

# Comment: Using Trend-in-Trend to Evaluate Drug Abuse

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# Presentation outline

1. Evaluating opioid analgesics with abuse-deterrent (AD) labeling
  - Category 4 labeling and postmarketing requirements
  - Goals for accurate evaluation
2. Comments on applying trend-in-trend
  - Exploratory method for evaluating AD opioids
  - Advantages, disadvantages, remaining questions
3. Future directions

# **EVALUATING OPIOID ANALGESICS WITH ABUSE-DETERRENT (AD) LABELING**



# Opioid analgesics with AD labeling

- Are not abuse-proof
- Are not designed to prevent addiction
- Have properties expected to deter abuse through specific routes (e.g., nasal, injection), as demonstrated in premarket assessments

# Opioid analgesics with AD labeling



- 10 products labeled as “expected to deter abuse” by specific routes
- Based on Category 1-3 (premarket) studies

OxyContin	Arymo ER*
Embeda	Roxybond* ( <i>first IR</i> )
Hysingla ER	<del>Troxyca ER</del>
MorphaBond	<del>Targiniq ER</del>
Xtampza ER	<del>Vantrela ER</del>

} **Withdrawn**

- All have postmarket requirements (PMRs) to study the impact of AD properties on abuse and related outcomes
- **None with Category 4 (postmarket) AD labeling**

\*Not currently marketed



# Evaluating AD opioid analgesics: Category 4 labeling supplement application

- 2015 Final Guidance<sup>1</sup>
  - “When postmarketing data become available that demonstrate a **meaningful reduction in abuse by one or more routes of administration**, these data should be added to the product labeling.”
  - Should not demonstrate a shift in routes of abuse that represents a greater risk (e.g., oral/nasal to injecting)
- “...flexible, adaptive approach...”

<sup>1</sup> *Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry*, Department of Health and Human Services, Food and Drug Administration, April 2015



# Evaluating AD opioids to inform regulatory decisions

- Results in meaningful reduction in abuse and its consequences
- People do not shift to riskier routes of abuse
- We have not settled on the definitive methods
- Ecologic designs, Trend-in-Trend, retrospective cohort studies are possible methods
  - Multiple data sources, study designs
  - Use active comparators



# Goals for evaluating AD opioids

- **Valid, precise estimates for causal inference**
- Sampling that allows inferences to defined target population
- Data are accurate and complete
  - Opioid analgesic products
  - Outcomes
- Design and analysis minimize confounding, bias
- Consistent results across multiple data sources, study designs, and sensitivity analyses





# Challenges for each goal

- **Make inferences to defined target population**
  - Finding exposed people and outcomes to study
  - Abuse is a covert behavior
  - AD opioid analgesics are low-volume
- **Complete and accurate data**
  - Research participants may misreport product names
- **Design and analysis minimize confounding, bias**
  - Ecologic time-series, retrospective cohort designs are vulnerable to confounding

# **CONSIDERATIONS FOR APPLYING TREND-IN-TREND TO REGULATORY QUESTIONS**



# Interesting descriptive findings from Dasgupta et al.<sup>1</sup>

- Each product had substantial spatial and temporal variation in utilization
  - Each profile was unique
- Few ZIP-quarters had any abuse cases
  - ZIP-quarters with any abuse often had only one case
  - Abuse was more likely in ZIP-quarters with any dispensing
- Association between dispensing and abuse was non-linear for many low-volume products

<sup>1</sup>Dasgupta N, Schwarz J, Hennessy S, et al. Causal inference for evaluating prescription opioid abuse using trend-in-trend design. *Pharmacoepidemiol Drug Saf* 2019;28(5):716-725.



# Trend-in-Trend Advantages

- Adjusts for important sources of confounding
  - Other interventions, secular trends
  - Geographic differences (probably, though no direct evidence of this in Dasgupta et al.)
  - Patient characteristics (possibly, though not examined by Dasgupta et al.)
- Uses a logistic regression model that appears to be more appropriate to the reality of the data distribution



# Disadvantage:

## Interpreting the odds ratio for Product X

	Any Abuse	No Abuse
Any Dispensing	A	B
No Dispensing	C	D

- $OR = (A/B) / (C/D)$
- **All Cells:** What other products were dispensed in that ZIP-quarter?
- **Cell C:** The outcome is product-specific, so, how did someone get exposed to Product X in that ZIP-quarter?



# Trend-in-Trend Disadvantages

- The interpretation is complicated, and the reference group is not clear
- Desirable to use active comparators, but that would not be feasible for many products
- Certain drugs cannot be studied with Trend-in-Trend if utilization is either high or very low
  - Very narrow application
  - Comparators?



# Trend-in-Trend does not address these challenges

Goals	Challenges
<b>Inferences to defined target population</b>	<b>Abuse is a covert behavior; AD opioid analgesic products are “low volume”</b>
<b>Data are accurate and complete</b>	<b>Product names may be misreported – bias aggravated by low volume products</b>

Address these challenges through careful study design:

- Study population definition
- Data collection and validation



# FDA's selected questions about Dasgupta et al.

- Used composite outcome from OTP/SKIP and PC
  - Differential coverage of ZIP-quarters
  - Are the odds ratios consistent across data sources?
- We would like to learn more about calculating the precision around the reported estimates from Trend-in-Trend model



# FUTURE DIRECTIONS



# Possible to study related outcomes?

- Route of abuse: intranasal, intravenous routes
  - Self-reported data
- Overdose from any opioid
  - Individual-level claims data linked to cause-of-death data



# Conclusions

- FDA currently considers Trend-in-Trend an exploratory method for evaluating AD opioid analgesics
  - Trend-in-Trend has distinct advantages and disadvantages
  - May hold promise for studying abuse, overdose, and related outcomes in selected situations
- For evaluating AD opioid analgesics, exposure and outcome ascertainment continue to be fundamental considerations

