

External Review of FDA Regulation of Opioid Analgesics

Final Report

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AUJ	1,822	12,349,000
EJK	3,400	238,681,000
HCL	1,362	85,678,000
KEE	465	8,349,000
NAH	8,569	189,301,000
OSP	6,502	102,698,000
TKK	890	24,697,000
WIG	6,280	76,002,000
AHD	2,434	57,610,000



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Table of Contents

Executive Summary	1
I. Introduction	3
A. Aim and Scope of the Report	4
B. Terminology	5
C. Abbreviations	6
II. Background on FDA’s Drug Authorities	7
III. FDA’s Approach to Opioid Analgesic Regulation	10
A. OxyContin	10
B. Opana ER	15
C. Zohydro ER	16
D. Dsuvia	18
E. Hydexor	20
F. Evolution of FDA’s Approach	22
IV. Generating Evidence about Opioid Analgesics	23
A. Actions to Implement NASEM Report Recommendations	23
B. Recommendations for Additional Actions	28
V. Opioid Analgesic Approvals (and Withdrawals of Approvals)	31
A. Actions to Implement NASEM Report Recommendations	31
B. Recommendations for Additional Actions	34
VI. Post-Approval Oversight of Opioid Analgesics	38
A. Actions to Implement NASEM Report Recommendations	39
B. Recommendations for Additional Actions	41
VII. Transparency	46
A. Actions to Implement NASEM Report Recommendations	46
B. Recommendations for Additional Actions	48
References	52
Appendix A: NASEM Report Recommendations Included in Review	A-1
Appendix B: List of Key Regulatory Decisions Included in Review	B-1
Appendix C: Example FDA Actions to Implement NASEM Recommendations	C-1
Appendix D: Biographical Sketches of Subject Matter Experts	D-1

Executive Summary

For over two decades, the overdose crisis has had staggering effects on the lives of the people in the United States. In 2021, a record high 107,000 people died from drug overdose—with a majority of those deaths involving opioids—and few, if any, U.S. communities remain untouched by the crisis (CDC, 2022c). Addressing the drug overdose crisis, and its varied root causes, while also ensuring that prescription opioids are available for the evidence-based management of pain, will require multiple policy tools, and long-term, comprehensive, and coordinated efforts from a wide range of stakeholders and regulators, including the U.S. Food and Drug Administration (FDA) (Chen et al., 2019; Dasgupta et al., 2018; HHS, 2021).

FDA is a public health agency (Hamburg & Sharfstein, 2009). Consistent with its public health mission, FDA has identified advancing its efforts to address the opioid crisis as one of its highest priorities. As part of these efforts, in 2016 the agency requested that the National Academies of Sciences, Engineering, and Medicine (NASEM) convene a committee to inform an agency reassessment of its benefit-risk framework for prescription opioids. In the report that the NASEM Committee issued in 2017, it advised that FDA use “a comprehensive, systems approach for incorporating public health considerations into its current framework for making regulatory decisions regarding opioids,” and provided additional recommendations for implementing this central advice in specific aspects of FDA’s prescription drug regulatory scheme (National Academies of Sciences, 2017).

FDA is now seeking to evaluate the progress that it has made in implementing the NASEM Committee’s 2017 recommendations, as part of its ongoing public health work on substance use and overdose prevention. In this report, we, the subject matter experts listed below, provide an external review of FDA’s implementation of the NASEM recommendations and of key FDA regulatory policies and decisions regarding opioid analgesics. Based on that review, this report provides actionable recommendations for FDA’s consideration, with the aim of helping the agency continue to improve its regulatory decision-making to support appropriate use of opioid analgesics.

We found that, over the last five and a half years, FDA has made clear, important progress on implementing the NASEM Committee’s recommendations across the board. Even with this progress, however, FDA has recognized that the drug overdose crisis is dynamic in nature and there is—and, for the foreseeable future, there will continue to be—more work to be done (FDA, 2022f). With the need for sustained attention to the evolving crisis in mind, we offer three overall recommendations:

- FDA should continue its efforts to comprehensively implement the recommendations in the 2017 NASEM Report, including evaluating scientifically-sound, inclusive study designs to inform a systems approach for regulatory decision-making that incorporates public health considerations.
- FDA should consider seeking from Congress certain additional authorities regarding opioid analgesic approvals and its review of the advertising and promotion for such products, as well as additional resources to implement such authorities, to strengthen the agency’s oversight of prescription opioid analgesics.

- FDA should be as transparent as possible regarding its decision-making for opioid analgesics, as increased transparency can encourage appropriate uses of prescription opioid analgesics, promote innovation in pain management and prevention of opioid use disorder, and enhance public trust.

No matter what the agency does, FDA action alone will not comprehensively address the complex, intertwining public health challenges presented by the drug overdose crisis and the medical, social, and economic consequences of pain. But the agency’s continued efforts to advance its regulatory approach to opioid analgesics are a critical component of a broader government strategy to mitigate the drug overdose crisis, and crucial to realizing FDA’s public health mission. While implementing the recommendations in this report may require substantial resources and time, our hope is that the findings and recommendations in this report will help FDA further strengthen its response to the overdose epidemic and its oversight of prescription opioid analgesics.

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I. Introduction

The opioid crisis is one of the most pressing public health challenges facing the United States. In 2021, over 107,000 people in the United States died from drug overdose—a record number—with over 80,000 of those deaths involving illicit or prescription opioids (CDC, 2022c). Studies have indicated that the increase in overdose death rates in recent years (2019 to 2020) have been disproportionately high among Black, Hispanic, and American Indian or Alaska Native people (CDC, 2022b; B. Han et al., 2022; Larochelle et al., 2021; SAMHSA, 2020). And deaths alone do not fully tell the story of the toll of the opioid crisis. In 2019, over 9.7 million people aged 12 years and older “misused” prescription opioid analgesics, and about 1.6 million people in the United States had an opioid use disorder (OUD) (SAMHSA, 2020). The potential economic cost of the opioid crisis to US society is astronomical; more than 1 trillion dollars is lost annually due to the opioid crisis (Florence et al., 2021; PEW, 2021).

At the same time, pain—including chronic pain—is a complex, widespread health condition, often treated with opioids, that has significant impacts on people’s health and lives. According to the Centers for Disease Control and Prevention (CDC), in 2019 20.4% people in the United States experienced chronic pain, with 7.4% experiencing high-impact chronic pain that frequently limited life or work activities (CDC, 2020), while disparities in pain treatment persist across many factors, including race/ethnicity, gender, socioeconomic status, and population density (Dowell et al., 2022). Pain also has a substantial economic impact, with a 2011 Institute of Medicine report estimating that chronic pain costs between \$560 to \$635 billion in annual direct medical costs, lost productivity, and disability (Institute of Medicine, 2011). Adequate treatment of pain, whether acute or chronic, is a vital component of equitable and appropriate health care (Bonnie et al., 2019; Dineen, 2016; National Academies of Sciences, 2017).

The public health challenge, accordingly, involves both addressing the overdose crisis and mitigating the myriad individual and public health risks of opioids, while also ensuring that safe and effective pain treatments are available for patients who need them. FDA’s authority to regulate prescription opioid analgesics throughout the drugs’ lifecycles is one critical tool for meeting this challenge.

As the epidemic of opioid-related overdose, and scientific understanding of this crisis, have both evolved over the years, FDA’s approach to regulating opioid analgesics likewise has evolved. To help inform the agency’s approach, in 2016 FDA requested that the National Academies of Sciences, Engineering, and Medicine (NASEM) convene a committee “to update the state of the science on pain research, care, and education” and “to identify actions the FDA and other organizations can take to respond to the opioid epidemic” (National Academies of Sciences, 2017). Although the safety and effectiveness of many drugs can be adequately assessed based on the benefits and risks of the drug as shown in the preapproval clinical trials and, after approval, when used according to the FDA-approved labeling, opioid analgesics have important effects that are not reflected in such information. Accordingly, in the 2017 report that resulted from the NASEM Committee’s work (the 2017 NASEM report), the central advice for FDA, in Recommendation 6-1, was that the agency use “a comprehensive, systems approach for incorporating public health considerations into its current framework for making regulatory decisions regarding opioids.” The

Committee’s other recommendations for FDA provided advice on how the agency can implement this comprehensive systems approach in specific areas of its regulatory authority. Since the report was published, FDA has continued to adapt its approach to overseeing opioid analgesics to address the NASEM committee’s recommendations, to implement changes to the agency’s statutory authorities, and to reflect new scientific information.

Yet, how the agency can and should oversee prescription opioid analgesics to best serve public health remains a particularly difficult regulatory question, given the products’ clear benefits for certain patients in certain circumstances, but also their clear risks to patients, families, and communities and their widespread effects on society and public health. Against this background, FDA commissioned this report to obtain an external review of the agency’s regulation of opioid analgesics.

A. Aim and Scope of the Report

We were asked to conduct a review of FDA’s implementation of the recommendations in the 2017 NASEM report (Appendix A) and of key regulatory policies and decisions made by the agency (Appendix B), to provide forward-looking lessons learned and actionable recommendations regarding FDA’s regulatory decisions for opioid analgesics. This report first provides background on FDA’s drug authorities and, based on a review of key, and controversial, FDA regulatory actions on prescription opioid analgesics, an overview of how FDA’s use of its authorities in the context of opioid analgesics has evolved over time. Then, organized around various areas of focus in the NASEM Committee’s recommendations (evidence generation, approval decisions, post-approval oversight, and transparency), this report describes (a) actions that FDA has taken to implement relevant recommendations from the 2017 NASEM report and (b) suggestions for actions to further implement recommendations from the 2017 NASEM report and strengthen FDA oversight of opioid analgesics, drawing on the review of key regulatory actions.

This report focuses on prescription opioid products approved for pain relief (*i.e.*, opioid analgesics). Opioid products approved for other indications (*e.g.*, the treatment of OUD), products approved for emergency treatment of known or suspected opioid overdose (*e.g.*, naloxone), non-opioid products to treat pain, and illicit drugs are generally outside the scope of this report, though such products and issues may be discussed where relevant to understanding FDA’s regulatory decision-making for prescription opioid analgesics.

To develop this report, five subject matter experts (Appendix D) reviewed laws, regulations, publicly-available FDA documents, publicly-available documents from other relevant agencies (*e.g.*, CDC), publicly available Congressional documents (*e.g.*, bills, and letters and statements from members of Congress), the 2017 NASEM report, media reports regarding FDA regulation of opioid analgesics, and research published in health sciences and law journals regarding FDA regulation of opioid analgesics. Our approach was framed around the following questions, which we applied to each relevant recommendation in the NASEM report¹:

¹ Appendix A provides the full text of each NASEM Report recommendation included in the review.

- Why was the recommendation made?
- What actions has FDA taken in response to the NASEM Report’s recommendation?
- What additional actions could FDA take to further comprehensively address the recommendations in the NASEM Report and strengthen the agency’s regulation of opioid analgesics?

We assumed that a NASEM Report recommendation has been addressed by FDA if the agency has taken action on a specific product and/or has taken a general regulatory action (*e.g.*, issued guidance or held public meetings/workshops) consistent with the NASEM Report recommendation. This report provides representative, but not exhaustive, examples of such FDA actions (Appendix C).² Although FDA did not provide input on this report’s assessments of the agency’s progress toward implementing the NASEM Report recommendations nor on recommendations offered in this report, FDA provided factual corrections on portions of this report, which were incorporated as appropriate.

B. Terminology

Over the past decade, increased attention has been paid to the language used to describe people who use drugs, people with substance use disorders, and substance use disorders (National Academies of Sciences, 2017). Studies have found that the use of stigmatizing terms negatively affects health care decision-making about people who use drugs (Kelly et al., 2010; Kelly & Westerhoff, 2010; Saitz et al., 2021; van Boekel et al., 2013), and the Office of National Drug Control Policy (ONDCP) and the American Society of Addiction Medicine (ASAM) have provided recommendations for humanizing, non-stigmatizing, and medically-precise terminology (ONDCP, 2017; Saitz et al., 2021).³ This report uses terminology consistent with the ONDCP and ASAM recommendations and avoids stigmatizing terms, such as “abuse,” unless directly quoting sources that use those terms or referring to “abuse-deterrent formulations” of opioid analgesics (*e.g.*, formulations with properties to prevent crushing or dissolving the drug for insufflation or injection).

² For the agency’s own extensive list of its activities and significant actions addressing opioid misuse, see FDA, Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse, <https://www.fda.gov/drugs/information-drug-class/timeline-selected-fda-activities-and-significant-events-addressing-opioid-misuse-and-abuse>.

³ Other groups, such as the Health Justice in Action Lab at Northeastern University School of Law, have also made similar recommendations. The Health Justice in Action Lab. Changing the Narrative. Words Matter. <https://www.changingthenarrative.news/stigmatizing-language>.

C. Abbreviations

AADPAC	Anesthetic and Analgesic Drug Products Advisory Committee
ADF	Abuse-Deterrent Formulation
ANDA	Abbreviated New Drug Application
ASAM	American Society of Addiction Medicine
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CRL	Complete Response Letter
DEA	Drug Enforcement Administration
DSaRM	Drug Safety and Risk Management Advisory Committee
EERW	Enriched Enrollment Randomized Withdrawal
ER/LA	Extended Release/Long-Acting
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
FDCA	Federal Food, Drug, and Cosmetic Act
GAO	Government Accountability Office
HHS	Department of Health & Human Services
HIV	Human Immunodeficiency Virus
IND	Investigational New Drug Application
IR	Immediate Release
NASEM	National Academies of Science, Engineering, and Medicine
NDA	New Drug Application
NIH	National Institutes of Health
ONDCP	Office of National Drug Control Policy
ODU	Opioid Use Disorder
PMR	Postmarketing Requirement
REMS	Risk Evaluation and Mitigation Strategy
SAMHSA	Substance Abuse and Mental Health Services Administration
SUPPORT	Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act of 2018
TIRF	Transmucosal Immediate Release Fentanyl

II. Background on FDA’s Drug Authorities

FDA is a science-based public health agency (Hamburg & Sharfstein, 2009). Section 1003(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) describes FDA’s public health mission with respect to drugs as two-fold: the agency “protect[s] the public health by ensuring that . . . drugs are safe and effective” and it “promote[s] the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner.”⁴ To those ends, FDA is responsible for ensuring the safety, effectiveness, and quality of drugs, advancing public health by helping to speed innovations that make drugs more effective, safer, and more affordable, and helping health care professionals and the public get the accurate, science-based information that they need to safely and effectively use medical products (FDA, 2021g).

Perhaps the most well-known mechanism through which FDA accomplishes this mission is its approval authority. A new drug usually cannot be marketed in the United States until and unless FDA approves it.⁵ To approve a new drug application (NDA), FDA must determine that the drug is safe and effective for its proposed indication (that is, that the drug’s benefits outweigh its risks), the drug’s labeling is truthful and non-misleading, and manufacturing methods are adequate to assure the drug’s identity, strength, quality, and purity.⁶ Accordingly, NDAs must contain a wide range of information about the drug, including data to show that the drug is safe and “substantial evidence” that the drug is effective, which typically consists of one or two “adequate and well-controlled” clinical investigations conducted by the drug’s manufacturer.⁷ For certain drugs, the agency’s benefit-risk assessment incorporates broader public health considerations, such as risks related to misuse, accidental exposure, or disease transmission (FDA, 2021b; Lurie & Sharfstein, 2021). The NDA approval standard, however, does not generally require a showing that a new drug is *more effective* or *safer* than currently available drugs.

The process of developing information sufficient to support NDA approval generally starts with the manufacturer conducting preclinical laboratory and animal testing. If the results of preclinical testing support conducting clinical trials in humans, the manufacturer submits an Investigational New Drug application (IND) to FDA.⁸ An IND helps ensure that the proposed research includes sufficient protections for participants and that study designs are adequate to produce information about the drug’s effects. Once the IND goes into effect—30 days after FDA receives it, unless the agency informs the manufacturer otherwise—the manufacturer may proceed with conducting clinical trials. The research then usually goes forward sequentially in Phase I, II, and III trials, which involve increasing numbers of subjects as the safety (initially studied in Phase

⁴ 21 U.S.C. § 393(b).

⁵ *Id.* § 331, 355(a).

⁶ *Id.* § 355(d).

⁷ *Id.*

⁸ *Id.* § 355(i); 21 C.F.R. §§ 312.1, 312.20. “Manufacturer” generally refers to an entity engaged in drug manufacturing, preparing, propagating, compounding, processing, packaging, or labeling, while “sponsor” is defined in FDA regulations for INDs as the entity that takes responsibility for and initiates a clinical investigation. 21 C.F.R. § 312.3. Although a drug’s manufacturer is not always the IND sponsor, manufacturers are frequently the sponsors of INDs covering investigational opioid analgesics. Accordingly, for simplicity, we generally use the term “manufacturer.”

I, further studied in Phases II, III) and efficacy (primarily Phases II, III) of the investigational drug are studied.⁹ While manufacturers are responsible for designing and conducting trials, manufacturers can, and frequently do, consult with FDA regarding trial design and outcomes at various times throughout the process (FDA, 2017c).

If research supports a conclusion that a drug is safe and effective for its intended use, there are two types of NDAs that might be submitted (FDA, 2019a).¹⁰ Many NDAs contain full reports of investigations of safety and effectiveness that were conducted by or for the manufacturer or for which the manufacturer has a right of reference. NDAs also may be “505(b)(2) applications,” which likewise contain full reports of investigations of a drug’s safety and effectiveness, but at least some of the information in a 505(b)(2) application comes from studies *not* conducted by or for the drug’s manufacturer and for which the manufacturer does *not* have a right of reference. Such 505(b)(2) applications have been used to obtain approval of numerous opioid analgesic reformulations or dosing changes (Heyward, Moore, et al., 2020).

Once a drug is approved, FDA continues to oversee drug safety and effectiveness through various means. FDA monitors information about marketed drugs’ safety and effectiveness through receiving adverse event reports required to be submitted by manufacturers (and voluntarily submitted by patients and health care professionals), actively surveying drug effects through FDA’s Sentinel Initiative, and reviewing data coming from postmarketing registries, observational studies, or trials that manufacturers either agree to conduct or are required by FDA to conduct (FDA, 2022h; National Academies of Sciences, 2017).

FDA also has tools to help ensure that the public has accurate information about marketed drugs. FDA approval of an NDA includes approval of drug labeling. After approval, the manufacturer is responsible for keeping the labeling up-to-date and FDA also may require changes to drug labeling based on new information.¹¹ When labeling changes related to safety are made after approval—or when otherwise necessary to inform health care professionals and the public about new safety issues associated with drugs—FDA may issue drug safety communications (Cortez, 2011; FDA, 2022e).¹² Additionally, FDA monitors and regulates manufacturers’ advertising and promotion of their approved prescription drugs to help ensure that such communications are truthful and non-misleading (FDA, 2022o).¹³

In addition to monitoring the risks of approved drugs, requiring post-approval studies, issuing agency communications about drugs’ effects, and overseeing manufacturer

⁹ 21 C.F.R. § 312.21.

¹⁰ There is also a pathway for approval that involves submitting an abbreviated new drug application (ANDA) for a generic drug product. 21 U.S.C. § 355(j). Instead of including preclinical and clinical data to establish safety and effectiveness as an NDA would, an ANDA must include scientific information sufficient to demonstrate that the generic drug product is bioequivalent to the relevant reference-listed drug (*i.e.*, that the generic drug performs in the same manner as the innovator drug). This report’s analysis, however, is limited to FDA decision-making for NDAs—for which the agency is assessing full reports of safety and effectiveness information regarding opioid analgesics—and we do not generally further discuss ANDAs.

