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PK/PD meta-analysis of abuse deterrent opioid drug products: PSG Development, Research and ANDA Assessment

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SBIA: Complex Drug Product Development Workshop
September 25-26, 2019

Outline

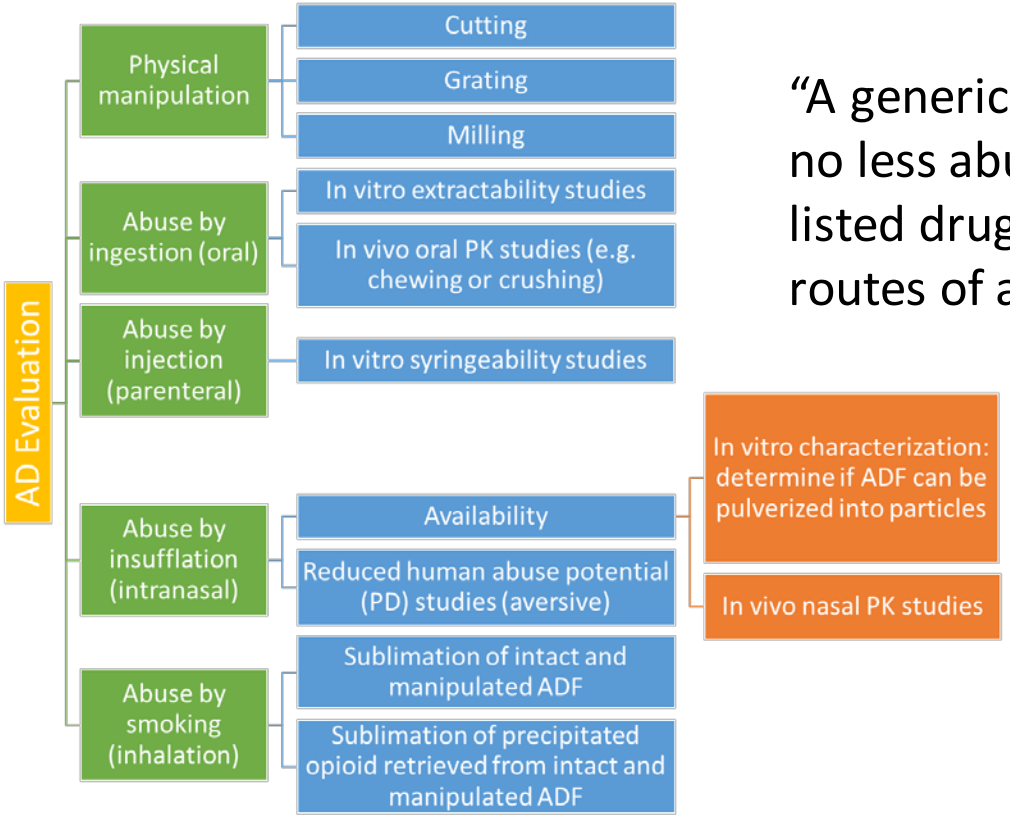
- Abuse-deterrent (AD) opioid drug products
- Pharmacokinetic/Pharmacodynamic (PK/PD) analysis facilitates guidance development
- PK/PD knowledge informs clinical research
- Assessment of comparative nasal PK studies in Abbreviated New Drug Applications (ANDAs)

Approved AD opioid drug products

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Vantrela ER Tablet	Hydrocodone bitartrate	Nasal, IV, oral	Withdrawn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Troxyca ER Capsule	Oxycodone HCl/naltrexone HCl	Nasal, oral	Withdrawn
Targiniq ER Tablet	Oxycodone HCl/naloxone HCl	Nasal, IV	Withdrawn

- AD technologies: physical/chemical barriers, agonist/antagonist combinations, delivery system etc.
- Basis of drug approval: in vitro AD testing, relative bioavailability, efficacy, and abuse potential studies

General principles for evaluating generic AD



"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"

Guidance for Industry - General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products. https://www.fda.gov/media/96643/download

What PK metrics should be used to compare brand vs generic AD?

