Overview of Emerging Technologies

Opioids with Abuse-Deterrent Properties and Claims (OADP)

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Synopsis

• This presentation will provide information about:
  – The reasons OADP are important innovations
  – The FDA’s direction to those developing OADP
  – Where to find Abuse-Deterrent Properties and Claims
  – Some technologies employed or under study for OADP
The Problems

• Concurrent public health problems in the United States:
  
  – Endemic nonmedical use/misuse of prescription pain medicines
  
  – Epidemic fatal overdoses involving opioid analgesics
  
  – Endemic chronic pain
National Survey on Drug Use & Health
NSDUH

- Authorized by federal statute, began in 1971
- Data used to implement and measure drug policy
- Annual, face-to-face, computer-assisted interview
- Approximately 70,000 persons, age 12 and older

- 2002-2014: Nonmedical use determined by: “Have you ever, even once, used any prescription pain reliever that was not prescribed for you, or that you took just for the experience or feeling it caused?”

Nonmedical Use (NMU) Opioid Analgesic Incidence Trends

Persons ≥12 y/o *Initiating* NMU in Past Year (%)

http://www.samhsa.gov/data/sites/default/files/NSDUH-DetTabs2014/NSDUH-DetTabs2014.htm#tab7-44a
National Survey on Drug Use and Health (NSDUH) Tables 7.44A&B
Nonmedical Use (NMU) Opioid Analgesic Prevalence Trends

Persons ≥12 y/o with Current (Past Month) NMU, by Year (%)

Use and Misuse
Prescription Pain Relievers (PPR)

• NSDUH changed some questions in 2015
• Asked about any use as well as misuse
• Misuse defined only by behaviors:
  – Use in any way a doctor did not direct, including use without a prescription of one’s own, use in greater amounts, more often, or longer than directed, or use in any other way not directed by a doctor.
• Change creates a break in trend for Rx drugs, but not heroin, cocaine, marijuana.
• Past Year Initiation of PPR Misuse = 2,126,000 (0.8%)
• Past Year Prevalence of PPR Misuse = 12,462,000 (4.7%)
• Past Month PPR Misuse = 3,775,000 (1.4%)

Main Reason for Last Episode of Misuse of Prescription Pain Relievers (2015)

Past Year Misuse = 12,462,000
97% of Respondents Provided a Reason*

- Relieve Physical Pain, 62.6%
- Feel Good Or Get High, 12.1%
- Relax or Relieve Tension, 10.8%
- Help With Sleep, 4.4%
- Help With Feelings/Emotions, 3.3%
- Experiment/See What It's Like, 2.5%
- Because I Am Hooked/Have To Have It, 2.3%
- Some Other Reason (Write-In Responses), 1.2%
- Increase/Decrease Effect of Other Drug, 0.9%

* Total = 100.1%: If respondent gave more than one reason, they were prompted to indicate the most important reason.

Accessed 10/11/2016

Sources of Pain Relievers for Most Recent Misuse (2015 Data)

* The **Other** category includes: “Write-in responses not already listed in source table” or “Responses with insufficient information that could allow for placement in another category.”

Accessed 10/11/2016
Sources of Pain Relievers for Nonmedical Use By Frequency of NMU (Combined 2008-2011 Data)

* The Other category includes: "Wrote Fake Prescription," "Stole from Doctor's Office/Clinic/Hospital/Pharmacy," and "Some Other Way."


Astor Crowne Plaza/NASCSA/New Orleans, LA  10/20/2016
Fatal Overdoses Involving Opioids

Benzodiazepines Involved:
- 1999 – 527 (13%)
- 2011 – 5,188 (31%)

Methadone Involved:
- 1999 – 784 (19.5%)
- 2007 – 5,518 (38%)
- 2011 – 4,418 (26%)

Synthetic Opioids other than Methadone Involved:
- 2014 – 5,544 (29%)
- 79% Increase over 2013
- Largely non-pharmaceutical fentanyl

http://www.cdc.gov/nchs/data/databriefs/db166_table.pdf#1 Tables 2 and 3
Chronic Pain is Endemic in the U.S.

