Ongoing FDA Work Related to Opioid Overdose Prevention

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Office of the Assistant Secretary for Health (OASH)
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Recent and Ongoing Activities Related to Naloxone

• Co-prescribing of Naloxone with RX Opioids
  – Results of recent public FDA Advisory Committee

• Over-the-Counter (OTC) Naloxone
  – Research to support labeling for OTC naloxone products to support product development

• Role of expanded naloxone availability in USG response to opioid crisis
  – Systems model of opioid crisis
The Opioid Crisis: FDA’s Priorities & Strategies

1. Decreasing Exposure & Prevent New Addiction
   - Appropriate Dose/Duration Labeling
   - Appropriate Packaging, Storage, and Disposal
   - Health Care Provider Education

2. Supporting the Treatment of Those With Opioid Use Disorder
   - Naloxone
   - Medication Assisted Treatment (MAT)

3. Fostering the Development of Novel Pain Treatment Therapies
   - Partnerships & Meetings
   - Abuse Deterrent Formulations (ADFs)
   - Pain Treatment Alternatives

4. Improving Enforcement & Assessing Benefit-Risk
   - Improving Enforcement
   - Assessing Benefit-Risk
I. Naloxone Co-Prescribing with Rx Opioids

• Naloxone prescriptions rising (336.1K dispensed in 2017) but still inadequate
• FDA received Citizen Petition from maker of one of the naloxone products requesting FDA require co-prescribing of patients prescribed opioids
• FDA Advisory Committee held December 17-18 to get input from advisors and public
Annual Cost of Requiring Co-Prescribing: FDA Model

All Opioid Analgesic Rx Scenario

- Increase in Demand:
  - 48.5 million new doses per year (4,689% increase)

- Increase in Prices:
  - With Generics: $52.63/dose → $1,287.87/dose
  - Without Generics: $478.41/dose → $11,707.95/dose

- Increase in Total Spending:
  - $579.2 billion/year (Without Generics)
  - $63.9 billion/year (With Generics)
Naloxone Advisory Committee (cont)

• In general:
  – Harm reduction advocacy groups very strong in their view that co-prescribing was not ‘enough’
  – Committee members not supportive of value of required co-prescribing
    • Concerns expressed about cost to healthcare system and diversion of resources (both money and naloxone) away from underserved areas
    • Focus should be on educating prescribers/patients and supporting harm reduction efforts

• In addition, Committee members called on USG to take on broader actions to ‘force’ expanded availability of naloxone. Examples:
  – Forced OTC switch
  – Revoking patents currently delaying generic/OTC product marketing
  – Manufacturing naloxone and making it available from USG stockpile(s)
  – Extending expiration dating for naloxone products
Next Steps

• FDA meeting internally on AC recommendations
  – Plan response to Citizen Petition
  – Discuss ideas raised by Committee members
  – Review AC Docket comments (>220 comments received so far)
  – Engage external stakeholders
  – Propose next steps to leadership
II. Over-The-Counter Naloxone: Why OTC Naloxone?

• Existing expanded access programs (such as pharmacy standing order programs) are a significant tool, but more is needed – not everyone can/wants to obtain the product through a healthcare professional

• Surgeon General’s 2018 Advisory
“I, Surgeon General of the United States Public Health Service, VADM Jerome Adams, am emphasizing the importance of the overdose-reversing drug naloxone. For patients currently taking high doses of opioids as prescribed for pain, individuals misusing prescription opioids, individuals using illicit opioids such as heroin or fentanyl, health care practitioners, family and friends of people who have an opioid use disorder, and community members who come into contact with people at risk for opioid overdose, knowing how to use naloxone and keeping it within reach can save a life.”
Development Programs for Nonprescription Drugs

- Often rely on safety and efficacy established for the prescription product
- New studies may be required if proposing a new indication or a new patient population for the OTC market
- Need to “translate” key elements of the prescription label into consumer-friendly terms
- Consumer studies needed to evaluate the “OTC-ness” of product
Translate the Approved RX Product Label....
To a Label for OTC Products.....

