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# Implementing a Public Health Perspective in FDA Drug Regulation

PATRICIA J. ZETTLER, MARGARET FOSTER RILEY, AND  
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## ABSTRACT

There is, without question, a public health crisis in the United States arising from both illicit and prescription opioid misuse, addiction, and overdose. The Food and Drug Administration (FDA) is one regulator with an important role to play in minimizing the harms associated with prescription opioids, while also ensuring that prescription opioids are available for the evidence-based management of pain. One question, however, is to what extent the agency can consider in its decisions to approve opioids and keep existing ones on the market the provider and patient behaviors contributing to the epidemic. This is, in part, because FDA's approval of drugs is often understood as narrowly focused on weighing the benefits and risks of the products as defined in the preapproval clinical trials that are used to set the drug's official FDA-approved indication. Such a limited focus would exclude important information about the real-world use and public-health impact of prescription opioids and other drugs with externalities. This Article argues that, to better regulate drugs like opioids that have such externalities, one step FDA should take is to use a "public health" perspective in its approval (and withdrawal) decisions. The Article describes how the federal Food, Drug, and Cosmetic Act authorizes FDA to take this broad

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approach in its drug approval and withdrawal decisions and offers some principles for implementing this approach systematically.

## INTRODUCTION

Although the steady increase in opioid prescribing that began in the 1990s has now begun to decrease, opioid prescribing in the United States remains high, far beyond prescribing rates in comparable countries around the world.<sup>1</sup> In 2015, the amount of morphine milligram equivalents prescribed per capita was approximately three times as high as it was in 1999,<sup>2</sup> and about 300 million opioid prescriptions were written.<sup>3</sup> Alongside this high level of prescribing, the United States has also experienced a dramatic increase in opioid misuse, addiction, and overdose over the past two decades—with opioids causing over 42,000 deaths in 2016, and prescription opioids contributing to about 40% of those deaths.<sup>4</sup> Minimizing the harms associated with both prescription and illicit opioids that have given rise to this crisis,<sup>5</sup> while also ensuring that prescription opioids are available for the evidence-based management of pain, will require a comprehensive, long-term effort from a wide range of stakeholders and regulators.<sup>6</sup> FDA, through its authority over the drug market, undoubtedly has an important role to play in this landscape.<sup>7</sup>

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<sup>1</sup> See, e.g., Eriko Onishi et al., *Comparison of Opioid Prescribing Patterns in the United States and Japan: Primary Care Physicians' Attitudes and Perceptions*, 30 J. AM. BRD FAM. MED. 248, 249 (2017); CTRS. FOR DISEASE CONTROL & PREVENTION: ANNUAL SURVEILLANCE REPORT OF DRUG-RELATED RISKS AND OUTCOMES (2017), <https://www.cdc.gov/drugoverdose/pdf/pubs/2017-cdc-drug-surveillance-report.pdf> [<https://perma.cc/N2AL-SWYG>] [hereinafter 2017 CDC Report]; see also Benedikt Fischer et al., *Non-Medical use of Prescription Opioids and Prescription Opioid-Related Harms: Why So Markedly Higher in North American Compared to the Rest of the World?*, 109 ADDICTION 177, 178 (2013) (“The United States consumes the vast majority of the world’s [prescription opioid] supply . . .”).

<sup>2</sup> See, e.g., Gery P. Guy Jr. et al., *Vital Signs: Changes in Opioid Prescribing in the United States, 2006–2015*, CTRS. FOR DISEASE CONTROL & PREVENTION: MORBIDITY & MORTALITY WKLY. REP. (July 7, 2017), <https://www.cdc.gov/mmwr/volumes/66/wr/mm6626a4.htm>; [<https://perma.cc/MU2W-8VEQ>].

<sup>3</sup> See Dina Gusovsky, *Americans Consume Vast Majority of the World's Opioids*, CNBC (Apr. 27, 2016), <http://www.cnbc.com/2016/04/27/americans-consume-almost-all-of-the-global-opioid-supply.html>. [<https://perma.cc/AM6C-ZKS2>].

<sup>4</sup> CTRS. FOR DISEASE CONTROL & PREVENTION, *Opioid Overdose*, <https://www.cdc.gov/drug-overdose/index.html>; see also Leo Beletsky et al., *Fatal Re-Entry: Legal and Programmatic Opportunities to Curb Opioid Overdose Among Individuals Newly Released from Incarceration*, 7 NE. U.L.J. 149, 150 (2015) (describing the “public health crisis” of opioid overdose); Ameet Sarpatwari et al., *The Opioid Epidemic: Fixing A Broken Pharmaceutical Market*, 11 HARV. L. & POL’Y REV. 463, 464 (2017) (“It is difficult to overstate the extent of opioid overuse and misuse in the United States.”).

<sup>5</sup> In addition to prescription opioids, illicit opioids, such as heroin and synthetic fentanyl, clearly also play a central role in the current U.S. opioid epidemic. The markets for prescription and illicit opioids cannot be viewed in isolation, and in recent years illicit, not prescription, opioids have driven much of the increase in overdose deaths. See, e.g., 2017 CDC Report, *supra* note 1, at 8, 20–22; see also Wilson M. Compton et al., *Relationship Between Non-medical Prescription Opioid Use and Heroin Use*, 374 NEW ENG. J. MED. 154, 160 (2016) (finding that a majority of heroin users report using prescription opioids before heroin initiation); Pradip K. Muhuri et al., *Associations of Nonmedical Pain Reliever Use and Initiation of Heroin Use in the United States*, CBHSQ DATA REVIEW (Aug. 2013), <https://www.samhsa.gov/data/sites/default/files/DR006/DR006/nonmedical-pain-reliever-use-2013.htm>. [<https://perma.cc/NZ9K-PSH2>] (finding same). But the focus of this Article is on FDA’s role in helping to address the ways that prescription opioids contribute to the problem while also ensuring that prescription opioids remain available for appropriate, evidence-based pain management.

<sup>6</sup> NATIONAL ACADEMIES OF SCIENCES, ENGINEERING AND MEDICINE, *PAIN MANAGEMENT AND THE OPIOID EPIDEMIC: BALANCING SOCIETAL AND INDIVIDUAL BENEFITS AND RISKS OF PRESCRIPTION*

A key question relating to FDA's role in the U.S. prescription opioid epidemic is to what extent FDA can consider, or regulate, the health care provider and patient behaviors that contribute to over-prescribing and misuse of these drugs. This is, in part, because the standard for approval in the federal Food, Drug, and Cosmetic Act (FDCA) describes drug safety and effectiveness in terms of "the conditions prescribed, recommended, or suggested in the proposed labeling."<sup>8</sup> Accordingly, FDA's evaluation of drugs is often understood as being what we call "drug-specific." That is, the agency is viewed as solely focused on the benefits and risks of the products as defined in the preapproval clinical trials that are used to set the drug's official FDA-approved indication, which are generally short-term studies in highly-selected populations. Likewise, after approval, FDA's regulatory decision making is traditionally conceived as being restricted to addressing the use of the drug as described in FDA-approved labeling, even though providers and patients prescribe or use drugs in ways that deviate from that labeling.<sup>9</sup>

For prescription opioids, such a drug-specific focus clearly would exclude important information about the real-world use and public-health impact of this drug class. In addition, although opioids provide a particularly salient example of a drug class with the potential for externalities, they are not the only such class of prescription drugs. Other FDA-approved prescription drugs and drug classes have effects beyond the individual being treated, including those with the potential for

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OPIOID Use 1–17 (Jonathan K. Phillips, Morgan A. Ford & Richard J. Bonnie eds., 2017), [https://www.ncbi.nlm.nih.gov/books/NBK458660/pdf/Bookshelf\\_NBK458660.pdf](https://www.ncbi.nlm.nih.gov/books/NBK458660/pdf/Bookshelf_NBK458660.pdf) [hereinafter NAS REPORT]; see also Richard J. Bonnie et al., *Both Urgency and Balance Needed in Addressing Opioid Epidemic: A Report from the National Academies of Sciences, Engineering, and Medicine*, 318 JAMA 423, 423–24 (2017).

<sup>7</sup> See, e.g., Scott Gottlieb & Janet Woodcock, *Marshaling FDA Benefit-Risk Expertise to Address the Current Opioid Abuse Epidemic*, 318 JAMA 421, 421 (2017).

<sup>8</sup> 21 U.S.C. § 355(d). There are other reasons that one might question FDA's ability to regulate provider and patient behaviors. For example, FDA oversight has long been characterized as distinct from medical practice regulation. See, e.g., Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the FDA, 37 Fed. Reg. 16,503, 16,504 (proposed Aug. 15, 1972). Notwithstanding this conventional wisdom, the agency indirectly regulates or influences provider behavior in various ways, such as through requiring Risk Evaluation and Mitigation Strategies (REMS). See, e.g., Lewis Grossman, *Drugs, Biologics, and Devices: FDA Regulation, Intellectual Property, and Medical Products in the American Healthcare System*, in THE OXFORD HANDBOOK OF U.S. HEALTH LAW 637 (I. Glenn Cohen, Allison Hoffman & William Sage eds., 2016) (describing FDA's indirect regulation of medical practice); Lars Noah, *Ambivalent Commitments to Federalism in Controlling the Practice of Medicine*, 53 U. KAN. L. REV. 149, 173 (2004) ("[T]he FDA undoubtedly affects the practice of medicine, even if only indirectly."); Margaret Foster Riley, *An Unfulfilled Promise: Changes Needed to the Drug Approval Process to Make Personalized Medicine A Reality*, 70 FOOD & DRUG L.J. 289, 308 (2015) ("In 2007, FDAAA introduced potentially far-reaching limits on the practice of medicine doctrine allowing FDA to impose restrictions (e.g. place and mode of use) on approved drugs."); Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427, 498 (describing FDA's REMS authority as indirectly regulating medical practice); see also Barbara J. Evans, *Distinguishing Product and Practice Regulation in Personalized Medicine*, 81 CLINICAL PHARMACOLOGY & THERAPEUTICS 288, 288 (2007) (describing "the crucial distinction between product and practice regulation"); Scott Gottlieb, *Drug Safety Proposals and the Intrusion of Federal Regulation into Patient Freedom and Medical Practice*, 26 HEALTH AFFAIRS 664, 672 (2007) (describing RiskMAPs as "put[ting] the FDA squarely in the role of dictating medical practice standards and promoting specific clinical behavior").

<sup>9</sup> See, e.g., Tewodros Eguale et al., *Drug, Patient, and Physician Characteristics Associated with Off-Label Prescribing in Primary Care*, 172 ARCHIVE INTERNAL MED. 781, 781 (2012) (describing the prevalence of off-label prescribing); Aaron S. Kesselheim, *Off-Label Drug Use and Promotion: Balancing Public Health Goals and Commercial Speech*, 37 AM. J.L. & MED. 225, 234 (2011) (describing same).

misuse, such as benzodiazepines approved to treat anxiety, and those without the potential for misuse, such as antibiotics, which, when used inappropriately, accelerate the development of resistant bacteria.<sup>10</sup>

Thus, to better regulate prescription opioids and other drugs with externalities, one step FDA should take is to use a broad perspective in its approval (and withdrawal) decisions, by incorporating information in addition to that used in a conventional, drug-specific approach. We call this a “public health” basis for decision-making. In fact, a close review of FDA regulatory history reveals that for some decisions about specific drugs and drug classes, including certain opioids, FDA already does this by incorporating information outside the approved labeling—such as population health impacts and how providers and patients actually use drugs—in its decisions.<sup>11</sup> In this Article, we review how the FDCA authorizes FDA to take such a public health approach not only in its efforts to influence provider and patient behavior through labeling, risk evaluation and mitigation strategies, and other tools, but also in its approval and withdrawal decisions. FDA would effectively serve its mission by consistently using its authority to incorporate public health considerations into approval and withdrawal decisions for drugs with a high potential for externalities.

This Article proceeds in three parts. Part I explains the challenges of regulating drugs with externalities, using prescription opioids as a paradigmatic example that demonstrates the need for the agency to incorporate public health considerations in its oversight of drugs. Part II describes FDA’s legal authority to take this broad approach in its drug approval and withdrawal decisions. Finally, Part III offers some principles for implementing this approach systematically to meet public health goals.

## I. PRESCRIPTION OPIOIDS AND THE CHALLENGE OF REGULATING DRUGS WITH EXTERNALITIES

For many drugs, safety and effectiveness can be well-understood through FDA’s traditional, drug-specific regulatory process that focuses on the benefits and risks of the drug as shown in preapproval clinical trials, and then used as described in FDA-approved labeling after marketing. Prescription opioids, however, are an example of when this regulatory model cannot provide a comprehensive picture of the drugs’ impact on patients and the public health. This Part first provides background on the role of prescription opioids in the current opioid epidemic, including how provider and patient behaviors influence the drugs’ risks. Then it describes how FDA has addressed this public health problem through its conventional, drug-specific regulatory approach, in the context of its shared jurisdiction with the Drug Enforcement Administration (DEA).

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<sup>10</sup> See, e.g., Xanax (alprazolam) Labeling, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/018276s052lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/018276s052lbl.pdf); [<https://perma.cc/M9GA-C6D5>]; FOOD & DRUG ADMIN., *Battle of the Bugs: Fighting Antibiotic Resistance*, <https://www.fda.gov/drugs/resourcesforyou/consumers/ucm143568.htm>. [<https://perma.cc/K6ZN-L4U8>]. For additional examples of other drugs and drug classes that, like opioids, may have externalities, see *infra* notes 170–174 and accompanying text.

<sup>11</sup> See Section II.A., *infra*.

### A. *The Current Opioid Crisis*

Prescription opioids are clearly associated with numerous risks for users that have given rise to the current opioid crisis.<sup>12</sup> These include some risks that might be easily understood to be medical, or public health, concerns, such as death resulting from overdose, developing a substance use disorder, or impaired cognitive function, as well as less severe, but still debilitating, symptoms like constipation.<sup>13</sup> The risks associated with prescription opioid use also include harms that may not as easily be understood to be matters of public health, but arguably ought to be. These include outcomes such as users transitioning from prescription to illicit opioids like heroin, or negative effects on users' families' well-being.<sup>14</sup>

How opioids are prescribed and used influence these risks associated with the products.<sup>15</sup> For example, the formulation (e.g., extended- or immediate-release), dosage, and number of days' supply all have an effect on the risk of developing a substance use disorder or of overdosing.<sup>16</sup> Similarly, the route of administration—which a patient or user might have control over, for example by crushing a pill to snort or inject it—affects the risks associated with opioids.<sup>17</sup>

Although many of the risks of opioids are now well-known, opioids also have been some of the most effective analgesics available, and pain is a widespread, complex, and serious public health problem.<sup>18</sup> Perhaps unsurprisingly given the potential benefits of prescription opioids for pain management and the way behaviors influence the drugs' risks, the current opioid crisis developed alongside increased prescribing of opioids and recognition of the under-treatment of pain, as well as industry marketing of prescription opioids.

