A Framework for Opioid REMS Assessment

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Background

- FDAAA authorizes FDA to require Risk Evaluation and Mitigation Strategy (REMS)
- A single class-wide REMS is proposed for certain products
  - Extended Release formulations of morphine, oxycodone, oxymorphone
  - Methadone, transdermal fentanyl
- Not included
  - All other formulations (IR, IV, transbuccal)
URDD = Unique Recipients of Dispensed Drug; equivalent to “projected patients”

<table>
<thead>
<tr>
<th>Non-REMS Opioids</th>
<th>REMS Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>58,079,471</td>
<td>3,836,899</td>
</tr>
</tbody>
</table>
How Can Surveillance Data Help?

• Goals of Opioid REMS
  – Ensure that the benefits of an opioid product achieve appropriate balance with the risks through:
    • Proper patient selection
    • Minimizing the risk of overdose, both accidental and intentional
    • Minimizing the risk of abuse
  – Ensure that prescribers, dispensers, and patients are aware and understand the risks and appropriate use of these products

Hertz S: http://www.fda.gov/cder/meeting/opioid/3Hertzsponsormeeting3-3-09.pdf
REMS Questions

• Evaluation of the REMS concept
  – Will the creation of a class-wide REMS affect misuse, abuse and diversion of drugs?

• Evaluation of the effect of REMS on specific medications
  – Will the creation of a class wide REMS affect misuse, abuse and diversion of MY drug?

• Will all drugs in the class respond similarly to class-wide REMS?
Framework Background

• Opioid REMS assessment must follow basic principles of surveillance and public health
  – Evaluation framework should be designed to monitor both the intended consequences (reduction in the unintended consequences of outpatient opioid use) and potential unintended consequences of the proposed opioid REMS
Framework for Opioid REMS: Basic Surveillance and Public Health Principles

- Evaluation should include effects on misuse, abuse, addiction, diversion and overdose
- All types of opioid products must be included in evaluation: branded and generic as well as extended-release and immediate-release.
- The risks unique to specific formulations of prescription opioids must be measured separately (e.g. patch, tamper resistant, etc)
- The evaluation should be comprehensive, including both the benefits and risks
Framework for Opioid REMS: Basic Surveillance and Public Health Principles

- Multiple perspectives on the natural history of substance use disorders are needed to assess opioid REMS, measured separately but in parallel.
- The impact on opioid treatment programs must be evaluated.
- Assessments must be conducted on pre-scheduled basis (required by Section 505-1).
Framework for Opioid REMS: Basic Surveillance and Public Health Principles

- Outcomes in specific populations must be monitored (e.g. young children, adolescents, etc). The effects of opioid REMS on patients and non-patients (e.g. abuse) must be included.
- Evaluation must assess whether existing disparities in access to opioid pain medications by vulnerable minorities is not exacerbated.
Analysis Objectives

• Effect of class-wide REMS on overall rates abuse, misuse and diversion
• Administration route
• Medical consequences
• Ages of individuals involved in abuse and misuse
• Source of drug abused
• Street price
• Evaluation of natural experiments

*for REMS and non-REMS opioids
Mosaic of Prescription Drug Abuse
Mosaic of Prescription Drug Abuse
RADARS® System

Researched Abuse, Diversion and Addiction-Related Surveillance System

• Prescription drug abuse, misuse and diversion surveillance system that collects timely product-and geographically-specific data.

• Measures rates of abuse, misuse and diversion throughout the US, contributing to the understanding of trends and aiding the development of effective interventions.

• Data assist pharmaceutical companies in fulfillment of their regulatory obligations such as REMS.
Prescription Medication Issues

- Hidden events & motives
- Indications
- Formulations

Drug Diversion
H. Surratt

Poison Center
R. Dart

Opioid Treatment
M. Parrino

SKIP
T. Cicero

Impaired HCW

College Survey
R. Dart

Criminal Justice

Acute Events

Dependent Patients

Abuse/Dependent Patients

Nurse Pharmacist Physician

College Students

304 rep
50 states

50 PC
45 states

75 prog
33 states

86 KIs
39 states

Subset of programs

2000 rep
50 states
RADARS System
Reporting 3-Digit ZIP Codes, 2009
# Class-Wide REMS - Opioids

<table>
<thead>
<tr>
<th>REMS</th>
<th>Non-REMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone products</td>
<td>Buprenorphine products</td>
</tr>
<tr>
<td>ER morphine products</td>
<td>Hydrocodone products</td>
</tr>
<tr>
<td>ER oxycodone products</td>
<td>Tramadol products</td>
</tr>
<tr>
<td>ER oxymorphone products</td>
<td>Hydromorphone products</td>
</tr>
<tr>
<td>ER hydromorphone</td>
<td>IR morphine products</td>
</tr>
<tr>
<td>Transdermal fentanyl</td>
<td>IR oxycodone products</td>
</tr>
<tr>
<td>products</td>
<td>IR oxymorphone products</td>
</tr>
<tr>
<td></td>
<td>Fentanyl products, transbuccal or IV</td>
</tr>
</tbody>
</table>
Objective #1:

Effect of class-wide REMS on abuse, misuse and diversion rates

If a class-wide REMS is effective:
1. Abuse, misuse, diversion of REMS opioids will decrease
2. Abuse of an individual product will decrease
RADARS System Poison Center Program

Intentional Exposure Rate per 100,000 Population

2006-2009

Intentional Exposure Mentions: Suspected Suicidal, Intentional Misuse, Abuse, Unknown, Withdrawal
RADARS System Poison Center Program

