Pain Management and the Opioid Epidemic

Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use

Report Release

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Board on Health Sciences Policy
Health and Medicine Division

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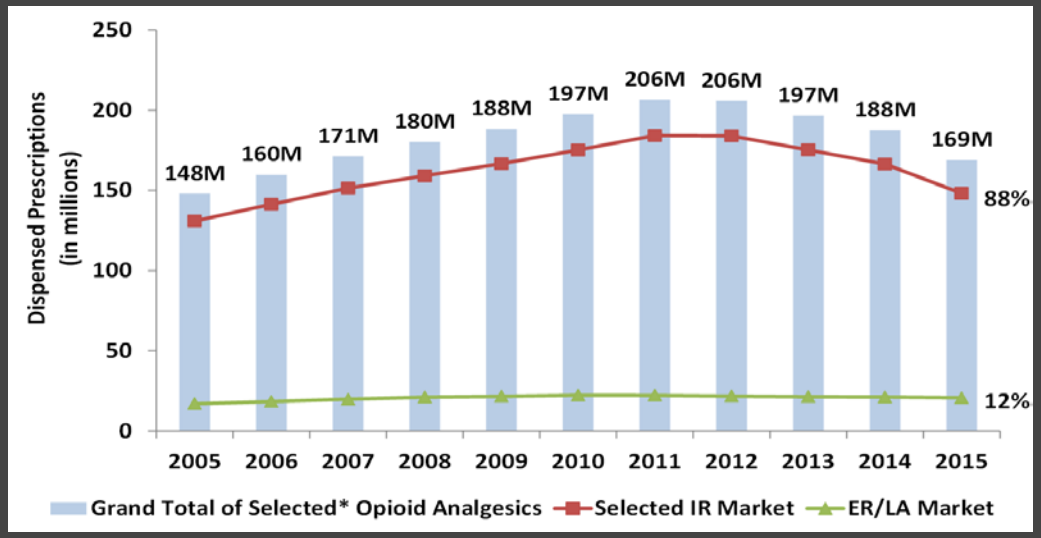
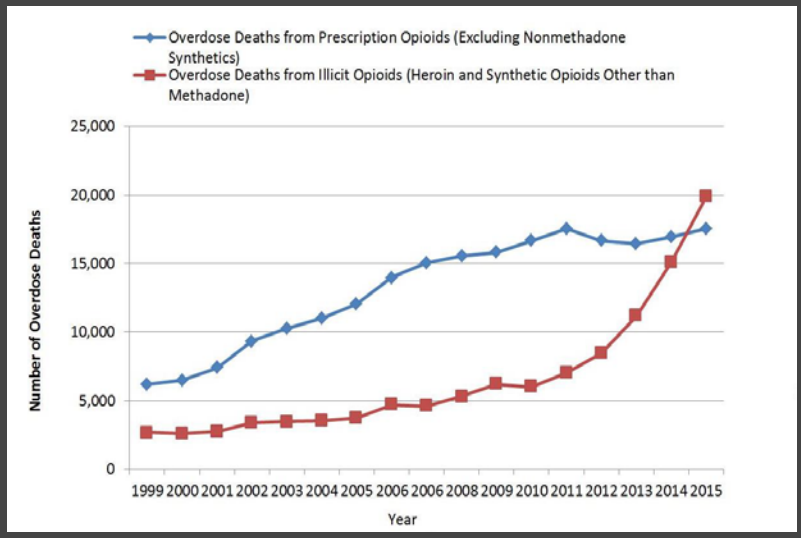
Background

- The ongoing opioid crisis lies at the intersection of two public health challenges—reducing the burden of suffering from pain and containing the rising toll of the harms that can arise from the use of opioid medications.



