ASCPT

FROM MOLECULE TO PATIENT

ASCPT 2019 ANNUAL MEETING

Evaluation of ADF Opioid Drug Products

Challenges, innovations and current practices related to evaluation of ADF opioid drug products

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Disclosures

- Alcobra
- BDSI
- Bonti
- Charleston Labs
- Daiichi Sankyo
- Depomed
- Egalet
- Indivior
- Inspirion
- Insys
- Kempharm
- Mallinckrodt
- Pain Therapeutics
- Pfizer
- Pernix
- Shionogi
- Teva
- Trevena
- Trevi

Abuse Deterrent Definition

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- Pharmaceutical product is formulated so its physical or chemical properties may reduce, deter or prevent abuse
- Changes impart properties that make extraction and purification of the active component difficult for abuse by another route
- Changes in the formulation might prevent inadvertent overdoses that can come about by chewing or cutting tablets to facilitate swallowing
- For “abuse deterrent” products to be an effective approach to reducing drug abuse, their development would have to apply to all drug products on the market: innovator and generic products

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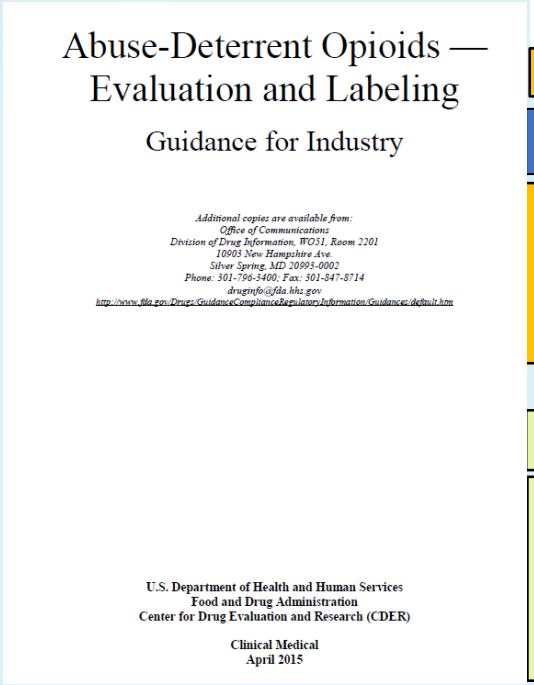
"Labeling is the first tool the Food and Drug Administration is looking at to incentivize the development of successful abuse-deterrence Opioids."

