Foundations of Pharmacokinetic Comparisons of Generic Opioids to RLDs with Labeling Describing Abuse-Deterrent Properties

Liang Zhao, Ph.D.
Director, Division of Quantitative Methods and Modeling
Office of Research and Standards
Office of Generic Drugs
Center for Drug Evaluation and Research, FDA

Public Meeting on Pre-market Evaluation of AD Properties of Opioid Drug Products
October 31st, 2016

General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products (2016 Draft)

- If the RLD's labeling describes properties that are expected to deter misuse or abuse, the potential ANDA applicant should evaluate its proposed generic drug product in comparative in vitro studies **and, in some cases, in relevant pharmacokinetic or other studies** to show that it is no less abuse-deterrent than the RLD with respect to all potential routes of abuse.
- FDA intends to consider the totality of the evidence when evaluating the abuse deterrence of a generic solid oral opioid drug product.

General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products (2016 Draft)

- **PK studies as mentioned in guidance** should be conducted to ensure the absence of significant difference in the rate and extent of absorption

- **Comparative abuse-potential studies** are generally not necessary, except in certain circumstances: e.g., comparing the abuse deterrence potential of an excipient that functions as an aversive agent.

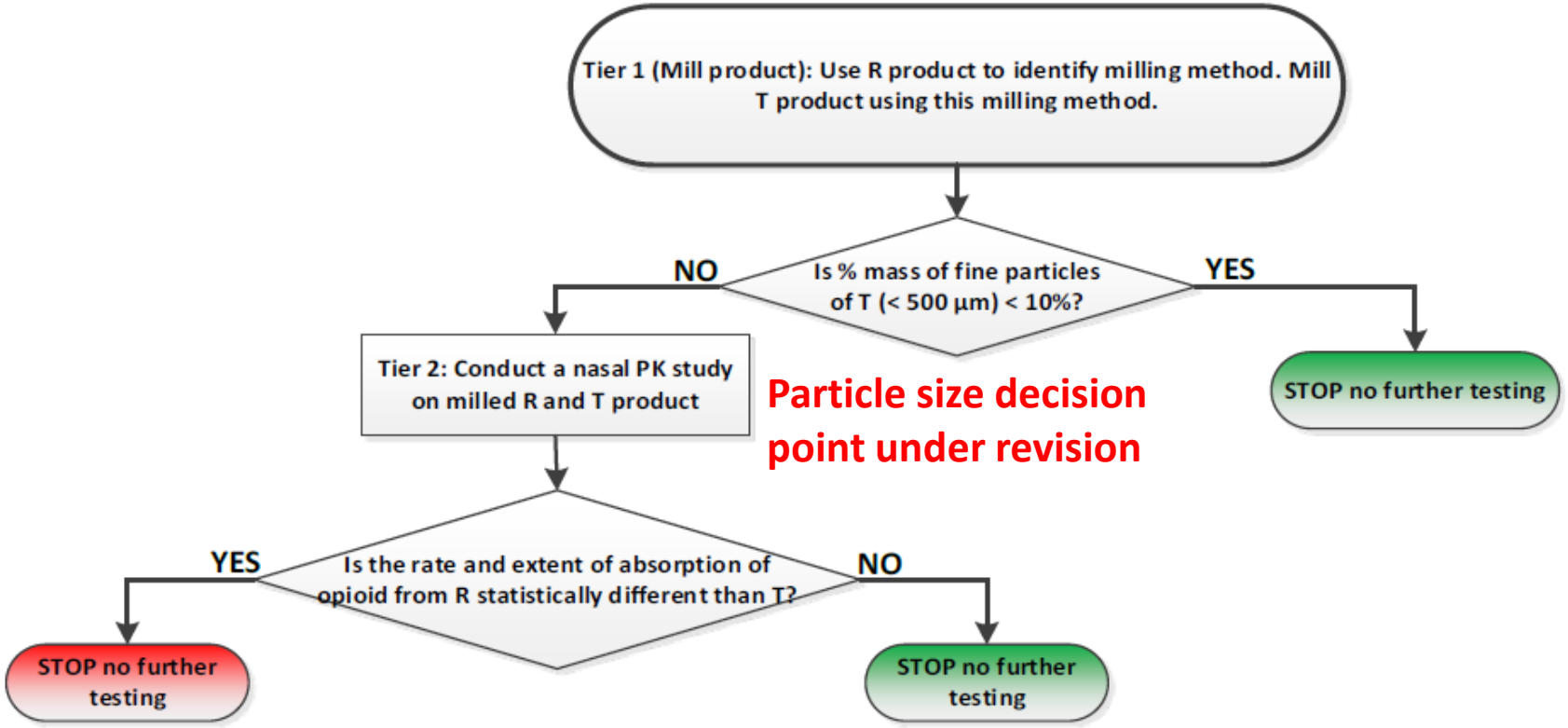
Deterrence of Abuse by Insufflation in All ADF Opioid Product Labels

