Implications of Draft Guidelines on Abuse Liability Testing for Generic Opioids

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ExL, Arlington VA
November 2, 2016

The opinions and information in this presentation are my own and do not necessarily reflect the views and policies of the FDA

Overall Messages

- FDA work on abuse deterrent formulations of generic opioids fits within a broader range of activities focused on improving the safe use of prescription opioids to appropriately treat pain
- Draft guidance on the development of generic AD opioids is a critical part of FDA work to support balanced development of effective abuse-deterrent (AD) opioids

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.

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

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 about prescription opioids
- Update Risk Evaluation and Mitigation Strategy (REMS) Program for ER-LA Opioids
- Expand access to abuse-deterrent formulations (ADFs) of opioids to discourage abuse
- Support better treatment for opioid substance use disorder
- Reassess the risk-benefit approval framework for opioid use

www.fda.gov/NewsEvents/Newsroom/FactSheets/ucm484714.htm

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 of Our 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

--http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm338566.htm

Summary of Recent Drug Approvals Aimed at Addressing the Opioid Crisis

- FDA has approved 7 opioids approved with features predicted to reduce their abuse
  - Numerous INDs for ADFs under development
- FDA has approved Probuphine, the first buprenorphine implant for the maintenance treatment of opioid dependence
- FDA has approved 2 new naloxone products to expand the availability and use of naloxone to prevent overdose deaths
  - Evzio – autoinjector naloxone product
  - Narcan nasal spray – intranasal naloxone product

Summary of Selected Actions Aimed at Addressing the Opioid Crisis

- March 2016: General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products
- August 2016: Stronger labeling on opioids and benzodiazepines warning about their combined use

IMPLEMENTATION OF A FRAMEWORK FOR AD OPIOID DEVELOPMENT AND USE

FDA Goals for Abuse Deterrent Opioid Formulations

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

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Development of AD Opioids: 7 Approved Products

- **OxyContin** (oxycodone, crush/extraction resistant): April, 2013
- **Targiniq** (oxycodone hydrochloride and naloxone, naloxone antagonist/precipitates withdrawal when abused): July, 2014
- **Embeda** (morphine/naltrexone, naltrexone is antagonist): October, 2014
- **Hysingla** (hydrocodone, crush/extraction resistant): November, 2014
- **MorphaBond** (morphine sulfate, crush/extraction resistant): October, 2015
- **Xtampza** (oxycodone, crush/extraction resistant): May, 2016
- **Troxyca** (oxycodone/naltrexone, naltrexone is antagonist): August, 2016

Future for AD Opioids-- Where Are We Headed?

- **Early**: market has a small number of AD products using early AD technology
  - Case by case decision-making
- **Intermediate**: multiple products approved as abuse deterrent using various technologies
  - Broader experience with AD technologies
  - Guidance outlining FDA's approach for brand name and generic development is refined
  - Actions potentially shift to class-wide scope
- **Late**: AD formulations of all major opioids marketed
  - Focus is on supporting iterative improvement in AD technologies

Future for AD Opioids-- How Will We Get There?

- **Series of potential regulatory actions:**
  - Data sufficient to support claim for the specific product
  - Data also sufficient to block approval of other drugs that lack the same (or better) abuse-deterrent properties
  - Data also sufficient for FDA to take action* against existing products with the same active ingredient
  - Data also sufficient for FDA to take action* against existing products, including those with different active ingredients

* Examples of actions could include withdrawal or imposition of REMS restrictions on the basis of safety

Implementation of This Framework

- Requires clear standards for assessment of formulation performance
  - *In vitro* testing **(focus of discussion at current meeting)**
  - Abuse liability testing
  - Assessment of real-world performance
- Requires policy development around criteria
  - What level of performance needed for each stage?
- Requires awareness of impact of actions on overall opioid market

Challenges in Implementing This Framework for AD Opioids

- Supporting brand name and generic product development
- Encouraging iterative development of effective abuse-deterrent formulations
  - Challenge to assess impact of individual formulations
  - Challenge to encourage uptake of effective products
- Managing expectations: abuse-deterrent opioids will not ‘prevent’ all abuse, and are not ‘silver bullets’

Challenges in Implementing This Framework for AD Opioids(cont): Need for Real-World Assessment

- DECIDE WHAT WORKS AND WHAT DOESN'T
- Current actions based on pre-market clinical and *in vitro* data to predict the formulation will reduce abuse
- Real-world assessment needed (and ongoing)

Assessment: Market Challenges

- Opioids market still dominated by non-AD formulations
- Market Share for AD Opioids limited:
  - AD formulation of OxyContin made up around 22% of the ER-LA opioids market in 2014
  - ER-LA opioids comprised around 10% of the total opioids market
  - Other AD opioids with limited market share to date

Assessment: Data Challenges

- Data sources often have limited information on individual products abused (e.g., generic vs brand name) and formulations (e.g., liquid, solid oral, patch)
- Patients abuse multiple products (and substances)
- Opioid abuse influenced by social factors
- Many other activities going on to address prescription opioid abuse, complicating conclusions about cause and effect

