



FDA Policies and Actions Related to the Development and Use of Opioids to Treat Pain

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Outline

- Context for FDA Efforts to Address Prescription Opioid Abuse
 - Other Federal Efforts
- FDA Action Plan and Goals
- Types of Activities FDA is Undertaking
 - Tools available to FDA
 - Selected examples of their application

Overall Message

- The FDA work to improve the safe use of opioids is taking place within a larger policy framework aimed at addressing opioid abuse while assuring appropriate access to pain treatment
- Ongoing and planned activities reflect the commitment by FDA to integrate the use of all of our available tools to achieve our goals related to the safe use of prescription opioids

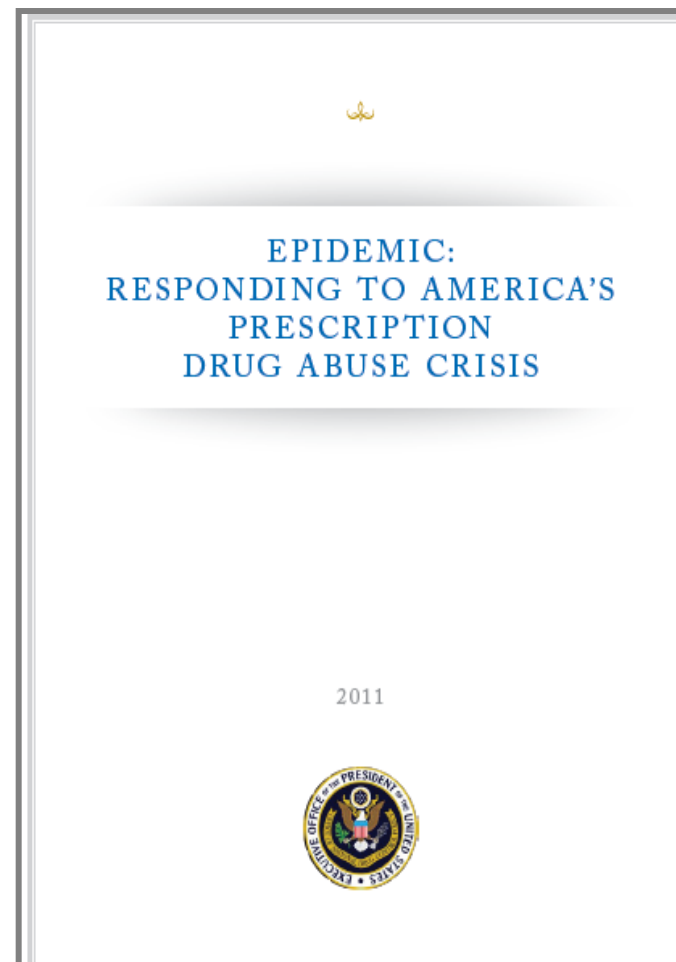


FDA is a Part of Larger Governmental Response to Opioids Abuse

Office of the National Drug Control
Policy Plan and
Health and Human Services
(HHS) Secretary's Plan

ONDCP National Drug Abuse Prevention Plan

- Issued April 2011
- Four major areas of focus to reduce prescription drug abuse and other harm from drugs
 - Education
 - Monitoring
 - Proper medication disposal
 - Enforcement



HHS Secretary's Initiative to Combat Opioid Abuse

- Improving opioid prescribing practices to reduce opioid use disorders and overdose
- Expanding use and distribution of naloxone to treat opioid overdoses
- Expanding Medication-assisted Treatment (MAT) to reduce opioid use disorders and overdose

Other Critical US Governmental Efforts FDA is Supporting

- **National Pain Strategy**

- Focuses on key areas of pain and pain care, including professional education and training, public education and communication, service delivery and reimbursement

