FDA Perspectives on Balancing the Risks and Benefits of Opioid Analgesics

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FDA’s Opioids Action Plan and Re-examining the Risk-Benefit Paradigm for Opioids
FDA’s Response to the Opioid Crisis

• FDA remains committed to
  – 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
FDA Opioids Action Plan

• “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

- Re-examine the risk-benefit paradigm for opioids and ensure that the agency considers their wider public health effects
- Expand use of Advisory Committees and outside engagement
- Strengthen immediate-release opioid labeling, including additional warnings and safety information that incorporate elements similar to the extended-release/long-acting (ER/LA) opioid analgesics
- Consider updates to the Risk Evaluation and Mitigation Strategy (REMS) Program for ER-LA Opioids
- Strengthen postmarket requirements to get needed real-world data
- Expand access to abuse-deterrent formulations (ADFs) to discourage abuse
- Support better treatment for opioid use disorder and to prevent opioid overdose deaths
- Support better pain management options, including alternative treatments
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
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:
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)
Principles of FDA Drug Regulation
FDA Authority to Regulate Drugs

• 505(a) of the Federal Food, Drug, and Cosmetic (FD&C) Act requires that “[n]o person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application...is effective with respect to such drug”

• FD&C Act requires drugs to be safe and effective for their labeled conditions of use
Investigational New Drugs

• 505(i) of the FD&C Act states that “[t]he Secretary shall promulgate regulations for exempting...drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs.”
• IND requirements apply to all human investigation of products under Section 505 of the FD&C Act and biologics under the Public Health Service Act
• 21 CFR Part 312 sets forth the requirements for an IND application
FDA’s Role in Drug Development and Approval Process

Pre-IND Meeting
End-of-Phase 2 Meeting
Pre-NDA Meeting

Pre-Clinical Testing → Phase 1 → Phase 2 → Phase 3 → NDA Review → Post-marketing Surveillance

Pre-IND → IND → NDA → Post-Approval
Expedited Programs for Serious Conditions

• Fast track designation, Breakthrough therapy designation, Priority review designation

• These programs are intended to help ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies’ benefits justify their risks

• These programs represent efforts to address an unmet medical need in the treatment of a serious condition
FDA’s Current Approach to the Risk-Benefit Paradigm for Opioids
Currently Available Tools to Evaluate the Risk-Benefit of Opioids

• Sponsors submit information in the New Drug Application (NDA) to inform the risk-benefit of the proposed product

• Our reviewers perform a qualitative risk-benefit analysis as part of an NDA review
  – Structured approach to the Benefit-Risk assessment
  – Postmarketing evaluation

• Advisory Committees
Structured Benefit-Risk Assessment

• In 2009, FDA initiated an effort to explore more systematic approaches to the benefit-risk assessment and communication as part of the human drug review process
  – Goal was to develop a structured approach for benefit-risk assessments that could serve as a template for product reviews, as well as a vehicle for explaining the basis for FDA’s regulatory decisions in drug approvals

• When FDA and industry began discussions on reauthorization of the Prescription Drug User Fee Act (PDUFA) in 2010, an enhanced structured approach to benefit-risk assessment was a key topic

• Those discussions resulted in a set of commitments during PDUFA V (FY 2013-2017) related to enhancing benefit-risk assessment in drug regulatory decision-making

• As part of these commitments FDA will revise its review templates to incorporate a structured benefit/risk assessment into the human drug review process

# FDA’s Benefit-Risk Framework

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**Benefit-Risk Summary Assessment**
Tools to Manage Risks Associated with Opioids

• Development of opioids with abuse-deterrent properties
• Postmarketing requirements
• Labeling
• Risk Evaluation and Mitigation Strategies (REMS)
  – A risk management plan to ensure that a drug’s benefits outweigh the risks
Opioids with Abuse-Deterrent Properties

- FDA supports development of these products as one component to addressing the opioid epidemic
  - Issued guidance for industry
  - Public meetings to discuss the development of these products
- FDA has approved 7 opioids with abuse-deterrent labeling
  - Generally based on premarketing evaluation of abuse-deterrence, these products are labeled to have properties that are expected to reduce abuse via certain routes. However, abuse of the drug product by these routes is still possible
- Postmarketing requirements to evaluate real world reductions in misuse and abuse, and their consequences, addiction, overdose, and death, due to the abuse-deterrent formulation
Measuring Abuse and Related Outcome Rates: Trends and Comparing Across Products

• No single national surveillance system for opioid abuse, misuse, addiction, overdose, and death

• All data sources have significant limitations
  – Most not product/formulation specific
  – Product-specific data sources
    • Represent unknown proportion of actual abuse occurring—can change over time
    • May not be able to reliably identify formulation, brand/generic, etc.

• When comparing rates across products and time periods, denominator choice is critical
  – population vs. prescriptions or tablets dispensed?

• Methods and data sources continue to evolve: how to best make regulatory decisions based on imperfect data and uncertain methods?
Labeling and Patient/Prescriber Education

• In 2013, FDA announced class-wide safety labeling changes to enhance the safe and appropriate use of extended-release and long-acting (ER/LA) opioids

• March 2016, FDA announced required class-wide safety labeling changes for immediate-release (IR) opioid pain medications, including expanded warnings and safety information and an updated indication statement to better reflect the intended population

• FDA Advisory Committee to discuss the Risk Evaluation and Mitigation Strategy (REMS) Program for ER-LA Opioids and to consider potential changes to improve prescriber education
Conclusions
Conclusions

• FDA has been consistently working over time to improve the safety of all medicines, including opioids
• The focus of this workshop is on the additional actions FDA can take to address the opioid epidemic
• In particular, we are seeking input from NASEM on how to formally incorporate the broader public health considerations surrounding opioids into the risk benefit analysis of individual opioid drug products
Thank You!