U.S. FOOD & DRUG ADMINISTRATION

Symposium 6: Hot Topic: Innovative Approaches in Combating the Opioid Crisis

1. **Regulatory Science in Action: Supporting Innovative Opioid Formulations Development & Advancing Overdose Treatments**
   Presenter: Manar Al-Ghabeish
2. **Design, Data, and Deterrence: Advancing Methodology and Overcoming Clinical and Formulation Challenges in Opioid Abuse Liability Studies**
   Presenter: John Oldenhof
3. **Regulatory History of Opioid Reversal Products and Recent Developments**
   Presenter: Zachary Dezman

Regulatory Science in Action: Supporting Innovative Opioid Formulations Development & Advancing Overdose Treatments

Symposium 6: Hot Topic: Innovative Approaches in Combating the Opioid Crisis

Presenter: Manar Al-Ghabeish, PhD

Disclosure and Disclaimer

- There are no relevant financial relationships to disclose.

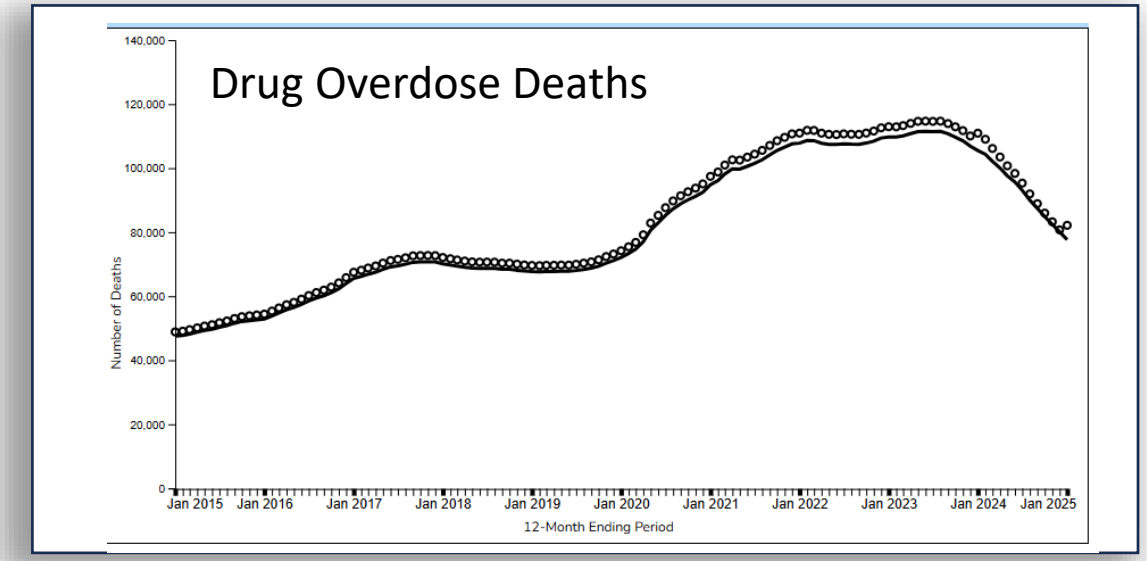
- This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Objectives

- Understand the FDA's regulatory framework and research in addressing the opioid crisis
- Describe how opioid agonist/antagonist combination products affect abuse deterrent properties, including drug liking measures
- Learn about innovative nasal delivery systems for opioid overdose reversal
- Highlight the clinical implications of long-acting injectable opioid antagonist systems

Background: The Opioid Crisis

- Declared a public health emergency and renewed in 2025
- High rates of opioid overdose deaths
- Market need for rescue products and opioid products designed to reduce abuse potential



https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2025/20250514.htm

FDA's Response to the Opioid Crisis

- Areas of focus have included:
  - Expedite the development of opioid products designed to reduce abuse potential (i.e., ADF)
  - Non-opioid alternatives for the treatment of pain
  - Expand availability of opioid overdose treatments such as naloxone:
    - Encourage healthcare providers to consider prescribing naloxone to patients at increased risk of opioid overdose
    - Prioritize research to support naloxone product approval

ADF: Abuse Deterrent Formulation

https://www.fda.gov/drugs/food-and-drug-administration-overdose-prevention-framework/timeline-selected-fda-activities-and-significant-events-addressing-substance-use-and-overdose

Generic Drugs Advance Access to Opioid and Overdose Treatments

- Generic Drug User Fee Amendments (GDUFA) Support for Regulatory Science:
  - Accelerates development of safe, effective generics including complex opioid and overdose treatments
  - Promotes science-based regulation through FDA-funded research
  - Supports complex opioid product approvals

April 2019

First Generic of Naloxone Nasal Spray

July 2023

First Generic of PLGA-based Long Injectable (Naltrexone)