NDA	API	Firm	Brand	Approval	Dosage Form	Abuse Deterrence
206627	Hydrocodone	PURDUE	Hysingla ER	11/20/14	ER Tablet	Oral, IN
208090	Oxycodone	COLLEGIUM	Xtampza ER	04/26/16	ER Capsule	IN
022272	Oxycodone	PURDUE	OxyContin	04/05/10	ER Tablet	IN
206544	Morphine	INSPIRION	MorphaBond	10/02/15	ER Tablet	IN
207621	Oxycodone/ Naltrexone	PFIZER	Troxyca ER	08/19/16	ER Capsule	Oral, IN
205777	Oxycodone/ Naloxone	PURDUE	Targiniq ER	07/23/14	ER Tablet	IN, IV
022321	Morphine/ Naltrexone	PFIZER	Embeda	08/13/09	ER Capsule	Oral, IN

As of 10/20/2016

IN: intranasal

Draft Guidance Decision Tree



For products with abuse deterrent claims by insufflation, applications quickly get to PK studies

In vitro characterizations of physicochemical properties cannot predict in vivo PK profile of nasal powder

Nasal PK Study in Current Draft Guidance

- PK study as mentioned
  - In healthy volunteers incorporating naltrexone to block the PD effects of opioids
  - Cmax, Tmax, AUC and pAUCs (when applicable) for opioid product and any active metabolites
  - Statistically significant difference in profiles
- Revisions to discuss today
  - Population should be experienced nasal abusers
  - Confidence interval criteria
  - When comparing R and T, the same level of mechanical or chemical manipulation to maximize the availability of R and T should be applied prior to administration through the proposed route
  - Questions via OGD control correspondence process

Other Routes Where PK Studies are Relevant

- For discussion today (Oral Route)
- For single API products with oral abuse deterrence claims when in vitro testing is not sufficient (eg, by chewing)
- Agonist/antagonist combinations:
  - All active ingredients (e.g. Oxycodone/Naltrexone) should be measured in the BE PK studies on intact products
  - PK studies to confirm oral absorption of sequestered actives after manipulation will be recommended in product specific guidance if needed

Standard BE Assessment for Generic Products

- Study Design:
  - Single-dose, two-way crossover, fasted + fed
  - Alternatives: Single dose parallel (fasted), single dose replicate, multiple dose two way cross over (fasted), clinical endpoint study

- Statistical Analysis:
  - 90% Confidence Intervals (CI) must fit between 80%-125%

PK Evaluations: Cmax, AUC, and Rate of Rise of the Initial PK Profile

- Evaluations on Cmax and AUC may not be sufficient
  - Conventional BE assessment typically based on Cmax and AUC following single dose
- FDA exploring relationships between PK metrics and abuse deterrence in terms of VAS including rate of rise of the initial PK profile
  - Focus is on relationship between PK metrics and VAS
  - Abuse deterrence can be correlated to the rate of drug onset
  - Equivalence in AUC and Cmax do not ensure similar rate of rise in the initial part of the PK profile

PK Evaluations: 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

Endpoints for Drug Liking and Abuse Deterrence from Clinical Studies

PD endpoints commonly measure include:

VAS: take drug again, drug liking, overall drug liking, high VAS, good effects, and any effect.