- Comparable Cmax and AUC may not be sufficient to establish comparable AD
- Literature reports suggest the rate of rise of drug concentration (Cmax/Tmax) contributes to differential abuse potential
- Research goal: explore potential relationships between PK metrics, especially measures of the ascending part of the PK curve, and opioid abuse potential for single active pharmaceutical ingredient (API) products

PK and PD metrics for clinical abuse potential studies

- 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
- Abuse potential metrics
  - 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

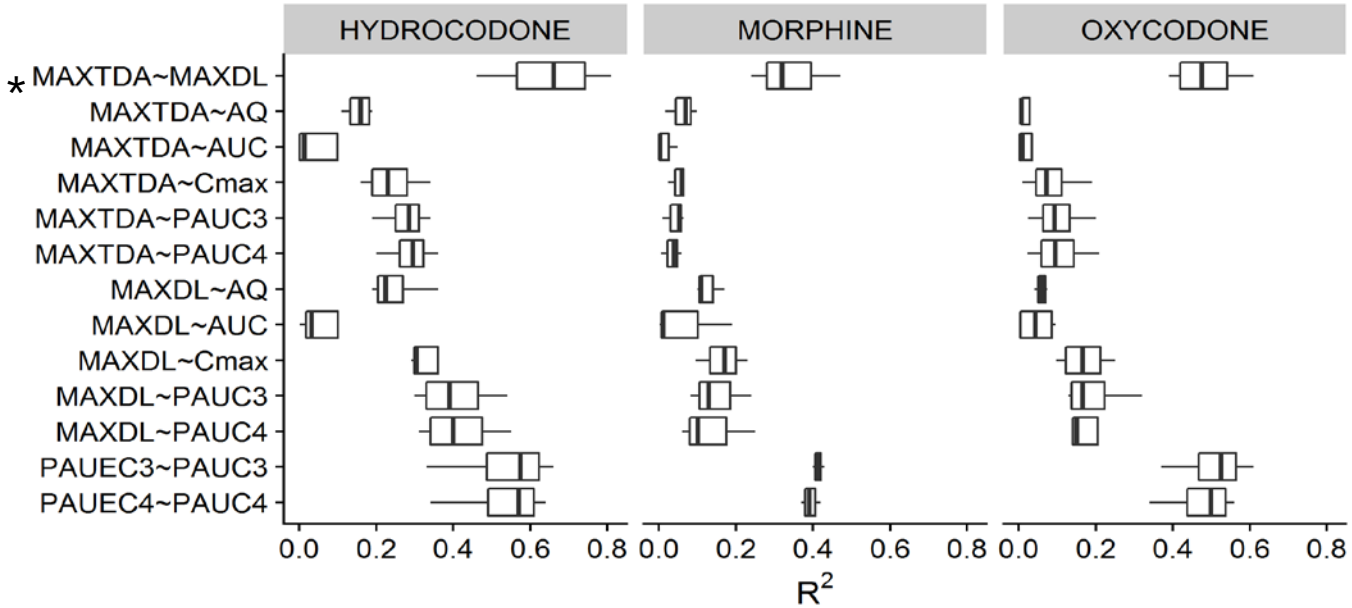
How are VAS measures assessed?

- 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”

PK/PD dataset for analysis: 11 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)