#### 1. *The Profound Difficulties of Treating Pain*

Pain is the perception manifest from nociceptive stimuli in internal tissues and external insults detected by peripheral sensors in the body.<sup>19</sup> It is a complex physiologic process, involving many different forms of pain encoded by a number of neural circuits.<sup>20</sup> Pain may be expressed in numerous forms, for example, stabbing, pricking, burning or aching, and may also produce diverse emotions and sensations.<sup>21</sup> Pain also arises in multiple clinical contexts, and each context, and sometimes each individual patient, raises specific issues that need to be addressed in distinct ways. For example, the pain requiring treatment may be acute, as a result of surgery or an injury, such as might occur from playing a sport. Likewise, dental procedures may

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<sup>12</sup> For a full examination of the risks of opioids, see, e.g., the NAS REPORT, *supra* note 6.

<sup>13</sup> NAS REPORT, *supra* note 6, at 120 (citing Howard L. Fields, *Should We Be Reluctant to Prescribe Opioids for Chronic Non-malignant Pain?*, 129 PAIN 233 (2007)).

<sup>14</sup> See *id.* at 388, 393.

<sup>15</sup> See, e.g., *id.* at 196.

<sup>16</sup> See, e.g., *id.* at 191–93.

<sup>17</sup> See, e.g., *id.*

<sup>18</sup> See *id.* at 120.

<sup>19</sup> Cedric Piers & Rebecca Seal, *Neural Circuits for Pain: Recent Advances and Current Views*, 354 SCIENCE 578 (2016).

<sup>20</sup> *Id.*

<sup>21</sup> *Id.*

cause acute pain. Pain may also be chronic, for example, from arthritis, fibromyalgia, and back pain. Pain also may be associated with cancer treatment and end-of-life care. Each individual setting, and patient within that setting, may present special characteristics that may make the pain treatments more or less likely to pose risks of misuse.

In the 1990s, the challenges of pain management, and more specifically, the under-assessment and under-treatment of pain, became a leading medical concern.<sup>22</sup> There was ample evidence of this problem; once asked, many patients reported pain that was not only untreated, but largely unnoticed.<sup>23</sup> Pain control advocates noted that patients were often left with long-term intractable pain. At the time, advocates also believed that physicians' reluctance to prescribe opioids because of concerns about the potential for addiction was misplaced. Among other things, they pointed to a now-widely-cited one-paragraph letter to the editor in a leading medical journal that reported that a review of medical records suggested that addiction was rare when opioids were used in hospitalized patients without a history of addiction.<sup>24</sup> Another article published in 1986 argued that opioids could safely be used for non-cancer-related pain.<sup>25</sup> Despite the relatively small sample size of that study, its premise was largely undisputed and follow up research was not conducted.

Such studies and efforts ultimately led to changes in the medical profession. In 1996, in what is now a well-known address, the president of the American Pain Society argued that pain should be deemed the fifth vital sign. The society subsequently developed algorithms for assessing pain to be included as part of vital sign assessments. By 1999, the Joint Commission issued standards requiring health care organizations to improve pain management and required vigorous treatment of pain.<sup>26</sup> In 2004, the Federation of State Medical Boards recommended that state boards consider punishment for under-treatment of pain. Physician thought-leaders regularly lectured that only 1 percent of the population was at risk for addiction.<sup>27</sup>

Yet despite this attention, all pain, and especially chronic pain, has remained notoriously difficult to treat. Finding appropriate therapies for pain requires understanding the various complex neural circuits involved in different types of pain, much of which is now better—but still incompletely—understood.<sup>28</sup> Nearly half of all dispensed opioid prescriptions in 2012 were prescribed by primary care

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<sup>22</sup> David W. Baker, *The Joint Commission's Pain Standards: Origins and Evolution* (May 5, 2017), [https://www.jointcommission.org/assets/1/6/Pain\\_Std\\_History\\_Web\\_Version\\_05122017.pdf](https://www.jointcommission.org/assets/1/6/Pain_Std_History_Web_Version_05122017.pdf). [<https://perma.cc/F8Z4-37B2>].

<sup>23</sup> Sarpatwari et al., *supra* note 4, at 465 (citing Marilee Donovan et al., *Incidence and Characteristics of Pain in a Sample of Medical–Surgical Inpatients*, 30 PAIN 69, 71, 73 (1987)).

<sup>24</sup> Jane Porter & Hershel Jick, *Addiction Rare in Patients Treated with Narcotics*, 302 NEJM 123 (1980); see also Pamela TM Leung et al., *A 1980 Letter on the Risk of Opioid Addiction*, 376 NEJM 2194 (2017).

<sup>25</sup> R.K. Portenoy & K.M. Foley, *Chronic Use of Opioid Analgesics in Non-malignant Pain: Report of 38 Cases*, 25 PAIN 171 (1986).

<sup>26</sup> Baker, *supra* note 22, at 3–4.

<sup>27</sup> Thomas Catan & Evan Perez, *A Pain-Drug Champion Has Second Thoughts*, WALL ST. J. (Dec. 17, 2012), <https://www.wsj.com/news/articles/SB10001424127887324478304578173342657044604?mg=prod/accounts-wsj>.

<sup>28</sup> *Id.*; Hance Clarke et al., *The Prevention of Chronic Postsurgical Pain using Gabapentin and Pregabalin: A Combined Systematic Review and Meta-Analysis*, 115 PAIN MEDICINE 428 (2012).

physicians, most of whom have only basic education in the details of pain management.<sup>29</sup> There are also insufficient numbers of pain specialists, meaning that other physicians may be unable to connect with a specialist in providing care.

## 2. *Pharmaceutical Industry Marketing*

Not only is pain difficult to understand and treat, it is widespread. Millions of Americans suffer from the burden of pain.<sup>30</sup> Pain poses a significant social and economic burden in the U.S., costing an estimated \$635 billion in treatment and management of pain alone,<sup>31</sup> not including the substantial economic costs from diminished work productivity for both pain sufferers and their families and other caregivers. This has led to an enormous market for pain management therapies, estimated at \$36.1 billion in 2017 with the expectation that it could grow to \$52.0 billion by 2022,<sup>32</sup> which has been long recognized by the pharmaceutical industry.

The pharmaceutical industry spends tens of billions of dollars per year on marketing in an effort to influence prescriber and patient behaviors, and marketing methods have become increasingly sophisticated over the years.<sup>33</sup> Such methods include setting up face to face meetings between health care providers and pharmaceutical sales representatives (detailing); providing health care providers with samples<sup>34</sup>; paying “thought leaders” for presentations at educational and professional meetings; funding Continuing Medical Education programs. All of these strategies have been demonstrated highly effective at increasing prescribing of the advertised drug. Approximately \$4 billion per year is spent on direct-to-consumer (DTC) advertising, which has been shown to lead exposed patients to ask for the advertised drug by name, which in turn makes physicians more likely to prescribe it.<sup>35</sup> In recent

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<sup>29</sup> NAS REPORT, *supra* note 6, at 57.

<sup>30</sup> The 2011 Institute of Medicine (IOM) Report, *Relieving Pain in America*, estimated that as many as 100 million Americans suffer from chronic pain. See INST. OF MEDICINE, RELIEVING PAIN IN AMERICA: A BLUEPRINT FOR TRANSFORMING PREVENTION, CARE, EDUCATION, AND RESEARCH (2011) [hereinafter 2011 IOM REPORT]. While that estimate is probably too high, see NAS REPORT, *supra* note 6, at 50, chronic pain is unquestionably one of the most common and intractable medical problems facing Americans today.

<sup>31</sup> 2011 IOM REPORT, *supra* note 30; Wayne Winegarden, *Estimating the Net Economic Benefit of Abuse-Deterrent Opioids*, ECONO STATS (March 2015), <http://econostats.org/estimating-the-net-economicbenefit-of-abuse-deterrent-opioids>.

<sup>32</sup> BCC RESEARCH, THE GLOBAL MARKET FOR PAIN MANAGEMENT DRUGS AND DEVICES (Aug. 2017), <https://www.bccresearch.com/market-research/healthcare/the-global-market-for-pain-management-drugs-and-devices-hlc026f.html>.

<sup>33</sup> *Persuading the Prescribers: Pharmaceutical Industry Marketing and its Influence on Physicians and Patients*, PEW CHARITABLE TRS. (Nov. 11, 2013), <http://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients>.

<sup>34</sup> *Id.* at 2.

<sup>35</sup> Ed Silverman, *All That Pharmaceutical Advertising May be a ‘Mixed Bag,’ After All*, STAT (Sept. 13, 2016), <https://www.statnews.com/pharmalot/2016/09/13/direct-to-consumer-drug-ads/>. This is not to say that DTC advertising’s public health effects are all negative. For example, DTC advertising can be used to promote awareness of new drugs and their risks. See, e.g., Elizabeth Almasi et. al, *What are the Public Health Effects of Direct-to-Consumer Advertising?* 3 PLOS MEDICINE e145 (2006). FDA is currently studying the effect of such advertising on the public, although it is not studying that effect specifically in the context of opioids. See U.S. Food & Drug Admin., Office of Prescription Drug Promotion (OPDP) Research, <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090276.htm#research>.



years, large pharmaceutical manufacturers have reduced early-pipeline internal research and development in favor of purchasing intellectual property from small biotech companies after they have established proof of concept and completed some clinical trials. The large companies then handle the later-phase trials required for approvals, and focus resources on sales and marketing.

Against this backdrop of an increased focus on marketing rather than research and development, opioids can be an especially attractive product because most opioids now entering the market involve tweaks on the existing technology and do not require extensive R&D, while offering a large potential market of patients.<sup>36</sup> Indeed, as professional organizations encouraged physicians to focus on pain assessment and management beginning in the 1990s, opioid manufacturers actively helped physicians meet these new standards. Until public health experts recently began sounding the alarm about increasing addiction and FDA began holding stakeholder meetings to discuss opioid misuse, manufacturers engaged in aggressive marketing of opioids. Purdue Pharma (Purdue) probably provides the most notorious example, although it was by no means alone. When Purdue introduced its extended-release oxycodone product (OxyContin) in 1995, it was the first formulation of oxycodone with an approved dosing schedule of every 12 hours rather than every 4 to 6 hours. It was indicated “for the management of moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days.”<sup>37</sup> Sales of OxyContin grew from \$44 million (316,000 prescriptions) in 1996 to over \$1 billion in 2000, with combined sales of almost \$3 billion in 2001-2002 (14 million prescriptions).<sup>38</sup> This was the result of a systematic and comprehensive marketing scheme.<sup>39</sup> In that period, Purdue held more than 40 all-expense paid conferences for more than 5000 physicians, pharmacists, and nurses. Purdue doubled its sales force, gave significant bonuses to sales representatives, and actively engaged the highest prescribers. In addition, Purdue greatly expanded its market by promoting Oxycontin for non-cancer related pain. Oxycontin prescriptions for non-cancer-related pain expanded from 670,000 in 1997 to 6.2 million in 2002.<sup>40</sup> Throughout that time, Purdue’s promotional materials argued that the risk of addiction was tiny.<sup>41</sup> Purdue, and three of its executives, ultimately pleaded guilty to criminal charges related to the misleading promotion of OxyContin in 2007.

Although FDA monitors and regulates prescription drug advertising, examples of troubling marketing of opioids and related products have continued to arise. For example, in 2016 the Department of Justice (DOJ) charged two former

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<sup>36</sup> Most research and development in the opioid market is focused abuse deterrent formulations (ADF). See *Report: Opioid Pain Sales to \$18.4B in the U.S. by 2020*, CENTERWATCH (July 17, 2017), <https://www.centerwatch.com/news-online/2017/07/17/report-opioid-pain-sales-hit-18-4b-u-s-2020> [<https://perma.cc/3UGK-4866>].

<sup>37</sup> U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-04-110, PRESCRIPTION DRUGS: OXYCONTIN ABUSE AND DIVERSION AND EFFORTS TO ADDRESS THE PROBLEM 35 (2003).

<sup>38</sup> Art Van Zee, *The Promotion and Marketing of OxyContin: Commercial Triumph, Public Health Tragedy*, 99 J. AM PUBLIC HEALTH 221, 223 (2009).

<sup>39</sup> *Id.* at 221.

<sup>40</sup> *Id.* at 223

<sup>41</sup> *Id.* OxyContin’s original label approved in 1996 stated that “Delayed absorption, as provided by OxyContin tablets, is believed to reduce the abuse liability of the drug.” See, e.g., *\$635 Million Settlement Resolves Oxycontin Charges*, 15 NO. 4 FDA ADVERT. & PROMOTION MANUAL NEWSLETTER 2.

pharmaceutical sales representatives with fraudulently using educational programs to promote sales of fentanyl sublingual spray (Subsys). The complaint alleged that physicians were compensated for providing educational presentations to healthcare professionals, but that the programs were pretense for social gatherings at expensive restaurants.<sup>42</sup> As another example, one of the most notorious advertisements aired during the 2017 Super Bowl was an advertisement for naloxegol (Movantik), a drug indicated for opioid-induced constipation. Although the drug was not an opioid, critics noted that the advertisement sought to normalize use of opioids for chronic pain.<sup>43</sup>

Marketing practices have also harnessed the power of patient advocacy groups. As these groups have proliferated in recent years, drug manufacturers can influence them by providing grant funding, which may garner endorsements for the manufacturers' positions.<sup>44</sup> Reuters reported that opioid manufacturers gave money to 45 of 158 patient advocacy and professional organizations that commented on the CDC's 2015 proposed guidelines on prescribing opioids for chronic pain. Organizations that had received funding from opioid manufacturers were more likely to oppose the guidelines.<sup>45</sup>

Pharmaceutical industry marketing and patient advocacy (some funded by the industry) were two leading factors that changed the culture around opioid prescribing and contributed to the explosion in use of opioids over the last few decades. These opioid use trends, in turn, revealed the substantial potential for misuse and overdose. In 2016, forty percent of all opioid related deaths in the U.S., roughly 16,000 people, were due to prescription opioids.<sup>46</sup> An estimated two million people misuse or are dependent on prescription opioids.<sup>47</sup> Many of the individuals who have moved on to stronger illicit drugs like heroin and fentanyl began by misusing prescription opioids.

