Selected FDA Activities on Opioids

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Disclosure Statement

I have no financial relationships with proprietary entities that produce health care goods and services

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

Over-Arching Public Health Goals

- Provide appropriate access to pain treatments for patients, including opioids drugs
- Reduce the misuse and abuse of prescription opioids

FDA Work To Support Goals*

- **Improving drugs used to treat pain**
  - **Abuse-deterrent formulations of opioids**
  - New classes of pain drugs that lack abuse risk
- **Improving safe use of opioids**
  - **Education of prescribers & patients to reduce risk of abuse through the ER-LA Opioid REMS**
    - Part of larger work in post-marketing surveillance to understand use of opioids
  - **Supporting research into best approaches to pain treatments, including opioids**
- **Improving drug treatments for opioid abuse**
- **Improving treatment of opioid overdose**
  - Naloxone autoinjector approval

* http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm338566.htm

Selected Recent FDA Activities

- **Abuse-Deterrent (AD) Formulations of Opioids**
  - **Public Meeting October 30, 31, 2014**
  - **Guidances to foster innovation and development**
- **Approval of Embeda and Hysingla**
- **Opioid REMS Assessment**
- **Non-regulatory activities: PASES**

Work to Support Development of Abuse Deterrent Opioids

ABUSE DETERRENT OPIOIDS GUIDANCES AND MEETING

Twin Goals for Abuse Deterrent (AD) Formulations of Opioids

- 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 Tools to Support AD Formulation Development

- **Scientific Research**
- **Regulatory Activities**
  - Decisions on applications
  - Sponsor discussions as a part of development
- **Guidances**
  - Draft Guidance on developing AD formulations of opioids issued January, 2013
  - Pending Guidance on generics development and testing
- **Public Discussion and Comment**
  - Public meetings, including meeting held October 30, 31, 2014
  - Comments on draft Guidance
  - Citizen Petitions

Focus of Meeting Oct 30, 31, 2014: Input

- FDA sought input in areas relevant to AD formulation development:
  - Comments from open public hearing
  - Presentations and comments from industry, academics, government reps, and patient advocates
  - Panel discussions
  - Docket submissions
  - **"…(S)upport the development of opioid medications with progressively better abuse-deterrent properties"**

Day One: Development and Evaluation of Abuse-Deterrent Opioid Formulations

- Manufacturing and formulation science related to abuse-deterrent formulations
  - FDA manufacturing experience with AD formulations
- Questions about potential approaches to assessing the *in vitro* performance of AD formulations of opioids, both generic and brand-name

Day Two: FDA Approach to the Overall Assessment and Regulation of AD Opioids

- **Discussion of potential FDA activities to support incremental AD formulation development and broad use**
  - Giving a labeling claim for specific product
  - Also blocking the approval of other drugs that lack the same (or better) abuse-deterrent properties
  - Also, taking action against existing products with the same opioid
  - Also, taking action against existing products, including those with different opioids

Important Outcome from Meeting: Continued Input to Inform AD Guidances

- Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling
  - Draft released Jan 2013
- Draft guidance to support development of AD generics
  - Work ongoing

Work to Support Development of Abuse Deterrent Opioids

EMBEDA AND HYSINGLA

New Products with Abuse-Deterrent Features: Embeda

- Morphine sulfate and naltrexone hydrochloride
- Embeda has properties that are expected to reduce, but not totally prevent, abuse of the drug when crushed and taken orally or snorted

New Products with Abuse-Deterrent Features: Hysingla ER

- Hydrocodone bitartrate
- Hysingla ER has properties that are expected to reduce, but not totally prevent, abuse of the drug when chewed and then taken orally, or crushed and snorted or injected

Points About Recent Approvals

- Utilized principles discussed publically and in the draft Guidance where appropriate
- Participating in ER-LA Opioid REMS
- Required post-marketing work to assess impact of new formulation on abuse
- g studied