Douglas Throckmorton, MD,

Deputy Director for Regulatory Programs

FDA's Center for Drug Evaluation and Research

FDA Guidance on Abuse-deterrent Opioids

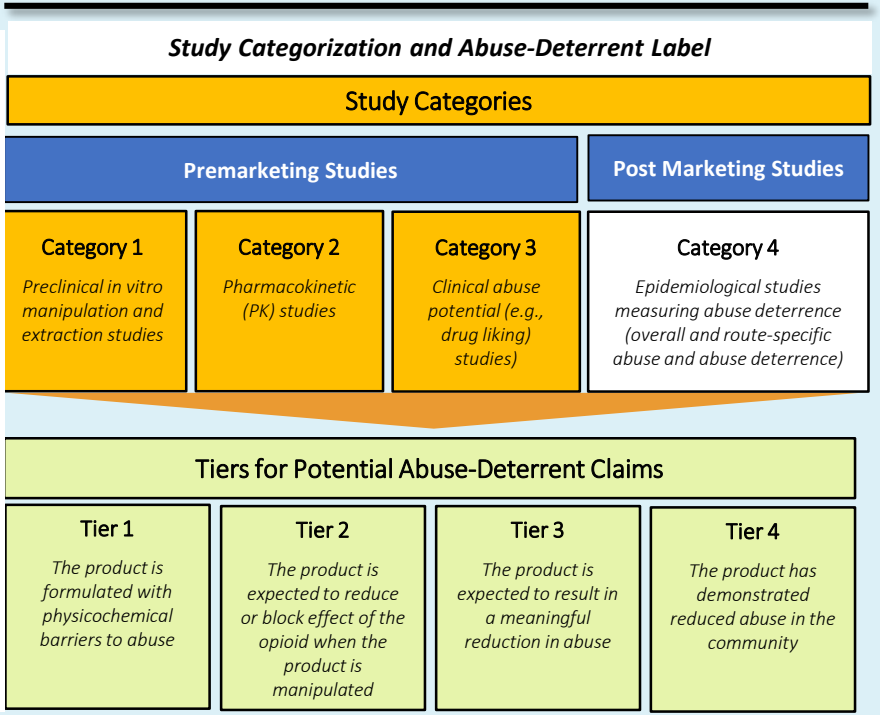

Abuse-Deterrent Opioids — Evaluation and Labeling

Guidance for Industry

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

Clinical Medical
April 2015

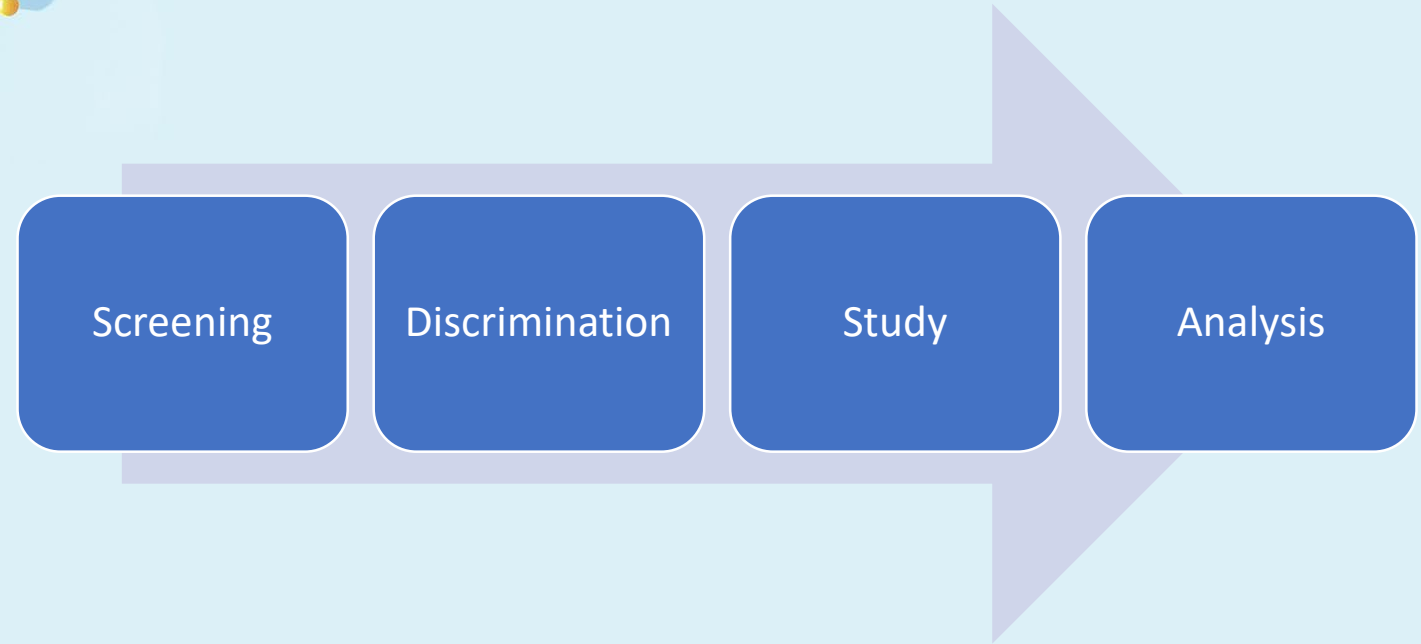


Mechanisms of abuse deterrence

Mechanism	Characteristics
Physical/chemical barriers (may not deter all of these)	Prevent chewing, crushing, cutting, grating, or grinding (physical barrier) Impede extraction of opioids with common solvents (chemical barrier)
Agonist/antagonist combinations	Addition of a sequestered or non-sequestered opioid antagonist
Aversion	Component(s) added that produces an unpleasant effect after manipulation, after administration by alternate routes (e.g. mucous membrane irritant), or if used at doses higher than indicated
Delivery system	Long-acting injectable or depot formulations that are difficult to manipulate
Prodrugs or new molecular entities	Require chemical or enzymatic transformation *in vivo* to active drug; may have inherent pharmacodynamic or pharmacokinetic properties that lower abuse potential
Combination of technologies	Contain greater than 2 of the other defined technologies
Novel approaches	Technologies that are not characterized by one of the defined categories (e.g. technology that provides protection against multiple-pill overdose)