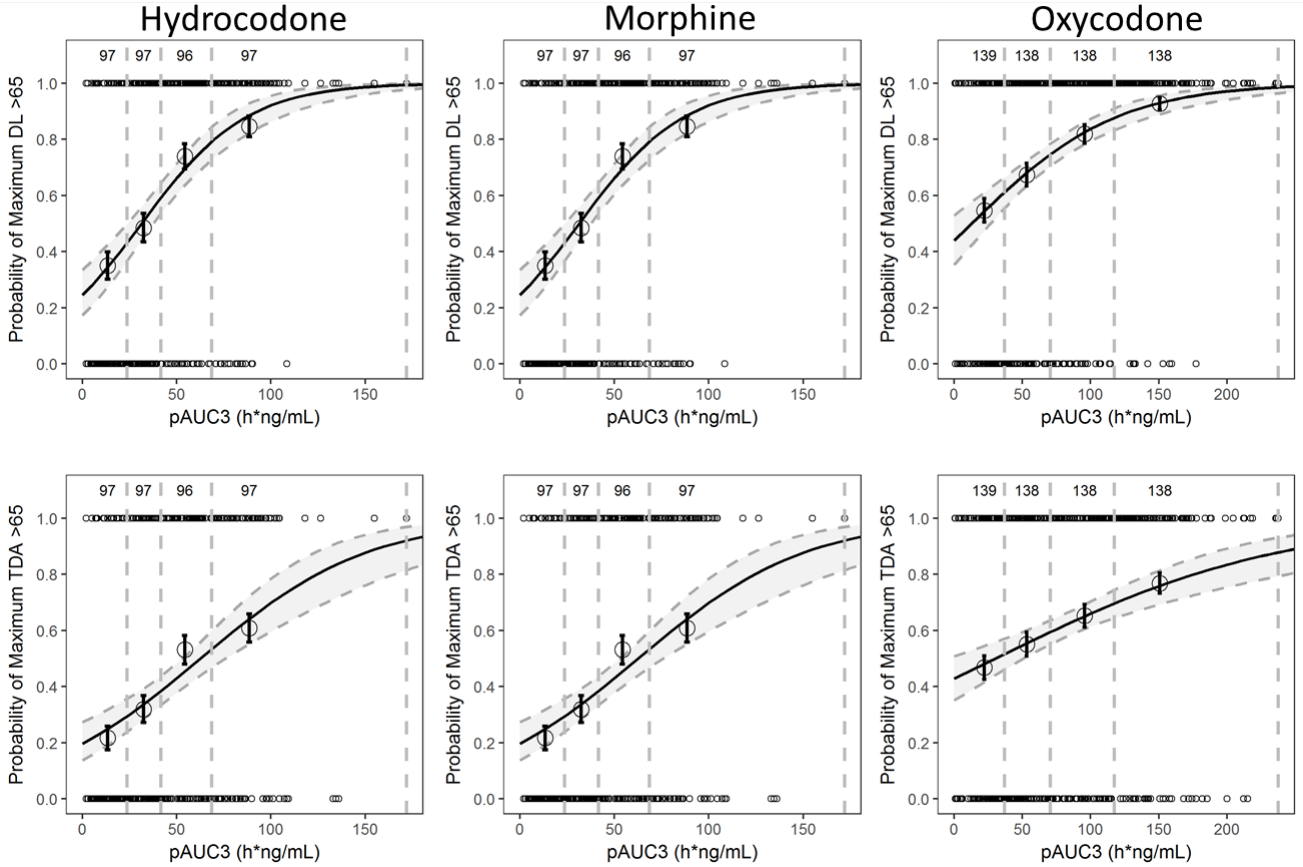
Highest correlation between early pAUEC and early pAUC among PK/PD metrics



- 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

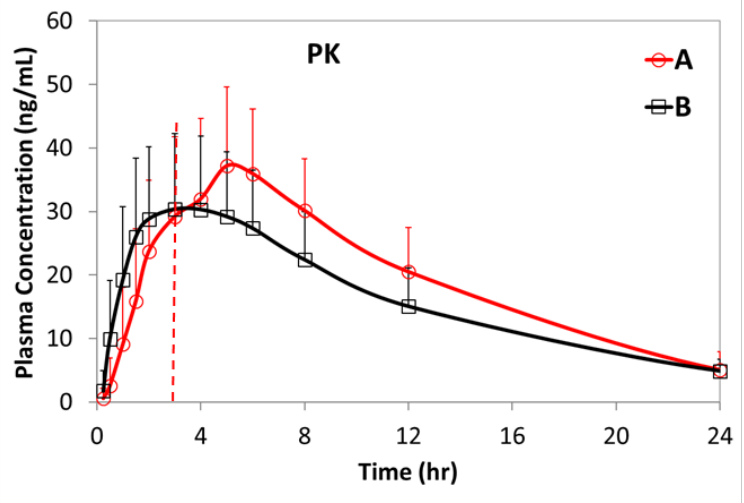
Adapted from presentation by Liang Zhao at 2019 ASCPT Annual Meeting