¹¹ 21 U.S.C. § 505(o)(4); 21 C.F.R. § 201.57.

¹² 21 U.S.C. § 375.

¹³ *Id.* §§ 321(n), 352. 21 C.F.R. § 202.1.

communications, at the time of approval (or after approval), FDA may require a Risk Evaluation and Mitigation Strategy (REMS).¹⁴ REMS are risk mitigation programs for drugs that FDA can require drug manufacturers to implement when such a program is necessary to ensure a drug's benefits outweigh its risks. Some REMS cover a single drug product, as the Dsuvia (sufentanil) REMS does. Others are “shared system” REMS covering multiple drug products and multiple drug manufacturers, including in some instances entire classes of drug products, as the Opioid Analgesic REMS does. A REMS may include a Medication Guide, a patient package insert, and/or a communication plan, as well as tools known as “elements to assure safe use” (ETASU) that, among other things, may require manufacturers to ensure that drug prescribers or dispensers have special training (*e.g.*, about the risks of misuse and overdose associated with opioids), that the drug is dispensed only in certain settings (*e.g.*, only in a hospital inpatient setting), or that certain tests results are documented before a drug is dispensed (*e.g.*, a negative pregnancy test for a drug known to cause birth defects) (FDA, 2023a). Additionally, every REMS for a drug marketed under an NDA must include a timetable for the submission of the manufacturer's assessments of the REMS, which are intended to evaluate whether a REMS is meeting its risk mitigation goals.

The FDCA also authorizes FDA to withdraw the agency's approval of an NDA for a marketed drug in various circumstances.¹⁵ For instance, similar to the approval standard, the agency may withdraw approval of an NDA if it finds that “scientific data” or “new evidence of clinical experience not contained in the application” show that the drug is unsafe, or, if considering new evidence as well as the evidence included in the NDA, the agency finds there is a lack of substantial evidence of effectiveness.¹⁶ Although the FDCA authorizes FDA to withdraw approval of an NDA without the manufacturer's agreement, FDA may also withdraw approval of an NDA at the request of the manufacturer.

But, in most cases when a manufacturer stops selling a drug, it does not involve FDA withdrawing approval of the NDA. Manufacturers often agree to FDA requests that they cease marketing a product for safety or effectiveness reasons, they sometimes decide to cease marketing for such reasons on their own, or they sometimes decide to cease marketing for reasons unrelated to safety or effectiveness.

At various points throughout the lifecycle of a drug, FDA may obtain independent expert advice on the scientific issues associated with the drug from its advisory committees (FDA, 2021a).¹⁷ For instance, FDA might seek recommendations from an advisory committee on proposals to approve, or withdraw approval of, an NDA, or on its evaluation of whether a REMS is necessary to approve a given drug or sufficiently mitigates the serious risks of a marketed drug. For opioids analgesics, FDA generally consults its Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and, often, also its Drug Safety and Risk Management Advisory

¹⁴ 21 U.S.C. § 355-1.

¹⁵ *Id.* § 355(e).

¹⁶ *Id.* § 355(e); 21 CFR § 314.150.

¹⁷ 5 U.S.C. app.; 41 C.F.R. § 101-6, 102-3; 21 C.F.R. part 14.

Committee (DSaRM) (FDA, 2022d, 2022a). Advisory committee meetings are generally open to the public, and materials presented to advisory committees are publicly available.¹⁸

III. FDA’s Approach to Opioid Analgesic Regulation

In order to illustrate how FDA has used its various authorities described in the Background section to regulate opioid analgesics, this section briefly summarizes certain FDA actions regarding five opioid analgesic products: OxyContin (oxycodone hydrochloride), Opana ER (oxymorphone hydrochloride), Zohydro ER (hydrocodone bitartrate), Dsuvia (sufentanil), and Hydexor (hydrocodone, acetaminophen, promethazine).¹⁹ As the discussion below demonstrates, FDA’s approach to opioid analgesic regulatory decision-making—including for approvals, labeling, REMS, advertising and promotion oversight, and the use of advisory committees—has sometimes been controversial. The agency’s approach also has evolved over time, as the opioid crisis and scientific understanding of the public health impacts of opioid analgesics likewise have evolved. A key part of the evolution in FDA’s approach has been the agency’s growing efforts to more clearly incorporate a broad perspective on the benefits and risks of opioid analgesics into its regulatory decision-making, including through asking its advisory committees to consider the public health risks related to misuse of and accidental exposure to specific opioid analgesics, citing the public health consequences of misuse in agency actions related to currently marketed opioid analgesics and NDAs for novel products, and discussing such issues in the agency’s public communications about its actions on opioid analgesic products.

A. *OxyContin*

The public understands, and research has suggested, that the marketing and use (including misuse) of OxyContin was a key factor in the emergence and acceleration of the opioid overdose crisis (Alpert et al., 2022). This section briefly summarizes some key FDA regulatory decisions relating to OxyContin, dating back to its initial approval in 1995. Because it is generally outside the scope of this review, this section does not review other important legal and regulatory developments related to OxyContin, including the civil and criminal litigation against Purdue Pharma LP (Purdue Pharma) and its executives, or the settlements and plea agreements that have resulted from such litigation.²⁰

¹⁸ 21 C.F.R. part 14.

¹⁹ This section does not seek to present fully comprehensive accounts of all FDA actions for each of these products. Rather, it highlights certain actions relevant to generally understanding FDA’s overall, and evolving, approach to opioid analgesics.

²⁰ The disclosure of more than 2 million pharmaceutical industry documents (from Purdue Pharma and others) as a result of legal settlements presents an unprecedented opportunity for FDA, and others, to study how the agency’s decisions were understood and acted upon by Purdue Pharma and other opioid analgesic manufacturers. University of California San Francisco, Opioid Industry Documents, <https://www.industrydocuments.ucsf.edu/opioids/>.

On December 12, 1995, FDA approved an NDA for OxyContin (oxycodone hydrochloride extended release tablets) submitted by Purdue Pharma (FDA, 1995). OxyContin was first offered in 10mg, 20mg, and 40mg doses; it was later offered in 80mg, and 160mg doses as well (FDA, 2022k).²¹ At the time of approval, FDA believed that approval of OxyContin would expand access to effective analgesics for those experiencing pain, and it thought the “controlled-release formulation of OxyContin would result in *less* abuse potential, since the drug would be absorbed slowly [in comparison to then-available oxycodone formulations that required more frequent dosing] and there would not be an immediate ‘rush’ or high that would promote abuse” (FDA, 2022p).

Following OxyContin’s approval, Purdue Pharma “conducted an extensive campaign to market and promote OxyContin using an expanded sales force and multiple promotional approaches to encourage physicians, including primary care specialists, to prescribe OxyContin as an initial opioid treatment for noncancer pain” (GAO, 2003), and sales grew from \$48 million in 1996 to more than \$1 billion in 2000 (Van Zee, 2009). Purdue Pharma downplayed the risks of addiction and misuse of OxyContin in its promotional efforts, but misuse of OxyContin escalated rapidly as sales increased (Van Zee, 2009). According to FDA, “the number of people who admitted to using OxyContin for non-medical purposes increased dramatically from approximately 400,000 in 1999 to 1.9 million in 2002 and to 2.8 million in 2003” (FDA, 2022p).

In a 2003 report, the U.S. Government Accountability Office (GAO) subsequently identified numerous factors that may have contributed to the extensive misuse of OxyContin. Among others, it noted that “the safety warning on the label that advised patients not to crush the tablets because a rapid release of a potentially toxic amount of the drug could result—a customary precaution for controlled-release medications—may have inadvertently alerted [people] to a possible method for misusing the drug” (GAO, 2003). The GAO report also explained that the Drug Enforcement Administration (DEA) concluded that OxyContin was targeted for diversion and misuse “because the tablet contained larger amounts of active ingredient and the controlled-release formulation was easy . . . to compromise” (GAO, 2003).

In 2001, FDA approved a revision to OxyContin’s labeling. The approved indication changed from “moderate to severe pain where use of an opioid analgesic is needed for more than a few days” to “management of moderate to severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time” (FDA, 2022p). FDA also added warnings to OxyContin’s labeling indicating that “Oxycodone is an opioid agonist of the morphine-type [and such] drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion,” and that “Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit” (GAO, 2003).²² At the same time, Purdue Pharma agreed to

²¹ FDA approved a supplemental application for the 80mg strength in January 1997, and for the 160 mg strength in March 2000. The 160 mg strength was only available for about a year. A 2003 GAO report explained that, “[i]n April 2001, Purdue [Pharma] discontinued distribution of the 160-milligram tablets because of OxyContin abuse and diversion concerns.” GAO. (2003). OxyContin Abuse and Diversion and Efforts to Address the Problem. <https://www.gao.gov/assets/gao-04-110.pdf>.

²² The new labeling also highlighted that the 80mg and 160mg strengths were “FOR USE IN OPIOID-TOLERANT PATIENTS ONLY” (emphasis in original).

implement a Risk Management Program (RMP) to mitigate the risks of OxyContin misuse, which including issuing a “Dear Healthcare Provider” letter about the labeling changes (FDA, 2022p).²³

FDA viewed the 2001 labeling change as narrowing the indication for OxyContin (FDA, 2022k). However, Purdue Pharma’s internal documents (subsequently released through litigation) show that the company viewed FDA’s action as “expand[ing] the indication” in a way that “created enormous opportunities,” because it applied generally to “any patient with moderate to severe around-the-clock persistent pain” (emphasis added) (Purdue Pharma, 2002).²⁴ The company’s internal assessment noted that the indication might “give OxyContin a competitive advantage” because “[t]his broad labeling is likely to never again be available for an opioid seeking FDA approval” (Purdue Pharma, 2002).

In the early 2000s, FDA also issued both an Untitled Letter and a Warning Letter that identified concerning violations in Purdue Pharma’s advertising and promotion of OxyContin (GAO, 2003).²⁵ More specifically, in May 2000, FDA issued an Untitled Letter to Purdue Pharma identifying several problems in an advertisement for OxyContin in a medical journal, including that the advertisement mischaracterized the patient population in which OxyContin had been studied and suggested, without support, that OxyContin could be used as the initial treatment for osteoarthritis pain. In January 2003, FDA sent a Warning Letter to Purdue Pharma regarding two advertisements for OxyContin in the *Journal of American Medical Association (JAMA)* that, according to FDA, “grossly overstate[d] the safety profile of OxyContin” (FDA, 2003). The advertisements in *JAMA* omitted information about the boxed warnings on OxyContin’s misuse and addiction potential, as well as information about the limits of OxyContin’s indication.

²³ Before Congress amended the FDCA in 2007 to authorize FDA to require REMS, FDA sometimes asked drug manufacturers to develop risk mitigation programs known as RMPs or Risk Minimization Action Plans (RiskMAPs). FDA, FDA’s Role in Managing Medication Risks, <https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/fdas-role-managing-medication-risks>.

²⁴ Though Purdue Pharma apparently saw the labeling change as broadening the indication, the indication approved in 1995 was similarly not limited to patients suffering from any particular source of pain.

²⁵ Warning Letters are issued for “violations of regulatory significance,” and are issued in part to achieve prompt voluntary compliance from individuals and firms. Untitled Letters are issued for violations that not meet the threshold of regulatory significance. FDA, Regulatory Procedures Manual §§ 4-1, 4-2, <https://www.fda.gov/media/71878/download>.

Consistent with FDA’s general practice in Warning Letters, the Warning Letter instructed Purdue Pharma to cease disseminating the *JAMA* advertisements and any similar campaigns, and to develop a plan for sharing corrective information with the audiences that received the misleading advertisements (*i.e.*, health care professionals). Purdue Pharma characterized the advertisements as “the result of an honest misunderstanding” about how risk information and warnings should be presented and ultimately it suspended the advertisements (“FDA Warns OxyContin Maker Over Ads,” 2003). In subsequent communication between FDA and Purdue Pharma, additional website-based violations were noted on a Purdue Pharma site called “Partners Against Pain.” Purdue Pharma responded by voluntarily removing the sections of concern (GAO, 2003).²⁶

In April 2010 FDA approved a reformulated version of OxyContin that was developed with properties intended to resist tampering for the purposes of insufflation or intravenous misuse (FDA, 2010a). As part of the approval, Purdue Pharma was required to conduct postmarketing studies about how successful the new formulation was in reducing misuse, as well as to implement a REMS, the main feature of which was prescriber education. In July 2012 FDA extended the REMS requirement to all extended release/long-acting (ER/LA) opioid analgesics, to form in a class-wide REMS for those products (FDA, 2023b). On April 16, 2013, FDA approved a supplemental application for the reformulated version of OxyContin allowing changes to the labeling to describe the product as an abuse-deterrent formulation (ADF) (FDA, 2013b). This was based on FDA’s review of “in vitro, pharmacokinetic, clinical abuse potential and postmarketing study data.”²⁷

Shortly after approving labeling describing the reformulated version of OxyContin as abuse-deterrent, FDA determined that the original version of OxyContin was withdrawn from sale for reasons of safety or effectiveness (and thus the agency would not accept or approve ANDAs for generic products referencing the original formulation of OxyContin).²⁸ When compared with original OxyContin, FDA concluded that the reformulation “resist[s] crushing, breaking, and dissolution using a variety of tools and ... when subjected to an aqueous environment, reformulated OxyContin gradually forms a viscous hydrogel ... expected to make abuse via injection difficult and ... reduce abuse via the intranasal route.”²⁹ Subsequently, in August 2013, FDA announced withdrawal of approval of the NDA for original OxyContin at the request of Purdue Pharma.³⁰

²⁶ In addition to these Untitled and Warning Letters, the federal government, with FDA’s participation in the relevant investigation, later prosecuted Purdue Pharma and three of its top executives for criminal violations arising from various promotional activities that the U.S. Attorney for the Western District of Virginia described as “a fraudulent marketing campaign that promoted Oxycontin as less addictive, less subject to abuse, and less likely to cause withdrawal.” In 2007 Purdue Pharma and the three executives plead guilty to felony misbranding. News Release United States Attorney’s Office Western District of Virginia (May 10, 2007), <https://www.health.mil/Reference-Center/Publications/2007/05/10/The-Purdue-Frederick-Company-Inc-and-Top-Executives-Plead-Guilty>.

²⁷ 78 Fed. Reg. 23273 (Apr. 18, 2013).

²⁸ Purdue Pharma notified FDA in August 2010, after initial approval of the reformulated version of OxyContin, that it had ceased distributing the original version. *Id.*

²⁹ *Id.*

³⁰ 78 Fed. Reg. 48177 (Aug. 7, 2013).

Though the reformulation of OxyContin reduced the drug’s misuse through non-oral routes, some studies suggest that it also had significant unintended consequences, as people who had been misusing OxyContin switched to using heroin or other illicit drugs (Cicero et al., 2012; Evans et al., 2019; Powell & Pacula, 2021). Deaths from heroin overdoses rose substantially and steadily between 2011 and 2015 after approval of the reformulation (NIDA, 2022). Research by FDA authors, however, found no evidence that the reformulation of OxyContin contributed to increases in heroin use or heroin use disorder (Wolff et al., 2020).

Against the background of scientific questions about the relationship between the reformulation of OxyContin and illicit drug use, FDA continued to monitor the abuse-deterrent benefits of the reformulated version OxyContin in the years after 2013. In October 2014, Purdue Pharma requested a labeling change to promote the benefits of the ADF OxyContin (FDA, 2020c). An Advisory Committee meeting was scheduled in July 2015 to review the postmarketing studies submitted to support the proposed labeling change, and FDA’s Center for Drug Evaluation and Research (CDER) prepared briefing materials for Committee members. In June 2015 these materials were given to Purdue Pharma, which subsequently requested that the supplement proposing the labeling change be withdrawn. As a result, the Advisory Committee meeting was canceled, and there was no public discussion of the supplement or the supporting studies.

In 2016, FDA then issued a postmarketing requirement (PMR) letter to Purdue Pharma requiring studies to evaluate whether reformulated OxyContin prevented misuse and related complications (FDA, 2020c). In September 2019 Purdue Pharma submitted the final study required by the March 2016 letter. In September 2020, FDA convened a joint meeting of DSaRM and AAPDAC to discuss findings of the required postmarketing studies evaluating the success of reformulated OxyContin’s abuse-deterrent properties. At the meeting, FDA tasked the committee members with discussing the evidence presented and voting on whether the reformulated version of OxyContin had meaningfully reduced “abuse of this product, relative to the original formulation, by one or more non-oral routes,” “overall abuse of this product, relative to the original formulation,” and “the risk of opioid overdose, relative to the original formulation” (emphasis in original) (FDA, 2020e). Additionally, members were tasked with discussing whether reformulated OxyContin led to important unintended adverse consequences, and the overall public health impact of the reformulation. Based largely on the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) ASI-MV study, which surveyed substance use in individuals entering or being evaluated for addiction treatment, the committee members voted 20-7 that available evidence did demonstrate a reduction in misuse through non-oral routes (Calderon, 2020; FDA, 2020e). However, by margins of 26-2 and 26-1 (one abstention), the committee members did not observe compelling data to demonstrate the success of reformulated OxyContin in reducing overall misuse of OxyContin or risk of opioid overdose, respectively. Much of these discussions centered on the quality of data presented and difficulty in designing studies to answer these questions. As the committee discussed unintended consequences of the reformulation, there was agreement that the substitution of heroin and other opioid products was probably an outcome of the transition to reformulated OxyContin, though establishing causality would be challenging in the context of an evolving overdose epidemic. An additional issue that committee members discussed were misconceptions that “abuse-deterrent” formulations are safer and prevent

addiction, and eliminating the term “abuse-deterrent formulation” in light of prescribers’ mistaken beliefs that these formulations are “safe opioids.”

B. Opana ER

Opana ER (oxycodone hydrochloride) was initially approved on June 22, 2006 for the management of moderate-to-severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time (FDA, 2018b). In July 2010, as the number of overdose deaths involving opioids continued to rise, Endo Pharmaceuticals (Endo), the manufacturer of Opana ER, submitted an NDA for a reformulated version of Opana ER using excipients intended to make tablets resistant to the physical and chemical manipulation necessary for intranasal and intravenous misuse. Using a polyethylene oxide matrix, the reformulated Opana ER deterred crushing, and thus potentially deterred insufflation and intravenous use by forming a viscous gel when in contact with liquids (FDA, 2017a). In January 2011, FDA issued a Complete Response Letter (CRL) asserting concerns that despite these new properties, the drug “... can still be...cut ...rendering it readily abusable by ingestion and intravenous injection, and possibly still by insufflation” (FDA, 2011b). It added that, “[o]f more concern, when chewed ... the new formulation essentially dose dumps like an immediate-release formulation” (FDA, 2011b). FDA ultimately approved the reformulated product in December 2011, because the agency concluded that the overall benefits of the drug outweighed its risks, but FDA did not approve labeling describing the reformulated product as abuse-deterrent (FDA, 2013a).

