Abuse Deterrent Formulations of Opioids and the Abuse Deterrent Coalition
Disclosures

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Views reflected herein are those of the author and do not necessarily represent the views of any affiliated entity
Agenda

• Understand how the Abuse Deterrent Coalition builds a sound medical, public policy and ultimately commercial case for abuse deterrent technology

• Strategize how to communicate scientific information to regulatory decision-makers, prescribers and consumers who may not have clinical backgrounds

• Identify how to best communicate with payers when those developing the formulary are most focused on the cost of the product and are less likely to understand the long-term benefits to the plan of abuse-deterrent products

• Understand the challenges abuse deterrent innovators faces when discussing a new product that prevents abuse, which is a huge yet unmeasurable benefit
Why We Do What We Do

Every day, 94 people die from an overdose of prescription painkillers in the United States – that’s more than 34,500 deaths annually.
Abuse Deterrence’s Place in the Paradigm
Age at first use of hydrocodone combination products is associated with subsequent abuse-related behaviors

Routes of administration use among those who believe non-medical use of hydrocodone combination products led to non-medical use of other prescription opioids
Deterrence vs. Prevention
Rising Toll
Climbing rates of U.S. overdose deaths from opioid painkillers and heroin have pushed the total number of drug overdose deaths above those from traffic accidents.

*Includes hydrocodone, oxycodone, morphine, codeine and others

Source: Centers for Disease Control and Prevention

THE WALL STREET JOURNAL.
The Abuse Deterrent Coalition was created to serve as a forum of Abuse Deterrent Formulation Technology Manufacturers, Patient & Issue Associations and Pharmaceutical Manufacturers to educate the public, policy makers and the FDA on the importance of ADF technologies in the fight against prescription drug abuse.
### U.S. Opioid Market in 2016

<table>
<thead>
<tr>
<th>Product Category</th>
<th>Total Rx MAT* (Dec 2016)</th>
<th>Relative percentage of market</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Opioid Analgesic Market</strong>*</td>
<td>236,327,570</td>
<td>100% of Total Opioid Analgesic Market</td>
</tr>
<tr>
<td>Branded IR</td>
<td>2,456,017</td>
<td>1.0% of Total Opioid Analgesic Market</td>
</tr>
<tr>
<td>Generic IR</td>
<td>210,050,806</td>
<td>88.9% of Total Opioid Analgesic Market</td>
</tr>
<tr>
<td><strong>Total IR (Immediate Release)</strong></td>
<td>212,506,823</td>
<td>89.9% of Total Opioid Analgesic Market</td>
</tr>
<tr>
<td>Branded ER</td>
<td>6,105,683</td>
<td>2.6% of Total Opioid Analgesic Market</td>
</tr>
<tr>
<td>Generic ER</td>
<td>17,715,064</td>
<td>7.5% of Total Opioid Analgesic Market</td>
</tr>
<tr>
<td><strong>Total ER (Extended Release)</strong></td>
<td>23,820,747</td>
<td>10.1% of Total Opioid Analgesic Market</td>
</tr>
<tr>
<td><em><em>Total OADP</em> Market (Opioids w/ Abuse-Deterrent Properties)</em>*</td>
<td>4,903,599</td>
<td>2.1% of Total Opioid Analgesic Market</td>
</tr>
</tbody>
</table>

*Total Rx = Total Prescriptions  
*MAT = Moving Annual Total  
**Total Opioid Analgesic Market = All oral and transdermal opioid analgesics, including liquids, excluding transmucosal, injectable, intranasal, and suppositories.  
*Total OADP* Market (Opioids w/ Abuse-Deterrent Properties)

**Source:** QuintilesIMS™  
*National Prescription Audit™ (NPA), 2016*
Investigating the Need for ADF Development

“Prescribing abuse-deterrent opioids implies that many patients will be switching from lower-priced generic drugs to higher-priced patented drugs – at least until generic versions of abuse-deterrent formulations become available. The question naturally arises: are the current higher prices for abuse-deterrent opioids worth the expense?”

- Wayne Winegarden

<table>
<thead>
<tr>
<th>Total Annual Benefits per Patient from Abuse-deterrent Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit per Patient</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Health expenses commercially-insured</td>
</tr>
<tr>
<td>Health expenses Medicaid/Uninsured</td>
</tr>
<tr>
<td>Non-health related expenses</td>
</tr>
</tbody>
</table>

A study that examined the medical cost savings associated with extended-release oxycodone with abuse deterrent technology found that reformulation was associated with medical cost savings of $430 million in the US.

Where are we today?
U.S. Healthcare System Remains Highly Inefficient

5% of patients represent 50% of healthcare costs

Drivers of Cost
- Pain costs more than cancer, diabetes & heart disease combined
- Focus on treatment not prevention
- “Rule Out” diagnosis and “Trial and Error” treatment decisions result in high costs of failure

Approximately $800 billion spent on chronic pain

What are the driving forces around ADFs

Societal concern about Rx drug abuse

“A US Public Health epidemic”

Societal concern about access to affordable pain medicines

“A US Public Health epidemic”

FDA
DEA
DAs
AGs
Lawmakers
Other authorities

Some care more about this....