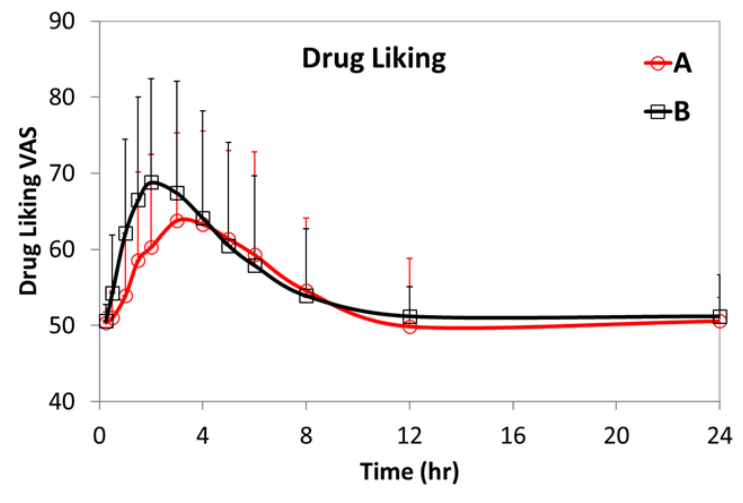
Probability of MAXDL/MAXTDA>65 is correlated with pAUC3



Adapted from presentation by Liang Zhao at 2019 ASCPT Annual Meeting

Use of early pAUC in addressing comments from Branded Industry Working Group





- BIWG commented that B had lower Cmax, but produced greater MAXDL compared to A
- 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)

Product-Specific Guidance (PSG) recommends pAUC metrics 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., $AUC_{0-3\ hours}$ and $AUC_{0-4\ hours}$) 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.

PK metrics included in guidances for morphine, oxycodone, and hydrocodone products:

"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., $AUC_{0-3\ hours}$ and $AUC_{0-4\ hours}$) as supportive data"

Clinical research to investigate factors (particle size and formulation) that influence nasal PK of milled oxycodone

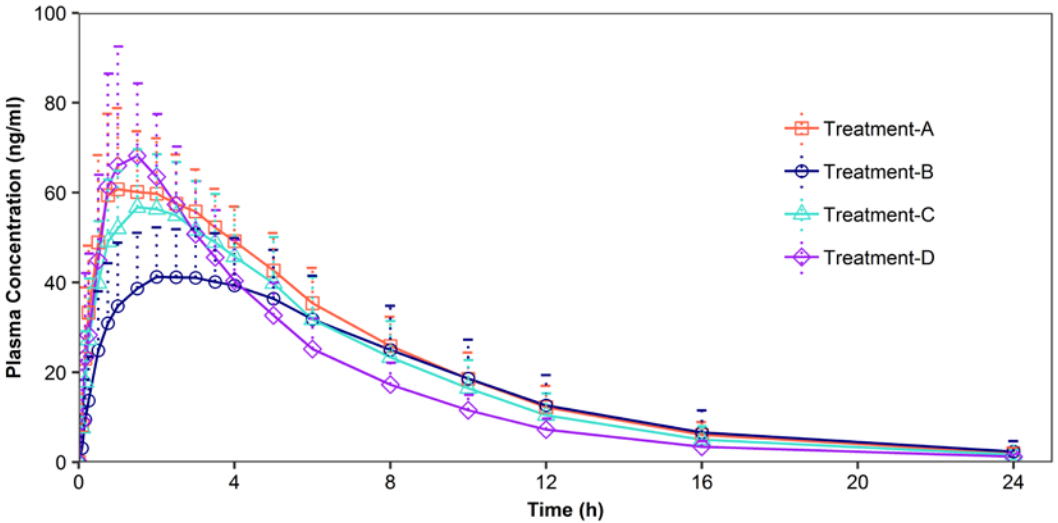
- Inconsistent impact of particle size on nasal PK of opioid products (New Drug Applications [NDAs] and literature reports)
  - Difference in manipulation methods
  - Variations in defined particle size ranges for “fine” and “coarse”
  - Differential drug loss during manipulation and nasal insufflation
- Unknown effect of excipient-to-drug ratio (EDR) on nasal PK of opioid products
  - AD labeling is based on human abuse potential studies with one strength only
  - Different strengths vary in the EDR
- FY15 contract awarded to Vince & Associates Clinical Research

