Center for Drug Evaluation and Research Progress Update on Opioid Action Plan

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Overall Messages

- FDA Opioids Action Plan is a valuable framework guiding FDA response to the challenge of opioids abuse epidemic
- Since the Action Plan was announced FDA has continued to make significant progress on the items identified in the plan, applying of all of our available tools to achieve our goals
  - Extensive use of outside groups and expertise to provide needed data and input on decisions
- FDA is one of many groups with a role to play in addressing these challenges

Challenge of Opioids and Pain Management

- US is experiencing a devastating epidemic of prescription opioid misuse and abuse, including a large number of overdose deaths from prescription opioids
- The treatment of pain in the US, particularly chronic pain, is not satisfactory, including an over-reliance on prescription opioids

BUT

- The science and data needed to inform best practices to address pain while preventing opioid misuse and abuse are often lacking

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."*

* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm484765.htm

FDA Opioids Action Plan

- Expand use of advisory committees and outside engagement
- Develop warnings and safety information for IR opioid labeling
- Strengthen postmarket requirements to get needed real-world data on prescription opioids
- Update Risk Evaluation and Mitigation Strategy (REMS) Program for Extended-Release Long-Acting (ER-LA) Opioids
- Expand access to abuse-deterrent formulations (ADFs) to discourage abuse
- Support better treatment for opioid substance use disorder and to prevent opioid overdose deaths
- Reassess the risk-benefit approval framework for opioid use to reflect the public health impact of opioids

Implementing the Action Plan: FDA Science Board Meeting (March 2016)

Tools Available to FDA to Address These Challenges

- 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

FDA Activities Related to Opioids Action Plan

- List of FDA activities and timeline can be found at:
  - http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm338566.htm

- Regulatory Activities
  - Review of the Extended-Release Long-Acting Opioids REMS
  - Requiring post-marketing studies to assess impact of regulatory decisions
    - Studies required of ER-LA opioid manufacturers on quantitative estimates of the serious risks of opioids
    - Studies required of manufacturers of abuse-deterrent opioids to assess their real-world effects on abuse

FDA Activities Related to Opioids Action Plan

- Policy Development
  - Guidances on development of abuse-deterrent opioids (brand name and generic)
- Science
  - Manufacturing science related to the development of AD opioids
- Communications/Collaboration
  - Partnership for Drugfree to develop and support opioids prescriber education campaign
  - Brandeis Univ in support of broadened data sharing

Updating FDA Work on the Action Plan since Science Board Meeting

Regulatory Activities: Labeling

- March, 2016: FDA requiring additional warnings on immediate-release (IR) opioids relabeling to match ER-LA opioids
  - Includes boxed warning about serious risks of misuse, abuse, addiction overdose and death
  - Includes additional warning about neonatal opioids withdrawal syndrome
  - Over 125 generic and over 75 brandname products
- August, 2016: FDA required additional warnings, including boxed warning, about concomitant use of benzodiazepines and opioids

Regulatory Activities: Drug Approvals

- 7 new opioids approved with abuse-deterrent formulations (latest August, 2016)
  - More than 30 active investigational new drug applications (INDs) being discussed for AD formulations
    - New technologies being explored (e.g., pro-drugs that require activation to prevent IV abuse and snorting)
- May, 2016: Approval of Probuphine, first subdermal implantable buprenorphine for management of opioid dependance
- September, 2016: Approval of a new dosage of naloxone

Policy Development: Abuse-Deterrent (AD) Opioids

- Generic drugs play a critical role in US healthcare, including important role in controlling costs and expanding access

- March, 2016: FDA released draft guidance: General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products
- October, 2016: FDA held 2-day meeting to discuss draft guidance and standardization of in vitro testing for AD opioids

From the Meeting

- Development of AD opioids important part of response to opioids abuse crisis
- Need to balance need for careful scientific assessment to support appropriate decision-making and the interest in supporting predictable product development pathway for generics
  - Balance between standardizing approach to assessment (where possible) and need to individualize analysis to reflect product characteristics and science

From the Meeting (cont)

- Challenges:
  - Science of AD manufacturing and evaluation is in early stages
    - Need to understand the relationship between opioid exposure (PK), outcomes of Human Abuse Potential studies and risk for abuse
    - Need to work on ways to assess complex nature of the effects of AD formulations beyond PK
  - Critical need to assess real-world impact of AD technologies

