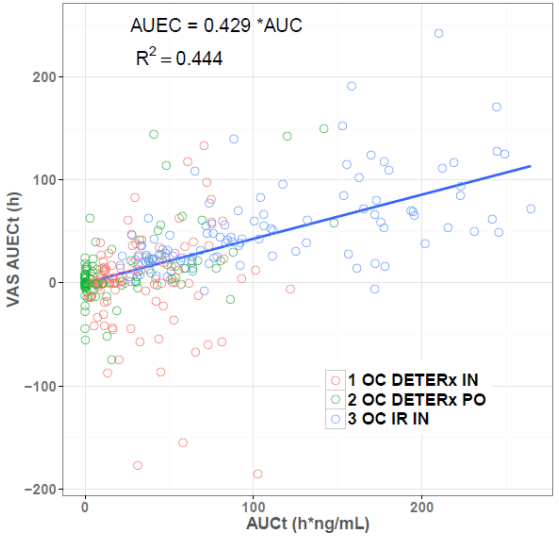
Morphine Oral



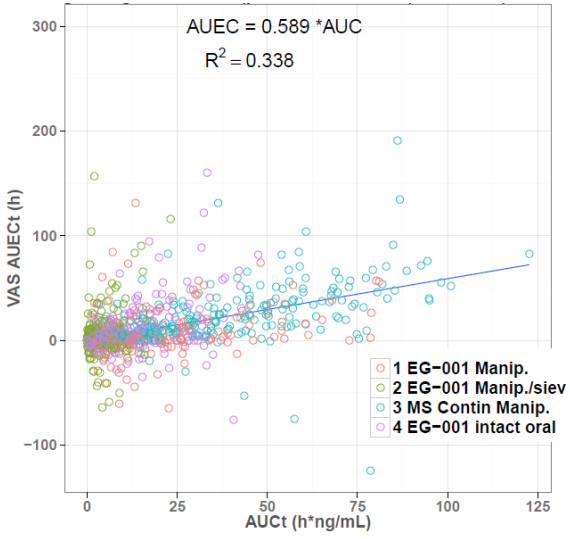
Hydrocodone IN



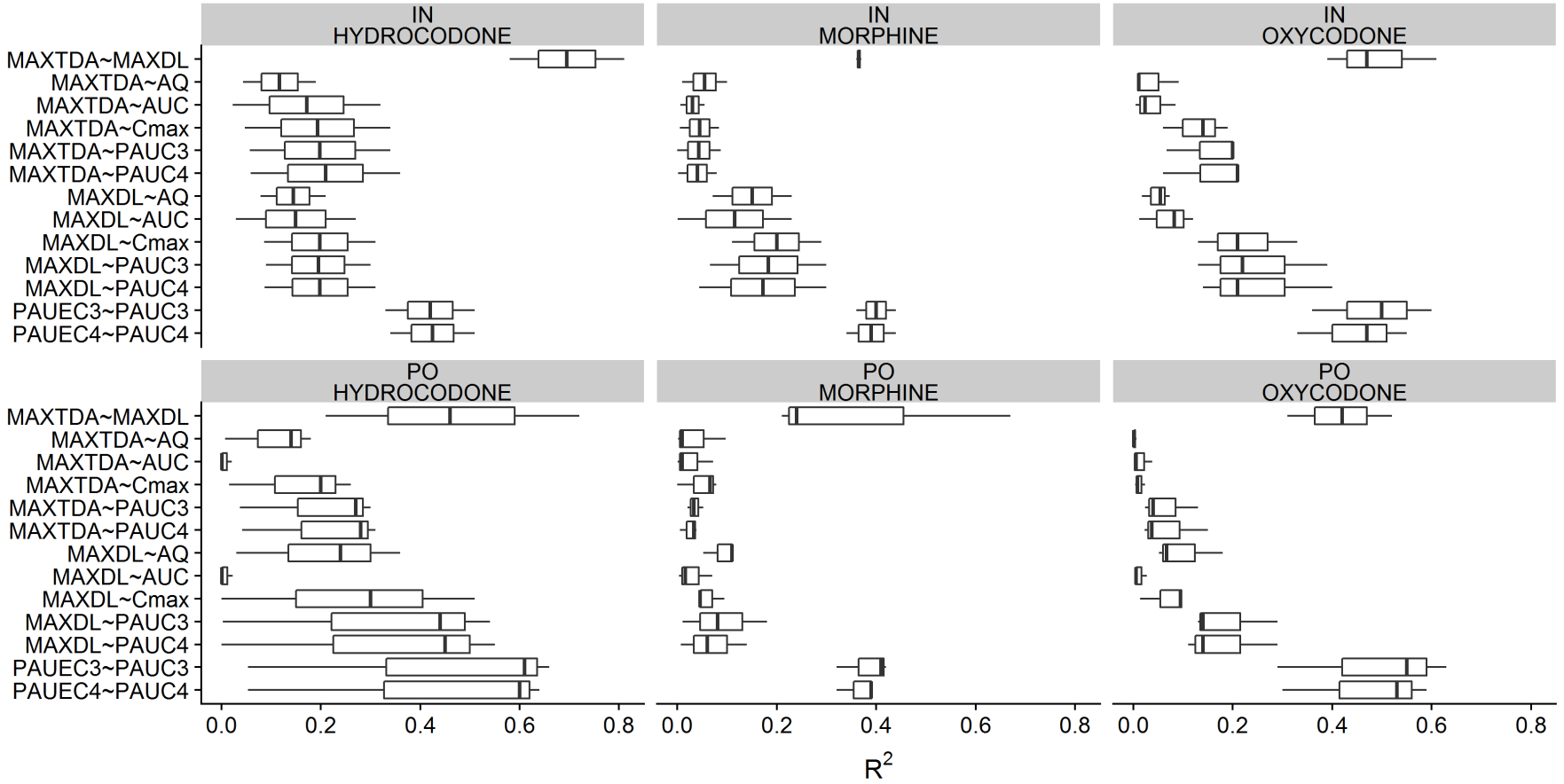
Oxycodone Capsule IN



Morphine IN