Drug Facts Label

<table>
<thead>
<tr>
<th>Active ingredient (in each tablet)</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpheniramine maleate 2 mg.</td>
<td>Antihistamine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>temporarily relieves these symptoms due to hay fever or other upper respiratory allergies:</td>
</tr>
<tr>
<td>- sneezing</td>
</tr>
<tr>
<td>- runny nose</td>
</tr>
<tr>
<td>- itchy, watery eyes</td>
</tr>
<tr>
<td>- itchy throat</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask a doctor before use if you have</td>
</tr>
<tr>
<td>- glaucoma</td>
</tr>
<tr>
<td>- a breathing problem such as emphysema or chronic bronchitis</td>
</tr>
<tr>
<td>- trouble urinating due to an enlarged prostate gland</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ask a doctor or pharmacist before use if you are taking tranquilizers or sedatives</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>When using this product</th>
</tr>
</thead>
<tbody>
<tr>
<td>- drowsiness may occur</td>
</tr>
<tr>
<td>- avoid alcoholic drinks</td>
</tr>
<tr>
<td>- alcohol, sedatives, and tranquilizers may increase drowsiness</td>
</tr>
<tr>
<td>- be careful when driving a motor vehicle or operating machinery</td>
</tr>
<tr>
<td>- excitability may occur, especially in children</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If pregnant or breast-feeding, ask a health professional before use.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Directions</th>
</tr>
</thead>
<tbody>
<tr>
<td>adults and children 12 years and over</td>
</tr>
<tr>
<td>take 2 tablets every 4 to 6 hours; not more than 12 tablets in 24 hours</td>
</tr>
<tr>
<td>children 6 years to under 12 years</td>
</tr>
<tr>
<td>take 1 tablet every 4 to 6 hours; not more than 6 tablets in 24 hours</td>
</tr>
<tr>
<td>children under 6 years</td>
</tr>
<tr>
<td>ask a doctor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Facts (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other information</td>
</tr>
<tr>
<td>store at 20-25°C (68-77°F)</td>
</tr>
<tr>
<td>protect from excessive moisture</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inactive ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>D&amp;C yellow no. 10, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch</td>
</tr>
</tbody>
</table>
OTC Consumer Studies

Label Comprehension Study
• Understanding the key label messages

Self-Selection Study
• Choosing the right product for “me”

Actual Use Study
• Using according to labeled directions

Human Factors Study
• Interacting with the product
FDA Proposed an Innovative Approach to Support OTC Naloxone Products:

• To develop a model Drug Facts Label (DFL) that could be understood by all potential consumers who might use OTC naloxone
• To iteratively refine the DFL and evaluate consumer comprehension through a contract with established consumer research firms with expertise in conducting label comprehension studies and interviewing substance abuse populations
• To conduct an independent review of the resulting data
FDA Proposed an Innovative Approach (cont’d):

• If study was successful, Sponsors could adapt the model DFL to their naloxone product
• Sponsors would only need to add information specific to their particular device and assess through human factors
• Label comprehension was the key study to be conducted – self-selection and actual use are likely not needed
**Status of Research**

- FDA-supported study completed December 2018
- Review by FDA scientists complete January 2019
  - FDA concluded that the results of this study are acceptable to support use of the tested naloxone DFL in the OTC setting
  - FDA in the process of making these results and findings public for use by manufacturers seeking to develop OTC naloxone products
    - FRN in clearance
    - Planned public announcement of results and article being written
Prototype Drug Facts
Box for OTC Naloxone
III. Systems Model of Opioids Crisis Including Role of Naloxone

• Deliverable for the BHCC
• Successful model will help identify high-impact actions and anticipate consequences of policy changes
• Experts from across HHS providing input
Every day, more than 115 people in the United States die after overdosing on opioids...

The total number of overdose death has been on the rise.

System architecture
- Feedback processes
- Stocks and flows
- Time delays

Information availability
- Delays, biases, error, gaps
- Access & transparency

Mental models (of any stakeholder)
- Actor goals and incentives
- Time horizon, model boundary
- Misperceptions of feedback
Elements of Opioid Use/Misuse/Abuse Model (Simplified)
**PROJECT TIMELINE**

**ESTIMATED DELIVERABLES:**
- Model ver. 1
- Model ver. 2
- Draft article ver. 1
- Draft article ver. 2

**Experts interviews (began in Nov.)**

**Literature research & data analysis (began in Sep.)**

**Model development (began in Sep.)**

**Policy evaluation & insight generation**

**Model validation & analysis**

Dec 18 | Jan 19 | Feb 19 | Mar 19 | Apr 19 | May 19 | Jun 19 | Jul 19 | Aug 19

**AGENDA | PROJECT CONTEXT | SYSTEMS MODEL | PROJECT TIMELINE | DISCUSSION**
Thank You
Backup Slides
FDA Estimates Differ from the Manufacturers Based on Several Key Assumptions