First Generic of ADF

March 2021

PLGA: Poly(lactic-co-glycolic acid)
ADF: Abuse Deterrent Formulation

2020-2025 Generic Drug Research Themes

- Assessment of Opioid Abuse Deterrent Formulations (ADFs)
- Opioid Antagonist Nasal Delivery for Opioid Overdose Reversal
- Computational Modeling of Nasal Drug Delivery and Regional Deposition
- Opioid Antagonist Long-Acting Injectable Systems

https://www.fda.gov/drugs/generic-drugs/fy-2024-gdufa-science-and-research-report

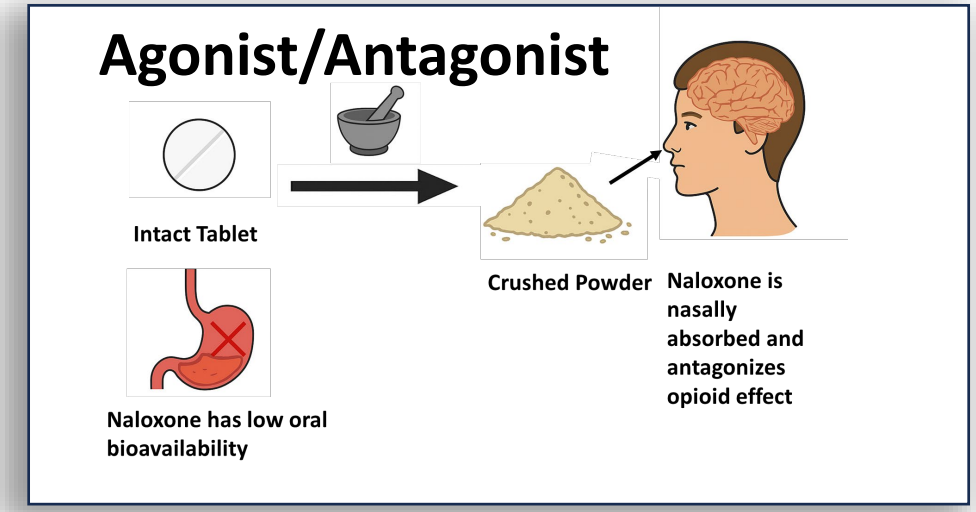
Formulation Innovation

A Focus on Opioid Agonist Products with an Antagonist Component

ADFs are NOT abuse proof. Providers must still assess risk and monitor patients

Opioid Abuse Deterrent Formulations (ADFs)

- The potential of abusing these products is more difficult and less rewarding
- Designed to deter misuse, even if they do not fully prevent abuse
- Different designs:
  - Opioid antagonist (e.g. naloxone or naltrexone) combined with an opioid agonist



Guidance for Industry: Abuse-deterrent opioids – evaluation and labeling

Understanding Intranasal Naloxone and Demonstrating Equivalence of Abuse Deterrent Properties

Background

- Goal of the Generic Drug Program was to identify in vivo study designs that could be used to demonstrate equivalence of the ADF characteristics for nasal administration
- Limited data on intranasal use of crushed ADF opioid
- First GDUFA-funded study evaluated intranasal administration of manipulated OxyContin*
- The methods from the first study support the approval of a generic version of an ADF opioid product

Scientific Goals for the Second GDUFA-funded Study

- Intranasal behavior of an ADF using naloxone (at the time we believed that ADF containing naloxone might be a more promising approach)
- Effects of manipulated particle size on pharmacokinetic (PK) of opioid agonist/antagonist
- Intranasal administration of powder naloxone and how that will impact its opioid antagonizing effect
- Impact of drug product manipulation methods on nasal absorption and onset

*Raofi, Saeid, et al. "Particle size affects pharmacokinetics of milled oxycodone hydrochloride tablet products following nasal insufflation in nondependent, recreational opioid users." *Clinical and Translational Science* 14.5 (2021): 1977-1987.

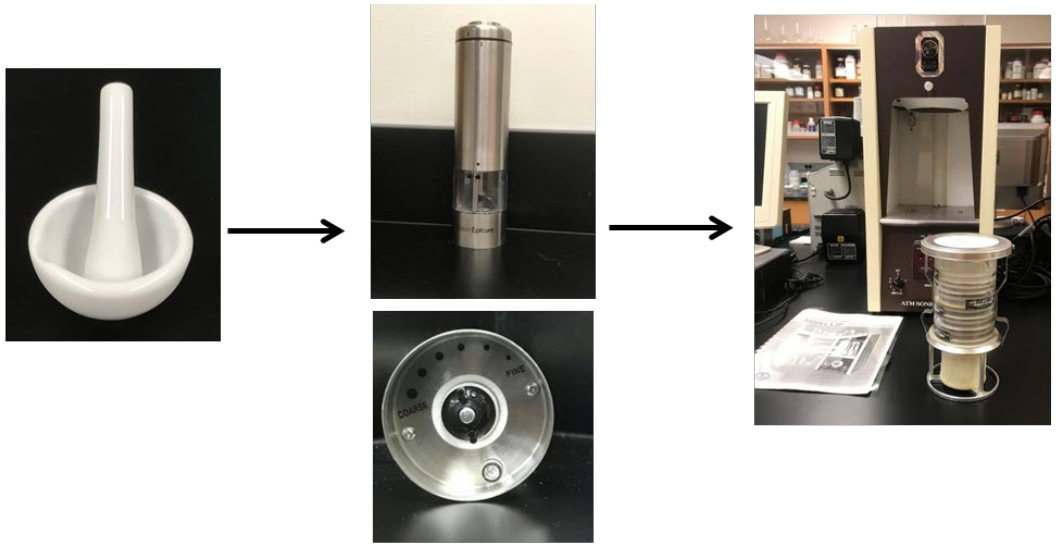
Impact of Different Manipulations of an ADF Containing Naloxone on Abuse deterrent Properties: Intranasal Pharmacokinetic (PK)/ Pharmacodynamic (PD) Study

