USPHS: Opioid Drug Product Formulation Approaches To "Deter" Abuse

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Financial Disclosures

“I, Joshua Hunt, declare no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.”

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The American Pharmacist Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Target Audience: Pharmacists and Pharmacist Technicians

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Activity Type: Knowledge-based
Learning Objectives

• Explain the role of abuse deterrent technology in relation to the current Rx opioid epidemic.
• List the types of studies required for determining abuse deterrence.
• Describe labeling language used for AD products versus non-AD and how this can provide market exclusivity. List the types of studies required for evaluating abuse deterrent properties.
Self-Assessment

1. Abuse-deterrent products are “abuse-proof.”
   
a. True
b. False
2. What the first product to obtain FDA-approved labeling claims for expected abuse deterrence?

   a. Oxycontin ®
   b. Opana ER
   c. Vantrela ER™
   d. Targiniq ER ™
3. Name the product that was voluntarily withdrawn from marketing in 2017, based upon a link to serious outbreaks of HIV (by sharing of infected needles) and thrombotic thrombocytopenic purpura (TTP) like illness seen among illicit drug users? **These were unexpected safety consequences of intravenous abuse with this formulation.**

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Overall Message

- FDA considers the development of abuse-deterrent formulations (ADF) to be a high public health priority.
- The work on ADFs is taking place within a broader framework aimed at addressing opioid abuse.
- Use of ADFs is still limited, impacting on the assessment of their actual role in decreasing abuse and misuse.
FDA Part of Larger Governmental Response to Opioids Abuse

Issued April 2011 - National Drug Abuse Prevention Plan

Four major areas of focus to reduce prescription drug abuse and other harm from drugs

- Education
- Monitoring
- Proper medication disposal
- Enforcement
FDA Activities to Improve Safe Use of Opioids and Reduce Prescription Opioid Abuse

• Improving the use of opioids through careful and appropriate regulations.
• Improving the use of opioids through education of prescribers and patients.
• Improving the safe use of opioids through partnership and collaboration.
• Improving the treatment of pain through improved science.

--http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm338566.htm
In response to the opioid abuse epidemic, the FDA Commissioner [Robert Califf], along with other FDA leaders, called for a far-reaching action plan to reassess FDA’s approach to opioid medications. The plan focuses on policies aimed at reversing the epidemic, while still providing patients in pain access to effective relief.
FDA Opioid Policy

- Examine opioid risk-benefits to ensure that wider public health effects are considered.
- Convene expert advisory committees before approving any new drug application for an opioid that does not have abuse-deterrent properties.
- Assemble and consult with the Pediatric Advisory Committee regarding a framework for pediatric opioid labeling before approval.
- Develop changes to Immediate Release (IR) opioid labeling, including additional warnings and safety information that incorporate elements similar to required labeling warnings for the Extended Release/Long-Acting (ER/LA) opioid analgesics.
- Update Risk Evaluation and Mitigation Strategies (REMS) requirement for opioids after considering advisory committee recommendations and review of existing requirements.
- Expand access to, and encourage development of, abuse-deterrent formulations of opioid products.
- Improve access to naloxone and Medication-Assisted Treatment (MAT) options for patients with opioid use.
- Support better pain management options, including alternative treatments.
Essential Features of Successful AD Formulations

- The product must deliver a consistent and effective dose of the opioid when used as labeled.
- The product’s potentially abuse-deterrent properties can be expected to, or actually does, result in a significant reduction in abuse of that product.

Two stages
- Labeling must be based on scientific data
- Labeling based on pre-market studies must be updated and confirmed based on post-market data


• Final Guidance released April 1, 2015
• Outline studies needed for assessing abuse deterrent formulation (ADF) opioids, and potential labeling claims based on these studies
• Identifies areas for future research, and takes a flexible approach recognizing that the science of abuse deterrence is relatively new, and rapidly evolving
• Applies to innovator products
Abuse Deterrent Technologies

Physical/Chemical barriers

- Formulations that resist particle size reduction and that compromise the extended release properties for the active pharmaceutical ingredient (API).
- API may have properties limiting manipulation and/or extraction.
- Excipients imparting barrier to physical manipulation or extraction.
  - Polymers affecting formulation hardness, regulating controlled release properties, and impacting syringeability
  - Use of wax compounds limiting syringeability and extractability
Abuse Deterrent Technologies

**Agonist/Antagonist combinations**, a mu opioid antagonist may deter abuse by non-oral routes due to released antagonist blocking the subjective effects of the mu opioid agonist

- Approaches taken
  - Sequestration of an opioid antagonist (e.g. naltrexone)
    - Release of naltrexone only following crushing