ARCI MBG Scale (euphoria), ARCI PCAG (sedative), and Pupillometry

2015 Guidance 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".

The Agency considers VAS to be the most important premarket testing endpoint in assessing the clinical relevance of the abuse-deterrent effects of a product

Case Example:

Hysingla ER Tablet
(hydrocodone bitartrate)

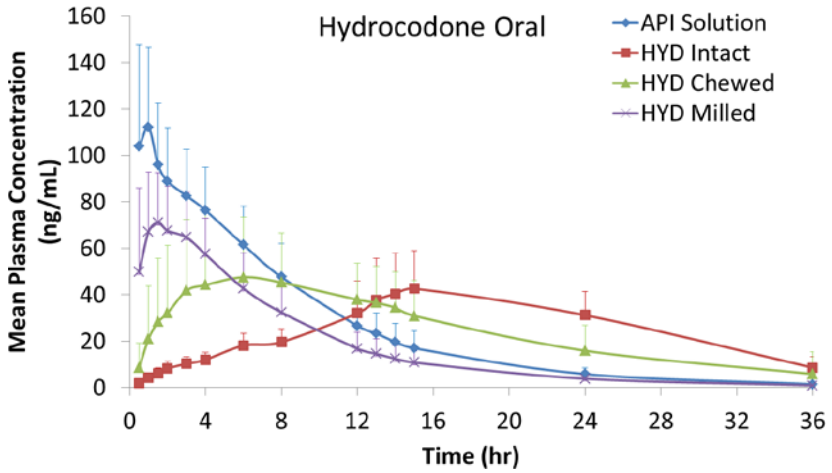
FDA has determined that this product has abuse-deterrence properties which are expected to deter intranasal abuse, oral abuse when chewed, intravenous abuse

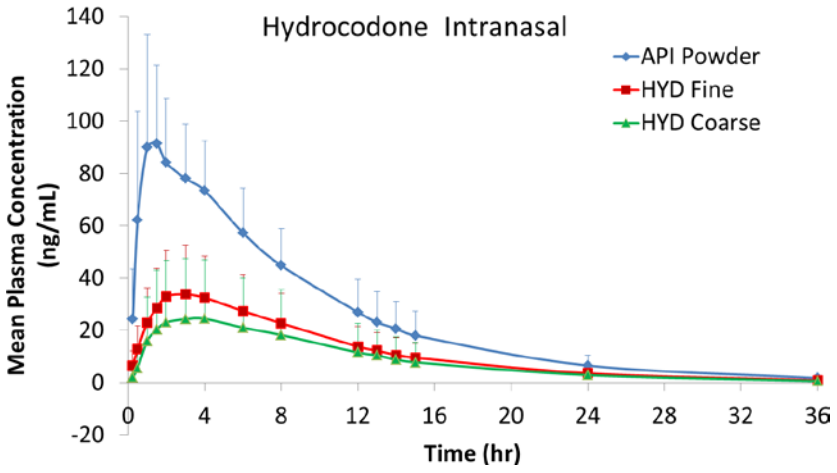
Clinical PK/Abuse Deterrence Studies for Hydrocodone

Opioids	**Hysingla ER Hydrocodone**	
Trial	HYD1013	HYD1014
Route	Oral	Intranasal
Study	Randomized, double-blind, placebo-controlled, crossover study	
Subject	35	25
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
Endpoints	**Take drug again VAS**, **Drug Liking VAS,** Overall drug liking VAS, High VAS, Good effects VAS, Any effect VAS, ARCI MBG Scale (euphoria), ARCI PCAG (sedative), and pupil size	