After the reformulated product was approved, Endo stopped marketing the original formulation of Opana ER and requested that FDA determine that it was withdrawn from the market for safety reasons.³¹ FDA concluded that the original formulation was not withdrawn for such reasons, noting that reformulated Opana ER “can be readily prepared for injection, despite Endo’s claim that these tablets have ‘resistance to aqueous extraction (i.e., poor syringeability)’” and that it “appears that reformulated Opana ER can be prepared for snorting using commonly available tools and methods” (FDA, 2013c). Moreover, although the postmarketing data on misuse of the reformulated version of Opana ER were, at the time, “preliminary” and “inconclusive,” FDA noted that “one of the postmarketing investigations suggests the troubling possibility that a higher (and rising) percentage of [misuse of the reformulated version] is occurring via injection than was the case with [the original formulation]” (FDA, 2013c).

Soon after FDA approved the Opana ER reformulation, state and local public health agencies began noticing patterns of injection-related HIV and Hepatitis C virus outbreaks as well as thrombotic microangiopathy (CDC, 2013, 2015). CDC reported these outbreaks as linked to Opana ER as early as 2015, and the association between thrombotic microangiopathy and Opana ER misuse as early as 2013.³² This prompted FDA to seek input, at a March 2017 meeting, from the AADPAC and DSaRM on the evidence regarding misuse patterns and safety of the

³¹ 78 Fed. Reg. 38053 (June 25, 2013).

³² Additionally, in its May 2013 denial of Endo’s citizen petition, FDA cited the 2013 CDC Morbidity and Mortality Report linking thrombotic microangiopathy to Opana ER use, as well as FDA’s own 2012 warnings regarding the link between the disorder and misuse of Opana ER. FDA. (2013c). Response to Endo Pharmaceuticals Citizen Petition, Docket No. FDA-2012-P-0895. <https://www.regulations.gov/document/FDA-2012-P-0895-0014>.

reformulated version of Opana ER. More specifically, FDA asked the advisory committees to discuss experimental and epidemiologic data to consider the risk/benefit balance for Opana ER; discuss potential consequences of regulatory action relating to reformulated Opana ER including on prescribing or use patterns for other products, and; (vote on whether the benefits of reformulated Opana ER continue to outweigh its risks. Materials presented to the advisory committee members suggested that these infectious disease outbreaks had been caused by misuse of the reformulated version of Opana ER via injection. Evidence presented to the committee members also discussed the high potency of oxymorphone relative to oxycodone, especially when administered intravenously (Fields, 2017); the short duration of action for oxymorphone, which led to more frequent use; the inability to crush reformulated Opana ER; the greater volume of solvent required to dissolve the medication prior to injection; and the high cost per pill (Brooks, 2017). Taken together, these factors led to a high rate of injection equipment sharing and created the conditions that could result in these outbreaks and devastating public health consequences.

Appreciating this shift in pattern of Opana ER misuse from intranasal to injection routes, the advisory committee members voted 18-8 that the benefits of reformulated Opana ER did not outweigh its risks (FDA, 2017e). Committee members who voted in the majority cited epidemiologic studies of misuse rates and significant morbidity and mortality in those populations. Those who voted in the minority noted that when taken as prescribed the drug remained an important analgesic option. There was disagreement about whether Opana ER should be removed from the market, though near unanimous agreement about limiting use through REMS or other mechanisms. In June 2017, FDA then requested that Endo remove the reformulated version of Opana ER from the market, which Endo announced it would do shortly thereafter. FDA explained that this action on Opana ER was “the first time the agency ha[d] taken steps to remove a currently marketed opioid pain medication from sale due to the public health consequences of abuse” (FDA, 2017b). In December 2020, FDA withdrew approval of the NDA for the reformulated version of Opana ER at Endo’s request.³³

C. Zohydro ER

In April 2012, Zogenix Inc (Zogenix) submitted an NDA for Zohydro ER (hydrocodone bitartrate extended-release capsules), in a formulation without abuse-deterrent properties and with a proposed indication for the “[m]anagement of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time” (FDA, 2013d).³⁴ In December 2012, FDA sought input from AADPAC on the risks and benefits of Zohydro ER. FDA’s review noted that “[i]f approved, Zohydro ER would be the first approved... single-entity hydrocodone product in the U.S.,” meaning the hydrocodone in Zohydro ER was not

³³ 85 Fed. Reg. 93972 (Dec. 23, 2020).

³⁴ Consistent with labeling changes that FDA required for all ER/LA opioids, FDA ultimately modified the proposed indication to “management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate,” emphasizing the need for providers to “assess[] the patient’s needs for adequate pain control in light of the patient’s previous experience with alternative analgesic treatments, and in balance with the risks specific to the patient[.]” FDA, Zohydro ER Summary Review, https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202880Orig1s000SumR.pdf[accessdata.fda.gov/drugsatfda_docs/label/2013/202880Orig1s000SumR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202880Orig1s000SumR.pdf).

combined with any other active pharmacological ingredient (FDA, 2013d). The key noted safety benefit was that Zohydro ER, because it did not include acetaminophen like then-available combination drugs, reduced the risk of liver toxicity associated with acetaminophen overuse, particularly for patients in need of higher doses of hydrocodone.

At the December 2012 meeting, AADPAC voted 11-2 (with one abstention) that the benefit-risk profile of Zohydro ER *did not* support the approval of the NDA (FDA, 2012b). According to the minutes of the meeting, “the committee agreed that the Applicant met the Agency standards for efficacy and safety,” but recommended against approval based on “public health concerns about abuse and misuse” of prescription opioids (FDA, 2012b). The committee concluded that “FDA should not approve ER/LA opioids without tamper-resistant or abuse-deterrent formulations, and that additional risk mitigation features should be adopted to strengthen the current ER/LA Opioid Analgesic REMS” (FDA, 2012b). In particular, some members of the committee predicted that “Zohydro ER would be more likely to be diverted [than then-available fixed-dose combination opioids] due to the lack of acetaminophen,” and there was accordingly a “need for additional postmarketing risk mitigation requirements beyond the current REMS” (FDA, 2012b).

Reaching a conclusion different from that of the AADPAC members, in October 2013, FDA approved the NDA for Zohydro ER (in 10mg, 15mg, 20mg, 30mg, 40mg, and 50mg capsules) with the indication proposed by Zogenix, Inc., though with some changes to the labeling initially proposed by Zogenix including additional boxed warnings highlighting the risks of “addiction, abuse and misuse and the potential for overdose and death” (FDA, 2013d). FDA’s approval memorandum noted the advisory committee’s views, but concluded that “the overall risk-benefit balance for patients who will be properly, thoughtfully and carefully prescribed Zohydro ER for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate, falls firmly on the side of approval of this application” (FDA, 2013d). FDA also noted that Zohydro ER would be the first newly-approved product subject to the ER/LA Opioid REMS.

FDA’s 2013 approval of the NDA for Zohydro ER was met with substantial concern from varied stakeholders. Shortly after the approval, for example, a bipartisan group of Attorneys General from 28 states and Guam wrote a joint letter to FDA expressing concern that the approval of Zohydro ER “has the potential to exacerbate our nation’s prescription drug abuse epidemic because this drug will be the first hydrocodone-only opioid narcotic that is reportedly five to ten times more potent than traditional hydrocodone products, and it has no abuse-deterrent properties” (State Attorneys General, 2013). They asked FDA to either reconsider its approval of Zohydro ER or to establish a “rigorous timeline for Zohydro ER to be reformulated to be abuse-deterrent while working with other federal agencies to impose restrictions on how Zohydro ER can be marketed and prescribed” (State Attorneys General, 2013).³⁵ Additionally, federal bills were introduced in

³⁵ These concerns were echoed by the Coalition to End the Opioid Epidemic, a coalition of “consumer safety organizations, health care agencies, addiction treatment providers, community-based drug and alcohol prevention programs, professional organizations” and others. A Coalition to End the Opioid Epidemic, Letter to Commissioner Hamburg, <https://www.citizen.org/wp-content/uploads/migration/2185.pdf>.

the Senate and the House that would have required FDA to withdraw approval of Zohydro ER's NDA and barred it from approving any "pure hydrocodone bitartrate extended-release capsules unless such drug is formulated to prevent abuse."³⁶ In an unusual move, in March 2014, the Massachusetts Department of Public Health (DPH) issued an emergency order to "prohibit the prescribing and dispensing of Zohydro ER until DPH determined that adequate measures to safeguard against diversion, overdose, and misuse had been implemented," which, had the order not been blocked by a federal court on preemption grounds, would have effectively banned Zohydro ER within Massachusetts.³⁷

In January 2015, FDA approved a modified formulation of Zohydro ER with excipients intended to form a viscous gel when the drug was crushed and dissolved in liquids or solvents. At the time, Zogenix announced its intent to seek approval for labeling that would include abuse-deterrent claims (Helfand, 2015). However, FDA never approved any such labeling change.³⁸ In 2022, FDA withdrew the approval of Zohydro ER's NDA at the request of its current sponsor (Recro Gainesville LLC), after the company had ceased marketing the drug.³⁹

D. Dsuvia

Dsuvia is the brand name for sufentanil sublingual tablets produced by AcelRx Pharmaceuticals, Inc. (AcelRx). Prior to the introduction of Dsuvia, sufentanil, a synthetic opioid analgesic, had been available in injection form (marketed as Sufenta), as an IV analgesic, and as an epidural analgesic used in labor and delivery. In 2018, AcelRx resubmitted⁴⁰ an NDA for Dsuvia (30 mcg sublingual tablets), seeking an indication "for the management of moderate-to-severe acute pain severe enough to require an opioid agonist and for which alternative treatments are inadequate, in adult patients in a medically supervised setting" (AcelRx, 2018). AcelRx's submission noted several potential benefits over then-available opioids used in medical settings, including individual packaging to reduce the possibility of dosing errors (particularly in comparison to the "large array of liquid opioid concentrations, volumes, and compounding variability" in IVs)⁴¹; more immediate relief of pain in comparison to IV administration; a delivery mechanism that avoided potential logistical delays and needle placement challenges associated with IV administration, and; use by patients with difficulty swallowing pills or with medical NPO (nothing by mouth) orders (AcelRx, 2018). Dsuvia was developed by AcelRx in collaboration with

³⁶ S.B. 2134, 113th Cong. (2014); H.R. 4241, 113th Cong. (2014).

³⁷ Zogenix, Inc. v. Patrick, No. CIV.A. 14-11,689-RWZ (D. Mass. Apr. 15, 2014).

³⁸ This statement is based on a review of Zohydro labeling available on FDA's webpage "Drugs@FDA" (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>).

³⁹ 87 Fed. Reg. 5827 (Feb. 2, 2022). In 2020, FDA approved an ANDA for a generic version of Zohydro; that ANDA is still approved. Brenda Sandburg, The Short & Controversial Life of Zohydro Comes to an End, Pink Sheet, Feb. 1, 2022, <https://pink.pharmaintelligence.informa.com/PS145619/The-Short-And-Controversial-Life-Of-Zohydro-Comes-To-An-End>.

⁴⁰ AcelRx had submitted an NDA for Dsuvia in December 2016. According to AcelRx, FDA issued a CRL in 2017 indicating it could not approve the NDA primarily because of "[t]he lack of sufficient safety data to support the initially proposed maximum available dose of 24 tablets (720 mcg) in a 24-hour period," and "[i]nadequate mitigation of the risk of dropped tablets." AcelRx. (2018). AcelRx Briefing Document Meeting of AADPAC. <https://www.fda.gov/media/118092/download>.

⁴¹ To reduce the possibility of dosing errors and misuse, Dsuvia tablets are individually packaged in a single-dose, tamper-evident pouch, with illustrated use instructions attached to each pouch.

the U.S. Department of Defense (DoD). DoD was particularly interested in the development of a potent opioid analgesic for use in battlefield settings when IV use may not be available or feasible (FDA, 2018c).

In October 2018, FDA convened a meeting of AADPAC to discuss the Dsuvia NDA. A majority of the members of the advisory committee concluded that “the proposed product and dispensing system is safe and effective for use by health care professionals in certified settings such as hospitals, emergency departments and surgical centers,” and committee members voted 10-3 in support of FDA approval (FDA, 2018d). The committee was directly asked about “public health risks related to abuse, misuse, and accidental exposure” (FDA, 2018d). Though committee members noted that “having a REMS program associated with this medication and its limited use in health care settings will . . . decrease the incidence and potential for abuse,” some members “found it difficult to compare public health risk and its benefit” as the only evidence provided consisted of a study conducted in hospital settings (FDA, 2018d).

In November 2018, FDA approved Dsuvia, with a REMS to help ensure that the drug is dispensed only in certified medically-supervised health care settings.⁴² A contemporaneous statement issued by then-Commissioner Scott Gottlieb emphasized the “very tight restrictions being placed on the use of this product” and the “unique aspects of Dsuvia, including those that make this drug a high priority for the Pentagon” (FDA, 2018c). The statement went on to suggest that, in the future, FDA “should consider whether we could do more in weighing approvals to ensure that new opioids are sufficiently better than existing drugs to justify their addition to the market in the context of the current crisis of abuse,” while considering “whether the individual drug meets the standard for safety and effectiveness.” Commissioner Gottlieb added that he was directing FDA staff to develop guidance about how FDA should incorporate such considerations into regulatory decisions. Though questions about Dsuvia’s advantages relative to other opioids were not asked of the advisory committee, Commissioner Gottlieb expressed confidence that Dsuvia’s approval was “consistent with population-based considerations for how it fits into the overall drug armamentarium.”

Even before FDA announced its approval of Dsuvia, concerns were raised about FDA’s process for reviewing the NDA. Public Citizen⁴³ wrote a letter to FDA criticizing “the failure of the FDA to have the full Drug Safety and Risk Management Advisory Committee [DSaRM] participate in the October 12, 2018 AADPAC meeting, therefore predictably increasing the odds of a vote favoring FDA approval” (Public Citizen, 2018).⁴⁴ The letter also raised substantive

⁴² In April 2022, FDA approved a modification to the Dsuvia REMS, reducing the frequency of required audits of health care settings that have received Dsuvia. Dsuvia REMS, REMS@FDA, <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=IndvRemsDetails.page&REMS=384>.

⁴³ A description of Public Citizen is available on the organization’s website. Public Citizen, About Us, <https://www.citizen.org/about/>.

⁴⁴ An op-ed later published in the Washington Post claimed that all but three members of the DSaRM had been “disinvited” from the meeting. Raeford Brown & Sidney Wolfe, The FDA Made the Wrong Call on this Powerful, New Opioid, Washington Post, Nov. 16, 2018, https://www.washingtonpost.com/opinions/the-fda-made-the-wrong-call-on-this-powerful-new-opioid/2018/11/16/39b212e2-e464-11e8-ab2c-b31dcd53ca6b_story.htmlhttps://www.washingtonpost.com/opinions/the-fda-made-the-wrong-call-on-this-powerful-new-opioid/2018/11/16/39b212e2-e464-11e8-ab2c-b31dcd53ca6b_story.html.

concerns about potential diversion of Dsuvia by “anesthesiologists and other medical personnel,” as well as about whether FDA is able to “predict the behavior of opioid drugs and to enforce postmarketing regulation.” One signatory to that letter was the chair of the AADPAC, who had been unable to attend the October meeting because of scheduling conflict.

A February 2019 letter from Sen. Edward Markey (D-MA) and Rep. Diana DeGette (D-CO) expressed similar concern about FDA’s decision not to consult the full DSaRM (Markey & DeGette, 2019). The letter also stated: “[W]hile we commend the agency’s plan to consider the broader public health context of future opioid approvals rather than merits of the individual drug application in question, it is difficult to understand why the FDA did not consider these questions before it approved Dsuvia.”

In February 2021, FDA issued a Warning Letter to AcelRx for “false and misleading promotion of Dsuvia” (FDA, 2021c). The Warning Letter cited the marketing claim “TONGUE AND DONE” as misleading because it implied that the “administration of Dsuvia consists of a simple, one-step process, when this is not the case” (FDA, 2021f). Rather, “the prescribing information outlines multiple administration steps including a separate, distinct step to visually confirm tablet placement in the patient’s mouth” (FDA, 2021c). AcelRx sent a corrective letter to health care professionals (AcelRx, 2021), and in March 2022, FDA issued a closeout letter to AcelRx acknowledging that it appeared to have adequately addressed the violations noted in the warning letter (FDA, 2022b).

E. Hydexor

An NDA for Hydexor, a fixed-dose combination oral tablet of hydrocodone, acetaminophen, and promethazine (an antiemetic), was first submitted to FDA by Õlas Pharma on March 31, 2016. The proposed indication was the relief of moderate to severe pain while preventing or reducing opioid-induced nausea and vomiting (OINV). Over the ensuing four years this medication underwent four separate review cycles that included two advisory committee meetings, three CRLs, and a request for dispute resolution procedures. The core issues around Hydexor center on the inclusion of promethazine, an antiemetic, with a more standard opioid/acetaminophen analgesic combination to prophylactically treat OINV.

In January 2017 the first CRL for Hydexor was issued by FDA, which cited four deficiencies including failure to establish bioequivalence of Hydexor to an already-approved hydrocodone/acetaminophen medication (FDA, 2020b). FDA received the manufacturer’s response to the initial CRL in October 2017, which it then discussed at a joint advisory committee meeting of AADPAC and DSaRM in February 2018. The committees voted 19-2 against approval citing several concerns. First, OINV seemed to decrease over time in the hydrocodone/acetaminophen comparator group in the submitted studies. Second, promethazine has “severe and concerning” adverse effects. Finally, committee members were concerned that the manufacturer failed to adequately identify a patient population that predictably requires concomitant analgesic and antiemetic therapies, a concern that carried into subsequent reviews of Hydexor. This last concern was the single deficiency identified in the second CRL, issued in April 2018 subsequent to the advisory committee meeting. At a post-action meeting held in May 2018

between Õlas Pharma and FDA, the manufacturer suggested changes to the proposed indication including limiting the indicated use to three to five days and narrowing the indicated population to “patients expected to be prone to nausea and vomiting.” FDA did not agree that the proposal addressed the safety concerns about the drug, noting the ongoing concerns raised by advisory committee members about unneeded exposure to promethazine by a significant number of patients who will never experience OINV.

The third review cycle of Hydexor began with a second resubmission of the NDA in August 2018, which included mutually agreed upon post-hoc analyses of subpopulations from the Phase 3 trials included in the initial NDA. In a February 2019 CRL (the third CRL), FDA again noted the failure to identify a patient population that would benefit from prophylactic antiemetic with every dose of an analgesic. Following this, Õlas Pharma requested a formal dispute resolution process to appeal the CRL’s conclusions in April 2019. This request was rejected in a letter signed by CDER’s Dr. Mary Thanh Hai on June 21, 2019 (FDA, 2020b). Among other things, the letter cited broader FDA priorities in addressing the opioid overdose crisis and the August 2016 announcement of class-wide boxed warning about co-administration of opioids and benzodiazepines. In a statement explaining the 2016 decision to require this class-wide warning, FDA emphasized safety concerns with concomitant use of both benzodiazepine and non-benzodiazepine central nervous system (CNS) depressants, which Dr. Thanh Hai noted would include antiemetics and antiemetic-containing medications like Hydexor (FDA, 2016a). Dr. Thanh Hai’s 2019 letter was the first time that an FDA official explicitly connected decision-making around whether to approve Hydexor to the overdose epidemic in general or, more specifically, the agency’s public health commitment to addressing it. Dr. Thanh Hai denied Õlas Pharma’s request for approval but instructed FDA to consider its proposed labeling revision as a resubmission in response to the third CRL. The letter instructed FDA to “make revisions so that labeling and instructions for use will sufficiently address the Agency’s concerns of respiratory depression when an opioid is used in combination with a CNS depressant,” which might include “restrictions to dosing, patient population, labeling claims, product packaging, and distribution that may require a Risk Evaluation and Mitigation Strategy (REMS) specific to Hydexor” (FDA, 2020b).

