Overview of Public Meeting & Day 1 Roadmap

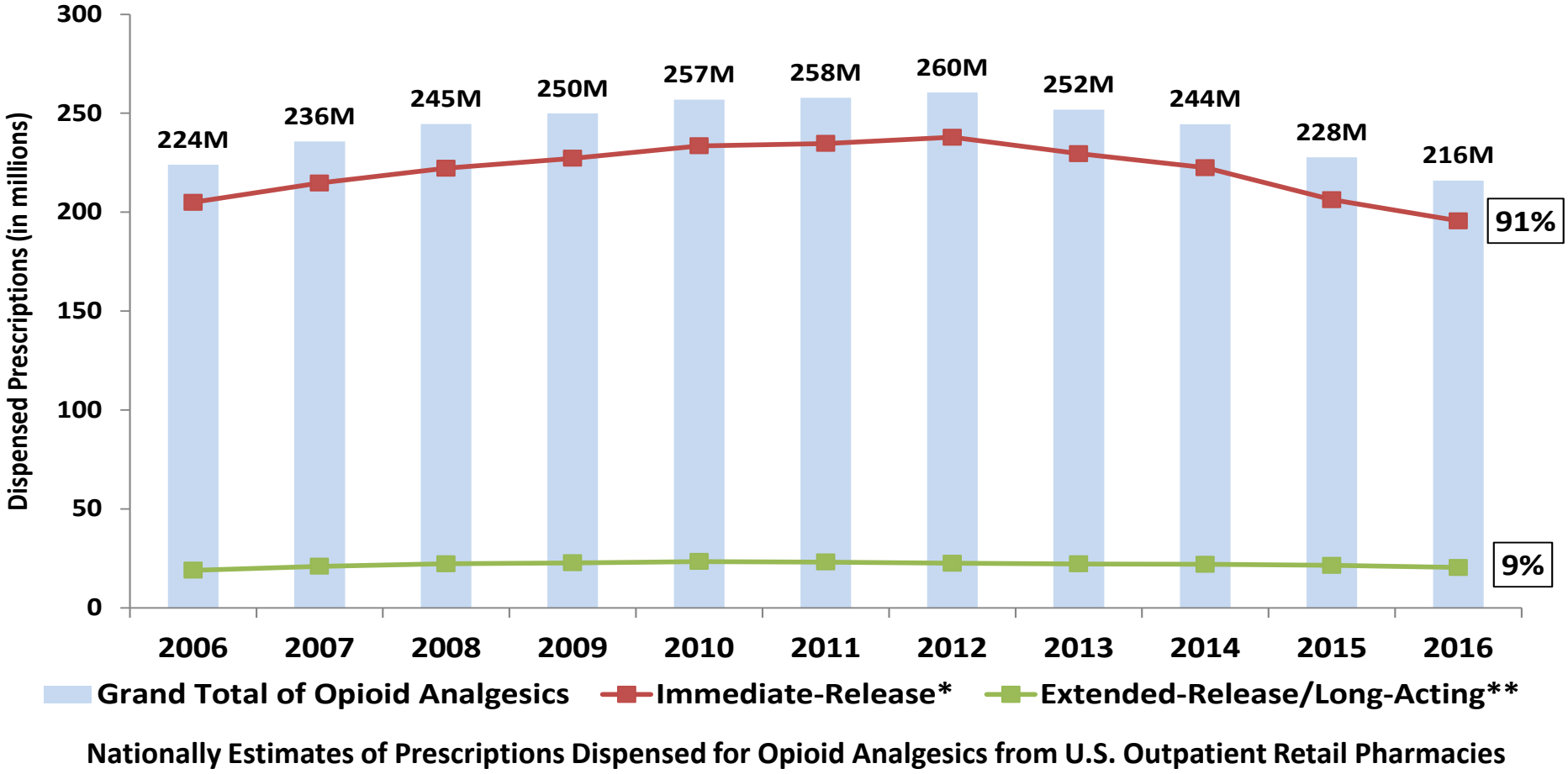
Judy Staffa, Ph.D., R.Ph.
Associate Director for Public Health Initiatives
Office of Surveillance & Epidemiology
Center for Drug Evaluation and Research
US Food and Drug Administration

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?