- <http://iprcc.nih.gov/docs/DraftHHSNationalPainStrategy.pdf>

- **National Pain Research Strategy**

- Strategic plan under development for pain research across federal agencies

- **CDC Guidelines for Prescribing Opioids for Chronic Pain**

- Provides recommendations for the prescribing of opioid pain medication focused on the use of opioids in treating chronic pain

- <http://www.cdc.gov/drugoverdose/prescribing/guideline.html>



FDA Response to Opioids Abuse



FDA Action Plan (February 4, 2016)

- In response to the opioid abuse epidemic, today Dr. Robert Califf, the FDA's Deputy Commissioner for Medical Products and Tobacco, along with other FDA leaders, called for a far-reaching action plan to reassess the agency's approach to opioid medications. The plan will focus on policies aimed at reversing the epidemic, while still providing patients in pain access to effective relief.

FDA Opioids Action Plan

- *Expand use of advisory committees*
- **Develop warnings and safety information for immediate-release (IR) opioid labeling**
- **Strengthen postmarket requirements to get needed data**
- **Update Risk Evaluation and Mitigation Strategy (REMS) Program**
- **Expand access to abuse-deterrent formulations (ADFs) to discourage abuse**
- **Support better treatment**
- **Reassess the risk-benefit approval framework for opioid use**

Center for Drug Evaluation (CDER) Activities Reflect the Action Plan

- Provide patients in pain access to effective relief
- Reduce the misuse and abuse of prescription opioids through:
 - Preventing prescription drug abuse
 - Treating opioid addiction
 - Saving lives from opioid overdose

CDER Will Accomplish These Goals Through the Use of All Available Tools

- Improving the use of opioids through careful and appropriate **regulatory activities**
- Improving the use of opioids through careful and appropriate **policy development**
- Improving the treatment of pain through **improved science**
- Improving the safe use of opioids through **communication, partnership and collaboration**

Improving the Safe Use of Opioids Through **Regulatory Activities:**

ER/LA Opioids and Continuing
Education

Post-Marketing Study
Requirements

Regulatory Activity: ER/LA Opioids and Prescriber Education

- In 2012, FDA required makers of extended-release, long-acting (ER/LA) opioids to make balanced and scientifically accurate Continuing Education (CE) materials available to prescribers
- Required content “Blueprint ” created by FDA
- Metrics to be used to determine success include:
 - Numbers of providers who successfully complete the CE
 - Changes in patterns of opioid use
 - Knowledge surveys

ER/LA Opioid Analgesic REMS

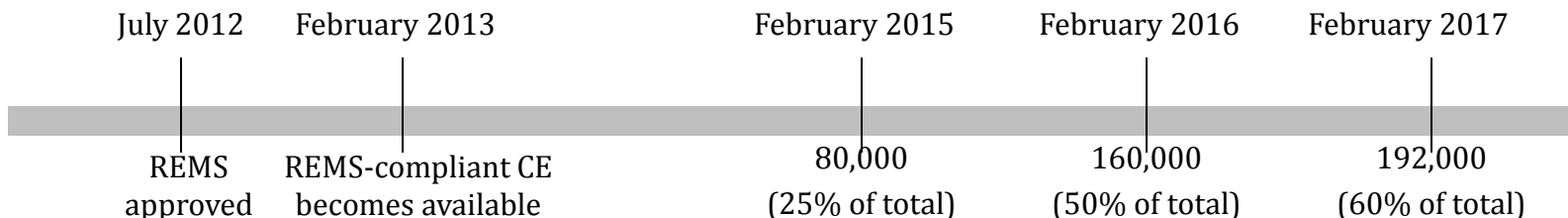
- **Goal of REMS**

- to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.