Study Objectives

- Determine that an opioid product with an antagonist* still reduces drug liking and take drug again albeit manipulated using three approaches
- Explore use of pupillometry as an alternative PD measure
- Evaluate these parameters against a positive control (i.e. the non-ADF version of the opioid product) and a negative control (i.e., inert powder)
- Establish a method to demonstrate abuse-deterrent equivalence

*Product is currently discontinued

Manipulation Method Used in the Study



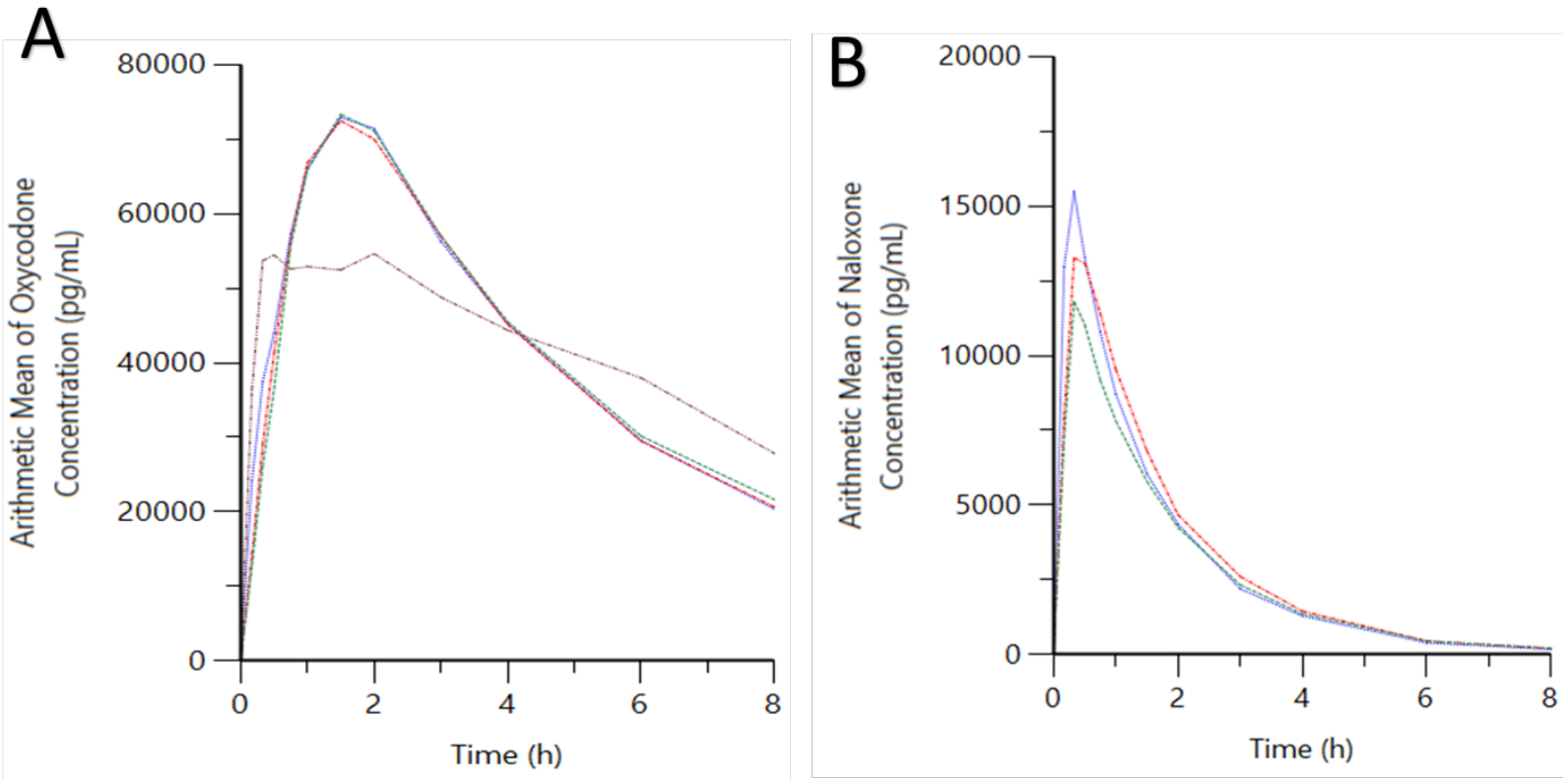
- Household tools used to stimulate common real-world manipulation
- Particles were sieved to obtain varied particle sizes
- Analytical testing ensured accurate content and consistent opioid-to-naloxone ratio
- Stability testing confirmed manipulated products remained stable during the study