The fourth review cycle began with a resubmission of the NDA in June 2019 that included new labeling and packaging, and a proposed REMS that would restrict locations where Hydexor may be administered. The proposed indication targeted, “management of acute post-operative pain severe enough to require an opioid analgesic, for a maximum of 3 days, in adults at high risk for nausea and vomiting with hydrocodone-containing products.” Acknowledging risks of respiratory depression, Hydexor was to be only used in certified, medically supervised health care settings. Proposed REMS requirements focused on the health care settings where Hydexor was to be dispensed, including establishing policies and procedures to manage acute opioid overdose and respiratory depression, fall precautions, Hydexor discontinuation after 3 days, and verification that Hydexor was not dispensed for use outside of the facility. The new proposed REMS requirements were the focus of a second Hydexor-focused joint meeting of the AADPAC and DSaRM, which took place in November 2020 (FDA, 2020f). Advisory committee members were asked if the concerns from the initial application had been addressed through proposed labeling and REMS. In a 14-7 vote, a majority of committee members did *not* find these proposals to satisfactorily address

the safety concerns regarding Hydexor (FDA, 2020f). Concerns remained about difficulty in prospectively identifying patients at high risk for OINV and lack of specific safety data in elderly patients, who are likely in the highest risk group for respiratory depression from combination drugs with overlapping CNS depression. New concerns also arose about ambiguous terminology in specifying certified, medically supervised health care settings and the potential that Hydexor would be used in unintended settings. Based on publicly available information, there appear to have been no subsequent resubmissions of an NDA for Hydexor since the conclusion of this fourth review cycle.

F. Evolution of FDA’s Approach

One lesson from the examples in this section is that FDA has long considered the public health effects of opioid analgesics in certain ways. For example, in the agency’s summary review document regarding the 2013 approval of Zohydro ER, it discussed “the increasingly serious public health problem of prescription drug . . . misuse” and in a *JAMA* article discussing the approval, FDA officials explained that “[p]reventing prescription opioid overdose deaths is a public health priority” and detailed FDA efforts to reduce the misuse of opioid analgesics as a class (FDA, 2013d; Jones et al., 2014). At the same time, while AADPAC recommended against Zohydro ER approval based on “public health concerns about abuse and misuse” (even though the committee was not expressly asked to consider “public health concerns” in its approval recommendation) (FDA, 2012b), FDA ultimately approved Zohydro ER, concluding “the overall risk-benefit balance for patients who will be properly, thoughtfully and carefully prescribed Zohydro ER for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate, falls firmly on the side of approval of this application.”

But, importantly, the examples in this section also demonstrate that FDA’s approach to its oversight of opioid analgesics has evolved over time. Consistent with FDA’s statutory authority and the evolving nature of the overdose crisis and scientific understanding of the public health effects of opioid analgesics (Zettler et al., 2018), in more recent years, FDA has increasingly and more transparently incorporated broader benefit and risk considerations into its actions. These considerations have included those relating to addiction, misuse of FDA-approved products, and transitions between use of FDA-approved opioid analgesics and illicit opioids—while at the same time FDA has kept in mind the need for patients to access effective medications for pain. In 2017, for instance, when FDA convened AADPAC and DSaRM to provide advice on whether the benefits of the reformulated version of Opana ER continued to outweigh its risks, the agency expressly asked advisory committee members to consider “the risk/benefit balance for Opana ER, relative to other oxymorphone products” and “effects on prescribing or abuse patterns for other products, including other oxymorphone products” should FDA take action on Opana ER (FDA, 2017e). These questions suggested the incorporation of broader public health systems concerns into FDA’s decision-making, and were posed in a public forum. FDA took action shortly after the meeting to request that Endo voluntarily cease marketing the drug, citing “the public health consequences of abuse” (FDA, 2017b). This trend is also apparent in other recent examples, such as when FDA posed a question about “public health risks” of Dsuvia at the 2018 AADPAC meeting about the drug (FDA, 2018d), asked AADPAC and DSaRM to consider whether

“OxyContin’s reformulation meaningfully reduced the risk of opioid overdose [from any source] relative to the original formulation” (emphasis in original) (FDA, 2020e), and explained in a 2020 briefing document for an AADPAC and DSaRM meeting about Hydexor that “for all regulatory decisions related to opioid analgesics, FDA considers the benefit-risk assessment to include broader public health risks, including those related to misuse and abuse in patients as well as others in the household and community” (FDA, 2020b).⁴⁵ This gradual and necessary shift toward a broader public health approach is in line with the NASEM recommendations, as discussed further in this report, and is important for the agency to continue to build on.

IV. Generating Evidence about Opioid Analgesics

Robust evidence about the full range of benefits and risks of opioid analgesics is necessary to address the opioid epidemic while also ensuring that safe and effective uses of opioid analgesics are available for patients. One function that FDA’s drug regulation authorities serve, including the agency’s premarket approval and postmarketing requirement authorities,⁴⁶ is to require manufacturers to generate evidence about their products’ risks and benefits (Eisenberg, 2007). FDA itself also can generate evidence on the benefits and risks of drugs, including opioids, through its own research, surveillance, and monitoring.

A. Actions to Implement NASEM Report Recommendations

The 2017 NASEM Report offered several recommendations regarding FDA’s role in helping to ensure that useful information about the risks and benefits of opioids is developed. First, the NASEM Report recognized that the licit and illicit markets for opioids are inextricably linked, and regulatory decisions for licit opioids are likely to affect markets for and the use of illicit opioids. Therefore, Recommendation 4-1 (Appendix A) advised FDA to “consider potential effects on illicit markets of policies and programs for prescription opioids.” This includes considering the “potential effects of [prescription opioid] interventions on illicit markets – including both the diversion of prescription opioids...and the increased demand for illegal opioids.” Second, Recommendation 6-2 (Appendix A) advised that FDA should “require additional studies and the collection and analysis of data needed for a thorough assessment of broad public health considerations.” Lastly, Recommendation 6-3 (Appendix A) suggested that FDA should “ensure that public health considerations are adequately incorporated into clinical development.” Since the NASEM Report was published, FDA has taken several clear steps to address the Report’s recommendations regarding evidence generation, as summarized in **Table 1**.

⁴⁵ Questions posed to the advisory committees, however, have not necessarily consistently included this broader public health framing.

⁴⁶ 21 U.S.C. §§ 355(d), (o)(3).

Table 1: Example FDA Actions to Address NASEM Recommendations on Evidence Generation.[†]

Example FDA Actions to Implement NASEM Recommendations	Action Date	Primary NASEM Recommendation(s)*
Issued final guidance document, “General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products”	November 2017	4-1
Launched SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects)	2018	4-1; 6-2
Held public meeting on Patient-Focused Drug Development for Opioid Use Disorder	April 2018	6-3
Held interagency meeting of federal partners (the National Institute on Drug Abuse and the National Center for Injury Prevention and Control at CDC), modeling teams, and data experts to improve SOURCE	April 2019	4-1; 6-2
Issued draft guidance document, “Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework”	June 2019	6-3
Held public hearing, “Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction”	September 2019	6-3

[†]This Table provides examples of agency actions to address the NASEM recommendations but is not intended to be an exhaustive list of all relevant agency actions.

*Each example action also may be relevant to additional NASEM Report Recommendations not listed in the Table.

One example of an area where FDA has made progress in implementing Recommendation 4-1 is in encouraging the development of ADF opioid analgesics through providing information to help ensure that study designs are sufficient to understand the abuse-deterrent qualities of products. Formulations can be abuse-deterrent through various strategies, such as:

- Physical and chemical barriers (*e.g.*, physical or chemical properties that prevent crushing the drug for snorting);
- Agonist/antagonist combinations,⁴⁷ which have a lower risk of overdose;
- Inclusion of a substance that produces an unpleasant effect if the drug is misused (known as “aversion”);
- Delivery systems that make misuse difficult;
- New molecular entities that are less prone to misuse, or;
- Any combinations of these strategies that may further reduce the potential for misuse.

In April 2015, FDA published a guidance document on the evaluation and labeling of abuse-deterrent opioids that includes recommendations on how to conduct and design studies to demonstrate that a product formulation is abuse-deterrent (FDA, 2015). In July 2017, contemporaneous with the publication of the 2017 NASEM Report, FDA held a public workshop with scientific experts and interested stakeholders about the currently available data and methods for assessing the impacts of opioid formulations with abuse-deterrent properties on opioid misuse, addiction, overdose, and death, as well as opportunities for improving research regarding abuse-

⁴⁷ Opioid agonists activate the opioid receptors in the brain. Full agonist opioids, such as oxycodone, activate the opioid receptors in the brain fully, resulting in the full opioid effect. Partial agonist opioids, such as buprenorphine, activate the opioid receptors in the brain to a lesser degree than a full agonist. Opioid antagonists, such as naloxone, block opioid agonists by attaching to the opioid receptors without activating them.

deterrent formulations.⁴⁸ In November 2017, FDA then published a guidance document entitled “General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products,” in which the agency provided additional information about designing and conducting studies of formulations intended to be abuse-deterrent (FDA, 2017d).

No ADF can completely eliminate the risk of misuse. ADFs, and reformulations in general, also may have unintended, harmful public health consequences. For example, as discussed in Section III of this report, injection of the reformulated version of Opana ER was linked to outbreaks of HIV and Hepatitis C virus, as well as cases of thrombotic microangiopathy,⁴⁹ and some studies have suggested that the introduction of the reformulated version of OxyContin, for which FDA approved labeling describing the drug as abuse-deterrent, may have led people who had been misusing OxyContin to transition to using heroin or other illicit drugs. That said, studies have suggested growing evidence that products with formulations adequately demonstrated to be abuse-deterrent may significantly decrease the likelihood of misuse, and ADFs are currently only a small proportion of available prescription opioids (Pergolizzi et al., 2018). FDA’s continued efforts to encourage research and development of ADFs are important for public health and illustrate FDA actions that are consistent with Recommendation 4-1’s advice that the agency “consider potential effects on illicit markets of policies and programs for prescription opioids.”

Another area where FDA has made clear progress is in developing means to thoroughly assess the broad public health considerations associated with opioid analgesics, in direct response to NASEM Recommendations 4-1 and 6-2. FDA, for example, has taken the following actions:

- Partnered with external subject matter experts to develop a national-level system dynamics model of the opioid crisis, known as SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects);
- Partnered with other institutions to support the development and use of the systems modeling framework, and;
- Worked with the Department of Health and Human Services (HHS) on systems modeling efforts.

SOURCE combines dynamic simulation modeling with systems thinking principles to enhance understanding of the crisis and guide policy decisions (FDA, 2022g). This model was developed by an Opioid Systems Modeling Workgroup that consisted of experts in decision science, modeling and data analysis, economics, and evaluation. SOURCE is a dynamic, continuous-time differential equation model that simulates the transitions of the U.S. opioid-using population through opioid misuse, OUD, and remission; treatment with medications for OUD (MOUD); and nonfatal and fatal opioid overdose (Lim et al., 2022). These simulations elucidate future scenarios under varying conditions based on population health and policy temporal dynamics. Regulators and policymakers could use the SOURCE model to perform rapid thought-experiment analyses to gain insights on trends and systems behavior, especially when there is high

⁴⁸ 82 Fed. Reg. 27271 (June 14, 2017).

⁴⁹ As discussed in Section III, FDA did not approve labeling for the reformulated version of Opana ER that described it as having abuse-deterrent properties.

uncertainty around a policy question. The SOURCE model is also useful for guiding analyses intended to inform decision-making with more quantitative precision.

In addition to developing SOURCE, FDA has engaged with external institutions to provide support for the implementation of the systems modeling framework, as well as with HHS (FDA, 2022g). For example, Harvard Medical School/Massachusetts General Hospital has led the SOURCE model development and enhancement while Booz Allen Hamilton supported the SOURCE model validation, maintenance, and implementation. These resources and services could be leveraged by other policymakers and decision-makers to perform independent assessments of the public health benefit-risk profile of opioids and the impacts of various policies. FDA has already partnered with academic institutions to independently conduct research on the application of a systems modeling framework to investigate opioid use/misuse and outcomes (FDA, 2022g). For example, the University of Maryland Center for Excellence in Regulatory Science and Innovation (CERSI) is currently conducting research on the utilization of treatments for OUD and the role of such treatments in the opioid system. FDA has also provided funds to support a collaboration between Yale University and Mayo Clinic Center for Excellence in Regulatory Science and Innovation (CERSI) to conduct research on factors that influence health care professional decisions regarding the prescribing of opioid analgesics. Notably, SOURCE has already been applied to model the impacts of evidence-based strategies on OUD prevalence and fatal opioid overdoses, as described in a paper published in June 2022 in *Science Advances* (Stringfellow et al., 2022). A total of eleven strategies spanning opioid misuse and OUD prevention, buprenorphine capacity, recovery support, and overdose harm reduction were tested in the model-based analysis. The largest impacts on reducing fatal opioid-related deaths were noted with harm reduction (e.g., fentanyl test strips and other drug-checking services; harm reduction education on how to adjust drug use behavior, such as titrating or decreasing dose), increased naloxone distribution, recovery support, and rapid increase of buprenorphine providers' capacity.

In spite of the incredible progress that has been achieved by FDA in developing a systems approach to assessing the public health benefits and risks of opioids, there are relevant data limitations identified by the 2017 NASEM Report. Without robust data sources, the SOURCE model, and any other systems modeling approaches, would not yield accurate results. The NASEM Committee, thus, recommended that FDA develop guidelines for the collection of less traditional data sources that would produce data necessary for accurate modeling and their integration in a systems approach for assessment. Current opioid use systems modeling relies on national-level quantitative data that can be grouped into four data sources: prescription opioid utilization data (e.g., claims data, survey data, etc.); illicit use of prescription opioids and heroin data (e.g., the National Survey on Drug Use and Health); OUD treatment data (e.g., The Treatment Episode Data Set), and; overdose, hospitalizations, and mortality data (e.g., National Emergency Medical Services Information System). Although these data sources have been useful in advancing knowledge about the opioid epidemic, it is important to acknowledge that they feature several limitations including:

- Untimeliness (delays in current data processing and quality controls limit the value of using data to inform planning and resource allocation);

- Data sparseness due to geographic and socioeconomic variation in the prevalence of opioid use and outcomes, which creates challenges in generating stable and precise estimates at local levels;
- Lack of comprehensive data on multilevel risk factors of opioid use and outcomes (e.g., while electronic medical records (EMR) data is rich in clinical information about opioid prescribing, opioid use, OUD and overdose, vital information about impacts on families and the role of systems-level policies are absent from EMR datasets), and;
- Lack of longitudinal data, which is critical for understanding opioid prescribing, opioid use, OUD, and overdose over time and for more accurate assessment of the relationships between risk factors and these outcomes.

These data challenges cannot be solved by FDA alone; multi-institutional partnerships and collaborations are required to create comprehensive and timely datasets to facilitate robust systems modeling. FDA responded to this challenge by convening an April 2019 interagency meeting of federal partners (the National Institute on Drug Abuse, and the National Center for Injury Prevention and Control at CDC), modeling teams, and data experts to address data needs and challenges to improve opioid systems modeling (Jalali et al., 2021). At this meeting, partners were encouraged to exchange national data sources, data needs, and data considerations for developing systems models, though it is not clear whether specific datasets have been created as a result of this interagency meeting (and what those datasets are).

The agency has also taken steps to implement Recommendation 6-3, which advised the agency to help ensure that public health considerations are incorporated into clinical development. FDA has responded to this recommendation, for example, by:

- Holding a public meeting on Patient-Focused Drug Development for Opioid Use Disorder in April 2018⁵⁰;
- Developing and issuing, in June 2019, a draft guidance on benefit-risk assessment for opioids (FDA, 2019c), and;
- Convening a public hearing entitled “Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction,” in September 2019.⁵¹

In the 2019 draft guidance document on benefit-risk assessment for opioids, FDA encouraged manufacturers to provide information on the potential public health consequences of opioids to enable FDA to perform more comprehensive benefit-risk assessments of the products. In this draft guidance document, FDA explained that it considers various benefits and risks of opioids related to the drugs’ public health impacts including:

- Risk of accidental exposure in children;
- Characteristics of the drug that increase or decrease the risk of misuse, OUD, and related adverse outcomes;
- Risks associated with the indicated method of delivery;
- Potential unintended adverse consequences of abuse-deterrent formulations;
- Safety of excipients by unintended routes of administration, and;

⁵⁰ 83 Fed. Reg. 11208 (Mar. 14, 2018).

⁵¹ 84 Fed. Reg. 29112 (June 21, 2019).

- The distinct benefit-risk profiles of opioids within subpopulations (e.g., adolescents, patients with mental health and/or substance use disorders, patients with certain other comorbidities).

In order to support FDA’s ability to consider such benefits and risks, the draft guidance recommended that manufacturers developing novel opioid drugs use traditional and non-traditional data sources to assess how these drugs may be misused in postmarketing settings.

Furthermore, in November 2020, FDA issued a final guidance document entitled “Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs” (FDA, 2020a). This guidance, while not specific to opioid analgesics, provides assistance for drug developers to broaden participant eligibility criteria and adopt more inclusive enrollment practices. Trial eligibility is often based on criteria that have been conventionally accepted without much scientific background or rationale, which can lead to the exclusion of important patient populations. The 2020 guidance document suggests integrating inclusive trial practices, such as enrichment approaches that would lead to enrolling representative samples of the populations that are expected to use the drugs. For opioid-related drugs, inclusive trial practices could include targeted recruitment of populations affected by documented social drivers of health⁵² that are related to opioid misuse and populations with relevant co-morbid conditions, such as mental health conditions and those living with HIV or Hepatitis C virus (B. H. Han et al., 2019; Martins et al., 2012; Sumetsky et al., 2019; Zibbell et al., 2018). Inclusive trial practices are important for fully understanding a drug’s real-world benefit-risk profile.

B. Recommendations for Additional Actions

Since the 2017 NASEM recommendations, FDA has taken clear steps to help support the development of evidence needed to consider illicit markets more robustly in policies and programs and to incorporate broader public health effects into benefit-risk assessments of opioid analgesics, as well as steps to help ensure that public health considerations are adequately incorporated into drug development programs. However, at this time, there are additional steps the agency could take to further implementation of the NASEM recommendations.

One example is updating SOURCE to further consider the potential effects of both illicit markets and social drivers of health. A major limitation of SOURCE is the exclusion of certain factors and data that are directly related to opioid misuse (Gladden et al., 2019). First, the model does not account for counterfeit opioid pills or other illicit drugs that are not opioids, but may be used in conjunction with opioids. CDC reported that over 60% of all opioid-related deaths in 2018 involved at least one other non-opioid drug. This estimate is likely to grow as the use of non-opioid

⁵² “Social drivers of health” has the same meaning as “social determinants of health,” and refers to “the conditions in which people are born, grow, work, live, and age, and the wider set of forces and systems shaping the conditions of daily life.” World Health Organization, Social Determinants of Health, https://www.who.int/health-topics/social-determinants-of-health#tab=tab_1. The term “drivers” (in place of “determinants”) is used to emphasize that factors such as housing conditions, educational opportunities, community safety, income, and access to health care—which all contribute to health inequities—are not predetermined, but instead are the product of societal decisions and are modifiable. Davies, S, Pearson-Stuttard J. (2020). The social drivers of health. In S. Davies & J. Pearson-Stuttard (Eds.), *Whose Health Is It, Anyway?* Oxford University Press. <https://doi.org/10.1093/oso/9780198863458.003.0004>

illicit drugs, commonly used in conjunction with opioids, continues to increase (Ellis et al., 2021). Including this data will likely lead to more accurate simulations, in turn increasing SOURCE's utility for informing policy decisions.