- **Prescribers:**

- Clinicians registered with DEA to prescribe CII/CIII
- Have written at least one ER/LA opioid analgesic prescription in the past year. (N=320,000)

- **Milestones (#'s of Prescribers completing CE):**





REMS Assessment After 36 Months

- Results submitted to FDA July 9, 2015
- Discussion at public Advisory Committee May, 2016, about results and any changes that need to be made to the REMS
- **Results of CE Training:**
 - 37,512 “ER/LA prescribers”*
 - Number represents 40% of the *total* healthcare providers who have completed an RPC-funded REMS compliant training

*Licensed to prescribe C2/3 and written at least one ER/LA Rx in past year

Regulatory Activity:

Postmarketing Requirements to Get Needed Data on Opioids

- FDA can require studies be conducted after a drug is marketed to answer safety questions under certain circumstances
- Important tool to improve the evidence on the serious risks of misuse and abuse associated with long-term use of opioids, and predictors of opioid addiction

Postmarketing Requirements I: Chronic Opioid Use

- Manufacturers of ER/LA opioids required to conduct 11 studies, related to safety of chronic ER/LA opioid use to assess:
 - Quantitative estimates of the serious risks of misuse, abuse, addiction, overdose, and death associated with long-term use of opioid analgesics
 - Estimate risks for hyperalgesia
 - Validate measures of abuse/misuse
 - Doctor/Pharmacy shopping, Medical codes for outcomes
- Each study is tracked for progress, with timelines for completion

Postmarketing Requirements II: Impact of Abuse-Deterrent Opioids

- Critical to understand the ‘real-world’ impact of abuse-deterrent formulations on actual abuse of opioids
 - Manufacturers of the 5 approved opioids with abuse-deterrent properties are required to conduct post-marketing studies to address this issue



Improving the Safe Use of Opioids Through **Policy Development**

Abuse-Deterrent (AD)
Formulations of Opioids

Twin FDA Policy Goals for Abuse Deterrent (AD) Formulations of Opioids

- Incentivize the development of opioid medications with progressively better AD properties and support their widespread use
- Assure appropriate development and availability of generics, reflecting their importance in US healthcare

Policy Formulation: Guidance on AD Opioid Formulations

- Promised as part of Office of National Control Policy (ONDCP) Rx Drug Abuse Plan (2011)
- Draft guidance release for comment:
January 9, 2013
- Final Guidance released April, 2015
 - <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf>

Results of Policy: Product Development

- 5 products given abuse-deterrent claims in label
 - OxyContin (oxycodone, crush/extraction resistant):
April, 2013
 - Targiniq (oxycodone hydrochloride and naloxone, naloxone aversive): July, 2014
 - Embeda (morphine/naltrexone, naltrexone is aversive/precipitates withdrawal when abused):
October, 2014
 - Hysingla (hydrocodone, crush/extraction resistant):
November, 2014
 - MorphaBond (morphine sulfate, crush/extraction resistant): October, 2015

Results of Policy: Product Development (cont)

- Manufacturers working on developing AD formulations of opioids
- More than 30 active investigational new drug applications (INDs) being discussed with CDER
 - New technologies being explored



Next **Policy Step**: Generics Abuse-Deterrent Opioids Guidance

- Generic products represent a significant fraction (>80%) of all prescriptions in the US today
- No current guidance for ANDA sponsors or reviewers

Additional Step: Need for Assessment of Impact on Real-world Abuse

- 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 limited (2% of total opioid prescriptions in 2014)
- DECIDE WHAT WORKS AND WHAT DOESN'T