**Institute of Medicine of the National Academies (2011) estimates:**

- “About 100 million” adult Americans experience chronic pain
- Cost range of $560 – $635 billion annually

**National Health Interview Survey (2012) estimates:**

- 126 million adults experience *some* pain in past 3 months
- 25.3 million adults suffer pain *daily*
- 23.4 million adults experience “*a lot*” of pain
- The 39.8 million adults with the *most severe pain* were more likely to:
  - Have worse health status
  - Suffer from disability
  - Use more health care

Opioid Prescriptions in the U.S.

**US Centers for Disease Control & Prevention (2012)**

- 259 MM prescriptions for opioids in 2012

**IMS Institute for Healthcare Informatics (2012)**

- ~ 75 MM persons prescribed an opioid at least once in 2012

**IMS NPA Market Dynamics Monthly Opioid Average (01/16-05/16)**

- ~ 13.2 MM persons on immediate-release (IR) opioid analgesic
- ~ 1.7 MM persons on extended-release or long-acting (ER/LA) opioid

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The Federal Solution

White House Office of National Drug Control Policy (ONDCP)

• Rx Drug Abuse Policy Approach Is Built on Four Pillars:
  – **Education** – Prescribers and consumers
  – **Monitoring** – PDMPs and clinical monitoring of progress
  – **Disposal** – Take back programs and FDA instructions in FPIs
  – **Enforcement** – Existing laws against trafficking and pill mills

• FDA to perform expedited review of NDAs for:
  – analgesics with no abuse potential
  – abuse-deterrent formulations for:
    o opioid medications and
    o other drugs with abuse potential

• FDA to provide guidance to industry on development and assessment of potentially abuse-deterrent drug formulations

Abuse-Deterrent Opioids—Evaluation and Labeling Guidance to Industry (April 2015)

• “FDA considers the development of these products a high public health priority.”
• Delineates four Categories of studies that can characterize product attributes as abuse deterrent.
• Defines “meaningful” deterrence as the standard for label claims.
• States that no absolute performance thresholds on studies.
• States that science of abuse-deterrence technology and its evaluation is relatively new and continually evolving.
• Abuse-Deterrent Properties and Claims will:
  – Generally be based on results from studies in more than one Category.
  – Include caveats about abuse by:
    o The route(s)/method(s) of abuse it deters.
    o Other routes/methods of abuse.
## Common Methods of Abuse

<table>
<thead>
<tr>
<th>Route</th>
<th>Dosage Form Manipulation (if any)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Intact dosage form(s) swallowed</td>
</tr>
<tr>
<td></td>
<td>Chewed dosage form(s) swallowed</td>
</tr>
<tr>
<td></td>
<td>Extract from dosage form(s) swallowed (eg, EtOH, water)</td>
</tr>
<tr>
<td>Inhaled</td>
<td>Intact or mechanically-compromised* dosage form(s) vaporized</td>
</tr>
<tr>
<td></td>
<td>Mechanically-compromised dosage form(s) inspired into nasal cavity</td>
</tr>
<tr>
<td>Injection†</td>
<td>Mechanically-compromised dosage form(s) dissolved, usually with aid of heat, aspirated into syringe, and injected</td>
</tr>
</tbody>
</table>

* Mechanically-compromised = break, crush, grind, mill, etc.

† Intravenous or subcutaneous

# Technological Approaches to Abuse Deterrence

<table>
<thead>
<tr>
<th>Technology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical/Chemical Barriers</td>
<td>Physical barriers: can prevent chewing, crushing, cutting, grating, or grinding. Chemical barriers: can resist extraction of the opioid using common solvents like water, alcohol, or other organic solvents. These barriers can limit drug release after manipulation or change the form of the drug, rendering less amenable to abuse.</td>
</tr>
<tr>
<td>Agonist/Antagonist Combinations</td>
<td>Antagonist added to interfere with, reduce, or defeat the euphoria associated with abuse. Antagonist may be sequestered and released only upon manipulation of the product, i.e., antagonist is not clinically active when the product is swallowed but becomes active if the product is crushed and injected or snorted.</td>
</tr>
<tr>
<td>Aversion</td>
<td>Substances can be combined to produce an unpleasant effect if the dosage form is manipulated prior to ingestion or a higher dosage than directed used.</td>
</tr>
</tbody>
</table>
Evaluation of Abuse Deterrence
(Study Categories Numbered per FDA Guidance)

Premarket Studies

1. In Vitro Manipulation & Extraction
   Evaluate the ease of defeating physical and chemical properties of the formulation

2. Pharmacokinetics
   Compare PK profiles of intact and manipulated product with those of a suitable comparator

3. Clinical Abuse Potential
   Assess abuse-related measures (eg, drug liking, willingness to take again)

Postmarket Studies

4. Epidemiology
   Assess real-world impact using postmarketing outcomes data

Guidance for Industry Abuse-Deterrent Opioids — Evaluation and Labeling Issued by Food and Drug Administration
Hypothetical Abuse-Deterrent Properties and Claims

Results from Studies in Category 1

[Tradename] has physical and chemical properties expected to deter intravenous abuse.