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<sup>42</sup> Press Release, U.S. Dep't of Justice, Former Pharmaceutical Company Employees Arrested for Participating in Fentanyl Kickback Scheme (June 9, 2016), <https://www.justice.gov/usao-sdny/pr/former-pharmaceutical-company-employees-arrested-participating-fentanyl-kickback-scheme> [https://perma.cc/4CP9-HW4W].

<sup>43</sup> Ahiza Garcia, *Super Bowl Drug Ad Spurs Big Backlash*, CNN (Feb. 12, 2016), <http://money.cnn.com/2016/02/11/news/super-bowl-painkiller-constipation-ad/index.html> [https://perma.cc/4Z2U-4D7T].

<sup>44</sup> C. Wick et al., *The Characteristics of Unsolicited Clinical Oncology Literature Provided by Pharmaceutical Industry*, 18 ANNALS OF ONCOLOGY 1580 (2007).

<sup>45</sup> Ronnie Cohen, *Industry Money May Taint Advice from Patient Groups, Regulators*, REUTERS (Jan. 17, 2017), <http://www.reuters.com/article/us-health-patients-advocacy-conflicts/industry-money-may-taint-advice-from-patient-groups-regulators-idUSKBN1512ZG>. [https://perma.cc/4BNA-FXNY]. Reuters also reported that United Therapeutics Corp. is paying \$210 million to settle claims that it used a patient-assistance charity to illegally pay Medicare patients' expenses for its blood pressure medications, thereby increasing its sales. This settlement is the first to come out of a broader investigation by the government into the financial relationships between various pharmaceutical manufacturers and patient groups. See Nate Raymond, *United Therapeutics to Pay \$210 Million to Resolve U.S. Kickback Probe*, REUTERS (Dec. 20, 2017), <https://www.reuters.com/article/us-utd-therapeut-settlement/united-therapeutics-to-pay-210-million-to-resolve-u-s-kickback-probe-idUSKBN1EE24U> [https://perma.cc/NJY7-EG5K].

<sup>46</sup> CTRS FOR DISEASE CONTROL AND PREVENTION, *Prescription Opioid Overdose Data* (2017), <https://www.cdc.gov/drugoverdose/data/overdose.html> [https://perma.cc/JVP7-E543].

<sup>47</sup> DEP'T OF HEALTH AND HUMAN SERVICES, SUBSTANCE ABUSE AND MENTAL HEALTH SERVICES ADMIN., CTR FOR BEHAVIORAL HEALTH STATISTICS AND QUALITY, NATIONAL SURVEY ON DRUG USE AND HEALTH (2014), <https://www.samhsa.gov/data/sites/default/files/NSDUH-FRR1-2014/NSDUH-FRR1-2014.pdf> [https://perma.cc/B6GN-PPZL].

The social cost of opioid misuse and dependence is nearly eighty billion dollars annually.<sup>48</sup> In short, the patient advocates who argued for better treatment of pain in the 1980s and 1990s were not wrong about the need to do so, but the fact that such advocacy led to the prescribing of more opioids became its own problem.<sup>49</sup>

### *B. Applying FDA's Regulatory Process to Opioids*

FDA oversight of prescription drugs covers the human clinical trials necessary to support approval and continues through the approval decision and the monitoring of drugs after they are marketed. Despite this regulation, one reason there has been little evidence of the comprehensive safety and effectiveness of opioids, particularly in the context of indirect effects, addiction, and third-party misuse, is that, as explained in this section, FDA's traditional, drug-specific regulatory scheme generally has not required such study.<sup>50</sup>

#### *1. The Approval Process*

The approval process for opioids has generally been the same as that for other new drugs.<sup>51</sup> FDA's approval process focuses on a particular drug's safety and efficacy as demonstrated in the setting of its clinical trials. In most situations, it does not factor in the practice of medicine or patient behavior. To initiate clinical investigation of a new compound, a drug sponsor must file an Investigational New Drug Application (IND) in which the sponsor lays out its general investigative plan, its projected clinical protocols as well as information about the drug's chemistry, pharmacology, and toxicology.<sup>52</sup> The investigative plan lays out the anticipated types of clinical trials that will be conducted, the number and characteristics of the participants in the clinical trials and any foreseeable risks to participants based on the drug's toxicology.

For approval, the FDCA requires that drugs be shown to have benefits that outweigh their risks.<sup>53</sup> A drug's efficacy is demonstrated by showing "substantial evidence" of its effects under the conditions of use prescribed. Clinical benefit is subject to the intended use of the drug; it may mean an improvement in symptoms,

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<sup>48</sup> Sarpatwari et al., *supra* note 4, at 464 (citing Curtis s. Florence et al., *The Economic Burden of Prescription Opioid Overdose, Abuse and Dependence in the United States*, 2013, 54 MED. CARE 901, 901 (2016)).

<sup>49</sup> NAS REPORT, *supra* note 6, at 51.

<sup>50</sup> Cf. Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. TECH. L. REV. 345, 347-48 (2007) (describing how FDA approval incentivizes research).

<sup>51</sup> Because some opioids have been on the market since before the Kefauver-Harris Amendments of 1962, and the FDCA itself, were enacted, certain drugs were subject to the Drug Efficacy Study Implementation (DESI) review rather than the modern drug approval process. However, like the modern drug approval process, the DESI review was focused on effectiveness for individual patients in the context of the drug's labeling, not on indirect effects. Much of the DESI review of opioids was not completed until the 1980s. See, e.g., NAS Report, *supra* note 6, at 359-60; Peter Barton Hutt & Robert Temple, *Commemorating the 50th Anniversary of the Drug Amendments of 1962*, 68 FOOD & DRUG L.J. 449, 454 (2013); FOOD & DRUG ADMIN., *Background Document, Pediatric Advisory Committee Meeting, Benefit/Risk Assessment of Prescription Opioid Antitussive Products for Treatment of Cough in Pediatric Patients* (Sept. 11, 2017), <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM575013.pdf>.

<sup>52</sup> 21 C.F.R. § 312.23.

<sup>53</sup> 21 U.S.C. § 355(d).

an improved mode of delivery or an improved side-effect profile as compared to no therapy (often a placebo) or a known effective therapy. Safety is measured within the studied cohort. Superiority is not required. FDA prefers two “adequate and well-controlled investigations” of a drug’s efficacy, but the FDCA was changed in 1997 to permit FDA to grant approval on the basis of only one such investigation with additional supporting evidence.<sup>54</sup> About one-third of drugs are now approved on the basis of a single pivotal trial.<sup>55</sup>

Because clinical trials often represent the greatest expense in the drug approval process for drug sponsors, sponsors are incentivized to eliminate as much human variability as possible in the clinical trial process. This means that there can be major differences between the study population and the population that ultimately uses the drug after it is approved. For example, in the case of the extended-release hydrocodone (Zohydro) approved in 2013, the clinical trial that supported the drug’s approval was limited to patients with lower back pain. No trials involving other patients who might use the drug for pain, such as patients with cancer or arthritis were required.<sup>56</sup> In addition, to further reduce the potential for human variability, opioid drug sponsors have used a controversial trial design called “enriched enrollment randomized withdrawal” (EERW). That method screens out patients who are non-responsive or suffer adverse effects so that they do not confound efficacy data. Critics, however, argue that the methodology further reinforces the disconnect between the clinical trials supporting regulatory approval and clinical practice in the real world.<sup>57</sup>

In addition, most opioids approved in recent decades have not been subject to the full clinical trial process required for novel drugs because they are reformulations of existing drugs. They have therefore been approved via an abbreviated pathway that relies heavily on the safety and efficacy data about the existing product.<sup>58</sup> Clinical trials are required to bridge any differences between the products or to address any new safety signals that may arise.<sup>59</sup> But those clinical trials are typically of a short duration that does not reflect how long opioids are frequently prescribed in clinical practice.

## 2. Post-Approval Monitoring

FDA continues to monitor and evaluate the safety and effectiveness of new drugs once they are approved and marketed. This is because some risks may not be apparent until after larger and more heterogeneous populations have used the drug. Likewise, some risks may become apparent when a drug has been used for a duration

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<sup>54</sup> *Id.*; see also The Food and Drug Administration Modernization Act of 1997 (FDAMA), Pub. L. No. 105-115 § 115, 11 Stat. 2296, 2313.

<sup>55</sup> Nicholas S. Downing et al., *Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005–2012*, 311 JAMA 368 (2014).

<sup>56</sup> NAS REPORT, *supra* note 6, at 364; FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION AND RESEARCH, *Summary Review [of Zohydro ER]* (Oct. 25, 2013), [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/202880Orig1s000SumR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202880Orig1s000SumR.pdf) [<https://perma.cc/NV69-AEXZ>].

<sup>57</sup> Jonah Campbell & Nicholas King, “Unsettling Circularity”: *Clinical Trial Enrichment and the Evidentiary Politics of Chronic Pain*, 12 *BIOsocieties* 191 (2017).

<sup>58</sup> 21 U.S.C. § 355(b)(2).

<sup>59</sup> 21 C.F.R. §§ 314.50, 314.54.

longer than that of the clinical trials supporting approval (two-thirds of drugs are approved based on trials lasting six months or shorter).

One primary way that FDA monitors marketed drugs is through adverse event reporting. FDA maintains a database, FDA's Adverse Event Reporting System (FAERS), that contains submitted adverse event reports relating to FDA regulated drugs and biologics.<sup>60</sup> Drug manufacturers are subject to various reporting obligations, including providing FDA with serious and unexpected adverse event reports within fifteen days.<sup>61</sup> But reports that come to FAERS from health care providers, lawyers, and patients, rather than manufacturers, are made voluntarily. Best estimates are that only 10 percent of adverse events are actually reported to FAERS.<sup>62</sup>

To address some of these weaknesses of FAERS, in 2007 Congress authorized FDA to create an active postmarket surveillance system, known as Sentinel. FDA launched Sentinel to better monitor postmarket safety issues with drugs in 2014. Sentinel gathers and analyzes data provided by participating organizations, including some of the nation's largest health insurers, disease registries as well as many hospitals. Although Sentinel should help FDA address some of the shortcomings of relying only on the information in FAERS, its ability to use its available data to accurately assess a drug's risk is still subject to major challenges.<sup>63</sup>

Beyond these general challenges of monitoring the safety and effectiveness of marketed drugs, adverse events relating to misuse of opioids are particularly challenging to observe because physicians or patients may have incentives to conceal them.<sup>64</sup> For example, patients may not report some psychological effects relating to opioids. Because of stigma or fear of criminal prosecution, there may be reluctance to report issues relating to substance misuse. In addition, in many contexts of misuse, it is difficult to know which drug caused the adverse event. There are many different surveillance networks for drug misuse at the national and state level.<sup>65</sup> The Researched Abuse, Diversion and Addiction-Related Surveillance System (RADARS) and the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO) are two that provide postmarketing surveillance data to the pharmaceutical industry. But those systems do not provide the product-level information that had been provided by the Drug Abuse Warning Network (DAWN).<sup>66</sup> That data allowed comparison of the impacts, mortality and morbidity

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<sup>60</sup> FOOD & DRUG ADMIN., *Questions and Answers on FDA's Adverse Event Reporting System (FAERS)*, <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects> [<https://perma.cc/2CMS-ZQJ7>].

<sup>61</sup> 21 C.F.R. § 314.80; Steven Findlay, *Health Policy Brief: The FDA's Sentinel Initiative*, HEALTH AFFAIRS (June 4, 2015), [http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief\\_id=139](http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=139). [<https://perma.cc/8SPG-XRKE>]. Other reporting requirements include that manufacturers must report non-serious or expected adverse events on a quarterly basis for the first three years after a drug is approved, and then annually thereafter. See 21 C.F.R. § 314.90.

<sup>62</sup> Findlay, *supra* note 61, at 2.

<sup>63</sup> *Id.* at 4.

<sup>64</sup> Richard C. Dart, *Monitoring Risk: Post marketing Surveillance and Signal Detection*, 105S DRUG AND ALCOHOL DEPENDENCE S26 (2009).

<sup>65</sup> See NAS REPORT, *supra* note 6, at app. C.

<sup>66</sup> NAS REPORT, *supra* note 6, at 228.

trends, of specific products. Such data would likely be useful for FDA in developing postmarket risk mitigation strategies. The DAWN networks were defunded in 2011.

FDA has the authority to require postmarketing studies if there is some evidence or signal of “serious risk.”<sup>67</sup> The FDCA directs FDA to conduct regular screenings of the FAERS database to identify such risks, and through this process, FDA has identified drugs that may warrant further regulatory action or investigation. Although FDA has rarely used its authority to require additional studies based on such information, opioids are one such instance in which the agency has required postapproval research.<sup>68</sup> However, FDA has limited authority to ensure that postmarket study commitments, in general, are completed.<sup>69</sup> In the specific context of opioids, FDA may be further hampered by a lack of product-specific information.

In addition to requiring studies and trials, FDA has the authority to require special risk mitigation programs, known as Risk Evaluation and Mitigation Strategies (REMS). The agency has required REMS for almost all opioids, and has recently expanded the demands of those requirements. But even these broader REMS requirements do not address the need for further systematic study and research to fully understand the relationships between specific opioids’ uses and misuses.<sup>70</sup> A recent meta-analysis of available studies on long-term opioid treatment found very few studies that extended for more than six weeks, and that methodologies and definitions varied widely.<sup>71</sup> The study found limited evidence on the effectiveness of varying opioid dosing strategies, and limited data on the effectiveness of risk assessment modalities for predicting potential abuse or misuse. The authors expressed an urgent need for well-designed studies to answer some of these questions.<sup>72</sup> Whether through pre-approval studies, postapproval surveillance, or other safety-related tools like REMS, FDA has not yet systematically used its authorities to require and assess comprehensive data on the indirect, public health impacts of opioids.

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<sup>67</sup> 21 U.S.C. § 355(o)(3).