Lynn R. Webster, John Markman, Edward J. Cone & Gwendolyn Niebler (2017) Current and future development of extended-release, abuse-deterrent opioid formulations in the United States, Postgraduate Medicine, 129:1, 102-110, DOI: 10.1080/00325481.2017.1268902

Stages of Human Abuse Potential (HAP) Studies



Stages of HAP Studies: Screening

Screening → Discrimination → Study → Analysis

IRB
- Does the IRB understand HAP?
  - Consent
  - Confidentiality
  - Compensation

Recruitment
- Gender (sex)
- Age
- Ethnicity
- Social

Population
- How experienced
- Route of exposure
- Poly substances
- Tobacco
- Marijuana

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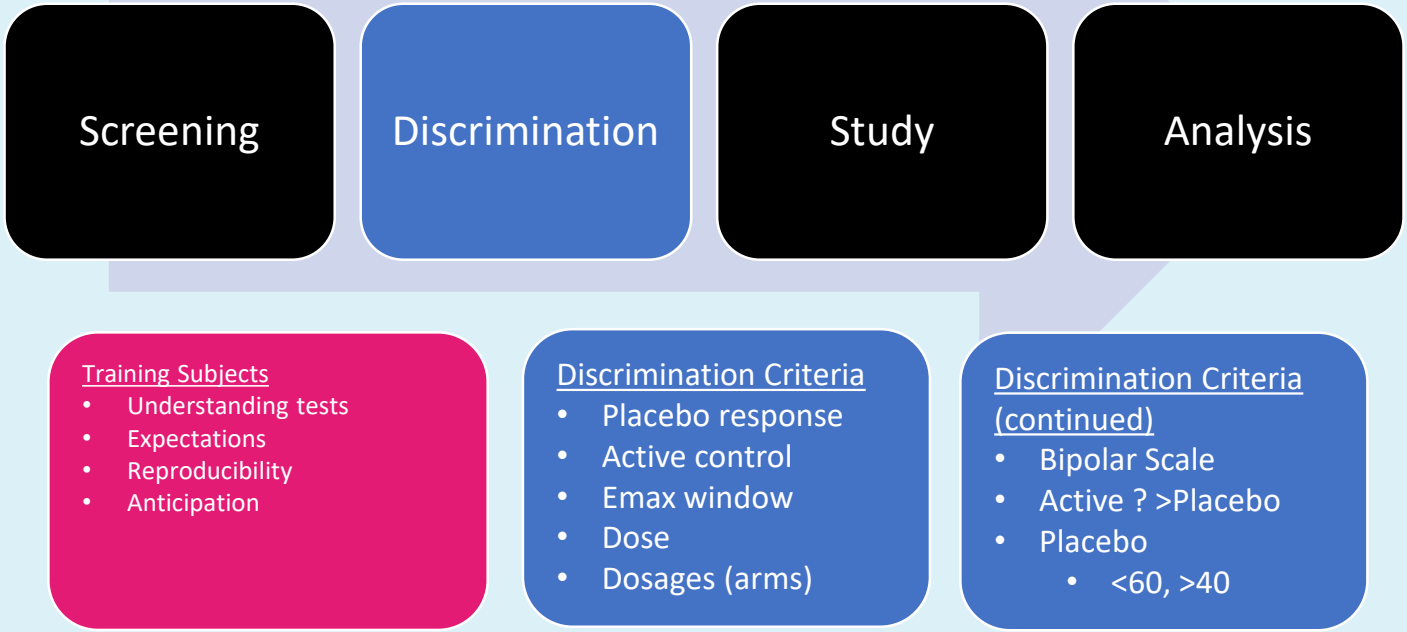
Stages of HAP Studies: Discrimination



Stages of HAP Studies: Study

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Screening → Discrimination → **Study** → Analysis

<u>Pharmacy Challenges</u>
- Drug preparation
  - Manipulation
  - Encapsulation
- Blinding
- Routes of Administration

<u>Manipulation Technique</u>
- Degree of effort
- Method of manipulation
- Time

<u>Assessment Tools</u>
- Scales
- Number of scales
- Cognitive
- Paper vs electronic
- Unipolar vs bipolar