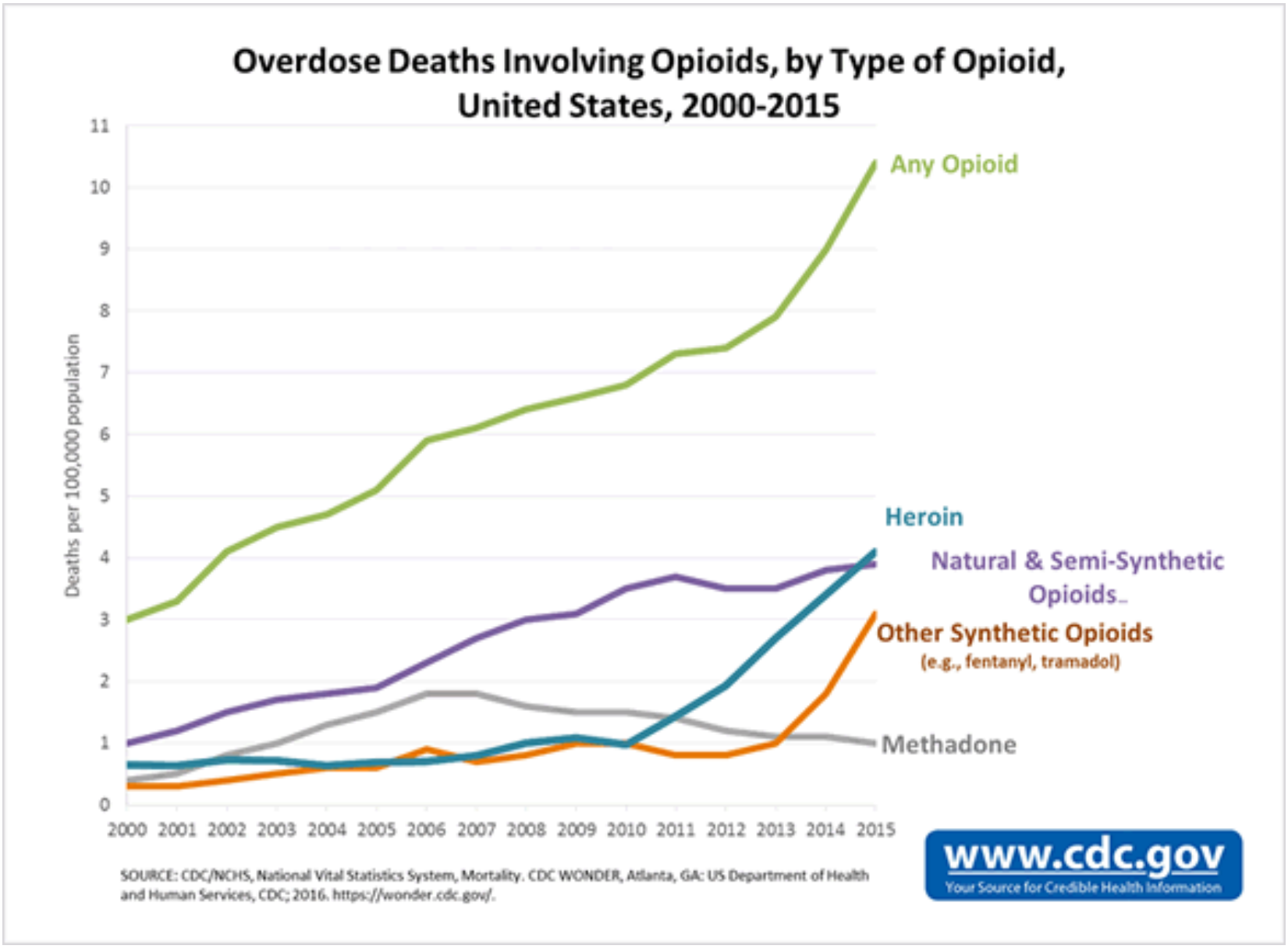
What is the impetus for today's meeting?

Nationally Estimated Number of Prescriptions Dispensed for Opioid Analgesics* Products from U.S. Outpatient Retail Pharmacies



Nationally Estimates of Prescriptions Dispensed for Opioid Analgesics from U.S. Outpatient Retail Pharmacies

Source: National Prescription Audit (NPA) and static data 2006-2011. January 2006-December 2016 Extracted March 2017.
* 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
Deaths per 100,000 population
0
1
2
3
4
5
6
7
8
9
10
11
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015
Any Opioid
Heroin
Natural & Semi-Synthetic Opioids
Other Synthetic Opioids
(e.g., fentanyl, tramadol)
Methadone
SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2016. https://wonder.cdc.gov/.
www.cdc.gov
Your Source for Credible Health Information

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:
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