<sup>68</sup> See, e.g., Letter from Bob A. Rappaport, Director, Division of Anesthesia and Analgesia Products, CDER, FDA, to Craig Landau, CMO & VP Clinical, Medical & Regulatory Affairs, Purdue Pharma L.P. (Apr. 5, 2010) (describing postmarket requirements for Oxycontin), [https://www.accessdata.fda.gov/drugsatfda\\_docs/applletter/2010/022272s000ltr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2010/022272s000ltr.pdf) [<https://perma.cc/RKE8-5W7H>]. For a database of all required postmarket studies, see FOOD & DRUG ADMIN., *Postmarket Requirements and Commitments*, <https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm> [<https://perma.cc/S579-UNL5>].

<sup>69</sup> Findlay, *supra* note 61, at 3; Kevin Fain et al., *The Food and Drug Administration Amendments Act and Postmarketing Commitments*, 310 JAMA 202, 202–03 (2013); see also Alison M. Pease et al., *Postapproval Studies of Drugs Initially Approved by the FDA on the Basis of Limited Evidence: Systematic Review*, 357 BRITISH MED. J. 1680 (2017).

<sup>70</sup> Until recently, FDA required REMS only for extended release/long acting opioids, which have higher risks for abuse because of their higher potency. But FDA moved to extend those requirements to immediate release opioids, still the most commonly prescribed class of opioids, in September 2017. See Scott Gottlieb, *FDA Takes Important Steps to Stem the Tide of Opioid Misuse and Abuse*, FDA VOICE (Sept. 28, 2017), <https://blogs.fda.gov/fdavoices/index.php/2017/09/fda-takes-important-steps-to-stem-the-tide-of-opioid-misuse-and-abuse>.

<sup>71</sup> Roger Chou et al., *The Effectiveness and Risks of Long-Term Opioid Therapy for Chronic Pain: A Systematic Review for a National Institutes of Health Pathways to Prevention Workshop*, 162 ANNALS OF INTERNAL MEDICINE 276, 280–81 (2015).

<sup>72</sup> *Id.*

### C. *The Role of DEA*

Because opioids are controlled substances,<sup>73</sup> FDA is not the only federal regulator that oversees the opioid market, which further complicates the regulatory landscape. Since 1973, FDA has shared jurisdiction over the regulation of opioids and other controlled substances with DEA. DEA was created to add intensified law enforcement mechanisms to the federal response to drug misuse pursuant to the Controlled Substances Act (CSA).<sup>74</sup> The CSA establishes a statutory framework for the regulation of production, possession, and distribution of *controlled substances*, defined as any drug or substance (excluding alcohol products) that has potential for abuse. Opioids have been treated as controlled substances and subject to some sort of scheduling since the advent of federal regulation in the 1920s. DEA licenses controlled substance manufacturers, sets supply quotas for the drugs, regulates prescribers and dispensing pharmacies, and prosecutes illicit or illegal use or production.

Under the CSA, FDA and DEA share responsibility for determining scheduling of controlled substances. Scheduling is intended to balance the need to limit supply of potentially addicting drugs while at the same time permitting sufficient supply for medicinal and research use.<sup>75</sup> The five schedules for drugs covered by the CSA are designed to provide a structure that would be responsive to the nuanced requirements of perceived danger, medical utility, and potential for abuse.<sup>76</sup> Scheduling status affects prescribing power (e.g. manner of prescribing and limits on refills), triggers requirements for supply chain record keeping, and determines the degree of criminal punishment for illicit trafficking. While all five schedules impose controls, the most significant controls are imposed on Schedule I substances (extremely limited use) and Schedule II substances. Indeed, in practice, scheduling can have a profound effect on the therapeutic use of a drug, but it functions as a very blunt instrument. Many physicians refuse to prescribe schedule II drugs. Since many opioids are scheduled or being rescheduled into schedule II, this should reduce opioid prescribing but it may also limit access for patients who need them.<sup>77</sup>

To make decisions about whether to schedule a drug and, if so, at what level, the CSA requires FDA and DEA to consider eight factors: (1) the drug's actual or potential for abuse, (2) scientific evidence of the drug's pharmacologic effect, (3) the state of current scientific knowledge regarding the drug, (4) the drug's history and current pattern of abuse, (5) the scope, duration and significance of abuse, (6) risk to public health, (7) the drug's psychic or physiologic dependence liability and (8) whether the substance is an immediate precursor of a substance already controlled

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<sup>73</sup> See, e.g., DRUG ENFORCEMENT ADMINISTRATION, *List of Controlled Substances*, <https://www.deadiversion.usdoj.gov/schedules> [<https://perma.cc/63VD-242V>].

<sup>74</sup> 21 U.S.C. §§ 801–904.

<sup>75</sup> See, e.g., John A. Gilbert, Jr., *DEA Regulation of Controlled Substances and Listed Chemicals*, 65 FOOD & DRUG L.J. 623, 624 (2010). For a detailed discussion of how FDA and DEA work together on scheduling decisions, including difficulties that may arise in the process, see, e.g., Lars Noah, *Challenges in the Federal Regulation of Pain Management Technologies*, 31 J. L. MED. & ETHICS 55 (2003).

<sup>76</sup> Joseph F. Spillane, *Debating the Controlled Substances Act*, 76 DRUG & ALCOHOL DEPENDENCE 17, 21–22 (2004).

<sup>77</sup> See Noah, *Challenges in the Federal Regulation of Pain Management Technologies*, *supra* note 75, at 62–63.

under the CSA.<sup>78</sup> Some of this data, such as the scientific evidence of the drug's pharmacologic effect, is readily accessible through FDA's approval process. But much of the data cannot be available until there is broad experience with the drug. Moreover, given the paucity of research about long-term use of many opioids, many scheduling decisions are made in a way that appears data-driven but are in reality based on limited data and anecdotal evidence or intuition.

Although DEA has an important role to play in responding to the opioid epidemic,<sup>79</sup> the focus of DEA's mission is one of law enforcement, rather than public health. Because of the complicated nature of the opioid crisis, including its intersection with pain management and prescriber and patient behaviors, it is critical that the regulatory response to the crisis include public health expertise.<sup>80</sup> FDA, in contrast to DEA, has a public health mission, the institutional expertise in assessing a drug's safety and effectiveness within the context of that mission, and the gatekeeping authority over prescription opioids. Accordingly, this Article focuses on FDA's application of its legal authority to opioids, with subsequent consideration of other drugs that raise similar population health concerns.

## II. FDA'S LEGAL AUTHORITY TO TAKE A BROAD REGULATORY PERSPECTIVE

The current opioid epidemic has arisen over the course of many years, and as a result of many complex factors.<sup>81</sup> Adequately addressing the problem will take a sustained effort on the part of many regulators and stakeholders, and no one action by FDA, alone, will be sufficient.<sup>82</sup> But there may be ways to improve FDA's regulatory approach for opioids and other drugs with externalities—such as by ensuring that the agency incorporates population health information, including provider and patient behaviors, into its approval and withdrawal decisions in a systematic way.

For many of its drug-related regulatory decisions, FDA's authority to take this broader, public health perspective on the evidence relevant to those decisions is expressly granted in the FDCA. For example, FDA may require a REMS when necessary to ensure that a drug's benefits outweigh its risks.<sup>83</sup> In conducting that benefit-risk analysis, the statute explicitly contemplates the agency considering uses and impacts beyond those described in the labeling. In requiring a REMS, FDA is to consider, among other things, “any known or potential adverse events,” including the risks of misuse and overdose from patients using the drug in ways not in the labeled instructions.<sup>84</sup> Additionally, for REMS with elements to assure safe use—the most

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<sup>78</sup> 21 U.S.C. § 811(c).

<sup>79</sup> See, e.g., Rebecca L. Haffajee, *Preventing Opioid Misuse with Prescription Drug Monitoring Programs: A Framework for Evaluating the Success of State Public Health Laws*, 67 HASTINGS L.J. 1621, 1637 (2016) (describing law enforcement's ability to limit diversion as important for public health).

<sup>80</sup> See, e.g., NAS REPORT, *supra* note 6, at 1–15.

<sup>81</sup> See Part I, *supra*.

<sup>82</sup> See, e.g., NAS REPORT, *supra* note 6, at 1–15.

<sup>83</sup> 21 U.S.C. § 355-1(a)(1).

<sup>84</sup> See 21 U.S.C. § 355-1(a)(1)(E), (b) (emphasis added); see also NAS REPORT, *supra* note 6, at 381 (making a similar point).



restrictive types of REMS—the agency must not only evaluate the benefits and risks of the drug, but also the impact of the REMS requirements on patient access and the health care delivery system.<sup>85</sup>

Yet, because the baseline drug approval language in the FDCA is not parallel in its express wording,<sup>86</sup> FDA’s approval decisions have been interpreted as “drug-specific”—needing to be focused on the benefits and risks and the use of the drug as described in the labeling. We argue that such a conception of FDA’s authority is too narrow, and that a broader, “public health” approach can be observed in past FDA decisions regarding approval or withdrawal. This Part first describes FDA’s practice of taking a public health approach in its drug approval and withdrawal decisions, providing examples of when FDA has done so, and then describes the legal authority permitting that approach.

### *A. The Public Health Regulatory Perspective in Practice*

The FDCA authorizes FDA to approve a drug when the drug is shown to be efficacious and safe enough “under the conditions prescribed, recommended, or suggested in the proposed labeling.”<sup>87</sup> As FDA recently explained in a memorandum, “[t]he separate weighing of benefit and risk for each intended use is critical” because evidence supporting safety and efficacy in one “setting” does not necessarily indicate that the same product is safe and efficacious in another setting.<sup>88</sup>

But the fact that a drug’s benefit-risk profile may be different in different settings does not mean that FDA must ignore the realities of how particular drugs are used, or likely to be used, in ways that deviate from the approved labeling and affect other patients or the public health.<sup>89</sup> Indeed, FDA has recognized that the kinds of evidence necessary to determine safety and efficacy vary across drugs. Since at least 1985, the agency’s regulations regarding approvals of new drug applications (NDAs) and abbreviated new drug applications (ANDAs, for generics) have explained:

While the statutory standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards. Thus, FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards.<sup>90</sup>

Similarly, for opioids and other drugs with the potential for misuse, since at least 1985, FDA regulations have required that NDAs include “studies or information

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<sup>85</sup> 21 U.S.C. § 355-1(f)(2); *see also* NAS REPORT, *supra* note 6, at 10-15 (making a similar point).

<sup>86</sup> If FDA determines that an approved drug no longer satisfies the standard for approval, the agency may withdraw its approval of the drug. 21 U.S.C. 355(e). Thus, FDA’s withdrawal actions can be viewed as involving the same questions about the expansiveness of the information that it may consider as its approval decisions do.

<sup>87</sup> 21 U.S.C. § 355(d); *see also* Am. Pharm. Ass’n v. Mathews, 530 F.2d 1054, 1055 (D.C. Cir. 1976) (McGowan, J., concurring) (arguing, based on 21 U.S.C. § 355(d), that “methadone is safe for its intended use notwithstanding the possibility that it will be employed in unintended fashions”).

<sup>88</sup> FOOD & DRUG ADMIN., MEMORANDUM: PUBLIC HEALTH INTERESTS AND FIRST AMENDMENT CONSIDERATIONS RELATED TO MANUFACTURER COMMUNICATIONS REGARDING UNAPPROVED USES OF APPROVED OR CLEARED MEDICAL PRODUCTS 4-2-3 (Jan. 2017), <https://www.regulations.gov/document/D-FDA-2016-N-1149-0040> [<https://perma.cc/ZA5U-4MXM>] [hereinafter FDA MEMO].

<sup>89</sup> *Cf.* Egualle et al., *supra* note 9 (describing the prevalence of off-label uses).

<sup>90</sup> 21 C.F.R. § 314.105(c); *see also* 50 Fed. Reg. 7452 (Feb. 22, 1985); NAS REPORT, *supra* note 6, at 380 (“[T]he agency also has acknowledged that it has ‘flexibility’ in applying the approval standard.”).

related to abuse of the drug,” in recognition of the risks to individual patients and their communities associated with such drugs.<sup>91</sup> FDA has implemented this regulatory language by taking a broad perspective on the evidence relevant to its benefit-risk determinations for approvals and withdrawals (or analogous decisions) for drugs subject to misuse and drugs with other kinds of clinical externalities.<sup>92</sup>

One example of FDA incorporating population health information into its assessments of drugs of misuse comes from OxyContin, which was originally approved for moderate to severe pain when continuous, around-the-clock treatment was needed.<sup>93</sup> In 2010, after FDA approved an abuse-deterrent formulation of OxyContin, Purdue, the drug’s manufacturer, took the original formulation off the market.<sup>94</sup> FDA was then faced with the possibility of generic manufacturers seeking approval for their formulations. Before a generic equivalent of a no-longer-marketed brand-name drug may be approved, FDA must determine whether the brand-name drug was withdrawn for reasons of safety or effectiveness, and this determination is, essentially, based on the same criteria that FDA uses to approve or withdraw approval of applications.<sup>95</sup> In this case, FDA concluded that the brand-name was withdrawn from the market for reasons of safety or effectiveness, a determination that was made based on widespread patient misuse of that non-abuse-deterrent formulation. FDA’s finding “that the benefits of original OxyContin no longer outweigh its risks” provides an example of the agency incorporating non-labeling-related patient experiences into its benefit-risk determination process.<sup>96</sup>

As another example, in June 2017, FDA asked Endo Pharmaceuticals to stop marketing its extended-released oxymorphone product, Opana ER, “due to the public health consequences of abuse,” and explained that if Endo Pharmaceuticals declined to voluntarily withdraw Opana from the market, FDA would “take steps to formally

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<sup>91</sup> 21 C.F.R. § 314.50(d)(5)(vii), 50 Fed. Reg. 7452 (Feb. 22, 1985); *see also* NAS REPORT, *supra* note 6, at 381 (“For drugs with the potential for misuse, for example, NDAs must include ‘studies or information related to abuse of the drug,’ which, of course, is not information about the use of the drug as directed in the proposed labeling.”).

<sup>92</sup> *See, e.g.*, NAS REPORT, *supra* note 6, at 380–85; Gottlieb and Woodcock, *supra* note 7; Peter Lurie, Associate Commissioner, FDA, Integrating the Broader Public Health Consequences of Opioid Abuse and Misuse into the Evaluation of New Opioid Products (Nov. 4, 2016), <http://www.nationalacademies.org/hmd/~media/Files/Activity%20Files/PublicHealth/PainResearch/LURIE2.pdf> [<https://perma.cc/T299-QM2L>] [hereinafter Lurie Presentation]; *see also* 82 Fed. Reg. 45,597, 45,599 (Sept. 29, 2017) (soliciting comment on what “public health considerations” should be incorporated into FDA’s benefit-risk assessment of opioids).