*Aversion*, excipients or second active ingredient may deter abuse by non-oral routes

- Contain Sodium Lauryl Sulfate, a nasal cavity irritant – deter intranasal abuse
Abuse Deterrent Technologies

**Delivery system**
- Depot injections or subdermal implants may deter abuse by making the drug unavailable for manipulation

**Prodrugs**
- New molecular entities (not reformulations), *AD effects are inherent in the pro-drug, not the excipients.*

**Combination**
- Physical/Chemical barriers/Aversion

**Novel approaches**
- This category encompasses novel approaches or technologies that are not captured in the previous categories.
Currently Marketed ADF Products

Ten approved ADF NDAs:

1. Hysingla™ ER Tablets (hydrocodone bitartrate)
2. Embeda™ ER Capsules (Morphine Sulfate + Naltrexone)
3. Morphabond™ ER Tablets (Morphine Sulfate)
4. OxyContin® (Oxycodone)
5. Xtampza ER Capsules (Oxycodone base) – MUST BE TAKEN WITH FOOD!
6. RoxyBond™ Tablets (IR containing oxycodone HCl)
7. Arymo™ (Morphine Sulfate) - discontinued
8. Vantrela™ ER Tablets (Hydrocodone Bitartrate), withdrawn
9. Troxyca® ER Capsules (Oxycodone HCl + Naltrexone HCl), withdrawn
10. Targiniq™ ER Tablets (Oxycodone HCl + Naloxone HCl), withdrawn
NDA 201655, OPANA ER (oxymorphone)

The product was an approved extended-release (ER) opioid formulation intended to have abuse-deterrent properties based on its physicochemical properties, however, such claims were not included in product labeling.

The limited absolute oral bioavailability for oxymorphone in humans may be an important reason that OPANA ER and other oxymorphone products are not frequently abused by the oral route. The absolute oral bioavailability of oxymorphone in humans is only approximately 10% (Endo 2011). By contrast, the absolute oral bioavailability of oxycodone is 60% to 87% (Purdue 2016).

Epidemiological data indicate that intravenous injection is an important route of abuse for reformulated OPANA ER. The difficulties associated with abuse of OPANA ER by oral administration and insufflation, may contribute to individuals abusing reformulated OPANA ER by injection. An additional factor contributing to the intravenous abuse of reformulated OPANA ER tablets upon manipulation is the feasibility of obtaining suitable solutions for injection upon manipulation of the reformulated OPANA ER tablets.
Assessment of Abuse-Deterrent (AD) Products

Pre-Market Abuse-Deterrent Assessment

• Types of Studies
  o Category 1 - *in vitro* manipulation and extraction studies
  o Category 2 - pharmacokinetic studies
  o Category 3 - human abuse potential (HAP) studies

  - Studies are designed with input from the Agency.
  - Studies intended to **PREDICT** possible AD effects once marketed
  - Results may be included in the product labeling - AD Claims

Category 4 - Post-Marketing Epidemiological Studies

• Required by the Agency
• Intended to determine whether an approved product actually deters abuse in the real world - by specific route
• Studies are designed with input from the Agency and take years to complete
Category 1 Physical Manipulation and Chemical Extraction Studies

• Essential part of the overall premarket abuse-deterrent assessment.

• Are discussed in the 2015 guidance for industry - Opioid Abuse-Deterrent - Assessment and Labeling document.

• To support labeling claims of abuse deterrent efficacy under an NDA, must be conducted on the to-be-marketed formulation.

• Under the overall premarket abuse-deterrent assessment, should be the first studies conducted to identify effective methods for manipulation to facilitate abuse by selected routes of administration - oral (ingestion or chewing), intranasal, intravenous.

• Results should be used in developing protocols for Category 2 and Category 3 studies.
  o Provide support of conducting HAP studies by selected routes of abuse
  o Provide the mode of manipulation to be used in HAP studies
Generic products represent a significant fraction (>80%) of all prescriptions in the U.S. today.

**General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products (Draft Guidance March 2016), Finalized November 2017**

Additional Steps: Need for additional assessment on impact of AD products

- Current labels based on clinical and *in vitro* data to predict the formulation will reduce abuse.
- Real-world assessment needed (and ongoing) as we know AD formulations are not silver bullets and can be defeated.
  - To date, prescription of AD opioids is limited (2% of total opioid prescriptions in 2018)
- DECIDE WHAT WORKS AND WHAT DOESN’T.
Assessment: Market Challenges

Even among ER/LA Opioid analgesics, market share for AD Opioids limited:

- AD formulation of OxyContin made up around 25% of the ER/LA opioids market in 2014
- ER/LA opioids comprise only around 10% of the total opioids market
Data Challenges to Post-Marketing Assessment

There are many reasons why post-marketing studies are difficult to conduct and to provide any conclusive answers as to whether an AD produce ACTUALLY in the REAL WORLD will reduce abuse.

