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

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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."

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

# 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 | Xtampza ER |
| Targiniq ER* | ~~Troxyca ER~~ |
| Embeda | Arymo ER |
| Hysingla ER | ~~Vantrela ER~~ |
| MorphaBond | Roxybond *(first IR)** |

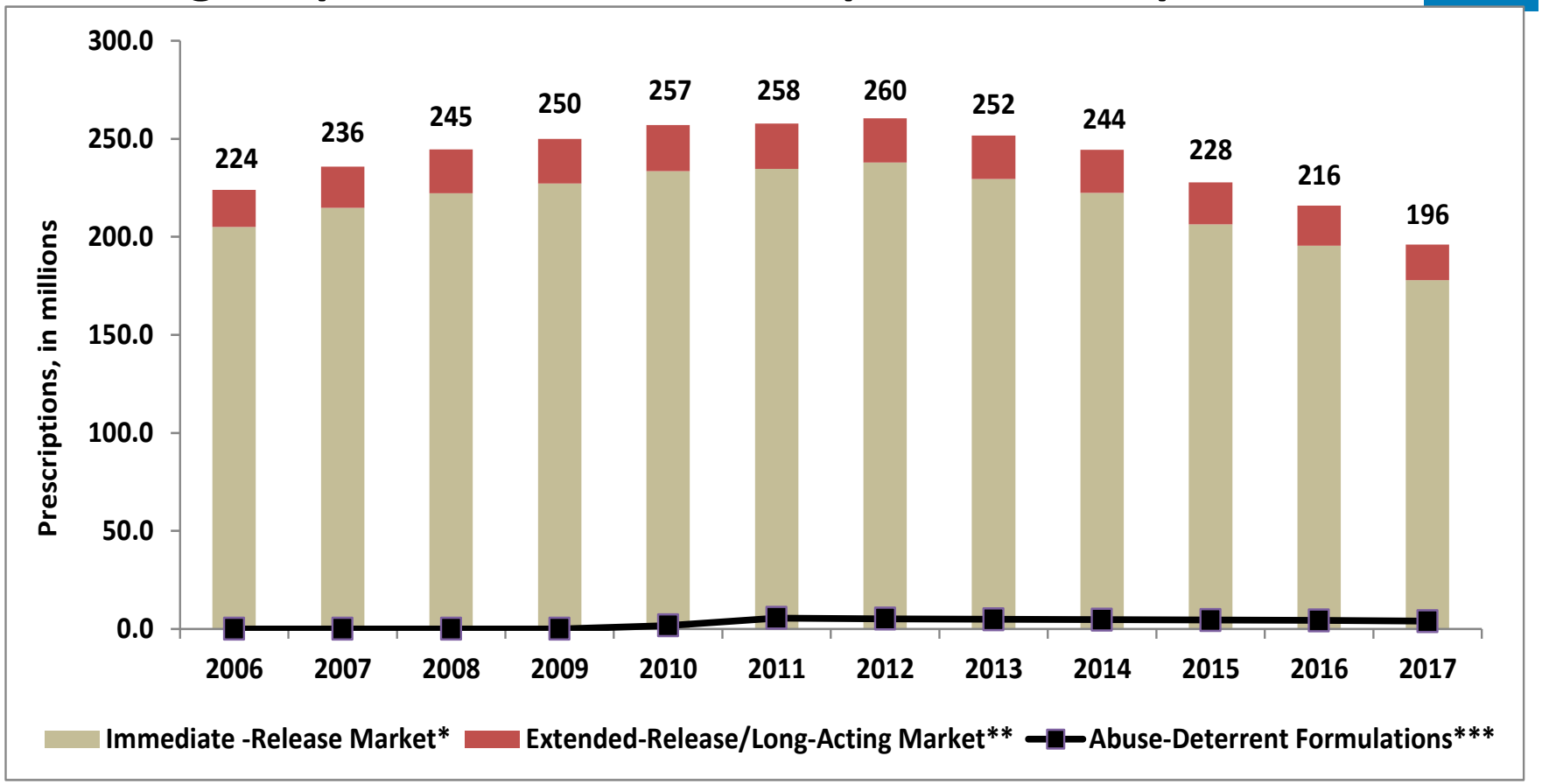
**Withdrawn on 5/2/2018**

- **<u>No products with Category 4 labeling</u>**
- All have postmarket requirements (PMRs) to evaluate the impact of these properties on abuse in the "real-world" post-approval setting