Prescriptions Dispensed



Overdose Deaths – Rx and Illicit

Background, continued

- Drug overdose is now the leading cause of unintentional injury death in the United States and most of these deaths involve an opioid.
- As of 2015, 2 million Americans aged 12 or older had an OUD involving prescription opioids, and nearly 600,000 had an OUD involving heroin.
- In the context of the growing opioid problem, the FDA launched an Opioids Action Plan in early 2016. One component of the FDA plan is to reassess the agency's risk-benefit approval framework for opioid approval and monitoring. The FDA commissioned this study to inform this reassessment.

Statement of Task

- Update the state of the science on pain research, care, and education since publication of the 2011 Institute of Medicine Report *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*, including the evolving role of opioids in pain management;
- characterize the epidemiology of the opioid epidemic and the evidence on strategies for addressing it;
- identify actions the FDA and others can take to respond to the epidemic, with a particular focus on the FDA's development of a formal method for incorporating individual and societal considerations into its risk-benefit framework for opioid approval and monitoring; and
- identifying research priorities.

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Committee Membership

Richard L. Bonnie (Chair), University of Virginia School of Law
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Linda Burnes Bolton, Cedars-Sinai Medical Center
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Consultants to the Committee: **Margaret Foster Riley**, University of Virginia
Patricia Zettler, Georgia State University

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Information Gathering

- Reviewed scientific literature relevant to statement of task and background materials provided by FDA.
- Held two public workshops to hear from researchers and FDA and other federal agency representatives on topics germane to the statement of task.
  - Workshop 1 (held September 22, 2016) focused on updating the state of the science on pain management and characterizing the epidemiology of the opioid epidemic and strategies to address it.
    - Summarized in a Proceedings of a Workshop—in Brief titled *Pain Management and Prescription Opioid-Related Harms: Exploring the State of the Evidence*.
  - Workshop 2 (held November 4, 2016) focused on regulatory aspects of the committee's charge, including how the FDA might incorporate public health considerations into is regulatory framework for evaluation of opioids.

Approach

- The committee interpreted its charge as focusing primarily on prescribed opioids. However, because markets for prescription and illicit opioids have been found to be intertwined, one of the main messages of the report is that policymakers must take account of the impact of their actions on the entire "opioid ecosystem."

- The committee believes that the FDA cannot address the opioid problem on its own. Therefore, the committee directs a number of its recommendations at other stakeholders, such as other federal and state agencies, and payors, among others.

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Pain Management and Progress and Future Directions in Research on Pain and Opioid Use Disorder

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- Opioids are prescribed in a variety of settings for treatment of both acute and chronic pain.

- While opioid analgesics are widely accepted as effective for acute pain as well as pain related to cancer or in end-of-life situations, data demonstrating benefits of long-term opioid therapy for chronic noncancer pain are lacking. Some data suggest worsened pain and functional outcomes.

- Long-term use of opioids is associated with increased risk of OUD, overdose, and other adverse outcomes (e.g., endocrine problems, mood disturbance, fractures and cardiovascular events).

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- Many nonopioid alternatives exist for the management of chronic pain:
  - Pharmacologic: NSAIDs, anticonvulsants, antidepressants, analgesic creams and patches
  - Psychological/behavioral: Cognitive-behavioral therapy, acceptance-commitment therapy, mindfulness meditation
  - Rehabilitative: Physical therapy, exercise
  - Interventional: Injections, nerve stimulators, medication pumps
  - Complementary medicine: Yoga, acupuncture, chiropractic, massage
  - Multidisciplinary rehabilitation programs
- While each nonopioid alternative has its own indications and risks, these treatments can in some patients be as or more effective than opioids for reducing pain, and often carry a lower risk of adverse outcomes when used appropriately.
- Comparative effectiveness and long-term outcome data are sparse for most of these alternative therapies.

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- Several advances in understanding pain and its treatment have occurred since the release of the 2011 IOM report *Relieving Pain in America*.
  - Improved understanding of the basic mechanisms related to MOPR (μ opioid receptor)-biased analgesia, inflammation, pain transmission, innate immunity, and use in the treatment of neuropathic pain
  - Advances in preclinical and translational research, including several developments related to the creation of nonaddictive alternatives to the opioid analgesics currently on the market
  - Movement toward pragmatic, practice-based trials emphasizing treatments delivered under real world rather than idealized conditions.
  - Advances in precision medicine to facilitate tailoring of pain management at the level of the individual patient, although further research is needed

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- Despite these advances, little is known about why individuals who use prescribed opioids to alleviate pain develop opioid dependence or OUD.