Highest Correlation between Early PAUEC and Early PAUC among PK/PD Metrics

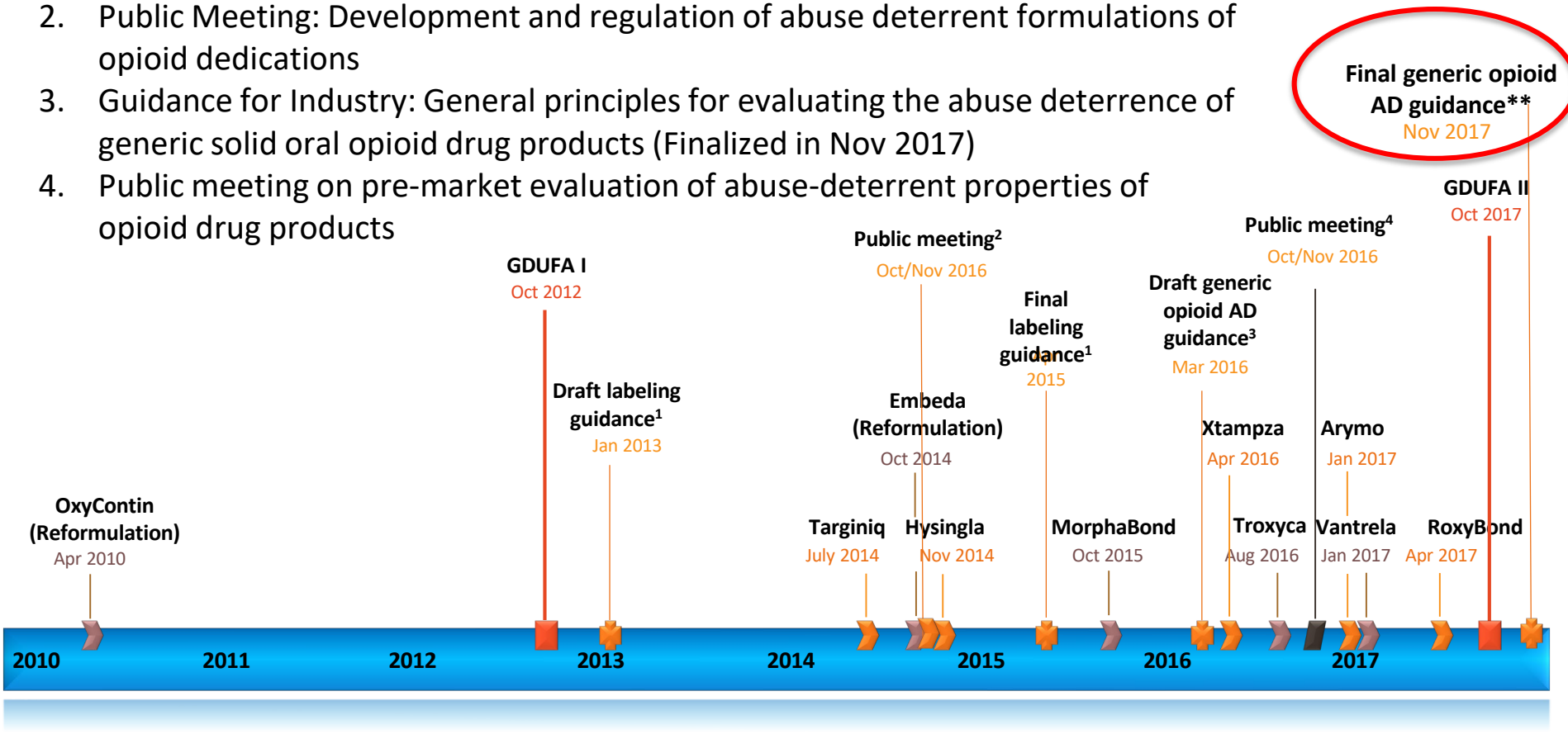


- PK metrics: Cmax, AUC, AQ, PAUC3, PAUC4
- PD metrics: MAXDL, MAXTDA, PAUEC3, PAUEC4
- R^2: variation in a PD metric that can be explained