Additionally, SOURCE does not seem to account for social drivers of health, nor for associated comorbidities with OUD such as mental health, trauma, and involvement in the criminal justice system. The opioid epidemic is a complex system of risk factors at the individual, interpersonal, communal, and societal levels (Jalali et al., 2020). Socioeconomic factors including poverty, unstable housing access, and structural racism, as well as biologic health comorbidities are associated with rates of higher opioid misuse and OUD. Integrating these factors, to the extent possible, should increase the accuracy and usefulness of SOURCE, just as including information on concomitant use of non-opioid drugs would. While FDA alone may not have the capacity to generate the types of datasets that are required to include such information, the agency could and should continue to develop multi-agency partnerships to link datasets, to do as much as it can to generate such information, and to make such data available to the research community and other stakeholders.

As noted above, FDA has taken clear steps to develop a systems modeling approach and to address the need to incorporate non-traditional data sources in these systems modeling approaches, but some gaps do remain. For instance, while social and structural drivers of health are important barriers and facilitators of opioid access, misuse, and overdose, there was little to no explicit discussion of plans to incorporate these non-clinical factors into existing data sources that are currently used in opioid systems modeling (Jalali et al., 2021). Although the 2017 NASEM Report did not discuss the important role of these factors in the opioid crisis in its recommendations, racial and ethnic minorities are now disproportionately experiencing the impacts of the opioid epidemic, and it is critical to consider how opioid systems modeling approaches can be leveraged to better understand the root causes of these growing disparities. The data needs for understanding and addressing the widening racial and ethnic disparities in the opioid crisis are unusually challenging for various reasons including that traditional data sources on opioid prescribing, OUD, and overdose rates (especially EMR and health insurance claims) often do not capture comprehensive information on racial and ethnic minorities because of lower health care access and utilization (*e.g.*, EMR and claims data are based on health care encounters). In other words, while understanding social and structural drivers are important to understanding most health disparities, including opioid use and outcomes, traditional data sources are often bereft of this information. Given the challenges associated with incorporating social drivers of health into a systems modeling approach, and in developing the data necessary to do so, one option for FDA might be to convene a public meeting, with experts in systems modeling and social drivers of health, as well as stakeholders (*e.g.*, community and patient organizations), to transparently solicit input on data challenges and possible approaches for the incorporation of social drivers in SOURCE.

A second example of additional steps the agency could take is furthering efforts to help ensure that the evidence necessary for benefit-risk assessment of opioid analgesics is developed. Although the 2019 draft guidance on risk-benefit assessment for opioids clarifies FDA's thinking

on how it will assess the benefits and risks of opioids, more could be done to clarify how drug manufacturers and other stakeholders can produce the scientific evidence necessary to inform FDA’s benefit-risk assessments. For example, certain information about the public health effects of opioids described in the draft guidance may only become available after a drug is approved and marketed. Guidance on what kinds of evidence manufacturers might be able to assess in the preapproval and post-approval contexts, and how that evidence can be generated, could help manufacturers better design studies in both contexts. Furthermore, the draft guidance lacks specific details on how to measure the public health outcomes that it describes, as some public commenters noted at FDA’s September 2019 Public Hearing on opioid benefit-risk assessments, and additional guidance on measuring such public health outcomes might be useful. As a final example, given the potential public health benefits of ADFs, as well as the potential for unintended adverse consequences associated with introducing ADFs into the market, FDA should continue to support advances in ADF research and technology, such as through seeking expert input on research designs for studying proposed ADF products or modeling of impacts of ADF products on illicit markets and drug use.

While the 2020 guidance document “Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs” is useful for a wide-range of drug developers, including manufacturers developing opioid analgesics, the agency has not released guidance on enhancing the diversity of clinical trial populations for opioid and pain-related clinical trials specifically. Given the public health considerations associated with opioid analgesics, including the societal and individual risks of prescription opioid use, guidance on the inclusion of diverse populations in opioid or pain treatment clinical trials could provide additional, helpful clarity to drug manufacturers developing these therapies. FDA could, for example, develop guidance to help manufacturers consider how to design studies to understand the potential impacts of opioid analgesics in subpopulations at high risk for misuse. This might include guidance on enrolling participants from geographic areas with high rates of misuse and overdose, or with commonly occurring co-conditions, such as depression or opioid-related infectious diseases. Furthermore, FDA should consider providing guidance on how to measure and assess the impact of social drivers of health on the safety and effectiveness of opioid analgesics; this would help elucidate the potential adverse impacts of opioids among populations burdened by multiple negative social drivers of health. FDA might also consider guidance on the length of clinical trials, to assess whether trials could be designed to better understand the risks and benefits of investigative opioid analgesics (*e.g.*, opioid analgesics proposed for long-term use).

Lastly, FDA should revisit the use of enriched enrollment randomized withdrawal (EERW) trials. EERW trials differ from conventional randomized control trials in that EERW designs do not randomize participants before trial product initiation but rather provide trial participants titrated active trial product to assess satisfactory efficacy and tolerability prior to randomization (McQuay et al., 2008; Moore et al., 2015). A primary motivation for EERW designs in opioid analgesic trials is to identify benefits among a small proportion of trial participants. Although FDA has explained that EERW trial design has been used for over thirty years to develop drugs in a range of therapeutic classes and the agency issued guidance in 2019 on enrichment strategies that is not specific to analgesic trials (FDA, 2019b, 2022k), there are several limitations of EERW

design that warrant additional consideration for opioid analgesics, in a public format, particularly given persistent questions from stakeholders about EERW designs for analgesic trials. First, EERW trial design involves prior exposure to the treatment during the initial open-label, which likely leads to partial unblinding of participants during the double-blind phase (Moore et al., 2015). This partial unblinding may directly decrease the trial’s validity (Gilron, 2016). Second, EERW trial designs are limited in their ability to inform results more generalizable to a broader population and, particularly with drugs like opioid analgesics that are widely used and have a wide range of public health impacts, are less informative than other trial designs (Staud & Price, 2008). Third, EERW trial designs are also known to underestimate adverse effects and, thus, may misguide evaluations for the agency’s benefit-risk assessment framework (Furlan et al., 2011). Given the documented methodological concerns with EERW designs, FDA should transparently review the use of EERW trial designs for studies used to support opioid analgesic NDAs and approval decisions. A useful first step might be for the agency to discuss the general appropriateness of EERW designs for opioid analgesic trials at an advisory committee meeting or other public meeting that includes scientific experts and other stakeholders, or to issue draft guidance on its thinking on EERW design for opioid analgesic trials specifically (on which the public could comment).

V. Opioid Analgesic Approvals (and Withdrawals of Approvals)

As described at the outset of this report, FDA’s authority to approve new drugs and, if necessary, to withdraw that approval, based on its expert evaluation of drugs’ benefits and risks are important tools through which FDA protects and promotes public health. For many drugs, safety and effectiveness can be adequately assessed—and FDA approval and withdrawal decisions made—based on the benefits and risks of the drug as shown in the preapproval clinical trials and, after approval, when used according to the FDA-approved labeling (Gottlieb & Woodcock, 2017; National Academies of Sciences, 2017). But some drugs, like opioid analgesics or products to treat or prevent communicable diseases, have important benefits or risks that may not be reflected in such information (Califf et al., 2016; Gottlieb & Woodcock, 2017; Lurie & Sharfstein, 2021; National Academies of Sciences, 2017; Zettler et al., 2018). For these drugs, FDA’s “benefit-risk assessment incorporates broader public health considerations for both the target patient population and others, such as risks related to misuse, accidental exposure, or disease transmission” (FDA, 2021b).⁵³

A. Actions to Implement NASEM Report Recommendations

The 2017 NASEM Report offered two recommendations particularly relevant for FDA’s approach to approving, and withdrawing approval of, opioid analgesics. First, in Recommendation

⁵³ For additional discussion of FDA’s statutory authority to incorporate public health considerations into its benefit-risk determinations, as well as examples of when it has done so, see the 2017 NASEM Report and Zettler et al. (2018). Additionally, after the NASEM Report published, Congress passed the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities (SUPPORT) Act, in which it expressly recognized that the approval and withdrawal of approval standards, in subsections (d) and (e) of section 505 of the FDCA, permit FDA to consider “misuse and abuse” in assessing the risks and benefits of drugs that are controlled substances. SUPPORT Act, Pub. L. No. 115–271 § 3001 (2018).

6-1 (Appendix A), the 2017 NASEM Report advised FDA to “utilize a comprehensive, systems approach for incorporating public health considerations into its current framework for making regulatory decisions regarding opioids,” including “when making approval decisions on applications for new opioids.” Second, in Recommendation 6-6 (Appendix A), the NASEM Report advised that FDA “should develop a process for reviewing, and complete a review of, the safety and effectiveness of all approved opioids, utilizing the systems approach described in Recommendation 6-1.” FDA has taken various steps to address these recommendations, as summarized in **Table 2**.

Table 2: Example FDA Actions to Implement NASEM Recommendations on Opioid Analgesic Approvals and Withdrawals of Approvals.[†]

Example FDA Actions to Implement Recommendations	Action Date	Primary NASEM Recommendation(s)*
Requested that reformulated Opana ER be voluntarily removed from the market	June 2017	6-1
Issued draft guidance document, “Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework”	June 2019	6-1
Held public hearing, “Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics To Treat Pain and Addiction”	September 2019	6-1
Withdrew approval of reformulated Opana ER	December 2020	6-1

[†]This Table provides examples of agency actions to address the NASEM recommendations but is not intended to be an exhaustive list of all relevant agency actions.

*Each example action also may be relevant to additional NASEM Report Recommendations not listed in the Table.

FDA has made clear progress toward implementing Recommendation 6-1. Some of this progress has come in the form of agency decisions about specific products. For example, in June 2017—shortly before publication of the 2017 NASEM Report—FDA requested that Endo stop marketing the reformulated version of Opana ER because the reformulation was associated with a shift from intranasal to intravenous non-medical use of the drug, leading to outbreaks of HIV and Hepatitis C virus, as well as cases of a thrombotic microangiopathy (FDA, 2017b). FDA identified this action on Opana ER as “the first time the agency ha[d] taken steps to remove a currently marketed opioid pain medication from sale due to the public health consequences of abuse” (FDA, 2017b). Shortly thereafter, Endo announced it would voluntarily remove the drug from the market.⁵⁴ In October 2017 Endo then requested that FDA formally withdraw approval of the product, which FDA did in December 2020.⁵⁵ As another example, in FDA’s 2019 letter denying Õlas Pharma’s request for a dispute resolution process to appeal conclusions in the 2019 CRL for the Hydexor NDA, the agency explicitly cited its commitment to addressing the opioid crisis (FDA, 2020b).

The agency has also taken steps to implement Recommendation 6-1 through general regulatory actions. For example, in June 2019, FDA issued a draft guidance document entitled “Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework” (FDA,

⁵⁴ 85 Fed. Reg. 93972 (Dec. 23, 2020).

⁵⁵ *Id.*

2019c). The draft guidance describes FDA’s benefit-risk assessment framework for opioids as one that not only accounts for the benefits and risks of an opioid when used as prescribed, but also the effectiveness and safety of a proposed opioid analgesic relative to currently available analgesics as well as the drug’s broader public health impacts. As it generally does for draft guidance documents,⁵⁶ the agency solicited public comment on the approach described in draft guidance.⁵⁷ The same day that FDA issued the draft guidance, it also announced a public meeting—held in September 2019—and opened a docket to solicit additional stakeholder input on the agency’s approach to regulating opioid analgesics, including aspects of opioid analgesic benefit-risk assessment.⁵⁸ The agency reiterated its view that its “benefit-risk assessment incorporates broader public health considerations” in certain circumstances, including for drugs that are controlled substances, in a draft guidance not specific to opioids that FDA published in 2021 (FDA, 2021b).

Each of these examples also shows progress toward incorporating public health considerations into FDA’s regulatory decisions regarding already-approved opioids, consistent with Recommendation 6-6. As noted previously both in this Section and in Section III of this Report, in 2017 FDA requested that Endo cease marketing the reformulated version of Opana ER “based on the public health consequences” of misuse of the drug, and the agency subsequently withdrew approval of the drug’s NDA at Endo’s request.⁵⁹ The agency’s efforts to clarify and revise its benefit-risk assessment framework for opioid analgesics, through the 2019 draft guidance document, public docket, and public meeting, are not only relevant to the agency’s approval decisions but also to its decisions to withdraw approval, because the approval and withdrawal standards are similar.⁶⁰ Additionally, this report is part of the agency’s efforts to address Recommendation 6-6 (FDA, 2022f).

But, based on publicly available documents, the agency does not appear to have implemented the NASEM Report’s specific recommendation that the agency develop a process for reviewing, and then complete a review of, the safety and effectiveness of all approved opioids, using a comprehensive, systems approach. This may, at least partly, be a result of resource constraints. The 2017 NASEM Report recommended that FDA’s review of approved opioids be an “Opioid Study Implementation (OSI),” “modeled on the Drug Efficacy Study Implementation (DESI) of the 1960s and 1970s” (National Academies of Sciences, 2017). For DESI, FDA “worked in concert with the National Academy of Sciences (NAS)/National Research Council (NRC) to classify the risk-benefit ratios of the purported indications for drugs approved between 1938 and 1962”—that is, those drugs approved before the FDCA required that new drugs be shown effective, as well as safe, to obtain FDA approval (National Academies of Sciences, 2017). The agency reviewed thousands of drug products and indications through DESI, but the process was resource- and time-intensive. For example, one reason FDA contracted with NAS/NRC to undertake DESI was that the agency lacked sufficient staff to undertake the process itself. At the start FDA anticipated the process taking two decades, and, in fact, as of the time of drafting this

⁵⁶ 21 C.F.R. § 10.115(g).

⁵⁷ 84 Fed. Reg. 29211 (June 21, 2019).

⁵⁸ 84 Fed. Reg. 29112 (June 21, 2019).

⁵⁹ 85 Fed. Reg. 93972 (Dec. 23, 2020).

⁶⁰ 21 U.S.C. §§ 355(d), (e).

Report, proceedings still remain open for a few drugs (Carpenter, 2010; Carpenter et al., 2015; FDA, 2011a, 2022c). Although an opioid review modeled on DESI would be smaller in scale, covering a single class of drugs about which much information already exists, it would likely require considerable agency resources.⁶¹ In addition to the resource challenges of such a review in general, research has indicated that withdrawing approval of drugs, when not at the request of the manufacturer, can require significant agency time and resources (which could be relevant should a review of currently approved opioid analgesics lead to such a decision) (Herder, 2019).

B. Recommendations for Additional Actions

FDA has made clear progress in implementing the NASEM recommendations relevant to approval and withdrawal of approval decisions and should continue its efforts. There are various ways the agency could do so under its existing authorities.

One example is finalizing the guidance document, “Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework.” As described in the draft guidance, the agency’s benefit-risk assessments for opioid analgesics “consider the positive and negative public health effects” of the products including a “drug’s potential effect on risks to both patients and nonpatients, such as members of the patient’s household,” “potential safety concerns” related to abuse-deterrent formulations such as “shift(s) to more dangerous routes” of use, and the “potential for subpopulations where the benefit-risk balance may be unfavorable” (FDA, 2019c). This is what the NASEM Report advised in Recommendation 6-1. To clarify that the agency intends to fully implement Recommendation 6-1, the final guidance could also expressly state that FDA may also consider the risk of people transitioning from prescription to illicit opioids as part of its evaluation of the positive and negative effects of products (as currently written, the draft guidance broadly describes the agency’s benefit-risk assessment so as to include these risks, but does not explicitly list such risks).⁶²

Importantly, finalizing the guidance can help clarify expectations for drug manufacturers in a format that still allows FDA to respond relatively nimbly to changes in the scientific evidence or the public health landscape. This, in turn, may help facilitate drug development as well as avoid some kinds of controversy that have arisen in FDA’s past regulatory actions on opioid analgesics. For example, greater clarity regarding FDA’s incorporation of public health impacts into its benefit-risk assessments for opioid analgesics may have helped the agency act more quickly to remove reformulated Opana ER from the market after it was determined, in 2015, that outbreaks of HIV and Hepatitis C virus were linked to injection-use of the drug (CDC, 2015; Peters et al., 2016).⁶³

⁶¹ The NASEM Report acknowledged that additional resources would be needed for the recommended OSI, suggesting among other things, that “user fees applied to NDAs could be adjusted to account for the . . . costs” in the next Prescription Drug User Fee Act or Congress could “add a very small surcharge to each opioid prescription” to fund this work.

⁶² For example, the draft guidance provides a few examples of the risks of ADFs that the agency considers and adds that the agency also considers “[a]ny other potential safety concerns related to the abuse-deterrent formulation.”

⁶³ Moreover, as noted in Section III, as early as 2013 CDC had linked cases of thrombotic microangiopathy to Opana ER use, and FDA issued a warning regarding the link between the blood disorder and misuse of Opana ER in 2012.

As the agency finalizes the guidance document on its overall benefit-risk framework, it also should consider whether additional guidance documents are needed on specific aspects of benefit-risk assessments for opioid-analgesics. For example, guidance on how drug manufacturers can use, and the agency intends to use, dynamic modeling analyses or other data sources to better understand opioid analgesics' public health effects could help provide additional clarity on how the benefit-risk framework can be incorporated into preapproval drug development and post-approval drug monitoring plans, and advance efforts not only to incorporate public health considerations into decision-making, but also to implement a systems approach for doing so.⁶⁴ As another example, if the agency anticipates future interest in developing fixed-dose combination drugs that include both opioid analgesics and other CNS depressants (similar to Hydexor), guidance on what is needed to demonstrate that the benefits of such products outweigh their risks, including how to prospectively identify appropriate patient populations, could help prevent the kind of back-and-forth between drug manufacturers and the agency that has happened with Hydexor.

There are also additional steps that FDA could take to further address Recommendation 6-6. Ensuring that the agency's benefit-risk framework, as generally articulated in the June 2019 draft guidance, applies to currently marketed, approved opioids, just as it would to novel products, is an important part of fully implementing the NASEM Report's central advice that FDA use "a comprehensive, systems approach for incorporating public health considerations" for regulatory decisions regarding opioids. Regardless of how FDA handles approval decisions going forward, there are numerous already-approved opioid analgesics.⁶⁵ These products can pose public health risks once marketed—as demonstrated by the reformulated version of Opana ER, for example—and there is little reason for FDA to assess approved products' benefits and risks differently than novel products.

Even if a comprehensive review is not feasible as precisely described in Recommendation 6-6, there are other steps that would be important advances for the public health, while also making more transparent how the agency is implementing a comprehensive, systems approach for incorporating public health considerations into its oversight of already-approved opioids. For example, FDA could use SOURCE to model effects of various regulatory decisions, including approval withdrawals, of existing opioid analgesics.