*Not currently marketed

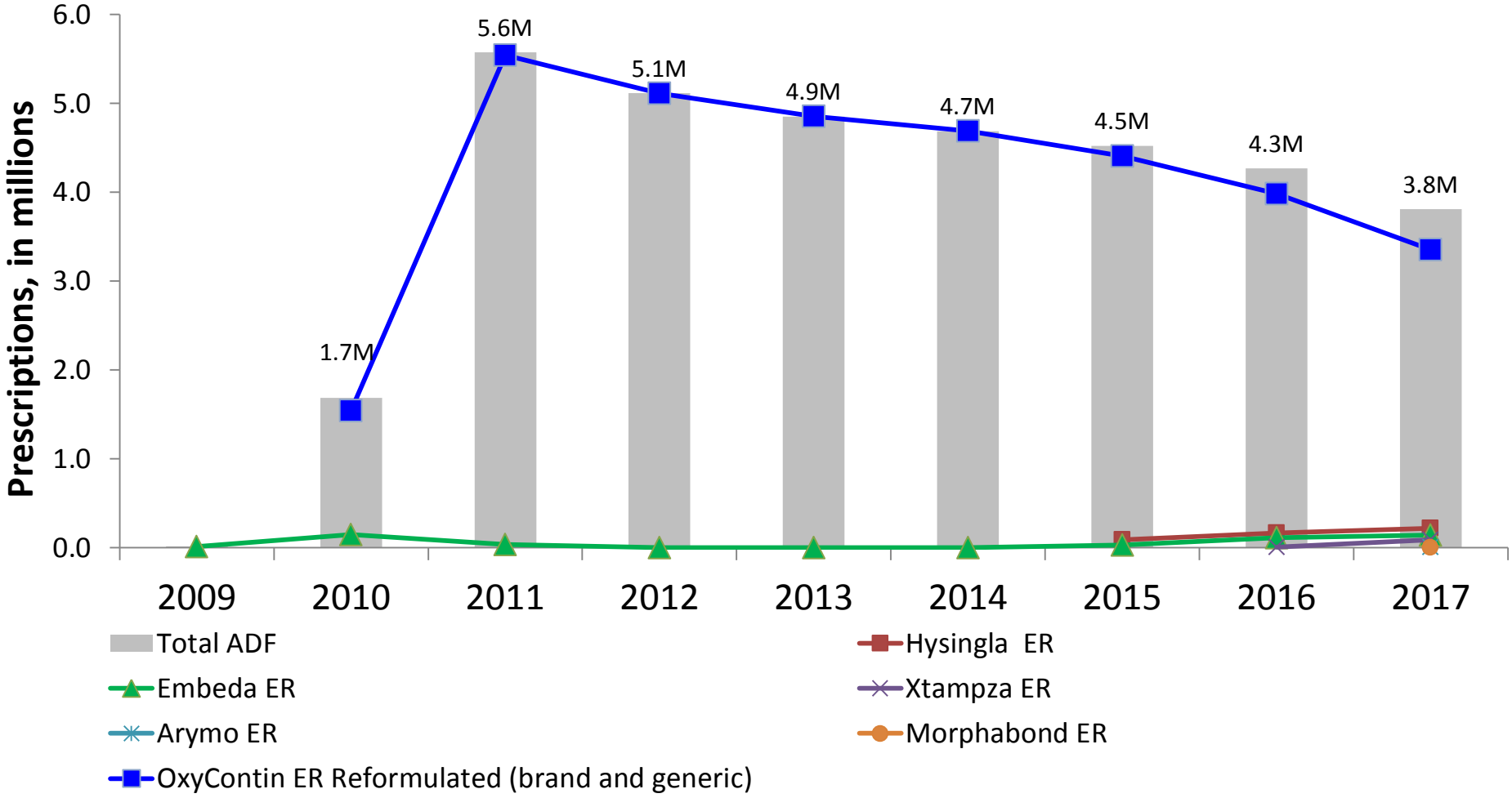
Troxyca ER and Vantrela ER were withdrawn on 5/2/2018, https://www.gpo.gov/fdsys/pkg/FR-2018-04-02/pdf/2018-06663.pdf