FDA Goals for Abuse Deterrent Opioid Formulations

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

FDA Work Supporting Generic AD Opioid Development

- **Policy development**
  - Draft Guidance (March 2016): General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products
- **Research by CDER on formulations science**
- **Focus on continued improvements to, and support for, generic drugs program under GDUFA**
  - Work under GDUFA I to build capacity for generics program as a whole
  - AD Opioids as 'complex products'
  - Product-specific support for generics development
    - Controlled correspondnce
    - Expanded meetings

FDA Public Meeting on Draft Generics Abuse-Deterrent Opioids Guidance (Oct 31-Nov 1)

- Summary of key points and comments on draft Guidance
  - Necessary and important compliment to guidance supporting brand name AD opioid development
  - Development of successful generic AD opioids important to public health to ensure abusers do not seek out generics as easier to abuse
- Discussion of standardizing *in vitro* test methodologies to use when assessing abuse-deterrent formulations
  - FDA work on the science of *in* vitro assessment of AD formulations
- Perspectives and comments on draft Guidance from public, payors, academics, brand name and generics industry

What I Heard at 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 for generics
  - Balance between standardizing approach to assessment and need to individualize analysis to reflect product characteristics and science

What I Heard at the Meeting

- Challenges
  - Science of AD manufacturing is in early stages
  - Small changes in the same formulation reported to have large effects on product performance
  - Identifying critical quality attributes essential and challenging
  - Need to understand PK-PD relationship between opioid exposure (PK), outcomes of Human Abuse Potential studies and risk for abuse (PD)
  - Need to work on ways to assess complex nature of the effects of AD formulations beyond PK

What I Heard at the Meeting

- Suggested Solutions
  - Broad support for value of providing Guidance
  - Support for product specific guidance as a means of updating recommendations to industry
  - Support for continued dialogue between industry, academics and FDA about finding balance between challenges in support of FDA decision-making