- Identification of individuals at risk of OUD requires better characterization of the neurobiological interaction between chronic pain and opioid use. In particular, research on the interactions among pain, emotional distress, and reward, including pain-induced alterations in the reward pathway, would help in understanding and reducing the misuse potential of opioids.

- Despite the prevalence of pain and OUD and related costs to society and repeated calls to action, research on pain remains poorly resourced.

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Recommendation 3-1. Invest in research to better understand pain and opioid use disorder. Given the significant public health burden of pain and opioid use disorder (OUD) in the United States, the National Institutes of Health, the Substance Abuse and Mental Health Services Administration, the U.S. Department of Veterans Affairs, industry, and other relevant research sponsors should consider greater investment in research on pain and OUD, including but not limited to research aimed at

- improving understanding of the neurobiology of pain;
- developing the evidence on promising pain treatment modalities and supporting the discovery of innovative treatments, including nonaddictive analgesics and nonpharmacologic approaches at the level of the individual patient; and
- improving understanding of the intersection between pain and OUD, including the relationships among use and misuse of opioids, pain, emotional distress, and the brain reward pathway; vulnerability to and assessment of risk for OUD; and how to properly manage pain in individuals with and at risk for OUD.

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Trends in Opioid Use and Harms

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Risk Factors and Vulnerable Populations

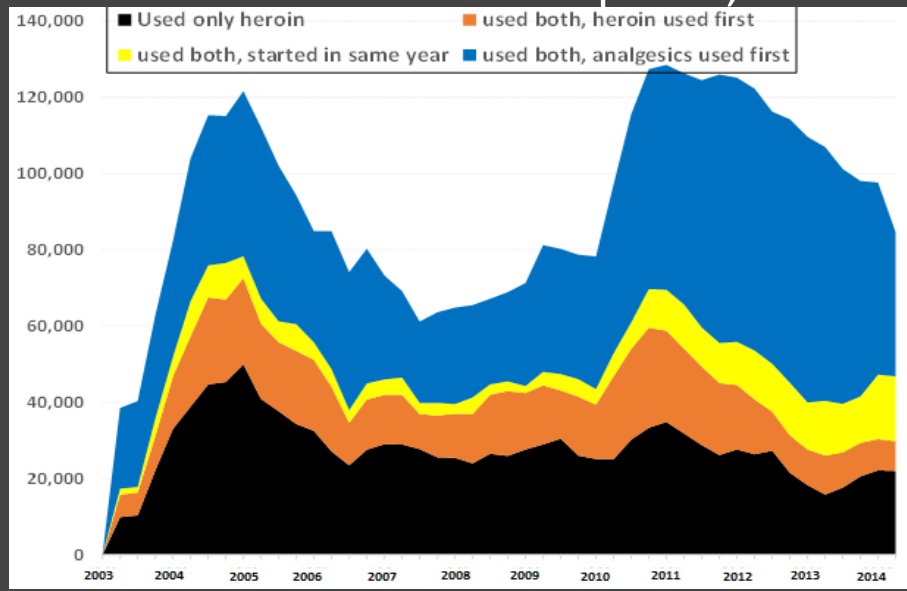
- The level and type of risk to a patient from a given opioid are influenced by several factors including features of the medication itself (e.g., compound, formulation, route of administration) and how it is prescribed (e.g., on an as-needed basis, at high doses, for prolonged periods of time)
- One consistent finding in the research is that risk of opioid overdose increases in a dose-response fashion with increasing morphine-equivalent milligram doses.
- Three populations with unique risks in the context of the opioid epidemic are discussed in the committee's report: pregnant women and neonates, people involved with the criminal justice system, and people who inject drugs.