Clinical Study

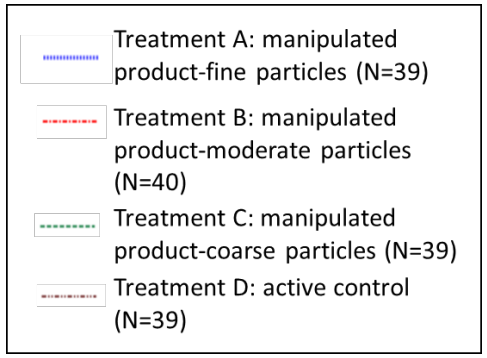
Study Design:	Single-dose, randomized, double-blind, active controlled, five-way crossover study (Phase 1 study)
Study Subject:	Non-dependent recreational opioid users who: underwent a naloxone challenge and discrimination test and can tolerate the study products
Treatments:	A: Manipulated product, fine particles [106–300 µm] B: Manipulated product, medium particles [300–600 µm] C: Manipulated product, coarse particles [600–1000 µm] D: Active control (oxycodone) E: Placebo
Dose and administration	Dose: oxycodone HCl: 40 mg, naloxone HCl :20 mg Administration: insufflation using plastic straw
Assessment	PK parameters: AUC, Cmax, etc. PD endpoints: Abuse potential, Pupillometry, SRAII, Ease of Snorts and Percentage of Dose Insufflated

AUC: Area under curve Cmax: peak concentration SRAII: Subject-rated assessment of intranasal irritation

Oxycodone and Naloxone Exposure



The PK Profiles of Oxycodone (A) and Naloxone (B) After the Intranasal Administration of Manipulated Products Compared to Active Control

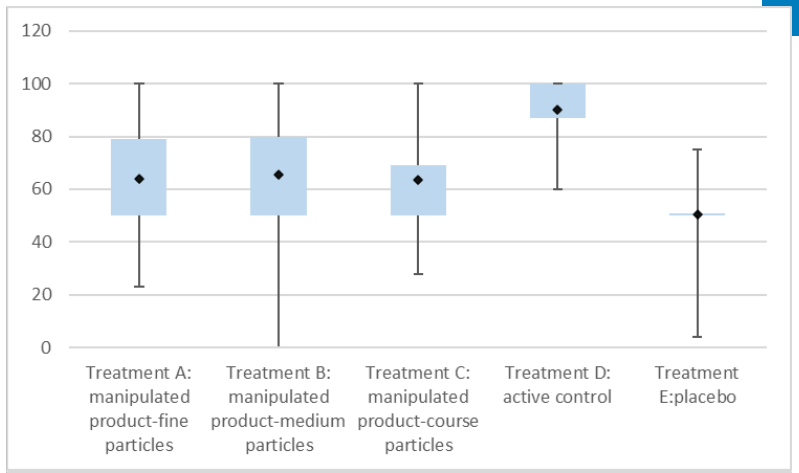


- **Oxycodone Bioequivalence (A)**: Rates and extents of absorption were comparable between three manipulated products, with 90% confidence intervals for Cmax and AUC falling within the 80.00-120.00% acceptance range
- **Oxycodone not in ADF (Treatment D) Profile**: Distinct double-peak profile in all subjects
- **Naloxone Absorption Pattern (B)**: Decreased absorption with larger particle size

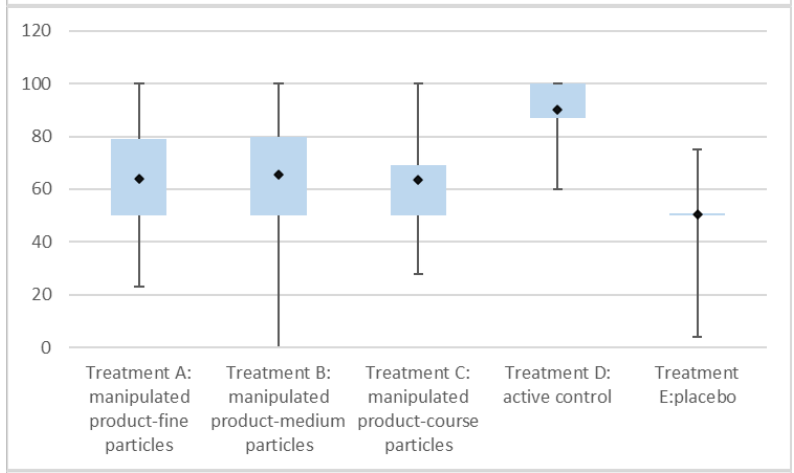
Drug Liking and Take Drug Again Scores Indicate Abuse Deterrent Properties Maintained

- **Visual Analog Scale (VAS) Assessment**: Abuse potential measured using VAS for subjective drug effects.
- **Validated Methodology**: Significant difference in drug liking between active control and placebo confirmed assessment validity ($p<0.001$).
- **Consistent Deterrence**: Abuse deterrent properties remained effective regardless of variations in manipulated products.