Stages of HAP Studies: Study

FROM MOLECULE TO PATIENT

Screening | Discrimination | **Study** | Analysis

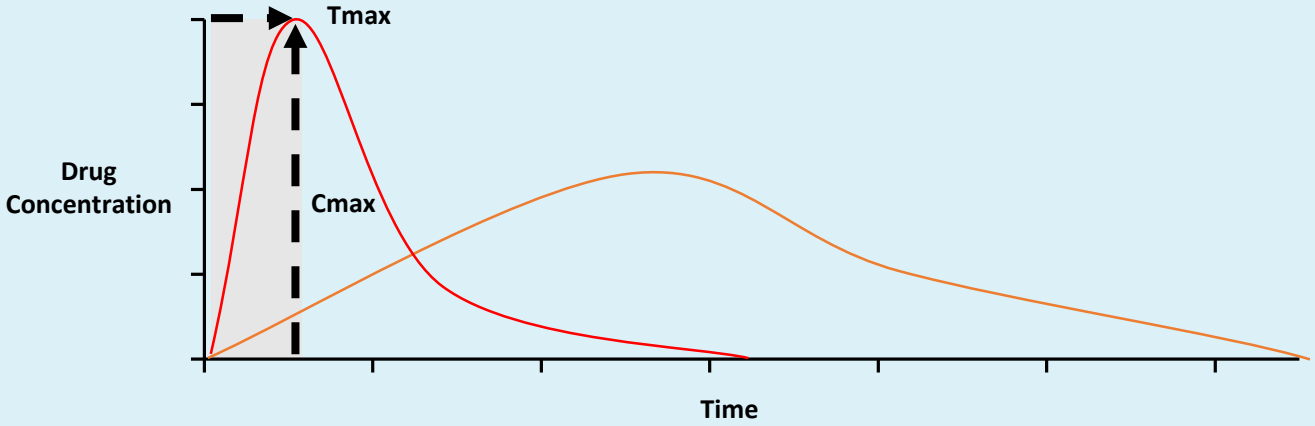
Blinding
- Particle size/volume
- Irritation
- Smell & taste
- Visual
- Texture
- Consistency

Blinding (continued)
- Color difference
- Blinding solution
- Placebo utilized
- Blinding method during dosing

Endpoints
- Maximum Effect (E_{max})
- AUE
- Abuse quotient (A/Q)

Rate of Rise May Contribute to Differential Abuse Potential

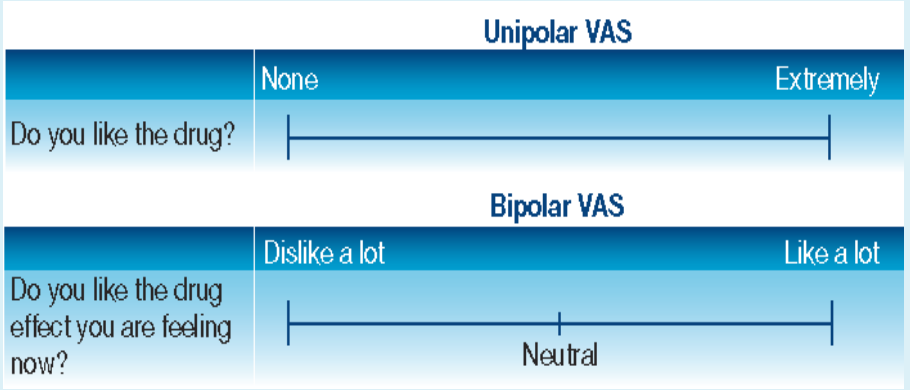
- Category 2 PK data intended to measure ‘rate of rise’, peak and early concentrations, as measured by
  - Early concentrations and partial AUCs
  - C_{max} and T_{max}
  - C_{max} / T_{max} ratio (“Abuse Quotient”)



Webster, 2015.

