Overview of Public Meeting & Day 1 Roadmap

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Rationale for this scientific workshop

• What is the impetus for today’s meeting?
• Why did we invite you here today?
• How will the meeting work?
• What do we envision as the output?
What is the impetus for today’s meeting?
Nationally Estimated Number of Prescriptions Dispensed for Opioid Analgesics* Products from U.S. Outpatient Retail Pharmacies


* Immediate-Release formulations included oral solids, oral liquids, rectal, nasal, and transmucosal products.
** Extended-Release/Long-Acting formulations included oral solids and transdermal patches.

Note: Included opioid analgesics only. Excluded injectable products, cough-cold products, and Medication-Assisted Treatment (MAT) products.
Overdose Deaths Involving Opioids, by Type of Opioid, United States, 2000-2015

- Any Opioid
- Heroin
- Natural & Semi-Synthetic Opioids (e.g., fentanyl, tramadol)
- Other Synthetic Opioids
- Methadone

FDA Opioids Action Plan

• Expand the use of advisory committees
• Develop warnings and safety information for immediate-release (IR) opioid labeling
• Strengthen postmarket requirements to get needed data
• Update Risk Evaluation and Mitigation Strategy (REMS) Program for Prescription Opioids
• Expand access to abuse-deterrent formulations (ADFs) to discourage abuse
• Support better treatment for prescription opioid abuse and overdose
• Reassess the risk-benefit approval framework for opioid use

--www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm
Abuse-Deterrent Opioids — Evaluation and Labeling
Guidance for Industry

Additional copies are available from:
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Terminology

• “Abuse deterrent formulations”
  – Are not “abuse proof”
  – Are designed to deter specific routes of abuse (e.g. intranasal, injection)
  – Are not designed to prevent addiction
  – Have properties intended to deter abuse, as demonstrated in pre-market assessments
    • In vitro studies
    • Human abuse potential (HAP) studies

• For brevity, we will refer to such formulations as “ADFs” throughout our talks
Products with approved abuse-deterrent labeling

- Based on *in vitro* and *in vivo* premarket data, ten opioid products labeled as having properties *expected to deter abuse*:

  - OxyContin
  - Targiniq ER
  - Embeda
  - Hysingla ER
  - MorphaBond
  - Xtampza ER
  - Troxyca ER
  - Arymo ER
  - Vantrela ER
  - Roxybond (*first IR*)

- All have postmarket requirements (PMRs) to evaluate the impact of these properties on abuse in the “real-world” post-approval setting
Nationally Estimated Number of Prescriptions Dispensed for Opioid Analgesic Products* with abuse deterrent properties from U.S. Outpatient Retail Pharmacies


*Not marketed during study period: Targiniq (oxycodone/naloxone ER) - Approved 07/2014; MorphaBond (morphine ER) - Approved 10/2015; Troxyca (oxycodone/naltrexone ER) - Approved 08/2016 – Roxybond (oxycodone IR) – Approved 04/2017
Goal of Postmarket Evaluation of Opioids with Abuse-deterrent Properties
(from FDA Guidance for Industry)

“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 Opioids 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, smaller
  – Provide context, aid interpretation of formal studies
Postmarket Evaluation of Opioids with Abuse-deterrent Properties

• Recently moved to 2-phase approach:

  **Phase 1:** Descriptive and feasibility
  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
Postmarket Abuse-deterrent Labeling

• Labeling dictates how a product can be legally marketed
• Claims in drug labels require
  – High quality studies (but here we don’t have RCTs!)
  – In-depth FDA review
  – Often, public discussion and outside expert input
• Goal is to provide informative and scientifically accurate information
• Currently, no opioid product label states that it reduces abuse in the community (Category 4 labeling) – only that it is “expected” to do so, based on pre-market evaluations
Challenges
How is abuse different from traditional pharmacoepidemiology safety outcomes?

• Abuse and related outcomes occur in patients and non-patients
• Traditional data sources (claims/EMR) are specific to patients under medical care
• Abuse is covert behavior—not captured well in these sources
• Outcomes associated with drug abuse are social/legal, as well as medical—manifest in multiple settings
Pathways to Abuse/Misuse of Prescription Drugs and Related Adverse Outcomes

Drug manufactured  Drug distributed  Drug prescribed/dispensed

Drug diversion

Patient supply

Patient use as prescribed

Outcome captured in...