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

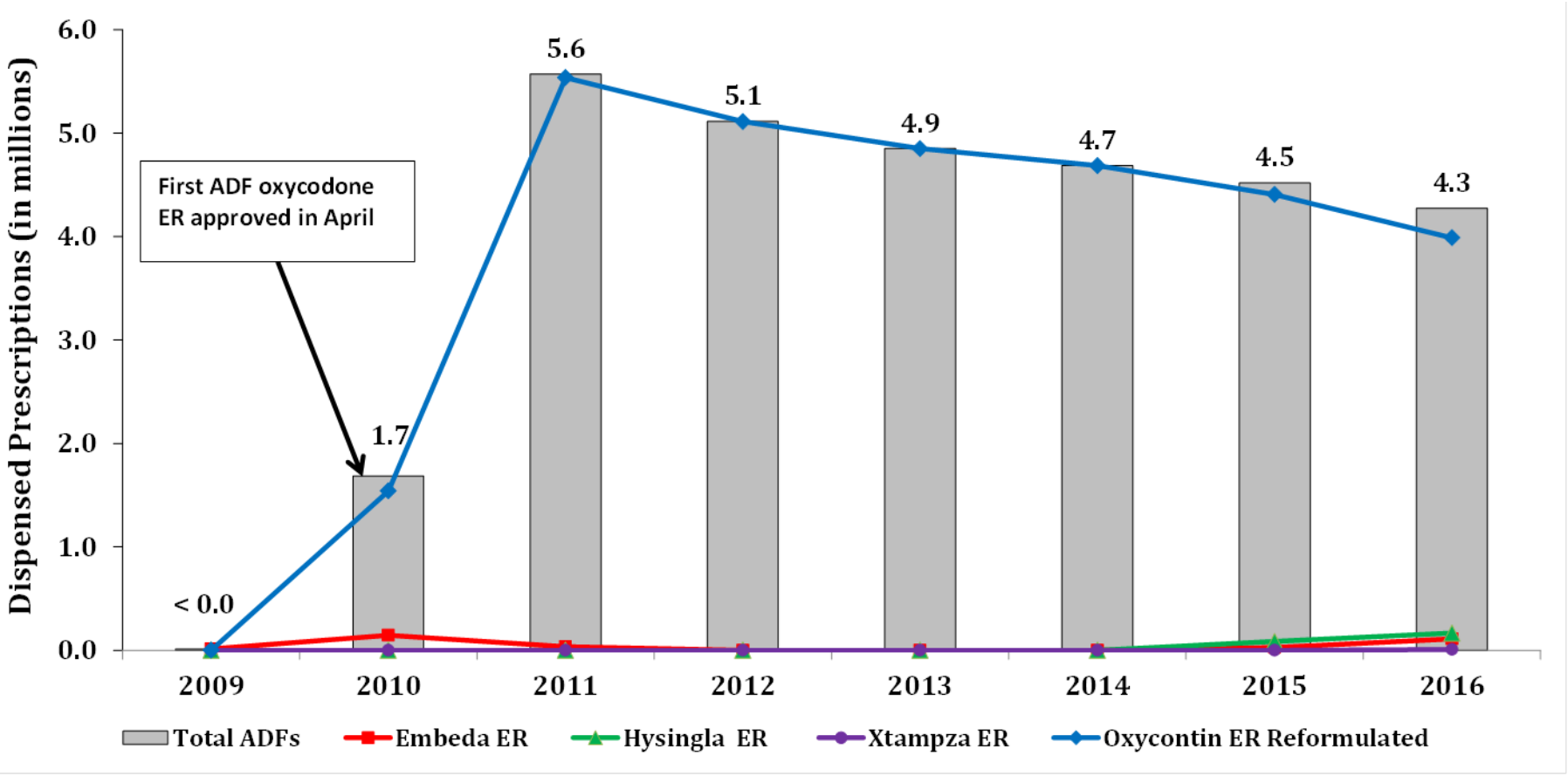
Products with approved abuse-deterrent labeling

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

OxyContin	Xtampza ER
Targiniq ER	Troxyca ER
Embeda	Arymo ER
Hysingla ER	Vantrela ER
MorphaBond	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



Source: QuintilesIMS National Prescription Audit™, Years 2009-2016. Data Extracted March 2017.
*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."

1. "Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry," FDA Center for Drug Evaluation and Research, April 2015

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

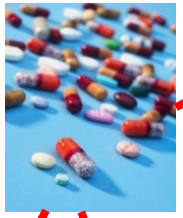
Challenges

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



Patient supply

Drug manufactured

Drug distributed

Drug prescribed/ dispensed

Patient use as prescribed

Drug diversion

Inappropriate use by patients

Abuse

Misuse

Addiction

Overdose

Death

Outcome captured in…

Population Surveys (self-report)

- **Nationally-representative household and school surveys**
- **Treatment center surveys**
- **Internet surveys**

Health Care Utilization data

- **Poison Center data**
- **Emergency Department Visit and Hospitalization data (claims, EMR)**
- **Addiction treatment admissions**

Mortality Records

- **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.htm

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.


FDA
U.S. FOOD & DRUG
ADMINISTRATION