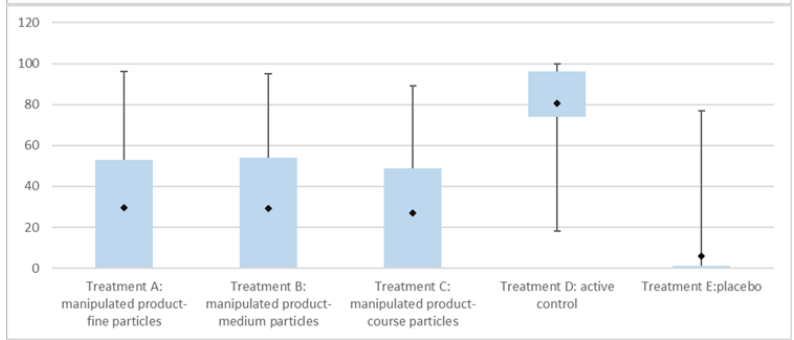
Drug Liking VAS Emax



Take Drug Again VAS Emax

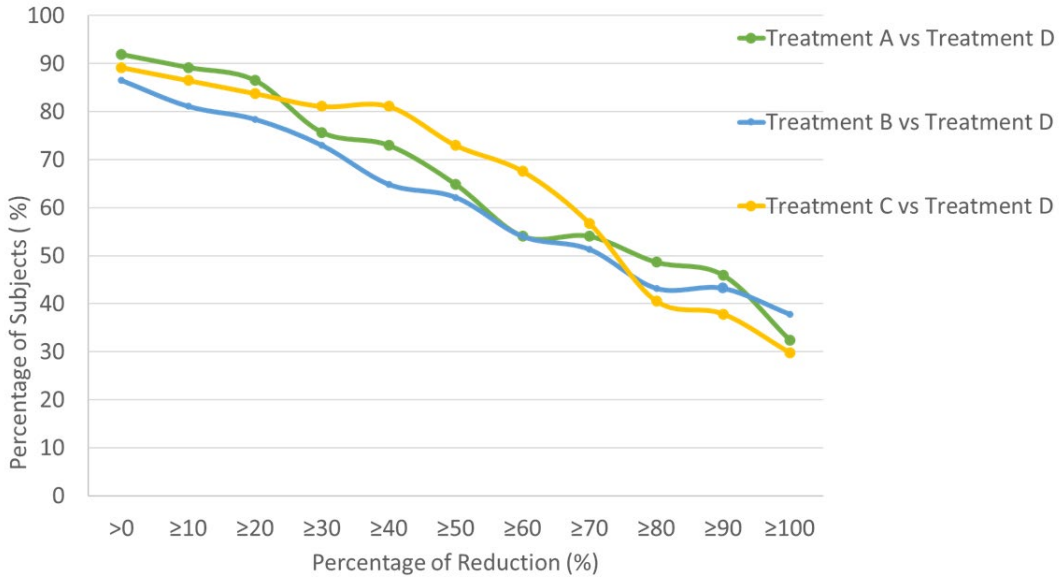


High VAS Emax



Box and Whisker Plots Where the Box Presents the 1st and 3rd Percentiles (Q1 and Q3), the Whiskers Present the Range (Min, Max) and the Diamond Symbol presents the Mean (N=37)