Guidance for Industry Abuse-Deterrent Opioids — Evaluation and Labeling Issued by Food and Drug Administration
Hypothetical Abuse-Deterrent Properties and Claims

Results from Studies in Categories 1 & 2

[Tradename] has physical and chemical properties that are expected to deter oral, nasal, and intravenous abuse.

Guidance for Industry Abuse-Deterrent Opioids — Evaluation and Labeling Issued by Food and Drug Administration
Hypothetical Abuse-Deterrent Properties and Claims

Results from Studies in Categories 2 & 3

PK data demonstrate crushing results in rapid absorption of the opioid and antagonist. These, with results of clinical abuse potential studies, show [Tradename] has properties expected to deter oral, nasal, and intravenous abuse.
Hypothetical Abuse-Deterrent Properties and Claims

Results from Studies in Category 4

These data demonstrated reduced abuse of [Tradename] in the community, which appears attributable to its formulation, which deters nasal and intravenous abuse.
Label Claims Also Include Caveats

- **Examples could include:**
  - [Tradename] has physical and chemical properties expected to deter crushing the tablet. However, [Tradename] can still be abused by swallowing intact tablets.
  - [Tradename] has properties expected to deter abuse by the oral, intranasal, and intravenous routes. However, abuse of [Tradename] by these routes is still possible.
  - Additional data, including epidemiological data, when available, may provide further information on the impact of [Tradename] on the abuse liability of the drug in the community. Accordingly, this section may be updated in the future as appropriate.
Abuse-Deterrent Properties and Claims

Appear in **Section 9.2** of a product’s FPI (or “Label”) when:

1) The drug product has attributes intended to discourage its abuse that have undergone the studies specified by the FDA AND

2) The results of those studies show that the drug product:
   – can be *expected* to result in or has *demonstrated a meaningful* reduction in its abuse.

*Guidance for Industry Abuse-Deterrent Opioids — Evaluation and Labeling Issued by Food and Drug Administration*  
Abuse-Deterrent Properties and Claims in FPIs

9. DRUG ABUSE AND DEPENDENCE

9.2 Abuse

• Descriptions of selected study design, conduct, and results

• Abuse-Deterrence Properties and Claims currently appear in the Summary at the end of Section 9.2

Note: Abuse-Deterrent Properties in Section 9.2 of an FPI does NOT mean the product is abuse proof.

Guidance for Industry Abuse-Deterrent Opioids — Evaluation and Labeling Issued by Food and Drug Administration
DailyMed
The official provider of FDA-approved Full Prescribing Information (FPI) for Human and Animal Drug Products and Biologics


Screen capture 06/21/2016
Abuse-Deterrent Properties
Drugs@FDA

The FDA approval history of drug products now has separate bulleted designation if FDA has determined that a product has abuse-deterrent properties.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
## Approved Opioids*  
**With Technology Designed to Impart Abuse Deterrence**

<table>
<thead>
<tr>
<th>Technology</th>
<th>Active Ingredients in Drug Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical/Chemical Barriers</td>
<td><strong>ER:</strong> hydrocodone (2); hydromorphone; morphine; oxycodone (2); oxycodone + APAP; oxymorphone; tapentadol</td>
</tr>
</tbody>
</table>
| Agonist-Antagonist Combinations | **ER:** morphine + naltrexone; oxycodone + naloxone  
|                             | **IR:** buprenorphine + naloxone† (multiple); pentazocine + naloxone |
| Aversion                    | **IR:** diphenoxylate + atropine†† |
| Delivery System             | **ER:** buprenorphine† |
| Prodrug                     | -- |
| Combination                 | **IR:** oxycodone (physical + aversive agent) |