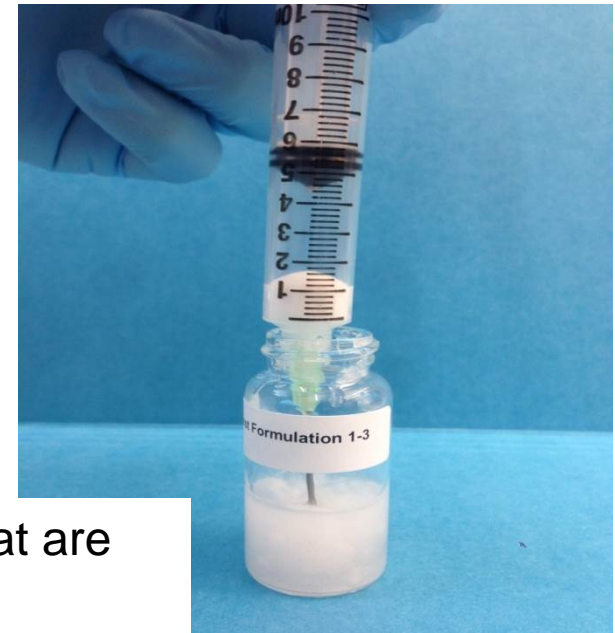
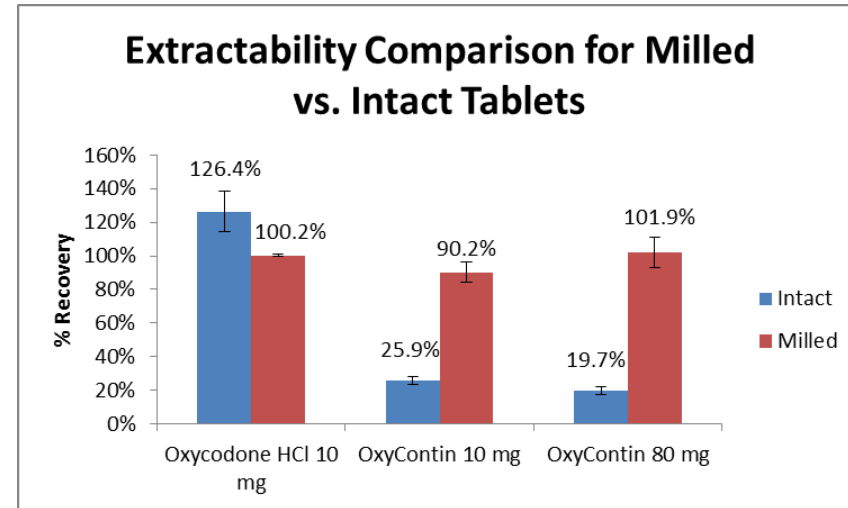
Improving the Safe Use of Opioids Through **Improved Science**

Advancing Development and
Assessment of Abuse-Deterrent
(AD) Formulations of Opioids

Understanding Formulation Science of AD Opioids

Scientific need: how to test AD formulations as new technologies are developed to support FDA policies related to AD opioids:

- Aid in regulatory review of new products
- Give advice to manufacturers to speed development of effective products



Some formulations become gels that are difficult to pull into a syringe

Understanding Formulation Science of AD Opioids (cont.)

- FDA laboratory activity: creation and testing of AD formulations in FDA labs
 - 30+ formulations manufactured
 - Working to identify the process conditions that are critical for AD formulation performance and product stability
 - Validations of the AD performance tests to be done using these formulations
- Goal: development and publication of a standardized *in vitro* ADF performance evaluation matrix



Improving the Safe Use of Opioids Through **Collaboration**

Educational Partnerships

Partnerships on Prescription Drug
Monitoring Programs (PDMPs)

Importance of Collaboration with Non-Governmental Partners

- Collaborations with non-governmental groups expands FDAs capacity to achieve our public policy goals
- Examples of partnerships:
 - Partnership for Drugfree to develop and support opioids prescriber education campaign
 - NCPIE & NCL to help educate consumers and patients about patient-provider communications and medication adherence
 - Brandeis U in support of broadened data sharing between Prescription Drug Monitoring Programs (PDMPs)

Summary

- FDA is using all of our available tools to address prescription opioid abuse while assuring availability of appropriate treatments for pain:
 - Regulatory actions, policy development, improved science, and improved communication and collaboration
- FDA is working to formally incorporate the broader public health impact of opioid abuse both to the patient and to others who may obtain them inappropriately into our regulatory decision-making

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 terrible crisis.



Thank You!