As another example, FDA could identify a subset of currently-approved opioid analgesics to prioritize for review,⁶⁶ such as opioid analgesics approved for long-term use.⁶⁷ The NASEM Report's review of the then-current scientific evidence identified long-term use of opioids for the management of chronic non-cancer pain as associated with risks of adverse outcomes, such as

⁶⁴ For additional discussion of the agency's efforts to develop such data sources, see Section IV.

⁶⁵ CDC reports that, in 2020, 142 million opioid prescriptions were dispensed. CDC, U.S. Opioid Dispensing Rate Maps, <https://www.cdc.gov/drugoverdose/rxrate-maps/index.html>.

⁶⁶ Even were the agency to seek, and Congress to supply, sufficient resources for a complete review of all currently marketed opioids as envisioned in Recommendation 6-6, the agency would likely need to prioritize products and indications within the review.

⁶⁷ OxyContin, for example, is currently approved for "the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." OxyContin Labeling, https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022272s047lbl.pdf.

OAD and overdose, while also lacking strong evidence supporting effectiveness (National Academies of Sciences, 2017). More recent scientific reviews have largely reached similar conclusions regarding long-term opioid analgesic use. A review of all NDAs for opioid analgesics approved from 1997 through 2018 concluded “approvals for chronic pain indications were generally based on a few trials of no more than 12 weeks, and few approvals for chronic pain included or referenced pooled safety analyses that incorporated systematic assessments of opioid-associated risks, such as tolerance, drug diversion, and nonmedical use” (Heyward, Moore, et al., 2020). A study of FDA files of prospectively-collected patient-level data from 12-month safety studies of extended-release opioids with abuse-deterrent properties found “about one-third of patients successfully titrated on opioids to treat chronic noncancer pain demonstrated continued benefit for up to 12 months” (Farrar et al., 2022). A systematic review conducted by the Agency for Health Care Research and Quality (AHRQ) in 2020 found that “evidence on long-term effectiveness [of opioid analgesics] is very limited, and there is evidence of increased risk of serious harms that appear to be dose dependent” (Chou et al., 2020). In CDC’s recently-issued November 2022 Clinical Practice Guideline for Prescribing Opioids for Pain, it concluded that there is “limited evidence of long-term effectiveness of opioids for chronic pain,” and for some conditions “evidence exists of worse outcomes” (CDC, 2022a). FDA, similarly, has explained that there “is very little research on the long-term benefits of opioids for treating chronic pain” (Califf et al., 2016), and that long-term use of opioids is “[a]n area of particular importance” (FDA, 2022f).

Given this context, an FDA review of opioid analgesics approved for long-term use could be important for both ensuring that drugs currently approved for that indication are supported by sufficient evidence of safety and effectiveness and promoting better understanding among health care professionals, patients, and other stakeholders. For example, this review could clarify for drug manufacturers and the public the kinds of evidence that the agency will expect to approve long-term use indications in the future.⁶⁸ It also could promote evidence-based prescribing through providing additional clarity for prescribers and patients about long-term opioid analgesic use, including with respect to the evidence on benefits and risks of different durations of use for different medical conditions, as well as identifying areas of both under- and over-use. As the NASEM Report recommended, any FDA report could, and should, account for any disadvantages to removing a given product from market or placing limits on its use, including risks posed to people who need treatment for pain. For instance, part of what motivated the CDC to issue a new clinical practice guideline in 2022 were concerns that the previous guideline had been misapplied in ways that contributed to patient harm, including through untreated and undertreated pain as well as rapid opioid tapers and abrupt discontinuations (Dowell et al., 2022). In other words, a review could serve the public health through promoting greater clarity for relevant stakeholders even if it did not ultimately result in changes to which products are currently marketed. Accordingly, the review should be done as transparently as possible, such as by discussing the relevant scientific

⁶⁸ Additional clarity among stakeholders, including drug manufacturers, also might help prevent controversies like that which occurred when the agency approved what it viewed to be a more limited long-term use indication, but others viewed to be a more expansive indication, for Oxycontin in 2001. For additional discussion of this controversy, see Section III.

evidence regarding long-term opioid treatment (including any relevant results from postmarket research conducted by drug manufacturers⁶⁹) with DSaRM and AADPAC, and with input from people with chronic pain, people with opioid use disorder, and health care professionals with expertise in treating both conditions.

The above suggested actions can be implemented under FDA’s current statutory authorities. One approach that FDA has identified as outside its current statutory authority is requiring that novel products be shown to offer material safety advantages (*e.g.*, a reduction in respiratory depression) over existing approved opioids analgesics (FDA, 2022a). Bills have been introduced in both the Senate and the House that would amend section 505 of the FDCA to specify that FDA “may deny approval of an [NDA] for an opioid analgesic drug if [FDA] determines that such drug does not provide a significant advantage or clinical superiority, in terms of greater safety or effectiveness, compared to an appropriate comparator drug, as determined by [FDA].”⁷⁰

Taking further steps under the agency’s existing authority to fully implement the NASEM Report’s central advice in Recommendation 6-1 could achieve many of the same goals of such a “comparative advantage” approach to opioid analgesic approvals. Additionally, FDA, at times, already incorporates similar considerations into its assessments of the benefits and risks of approved products. For example, although a different regulatory context than when FDA is determining whether to approve an NDA or withdraw approval of an NDA, in FDA’s 2013 response to Endo’s Citizen Petition requesting that the agency determine that the original version of Opana ER was withdrawn from the market for reasons of safety, the agency explained that it “recognize[s] that a drug’s benefit/risk profile can change to due to the availability of alternative products” (FDA, 2013c). As another example, again in a context different than decisions about whether to approve or withdraw approval of an NDA, when the agency determined, in 2013, that the original formulation of OxyContin was withdrawn from sale for safety or effectiveness reasons, it explained “Original OxyContin has the same therapeutic benefits as reformulated OxyContin. Original OxyContin, however, poses an increased potential for abuse by certain routes of administration, when compared to reformulated OxyContin. Based on the totality of the data and information available to the Agency at this time, FDA concludes that the benefits of original OxyContin no longer outweigh its risks.”⁷¹

Nevertheless, additional authority that expressly allows FDA to require a showing of a comparative advantage for opioid analgesics at the time of approval would give the agency even more flexibility than it already has to assess the public health impacts of novel opioids in its

⁶⁹ Other research, such as that conducted by researchers at the University of Pennsylvania that FDA engaged to evaluate long-term efficacy of chronic opioid use in chronic pain patients, of course might also be relevant. FDA. (2022k). Letter to the Honorable Maggie Hassan. <https://www.hassan.senate.gov/imo/media/doc/FDA%20RESPONSE%20HASSAN%201.21.20.pdf>.

⁷⁰ S.B. 4340, 117th Cong. (2022); H.R. 8586, 117th Cong. (2022).

⁷¹ 78 Fed. Reg. 23273, 23274 (Apr. 18, 2013). As a third example, and one from outside the opioid analgesic context, when FDA determined in 2012 that Chloromycetin (chloramphenicol), an antibiotic, was withdrawn from sale for reasons of safety or effectiveness, it explained “At the time of the approval of CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, there was significant unmet medical need. With the approval of additional therapies with less severe adverse drug effects, FDA has determined that the risks associated with CHLOROMYCETIN (chloramphenicol) Capsules, 250 mg, as currently labeled, outweigh the benefits.” 77 Fed. Reg. 41412, 41412 (July 13, 2012).

approval decisions, and help the agency further strengthen its approach to opioid analgesics.⁷² For instance, in a *JAMA* publication discussing the 2013 Zohydro approval, FDA officials explained that at the relevant 2012 advisory committee meeting the chair of [AADPAC] explained his view that “the committee felt most strongly, first, that the sponsor met the requirements [for approval] that they were asked to meet” and “the committee believes that the public health is not served by *this addition to the class* until and unless the [ER/LA Opioid Analgesic] Risk Evaluation and Mitigation Strategy (REMS) program is strengthened and/or this application is brought back to the committee in an abuse-deterrent form” (emphasis added) (Jones et al., 2014). Additional authority may have helped the agency address some of the concerns raised about Zohydro by AADPAC, including the recommendation that FDA decline to approve additional ER/LA opioid analgesics unless those products have effective tamper- or abuse-deterrent properties.

At the same time, it is crucial that FDA retain its ability to incorporate similar considerations into its assessments of the benefits and risks of approved products. Currently approved opioid analgesics have significant public health impacts, the full public health impacts of an opioid analgesic may often remain uncertain until the product is marketed and information about actual use is available, and it is critical to avoid creating a legacy market of less safe or less effective opioid analgesics as innovative novel products come on the market. In other areas, such as tobacco products, older products that are primary drivers of health risks remain on the market (United States Surgeon General, 2014), while newer products that may have the potential to reduce harm are subject to more stringent premarket oversight.⁷³ Accordingly, should the agency seek additional authority to allow it to require a showing of a comparative advantage for novel opioid analgesic approvals, it will be vital to FDA’s ability to implement an effective regulatory approach for all drugs to clarify that FDA also is authorized, for both opioids and non-opioid products, to determine that the benefits of an approved drug no longer outweigh its risks based on similar considerations.

VI. Post-Approval Oversight of Opioid Analgesics

FDA’s regulatory authority does not end with a decision to approve a new drug. Although NDAs contain substantial amounts of information about the safety and effectiveness of drugs, it is unlikely that a premarket research program can uncover all risks associated with a drug and remove all uncertainties about a drug’s effects. As described in Section II of the report, after a drug is approved, FDA can monitor the risks and effects of approved drugs, require manufacturers to continue to study their drugs, help ensure that health care professionals and the public have truthful, non-misleading, and up-to-date information about approved drugs through its own

⁷² In deciding whether to seek this authority, the Agency should, however, consider whether such authority has the potential for unintended consequences, such as by creating new incentives to be the first drug to market that might affect drug development, and whether any negative unintended consequences could be mitigated through statutory drafting or agency implementation.

⁷³ This is not to say that premarket review processes for novel tobacco and nicotine products are not important for promoting and protecting public health. Rather, we aim to highlight that finding feasible ways to transition from older, riskier technologies to newer technologies, while also ensuring that those newer technologies represent genuine innovations that have their claimed effects or otherwise do not repeat the problems associated with previous technologies, is a difficult regulatory question, and one that is integral to successful public health oversight.

communications and its oversight of advertising and promotion, and mitigate drug risks through requiring and overseeing REMS.⁷⁴

A. Actions to Implement NASEM Report Recommendations

The NASEM Report offered three recommendations particularly relevant to FDA’s post-approval oversight of opioid analgesics. First, in Recommendation 6-5 (Appendix A), the Report offered its primary advice for FDA, recommending that the agency “should take steps to improve post-approval monitoring of opioids and ensure the drugs’ favorable benefit-risk ratio on an ongoing basis,” including implementing “[REMS] that have been demonstrated to improve prescribing practices, close active surveillance of the use and misuse of approved opioids, periodic formal reevaluation of opioid approval decisions, and aggressive regulation of advertising and promotion to curtail their harmful public health effects.” The Report offered two additional recommendations for various stakeholders that also are relevant to FDA’s post-approval oversight. In Recommendation 4-1 (Appendix A), the NASEM Report advised that in “policies and programs pertaining to prescribing of, access to, and use of prescription opioids,” FDA 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.” Finally, in Recommendation 5-2 (Appendix A), the NASEM Report advised that “medical schools and other health professional schools should coordinate” with FDA and other state and federal agencies “to develop an evidence-based national approach to pain education encompassing pharmacologic and nonpharmacologic treatments and educational materials on opioid prescribing.” FDA has made clear progress on each of these recommendations, as summarized in **Table 3**.

Table 3: Example FDA Actions to Implement NASEM Recommendations on Post-Approval Oversight of Opioid Analgesics.[†]

Example FDA Actions to Implement NASEM Recommendations	Action Date	Primary NASEM Recommendation(s)*
Launched SOURCE, an opioid systems modeling effort	2018	6-5, 4-2
Contracted NASEM to study opioid analgesic prescribing for acute pain	August 2018	6-5
Approved Opioid Analgesic REMS, extending the requirements of the ER/LA Opioid REMS to cover IR products	September 2018	6-5
Approved modifications to TIRF REMS to better monitor risks and address inappropriate prescribing to opioid-non-tolerant patients	December 2020	6-5
Issued Warning Letter to AcelRx for false or misleading promotion of Dsuvia	February 2021	6-5
Issued Closeout Letter to AcelRx	March 2022	6-5
Held public workshops on prescriber education	Oct. 2021, Apr. 2022	6-5, 5-2

[†]This Table provides examples of agency actions to address the NASEM recommendations but is not intended to be an exhaustive list of all relevant agency actions.

*Each example action also may be relevant to additional NASEM Report Recommendations not listed in the Table.

⁷⁴ FDA also can withdraw its approval of an NDA pursuant to section 505(e) of the FDCA (21 U.S.C. § 355(e)), a postmarketing authority that is addressed in Section V.

For Recommendation 6-5, the agency has taken various steps to improve its post-approval oversight of opioid analgesics. One way it has done so is through actions to modify specific REMS (FDA, 2022f). In 2012 FDA approved a shared system REMS for ER/LA opioid analgesics to “reduce adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics, while maintaining patient access to pain medications,” primarily through a voluntary education program for prescribers (HHS Office of Inspector General, 2020). In September 2018, FDA approved a modification to that REMS—now known as the Opioid Analgesics REMS—to expand its coverage to include immediate release (IR) opioid analgesics, in addition to ER/LA opioid analgesics (FDA, 2018a), and to improve measurability of the REMS goal by focusing on prescriber education rather than adverse outcomes (HHS Office of Inspector General, 2020).

The shared system REMS for transmucosal immediate-release fentanyl (TIRF) products provides a second example. TIRF products are short-acting, high-potency opioid analgesics approved for breakthrough cancer pain in patients who are opioid-tolerant. Because TIRF products pose various risks, including a risk of overdose if used by patients without opioid tolerance, the TIRF REMS includes restrictive ETASU designed to ensure prescribing and dispensing only to appropriate patients, among other goals (HHS Office of Inspector General, 2020). After finding evidence of unacceptable rates of prescribing to non-opioid-tolerant patients in two consecutive REMS assessments,⁷⁵ in August of 2018 FDA convened a joint meeting of DSaRM and AADPAC to evaluate the TIRF REMS (HHS Office of Inspector General, 2020; Rollman et al., 2019). Consistent with the advisory committees’ recommendations, in March 2019 FDA then notified manufacturers of TIRF products that modifications to the REMS would be required to help ensure that only patients who are opioid tolerant are prescribed and dispensed TIRF products and to better monitor adverse events through a patient registry; the agency approved those modifications in December 2020 (FDA, 2020g).

Beyond these actions on specific REMS, and relevant to both Recommendations 6-5 and 5-2, FDA also has continued to assess how to best provide guidelines and education to health care professionals who prescribe opioid analgesics. The education component of the Opioid Analgesic REMS has been voluntary for prescribers since the REMS was first approved in 2012.⁷⁶ In September 2021 FDA announced it was reconsidering whether prescriber education through the REMS should be mandatory, opened a public docket to receive stakeholder input, and announced it would be holding a public workshop on the topic to be held in October 2021.⁷⁷ Consistent with the advice in Recommendation 5-2 that medical and health care professional schools, state agencies, and federal agencies coordinate, that public workshop included speakers from FDA, other federal agencies (*e.g.*, NIH), state agencies, medical and other health care professional

⁷⁵ In its review of both the 48-month REMS assessment (submitted in December 2015 and for which FDA completed its review in June 2016) and the 60-month assessment (submitted in December 2016, and for which FDA completed its review in December 2017), FDA concluded that the REMS was not meeting its goal of ensuring prescribing and dispensing of TIRF drugs only to appropriate patients. HHS Office of Inspector General. (2020). FDA’s Risk Evaluation and Mitigation Strategies: Uncertain Effectiveness in Addressing the Opioid Crisis. <https://oig.hhs.gov/oei/reports/OEI-01-17-00510.asp>.

⁷⁶ 86 Fed. Reg. 50541 (Sept. 9, 2021).

⁷⁷ *Id.*

schools, continuing medical education organizations, health care professional organizations, and patient organizations (Duke University, 2021). FDA then held another public workshop, in April 2022, on core competencies that should be included in prescriber education (FDA, 2022j). In addition to these workshops, in 2018 FDA contracted NASEM to study how evidence-based clinical practice guidelines for prescribing opioids for acute pain might help mitigate the risks of opioid analgesics while also reducing the burden of acute pain, resulting in a report published in December 2019 (National Academies of Sciences, 2019). In 2021 FDA also announced a cooperative research project with researchers at Brigham and Women’s Hospital and Harvard Medical School to study how REMS programs have operated in practice (Sarpawari, Mitra-Majumdar, et al., 2021). While not limited to opioid analgesics REMS, this research has the potential to produce information useful to improving the agency’s approach to REMS for opioids.

In addition to REMS-related actions, FDA also has taken steps to implement Recommendation 6-5 in its surveillance of the benefits and risks of approved opioid analgesics—some of which are also relevant to implementing Recommendation 4-1—such as SOURCE, the systems modeling effort that the agency began in 2018 (FDA, 2022g).⁷⁸ FDA has also required opioid analgesic manufacturers to conduct various postmarketing studies and trials (FDA, 2022i). Although FDA has not publicly announced a plan for a periodic formal reevaluation of opioid approval decisions, it has made efforts to incorporate public health considerations into its benefit-risk assessments for approved opioid analgesics (such as when the agency asked that reformulated Opana ER be removed from the market in 2017).⁷⁹ Additionally, since the 2017 NASEM Report was published, FDA has issued at least one Warning Letter regarding false or misleading promotion of an opioid analgesic (FDA, 2021f). Roughly one year later, the agency concluded that the manufacturer’s corrective actions in response to the Warning Letter addressed the violations (FDA, 2022b).

B. Recommendations for Additional Actions

FDA has made clear progress in implementing the NASEM Recommendations related to post-approval oversight of opioid analgesics, and the agency should continue these efforts. There are various actions that the agency could take to continue its implementation of the recommendations.

REMS is one example of an area on which the agency should continue to focus. REMS can be powerful tools to mitigate the risks of drugs, enabling FDA to approve, and patients to access, drugs for which benefits would otherwise be outweighed by risks (Avorn et al., 2018; Brandenburg et al., 2017; DiSantostefano et al., 2013; Sarpawari et al., 2015). At the same time, HHS Office of Inspector General reports have identified concerns about the effectiveness of REMS as a general matter (HHS Office of Inspector General, 2013), as well as concerns about REMS ability to quickly address the opioid crisis specifically (HHS Office of Inspector General, 2020). Research also has identified evidence that certain REMS, including the TIRF REMS, have, at

⁷⁸ For additional discussion of steps related to surveilling and studying the benefits and risks of opioid analgesics, including SOURCE, see Section IV of this report.

⁷⁹ For additional discussion of steps related to implementing a comprehensive, systems approach for incorporating public health considerations into benefit-risk assessments of approved opioid analgesics, see Section V of this report.

times, not achieved all their risk mitigation goals (Blanchette et al., 2015; HHS Office of Inspector General, 2020; Rollman et al., 2019; Sarpatwari, He, et al., 2021), that assessments sometimes have not been sufficient to allow FDA and drug manufacturers to evaluate whether certain REMS, including the Opioid Analgesic REMS, were meeting goals (Heyward, Olson, et al., 2020; HHS Office of Inspector General, 2020), and that some patients experience burdens on access to REMS-covered drugs (Sarpatwari et al., 2022). Given the dynamic nature of the overdose crisis and the potential of REMS to help mitigate the risks of opioid analgesics if appropriately designed (alongside evidence that certain REMS have fallen short of this potential), it is important for FDA to continue to study and evaluate how to best design and assess REMS for opioid analgesics, adjusting its approach as quickly and as transparently as possible when warranted.