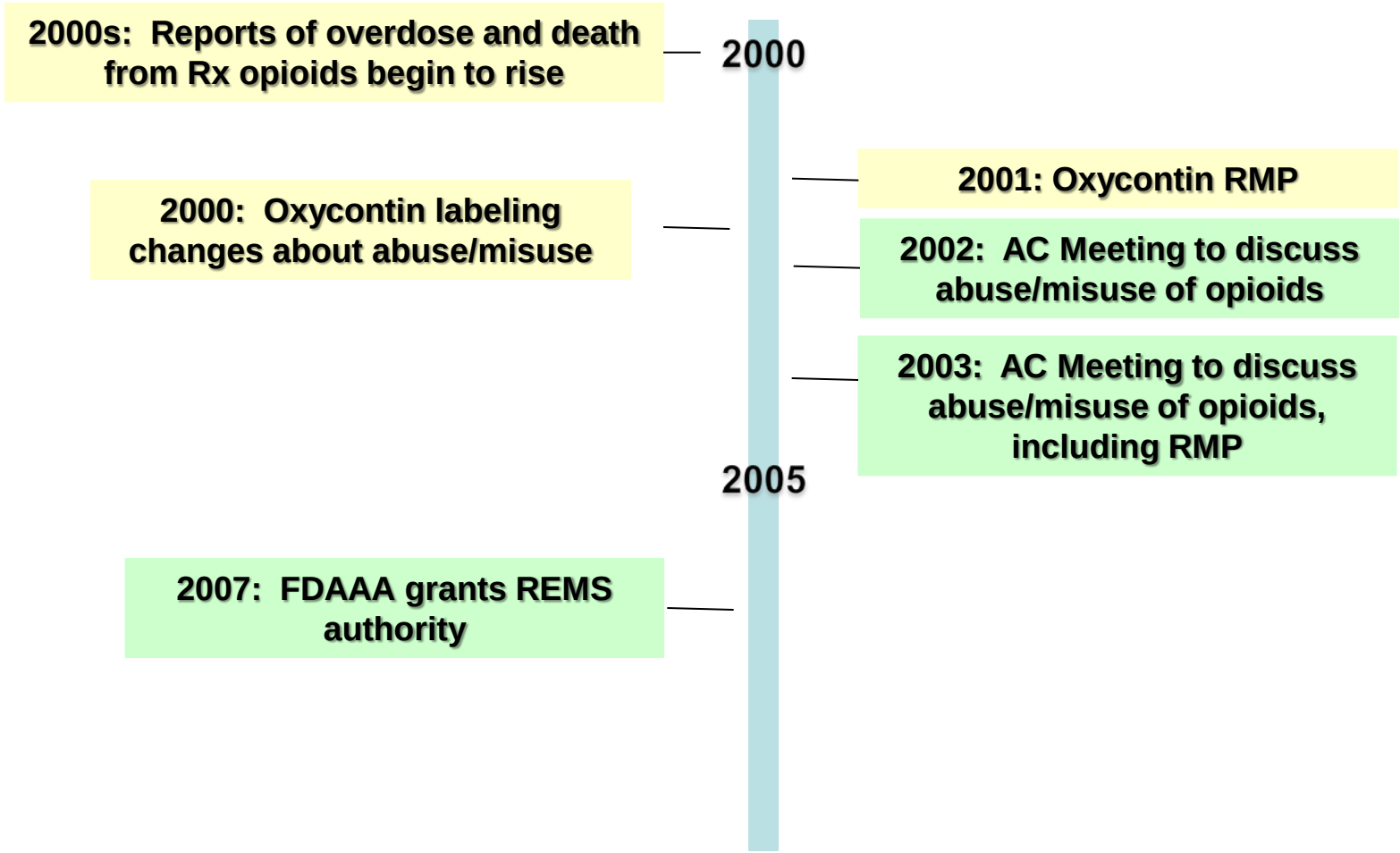
Points About Recent Approvals

- Reflects important new work developing new AD formulations of opioids
  - Around 30 products under IND, most extended-release, long-acting opioid formulations
  - Work to date has often focused on use of crush/extraction-resistant and aversion technologies but many new approaches being explored
- Similar levels of interest in generics development
  - Reinforces importance of guidance in this area