Vulnerable Populations: Pregnant Women and Neonates

- Illustrates considerations of opioid use beyond the prescribed patient.
- The proportion of babies born with neonatal abstinence syndrome (NAS) in the United States has increased in recent years concurrently with a significant increase in opioid use and misuse among women of childbearing age and subsequently among pregnant women.
- Approaches to improve maternal and NAS outcomes can be better refined by earlier identification and supports for pregnant women using opioids, whether the use results from taking opioid medication as prescribed or due to opioid misuse.
  - Taper off opioid
  - Sustain opioid, manage and minimize NAS
  - Initiation of MAT, manage and minimize NAS
  - Maintenance of MAT, manage and minimize NAS

Prescription and Illicit Opioid Epidemics Intertwined

- A critical feature of the opioid crisis—and of this report-- is that the prescription and illicit opioid epidemics are intertwined.
- Research indicates that a majority of heroin users report that their opioid misuse or OUD began with prescription opioids.
- In addition, the declining price of heroin and efforts to restrict access or to deter certain ways of using prescription opioids (e.g., abuse-deterrent formulations [ADFs]), may contribute to increased use of heroin and other illicit opioids, and ultimately to greater public health risk.



Heroin initiation reported in 2003-2014 NSDUH surveys, by whether analgesics were used non-medically before heroin.
SOURCE: Muhuri et al., 2013

Abuse-deterrent Formulations

- Given the lack of evidence supporting the use of opioids for chronic noncancer pain, and the intertwined nature of prescription and illicit opioid use, reliance on ADFs may undermine a successful public health response to the opioid epidemic.
- Abuse-deterrent formulations (ADFs) have the potential for benefit, but this is counterbalanced by recent examples of unexpected harm.
- Ongoing studies will help clarify the optimal role for ADFs as a strategy for reducing misuse of prescription opioids. The committee advises caution.

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Recommendation 4-1. Consider potential effects on illicit markets of policies and programs for prescription opioids. In designing and implementing policies and programs pertaining to prescribing of, access to, and use of prescription opioids, the U.S. Food and Drug Administration, other agencies within the U.S. Department of Health and Human Services, state agencies, and other stakeholders should consider the potential effects of these interventions on illicit markets—including both the diversion of prescription opioids from lawful sources and the effect of increased demand for illegal opioids such as heroin among users of prescription opioids—and take appropriate steps to mitigate those effects.

Status of Surveillance Data

- Gaps exist in the reporting of data with which to accurately describe the epidemiology of pain, OUD, and other opioid-related harms in the United States, including overdose, counterfeit medications, and how pain and OUD co-occur and relate to one another.
- The absence of publicly accessible surveillance data during the rise of nonmedical use of prescription opioids contributed to the epidemic and continues to impair national responses. To address the nuances of the evolving prescribed, illicit, and illicitly manufactured synthetic use trends, multiple, more sophisticated, and more responsive designs are warranted.
- Closing these data gaps would improve understanding of pain, OUD, and overlapping prescription and illicit opioid use and enable more effective and measurable policy interventions.

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Recommendation 4-2. Improve reporting of data on pain and opioid use disorder. The Substance Abuse and Mental Health Services Administration, the U.S. Food and Drug Administration, the National Institutes of Health, and the Centers for Disease Control and Prevention should collaborate to identify best practices and reporting formats that portray the epidemiology of both pain and opioid use disorder accurately, objectively, and in relation to one another.

Recommendation 4-3. Invest in data and research to better characterize the opioid epidemic. The National Institute on Drug Abuse and the Centers for Disease Control and Prevention should invest in data collection and research relating to population-level opioid use patterns and consequences, especially nonmedical use of prescription opioids and use of illicit opioids, such as heroin and illicitly manufactured fentanyl.