Intentional Exposure Rate per 1,000 URDD

2009

Intentional Exposure Mentions: Suspected Suicidal, Intentional Misuse, Abuse, Unknown, Withdrawal
RADARS System Drug Diversion Program
Rate per 100,000 Population
2006-2009

- REMS Opioids
- Non-REMS Opioids
RADARS System Drug Diversion Program
Rate per 1,000 URDD
2009

REMS Opioids
Non-REMS Opioids
RADARS System **Drug Diversion Program**

Rate per 1,000 URDD

2009
RADARS System Drug Diversion Program
Rate per 1,000 URDD
2005-2009

REMS Implementation
Implications

• The massive use of IR formulations causes a much greater number of events.
• But when examining a single use of a drug, the risk is greater for REMS drugs.
• We need both population and URDD views to understand what transpires.
• Will increased intervention on REMS drugs without corresponding effort on IR result in ‘squeezing the balloon’?
Pain Patients vs. Non-Patients

• Poison Center Program
  – Intentional exposures are defined: suspected suicide, misuse, abuse, unknown, withdrawal
  – *Pain Patients*: intentional misuse exposure
  – *Non-Patients*: intentional exposure excluding misuse

• Opioid Treatment Program
  – *Pain Patients*: enrolling in substance use disorder treatment to treat bodily pain
  – *Non-Patients*: pursuing treatment for other reasons
RADARS System **Poison Center** Program

**Pain Patients vs. Non-Patients**

2009

- REMS Opioids Only (n=5,310)
- Non-REMS Opioids Only (n=27,153)
- REMS and Non-REMS Opioids (n=1,101)
RADARS System Poison Center Program
Pain Patients vs. Non-Patients
2009

- Exposures to An Opioid Excluding Benzodiazepine (n=1,002)
- Exposures to An Opioid Including Benzodiazepine (n=252)
Objective #2:

Route of Abuse

If a class-wide REMS is effective:
1. Higher risk routes of abuse of REMS opioids will decrease
2. Higher risk routes of abuse for an individual product will decrease
RADARS System College Survey
Route of Abuse
2009

Percent of Self-Reported Non-Medical Use Cases

- REMS Opioids Alone or in Conjunction with Non-REMS Opioids (n=210)
- Non-REMS Opioids (n=490)

Swallowed Whole  | Chewed & Swallowed  | Inhaled  | Injected  | Dermal  | Other
Objective #3:

Medical Consequences

If a class-wide REMS is effective:
1. Major events and deaths will decrease for REMS opioids
2. Major events and deaths for an individual product will decrease
Minor, Self-Resolving Conditions: no effect, minor effect, not followed – nontoxic, not followed – minimal clinical effects, unrelated effect, confirmed non-exposure

Intentional Exposures: Suspected Suicidal, Intentional Misuse, Intentional Abuse, Intentional Unknown, Withdrawal
RADARS System College Survey
DAST-10 Score Categories
2009

Percent of Self-Reported Non-Medical Use Cases

- REMS Opioids Alone or in Conjunction with Non-REMS Opioids (n=210)
- Non-REMS Opioids (n=490)

DAST-10 Degree of Problems Related to Drug Abuse
Objective #4:

Age of individuals reporting abuse and misuse

If a class-wide REMS is effective:
1. Frequency will decrease for all age groups in REMS drugs without an increase in non-REMS drugs
2. Frequency will decrease for individual drug
RADARS System Poison Center Program

Age Category (years)

2009

Intentional Exposures: Suspected Suicidal, Intentional Misuse, Intentional Abuse, Intentional Unknown, Withdrawal

Percent of Intentional Exposure Cases

REM S Opioids Only (n=5,310)
Non-REM S Opioids Only (n=27,153)
REM S and Non-REM S Opioids (n=1,101)
RADARS System **Poison Center** Program

Age Category (years)

2009

Intentional Exposures: Suspected Suicidal, Intentional Misuse, Intentional Abuse, Intentional Unknown, Withdrawal

### Graph Details

- **Number of Intentional Exposure Cases**

- **Age Categories:**
  - 0-5
  - 6-12
  - 13-19
  - 20-29
  - 30-39
  - 40-49
  - 50-59
  - 60+
  - Unknown

- **Legend:**
  - REMS Opioids Only
  - Non-REMS Opioids Only
  - REMS and Non-REMS Opioids
  - Mortality Data

Intentional Exposures: Suspected Suicidal, Intentional Misuse, Intentional Abuse, Intentional Unknown, Withdrawal
Objective #5:

Opioid Source

If a class-wide REMS is effective:

1. Frequency of diversion will decrease for REMS drugs without an increase in non-REMS drugs

2. Frequency will decrease for individual drug
RADARS System College Survey
Source of Prescription Opioids
2009

Percent of Self-Reported Non-Medical Use Cases

- REMS Opioids Alone or in Conjunction with Non-REMS Opioids (n=210)
- Non-REMS Opioids (n=490)

- Doctor Prescription
- Not Family or Friend
- Family Member
- Friend
- Internet
- Other
- Purchased
- Stolen
Future Directions

• Street price data will be obtained from Drug Diversion Program
  – A difference in street price between REMS and non-REMS opioids may indicate the demand for one drug category over another

• Natural experiments will be identified for additional analyses after the launch of class-wide REMS
Closing Comments

• Class-wide opioid REMS discussions continue
• Data will be needed to evaluate both intended and potential unintended consequences on opioid use
• RADARS System data can evaluate some of the anticipated and unanticipated effects of REMS
• The evaluation will not be simple depending on the outcome measures chosen
RADARS System Contacts

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