# Nationally estimated number of prescriptions dispensed for opioid analgesic products from U.S. outpatient retail pharmacies




Source: IQVIA, National Prescription Audit (NPA) and static data 2006-2011. January 2006-December 2017.
Static data extracted March 2017 and 2012-2017 data extracted February 2018.
*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




**Source: IQVIA, National Prescription Audit™, Years 2009-2017. Data Extracted February 2018.**

***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**

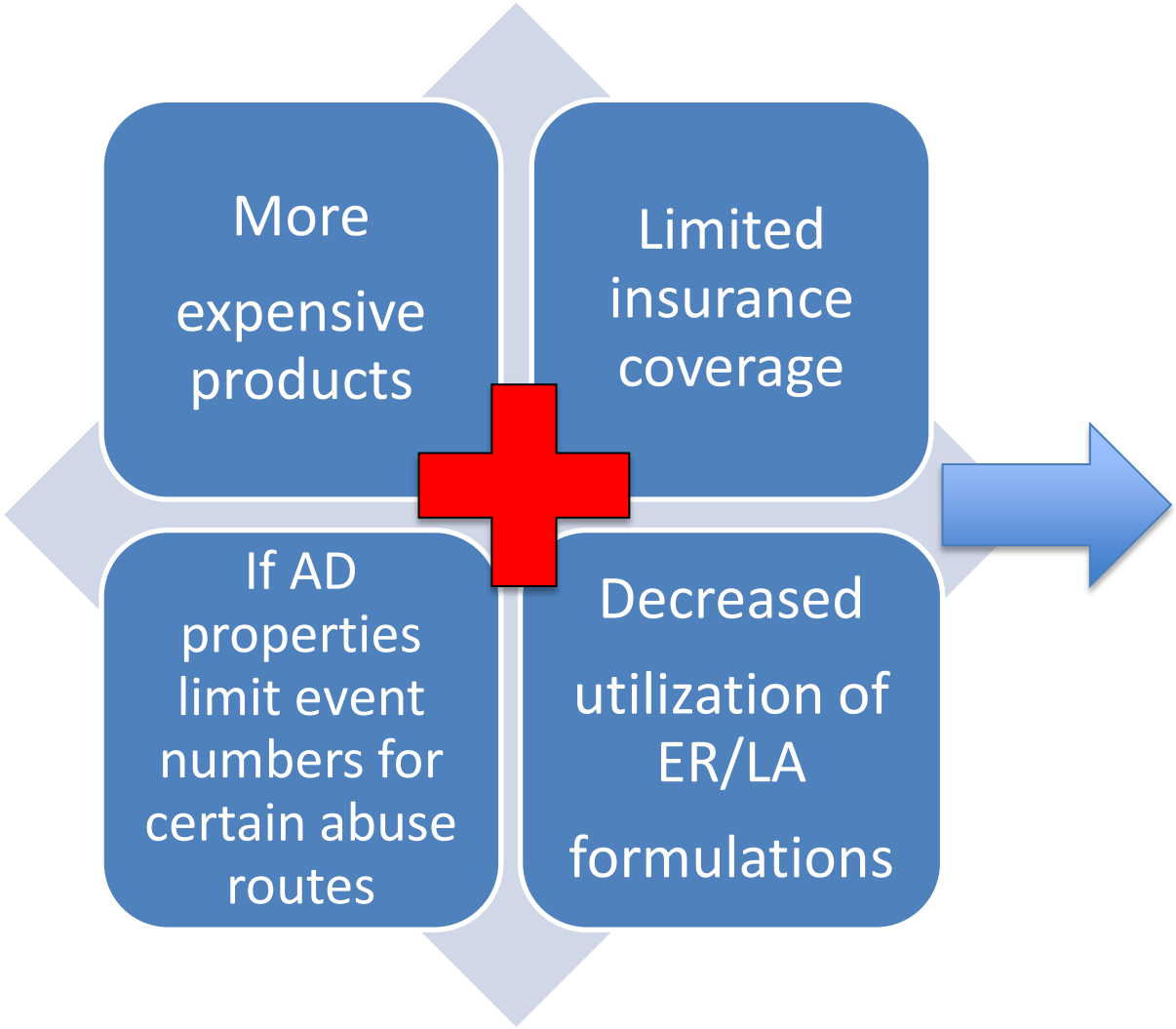
**…and many more**

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