Key Assessments

- Subjective Abuse Liability Assessments
  - Bipolar VAS
    - Drug Liking
    - DEQ
  - Unipolar VAS
    - Drug High
    - DEQ



Example of Individual Discrimination Data & Interpretation

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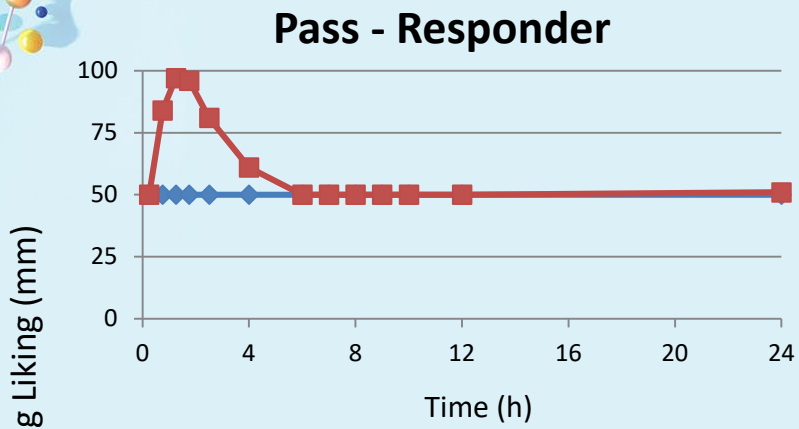
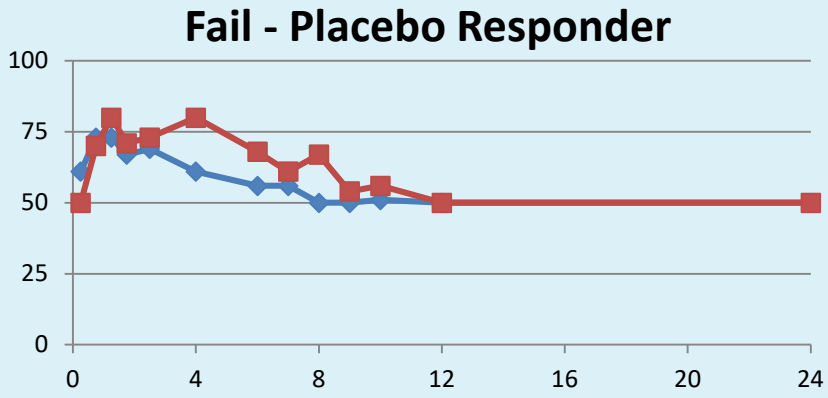
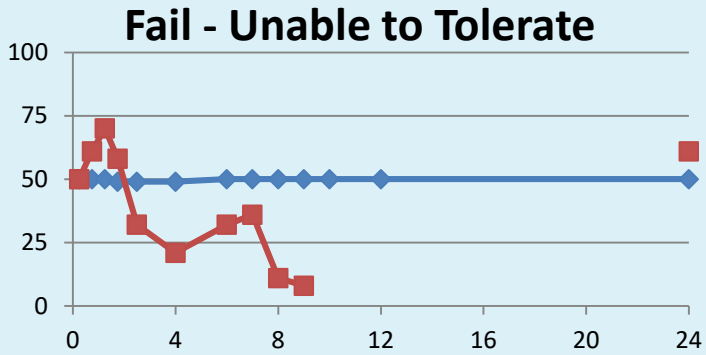
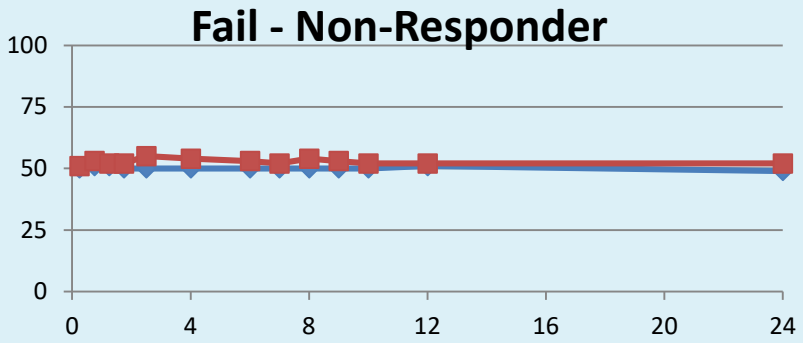
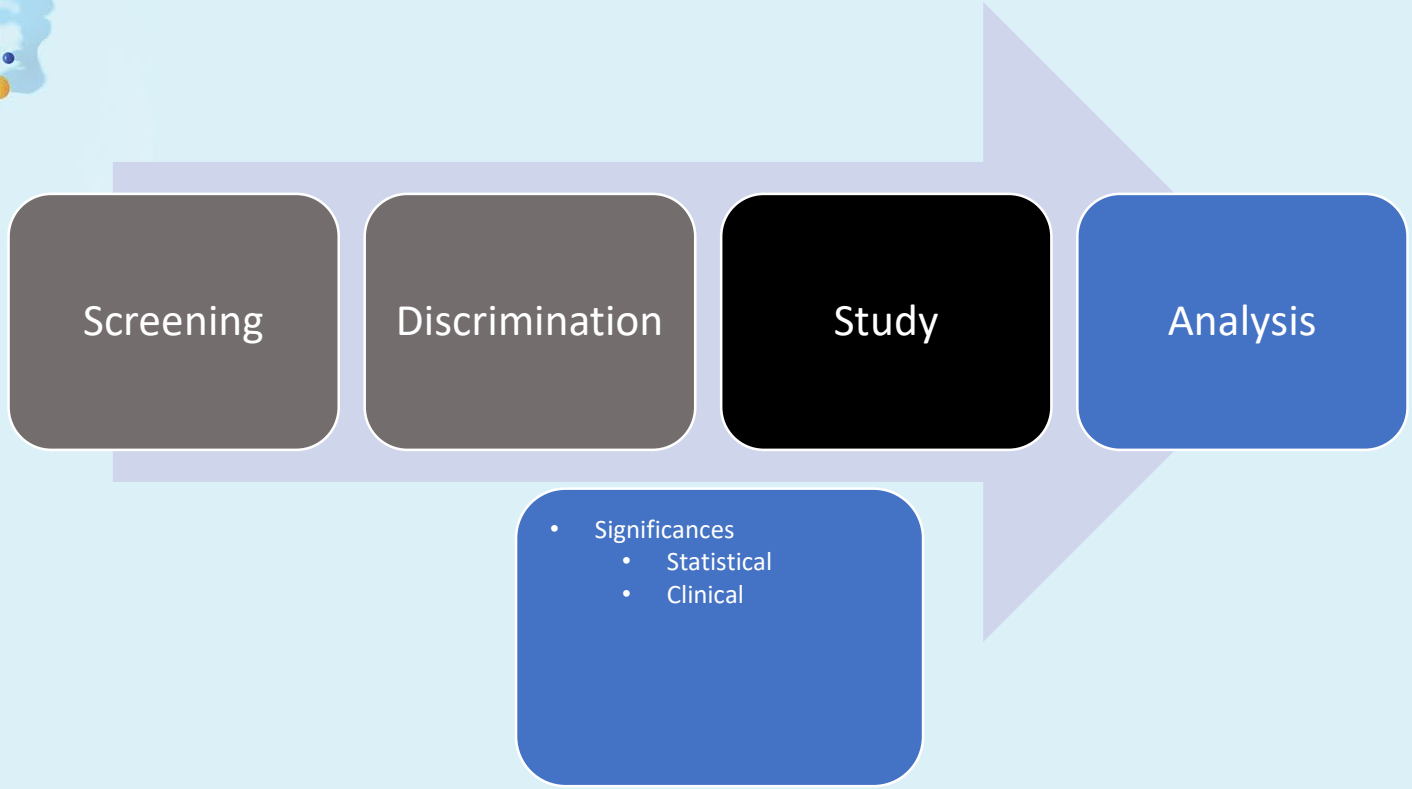