<sup>93</sup> 78 Fed. Reg. 23,273 (Apr. 18, 2013) [hereinafter OxyContin Notice].

<sup>94</sup> *Id.*

<sup>95</sup> *See* 21 U.S.C. § 355(j)(7)(C); *see also* OxyContin Notice, *supra* note 93, at 23,274 (“FDA concludes that the benefits of original OxyContin no longer outweigh its risks.”). *But see* DONALD. O. BEERS & KURT R. KARST, *GENERIC AND INNOVATOR DRUGS: A GUIDE TO FDA APPROVAL REQUIREMENTS* § 3.02[B] (8th ed., 2017) (“How FDA is supposed to determine whether a drug has been withdrawn from sale for safety or effectiveness reasons is not spelled out in the statute.”).

<sup>96</sup> OxyContin Notice, *supra* note 93, at 23,274. FDA’s decision on OxyContin did not amount to a decision that all non-abuse deterrent formulations were no longer safe and effective. For example, shortly after the agency published its determination that original OxyContin was removed from the market for safety and effectiveness reasons, the agency determined that original Opana ER (oxymorphone), which also lacked an abuse deterrent formulation, was *not* removed from the market for safety and effectiveness reasons after the newer abuse deterrent formulation was approved. The agency distinguished reformulated Opana ER from reformulated OxyContin based on data suggesting that reformulated Opana, unlike OxyContin, could still be easily crushed and snorted. *See* 78 Fed. Reg. 38,053 (June 25, 2013).

require its removal by withdrawing approval.”<sup>97</sup> Opana was first approved in 2006, and then reformulated in 2012.<sup>98</sup> The reformulated version, while intended to be more resistant to manipulation for misuse, proved to still be easy to inject, and the injection of the drug was linked to an HIV and HCV outbreak in Indiana.<sup>99</sup> Although FDA has not, as of yet, officially withdrawn approval of reformulated Opana,<sup>100</sup> Endo Pharmaceuticals voluntarily stopped marketing the drug in July 2017, and FDA’s request that Endo do so represents the agency incorporating non-labeling-related patient experiences into its drug evaluations.<sup>101</sup>

In certain instances, the agency has also incorporated a public health perspective into its assessments of drugs that are not controlled substances associated with misuse. For example, in its benefit-risk assessment of antibiotics for both animal and human use, the agency has long considered the risk that inappropriate use will lead to greater antibiotic resistance.<sup>102</sup> Resistance can render antibiotics ineffective, and all uses of antibiotics, including appropriate uses, contribute to the development of resistance by killing the bacteria that are not resistant.<sup>103</sup> But inappropriate uses—such as use in animals for growth promotion rather than for treating infection, use in patients who do not have signs of a bacterial infection, or use in patients who fail to complete a full course of treatment to eradicate the entire infection—contribute to the rise of resistance without offering commensurate health benefits.<sup>104</sup> Actions that

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<sup>97</sup> See Press Release, Food & Drug Admin., FDA Requests Removal of Opana ER for Risks Related to Abuse (June 8, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm562401.htm>. [<https://perma.cc/ZE22-3VQF>].

<sup>98</sup> See *id.*

<sup>99</sup> See *id.*; see also FOOD & DRUG ADMIN., SUMMARY MINUTES OF THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE AND ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE JOINT MEETING (Mar. 13–14, 2017), <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM551226.pdf>. [<https://perma.cc/75G7-ESFW>].

<sup>100</sup> Nor, as of the time of writing, has FDA determined that reformulated Opana was withdrawn from the market for reasons of safety or effectiveness. But given FDA’s June 2017 request, it seems likely FDA would make such a determination should a company seek to market a generic version of the drug.

<sup>101</sup> Moreover, there are signs that the agency may take a similar approach for other opioid products in the future. For example, in November 2017 FDA sent a complete response letter to Pharmaceutical Manufacturing Research Services (PMRS) declining to approve the company’s immediate release oxycodone product. After PMRS requested an opportunity for a hearing pursuant to 21 C.F.R. § 314.110(b)(3), FDA published a Federal Register Notice explaining that it declined to approve the drug for various reasons, including that “the data submitted were not sufficient to rule out the possibility that the proposed formulation could result in a greater proportion of abuse by injection of PMRS’s product compared to a conventional IR oxycodone formulation.” Although, as of the time of writing it is not clear whether FDA ultimately will refuse to approve the drug, the agency’s reasoning appears similar to that it applied to Opana. 83 Fed. Reg. 6196, 6197 (Feb. 13, 2018).

<sup>102</sup> See, e.g., NAS REPORT, *supra* note 6, 383–84; see also Aaron S. Kesselheim & Kevin Outterson, *Improving Antibiotic Markets for Long Term Sustainability*, 11 YALE J. HEALTH POL’Y, L. & ETHICS 101, 113–14 (2011) (describing the ways patient and provider behaviors contribute to resistance). Although the agency’s statutory authority for regulating animal drugs differs in some ways from human drugs, the approval standard for animal drugs similarly describes the safety and effectiveness of the drugs “under the conditions prescribed, recommended, or suggested in the proposed labeling thereof.” 21 U.S.C. § 360b(d)(1)(A).

<sup>103</sup> See Brad Spellberg et al., *The Future of Antibiotics and Resistance*, 368 NEW ENG. J. MED. 299, 299–300 (2013).

<sup>104</sup> See, e.g., Kesselheim & Outterson, *supra* note 102, at 114; FOOD & DRUG ADMIN., *Phasing Out Certain Antibiotic Use in Farm Animals* (2013), <https://www.fda.gov/ForConsumers/>

the agency has taken based on this risk included attempting, ultimately unsuccessfully, to withdraw approval of certain animal antibiotics used for growth promotion, issuing guidance on mitigating the risks of resistance associated with antibiotic use in animals, and requiring language in the labeling for antibiotics intended for human use to encourage judicious prescribing.<sup>105</sup>

There are other examples in which FDA incorporates a broad range of evidence into certain approval and withdrawal decisions. These include considering the herd immunity benefits of vaccines<sup>106</sup>; FDA's decision to withdraw approval of certain acetaminophen-containing prescription drugs based in part on the risk of liver damage when patients do not use the products as directed<sup>107</sup>; and certain considerations for over-the-counter drug approvals, such as studies of their actual, rather than intended, use.<sup>108</sup>

### *B. Interpreting the Statutory Standard for Approval*

Although FDA in some instances has incorporated broader, population-level information into its assessments of the safety and efficacy of drugs “under the conditions prescribed, recommended, or suggested in the proposed labeling,”<sup>109</sup> it has not clearly described its authority to do so either in the preambles to its

ConsumerUpdates/ucm378100.htm [https://perma.cc/J76D-KFB6]; see also CTRS. FOR DISEASE CONTROL & PREVENTION, ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES 11 (2013), <http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf> [https://perma.cc/K8C4-GW22] (finding that up to fifty percent of antibiotics used in the United States are used inappropriately).

<sup>105</sup> See, e.g., NAS REPORT, *supra* note 6, at 383–84.

<sup>106</sup> In addition to conferring benefits to the patients who receive vaccines, one well-known public health benefit of vaccination is “herd” or “community immunity.” If a large enough portion of the population is immunized against a contagious disease, the whole community—including those who are not immunized—benefits because the likelihood of an outbreak of the disease is reduced. Consistent with this important function of vaccination, FDA-approved labeling for certain vaccines, such as Gardasil (the human papillomavirus (HPV) vaccine) and the measles, mumps, rubella (MMR) vaccine, includes discussion of the population impact of the vaccines—although herd immunity does not appear to have been studied as part of the pivotal trials. See, e.g., Gardasil Labeling 21, <https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm111263.pdf> [https://perma.cc/BT38-82NV]; MMR Labeling 3, <https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM123789.pdf> [https://perma.cc/DT8M-FASK]. FDA's decision to approve Gardasil for boys and men may provide another indicator that the agency considers the population effects of vaccines. In making that decision, the agency appears to have considered both the vaccine's effectiveness in preventing HPV-caused genital warts, anal cancer, and certain precancerous lesions in vaccinated boys and men as well as the role that boys and men play in transmitting HPV to girls and women. See, e.g., Lurie Presentation, *supra* note 92; cf. FOOD & DRUG ADMIN., VACCINE AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE, Transcript of Proceeding at 183 (Sept. 9, 2009) (quoting the Gardasil sponsor as explaining that “men play an important role in transmitting HPV to women”), <https://wayback.archive-it.org/7993/20170113080600/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/UCM183640.pdf> [https://perma.cc/7EHW-ZTCF].

<sup>107</sup> See, e.g., NAS REPORT, *supra* note 6, at 384–85; 76 Fed. Reg. 2691 (Jan. 14, 2011).

<sup>108</sup> See, e.g., FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: SELF-SELECTION STUDIES FOR NONPRESCRIPTION DRUGS (Apr. 2013), <https://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm272122.pdf>, [https://perma.cc/D8GN-TU3Q].

<sup>109</sup> 21 U.S.C. § 355(d).

regulations on new drug applications or to justify individual regulatory actions.<sup>110</sup> In this Part, we evaluate the agency's statutory authority to consider such health impacts in applying the statutory standard for approval (or withdrawal of a drug's approval), concluding that it, indeed, possesses that authority.

As a preliminary matter, for the subset of drugs with externalities that are controlled substances, the FDCA's relationship to the CSA is relevant to determining the scope of FDA's authority because "the meaning of one statute may be affected by other Acts."<sup>111</sup> In *FDA v. Brown & Williamson Tobacco Corp.*, the Supreme Court concluded—based on federal law before the enactment of the 2009 Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act)<sup>112</sup>—that Congress did not intend for FDA to regulate tobacco products in part because Congress had "directly addressed the problem of tobacco" through federal legislation that did not provide a role for the agency.<sup>113</sup> The context for controlled substances is quite different. The CSA clearly envisions a role for FDA in regulating controlled substances, and, importantly, does not change FDA's approval standard or the agency's ability to determine independently which controlled substances have met that standard.<sup>114</sup>

For all drugs with externalities (including controlled substances), the agency's mission—of protecting and promoting the public health by "taking appropriate action on the marketing of regulated products"<sup>115</sup>—and the evolving nature of technology and scientific understanding suggest that the FDCA ought to be interpreted broadly.<sup>116</sup> Under this view, Congress did not intend to "specify every detail of regulation" when enacting the FDCA and its numerous amendments.<sup>117</sup> Rather, Congress intended the FDCA to be nimble enough to allow FDA to address emerging and evolving technologies and problems.<sup>118</sup> For example, as a practical matter, it is difficult to imagine that Congress would not want FDA to consider the full range of risks associated with drugs such as opioids when making its approval decisions.<sup>119</sup>

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<sup>110</sup>*See, e.g.*, 50 Fed. Reg. 7452 (Feb. 22, 1985) (final rule for relevant revisions to 21 C.F.R. pt. 314); 47 Fed. Reg. 46,622 (proposed rule for relevant revisions to 21 C.F.R. pt. 314).

<sup>111</sup>*Food & Drug Admin. v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000).

<sup>112</sup>Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, 123 Stat. 1776 (2009).

<sup>113</sup>*Brown & Williamson*, 529 U.S. at 137.

<sup>114</sup>*See* notes 73–80, *supra*, and accompanying text.

<sup>115</sup>21 U.S.C. § 393(b).

<sup>116</sup>*See, e.g.*, Peter Barton Hutt, *Philosophy of Regulation under the Federal Food, Drug and Cosmetic Act*, 28 FOOD DRUG COSMETIC L.J. 177, 178 (1973); *see also* *United States v. Article of Drug Bacto-Unidisk*, 394 U.S. 784, 798 (1969) ("[R]emedial legislation such as the Food, Drug, and Cosmetic Act is to be given a liberal construction consistent with the Act's overriding purpose to protect the public health."); *cf.* ANTONIN SCALIA & BRYAN A. GARNER, *READING LAW: THE INTERPRETATION OF LEGAL TEXTS* 63 (2012) ("A textually permissible interpretation that furthers rather than obstructs the document's purpose should be favored.").

<sup>117</sup>Hutt, *supra* note 116, at 178.

<sup>118</sup>*See id.*

<sup>119</sup>*Cf. The Federal Response to the Opioid Crisis: Hearing Before S. Comm. on Indian Affairs*, (2017) (written testimony on behalf of witnesses from the Department of Health and Human Services) <https://www.fda.gov/NewsEvents/Testimony/ucm579512.htm> [<https://perma.cc/GY3A-T22L>].

In addition to this general principle of interpreting the FDCA broadly, through considering the FDCA in light of the agency's public health mission,<sup>120</sup> we conclude that there are specific legal arguments that support the agency's authority to consider a broad range of evidence in its approval and withdrawal decisions. To be clear, we are not arguing that FDA's approvals are for anything other than the indication in the approved labeling, nor should our discussion be viewed as undermining the regulatory focus on a product's intended use. FDA approvals are focused on the specific indication in a drug's proposed labeling because evidence establishing effectiveness is typically limited to that indication and a drug's risks may be outweighed by its benefits for one clinical scenario but not for others.<sup>121</sup> Likewise, there are vital public health rationales for current FDA rules that limit pharmaceutical marketing to the specific approved indication such as helping to ensure that such marketing is informative and non-misleading, encouraging rigorous studies of the safety and effectiveness of new indications, and maintaining the integrity of the drug approval framework.<sup>122</sup> But in weighing the benefits and risks of a drug for an intended use, FDA is not required to ignore the ways that provider and patient behaviors—actual use of the drug—influence that weighing for individual patients, and for the broader population.

### 1. *Whole Text*

The Supreme Court has explained that “[s]tatutory construction [ ] is a holistic endeavor.”<sup>123</sup> This means that a statutory provision should be read to be “compatible with the rest of the law,” including its other provisions, its structure, and its subsequent amendments<sup>124</sup> to “fit, if possible, all parts into a harmonious whole.”<sup>125</sup> Consistent with this idea, the drug approval language in section 505(d) of the FDCA cannot be read apart from the rest of the FDCA. Numerous provisions in the FDCA contemplate FDA relying on evidence about how a drug is actually used to weigh the

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<sup>120</sup>See, e.g., *Bacto-Unidisk*, 394 U.S. at 798.