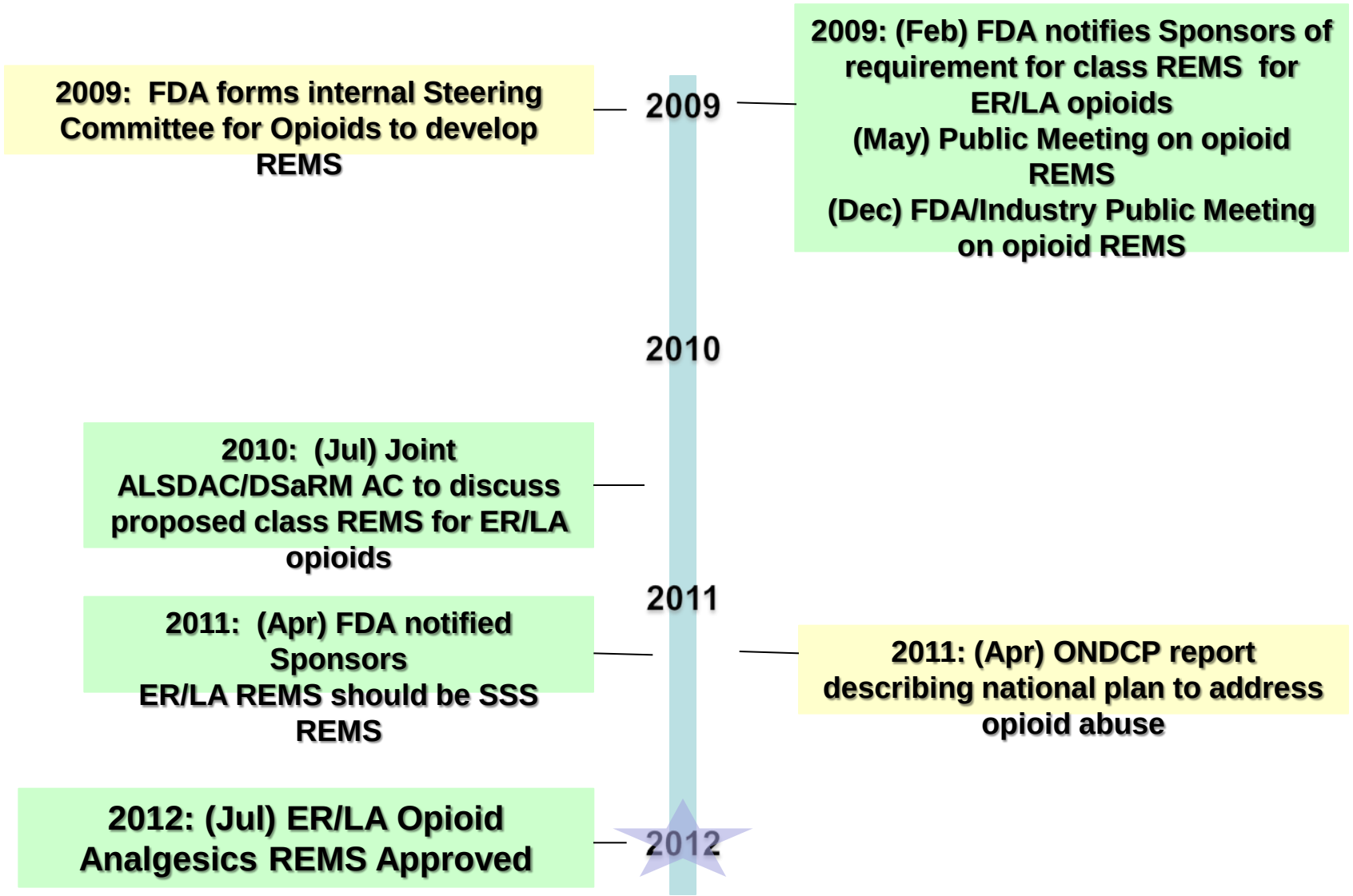
Measuring Impact of Regulatory Activities on Opioids