- Selection of appropriate comparators
- Databases often do not collect information on individual products (e.g., generic vs brand name) and formulations (e.g., liquid, solid oral, patch)
- Patients abuse multiple products (and substances)
- Concurrent MULTIPLE programs in effect by other agencies (i.e., new CDC opioid prescribing guidelines, law enforcement, enhanced Prescription Drug Monitoring Program (PDMP) at the state level, rescheduling of combination hydrocodone products from Schedule III to Schedule II) to reduce the opioid epidemic
If Category 2/3 studies provide positive results that are predictive of a clinically meaningful reduction in abuse potential, then labeling text could state the following, for example:

The pharmacokinetic data demonstrate that crushing Tradename results in the simultaneous release and rapid absorption of opioid and antagonist. These data along with the results from oral and intranasal clinical abuse potential studies and a clinical abuse potential study of intravenous opioid and antagonist to simulate crushed Tradename indicate that Tradename has properties that are expected to deter abuse via the oral, intranasal, and intravenous routes. However, abuse of Tradename by these routes is still possible.
IF post-market study results and other supportive information demonstrate ACTUAL evidence of a reduction in abuse, then labeling text could state the following, for example:

*These data demonstrated a reduction in the abuse of Tradename in the community setting compared to the levels of abuse, overdose, and death that occurred when only formulations of the same opioid without abuse-deterrent properties were available. This reduction in abuse appears to be attributable to the product’s formulation, which deters abuse by injection or snorting of the manipulated product. However, such abuse of this product is still possible, and the product’s abuse deterrence properties do not deter abuse associated with swallowing the intact formulation.*

### Table 5. Summary of Maximum Drug Liking \((E_{\text{max}})\) and Take Drug Again \((E_{\text{max}})\) Following Intranasal (IN) Administration of TARGINIQ ER, Oxycodone, and Placebo in Non-Dependent, Opioid Abusers (N=23)

<table>
<thead>
<tr>
<th>VAS</th>
<th>TARGINIQ ER 40 mg/20 mg (finely crushed)</th>
<th>Oxycodone HCl 40 mg (powdered)</th>
<th>Placebo (lactose powder)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Liking*</td>
<td>Mean (SE) 59.1 (2.8)</td>
<td>94.8 (2.2)</td>
<td>53.2 (2.1)</td>
</tr>
<tr>
<td></td>
<td>Median (Range) 51 (50-100)</td>
<td>100 (61-100)</td>
<td>51 (50-100)</td>
</tr>
<tr>
<td>Take Drug Again**</td>
<td>Mean (SE) 42.6 (6.4)</td>
<td>93.6 (2.3)</td>
<td>30.7 (6.1)</td>
</tr>
<tr>
<td></td>
<td>Median (Range) 50.0 (0-100)</td>
<td>100 (62-100)</td>
<td>50 (0-100)</td>
</tr>
</tbody>
</table>

VAS: visual analog scale  
SE: standard error  
* Drug Liking Question text: “At this moment, my liking for this drug is”; scale: 0 = maximumdisliking, 50 = neither liking nor disliking (neutral response), 100 = maximum liking.
Figure 1. Percent Reduction in Maximum Drug Liking for Finely Crushed TARGINIQ ER 40 mg/20 mg vs. Powdered Oxycodone HCl 40 mg Following Intranasal Administration in Non-Dependent Opioid Abusers
Recent ADF related legislation

On October 24, 2018, the President signed into law the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act. The bipartisan legislation granted federal agencies additional authorities that will meaningfully advance efforts to combat the opioid crisis. Under Section 6012, the Secretary of Health and Human Services is required to conduct a study and submit to Congress a report on: 1) the adequacy of access to abuse-deterrent formulations (ADFs) of opioid analgesics under Medicare and 2) the effectiveness and impact of ADFs.

In response to this directive, the U.S. Food and Drug Administration (FDA) is preparing a report, summarizing the findings from FDA and the Center for Medicare and Medicaid (CMS) on ADFs.
Conclusions

• FDA will act within its authorities in support of our public health mission to help defeat the epidemic of opioid abuse through a science-based and continuously evolving approach.

• Our aim is to make a difference in the lives of the many people who are struggling under the weight of this crisis.
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