Next Steps

- Comment period for the public meeting open until December 1, 2016
  - https://www.federalregister.gov/documents/2016/10/06/2016-24234/public-meeting-on-pre-market-evaluation-of-abuse-deterrent-properties-of-opioid-drug-products
- FDA committed to careful review of comments from meeting, comments to Docket as a part of finalizing Guidance

Policy Development: 2016 Study on Opioids for FDA with National Academies of Science Engineering & Medicine (NASEM)*

- **Follow-up to 2011 Institute of Medicine study**
  - "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research"
- **Goals for Committee:**
  - Update the state of the science regarding pain management and prescription opioid abuse and misuse
  - Make recommendations on additional actions FDA can take to address the opioid overdose epidemic, from both the individual and public health perspectives

* http://www.nationalacademies.org/hmd/Activities/PublicHealth/AddressPrescriptionOpioidAbuse.aspx

NASEM Study: Charge to the Committee

- Particular area of focus: public health framework for benefits and risks of prescription opioids
  - FDA is seeking help to develop a framework for opioid review, approval and monitoring that balances individual need for pain control with considerations of the broader public health consequences of opioid misuse and abuse
- NASEM prepublication Report expected June/July 2017

FDA's Benefit-Risk Framework

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		
Benefit-Risk Summary Assessment		

http://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm329758.pdf

Improved Science: Epidemiologic Assessment of Opioid Use/Abuse

- Office of Surveillance & Epidemiology (OSE)
  - Dedicated staff focused on identifying patterns of prescription drug use, misuse and abuse
  - 2016: New contracts allowing us to directly access data sources
    - Inflexxion, RADARS
    - AAPCC (poison control centers)
  - 2016: Collaborating with CDC to develop new data sources/capabilities for measuring abuse and its sequelae (NHCS, NEISS-CADES, finding literals on death certs)
  - Backup slide with recent references

Communication and Outside Engagement: Public Meetings

- Committed to expanded use of public meetings to discuss FDA work in this area
- In 2016 FDA has held 7 public meetings
  - 5 Advisory Committee meetings
  - Science Board
  - Additional meeting planned for remainder of the year
- Participated in numerous public meetings held by others
  - National Prescription Drug Abuse Summit
  - 3 NASEM public meetings

Communication and Outside Engagement: Advisory Committee on ER-LA REMS Assessment (May, 2016)

- In 2012, FDA required makers of extended-release, long-acting (ER/LA) opioids to provide funding for accredited Continuing Education (CE) coursed for 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

- http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm

REMS Assessment After 36 Months

- Results submitted to FDA July 9, 2015
- Discussion at pubic 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

FDA Advisory Committee on ERLA REMS

- Discussions focused on several areas:
  - Challenge of assessing impact of one activity related to opioids given the wide variety of actions taking place in this area
  - Need to expand ER-LA REMS to include immediate-release opioids
  - Need to expand education to include broader aspects of pain management beyond opioids
  - Need for mandatory education for all opioid prescribers
  - Inclusions of additional healthcare workers in educational efforts

Comments on Prescriber Education

- Advisory Committee themes reflected in other public comments made to Docket from RFI issued by HHS asking for input on opioid education, including:*
  - Need for multi-modal pain management education
  - Need to extend education to all members of the multidisciplinary team, not just prescribers
  - Expand ER/LA REMS to all schedule II opioid products
  - Flexibility in instructional design and content
  - Requirement should be tied to a clinician's application for a DEA registration to prescribe controlled substances
  - Incorporating recommendations from the CDC Guideline for Prescribing Opioids for Chronic Pain into education

- https://www.regulations.gov/document?D=HHS-ASPE-2016-0011-0001

HHS RFI: Prescriber Education

- Professional organizations (AMA, AAFP, AANP, ACP, ASA) were not supportive of a federal mandate requiring opioid education