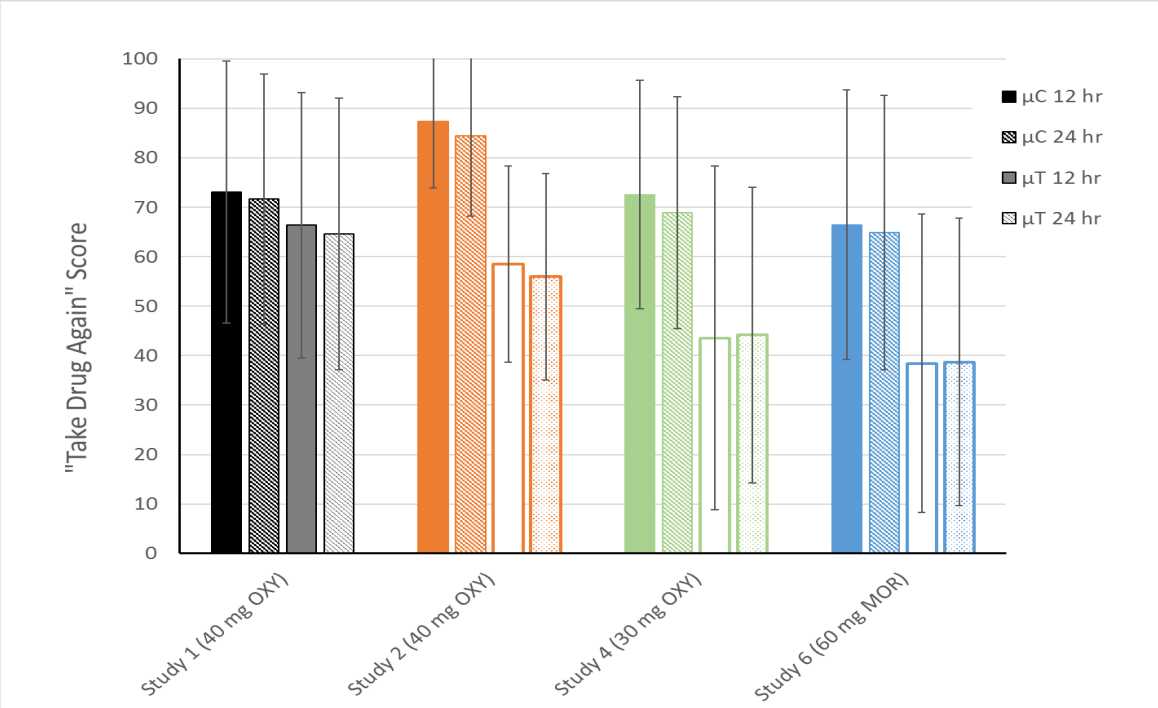




Stages of HAP Studies: Study

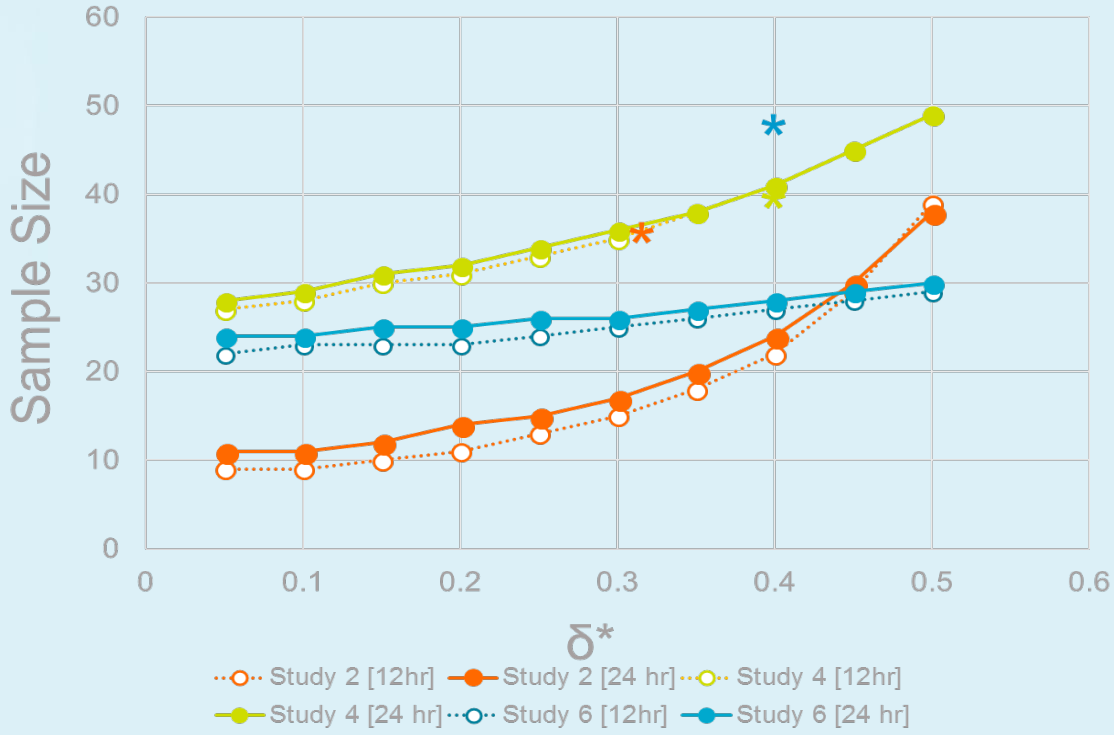


Take Drug Again Scores following Intranasal Administration in Selected HAP Studies of Opioid ADFs



Hansen, E., He, J., Webster, L., Turncliff, R. Considering "Take Drug Again" as the Primary Endpoint in Clinical Studies of Abuse Deterrent Formulations. Poster session presented at: annual meeting of the College on Problems of Drug Dependence; 2018; San Diego, California.