Hydrocodone PK Profiles

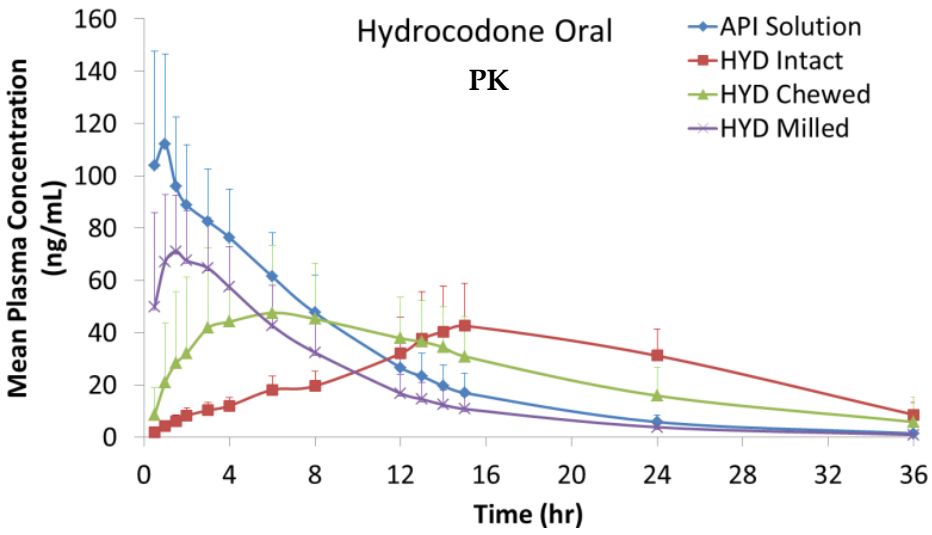
ADF vs non ADF, Intact vs Manipulated

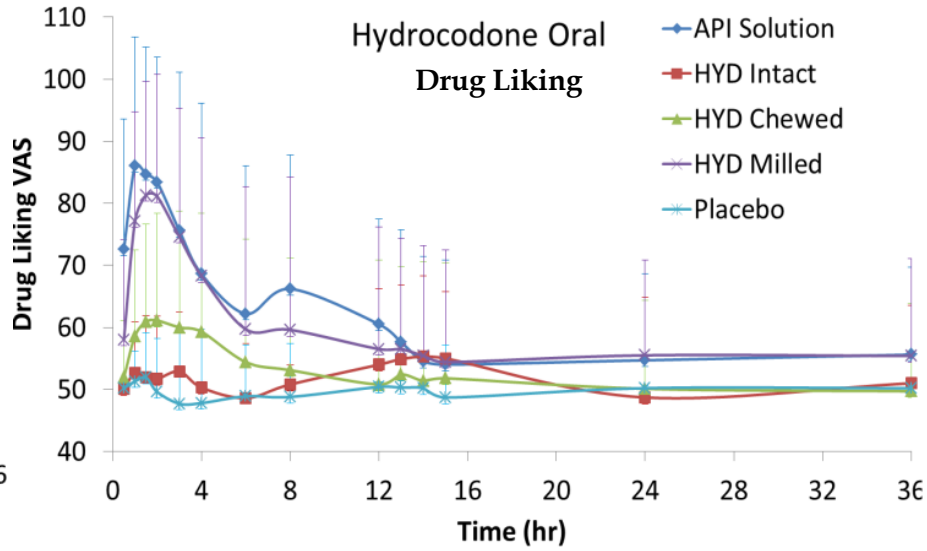




- In comparison to the positive controls (API solution or powder), ADF has lower Cmax and longer Tmax
- Manipulated tablet has higher Cmax and shorter Tmax than intact tablet
- Changes in $AUC_{0\text{-last}}$ are less prominent following oral route of administration