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OPIOID EPIDEMIC

Evidence on Strategies for Addressing the Opioid Epidemic

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- A constellation of policies, interventions, and tools are available to reduce opioid-related harms while meeting the needs of patients with pain. These strategies include
  - Influencing prescribing practices ,
  - Public education regarding safe pain management,
  - OUD treatment,
  - Reducing harm (e.g., preventing fatal overdoses), and
  - Regulating lawful access to opioid products .

Influencing Prescribing Practices

Education

- Current efforts to improve pain education and knowledge about prescription opioid misuse and OUD among prescribers are inadequate.
- If educational efforts are not substantially improved and resourced across all health care disciplines – especially medicine, it will undermine efforts to reverse the opioid epidemic.
- Prescribing guidelines may be able to improve provider opioid prescribing behavior, but may be most effective when accompanied by enhanced education and other measures to establish basic competencies in pain management and opioid prescribing practices.
- **Recommendation 5-2. Establish comprehensive pain education materials and curricula for health care providers.** State medical schools and other health professional schools should coordinate with their state licensing boards for health professionals (e.g., physicians, nurses, dentists, pharmacists), the National Institutes of Health's Pain Consortium, the U.S. Food and Drug Administration, the Centers for Disease Control and Prevention, and the Drug Enforcement Administration to develop an evidence-based national approach to pain education encompassing pharmacologic and nonpharmacologic treatments and educational materials on opioid prescribing.

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Reimbursement

- Insurance-based policies have substantial potential to reduce the use of specific prescription drugs such as opioids, and improve the overall well-being and function of persons suffering from chronic painful conditions. However, their impact on health outcomes remains uncertain.

- Current reimbursement systems appear to have misaligned incentives effectively limiting behavioral, mental health, and other non-opioid approaches to pain management. The judicious deployment of insurer policies related to analgesics would benefit from a commensurate increase in coverage of and access to comprehensive pain management, encompassing both pharmacologic and non-pharmacologic modalities.

- **Recommendation 5-3. Facilitate reimbursement for comprehensive pain management.** Public and private payers should develop reimbursement models that support evidence-based and cost-effective comprehensive pain management encompassing both pharmacologic and nonpharmacologic treatment modalities.

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Prescription Drug Monitoring Programs

- PDMPs help address the opioid epidemic by enabling prescribers and other stakeholders to track prescribing and dispensing information.

- However, state laws differ widely with respect to health care provider and related agency's access to PDMP data and requirements for use. These data are therefore not being used to their full potential.

- **Recommendation 5-4. Improve the use of prescription drug monitoring program data for surveillance and intervention.** The U.S. Department of Health and Human Services, in concert with state organizations that administer prescription drug monitoring programs, should conduct or sponsor research on how data from these programs can best be leveraged for patient safety (e.g., data on drug–drug interactions), for surveillance of policy and other interventions focused on controlled substances (e.g., data on trends in opioid prescribing, effects of prescriber guidelines), for health service planning (e.g., data on discrepancies in dispensing of medications for treatment of opioid use disorder), and for use in clinical care (i.e., in clinical decision making and patient–provider communication).

Patient/Public Education

- The committee's recommended changes to provider education and payer policy should be accompanied by a change in patient expectations with respect to the treatment and management of chronic pain.

- **Recommendation 5-5. Evaluate the impact of patient and public education about opioids on promoting safe and effective pain management.** The nation's public health leadership, including the surgeon general, the Centers for Disease Control and Prevention, and heads of major foundations and professional organizations, should convene a body of experts in communication and in pain and opioid use disorder to evaluate the likely impact (and cost) of an education program designed to raise awareness among patients with pain and the general public about the risks and benefits of prescription opioids and to promote safe and effective pain management.

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MAT

- Use of medication in treatment is the standard of care for OUD, even for special populations such as pregnant and postpartum women. Although several efficacious medications for treatment of OUD are available, they are underutilized because of an array of factors, including insufficient numbers of providers eligible to provide OUD treatment, coverage barriers, and other limitations on access.