... and many care about this as well.
# ADF Labeling to Date

- Of 10 FDA-approved ADFs, 9 are extended-release formulations and rely on physical/chemical or agonist/antagonist combinations

<table>
<thead>
<tr>
<th>Product</th>
<th>Drug Substance</th>
<th>Sponsor</th>
<th>Approval</th>
<th>Marketed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycontin</td>
<td>oxycodone</td>
<td>Purdue Pharma</td>
<td>4/5/2010</td>
<td>YES</td>
</tr>
<tr>
<td>Targiniq ER</td>
<td>oxycodone + naloxone</td>
<td>Purdue Pharma</td>
<td>7/23/2014</td>
<td>NO</td>
</tr>
<tr>
<td>Embeda</td>
<td>morphine + naltrexone (sequestered)</td>
<td>Pfizer</td>
<td>10/17/2014</td>
<td>YES</td>
</tr>
<tr>
<td>Hysingla ER</td>
<td>hydrocodone</td>
<td>Purdue Pharma</td>
<td>11/20/2014</td>
<td>YES</td>
</tr>
<tr>
<td>Morphabond</td>
<td>morphine</td>
<td>Inspirion</td>
<td>10/2/2015</td>
<td>NO</td>
</tr>
<tr>
<td>Xtampza ER</td>
<td>oxycodone</td>
<td>Collegium</td>
<td>11/6/2015</td>
<td>YES</td>
</tr>
<tr>
<td>Troxyca ER</td>
<td>oxycodone + naltrexone</td>
<td>Pfizer</td>
<td>8/19/2016</td>
<td>NO</td>
</tr>
<tr>
<td>Arymo ER</td>
<td>morphine</td>
<td>Egalet</td>
<td>1/9/2017</td>
<td>Limited</td>
</tr>
<tr>
<td>Vantrela ER</td>
<td>hydrocodone</td>
<td>Teva</td>
<td>1/18/2017</td>
<td>NO</td>
</tr>
<tr>
<td>RoxyBond</td>
<td>oxycodone hydrochloride</td>
<td>Inspirion</td>
<td>4/20/2017</td>
<td>NO</td>
</tr>
</tbody>
</table>
ADF Approval Process
“One fundamental obstacle is how industry and the U.S. Food & Drug Administration (FDA) determine which products receive what type of ADF. Even more basic, there is not yet agreement between the regulators and industry on what it means to be abuse deterrent and how to measure success.”
Non-Interference As an ADF Approval Standard
The Clinic v. Real World Abuse

“The **non-inferiority** study is dependent on knowing something that is not measured in the study. A “successful” non-inferiority trial shows what appears to be an acceptably small difference between treatments, may or may not have had assay sensitivity and therefore may or may not support a conclusion that the test drug was effective.”

“**Non-Interference**” is dependent on the presumed ADF not affecting the pharmacologically designed safety and efficacy standards in the intended patient population for the therapy. A “successful” non-interference ADF demonstrates in the post-approval environment a deterrence from diversion, abuse, misuse and abuse progression that is in additive to the intended medical therapy.”
FDA Guidance for ADF

Current Guidance for ADF Label Approval in Section 9.2

PREMARKET STUDIES
- Laboratory Manipulation and Extraction Studies (Category 1)
- Pharmacokinetic Studies (Category 2)
- Clinical Abuse Potential Studies (Category 3)

POSTMARKET STUDIES (CATEGORY 4)

Proposed Change

New Guidance for ADF Label Language in Section 9.2

PREMARKET STUDIES
- Laboratory Manipulation and Extraction Studies (Category 1)
- Pharmacokinetic Studies (Category 2)
- Clinical Abuse Potential Studies (Category 3)

POSTMARKET STUDIES (CATEGORY 4)
“Non-Interference” Standard

Clinical measurement of Abuse Deterrence for product labeling by the FDA should be limited to a “Non-Interference” standard.” ADF only need to demonstrate that the addition (matrixed technology or agonist/antagonist formulation) is safe in combination with the underlying drug and does not interfere with the intended patient population treatment.

- For NME/Prodrugs that create an entity in which the moiety itself has inherent deterrent characteristics, the FDA role is even cleaner – the product must meet existing safety and efficacy standards for treating the intended patient population.
- The FDA should not be placed in the position of having to determine by clinical standards the actions/reactions of a non-prescribed, unintended non-patient population. Product labels and FDA approvals under the non-interference standard could be limited to a description of the intended mechanism of action that would be used to deter an opiate naïve or early-stage recreational abuser from misusing the product.
- Sec. 9.2 Label information for the physician would include clinical evidence and results of studies demonstrating potential expected ADF effects

Under Non-interference, the FDA not be required to determine what clinical outcomes (VAS scale measures of High and Take Drug Again, e.g.) replicate “real world” abuse.

- FDA focus remains on product safety and efficacy in product development.