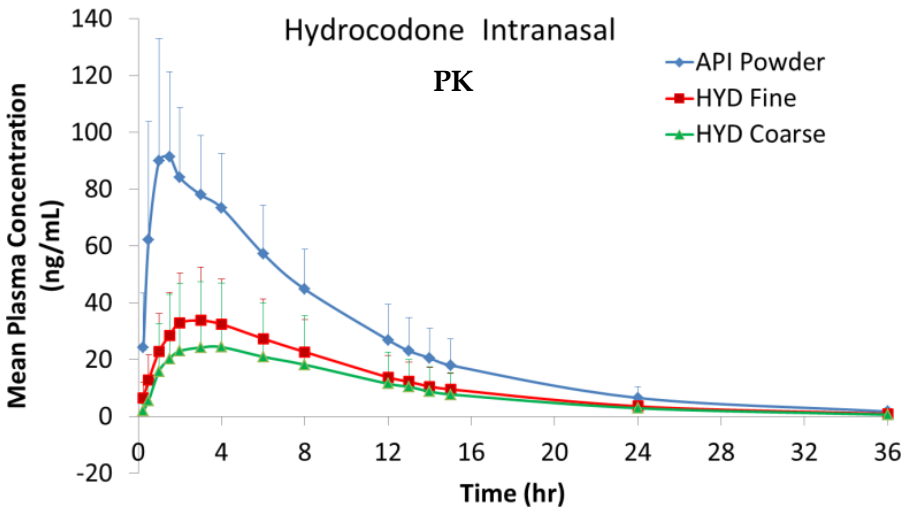
Hydrocodone PK-PD Profiles: Oral

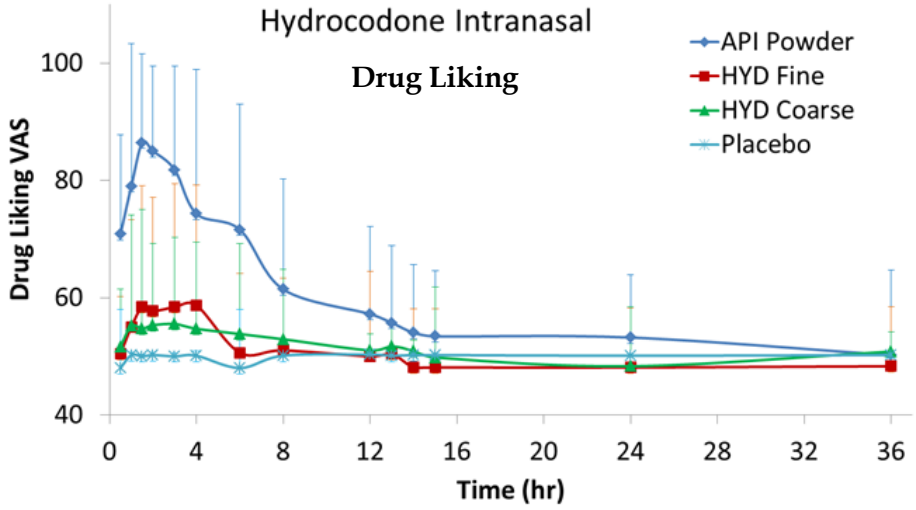




Maximum Take Drug Again VAS (Emax) from Oral Route					
Treatments	API Solution	HYD Intact	HYD Chewed	HYD Milled	Placebo
Mean (SD)	89.7 (21.2)	34.3 (36.0)	44.3 (40.8)	84.1 (28.1)	3.9 (15.9)

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)

Conclusions

- For the hydrocodone product with abuse deterrent properties
  - Drug liking VAS curves follow a similar pattern as observed in PK curves
  - Based on take drug again VAS, the manipulated products show less abuse potential than control for the routes of abuse deterrent property as described in its labeling (ie, intranasal route and oral abuse when chewed)
  - PD endpoints have higher variability
- Ongoing internal assessment to quantitatively explore the relationship between PK metrics and PD endpoints including take drug again VAS for other opioid APIs with abuse deterrent formulations

Summary of Guidance Regarding Use of PK Data

- PK studies are important for products with abuse-deterrent claims
  - For Agonist/Antagonist combinations: PK studies to confirm oral absorption of sequestered actives after manipulation will be recommended in product specific guidance
- PK studies are generally expected for abuse deterrent claims
  - By insufflation and
  - By ingestion when in vitro testing is not sufficient

Acknowledgement

- **ORS/OGD**

  Zhichuan (Matt) Li PhD

  Yehua (Josh) Xie PhD

  Xiaoyan Yang PhD

  Nan Zheng PhD

  Lanyan (Lucy) Fang PhD

  Myong-Jin Kim PharmD

  Robert Lionberger PhD

- **OCP/OTS**

  Srikanth Nallani PhD

- **OND**

  Sharon Hertz MD

- **The Opioid Abuse Deterrent Planning Team**

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				