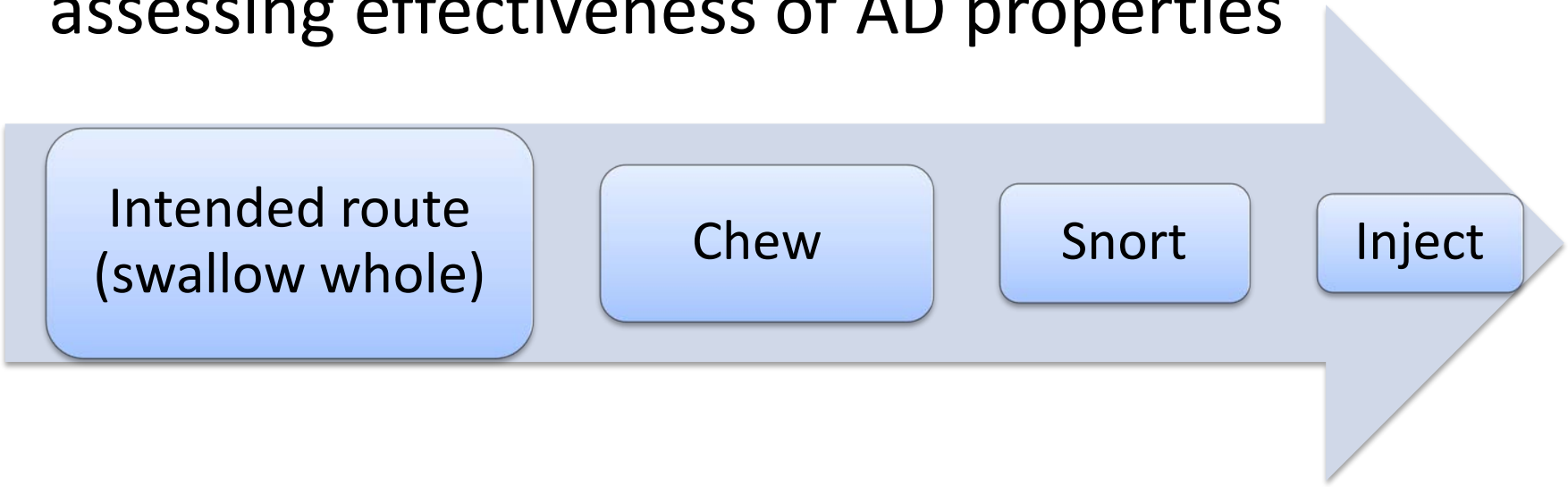
# Underpowered for hypothesis testing




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

AD, abuse-deterrent

# 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

AD, abuse-deterrent

# Assessing public health risk and benefits for new opioid approvals

- 2017 NASEM Report[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.

1. National Academies of Sciences, Engineering, and Medicine. 2017. *Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use*. Washington, DC: The National Academies Press.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