Clinical study design

- Study Design: Single center, randomized, open-label, single dose, 4-sequence, 4-period, 4-treatment crossover design
- Treatments (30 mg of API available for insufflation)
  - Finely milled oxycodone ER 30 mg tablets (Treatment-A)
  - Coarsely milled oxycodone ER 30 mg tablets (Treatment-B)
  - Finely milled oxycodone ER 80 mg tablets - administered as a 30 mg dose (Treatment-C)
  - Finely milled oxycodone IR 30 mg tablets (Treatment-D)
- Particles sizes
  - Finely milled - 106 to 500 µm
  - Coarsely milled - 500 to 1,000 µm
- 40 opioid users with a history of recreational intranasal drug uses
- Naltrexone block
- PK sampling: pre-dose to 48 hours after each dose
- Washout: 72 hours between administrations

Adapted from the presentation by Bradley D. Vince at 2019 ASCPT Annual Meeting

Plasma concentration-time profiles



- Treatment-A: finely milled oxycodone ER 30 mg tablets
- Treatment-B: coarsely milled oxycodone ER 30 mg tablets
- Treatment-C: finely milled oxycodone ER 80 mg tablets (30 mg dose)
- Treatment-D: finely milled oxycodone IR 30 mg tablets

- Fine ER (A) vs. Coarse ER (B)
  - Higher Cmax, overall exposure, and early AUCs (AUC0-3, AUC0-4)
- Fine ER 80 mg (C) vs. Fine ER (A)
  - Similar Cmax, overall exposure, and early AUCs
- Fine ER (A) vs. Fine IR (D)
  - Lower Cmax and higher overall exposure (upper bound > 1.25)

Research findings and impact on guidance

- Research findings
  - A significant effect of particle size on the PK of nasally administered milled oxycodone ER in healthy non-dependent, recreational opioid users
  - Not a significant effect of the evaluated EDR on the PK of oxycodone ER, when administered intranasally and finely milled (106-500 µm)
- Guidance on comparative nasal PK studies for AD assessment
  - "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"

Assessment of comparative nasal PK studies in ANDAs

- Take scientifically appropriate and ethical steps to protect each human subject
  - NOT physically dependent on opioids (e.g., through a naloxone challenge test)
  - Has NOT been seeking or undergoing treatment for abuse of controlled substances such that participating in the study could make them vulnerable to relapse
- Determine relevant PK parameters
  - Maximum concentration (Cmax), area-under-the-curve (AUC0-t and AUC0-∞), and time to maximum concentration (Tmax)
  - Partial AUCs (e.g., AUC0-3 hours and AUC0-4 hours) as supportive data
- Characterize manipulated test and reference drug products
  - formulation recovery
  - drug content
  - particle size distribution

Closing remarks

- AD opioid drug products are complex products
- The PSG reflects the Agency's current thinking on comparative in vivo PK studies for AD evaluation
- Encourage industry to consider
  - Pre-ANDA program
    - Controlled correspondence
    - Product development meetings
    - Pre-submission meetings
  - Mid-review-cycle meetings

Guidance for Industry - Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA. https://www.fda.gov/media/107626/download