<sup>121</sup>See, e.g., FDA MEMO, *supra* note 88, at 7.

<sup>122</sup>See, e.g., FDA MEMO, *supra* note 88, at 10–11; Nathan Cortez, *The Statutory Case Against Off-Label Promotion*, 83 U. CHI. L. REV. ONLINE 124 (2016); Kesselheim, *Off-Label Drug Use and Promotion*, *supra* note 9, at 231; Joshua M. Sharfstein & Alta Charo, *The Promotion of Medical Products in the 21st Century: Off-Label Marketing and First Amendment Concerns*, 314 JAMA 1795, 1796 (2015). But see Coleen Klasmeier & Martin H. Redish, *Off-Label Prescription Advertising, the FDA and the First Amendment: A Study in the Values of Commercial Speech Protection*, 37 AM. J.L. & MED. 315, 316 (2011) (“[I]n many instances [as a result of FDA’s policies on off-label promotion] doctors are likely to be deprived of valuable information about important off-label uses that are totally lawful and extremely beneficial to some very sick people.”).

<sup>123</sup>*United Sav. Ass’n of Texas v. Timbers of Inwood Forest Assocs., Ltd.*, 484 U.S. 365, 371 (1988); see also *Food & Drug Admin. v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 132 (2000) (discussing whole-text canon); SCALIA & GARNER, *supra* note 116, at 167 (explaining that statute “must be construed as a whole”); WILLIAM N. ESKRIDGE JR., PHILIP P. FRICKEY & ELIZABETH GARRETT, *CASES AND MATERIALS ON LEGISLATION: STATUTES AND THE CREATION OF PUBLIC POLICY*, app. B at 2021 (4th ed. 2007) (“Statutory interpretation is a ‘holistic’ endeavor.”).

<sup>124</sup>*United Sav. Ass’n.*, 484 U.S. at 371; see also Cortez, *supra* note 122, at 138–39 (describing the whole-text canon).

<sup>125</sup>*Brown & Williamson*, 529 U.S. at 133 (quoting *FTC v. Mandel Brothers, Inc.*, 359 U.S. 385, 389 (1959)) (internal quotations omitted).

drug's benefits and risks, including provider and patient behaviors that affect the benefit-risk balance.<sup>126</sup>

One clear example comes from the requirements for information that must be included in a drug's application and reported after approval. Section 505(b) of the FDCA requires that sponsors of new drug applications submit, as part of their application, "full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use" without limiting the required information to that about the uses described in the drug's proposed labeling.<sup>127</sup> In its regulations, FDA has noted that the type of information necessary to make approval decisions varies across drugs,<sup>128</sup> and studies and information related to misuse of the drug are required specifically for drugs with that potential.<sup>129</sup>

After approval, section 505(k)(1) requires sponsors to report to FDA any information about an approved drug relevant to FDA's ability to determine whether to withdraw approval.<sup>130</sup> One requirement that FDA has imposed pursuant to this authority is that sponsors must submit "adverse drug experience information" to the agency, which includes information about "any" adverse event regardless of whether it is associated with a use described in the approved labeling.<sup>131</sup> For over-the-counter (OTC) drugs marketed under a monograph rather than an approved application, the FDCA requires broad reporting of adverse events including those that reflect uses not described in the drug's labeling, such as overdose and misuse.<sup>132</sup>

Similarly, in the Food and Drug Administration Amendments Act (FDAAA) of 2007, Congress instructed FDA to create a system for proactive post-market surveillance of marketed drugs, known as Sentinel.<sup>133</sup> The statute requires FDA "to provide for active adverse event surveillance" using data from a wide range of sources, including electronic health records and insurance claims—sources that contain information about how drugs are actually used, not limited to the intended uses described in the labeling.<sup>134</sup> This provision also required FDA to establish standardized procedures for reporting "all serious adverse drug experiences,"

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<sup>126</sup>Cf. Patricia J. Zettler, *The Indirect Consequences of Expanded Off-Label Promotion*, 78 OHIO STATE L.J. 1053, 1087–88 (2017) (making a similar argument with respect to the agency's authority to consider off-label uses in its approval decisions).

<sup>127</sup>21 U.S.C. § 355(b); see Zettler, *Expanded Off-Label Promotion*, *supra* note 126, at 1087 (citing the same provision).

<sup>128</sup>21 C.F.R. § 314.105(c).

<sup>129</sup>21 C.F.R. § 314.50(d)(5)(vii).

<sup>130</sup>21 U.S.C. § 355(k).

<sup>131</sup>21 C.F.R. § 314.80(a), (c); see also 44 Fed. Reg. 19,434, 19,434 (Apr. 3, 1979) (explaining that adverse experience reporting is required to enable FDA to make determinations about whether there are grounds for withdrawing approval).

<sup>132</sup>21 U.S.C. § 379aa.

<sup>133</sup>21 U.S.C. § 355(k)(3); FOOD & DRUG ADMIN., *FDA's Sentinel Initiative* (2017) <https://www.fda.gov/safety/fdassentinelinitiative/ucm2007250.htm>; [<https://perma.cc/6TN8-G5W3>]; see Barbara J. Evans, *Authority of the Food and Drug Administration to Require Data Access and Control Use Rights in the Sentinel Data Network*, 65 FOOD & DRUG L.J. 67, 73–75 (2010) (describing Sentinel); Efthimios Parasidis, *Patients over Politics: Addressing Legislative Failure in the Regulation of Medical Products*, 2011 WIS. L. REV. 929, 951 (2011) (describing same).

<sup>134</sup>21 U.S.C. § 355(k)(3).

without restriction, including those that occur from overdose and misuse.<sup>135</sup> Thus, in requiring FDA to create Sentinel and standardized reporting procedures, Congress envisioned FDA monitoring the full range of safety and effectiveness information associated with marketed drugs as they are actually used.<sup>136</sup>

The recently-enacted 21st Century Cures Act (Cures Act) underscores that an expansive range of information is available to FDA when it makes its benefit-risk determinations.<sup>137</sup> For example, Sections 3001 and 3002 amended the FDCA to require that FDA, after approving a new drug, publicly describe the patient experience data, if any, that it reviewed and to develop a plan for issuing guidance on “the collection of patient experience data, and the use of such data.”<sup>138</sup> The law defines patient experience data as including information about “the impact of . . . a . . . therapy [] on patients’ lives” and “patient preferences with respect to treatment.”<sup>139</sup> This language appears broad enough to include a wide variety of information and in the context of opioids would certainly encompass how using the drug is affecting a patient’s family’s well-being.<sup>140</sup> Indeed, as of the time of writing, FDA is planning to hold a public meeting on patient-focused drug development for opioid use disorder (OUD), at which it will be soliciting patient perspectives on the “emotional or social effects of OUD,” as well as OUD’s impact on patients’ “ability to function in [their] personal . . . life.”<sup>141</sup> Additionally, Section 3022 of the Cures Act requires FDA to “establish a program to evaluate the potential use of real world evidence” in its approval decisions for new indications for already-approved drugs.<sup>142</sup> Real world evidence is defined as including “data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.”<sup>143</sup> Accordingly, it is likely to include information about how a drug is actually used—again suggesting that FDA is authorized to consider a broad range of information in its benefit-risk determinations at the time of approval.

These provisions exemplify how a broad spectrum of information—including information about how a drug may be actually prescribed and used by providers and patients—will be evaluated by FDA when it is determining whether the standard for approval is initially met, and whether drugs continue to meet that standard after

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<sup>135</sup>21 U.S.C. § 355(k)(3)(C)(i)(II) (emphasis added).

<sup>136</sup>See, e.g., Barbara J. Evans, *Seven Pillars of A New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 NOTRE DAME L. REV. 419, 482 (2010); cf. Michael J. Malinowski, *Doctors, Patients, and Pills—A System Popping Under Too Much Physician Discretion? A Law-Policy Prescription to Make Drug Approval More Meaningful in the Delivery of Health Care*, 33 CARDOZO L. REV. 1085, 1121 (2012) (“[FDAAA] expresses a belief that drawing more information from the physician-patient experience into the regulatory process with enhanced FDA market presence will shore up the reliability of prescription drugs.”).

<sup>137</sup>Pub. L. No. 114-255, 130 Stat. 1033 (2016).

<sup>138</sup>*Id.* at §§ 3001, 3002.

<sup>139</sup>*Id.* at § 3001.

<sup>140</sup>*Cf.* NAS REPORT, *supra* note 6, at 393 (describing the “benefits and risks to members of a patient’s household” as something FDA should consider in its regulation of opioids).

<sup>141</sup>83 Fed. Reg. 11,208, 11,209 (Mar. 14, 2018). This Federal Register Notice provides the full list of the topics related to patient-focused drug development for OUD on which FDA is soliciting information.

<sup>142</sup>Pub. L. No. 114-255 § 3022, 130 Stat. 1033 (2016).

<sup>143</sup>*Id.*



marketing. In the provisions added by the Cures Act, Congress expressly described FDA taking a broad perspective on the information relevant to its benefit-risk determinations in additional contexts. It seems inconsistent with the FDCA to require that sponsors submit such information to FDA, and to authorize FDA to gather such information itself through Sentinel, but at the same time prohibit the agency from considering that full range of information in making its benefit-risk determinations.

## 2. Absurdity

A second, related argument supporting FDA's authority to permit use of population-level information that it deems relevant to its drug-specific benefit-risk determinations comes from the "absurdity doctrine."<sup>144</sup> Under this doctrine, courts have departed "from the plain meaning of statutory text when its literal application would lead to an 'absurd' result" in light of the statutory context.<sup>145</sup> Looking at other provisions in the FDCA, one could argue that it would be absurd to read the statutory standard for approval as limiting FDA to only considering information about the safety and effectiveness of a drug when used as described in FDA-approved labeling or only by populations described in the approved labeling.

One could make this argument based on many of the provisions described in the previous section. It would be strange to require sponsors submit a wide range of information to FDA, including information about drugs arising from uses that depart from the approved labeling, while at the same time prohibiting FDA from considering that information in its benefit-risk determinations.<sup>146</sup>

Another example might come from some of the additional powers granted to FDA in FDAAA.<sup>147</sup> These drug safety tools include the authority to require a REMS and postapproval safety labeling changes, studies, and trials.<sup>148</sup> In deciding whether to require any of these risk mitigation measures, the FDCA explicitly authorizes FDA to consider information about drug uses that depart from those described in the approved labeling, and from sources that will include information about how drugs are actually used, including Sentinel.<sup>149</sup> It would be absurd to permit FDA to impose

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<sup>144</sup>See, e.g., SCALIA & GARNER, *supra* note 116, at 234; see also *Mova Pharm. Corp. v. Shalala*, 140 F.3d 1060, 1068 (D.C. Cir. 1998) ("In deciding whether a result is absurd, we consider not only whether that result is contrary to common sense, but also whether it is inconsistent with the clear intentions of the statute's drafters—that is, whether the result is absurd when considered in the particular statutory context.").

<sup>145</sup>Glen Staszewski, *Avoiding Absurdity*, 81 IND. L.J. 1001, 1002 (2006); *Mova Pharm. Corp.*, 140 F.3d at 1068; see also *United States v. Ron Pair Enterprises, Inc.*, 489 U.S. 235, 242 (1989) ("The plain meaning of legislation should be conclusive, except in the 'rare cases [in which] the literal application of a statute will produce a result demonstrably at odds with the intentions of its drafters.'"); *Holy Trinity Church v. United States*, 143 U.S. 457, 460 (1892) (If a literal construction of the words of a statute be absurd, the act must be so construed as to avoid the absurdity.); *ESKRIDGE ET AL.*, *supra* note 123, at app. B at 20 ("Avoid interpreting a provision in a way inconsistent with the overall structure of the statute or with another provision . . .").

<sup>146</sup>*Cf. Mova Pharma Corp.*, 140 F.3d at 1068 (connecting "absurdity" to the "statutory context"); SCALIA & GARNER, *supra* note 116, at 167 (explaining that the "whole-text doctrine" overlaps with other tools of statutory construction).

<sup>147</sup>See Pub. L. No. 110-85, 121 Stat. 823 (2007); cf. Zettler, *Toward Coherent Federal Oversight*, *supra* note 8, at 454, 456, 462 (making a similar argument with respect to the agency's REMS authority and its ability to consider off-label uses in its approval decisions).

<sup>148</sup>21 U.S.C. §§ 355(o)(3), (4); 355-1.

<sup>149</sup>21 U.S.C. § 355-1(b) (defining adverse drug experience and new safety information).

requirements for studying and mitigating drugs' risks based on their real-world effects, but prohibit the agency from making approval or withdrawal decisions—which could be characterized as the agency's most powerful risk mitigation tools—based on the same information.<sup>150</sup> This argument is perhaps strongest for FDA's REMS authority. FDA may require a REMS when necessary to ensure that a drug's benefits outweigh its risks—that is, to ensure that drug meets the approval standard in the FDCA.<sup>151</sup> If FDA can consider a drug's real-world effects to determine whether a REMS is needed, it would be odd to conclude that FDA cannot consider that same information in deciding whether to approve, or withdraw approval of, a drug.

### 3. Congressional Acquiescence

The theory of Congressional acquiescence or approval also supports an interpretation of the FDCA that permits FDA to take a broad perspective on the evidence relevant to its benefit-risk determinations. Although Congressional inaction is not generally a good indicator of legislative intent, the Supreme Court has explained that “the silence of Congress . . . may sometimes give rise to an implication as to the Congressional purpose,” particularly when the interpretation of a statute is long-standing and there has been “abundant opportunity” for amendments.<sup>152</sup> In this case, FDA has had regulations in place since 1985 interpreting the FDCA as giving the agency “flexibility” in determining what information is needed for it to determine whether a drug meets the statutory standard for approval.<sup>153</sup> Although FDA has not formally interpreted this flexibility as encompassing a public health basis for approval decisions, the language is broad enough to cover such an approach. Additionally, FDA has implemented a public health perspective publicly in specific cases since the regulation was originally promulgated.<sup>154</sup> Over the past three decades, Congress has had ample opportunity to revise the FDCA, with FDA's authority being amended over 20 times since 1985,<sup>155</sup> and Congress revisiting the FDCA at least every five years since 1992 to re-authorize medical product user fees.<sup>156</sup> Thus, a court could conclude that Congress has

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<sup>150</sup>On the other hand, one might also argue that this result would not be absurd, because it makes sense for FDA to consider different information in restrictions that fall short of a complete ban on marketing.