Label claims could be limited to initially mechanisms of action, and later, validated observational data of rates of diversion and impact on misuse. Non-interference would not change existing patent claims, nor Hatch-Waxman Exclusivity concerns. False claim concerns could be appropriately adjudicated in other venues such as the District Courts or at the Federal Trade Commission.
ADFs have an impact on Rx Drug abuse

Source: RADARS System data. – Presented by Richard C. Dart, MD, PhD - Director, RMPDC; Professor, University of Colorado
Figure 3. Temporal relation of RADARS Poison Center Intentional Abuse case rate and interventions to reduce prescription drug abuse
Number of Prescriptions ER vs. IR

IR and ER/LA Opioid

Nationally estimated number of prescriptions dispensed for selected IR and ER/LA opioid analgesics from U.S. outpatient retail pharmacies

Source: IMS Health, National Prescription Audit™ Extracted May and August 2015
Need for Additional ER ADFs

- A number of factors suggest that a next generation of ADFs will be necessary to provide incremental improvements in opioid abuse epidemic
  - Patterns of abuse change over time due to a variety of factors:
    - Availability of opioids
      - 60% of variance in abuse prevalence estimates explained by prescription volume
    - Treatment guidelines
    - DEA scheduling/rescheduling
    - Fads
    - Approval of ADFs
    - Availability of illicit opioids
    - Availability of non-opioid substances (e.g., stimulants, benzodiazepines, etc)
  - Abusers over time can become proficient at defeating AD properties of opioids
    - Shared knowledge on internet forums
  - Abusers may alter route of abuse based on presumed “weaknesses” of AD product
  - Mitigating oral abuse of supratherapeutic doses of opioids remains a unique challenge

IR Opioid abuse patterns

Adult substance abusers assessed for abuse treatment planning (N=151,704)

Figure 1. Past 30-Day Abuse per 100 Assessments

Source: Cassidy et al.; "Abuse prevalence and patterns for immediate-release hydrocodone combination products"; PAINweek 2015
IR Opioid abuse patterns
Internet survey among adult abusers (N=304)

Figure 1. Age at first hydrocodone IR product use among lifetime users

Source: Cassidy et al.; "Patterns of abuse of hydrocodone combination products: Results from an Internet survey of recreational drug users"; PAINweek 2015
Reasons for Preference of IR Opioids

• Faster “high” (presumably with oral administration)
  – “If I’m going to take a drug I like to feel high and the effects right away. I don’t want to wait half an hour until the high hits me because you never know how long or when exactly it will hit and I end up taking too many, wanting a faster effect. If I’m gonna do a drug I want to get high right there and then.”
  – “When I wanted to get high, I prefer the immediate release, because it hits you all at once. Extended release does not give you the ‘rush’.”

• Ease of manipulation (presumably for non-oral administration)
  • “Throughout the years the extended-release opioids have gotten harder to abuse. It’s easier to crush up immediate-release oxycodone and then snort or shoot them. Even the generic extended-release pain pills gel up if you mix them with water.”
  • “To get a good feeling from extended release opioids, one must apply a good deal of chemistry and/or preparation. It takes some filing, some powdering, and some use of an acidic liquid, like coca cola in order to break down the extended release properties.”
Progression of Abuse

- Limiting or preventing progression of abuse remains an important goal of ADFs.
- Approximately 60% of lifetime IR hydrocodone combination product abusers were 14-18 years at first use.
- In a survey of non-medical users of opioids (n=472) being evaluated for substance abuse treatment, nearly 74% reported the same age for
  - Age at first non-medical use of hydrocodone IR combination products, AND
  - Age at first non-medical use of any prescription opioid.
- Nearly 50% (n=235) believed that non-medical use of IR hydrocodone combination products led them to use other prescription opioids non-medically in the future.

<table>
<thead>
<tr>
<th>Frequency of use (n = 235)</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>109</td>
<td>46.4*</td>
</tr>
<tr>
<td>A few times a week</td>
<td>40</td>
<td>17.0</td>
</tr>
<tr>
<td>A few times a month</td>
<td>36</td>
<td>15.3</td>
</tr>
<tr>
<td>Less than a few times a month</td>
<td>33</td>
<td>14.0</td>
</tr>
<tr>
<td>I only used them once or twice</td>
<td>17</td>
<td>7.2</td>
</tr>
</tbody>
</table>

* Among daily nonmedical users of opioids, 44% reported using >4 times daily.
Concern for opioid abuse remains high but there is need for support of ADF policy

- The DEA rescheduled hydrocodone from Class III to Class II, effective as of October 2014\(^1\)
- More and more states introduce abuse-deterrent properties (ADP) legislation
- In general, plans must provide equal or preferred coverage for ADF as for non-ADF products

Summary

- ADFs are being recognized as a valuable component in the combat against Rx drug abuse – Opioids & Stimulants
- FDA increasingly acknowledges its responsibility to provide guidance to industry for ADF development and to bring more ADF products (incl. IR opioids) to market
- Real-life incentives are still missing and adequate labeling and support from payers are key hurdles
- Working with all relevant stakeholders to create awareness, acceptance and incentives is still to be improved and intensified
Abuse Deterrent Coalition Members

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