- AMA does not support
  - Federal education initiatives being developed collaboratively by drug manufacturers (i.e. instead work collaboratively with physician experts)
  - Federal government-proposed educational requirement being undertaken as a law enforcement program, but rather a health care initiative

https://www.regulations.gov/document?D=HHS-ASPE-2016-0011-0001

Communication and Outside Engagement: Support for Appropriate Drug Disposal

- Part of administration efforts to prevent unneeded opioids from being diverted and/or misused
- Drug Disposal and Drug Take-back Day
- 2016: DEA has collected approximately 1.6 million pounds of drugs
  - FDA White Oak: 255 pounds last collection

Communication and Outside Engagement: Appropriate Drug Disposal

- CDER maintains USG website on drug disposal
- #1 most-visited consumer webpage in 2016
  - > 425,000 page views since January, averaging almost 3 minutes in length

http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/ensuringsafeuseofmedicine/safedisposalofmedicines/ucm186187.htm

Shared Responsibility

- FDA is one of many stakeholders in supporting appropriate pain management, and addressing opioids misuse and abuse
- Industry has an important role to play:
  - "I believe this is a matter of corporate responsibility, not just a government requirement. Corporate boards and executives have been noticeably silent on this issue. They have a duty to examine what their companies can do to stem this epidemic that goes beyond the minimum requirements, including careful examination of promotional practices."
    - Rob Califf, May 2016 RX Drug Abuse Summit

Summary: Overall Messages

- The FDA's work to improve the safe use of opioids is taking place within a larger policy framework aimed at addressing opioid abuse while supporting appropriate access to pain treatment
- Ongoing and planned activities reflect the commitment by FDA to work with other stakeholders to integrate the use of all of our available tools to achieve our goals related to the safe and appropriate use of prescription opioids
- Engagement with outside experts, including help from Science Board, continues to be an important focus of FDA activities

Thank you

BACK UP SLIDES

NASEM Opioid Study

- FDA has asked NASEM to help develop a framework for opioid review, approval and monitoring that balances individual need for pain control with considerations of the broader public health consequences of opioid misuse and abuse

NASEM Study Statement of Task

- Given the state of the available data, the Committee should identify additional actions FDA and others should consider now, with a particular focus on those actions the FDA can undertake, to balance the needs of pain patients and the need to address opioid misuse and abuse.
- FDA actions to be taken as a part of development, review and approval, and safe use of pain medicines, could include:

NASEM Study Statement of Task

- **Development of a formal method to incorporate the broader public health impact of opioid abuse in future FDA approval decisions regarding opioid**
- The development of non-opioid pain medicines to treat severe pain;
- The development of abuse-deterrent opioids
- The incorporation of prevention strategies into safe opioid prescribing, including modification of the standard opioid indication statements
- The development of medicines for medication assisted treatment for patients with opioid use disorder
- The development of medicines to treat opioid overdose
- The education of prescribers and patients about safe use of pain medications
- The education of prescribers and patients about appropriate medication storage and disposal

- Actions by prescribers, professional societies, and government agencies (local, state, and federal)

Improved Science: Epidemiologic Assessment of Opioid Use/Abuse

- OSE Publications
  - Measures to quantify the abuse of prescription opioids: a review of data sources and metrics.
    - *Secora AM, Dormitzer CM, Staffa JA, Dal Pan GJ. Pharmacoepidemiol Drug Saf. 2014 Dec;23(12):1227-37.*
  - Emergency Department Visits and Overdose Deaths From Combined Use of Opioids and Benzodiazepines.
    - *Jones CM, McAninch JK. Am J Prev Med. 2015 Oct;49(4):493-501.*
  - Trends in the Concomitant Prescribing of Opioids and Benzodiazepines, 2002-2014.
    - *Hwang CS, Kang EM, Kornegay CJ, Staffa JA, Jones CM, McAninch JK. Am J Prev Med. 2016 Apr 11. pii: S0749-3797(16)00094-5.*
  - Adverse Event Detection Using the FDA Postmarketing Drug Safety Surveillance System: Cardiotoxicity Associated with Loperamide Abuse and Misuse
    - *Swank KA, Wu E, Kortepeter C, McAninch J, Levin RL. Journal of the American Pharmaceutical Association, in press.*
  - Drug availability adjustments in population-based studies of prescription opioid abuse
    - *Secora AM, Trinidad JP, Zhang R, Gill R, Dal Pan GJ. Pharmacoepidemiol Drug Safety, in press.*