by a PK metric using a linear regression model

Adapted from the presentation by Zhichuan (Matt) Li in 2018 OGD Science Forum

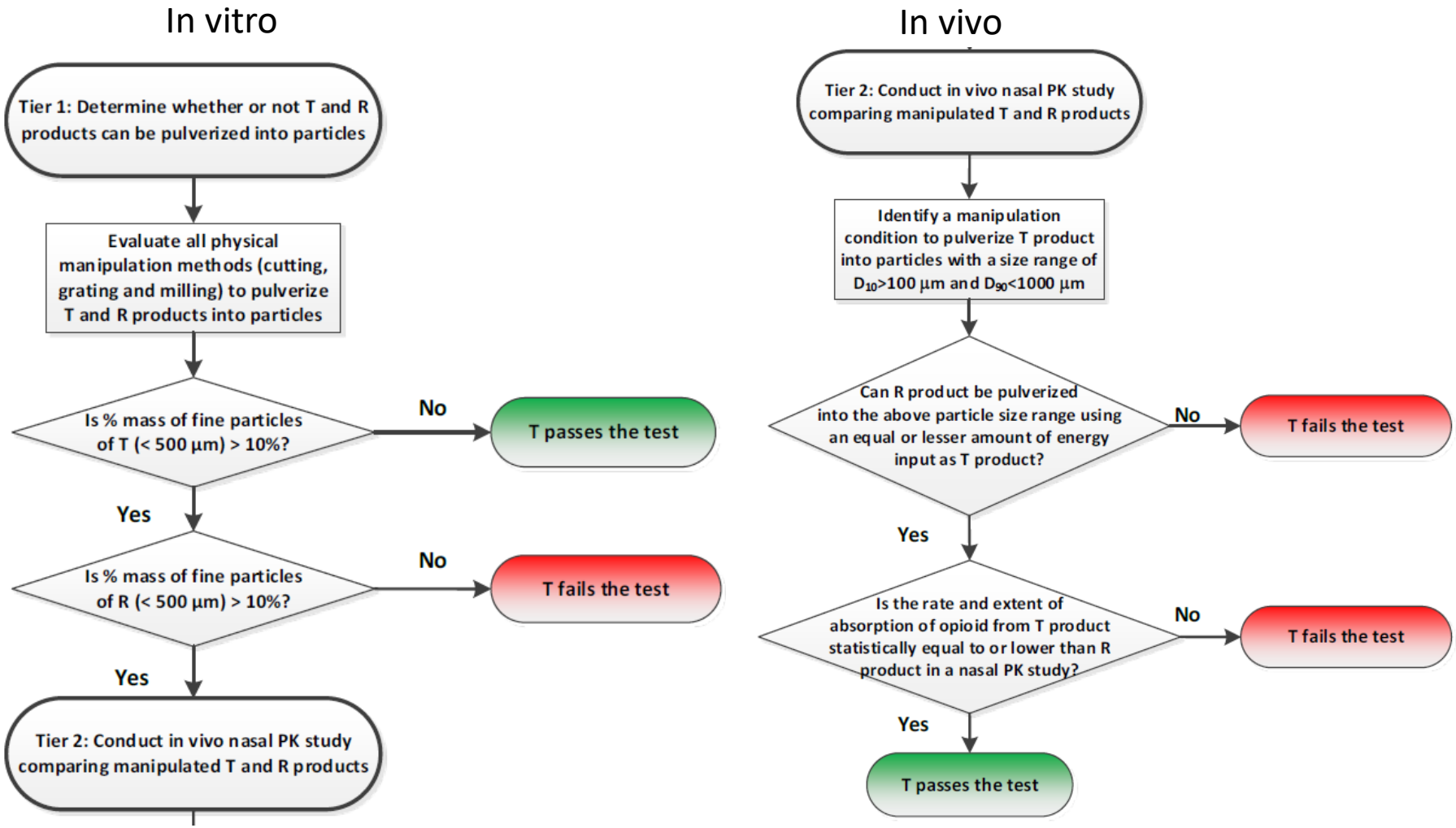
Regulatory Activities Related to Generic Opioid ADF