* Not all opioid drug products are indicated for use as analgesics, eg:  
† Indication: use in Opioid Dependence (ie, Opioid Addiction)  
†† Indication: Antidiarrheal  
** Not all have Labeled Abuse-Deterrence Properties and Claims  

NB: Information Current as of 10/10/2016

http://www.sciencedirect.com/science/article/pii/S0376871614000061 and specific product’s FPIs
## Opioids in Development

With Technology Designed to Impart Abuse Deterrence

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<td>Physical/Chemical Barriers</td>
<td><strong>ER</strong>: levorphanol; morphine; oxycodone; oxymorphone; tapentadol</td>
</tr>
<tr>
<td>Agonist-Antagonist Combinations</td>
<td><strong>ER</strong>: oxycodone + naltrexone (sequestered)</td>
</tr>
<tr>
<td>Aversion</td>
<td><strong>IR</strong>: oxycodone + aversive agent; oxycodone/APAP + aversive agent</td>
</tr>
<tr>
<td>Delivery System</td>
<td><strong>ER</strong>: hydromorphone</td>
</tr>
<tr>
<td>Prodrug</td>
<td><strong>ER</strong>: hydrocodone; hydromorphone</td>
</tr>
<tr>
<td></td>
<td><strong>IR</strong>: hydrocodone; hydromorphone</td>
</tr>
<tr>
<td>Combination</td>
<td><strong>IR</strong>: oxycodone (physical) + aversive agent</td>
</tr>
<tr>
<td>New Chemical Entity</td>
<td>MOR agonist with slow crossing of BBB</td>
</tr>
</tbody>
</table>
Physical/Chemical Barriers Example

• Polyethylene oxide (high MW)
• Heat and pressure during manufacturing process

Difficult to crush: physical barrier to obtaining fine powder.

Hard to dissolve: if mixed with liquid, it turns into a viscous gel.

Physical/Chemical Barriers (selected example)

- Drug substance binds to inactive constituents (fatty acid, waxes) within microspheres that fill a capsule.
- Each microsphere has ER properties.

http://www.collegiumpharma.com/technology-platform/overview Accessed 03/11/2015
Capable of containing many pellets

- Each pellet contains ER morphine sulfate surrounding a sequestered core of IR naltrexone

Rate-controlling membrane
Morphine sulfate
Sequestering membrane
Naltrexone

Pellets are between 1.0 - 1.7 mm dia.

Modified from: https://www1.pfizerpro.com/hcp/embeda/technology   Accessed 03/11/2015
Agonist/Antagonist (selected example)

- Capsule contains beads
- Some beads contain ER oxycodone
- Some beads contain sequestered IR naltrexone
- Beads are same size, color, weight, and density
- Crushing, dissolving, or extracting releases both oxycodone and naltrexone, blunting or preventing euphoria from opioid agonist

Modified from: http://www.elitepharma.com/how-it-works/ Accessed 03/11/2015
Combination

- **Gelling** agents to deter extraction and intravenous abuse

- **Aversive** agents to deter intranasal abuse

Delivery System Example

• Biodegradable, controlled-release, implant

• Polymer blended with drug substance and extruded

• Can be made to have delivery times from weeks to months

**Prodrug Example**

- A drug substance bound to a ligand

- After oral administration, ligand is cleaved away by enzymatic action/pH, releasing drug substance to exert effects at the receptor

![Diagram](image-url)
Draft Guidance for Generic Opioids

• On March 24, 2016, FDA issued a draft Guidance for generic drug developers intending to submit applications for products that reference an opioid with abuse-deterrent properties.

• Comment period closed May 24, 2016.

Summary

- OADP will have their maximal public-health impact only when substantially all opioids have Abuse-Deterrent Properties and Claims in their FPIs.

- Abuse-deterrent technologies are one part of a comprehensive intervention strategy to promote safe prescription opioid use:
  - Additional components, including governmental, community, and educational initiatives, are also needed.

- Public- and private-sector policies should encourage the use of OADP where appropriate, eg:
  - availability of OADP on drug formularies
  - removal of barriers to their use:
    - higher co-pays
    - step edits
Questions about

• The reasons OADP are important innovations?
• The FDA’s direction to those developing OADP?
• Abuse-Deterrent Properties and Claims in FPIs?
• The technologies considered for imparting abuse deterrence to formulations of opioid drug products?