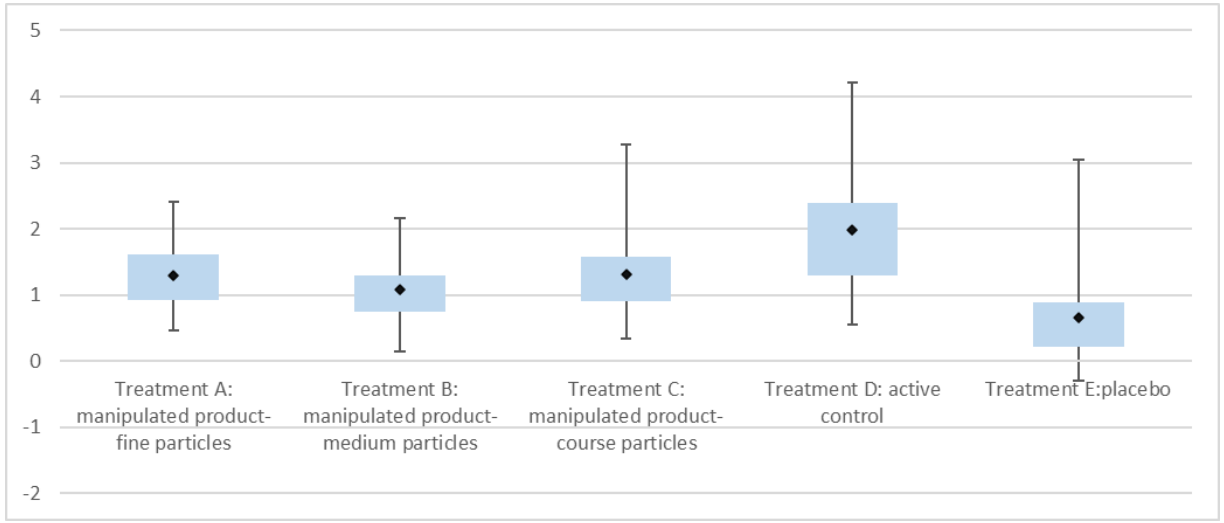
Significant Reduction in Drug Liking Demonstrated for Manipulated Products



Percent Reduction Profiles for Emax of Drug Liking VAS Manipulated Products of Oxycodone HCl And Naloxone HCl ER Tablet (Treatment A, B, And C) Compared to Active Control (Treatment D)

- All three manipulated products showed statistically significant reduction in drug liking compared to the active control ($p<0.001$)
- A cumulative of 65%, 62 % and 73 % of subjects (Treatment A, B, and C, respectively) showed at least 50 % reduction in Drug Liking Emax compared to active control

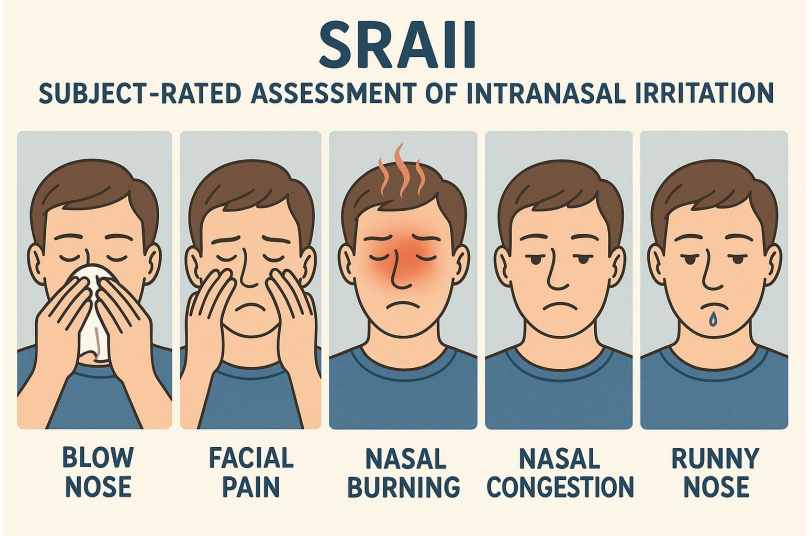
Objective Pupillometry Method Demonstrates Equivalent Opioid Antagonism



Box and Whisker Plots Where the Box Presents the 1st and 3rd Percentiles (Q1 and Q3) , the Whiskers Present the Range (Min, Max) and the Diamond Symbol represents the Mean (N=37)

- **Objective Methodology**: Pupillometry provides involuntary autonomic responses unaffected by subject bias, with high sensitivity to central opioid action and resistance to tolerance development.
- **Control Group Results**: Predose pupil diameter was consistent (4.079-4.291 mm); active control showed constriction beginning at 0.17 hours with maximum effect (2.568 mm) at 2 hours, while placebo showed no notable changes.
- **Treatment Efficacy**: All three manipulated products demonstrated significantly lower maximum pupil constriction (MPC) versus active control ($p<0.0001$), with no statistical differences between them ($p=0.4544$-0.7394).
- **Clinical Implication**: Particle size effects were minimal, indicating that differences in naloxone PK did not substantially impact opioid antagonism efficacy.

Coarse Particles Show Greater Nasal Irritation Effects Despite Overall Low Adverse Event Incidence



- **Assessment Method**: Subject-Rated Assessment of Intranasal Irritation (SRAII) evaluated five nasal symptoms including congestion, burning, and runny nose
- **Safety Profile**: Low overall adverse event incidence with all reported effects occurring only with placebo administration
- **Particle Size Impact**: Coarse particles showed significantly different maximum effects versus fine particles for nasal congestion and blow nose symptoms
- **Timing**: Consistent 0.5-hour time to maximum effect across all treatments