1. Guidance for Industry: Abuse-deterrent opioids – evaluation and labeling
2. Public Meeting: Development and regulation of abuse deterrent formulations of opioid dedications
3. Guidance for Industry: General principles for evaluating the abuse deterrence of generic solid oral opioid drug products (Finalized in Nov 2017)
4. Public meeting on pre-market evaluation of abuse-deterrent properties of opioid drug products



www.fda.gov

Decision Tree for Evaluation of Abuse Deterrence Potential (Abuse by Insufflation)



Abuse-Deterrence Nasal PK Studies

- T is no less resistant to physical manipulation than R and both can be pulverized to a particle size range considered safe and tolerable for human insufflation studies
- Be conducted using the same dose that was used in in vitro testing
- Characterize the particle size distribution of physically manipulated T and R products
- Be conducted in recreational opioid users
- Incorporate naltrexone or other opioid antagonist to block the PD effects of the opioids except for the agonist/antagonist combination products
- PK parameters include Cmax, Tmax, and AUC(0-t) and AUC(0-∞)
- A potential ANDA applicant should also determine the partial AUCs (p-AUCs)
  - E.g., in the case in which there is a clear relationship between the truncated partial area in the PK profiles at specific time points and a clinically relevant PD measure (e.g., likability or take-drug-again)

Potential Routes of Abuse

- Ingestion (oral route)—evaluate oral bioavailability of physically manipulated or chewed products
- Injection (parenteral route)—evaluate the extractability and syringeability of intact and manipulated products
- Insufflation (nasal route)—evaluate the nasal bioavailability and pharmacodynamic (PD) effects
- Smoking (inhalation route)—evaluate the ability to sublimate intact and manipulated products