ER-LA OPIOID REMS ASSESSMENT

History of ER/LA REMS



History of ER/LA REMS



Goal of ER/LA REMS

"…to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of extended-release or long-acting (ER/LA) opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death"

Multi-Sponsor/Multi-Product REMS

- Active ingredients in ER/LA products:

Buprenorphine	Fentanyl	Tapentadol
Hydrocodone	Hydromorphone	Methadone
Morphine	Oxycodone	Oxymorphone

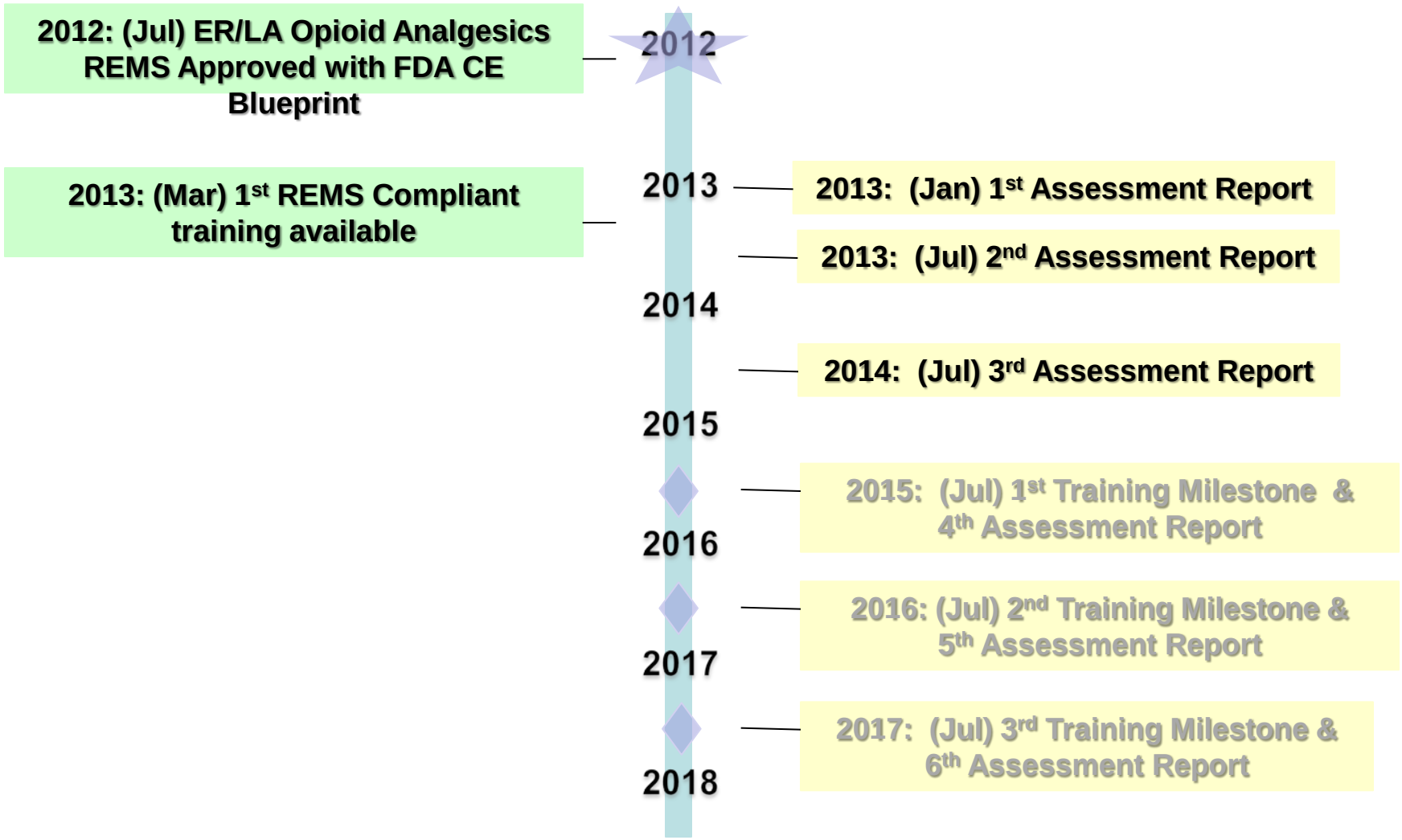
- Numerous applications represented by 24 Sponsors, who comprise the ER/LA REMS Product Companies(RPC)
  - Multiple NDA's