Acknowledgements

- **ORS/OGD:**
  - Zhichuan (Matt) Li PhD
  - Minori Kinjo PhD
  - Yehua (Josh) Xie PhD
  - Xiaoyan Yang PhD
  - Myong-Jin Kim PharmD
  - Mitchell Frost MD
  - Markham Luke MD
  - Liang Zhao PhD
  - Robert Lionberger PhD

- **Vince & Associate Clinical Research**

- **OCP/OTS:**
  - Srikanth Nallani PhD
  - Yun Xu PhD
  - Chandra Sahajwalla PhD
  - Issam Zineh PhD PharmD
- **OND/ODEII/DAAAP**
  - Sharon Hertz MD
- **CDER Controlled Substance Staff**
- **CDER Opioids Task Force**
- **Working Groups**
  - Opioid PK-PD working group
  - General guidance development
  - PSG development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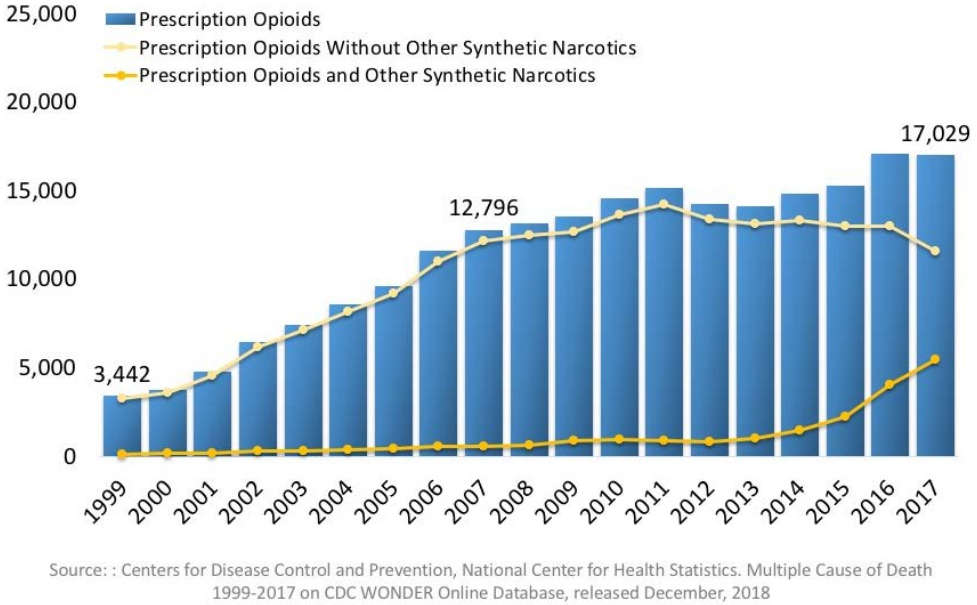
Backup slides

Opioid epidemic in the U.S.



Source: : Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2017 on CDC WONDER Online Database, released December, 2018

Rx opioids: morphine, oxycodone, hydrocodone etc.

Oral
Swallow the intact or crushed; chew

Nasal
Snort the crushed

Inhalation
Heat the intact or crushed, then inhale

Injection
Dissolve the intact or crushed, then inject

Human abuse potential studies in NDAs

Screening phase	• Naloxone challenge
Qualification phase	• Ability to distinguish placebo and positive control[1] • Tolerability to positive control
Treatment phase	• Arms: placebo, positive control(s), and test product(s) • Routes: nasal (IN) or oral (PO) • Abuse potential endpoints: Drug Liking (DL) Visual Analogue Scale (VAS)[2], Take Drug Again (TDA) VAS[3] etc. • PK: Cmax, Tmax, AUC

[1], VAS for DL in positive control should be at least 15 points more than that in placebo

[2], VAS for DL – "at this moment, my liking for this drug is":
0="strong disliking"; 50="neither like or dislike"; 100="strong liking"

[3], VAS for TDA – "I would take this drug again"

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 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".

Comparison of PK parameters across treatment arms