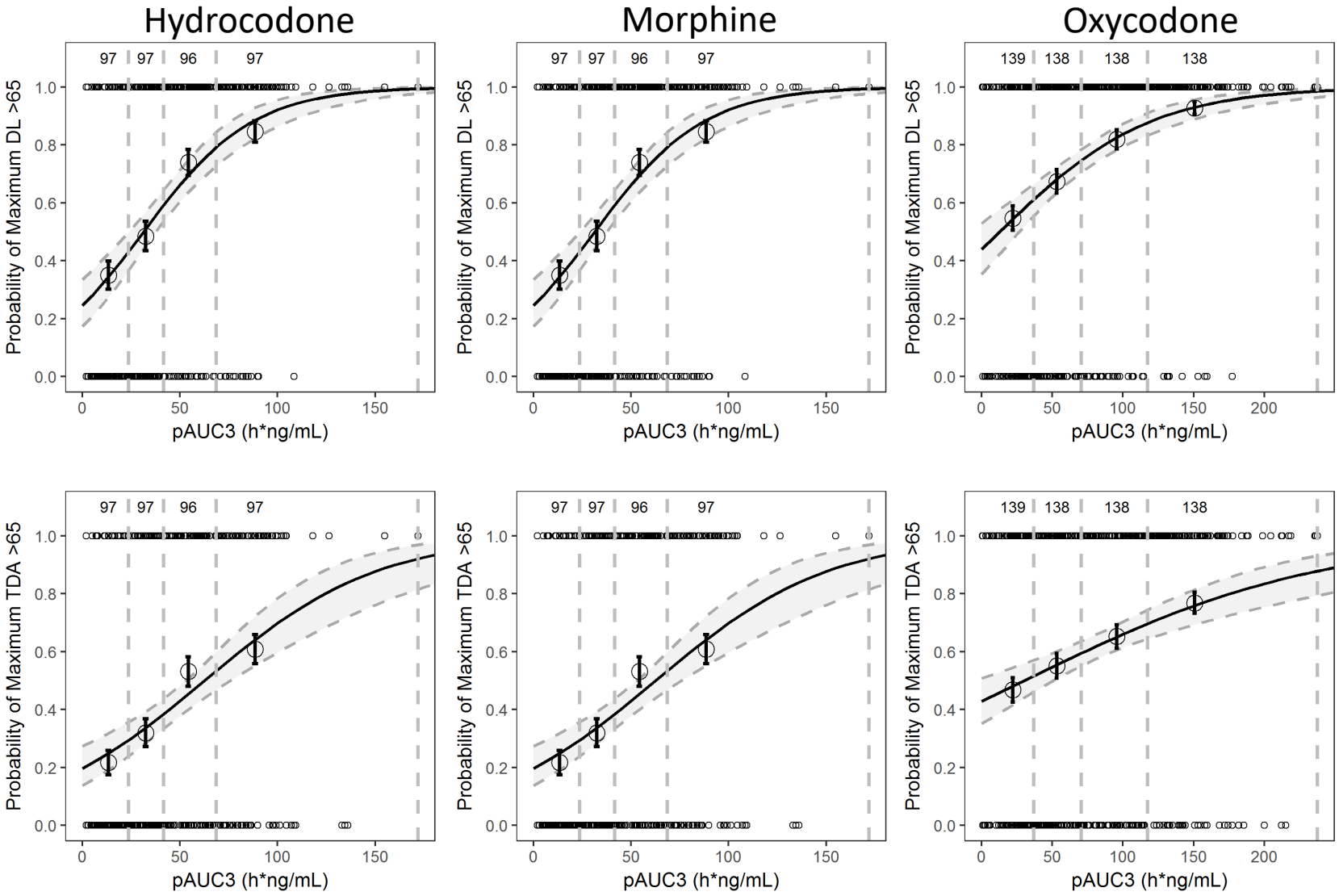
Clinical PK/Abuse Deterrence Studies Available for PK – PD Relationships For Single API Products: Hydrocodone, Oxycodone, and Morphine

Opioids	Hysingla ER Hydrocodone		Xtampza ER Oxycodone	OxyContin Oxycodone	MorphaBond Morphine
Trial	HYD1013	HYD1014	OXYDET-21	OTR-1018	M-ARER-002
Route	Oral	Intranasal	Intranasal	Intranasal	Intranasal
Study	Randomized, double-blind, placebo-controlled, crossover study				
Subject	40	25	36	30	27
Arms	A: API Solution 60 mg B: HYD 60 mg intact C: HYD 60 mg chewed D: HYD 60 mg milled E: Placebo	A: API 60 mg B: HYD 60 mg fine C: HYD 60 mg coarse D: Placebo	A: DETERx 40 mg crushed IN B: DETERx 40 mg intact PO C: OC IR 40 mg crushed IN D: Placebo	A: OTR 30 mg fine B: OTR 30 mg coarse C: OC 30 mg fine D: API powder 30 mg E: Placebo	A: IDT-001 60 mg crushed B: IDT-001 60 mg intact C: MS Contin 60 mg crushed D: Placebo
Endpoints	**Drug Liking VAS, Take drug again VAS**, Overall drug liking VAS, High VAS, Good effects VAS, Any effect VAS, ARCI MBG Scale (euphoria), ARCI PCAG (sedative), and pupil size				

Abuse-Deterrence PK Studies

- Oral (chewed or crushed) PK studies
  - The summary in Section 9.2 of the RLD labeling indicates AD properties to deter abuse by the oral route
  - For PK studies of crushed ADF, T and R should be physically manipulated into a particle size range that can discriminate the ability to deter abuse. For PK studies of chewed ADF, patient-relevant chewing conditions should be identified
  - Studies should be conducted in **healthy** volunteers
- Nasal PK studies
  - In vitro testing shows that T is no less resistant to physical manipulation than R and T and R can be pulverized to a particle size range that is considered safe and tolerable for human insufflation (i.e., D_{10}>100 μm and D_{90}<1000 μm)
  - Physically manipulated T and R products used in the nasal PK study should be characterized (e.g. particle size distribution, formulation recovery, drug content)
  - Studies should be conducted in **recreational opioid users**

Probability of MAXDL/MAXTDA>65 is correlated with PAUC3



Correlation between PAUC3 and categorized VAS (cutoff = 65) for each API