- **Recommendation 5-6. Expand treatment for opioid use disorder.** States, with assistance from relevant federal agencies, particularly the Substance Abuse and Mental Health Services Administration, should provide universal access to evidence-based treatment for opioid use disorder (OUD), including use of medication, in a variety of settings, including hospitals, criminal justice settings, and substance use treatment programs. Efforts to this end should be carried out with particular intensity in communities with a high burden of OUD. State licensing bodies should require training in treatment for OUD for all licensed substance use disorder treatment facilities and providers.

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- **Recommendation 5-7. Improve education in treatment of opioid use disorder for health care providers.** Schools for health professional education, professional societies, and state licensing boards should require and provide basic training in the treatment of opioid use disorder for health care providers, including but not limited to physicians, nurses, pharmacists, dentists, physician assistants, psychologists, and social workers.
- **Recommendation 5-8. Remove barriers to coverage of approved medications for treatment of opioid use disorder.** The U.S. Department of Health and Human Services and state health financing agencies should remove impediments to full coverage of medications approved by the U.S. Food and Drug Administration for treatment of opioid use disorder.

Harm Reduction

- Life-saving medication for treating opioid overdose is available. Provision of naloxone to overdose victims by laypersons or health professionals in the prehospital setting is the standard of care, and community-based programs and other first responder agencies adopted this protocol for treating opioid overdose as a harm reduction approach. The committee's recommendations convey the insistence upon low-cost, ready access to naloxone and unfettered access to sterile syringe equipment, to reduce harm:

- **Recommendation 5-9. Leverage prescribers and pharmacists to help address opioid use disorder.** State medical and pharmacy boards should educate and train their members in recognizing and counseling patients who are at risk for opioid use disorder and/or overdose, and encourage providers and pharmacists to offer naloxone when an opioid is prescribed to these patients or when a patient seeks treatment for overdose or other opioid-related issues.

- **Recommendation 5-10. Improve access to naloxone and safe injection equipment.** **S**tates should implement laws and policies that remove barriers to access to naloxone and safe injection equipment by
  - permitting providers and pharmacists to prescribe, dispense, or distribute naloxone to laypersons, third parties, and first responders and by standing order or other mechanism;
  - ensuring immunity from civil liability or criminal prosecution for prescribers for prescribing, dispensing, or distributing naloxone, and for laypersons for possessing or administering naloxone;
  - permitting the sale or distribution of syringes, exempting syringes from laws that prohibit the sale or distribution of drug paraphernalia, and explicitly authorizing syringe exchange.

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Interventions by the Food and Drug Administration