Continuing to consider how to best design and assess REMS may be particularly important, and particularly difficult, for the Opioid Analgesics REMS. Overprescribing of the products covered by the Opioid Analgesic REMS has been identified as one of the key factors that led to the current overdose crisis (National Academies of Sciences, 2017). But patients also need the products in many circumstances (National Academies of Sciences, 2017). The Opioid Analgesic REMS products, therefore, are somewhat unusually positioned relative to other drugs subject to REMS, in that they are associated with grave risks while also having a wide range of possible appropriate uses throughout the health care system in many different patient populations. Designing the Opioid Analgesic REMS to balance risk mitigation, patient access, and burdens on the health care system—as FDA is required to do for REMS with ETASU under section 505-1(f) of the FDCA⁸⁰—may be particularly complex, requiring sustained attention and adjustments from the agency as evidence about the effectiveness of the REMS and the overall drug overdose crisis evolves.⁸¹

One question that has been raised is whether the Opioid Analgesic REMS should include mandatory education for prescribers. As currently structured, the Opioid Analgesic REMS requires drug manufacturers to make education available for health care professionals, through continuing education providers, that includes all elements required in the FDA-approved blueprint for the education (FDA, 2023b). In its 2020 report on the use of REMS for opioids, the HHS Office of Inspector General recommended that FDA modify the Opioid Analgesic REMS to require not only that manufacturers make training available, but also that manufacturers ensure that health care professionals complete the training before prescribing (HHS Office of Inspector General, 2020). At that time, FDA explained that, although it agreed that effective education for health care professionals is important, such mandatory education could have “serious, detrimental unintended consequences,” including on appropriate patient access (HHS Office of Inspector General, 2020). At the 2021 public workshop on prescriber education that FDA subsequently held, panelists expressed doubt that mandatory prescriber education through a REMS would be effective, instead recommending other approaches, such as targeted education that is not funded by drug manufacturers (Duke University, 2021). The panelists’ views at the 2021 workshop were

⁸⁰ 21 U.S.C. § 355-1(f).

⁸¹ One possibility is that FDA could consider whether SOURCE could be leveraged to help evaluate the complex questions about risk mitigation, patient access, and burdens on the health care system that are raised by the Opioid Analgesic REMS.

consistent with recommendations from AADPAC and DSaRM at a joint meeting of those advisory committees in May 2016 at which, according to meeting minutes, committee members expressed that any mandatory education ideally would be accomplished through a means other than the REMS (FDA, 2016b).

Although there is evidence that reducing prescribing can reduce misuse initiation and OUD (Stringfellow et al., 2022), in the absence of evidence that modifying the educational component of the REMS to be mandatory is a change that will meaningfully improve opioid prescribing practices, it is reasonable for the agency to conclude—as other experts have—that risks to patient access and burdens on the health care system associated with mandatory prescriber education counsel against such a requirement. Moreover, the Omnibus Appropriations Bill enacted on December 29, 2022 amended the federal Controlled Substances Act to require prescriber training as a condition of the registration required under that law, and it would make sense for FDA to assess the impacts of that training before considering modifications to the REMS that would make the REMS educational component mandatory.⁸² That said, the agency should continue to monitor and evaluate whether to modify the Opioid Analgesic REMS to include mandatory prescriber education. Additionally, other modifications to improve the impact of the educational component of the REMS deserve careful consideration. For example, the agency could explore additional mechanisms to protect the independence of REMS prescriber education, or ways to ensure that prescriber education funded by independent sources rather than drug manufacturers is available, as well as to incorporate into the REMS educational strategies that have been shown to promote evidence-based prescribing, such as academic detailing (Duke University, 2021; Sarpatwari & Curfman, 2019; Trotter Davis et al., 2017).⁸³

In addition to REMS, another example of an area that merits sustained agency attention is Recommendation 6-5's advice that the agency conduct periodic formal reevaluations of opioid approval decisions.⁸⁴ Although FDA has taken various steps to incorporate public health considerations into its benefit-risk assessments for opioid analgesics, including for approved products, there are various ways the agency could further implementation of this aspect of Recommendation 6-5. For example, given that some level of nonmedical use of opioid analgesics is expected, FDA could consider issuing general guidance explaining the kinds of adverse events—such as rates or routes of misuse—that are likely to trigger agency review of an approved product's benefits and risks, or FDA could solicit input at an advisory committee meeting on such questions about a specific product before it is marketed, when the agency is considering whether to approve an NDA. Whether in a general or product-specific format, transparently discussing what kinds of information are likely to lead to FDA reconsidering the benefits and risks of an approved product could help provide certainty to drug manufacturers and help the agency move quickly to reassess benefits and risks when necessary. Setting out such expectations, for instance, might have helped the agency more quickly review the benefits and risks of reformulated Opana ER with DSaRM

⁸² The text of the law is available at <https://www.congress.gov/117/bills/hr2617/BILLS-117hr2617enr.pdf>.

⁸³ Academic detailing is intended to promote “medical decisions [] based on evidence-based information” and refers to “one-on-one educational outreach to physicians using similar methods as the pharmaceutical industry that sends ‘detailers’ to market their products to physician practices. Trotter Davis et al. (2017).

⁸⁴ For additional discussion of agency benefit-risk assessments for approved products, see Section V.

and AADPAC after outbreaks of HIV and Hepatitis C virus, and cases of thrombotic microangiopathy, were linked to injection-use of the drug. Another possibility might be for the agency to commit to periodically discussing certain types of products with AADPAC and DSaRM after approval.

FDA has authority to incorporate consideration of public health impacts into its post-approval monitoring and oversight of opioids in many ways, including with respect to opioid analgesic advertising and promotion. For instance, FDA regulations require that drug manufacturers submit to FDA “labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement,” which gives FDA a tool for monitoring and considering the impacts of promotional materials.⁸⁵ But drug manufacturers are generally *not* required to submit advertising and promotional materials in advance of dissemination, with time for review or authorization by FDA *before* the materials reach and influence audiences (FDA, 2021d).

A requirement for some form of pre-dissemination review or authorization would not be entirely without precedent. In 2007, for example, Congress amended the FDCA to allow FDA to “require the submission of any television advertisement for a drug . . . not later than 45 days before dissemination of the television advertisement,” and to “make recommendations” with respect to submitted advertisements.⁸⁶ FDA guidance issued in 2012 explained that the agency intended to apply this requirement to direct-to-consumer television advertisements for various categories of drugs, such as drugs subject to REMS with ETASU and drugs that are schedule II controlled substances, which would include opioid analgesics (FDA, 2012a). As another example, albeit one outside the prescription drug context, in the Family Smoking Prevention and Tobacco Control Act of 2009 (Tobacco Control Act), Congress amended the FDCA to give FDA jurisdiction over tobacco products. The Tobacco Control Act includes a requirement that before marketing any tobacco product with labels, labeling, and advertising that makes any claim that such product “reduce[s] harm or the risk of tobacco-related disease” in comparison to other tobacco products, FDA must review the evidence supporting such a “modified risk” claim and authorize it.⁸⁷ This requirement has been upheld against First Amendment challenges,⁸⁸ with one federal Court of Appeals writing that such pre-dissemination review of advertising claims may be particularly

⁸⁵ 21 C.F.R. § 314.81(b)(3)(i).

⁸⁶ 21 U.S.C. § 353c. In limited circumstances, this provision empowers FDA to not only “make recommendations” with respect to the submitted advertisements, but also to directly require changes to them.

⁸⁷ 21 U.S.C. § 387k. As a condition for authorizing a “modified risk” claim, FDA may require postmarket surveillance to assess the impact of such claims on “consumer perception, behavior, and health.” 21 U.S.C. § 387k(g)(2)(c). Under a separate provision of the Tobacco Control Act, tobacco product manufacturers are required to notify FDA 30 days before disseminating certain advertising and labeling, and in that notification to describe “the medium and discuss the extent to which the advertising or labeling may be seen by persons younger than 18 years of age.” 21 C.F.R. § 1140.30(a)(2)

⁸⁸ See, e.g., *Nicopure Labs, LLC v. Food & Drug Admin.*, 944 F.3d 267, 282–83 (D.C. Cir. 2019) (“[E]ven if we were to scrutinize the FDA’s reliance on new tobacco product descriptors as a burden on the Industry’s commercial speech, the modified risk product pathway clears First Amendment scrutiny because it is reasonably tailored to advance the substantial governmental interest in protecting the public health and preventing youth addiction.”).

important “in the context of a deadly and highly addictive product, [where] it would be a virtual impossibility to unring the bell of misinformation after it has been rung.”⁸⁹

Pre-dissemination review or authorization of opioid analgesic advertising and promotion that is not on television, and the resources to efficiently conduct such a review process, could serve an important public health function, because industry advertising and promotion practices are drivers of product use and health and are present in many forms of media beyond television (National Academies of Sciences, 2017; Pettigrew & Jones, 2022). Notwithstanding current legal requirements, some opioid analgesic manufacturers have engaged in advertising and promotion about unapproved uses (“off-label uses”) or advertising and promotion that otherwise overstated their products’ benefits and downplayed the risks of addiction (National Academies of Sciences, 2017; Van Zee, 2009). In some instances, such advertising and promotion has led to criminal prosecutions and convictions (Daval, Avorn, et al., 2022; Department of Justice, 2019; Meier, 2007) and much of the recent civil opioid litigation has included claims asserting deceptive marketing practices by opioid analgesic drug manufacturers (Haffajee & Mello, 2017). The HHS Office of Inspector General identified the history of such advertising and promotion practices among opioid analgesic manufacturers as undermining the effectiveness of REMS (HHS Office of Inspector General, 2020). Even when corrective actions are later taken, as happened after FDA’s 2021 Warning Letter regarding Dsuvia, some may continue to believe the initial false or misleading messages for various reasons (or may have already experienced negative health consequences stemming from the misleading information)—that is, the bell of misinformation, and its public health impacts, is difficult to unring. FDA could consider whether a pre-dissemination review and comment process, or a pre-publication agency authorization process, would be more appropriate. It also could consider whether such processes are needed for all opioid analgesic advertising and promotion, or for a subset, such as for opioid analgesics with labels, labeling, or advertising that explicitly or implicitly represent the products as presenting lower risks of misuse and addiction. Although authority and resources to require pre-dissemination review or authorization of advertising and promotion would be unlikely to eliminate all potentially false or misleading advertising and promotion, it would give FDA additional tools to implement the NASEM Report’s advice, in Recommendation 6-5, that the agency “aggressive[ly] regulat[e] . . . advertising and promotion to curtail their harmful public health effects.”⁹⁰

Finally, it is important to note that there are limits to what post-approval authorities, alone, can accomplish. Research has found that FDA generally faces more difficulty enforcing requirements in the post-approval context than at earlier points in the drug lifecycle (Herder, 2019),

⁸⁹ Disc. *Tobacco City & Lottery, Inc. v. United States*, 674 F.3d 509, 537 (6th Cir. 2012).

⁹⁰ Such pre-dissemination review may raise First Amendment issues that FDA also would need to consider. As noted above, however, courts have upheld pre-dissemination review for “modified risk” claims in the context of FDA tobacco regulation, emphasizing the tobacco industry’s history of misleading marketing and FDA’s inability to “unring the bell” of misinformation once widely disseminated. Discussing FDA’s pre-authorization requirement for “modified risk” claims, the Court of Appeals for the D.C. Circuit stated in 2019, “FDA is entitled to impose these reasonable requirements on manufacturers of products containing nicotine—like makers of dangerous or potentially dangerous pharmaceuticals—to show at the threshold that their marketing claims are accurate and not misleading.” *Nicopure Labs, LLC v. Food & Drug Admin.*, 944 F.3d 267, 287 (D.C. Cir. 2019).

and, as noted above, certain REMS have not always accomplished their risk mitigation goals (Blanchette et al., 2015; HHS Office of Inspector General, 2020; Rollman et al., 2019; Sarpatwari, He, et al., 2021). One way to help promote public trust and understanding, even when the agency faces such challenges, is to be as transparent as possible. For example, to the extent legally permissible, FDA could routinely make public information about how well opioid REMS are achieving their goals, including by presenting such information at advisory committee meetings (Sarpatwari & Curfman, 2019).⁹¹ Additionally, while FDA’s post-approval authorities are critical to the agency’s ability to protect and promote public health and it is important that FDA continue to evaluate and improve its approach to post-approval drug oversight, it is also important to recognize the limitations of post-approval action, perhaps particularly when post-approval measures are being considered as solutions for fully addressing concerns about safety or effectiveness when a product is being considered for approval.⁹² Post-approval oversight will be most effective when part of a comprehensive approach across drugs’ entire lifecycle, combined with robust preapproval evidence generation and approval processes.

VII. Transparency

Across a drug’s lifecycle and the various regulatory decisions that FDA makes, the agency can serve its public health mission through disseminating information about regulated products and FDA processes, while also protecting legitimately proprietary information (Califf, 2017). Advisory committees are one key tool for transparency, particularly when FDA is considering a potential regulatory decision on a specific product. Not only do advisory committees provide independent advice to the agency to inform its decision-making, but because meetings and meeting materials are generally public, advisory committee meetings also often provide the first publicly available information about the scientific information informing a decision that is before the agency (GAO, 2020; Sharfstein et al., 2017).⁹³

A. Actions to Implement NASEM Report Recommendations

In Recommendation 6-4 (Appendix A), the 2017 NASEM Report advised FDA to “commit to increasing the transparency of its regulatory decisions for opioids to better inform manufacturers and the public about optimal incorporation of public health considerations into the clinical development and use of opioid products.” FDA has made clear progress on this recommendation, as summarized in Table 4.

⁹¹ FDA publishes REMS documents and other information about REMS on its REMS@FDA website, and in 2021 the agency launched a “REMS Public Dashboard,” which provides information about all REMS to promote more efficient public access to REMS information and enable visualization of that information. While these resources are useful for understanding many aspects of REMS, the agency does not publish to these resources information about the substance of REMS assessments or other information about how well REMS are meeting their goals. FDA, REMS, <https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems>.

⁹² With Zohydro, for example, at the 2012 AADPAC meeting, committee members expressed concern about whether the then-existing ER/LA Opioid REMS could fully address the committee’s safety concerns about the drug.

⁹³ 21 C.F.R. part 14.

Table 4: Example FDA Actions to Implement NASEM Recommendations on Transparency.[†]

Example FDA Actions to Implement NASEM Recommendations	Action Date	Primary NASEM Recommendation(s)*
Maintaining and updating webpage, “Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse”	Ongoing	6-4
Convened advisory committee meeting on the clinical utility and safety concerns associated with higher range of opioid analgesic dosing	June 2019	6-4
Published white paper explaining the agency’s opioid systems modeling effort	March 2021	6-4
Announced and explained FDA’s “Overdose Prevention Framework”	August 2022	6-4
Published statement on website affirming agency commitment to transparency	September 2022	6-4

[†]This Table provides examples of agency actions to address the NASEM recommendations but is not intended to be an exhaustive list of all relevant agency actions.

*Each example action also may be relevant to additional NASEM Report Recommendations not listed in the Table.

FDA has made statements affirming a commitment to transparency, for example explaining in a post to the agency website in September 2022 that the agency “is committed to being transparent about regulatory decisions to the extent possible for all topics, and opioids are no exception” (FDA, 2022f).

In addition to such statements, FDA’s actions demonstrate clear progress on Recommendation 6-4. Some of these actions involve decisions on specific products. For example, FDA has continued to seek advisory committee input to inform its decisions on whether to approve opioid analgesic NDAs, including discussing questions regarding the safety and effectiveness of Dsuvia and Hydexor at advisory committee meetings in February 2018 (Hydexor), October 2018 (Dsuvia), and November 2020 (Hydexor). Additionally, at the October 2018 meeting at which FDA sought input on the safety and effectiveness of Dsuvia, the agency specifically asked AADPAC to discuss whether “based on the available data, the benefits to patients are expected to outweigh public health risks related to abuse, misuse, and accidental exposure” (FDA, 2018d).

FDA has also taken steps to implement Recommendation 6-4 through general regulatory actions. Some of these actions, such as the 2019 draft guidance and public meeting on opioid analgesic benefit-risk assessments, the 2021 and 2022 public workshops on prescriber education, and publishing REMS documents and information on the REMS@FDA webpage and the public REMS dashboard, are discussed elsewhere in this report (Duke University, 2021; FDA, 2019c, 2019d, 2021e, 2022j, 2022n). There are other examples as well. For instance, FDA maintains on its website a “Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse,” describing the agency’s opioid-related activities going back over 45 years to the agency’s 1987 approval of MS Contin, (morphine sulfate) (FDA, 2022p). In June 2019, FDA convened a joint meeting of DSaRM and AADPAC to solicit “public input on the clinical utility and safety concerns associated with the higher range of opioid analgesic dosing (both in terms of higher strength products and higher daily doses) in the outpatient setting.”⁹⁴ In March 2021, FDA

⁹⁴ 84 Fed. Reg. 18053 (Apr. 29, 2019).

posted to its website a white paper explaining SOURCE, the agency’s opioid systems modeling effort (and in 2022, two research articles were published) (FDA, 2022g; Lim et al., 2022; Stringfellow et al., 2022). And as a final example, in August 2022 FDA announced the launch of its “Overdose Prevention Framework,” explaining in that announcement FDA’s priorities for its actions to prevent drug overdoses and reduce deaths (FDA, 2022i).

B. Recommendations for Additional Actions

Continuing the agency’s clear progress in implementing the NASEM Committee’s recommendation to commit to increasing the transparency of regulatory decisions for opioid analgesics is critical for FDA’s public health mission. Transparency can help improve patient care, promote development of innovative products, and advance public understanding of FDA decisions—and research has indicated public support for increased transparency at FDA (Azad et al., 2022; Califf, 2017; National Academies of Sciences, 2017; Schwartz, 2020; Sharfstein et al., 2017). Increased transparency can also help prevent inappropriate influence on agency decisions, or the perception that such influence has occurred, while transparency about how FDA is using a systems approach to incorporate public health considerations into its decision-making can encourage drug manufacturers to generate data and information necessary for such an approach. Additionally, the agency has identified as a general priority countering misinformation and misunderstandings about both scientific evidence and FDA processes (FDA, 2022m), and transparency will be a necessary aspect of any such efforts related to opioid analgesics.

There are various actions that the agency could consider to further increase transparency around its regulatory decisions for opioid analgesics. One step could be to commit to using only public meetings and workshops for discussing policies related to opioid analgesic regulation, such as questions about appropriate trial design for classes of products (rather than for a specific NDA). When meetings are needed, using and participating in only public meetings would increase transparency by helping to ensure that meeting participation is available to more stakeholders. This could help avoid concerns about inappropriate industry influence on agency decision-making, similar to those raised about the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) meetings, held in the 2000s and 2010s, being a non-public forum at which industry and FDA officials discussed EEWR trial design (Campbell & King, 2017; Kolodny, 2020; Whoriskey, 2013).