<table>
<thead>
<tr>
<th>Key Assumption</th>
<th>FDA Model</th>
<th>Industry Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeted Patient Population(s)</td>
<td>0.3-58.0 million</td>
<td>34.0 million</td>
</tr>
<tr>
<td>Compliance Rate</td>
<td>100% Prescribing; 70% Fill</td>
<td>8-10% Dispensed</td>
</tr>
<tr>
<td>Price Increase</td>
<td>Yes (up to 2,347%)</td>
<td>No</td>
</tr>
<tr>
<td>Prescription Fill Costs</td>
<td>Yes ($3.94/dose)</td>
<td>No</td>
</tr>
</tbody>
</table>

**FDA Estimate for Industry Population With 70% Adoption:**
$24.7 Billion/Year - $224.0 Billion/Year

**FDA Estimate for Industry Population With 8% Adoption:**
$0.5 Billion/Year - $4.7 Billion/Year
(Industry: $150 Million/Year)
Total **Annual Costs—Naloxone Co-prescribing** for All Opioid Analgesic Rx Estimated At **$63.9 Billion - $579.2 Billion**

**New Doses (With Generics):**
48.5 Million x ($1,287.87 + $3.94\textsuperscript{1,2} ) = $62.6 billion

**Existing Doses (With Generics):**
1.0 Million x ($1,287.87 - $52.63) = $ 1.3 billion

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**Total (With Generics):** = **$63.9 billion**

\textsuperscript{1}Coalition for Community Pharmacy Action. The Cost of Dispensing Study. September 2015.

\textsuperscript{2}Takes the payroll and prescription department costs per prescription and divides this number by 2 to convert it to a per-dose basis
## Results: Patient Groups That Interact With the Health System

<table>
<thead>
<tr>
<th>Population</th>
<th># Patients (Millions)</th>
<th>Annual Cost w/ Generics ($ Billions)</th>
<th>Annual Cost w/o Generics ($ Billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Opioid Analgesic Rx</td>
<td>58.0</td>
<td>63.9</td>
<td>579.2</td>
</tr>
<tr>
<td>High-Impact Chronic Pain</td>
<td>19.6</td>
<td>9.5</td>
<td>85.5</td>
</tr>
<tr>
<td>Rx Opioid Analgesics with CNS Depressants</td>
<td>3.5</td>
<td>0.6</td>
<td>5.3</td>
</tr>
<tr>
<td>Medication Assisted Treatment (MAT)</td>
<td>1.4</td>
<td>0.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Opioid-Related ED Visit</td>
<td>0.8</td>
<td>0.1</td>
<td>0.7</td>
</tr>
</tbody>
</table>
## Results: Patient Groups That Don’t Interact With the Health System

<table>
<thead>
<tr>
<th>Population</th>
<th># Patients (Millions)</th>
<th>Annual Cost w/ Generics ($ Billions)</th>
<th>Annual Cost w/o Generics ($ Billions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misusing Opioids</td>
<td>11.4</td>
<td>3.8</td>
<td>34.0</td>
</tr>
<tr>
<td>Opioid Use Disorder</td>
<td>2.1</td>
<td>0.3</td>
<td>2.5</td>
</tr>
<tr>
<td>Recent Criminal Justice and Rx Opioid Misuse</td>
<td>0.9</td>
<td>0.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Recent Criminal Justice and Heroin Use</td>
<td>0.4</td>
<td>&lt;0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Recent Criminal Justice and Opioid Use Disorder</td>
<td>0.3</td>
<td>&lt;0.1</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Every day, more than 115 people in the United States die after overdosing on opioids...

The total number of overdose deaths has been on the rise.

System architecture
- Feedback processes
- Stocks and flows
- Time delays

Information availability
- Delays, biases, errors, gaps
- Access & transparency

Mental models (of any stakeholder)
- Actor goals and incentives
- Time horizon, model boundary
- Misperceptions of feedback
Illustrative pathway (simplified)
Illustrative pathway (detailed)