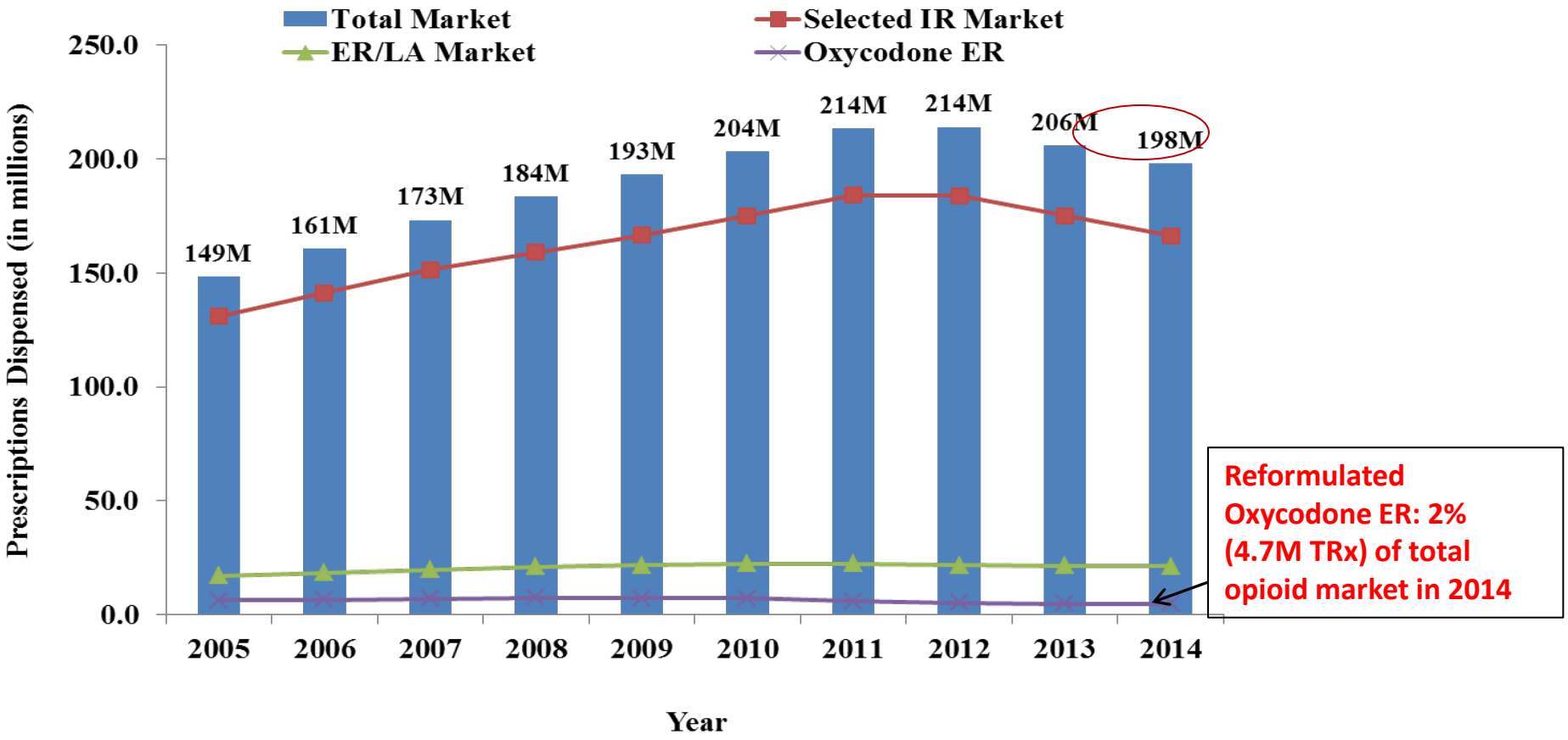
Overall Messages

- The FDA 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 integrate the use of all of our available tools to achieve our goals related to the safe and appropriate use of prescription opioids
- This meeting focuses on one important aspect of FDA's work in this area, the development and pre-market assessment of AD opioids, both brand name and generic

Thank you

TRENDS IN PRESCRIPTION OPIOIDS

IR and ER/LA Opioid Prescriptions



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

- No prescriptions captured for Hysingla ER or Embeda in 2014

Source: IMS Health, National Prescription Audit ™ Extracted May and August 2015

Prescriptions for Opioids with Abuse Deterrent Properties

Nationally Estimated Number of Prescriptions Dispensed for Opioids* with Abuse Deterrent Properties from U.S. Outpatient Retail Pharmacies

	Year 2015	
	Prescriptions (N)	Share%
Total Selected Opioids	4,520,013	100%
Oxycodone ER*	4,406,304	97.5%
Hysingla ER	85,934	1.9%
Embeda	27,775	0.6%

Source: National Prescription Audit (NPA™). Year 2015. Extracted February 2016

***Includes authorized generic oxycodone ER, Brand OxyContin (reformulated) accounted for 96% of total oxycodone ER prescriptions. No prescription data for Targiniq and Morphabond and other approved AD Opioids in 2015**

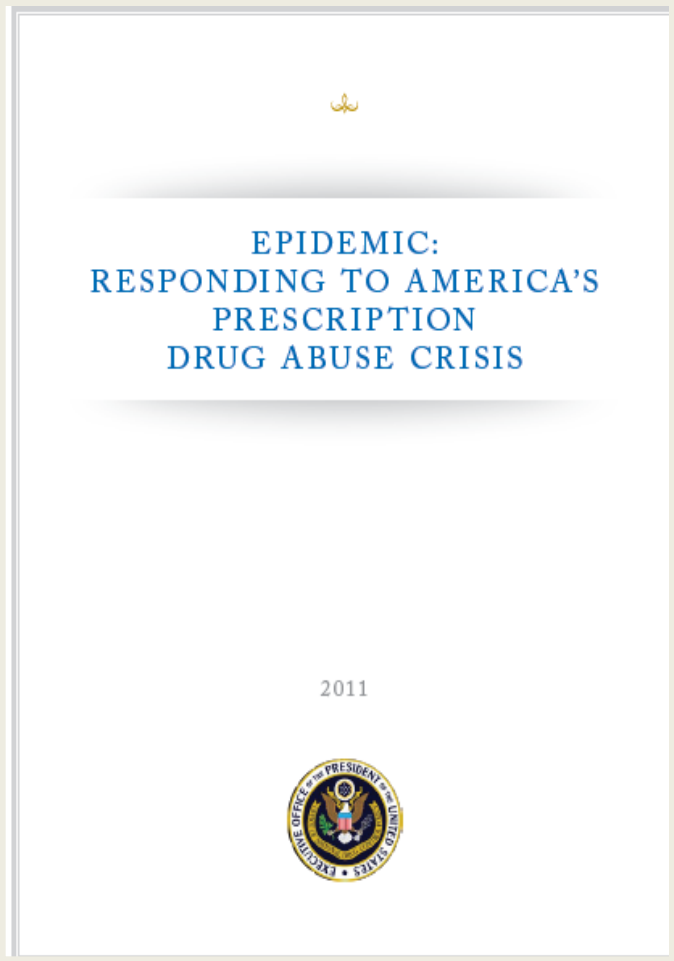
BROADER CONTEXT OF FDA WORK ON PRESCRIPTION OPIOIDS

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

--http://aspe.hhs.gov/basic-report/opioid-abuse-us-and-hhs-actions-address-opioid-drug-related-overdoses-and-deaths

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

Focus of Current Meeting: Day Two--Science of Assessing AD Formulations

- Standardizing *in vitro* test methodologies to use when assessing abuse-deterrent formulations
- FDA work on the science of *in* vitro assessment of AD formulations
- Perspectives and comments from public, academics, brand name and generics industry