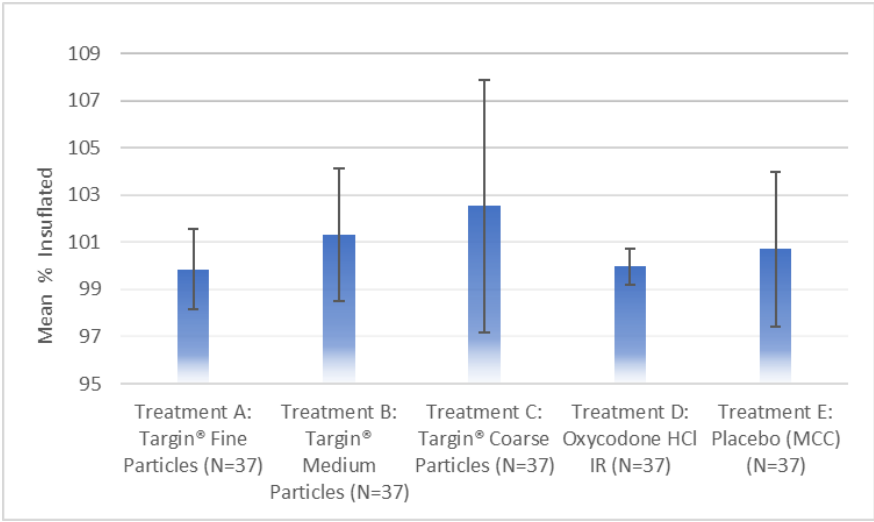
User Experience Results: Ease of Administration and Dose Delivery

- Comparable ease of administration (Fig. 1) was demonstrated with no significant differences observed in Ease of Snorting VAS scores

- Complete dose delivery achieved (Fig. 2)

Figure 1: Digital Image of Manipulated Products Showing Particle Characteristics That Support Ease of Administration Findings

Figure 2: Mean Percent (%) Insufflated of All Treatments



Summary

- All milled products showed significant abuse deterrent properties with both subjective and objective measures ($p<0.001$) with bioequivalent oxycodone exposure.
- Abuse deterrent properties remained robust (not statistically different) across all milled products despite variable naloxone absorption.
- This intranasal study confirmed that common manipulation methods do not compromise naloxone-mediated abuse deterrent properties.
- This study demonstrated that naloxone's opioid antagonist activity effectively counters abuse potential regardless of particle size variations.

Opioid Antagonist Nasal Delivery for Opioid Overdose Reversal

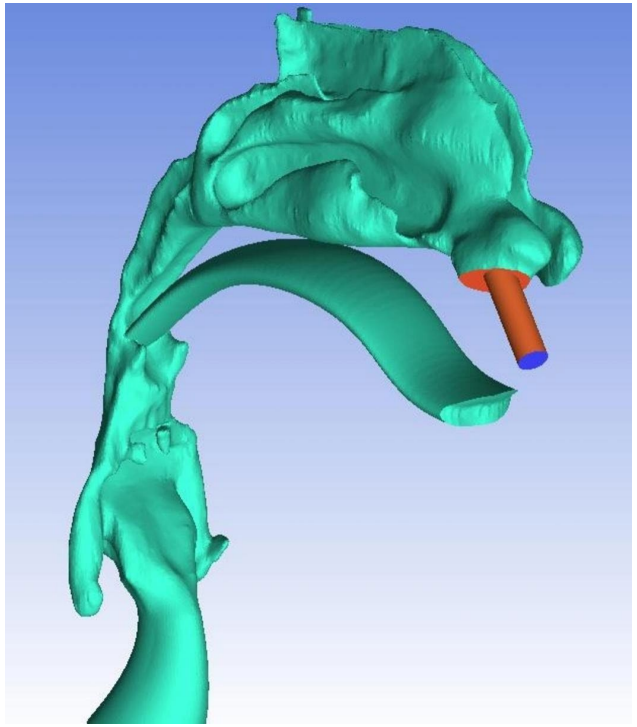
Focus of nasal deposition and absorption

Optimized nasal delivery ensures rapid reversal — important for out-of-hospital overdose response

Area 1: Opioid Antagonist Powder Formulation and Deposition

- Goal: Develop tools that guide the development of effective rescue formulation physician can rely on
- This area includes the following:

1. Use of computational fluid dynamics (CFD) for predicting nasal powder deposition
2. Development of physiologically-based pharmacokinetic (PBPK) models to predict absorption of naltrexone from milled ADF administered intranasally
3. Determination of critical quality attributes spray-dried naloxone nasal powder