<sup>151</sup>21 U.S.C. § 355-1(a); see Ameet Sarpatwari et al., *Using a Drug-Safety Tool to Prevent Competition*, 370 NEW ENG. J. MED. 1476, 1476–77 (2014) (“REMS requirements have also been hailed as a means for the FDA to approve important new drugs that might otherwise have been rejected.”).

<sup>152</sup>See *Graves v. New York*, 306 U.S. 466, 479 (1939); 73 AM. JUR. 2D STATUTES § 82; see also *Food & Drug Admin. v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 155 (2000) (discussing Congressional acquiescence); Cortez, *supra* note 122, at 141–42 (discussing same).

<sup>153</sup>21 C.F.R. §§ 314.50(d)(5)(vii), 314.105(c); 50 Fed. Reg. 7452 (Feb. 22, 1985) (final rule for relevant revisions to 21 C.F.R. pt. 314).

<sup>154</sup>See Part II.A, *supra*.

<sup>155</sup>See, e.g., Peter Barton Hutt, *The State of Science at the Food and Drug Administration*, 60 ADMIN. L. REV. 431, 467 (2008); FOOD & DRUG ADMIN., *Milestones in U.S. Food & Drug Law History*, <https://www.fda.gov/aboutfda/whatwedo/history/milestones/ucm128305.htm> [https://perma.cc/UL8J-L7LB].

<sup>156</sup>See, e.g., Jonathan J. Darrow, et al., *Speed, Safety and Industry Funding: From PDUFA to the FDA Reauthorization Act of 2017*, 377 NEW ENGL. J. MED. 2278, 2278–80 (2017).

acquiesced to FDA's interpretation of the FDCA as enabling it to consider a wide range of evidence in its approval and withdrawal decisions.

#### 4. Deference

There are, of course, weaknesses to these arguments that FDA may incorporate population health considerations into its benefit-risk determinations for drugs. Perhaps most obviously, although the context of the statute cannot be ignored, one might nevertheless point to the precise language of the approval standard—specifying that safety and effectiveness is determined “under the conditions prescribed, recommended, or suggested in the proposed labeling.”<sup>157</sup>

This language can be compared to the amendments to the FDCA enacted through the Tobacco Control Act. The Tobacco Control Act amended the FDCA to give FDA jurisdiction over tobacco products, requiring, among other things, pre-market authorization for “new tobacco products.”<sup>158</sup> The standard for the agency to authorize the marketing of a new tobacco product is that marketing it “would be appropriate for the protection of the public health,”<sup>159</sup> considering “the risks and benefits to the population as a whole, including users and nonusers of the tobacco product.”<sup>160</sup> Congress, therefore, can clearly articulate an approval standard that permits FDA to incorporate public health considerations into its approval determinations. Because such precise language is not found in the drug approval parts of the statute, one might argue that Congress did not intend to authorize FDA to apply a similar standard to its drug approval (and withdrawal) decisions.<sup>161</sup>

But no one canon of statutory interpretation trumps all others, and courts may be likely to defer to FDA's inclination to include considerations such as provider and patient behaviors in its benefit-risk determinations for drugs as a reasonable interpretation of the FDCA. Under *Chevron U.S.A. Inc. v. Natural Resources Defense Council, Inc.*,<sup>162</sup> courts defer to “permissible” agency interpretations of ambiguous statutory provisions.<sup>163</sup> In light of the arguments described above, courts would have sufficient grounds to conclude that the FDCA is at least ambiguous as to the scope of information that FDA may incorporate into its benefit-risk determinations for drugs, and that FDA has appropriately interpreted the FDCA as giving the agency flexibility in special cases, as set forth in its regulations. Even if *Chevron* was overturned,<sup>164</sup> courts may be likely to agree with FDA's interpretation

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<sup>157</sup>See, e.g., ESKRIDGE ET AL, *supra* note 123, app. B at 19 (“Plain meaning rule: follow the plain meaning of the statutory text.”); SCALIA & GARNER, *supra* note 116, at 56 (“When deciding an issue governed by the text of a legal instrument, the careful lawyer or judge . . . examines the very words of the instrument.”).

<sup>158</sup>Family Smoking Prevention and Tobacco Control Act, Pub. L. No. 111-31, 123 Stat. 1776 (2009).

<sup>159</sup>21 U.S.C. § 387j(c)(2)(A).

<sup>160</sup>*Id.* at § 387j(c)(4).

<sup>161</sup>*Cf.* Whitfield v. United States, 543 U.S. 209, 216 (2005) (“Congress has included an express overt-act requirement in at least 22 other current conspiracy statutes, clearly demonstrating that it knows how to impose such a requirement when it wishes to do so.”).

<sup>162</sup>467 U.S. 837 (1984).

<sup>163</sup>*Id.* at 842–43; see also Cortez, *supra* note 122, at 136–37 (describing the “*Chevron* two-step”).

<sup>164</sup>See, e.g., Regulatory Accountability Act, H.R. 5, 115<sup>th</sup> Congress (as passed by House, Jan. 11, 2017); *The Chevron Doctrine: Constitutional and Statutory Questions in Judicial Deference to Agencies:*

in this instance. Because the FDCA’s “primary objective” is “protect[ing] the public health,”<sup>165</sup> courts may view an interpretation of the FDCA as authorizing the agency to exercise flexibility in what information it deems necessary to analyze the benefits and risks of drugs as well-founded.<sup>166</sup>

### III. IMPLEMENTING FDA’S BROAD AUTHORITY

Because of the clear and extensive public health harms associated with opioid use and misuse, as well as the history of misleading industry marketing, opioids present a particularly compelling case for FDA to consider a broad range of evidence, such as provider and patient behaviors that affect the benefits and risks of drugs, in its regulatory decisions, including approval and withdrawal decisions.<sup>167</sup> But FDA’s legal authority does not require that the agency limit this approach only to the opioids context,<sup>168</sup> as there are other drugs for which this approach may be necessary.<sup>169</sup>

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*Hearing Before the Subcomm. On Regulatory Reform, Commercial and Antitrust Law of the H. Comm. on the Judiciary*, 114th Cong. (2016); *Examining Agency Use of Deference: Hearing Before the Subcomm. on Regulatory Affairs and Federal Management of the S. Comm. on Homeland Security and Governmental Affairs*, 114th Cong. (2016); Jonathan H. Adler, *Restoring Chevron’s Domain*, 81 MO. L. REV. 983 (2016); Christopher J. Walker, *Attacking Auer and Chevron: A Literature Review*, 16 GEO. J.L. & PUB. POL’Y 103 (2018). *But see* Kristin E. Hickman & Nicholas R. Bednar, *Chevron’s Inevitability*, 85 GEO. WASH. L. REV. 1392 (2017) (“[C]laims that *Chevron* is in decline are overblown.”).

<sup>165</sup>Pharm. Mfrs. Ass’n v. Food & Drug Admin., 484 F. Supp. 1179, 1183 (D. Del. 1980), *aff’d*, 634 F.2d 106 (3d Cir. 1980); *see* *United States v. Article of Drug Bacto-Unidisk*, 394 U.S. 784, 798 (1969).

<sup>166</sup>Moreover, some scholars have argued that *Chevron* did not, in fact, bring about a significant change in how frequently agencies prevail in litigation—that is, the standard of review may not affect the outcome of challenges to agencies’ practices. *See, e.g.*, William N. Eskridge, Jr. & Lauren E. Baer, *The Continuum of Deference: Supreme Court Treatment of Agency Statutory Interpretations from Chevron to Hamdan*, 96 GEO. L.J. 1083, 1120 (2008) (“Contrary to the conventional wisdom, *Chevron* is not the alpha and the omega of Supreme Court agency-deference jurisprudence.”); David Zaring, *Reasonable Agencies*, 96 VA. L. REV. 135, 169 (2010) (reporting a study finding “[c]ourts reverse agencies at roughly the same rate, regardless of the standard of review”); *cf.* Peter H. Schuck and E. Donald Elliott, *To the Chevron Station: An Empirical Study of Federal Administrative Law*, 1990 DUKE L.J. 984, 985 (1990) (finding that agencies prevailed more frequently immediately after *Chevron*, but that this effect lessened over time). *But see* Adler, *supra* note 164, at 986 (“*Chevron*’s significance grew over time.”); Kent Barnett and Christopher J. Walker, *Chevron in the Circuit Courts*, 115 MICH. L. REV. 1 (2017) (an empirical analysis finding that agencies prevail more often in the lower courts when *Chevron* applies, but not at the Supreme Court). Consistent with this view, courts often deferred to FDA’s positions before *Chevron*. *See, e.g.*, *United States v. Article of Drug Bacto-Unidisk*, 394 U.S. 784, 791–92 (1969) (“It is enough for us that the expert agency charged with the enforcement of remedial legislation has determined that such regulation is desirable for the public health, for we are hardly qualified to second-guess the Secretary’s medical judgment.”); *United States v. Rutherford*, 442 U.S. 544, 553 (1979) (“[T]he construction of a statute by those charged with its administration is entitled to substantial deference . . . . Such deference is particularly appropriate where, as here, an agency’s interpretation involves issues of considerable public controversy, and Congress has not acted to correct any misperception of its statutory objectives.”); *Premo Pharmaceutical Laboratories, Inc. v. United States*, 629 F.2d 795 (2d Cir. 1980) (“The rule that the FDA rather than the courts must first determine the safety and effectiveness of a drug is but an extension of the general principle that the agency is usually better equipped by reason of its expertise to make the determination than the court.”); *cf.* Eskridge and Bauer, *supra*, at 1120 (“[T]he Court was highly deferential to agency interpretations *before Chevron*.”).

<sup>167</sup>*See, e.g.*, Gottlieb & Woodcock, *supra* note 7; NAS REPORT, *supra* note 6.

<sup>168</sup>*See* Part II.B, *supra*.

<sup>169</sup>*See* Part II.A, *supra*; *cf.* Scott Gottlieb, *Reducing the Hurdles for Complex Generic Drug Development*, FDA VOICE (Oct. 2, 2017), <https://blogs.fda.gov/FDAvoice/index.php/2017/10/>

Other drugs with the potential for misuse on their own or along with opioids, include benzodiazepines approved to treat anxiety and gabapentin (Neurontin), a treatment for neuropathic pain.<sup>170</sup> But the approach we have outlined may also be applicable to drugs without the potential for misuse. For example, appropriate prescribing of antimicrobial drugs is essential to minimize the development of resistant bacteria that can then infect others, while vaccines provide benefits to the population through “herd immunity” apart from their benefits for individual patients.<sup>171</sup> Any prescription drug with common “off-label” uses—for indications not formally reviewed and approved by FDA—that substantially alter its population-level benefit-risk profile might be viewed as having externalities. As one example, drugs approved for dementia, narcolepsy, and attention deficit disorders have received attention for their potentially dangerous off-label uses as cognitive enhancers in healthy individuals.<sup>172</sup> As another example, we might expect a highly effective weight loss drug approved for patients with obesity or severe obesity to be used widely outside of that patient population, because of the social stigma associated with being even moderately overweight.<sup>173</sup> If use of such drugs outside of severely obese patients becomes commonplace, whether or not actively encouraged by the pharmaceutical manufacturer—as occurred in the 1990s with the use of fenfluramine/phentermine<sup>174</sup>—it may alter the population-level benefit-risk profile of the drug, because these patients are not at the same risk of adverse health outcomes.

Thus, there are a variety of drugs and drug classes for which FDA could incorporate a wide range of evidence in its benefit-risk determinations, including how patients and providers actually use a drug. Yet it is not clear precisely when and how the agency will do so in its approval and withdrawal decisions. Accordingly, in this Part, we offer some considerations for systematically and sensibly assessing the benefits and risks of drugs with externalities. Although not a comprehensive list of all considerations for, or practical consequences of, implementation,<sup>175</sup> these

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[<https://perma.cc/T2CK-39BF>] (describing drug prices as a “public health concern that FDA should address”).

<sup>170</sup>See, e.g., Xanax (alprazolam) Labeling, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/018276s052lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/018276s052lbl.pdf) [<https://perma.cc/QJ57-9BVK>]; Carmen Heredia Rodriguez, *New on the Streets: Drug for Nerve Pain Boosts High for Opioid Abusers*, KAISER HEALTH NEWS (July 6, 2017), <https://khn.org/news/new-on-the-streets-drug-for-nerve-pain-boosts-high-for-opioid-abusers> [<https://perma.cc/3R65-XDUM>].

<sup>171</sup>See, e.g., FOOD & DRUG ADMIN., *Battle of the Bugs*, *supra* note 10; Vaccines.gov, *Community Immunity (“Herd Immunity”)*, <https://www.vaccines.gov/basics/protection/index.html> [<https://perma.cc/QG2L-VUNU>].

<sup>172</sup>See, e.g., Martha J. Farah et al., *Neurocognitive Enhancement: What Can We Do and What Should We Do?*, 5 NATURE REV. NEUROSCIENCE 421 (2004).

<sup>173</sup>*Cf.* Zettler, *Expanded Off-Label Promotion*, *supra* note 126, at 1089 (describing a similar example).

<sup>174</sup>See, e.g., Steven R. Salbu, *The FDA and Public Access to New Drugs: Appropriate Levels of Scrutiny in the Wake of HIV, AIDS, and the Diet Drug Debacle*, 79 B.U. L. REV. 93, 124 (1999).

<sup>175</sup>As one example, systematically incorporating population health information into approval decisions for certain drugs may alter industry’s willingness to develop potentially beneficial drugs or drug classes if they also have the potential for significant externalities—particularly if evaluating population health information significantly lengthens the time necessary to develop a drug or is perceived as doing so. *Cf.* Yaniv Heled, *Regulatory Competitive Shelters*, 76 OHIO ST. L.J. 299, 301 (2015) (describing the “goal of creating incentives for innovation in pharmaceuticals and production of socially valuable data”).

suggestions are intended to aid in thoughtful administration of the agency's authority to take a public health perspective in its approval and withdrawal decisions.

### A. *When to Implement*

Consistent with its statutory authority, current regulations, and public health mission,<sup>176</sup> FDA can, and should, incorporate all relevant evidence into its benefit-risk determinations whenever warranted by the particular drug or drug class that the agency is reviewing. This approach will not be necessary or helpful for all drugs. FDA's traditional approach to assessing the benefits and risks of drugs, focused on the clinical trials of their intended uses as described in FDA-approved labeling, works well for many drugs. Apart from situations such as opioids—in which there is widespread recognition of the drugs' population health impacts, including in FDA regulations and guidance,<sup>177</sup> and of the influence that misleading marketing may have had on prescribing decisions—there may be considerable disagreement about when a drug or drug class can be adequately evaluated through the conventional approach, or, instead, has the potential to impact population health such that FDA must consider a wider body of evidence.