Population Surveys (self-report)

Abuse

Misuse

Addiction

Overdose

Death

Health Care Utilization data

Mortality Records

Nationally-representative household and school surveys

Treatment center surveys

Internet surveys

Poison Center data

Emergency Department Visit and Hospitalization data (claims, EMR)

Addiction treatment admissions

National Vital Statistics, linked death registry data

Medical Examiner data (limited availability)

National death certificate literal text (in development)
Challenges with Current Postmarketing Data used to Evaluate Abuse-Deterrence

• Most studies use ecologic time series design: pre-post comparison of abuse rates
• Goal is to isolate effect of abuse-deterrent formulation, support causal inference
• Must minimize other changes over time that could bias/confound pre-post comparison
Challenges with Current Postmarketing Data used to Evaluate Abuse-Deterrence

- No nationally-representative data that can reliably estimate national abuse, addiction, overdose rates for specific opioid products – by route
- Attempt “mosaic approach,” looking for consistency in multiple imperfect data sources
- Currently available data sources have significant limitations that can bias pre-post comparisons over time
Why did we invite you here today?

• It’s time for an open discussion around the **scientific issues**, rather than around specific products

• Invited a diverse group of scientists outside of FDA who are knowledgeable about:
  
  – Studying drug abuse, using currently available data (licit or illicit drugs)
  
  – Conducting surveillance on/building data systems to study other public health problems at a national level
  
  – Possibly relevant data sources NOT used widely to study prescription drug abuse
  
  – Survey design methodology/projection science
  
  – The scientific rigor needed for regulatory decision-making (us)

• Our goal: draw various areas of expertise into 1 conversation to brainstorm solutions to the current challenges
How will the meeting work?
Overall Roadmap

- **Day 1**: Focused on improving the use of existing data sources

- **Day 2**: Focused on development and use of new data sources and capabilities
Day 1 Sessions: Improving the use of existing data sources

• **Session 1** Data resources used to investigate drug products with properties intended to deter abuse

• **Session 2** Sampling, metrics and denominators

• **Session 3** Causality and control for confounding

• **Session 4** Strategies to overcome/mitigate some of the identified challenges
Day 2 Sessions: Use and development of new sources and capabilities

• **Session 5** National surveys: Opportunities for Evaluation of ADFs

• **Session 6** Designs That Assess Exposure and Outcome in the Same Individuals Over Time

• **Session 7** Leveraging other data: Linking and Benchmarking

• **Session 8** Next steps
Format for each session

• FDA epidemiologist and statistician will present brief overview of the issues (15 min) and discussion questions
• They will moderate group discussion (60 min)
• Opportunity for brief audience comments (15 min)
  – Please focus comments on the topic of the session
  – Not an FDA Advisory Committee
• Opportunity for detailed comments to be submitted to docket – open till 9/11/17 - Docket Number is FDA-2017-N-2903
• [https://www.fda.gov/Drugs/NewsEvents/ucm540845.html](https://www.fda.gov/Drugs/NewsEvents/ucm540845.html)
What do we envision as the output?
Path Forward - immediate

• FDA continues to support development of effective abuse-deterrent opioid products and rigorous evaluation of their impact -- just one part of multi-pronged effort to address opioid crisis
  – Continue to work with drug manufacturers through PMRs to improve postmarket studies – publicly share results
  – Use what we learn in this meeting to inform our conversations with industry and update our guidance
Path Forward - intermediate

– FDA contracted access to poison control center and treatment center data in 2016
  – AAPCC, RADARS treatment centers, NAVIPPRO

– Working with other federal agencies to develop new data resources and enhance existing ones
  – NCHS/SAMHSA – National Hospital Care Survey (“new DAWN”)
  – CDC - NEISS/CADES – adding in abuse-related cases
  – NCHS/Vital Statistics - Extraction of specific drugs from literal text on death certificates

– Collaborative project - Yale-Mayo Center for Excellence in Regulatory Science Innovation (CERSI) grant
  – Linking disparate data sources together across CT to study fatal and nonfatal opioid overdoses
Path Forward – long term

• Broad Agency Announcement (BAA) issued in 2016, soliciting research proposals in this area for possible FDA funding

• Ideas can also be shared with a new working group in HHS that is interested in stakeholder ideas about ways to build data infrastructure to study opioid abuse.