Additionally, although FDA routinely makes available on its website substantial amounts of information about approved NDAs as well as approved REMS (FDA, 2021, 2022a), there are key pieces of information informing or describing FDA’s own analysis and decision-making that are not typically disclosed. For example, as discussed in Section VI in the report, FDA could consider whether it is able to routinely make publicly available REMS assessments, or other summary information, to help promote public understanding about how well opioid REMS are achieving their goals. As another example, when opioid analgesic NDAs are not approved or development of an opioid analgesic is otherwise abandoned, FDA could consider means for routinely disclosing CRLs, summaries of CRLs, or other information about why drug development is not moving forward, that promote transparency without undermining drug manufacturers’

willingness to share information with FDA.⁹⁵ The 2017 NASEM Report recommended that FDA consider releasing CRLs, or summaries of CRLs, when opioid analgesics are not approved—something that an FDA Transparency Task Force and a team of academic researchers that included a former FDA official recommended for all prescription drug NDAs in 2010 and 2017, respectively (FDA, 2010b; National Academies of Sciences, 2017; Sharfstein et al., 2017). Information about why FDA declines to approve an opioid analgesic, or why a drug manufacturer otherwise does not move forward with a product, is potentially valuable for scientific understanding and promoting efficient drug development, particularly because research has found mismatches between drug manufacturers’ public communications about why a product is not approved and FDA’s rationales for such decisions as described in CRLs (Lurie et al., 2015). If FDA were to conclude there are legal barriers to releasing information about REMS assessments or CRLs for opioid analgesics, or resource-constraints that make releasing such information infeasible, it could publicly explain that—and consider possible solutions.

For advisory committees, specifically, there are also additional steps FDA could take to be more transparent about, and further improve, how it is implementing a comprehensive, systems approach for incorporating public health considerations into its regulatory decisions for opioid analgesics. For example, when FDA is seeking input about opioid analgesics—on both specific products and general regulatory issues—the questions that the agency poses to the advisory committee should expressly and consistently ask about relevant public health considerations. This would standardize the approach that the agency has already adopted in certain instances, such as when, in March 2017, FDA asked DSaRM and AADPAC to consider the data on the shift from intranasal to injection use of reformulated Opana ER, as well as the impacts on prescribing and misuse that a regulatory action may have, and when in October 2018 FDA asked AADPAC to consider public health risks related to misuse of and accidental exposure to Dsuvia. Developing standardized questions about the public health consequences of opioid analgesics, to the extent possible given differences between individual products and the scientific questions associated with them, can help ensure that the agency receives advice on all factors relevant to its benefit-risk assessments for opioid analgesics, provide stakeholders, including drug manufacturers, with certainty regarding expectations for the advisory committee meeting, and promote public trust in the process (Daval, Kesselheim, et al., 2022).

Beyond consistently including questions about public health considerations, to enable advisory committees to provide FDA with useful input, the agency should, whenever possible, present evidence regarding the public health impacts of the relevant product or regulatory decisions, including from FDA’s SOURCE modeling system. Similarly, the agency should consider whether additional expertise, for example in systems modeling, epidemiology, health behavior, health communications, or public health ethics, is needed among the members of DSaRM and AADPAC to enable the committees to optimally provide advice to FDA on the public health considerations associated with opioid analgesics. If the agency determines such additional

⁹⁵ This would be consistent with FDA’s approach to Hydexor, for example, where the agency has discussed such issues at advisory committee meetings.

expertise is needed, nominations for members could be solicited and members could be added either as permanent members of a committee or as temporary voting members for the relevant meeting (FDA, 2020d).

In addition, it is important that agency and advisory committee discussions are informed by perspectives from people with lived experience with OUD and with lived experience with pain. To help ensure this, to the extent the agency does not already do so, the agency could consider adding such perspectives to committee membership (including considering scientific experts who also have such lived experience as committee members) or proactively raising awareness about opportunities for public comment. Likewise, although state government officials have the opportunity to participate in the advisory committee process as any member of the public does, FDA might consider proactive outreach or some other form of consultation with such officials, if it is not already doing so, given serious state concerns about the opioid crisis as illustrated, for example, by state actions following the 2013 approval of Zohydro ER.

Finally, as much transparency as possible about the advisory committee process, and how FDA incorporates advisory committee input into any agency decision that follows advisory committee input, would be beneficial for public understanding and promoting the legitimacy of agency decision-making. This might include explaining, to the extent legally permissible, any aspects of meeting structures that have the potential to be perceived as irregularities—for example if key members of a committee are unavoidably unavailable for meetings about opioid analgesics or if the agency elects to solicit input from only AADPAC and not DSaRM for safety-related opioid analgesic questions. These steps could help prevent public perceptions that appropriate procedures were not followed, as when members of Congress raised such concerns about the advisory committee meeting at which the agency sought input only from AADPAC on the safety and effectiveness of Dsuvia, at a meeting held when the chair of the AADPAC was unable to attend (Markey & DeGette, 2019). Another possibility might be considering ways to transparently establish procedures for rapidly convening an advisory committee meeting when emerging evidence suggests serious public health consequences associated with an opioid analgesic, which is another example of a step that might have helped the agency more quickly reconsider the benefits and risks of reformulated Opana ER after intravenous use of the drug was linked to outbreaks of HIV, Hepatitis C virus, and thrombotic microangiopathy and one that also could help provide additional clarity to manufacturers.

This might also include taking additional steps to clarify how advisory committee recommendations informed an agency decision, when that decision differs from what the advisory committee recommended. Agency decisions that differ from advisory committee recommendations are not inherently problematic and are to be expected given the complex nature of many decisions and inevitable uncertainties in data. But it is also the case that the majority of FDA decisions are consistent with advisory committee advice (Zhang et al., 2019). For that reason, the public may have more questions about agency decisions that depart from advisory committee recommendations than about those decisions that are consistent with advisory committee recommendations. This may be particularly true for opioid analgesics where the public is likely to be highly interested in agency decision-making and benefit-risk assessment may be particularly

complicated. When agency decisions differ from advisory committee recommendations there is often some explanation in regulatory documents (*e.g.*, an approval package for an NDA). But for such decisions on opioid analgesics the agency should consider whether it could routinely explain how the advisory committee recommendations informed the regulatory decision and why the agency made a decision that differed from the recommendations, in a format that is easily accessible to the public.⁹⁶ Additionally, if the agency’s thinking is that concerns previously raised by an advisory committee have been resolved, for example by new data or changes to proposed labeling or a proposed REMS, the agency could consider reconvening an advisory committee to publicly solicit input on the question of whether the concerns have been resolved before making the relevant regulatory decision.

⁹⁶ Although not specific to FDA’s use of advisory committees nor to the opioid analgesic context, a 2020 GAO report on advisory committees similarly recommended that the Government Services Administration “encourage FACA committees to make information on agencies’ responses to and implementation of specific recommendations publicly available online, unless exempted from public disclosure under the Freedom of Information Act.” GAO. (2020). Federal Advisory Committees: Actions Needed to Enhance Decision-Making Transparency and Cost Data Accuracy. <https://www.gao.gov/products/gao-20-575>.

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Appendix A: NASEM Report Recommendations Included in Review

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.

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 U.S. Centers for Disease Control and Prevention, and the U.S. Drug Enforcement Administration to develop an evidence-based national approach to pain education encompassing pharmacologic and nonpharmacologic treatments and educational materials on opioid prescribing.

Recommendation 6-1. Incorporate public health considerations into opioid-related regulatory decisions. The U.S. Food and Drug Administration (FDA) should utilize a comprehensive, systems approach for incorporating public health considerations into its current framework for making regulatory decisions regarding opioids. The agency should use this approach, in conjunction with advisory committee input, to evaluate every aspect of its oversight of prescription opioid products in order to ensure that opioids are safely prescribed to patients with legitimate pain needs and that, as actually used, the drugs provide benefits that clearly outweigh their harms. When recommending plans for opioids under investigation; making approval decisions on applications for new opioids, new opioid formulations, or new indications for approved opioids; and monitoring opioids on the U.S. market, the FDA should explicitly consider:

- Benefits and risks to individual patients, including pain relief, functional improvement, the impact of off-label use, incident opioid use disorder (OUD), respiratory depression, and death;
- Benefits and risks to members of a patient’s household, as well as community health and welfare, such as effects on family well-being, crime, and unemployment;
- Effects on the overall market for legal opioids and, to the extent possible, impacts on illicit opioid markets;
- Risks associated with existing and potential levels of diversion of all prescription opioids;
- Risks associated with the transition to illicit opioids (e.g., heroin), including unsafe routes of administration, injection-related harms (e.g., HIV and hepatitis C virus), and OUD; and
- Specific subpopulations or geographic areas that may present distinct benefit-risk profiles.

Recommendation 6-2. Require additional studies and the collection and analysis of data needed for a thorough assessment of broad public health considerations. To utilize a systems approach that adequately assesses the public health benefits and risks described in Recommendation 6-1, the U.S. Food and Drug Administration (FDA) should continue to require safety and efficacy evidence

from well-designed clinical trials while also seeking data from less traditional data sources, including nonhealth data, that pertain to real-world impacts of the availability and use of the approved drug on all relevant outcomes. The FDA should develop guidelines for the collection of these less traditional data sources and their integration in a systems approach.

Recommendation 6-3. Ensure that public health considerations are adequately incorporated into clinical development. The U.S. Food and Drug Administration (FDA) should create an internal system to scrutinize all Investigational New Drug (IND) applications for opioids. This review should examine whether public health considerations are adequately incorporated into clinical development (e.g., satisfactory trial design; see Recommendation 6-2). In implementing this recommendation, the FDA should rarely, if ever, use expedited development or review pathways or designations for opioid drugs and should review each application in its entirety.

Recommendation 6-4. Increase the transparency of regulatory decisions for opioids in light of the committee’s proposed systems approach (Recommendation 6-1). The U.S. Food and Drug Administration should commit to increasing the transparency of its regulatory decisions for opioids to better inform manufacturers and the public about optimal incorporation of public health considerations into the clinical development and use of opioid products.

Recommendation 6-5. Strengthen the post-approval oversight of opioids. The U.S. Food and Drug Administration should take steps to improve post-approval monitoring of opioids and ensure the drugs’ favorable benefit-risk ratio on an ongoing basis. Steps to this end should include use of risk evaluation and mitigation strategies that have been demonstrated to improve prescribing practices, close active surveillance of the use and misuse of approved opioids, periodic formal reevaluation of opioid approval decisions, and aggressive regulation of advertising and promotion to curtail their harmful public health effects.

Recommendation 6-6. Conduct a full review of currently marketed/approved opioids. To consistently carry out its public health mission with respect to opioid approval and monitoring, the U.S. Food and Drug Administration should develop a process for reviewing, and complete a review of, the safety and effectiveness of all approved opioids, utilizing the systems approach described in Recommendation 6-1.

Appendix B: List of Key Regulatory Decisions Included in Review

Actions on OxyContin (oxycodone hydrochloride), starting with the initial approval of the NDA in 1995

Approval of the NDA for the reformulated version of Opana ER (oxymorphone hydrochloride) in 2011, and subsequent actions to remove the drug from the market starting in 2017

Approval of the NDA for Zohydro ER (hydrocodone bitartrate) in 2013

Approval of the NDA for Dsuvia (sufentanil) in 2018

Review, through multiple cycles, of the NDA for Hydexor (hydrocodone, acetaminophen, promethazine)

Appendix C: Example FDA Actions to Implement NASEM Recommendations

Table 5: Example FDA Actions to Implement NASEM Recommendations.[†]

Example FDA Actions to Implement Recommendations	Action Date	Primary NASEM Recommendation(s)*
Maintaining and updating webpage, “Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse”	Ongoing	6-4
Requested that reformulated Opana ER be voluntarily removed from the market	June 2017	6-1
Issued final guidance document, “General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products”	November 2017	4-1
Launched SOURCE (Simulation of Opioid Use, Response, Consequences, and Effects)	2018	4-1, 6-2, 6-5
Held public meeting on Patient-Focused Drug Development for Opioid Use Disorder	April 2018	6-3
Contracted NASEM to study opioid analgesic prescribing for acute pain	August 2018	6-5
Held interagency meeting of federal partners (the National Institute on Drug Abuse, and National Center for Injury Prevention and Control at CDC), modeling teams, and data experts to improve SOURCE	April 2019	4-1, 6-2
Convened advisory committee meeting on the clinical utility and safety concerns associated with higher range of opioid analgesic dosing	June 2019	6-4
Issued draft guidance document, “Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework”	June 2019	6-1, 6-3
Held public hearing, “Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction”	September 2019	6-1, 6-3
Approved modifications to TIRF REMS to better monitor risks and address inappropriate prescribing to opioid-non-tolerant patients	December 2020	6-5
Withdrew approval of reformulated Opana ER	December 2020	6-1
Issued Warning Letter to AcclRx for false or misleading promotion of Dsuvia	February 2021	6-5
Published white paper explaining the agency’s opioid systems modeling effort	March 2021	6-4
Issued Closeout Letter to AcclRx	March 2022	6-5
Held public workshops on prescriber education	Oct. 2021, Apr. 2022	6-5, 5-2
Announced and explained FDA’s “Overdose Prevention Framework”	August 2022	6-4
Published statement on website affirming agency commitment to transparency	September 2022	6-4

[†]This Table provides examples of agency actions to address the NASEM recommendations but is not intended to be an exhaustive list of all relevant agency actions.

*Each example action also may be relevant to additional NASEM Report Recommendations not listed in the Table.

Appendix D: Biographical Sketches of Subject Matter Experts

Institutional affiliations are provided for informational purposes only. The views expressed in this report are those of the authors and do not necessarily represent the views of The Ohio State University.

Micah Berman, JD is an associate professor of public health and law at The Ohio State University's College of Public Health and Moritz College of Law, and a member of Ohio State's Comprehensive Cancer Center. His research explores the intersection of public health research and legal doctrine, with a focus on the regulation of addictive products. He is a co-author of *The New Public Health Law: A Transdisciplinary Approach to Practice and Advocacy* (2nd. edition 2022) and has published extensively in both legal and scientific journals. Professor Berman has served as a senior advisor to the FDA's Center for Tobacco Products, as a visiting scholar at the World Health Organization's Center for International Cooperation on Tobacco Control (in Montevideo, Uruguay), and as a member of the National Institutes of Health's Council of Public Representatives. Prior to joining Ohio State, Professor Berman established and directed policy centers in Ohio and Massachusetts that developed innovative model ordinances and provided policy support to state and local public health programs. In 2021, the American Public Health Association honored Professor Berman with the David P. Rall Award for Advocacy in Public Health for his commitment to science-based prevention of tobacco-related illness and death. He holds a JD with distinction from Stanford Law School, a Certificate in Risk Sciences and Public Policy from the Johns Hopkins Bloomberg School of Public Health, and a BA with highest honors in Public Policy from Brandeis University.

Macarius M. Donneyong, PhD, MPH is an assistant professor of pharmacy and public health with joint faculty appointments in the Division of Outcomes and Translational Sciences, College of Pharmacy, and the Division of Health Services Management and Policy, College of Public Health at The Ohio State University. Dr. Donneyong's research agenda is driven by his passion to improve health equity especially with respect to the effectiveness, safety and adherence to prescribed medications. To achieve this, Dr. Donneyong's research focuses on how to prevent the risk of adverse drug events associated with polypharmacy practice in real-world settings, especially among older adults and racial/ethnic minority populations. His research also seeks to understand the multilevel barriers/facilitators of suboptimal medication adherence among racial/ethnic minorities that emanate from the individual patient, provider, health care system and the communities where patients reside (especially contextual social determinants of health). Dr. Donneyong's research is currently supported with funding from the National Institute on Ageing (NIA)/National Institutes of Health (NIH), National Cancer Institute (NCI)/NIH, the American Foundation for Suicide Prevention (AFSP) and pilot grants from The Ohio State University's Centers for Clinical and Translational Sciences. Dr. Donneyong's research has been published in some of the top-tier peer-reviewed journals in medicine including, the *British Medical Journal*, *JAMA Internal Medicine*, and *Circulation - Heart Failure*, among others. He has also given several invited talks at some of the top universities in the United States. Dr. Donneyong is actively involved in professional scientific societies and has served in multiple leadership roles in these societies, including currently serving as an elected Board Member of the American College of

Epidemiology. Dr. Donneyong teaches and mentors several students at the undergraduate, graduate and postdoctoral levels at The Ohio State University.

Martin Fried, MD, FACP is an assistant professor of clinical medicine in the Division of General Internal Medicine at The Ohio State University College of Medicine. His research and clinical interest focuses on the integration of addiction medicine within primary care. Dr. Fried founded The Ohio State University Primary Care Addiction Medicine Clinic in 2018 and has core roles in research projects funded by the National Institute on Drug Abuse (NIDA), the National Institutes of Health (NIH) and Ohio State's Addiction Innovation Fund. He is deeply involved in both undergraduate and graduate medical education at OSU and serves as the Assistant Director of Ambulatory Education for Ohio State's Department of Internal Medicine Residency Program. Dr. Fried received his BS from the University of Wisconsin-Madison and is an alumnus of Teach For America (Connecticut '08). He received his MD from Albert Einstein College of Medicine and completed his residency training in Primary Care Internal Medicine at New York University where he served as Chief Resident of the Community Health Residency Program of NYU Langone Hospital-Brooklyn.

Kathryn E. Lancaster, PhD, MPH is an associate professor of epidemiology at The Ohio State University's College of Public Health. Her research examines intervention and policy impacts on the interrelationships among substance use (e.g., drugs and alcohol), stigma, and HIV/HCV. Dr. Lancaster's work has resulted in over 70 peer reviewed papers in leading journals including the *Journal of the International AIDS Society (JIAS)*, *Lancet*, *International Journal of Drug Policy*, *PLoS One*, and the *Journal of Medical Ethics*. She has received funding as a Principal Investigator and site Principal Investigator through the National Institute on Drug Abuse (NIDA), National Institute of Mental Health (NIMH), National Institute of Allergy and Infectious Diseases (NIAID), and the National Center for Advancing Translational Sciences (NCATS). In 2017, Dr. Lancaster launched the Substance Use Working Group within the International Epidemiological Databases to Evaluate AIDS (IeDEA) Network, where she serves as the Chair working with IeDEA regional representatives as well as program staff from NIAID, NIMH, NICHD, NIAAA, and NIDA, to generate real-world evidence on substance use and HIV.

Patricia J. Zettler, JD is an associate professor of law at The Ohio State University Moritz College of Law and a faculty member of Ohio State's Drug Enforcement and Policy Center and its Comprehensive Cancer Center. Her research and teaching focus on FDA law and policy. Her scholarship has appeared in leading legal and health sciences journals such as the *Boston College Law Review*, *Food and Drug Law Journal*, *Journal of Law and the Biosciences*, *New England Journal of Medicine*, *JAMA*, and *Science*. Professor Zettler also is a co-author of the 5th edition of *Food and Drug Law: Cases and Materials*. She currently serves as a member of the Food and Drug Law Institute's (FDLI) Board of Directors and as co-chair of the International Society of Cell & Gene Therapy's (ISCT) Committee on the Ethics of Cell and Gene Therapy, also chairing its subcommittee on expanded access. Previously, she served on the National Academies of Sciences, Engineering, and Medicine's (NASEM) Committee on Reviewing the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) and as a consultant to the NASEM Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse,

among other things. Before her academic career, Professor Zettler served as an attorney in the Office of the Chief Counsel at FDA. She received her undergraduate and law degrees from Stanford University, both with distinction.