Multiple Sponsors, products, and applications result in very complex logistical considerations

ER/LA REMS Elements

- Medication Guide- Novel one-page format
- Elements to Assure Safe Use: Prescriber Training via sponsor-funded CE guided by the FDA Blueprint
- Additional REMS materials include:
  - Patient Counseling Document
  - Letters to healthcare professionals
  - REMS website
- Timetable for Submission of Assessment
  - 6 and 12 months post-approval and annually thereafter; components of each assessment change until year 4

History of ER/LA REMS



Some Milestones Under Assessment

- Prescriber CE Training
- CE Auditing Compared with FDA Blueprint
- Drug Utilization
- Patient Understanding
- Changes in prescriber behavior
- Changes in trends for misuse, abuse, overdose and death
- Patient Access

Ongoing Assessment

- ER/LA Opioid Analgesics REMS is early in its life-cycle
- Analysis of 3rd REMS Assessment Report is ongoing
- Consideration for significant modifications to the overall risk mitigation strategies will be dependent upon the findings in future REMS assessment reports

Non-Regulatory Work Through Safe Use Initiative

GOAL: IMPROVE THE TREATMENT OF PAIN, INCLUDING THE USE OF OPIOIDS

CDER's Safe Use Initiative

- **What?** FDA's non-regulatory activities to reduce risks (*preventable* harm) from Rx and OTC drugs
- **Why?** FDA's regulatory authority alone may not be sufficient to prevent harm
- **How?** Partnering with those involved in healthcare who can control, modify or influence behavior and practices (practices FDA doesn't regulate)
- **How?** Supporting targeted research that will yield important information about improving the use of pain drugs including opioids

Ongoing Safe Use Opioid Projects

Project Title	Description
Opioid Patient- Prescriber Agreement (PPA)	Working group comprised of federal and non-federal stakeholders to develop a model opioid PPA to be used voluntarily by prescribers
Urine Drug Testing for Opioid Use/Abuse	Collaboration with Oregon Health and Science University to identify factors that predict use of urine drug tests among patients prescribed chronic opioid therapy and generate qualitative data from clinicians on barriers to urine drug testing
Brandeis University Prescription Drug Monitoring Program	CERSI project with Brandeis University to develop an early warning surveillance and evaluation tool for opioid use (Prescription Behavior Surveillance System) based on data from state prescription drug monitoring programs

New Tool to Support Research: Safe Use 2014 BAA Contracts

Project Title	Description
Nurse Pain Education Pilot Program (NPE)	Development of a clinical decision support system using nurse pain educators to guide safe and pragmatic use of opioid analgesics in ***primary care settings*** to prevent AEs.
Reducing use of Opioid Therapy following Surgery: A Randomized Controlled Trial	Evaluation of methods for mitigating long-term, high dose of opioids following surgery, by refining a prediction tool to identify ***inpatients*** at high risk for opioid use following orthopedic surgery.

Summary

- FDA is working across many areas to
  - Improve the use of opioids
  - Preserve appropriate access to pain treatment
  - Encourage the development of new products in the area of pain treatment that will offer improved safety and efficacy
- Within this broadened range of activities, our regulatory mission remains at the heart of FDA role in opioids
  - FDA will act within its authorities, based on science, in support of our public health mission