FDA’s Current Approach to the Postmarket Evaluation of Opioid Analgesic Products with Properties Intended to Deter Abuse

Tamra Meyer, PhD, MPH
Team Lead: Prescription Drug Abuse Team
Office of Surveillance & Epidemiology
Center for Drug Evaluation & Research
Food and Drug Administration

RADARS annual meeting – May 10, 2018
The opinions in this presentation are my own and do not necessarily reflect the views and policies of the FDA
Addressing the opioid crisis is an agency priority

“Opioid formulations with properties designed to deter abuse are not abuse-proof or addiction-proof. These drugs can still be abused, particularly orally, and their use can still lead to new addiction. Nonetheless, these new formulations may hold promise as one part of a broad effort to reduce the rates of misuse and abuse. One thing is clear: we need better scientific information to understand how to optimize our assessment of abuse deterrent formulations ...”

Statement from FDA Commissioner Scott Gottlieb, M.D. – FDA is taking new steps to help assess opioid drugs with abuse-deterrent properties

https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm562961.htm
Terminology

• “Abuse-deterrent formulations”
  – 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
Abuse-deterrent mechanisms

1. Physical/chemical barriers
2. Agonist/antagonist combinations
3. Aversion
4. Novel delivery system
5. New molecular entities and prodrugs
6. Combination of two or more methods
7. Other novel approaches
Policy development

• April 2015: FDA released final guidance: Abuse-Deterrent Opioids-Evaluation and Labeling

• November 2017: FDA released final guidance: General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products
Premarket studies (Category 1-3)

1. Laboratory-based in vitro manipulation and extraction studies (Category 1)

2. Pharmacokinetic studies (Category 2)

3. Clinical abuse potential studies (Category 3)
Postmarket evaluations of abuse-deterrence (Category 4)

“Goal of postmarket studies is to determine whether the marketing of a product with abuse-deterrent properties results in **meaningful reductions** in abuse, misuse and related adverse clinical outcomes, including addiction, overdose, and death in the post-approval setting...Given the changing landscape, a numerical threshold cannot define what would be consider a meaningful reduction.”

Postmarket evaluation of opioid analgesics with abuse-deterrent properties

(from FDA Guidance for Industry)

• **Formal studies**
  – Hypothesis-driven
  – Meaningful measures of abuse (including route) and related adverse outcomes
  – National or multiple large geographic regions
  – Sufficiently powered to examine trends

• **Supportive information**
  – Can be qualitative, descriptive
  – Provide context, aid interpretation of formal studies
Products with approved abuse-deterrent labeling based on pre-market data

- Ten opioid analgesic products labeled as having properties expected to deter abuse (Category 1-3):
  - OxyContin
  - Targiniq ER *
  - Embeda
  - Hysingla ER
  - MorphaBond
  - Xtampza ER
  - Troxyca ER
  - Arymo ER
  - Vantrela ER
  - Roxybond (first IR) *

- No products with Category 4 labeling
- All have postmarket requirements (PMRs) to evaluate the impact of these properties on abuse in the “real-world” post-approval setting

*Not currently marketed
Nationally estimated number of prescriptions dispensed for opioid analgesic products from U.S. outpatient retail pharmacies

*Immediate-Release formulations include oral solids, oral liquids, rectal, nasal, and transmucosal
**Extended-Release/Long-Acting formulations include oral solids and transdermal patches
***Abuse-deterrent formulation opioid products include Arymo ER, Embeda ER, Hysingla ER, Morphabond ER, Xtampza ER, OxyContin ER
Reformulated (Approval in April 2010)
Note: Include opioid analgesics only, excluding injectable formulations as well as opioid-containing cough-cold products and opioid-containing medication-assisted treatment (MAT) products
Nationally estimated number of prescriptions dispensed for abuse-deterrent formulation (ADF) opioid analgesic products* from U.S. outpatient retail pharmacies


*ADF Products not marketed during study period: RoxyBond (Oxycodone IR) - Approved 04/2017; Targiniq ER (oxycodone/naloxone ER) - Approved 07/2014; Troxyca ER (Oxycodone/naltrexone ER) - Approved 08/2016; Vantrela ER (Hydrocodone ER) - Approved 01/2017
Challenges with current postmarketing data used to evaluate abuse-deterrence

- Abuse is a covert behavior that can occur in patients and non-patients
- Claims/EMR data insufficient to capture route-specific abuse
- Mosaic approach to look at several data sources that show different slices of the relevant populations/outcomes
- Most studies use ecologic time series design: pre-post comparison of outcome rates (per population, prescriptions, or dosage-units)
- Must minimize time-related bias/confounding of pre-post comparison
- Low/slow market uptake for most approved products with abuse-deterrent labeling