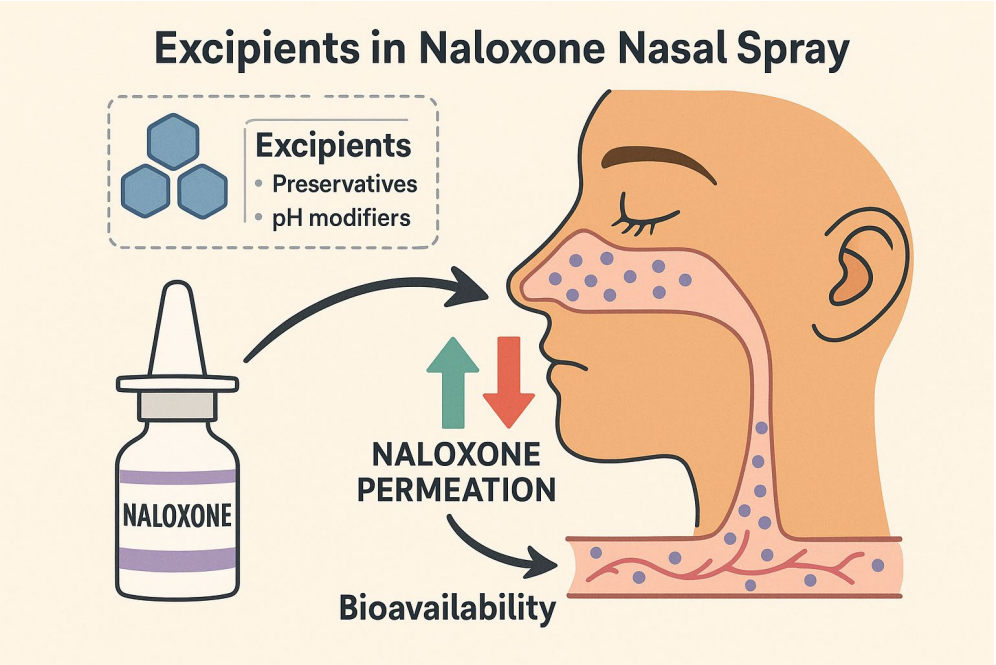
CAD model of nasal cavity

Walenga RL, et al. Nasal absorption of oxycodone predicted using a novel computational fluid dynamics-physiologically based pharmacokinetic model. J Control Release. 2025 Feb 10;378:982-996.

Area 2: Absorption and Permeation of Naloxone from Naloxone Spray Solutions

- Goal: Understanding what contribute to the bioavailability of opioid antagonist to support access to effective emergency kits
- This area includes the following:

1. Formulation variables and their impact on the permeation of naloxone
2. Identifying administration factors affecting the nasal bioavailability of naloxone and developing biopredictive in vitro permeation testing



Hsu, HJ., et al. Effect of Formulation Variables on the Nasal Permeability and Stability of Naloxone Intranasal Formulations. AAPS PharmSciTech 20, 232 (2019).

Opioid Antagonist Long-Acting Injectable Systems

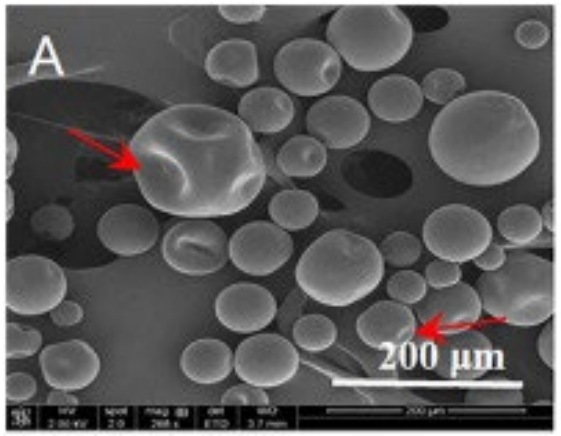
Focus on formulation characterization

Potential to support medication-assisted treatment in outpatient or correctional settings with minimal adherence burden

PLGA-based Product GDUFA Research

- **10-year research program** systematically advanced scientific understanding of PLGA-based products
- **Research Focus Areas**

1. Polymer characterization and selection for suitable PLGA polymers in generic development
2. Analytical method development for characterizing complex PLGA microsphere formulations
3. In vitro drug release testing to understand naltrexone release mechanisms and manufacturing impacts



SEM micrographs of naltrexone PLGA-based microspheres

PLGA: Poly(lactic-co-glycolic acid)

Janki V. Andhariya, et al, Development of in vitro-in vivo correlation of parenteral naltrexone loaded polymeric microspheres, Journal of Controlled Release,255 (2017):27-35

Regulatory Impact & Outcomes

FDA approved first generic naltrexone extended-release injectable

Established clear criteria for evaluating bioequivalence of generic PLGA products

Supports reduction in overdose fatalities and relapse — key public health outcomes for clinicians

Summary

- Computational modeling (PBPK/CFD) enables a prediction of nasal drug delivery for opioid antagonist
- Naloxone formulation optimization of spray-dried powders and spray solutions
- PLGA microsphere advancement through polymer characterization and in vitro-in vivo correlations

Public Health & Regulatory Impact

- Enhanced overdose response through improved nasal delivery systems ensuring rapid, reliable naloxone absorption
- Extended addiction treatment via long-acting injectable naltrexone providing sustained opioid antagonism and reduced relapse rates
- Accelerated access to life-saving treatments through science-based regulatory pathways that maintain safety standards while enabling faster market entry
- Regulatory framework established for complex drug delivery systems addressing public health emergencies

References

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