TDA Sample Size Calculations



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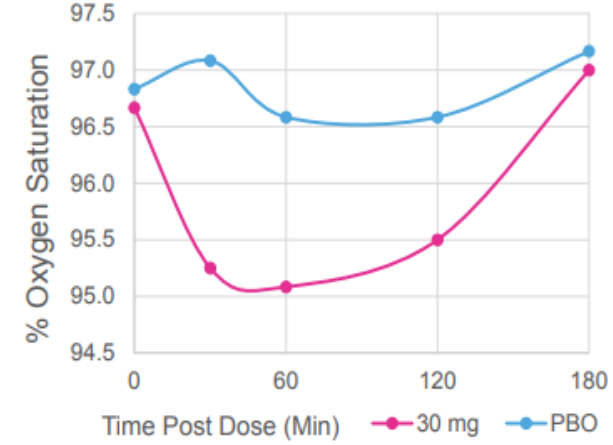
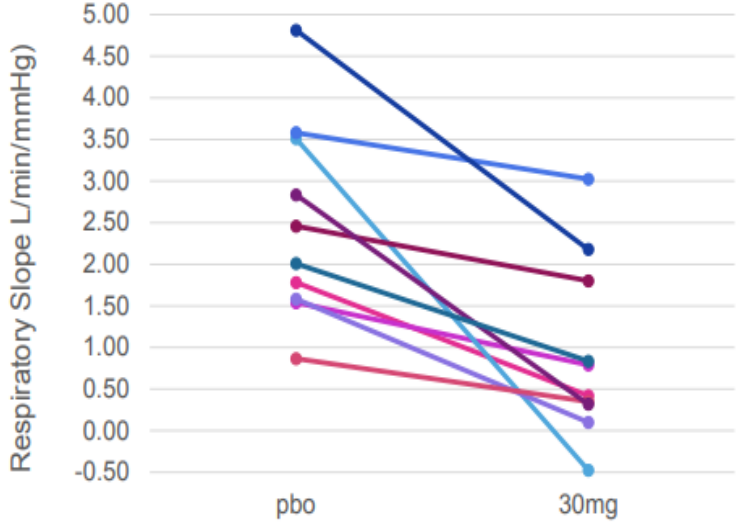
Overdose Protection ADFs

Average Change in Oxygen Saturation



Subject average Oxygen Saturation from predose (0 hours) to 3 hours (180 min) after oral administration of 30mg oxycodone and placebo

Difference in Respiratory Slope at One Hour Post Dose



Individual subject change in Respiratory Slope between placebo (pbo) and 30 mg oxycodone (30mg)

L Webster et. al. Oxycodone Effect on Ventilatory Drive. https://www.cdc.gov/media/releases/2018/p0329-drugoverdose-deaths.htm

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Overdose Protection ADFs

Time-Matched Average Respiratory Results of Subjects

Results at 60 min post dose	Placebo	30 mg Oxycodone	LS Mean Difference (95% CI)	Resultant Change
S – Slope of Regression (MV vs. $ETCO_2$)	2.28	1.13	**-1.15** (-2.08, -0.23)	↓ 50%
MV – Minute Ventilation (L/min)	20.81	15.13	**-5.68** (-9.56, -1.82)	↓ 27%
R – Ratio of MV/$ETCO_2$ (L/min/mmHg)	0.44	0.30	**-.14** (-0.23, -0.5)	↓ 31%
RR – Respiration Rate (Breaths/min)	12.7	12.9	**0.2** (-3.86, 3.44)	↓ 2%
$ETCO_2$ – End-tidal CO_2 (mmHg)	47.9	51.4	**3.5** (1.2, 5.8)	↑ 7%

L Webster et. al. Oxycodone Effect on Ventilatory Drive.
https://www.cdc.gov/media/releases/2018/p0329-drugoverdose-deaths.htm

What's next?

- Pharmacokinetic measurements for generic ADFs as surrogates for HAP
- Develop statistical analysis that is proven to have clinical meaningfulness
- Develop accepted endpoints for emerging overdose protection technology

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Thank you!

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