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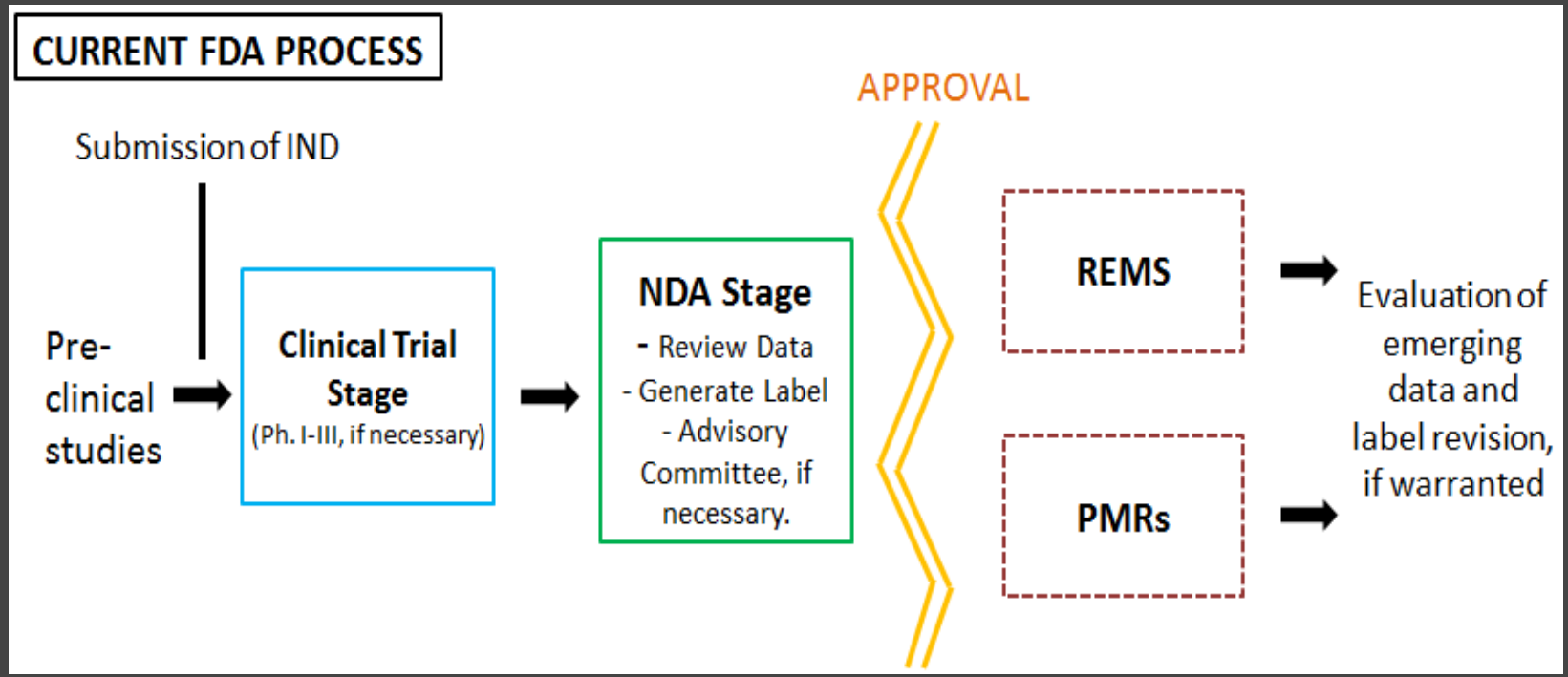
Current FDA approval process



Pre-approval Testing

- Testing in subpopulations at high risk of harmful outcomes, including those in locations of the country with high rates if misuse, OUD, or diversion
  - Including patients with mental health disorders, OUD, and other populations in which opioid drugs are known to be widely used
- Measuring outcomes reported by household members or other third parties expected to be affected by the product
  - Understanding interactions with other drugs commonly used with opioids or by people who use opioids illicitly
  - Seeking out non-traditional data sources

Approval Process: Integrating Public Health Considerations

- Current model:

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

Approval Process: Integrating Public Health Considerations

- New model:

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Characteristics of opioid		
How opioid fits among currently available pain treatment options		
Benefits observed in clinical trials, overall • To patients • Public health		
Risks observed in clinical trials, overall • To patients • Public health		
Predicted benefits/risks to families of patients		
Predicted benefits/risks to society, overall • Special communities • Subpopulations		
Diversion potential		
Predicted effects on use of other opioids or illicit drugs		
Risk management, overall • Potential for off-label use • Advertising/promotion		

Post-approval Monitoring

- Evidence-based strategies to influence safe and appropriate prescribing and dispensing practices (REMS, labeling, etc.)
- Re-evaluate after 1, 4, and 7 years
- Restricting advertising and promotion
- Active post-approval monitoring via Sentinel and other systems
- "Opioid Study Implementation"
  - Evaluation of approved indication, labeling, oversight systems, formulations

Recommendations: Opioid Exceptionalism

1. Incorporate public health considerations into opioid-related regulatory decisions
2. Require additional studies and the collection and analysis of data needed for thorough assessment of broad public health considerations
3. Ensure public health considerations adequately incorporated into clinical development
4. Increase transparency of regulatory decisions for opioids
5. Strength post-approval oversight of opioids
6. Conduct full review of currently marketed/approved opioids
7. Apply public health considerations to opioid scheduling decisions

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