...and many more

FDA Public Meeting July 10-11, 2017: Data and Methods for Evaluating the Impact of Opioid Formulations with Properties Designed to Deter Abuse in the Postmarket Setting:
https://www.fda.gov/Drugs/NewsEvents/ucm540845.htm

EMR, electronic medical record
Underpowered for hypothesis testing

More expensive products
Limited insurance coverage
If AD properties limit event numbers for certain abuse routes
Decreased utilization of ER/LA formulations

Low power for testing meaningful differences in route-specific abuse and related outcomes

AD, abuse-deterrent; ER/LA, extended-release/long-acting opioid analgesics
Especially underpowered for route-specific abuse

- Route-specific abuse is a critical component for assessing effectiveness of AD properties

---

AD, abuse-deterrent
Postmarket evaluation of opioid analgesics with AD properties (Category 4)

• Moved to 2-phase approach in 2017:

Phase 1: Descriptive, feasibility, safety surveillance
Provide surveillance data on utilization, scope, and patterns of abuse

Phase 2: Hypothesis Testing
Once market uptake is sufficient, conduct studies to evaluate for meaningful reduction in abuse and related outcomes
Surveillance for unanticipated outcomes with reformulated products

• Reformulated Opana® ER (oxymorphone)
  – Approved without AD labeling in December 2011 and replaced original Opana ER in February 2012
  – Polyethylene oxide matrix to make crushing and syringeability more difficult by forming a viscous gel when in contact with liquids
  – Shift in route of abuse from intranasal to IV abuse
  – Unsafe tampering/preparation practices specific to Opana ER led to HIV outbreak in Indiana
  – New potentially excipient-related adverse effects – TTP-like illness

AD, abuse-deterrent; ER, extended-release; IV, intravenous; TTP, Thrombotic thrombocytopenic purpura
Phase 1 PMR language

...provide meaningful baseline data to support the hypothesis-testing studies ..., conduct a descriptive study...:

1) **Utilization of PRODUCT and selected comparators**: ...include nationally-projected quarterly dispensing data, overall and by age group and census region;

AND

2) **Abuse of PRODUCT and related clinical outcomes**. ...utilize multiple data sources in different populations ... for PRODUCT as well as mutually agreed-upon, selected comparators to provide context.

• ...include route-specific abuse..., be **nationally-representative** or from multiple large geographic areas...

• Additional information..., from sources such as internet forums, spontaneous adverse event reporting, or small cohort studies...to help better understand abuse...

• **Formal hypothesis testing is not necessary during this phase**...
Phase 2 PMR language

Following satisfactory fulfillment of [Phase 1 studies]...:

• Conduct formal observational studies to assess whether the properties intended to deter misuse and abuse of PRODUCT actually result in a meaningful decrease in misuse and abuse, and their consequences, addiction, overdose, and death, in post-approval settings. ...Assessing the impact of the abuse-deterrent formulation on the incidence of clinical outcomes, including overdose and death, is critical to fulfilling this PMR. Any studies using electronic healthcare data should use validated outcomes and adhere to guidelines outlined in FDA’s guidance for industry and FDA staff...
Phase 1 to Phase 2?

- All outcomes covered (route-specific abuse, misuse, addiction, overdose, death, other clinical outcomes)?
  - Valid outcome definitions/algorithms?
    - Valid exposure assessment?
    - Nationally-representative/good geographic coverage?
    - Sufficient utilization/outcome precision for hypothesis testing?

Phase 1: Descriptive, feasibility, safety surveillance

Phase 2: Hypothesis Testing
Public health impact of AD opioid analgesics

• Potential Positives?
  • Shift to less-dangerous routes of abuse for some products
  • Prevention of transition to more severe opioid use disorder
  • Less diversion of some products

• Potential Negatives?
  • Excipient harms
  • Shift to more dangerous route of abuse
  • Misunderstanding of “abuse-deterrent” terminology by providers and patients
  • Costs to patients/health systems
  • Shift to other drugs of abuse, such as heroin
Assessing public health risk and benefits for new opioid approvals

• 2017 NASEM Report\textsuperscript{1} recommends developing a regulatory framework for opioids that balances individual need for pain control with considerations of the broader public health consequences of opioid misuse to ensure that ... as actually used, the drugs provide benefits that clearly outweigh their harms.