Furthermore, it may be difficult for the agency to articulate general guidelines about when it will implement a broad approach that are not specific to a drug product or class. FDA regulations explain only that it must “exercise its scientific judgment” in determining the information necessary to assess a drug's benefits and risks.<sup>178</sup> In a preamble, the agency further explained that “applications for new members of an established class of drugs should take into account experience gained with that class . . . This may involve, for example, more detailed safety data if marketing experience with the class has revealed special safety concerns.”<sup>179</sup> But beyond these statements, there is little public information about when the agency will incorporate broader information into its decision-making.

There, however, may be a few steps the agency could take to help ensure a consistent application of its authority to incorporate population health impacts into its decision-making, and clarify its thinking for stakeholders. First, FDA should be consistent, treating like cases alike. Such consistency is necessary under the Administrative Procedures Act, which authorizes courts to set aside arbitrary and capricious agency actions,<sup>180</sup> and is good policy.<sup>181</sup> It is fair to, and provides

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<sup>176</sup>See, e.g., 21 U.S.C. § 393(b); 21 C.F.R. § 314.105(c).

<sup>177</sup>See, e.g., 21 C.F.R. § 314.50; FOOD & DRUG ADMIN., *Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling* (Apr. 2015), <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf> [<https://perma.cc/7JKX-N67V>].

<sup>178</sup>21 C.F.R. § 314.105(c).

<sup>179</sup>50 Fed. Reg. 7452, 7483 (Feb. 22, 1985).

<sup>180</sup>See, e.g., 5 U.S.C. § 706(2)(A); *Etelson v. Off. of Pers. Mgmt.*, 684 F.2d 918, 926 (D.C. Cir. 1982); see also *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27 (D.D.C. 1997) (“[FDA] must treat similar cases in a similar manner unless it can provide a legitimate reason for failing to do so.”). Consistency may also make courts more likely to defer to the agency's positions. See, e.g., Christopher J. Walker, *How to Win the Deference Lottery*, 91 TEX. L. REV. 73, 80 (2013).

<sup>181</sup>See, e.g., I. Glenn Cohen, *Therapeutic Orphans, Pediatric Victims? The Best Pharmaceuticals for Children Act and Existing Pediatric Human Subject Protection*, 58 FOOD & DRUG L.J. 661, 680 (2003); Yoav Dotan, *Making Consistency Consistent*, 57 ADMIN. L. REV. 995, 999 (2005); Miranda Oshige McGowan, *Against Interpretation*, 42 SAN DIEGO L. REV. 711, 724 (2005); Laurens Walker & John

predictability for, regulated entities, and demonstrates rational decision-making.<sup>182</sup> If generalizable principles do emerge through the agency's experience, FDA should issue guidance on how it will consistently implement its "flexibility" in applying the approval standards for drugs.<sup>183</sup>

As part of the numerous communications that FDA schedules with manufacturers during the drug development process,<sup>184</sup> FDA also should communicate to a drug's manufacturer the range of evidence it will need to assess a particular drug's benefits and risks as early as possible, so that the manufacturer has sufficient notice of the agency's expectations. For some drugs, such as novel opioids that are likely to be associated with the same risks as currently-marketed opioids, this will be clear early in drug development, perhaps even before the drug's clinical trials begin.<sup>185</sup> For other drugs, the need for a broad range of evidence may not become apparent until later in development, or after approval when it is known how the drug is actually used by providers and patients and new risks emerge.<sup>186</sup>

To help all regulated entities understand FDA's thinking in this area, the agency could make public what has triggered a need for population health impact information about a particular drug or drug class, and what kind of information or data is needed, as early as the law allows such transparency.<sup>187</sup> This would be concordant with ongoing work at FDA to improve transparency, as well as a growing consensus about the importance of transparency among regulators in other countries and the biomedical community generally.<sup>188</sup> FDA also could use its advisory committees to help the agency decide whether a public health perspective is needed

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Monahan, *Scientific Authority: The Breast Implant Litigation and Beyond*, 86 VA. L. REV. 801, 821 (2000).

<sup>182</sup>See, e.g., *id.*; see also Patricia J. Zettler et al., *Closing the Regulatory Gap for Synthetic Nicotine Products*, 59 B.C. L. REV. (forthcoming 2018) (making a similar argument), [https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=3045317](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3045317).

<sup>183</sup>21 C.F.R. § 314.105(c) ("FDA makes its views on drug products and classes of drugs available through guidance documents, recommendations, and other statements of policy.").

<sup>184</sup>See, e.g., 21 C.F.R. § 314.102(a) ("During the course of reviewing an application[,] . . . FDA shall communicate with applicants about scientific, medical, and procedural issues that arise . . ."); OFFICE OF INSPECTOR GEN., DEP'T OF HEALTH & HUMAN SERVS., OEI-01-01-00590, FDA'S REVIEW PROCESS FOR NEW DRUG APPLICATIONS (Mar. 2003) ("FDA works collaboratively with sponsors.").

<sup>185</sup>See, e.g., NAS Report, *supra* note 6, at 392–96; 50 Fed. Reg. 7452, 7483 (Feb. 22, 1985).

<sup>186</sup>FDA, policymakers, and scholars acknowledge that many drugs are associated with risks that do not become apparent until after approval. See, e.g., INST. OF MEDICINE, THE FUTURE OF DRUG SAFETY: PROMOTING AND PROTECTING THE HEALTH OF THE PUBLIC 38 (2007) [hereinafter "IOM DRUG SAFETY REPORT"]; Nicholas S. Downing et al., *Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010*, 317 JAMA 1854 (2017); Parasidis, *supra* note 133, at 949.

<sup>187</sup>See, e.g., NAS REPORT, *supra* note 6, at 9, 400, 412 (describing a "commitment to transparency" as necessary in FDA regulation of opioids).

<sup>188</sup>See, e.g., Afia K. Asamoah & Joshua M. Sharfstein, *Transparency at the Food and Drug Administration*, 362 NEW ENG. J. MED. 2341 (2010); Peter Lurie et al., *Comparison of Content of FDA Letters Not Approving Applications for New Drugs and Associated Public Announcements from Sponsors: Cross Sectional Survey*, 350 BRITISH MED. J. h2758 (2015); Joshua M. Sharfstein and Michael Stebbins, *Enhancing Transparency at the US Food and Drug Administration: Moving Beyond the 21st Century Cures Act*, 317 JAMA 1621 (2017); Joshua M. Sharfstein et al., *Blueprint for Transparency at the U.S. Food and Drug Administration: Recommendations to Advance the Development of Safe and Effective Medical Products*, 45 J. L. MED. ETHICS 7 (2017).

for a particular drug, to incorporate population health information into its benefit-risk determination, or both. Because advisory committee meetings must be public,<sup>189</sup> routinely seeking advisory committee advice would also promote transparency and public accountability.

Even if FDA is transparent about the data needed for approval as early as possible, explicitly taking a public health approach may spark concerns that the agency is slowing the approval process.<sup>190</sup> But, because the public health approach would be applied to approval (and withdrawal) decisions for only for those drug products and classes that have population health impacts that affect their benefit-risk profiles—such as opioids—concerns about generalized changes to the approval process are not merited. Moreover, we are not arguing that FDA should refuse to approve, or withdraw approval of, any particular drug product or drug class subject to additional analysis of their social or clinical externalities.<sup>191</sup> If it determines that the benefit-risk profile still merits approval, FDA first could turn to risk mitigation tools, such as REMS, to address such externalities.<sup>192</sup> Indeed, FDA is reportedly currently in the process of revising the REMS for extended release opioids, and has expanded REMS requirements to also apply to immediate release opioids.<sup>193</sup> Similarly, before FDA requested that Endo Pharmaceuticals remove Opana ER from the market,<sup>194</sup> the agency likely considered whether the REMS could have been changed to sufficiently mitigate the drug's risks.<sup>195</sup> In those instances, such as for Opana ER, in which other risk mitigation tools are not sufficient to address the population health impacts of a

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<sup>189</sup>5 U.S.C. app. 2 § 10(a).

<sup>190</sup>*Cf.* Leah Isakov et al., *Is the FDA Too Conservative or Too Aggressive?: A Bayesian Decision Analysis of Clinical Trial Design 1* (Nat'l Bureau Econ. Research, Working Paper No. 21499, 2015), [https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=2641547](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2641547) [<https://perma.cc/J4JW-WSR6>] (arguing generally that FDA can be too conservative); Robert Kocher & Bryan Roberts, *The Calculus of Cures*, 370 *NEW ENG. J. MED.* 1473, 1474 (2014) (arguing same). *But see* Chul Kim & Vinay Prasad, *Strength of Validation for Surrogate Endpoints Used in the US Food and Drug Administration's Approval of Oncology Drugs*, 91 *MAYO CLINIC PROC.* 713, 723 (2016) (arguing that FDA can be too lenient); Matthew Herper, *The FDA Is Basically Approving Everything. Here's the Data to Prove It*, *FORBES* (Aug. 20, 2015), <https://www.forbes.com/sites/matthewherper/2015/08/20/the-fda-is-basically-approving-everything-heres-the-data-to-prove-it/#65b42fb45e0a> [<https://perma.cc/VN8E-29DH>] (same).

<sup>191</sup>It is also worth noting that individual regulatory decisions, including approval and withdrawal decisions, may have unintended consequences. For example, the approval of abuse deterrent formulations of prescription opioids, and their introduction into the market, may be linked to the increasing use of illicit opioids such as heroin. *See, e.g.*, NAS REPORT, *supra* note 6, at 6. The potential for such indirect consequences may need to be part of regulatory decisions for particular drugs or drug classes.

<sup>192</sup>*See, e.g.*, FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: SAFETY LABELING CHANGES 3 (July 2013), <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf> [<https://perma.cc/5YSK-UMKP>] (explaining that withdrawing approval is “not normally desirable if some patients [a]re benefitting from the drug despite its risks”).

<sup>193</sup>*See, e.g.*, FOOD & DRUG ADMIN., *Risk Evaluation and Mitigation Strategies (REMS) for Opioid Analgesics* (Sept. 28, 2017), <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm> [<https://perma.cc/8Z3F-4YUV>].

<sup>194</sup>*See supra* notes 97–101, and accompanying text.

<sup>195</sup>*Cf.* FOOD & DRUG ADMIN., *Summary Minutes of the Drug Safety and Risk Management Advisory Committee and Anesthetic and Analgesic Drug Products Advisory Committee Joint Meeting* (Mar. 13–14, 2017), <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM551226.pdf> [<https://perma.cc/75G7-ESFW>] (explaining that some advisory committee members “doubted the ability of either labeling or REMS to mitigate [Opana's] risk of abuse and related adverse health effects”).



particular product or drug class, the agency can, and should, take into account those population health impacts in its approval and withdrawal decisions in a fair and transparent manner.

### *B. Obtaining Data Necessary for Implementation*

If FDA were to determine that additional information about a drug's public health impacts is necessary, it also needs to consider how that information should be obtained. Randomized, controlled trials (RCTs) will continue to be the gold-standard for evaluating the benefits and risks of all drugs, including those with population health impacts. But obtaining the data and information about public health impacts, including how provider and patient behaviors affect a drug's benefits and risks is, of course, critical for enabling FDA to incorporate such information into its decision-making, and traditional RCTs may be insufficient to assess such factors.<sup>196</sup> For example, the agency may need to understand the risks associated with patients who use opioids or other drugs of misuse and then transition to illicit drugs, the sort of question that is not readily addressed in a randomized prospective trial.<sup>197</sup> For example, in July 2017, the agency held a public workshop to discuss methods for studying the effects of abuse-deterrent formulations of opioids.<sup>198</sup>

Accordingly, other methods for understanding the benefit-risk profiles of drugs with externalities should be developed. Although assessing the risk-benefit profiles of drugs through means other than traditional RCTs may seem like a significant shift in how Center for Drug Evaluation and Research (CDER) has historically operated, it is consistent with ongoing efforts at CDER.<sup>199</sup> Indeed, in some, and perhaps many, instances, CDER may be able to obtain the data and information that it needs to assess population health impacts of drugs through initiatives that are already underway. Sentinel, and the incorporation of real-world evidence and patient experience data into its drug and device regulation, are sources that are likely to provide the agency useful information about the population health impacts of drugs, including those associated with provider and patient behaviors.<sup>200</sup>

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<sup>196</sup>*Cf.* Laura E. Bothwell et al., *Assessing the Gold Standard—Lessons from the History of RCTs*, 374 NEW ENG. J. MED. 2175 (2016) (discussing strengths and limitations of RCTs); Thomas R. Frieden, *Evidence for Health Decision Making—Beyond Randomized, Controlled Trials*, 377 NEW ENG. J. MED. 465, 466 (2016) (asserting that the limitations in RCTs “do[] not suggest that the Food and Drug Administration should be less stringent in their review of drug safety and efficacy, but rather that there should be rigorous review of all potentially valid data sources”).

<sup>197</sup>*See, e.g.*, NAS Report, *supra* note 6, at 388–409.

<sup>198</sup>*See, e.g.*, 82 Fed. Reg. 27,271 (June 14, 2017).

<sup>199</sup>*See, e.g.*, Nina L. Hunter et al., *Flexibility in the FDA Approach to Orphan Drug Development* 16 NATURE REV. DRUG DISCOVERY 737, 738 (2017) (describing FDA's use of real-world evidence to overcome limitations of RCTs in the context of orphan drugs); Riley, *supra* note 8, at 311–12 (describing FDA's as “allow[ing] increased flexibility” in clinical trial design in the context of precision medicine); *cf.* IOM DRUG SAFETY REPORT, *supra* note 186, at 4 (describing the limited safety information provided by pre-approval and recommending that FDA take a “lifecycle” approach to drug regulation).

<sup>200</sup>*See, e.g.*, 21 U.S.C. 355(k)(3); 21st Century Cures Act, Pub. L. No. 114-255, §§ 3001, 3022, 130 Stat. 1033, 1083–84, 1096–98 (2016); FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FDA STAFF: USE OF REAL-WORLD EVIDENCE TO SUPPORT REGULATORY DECISION-MAKING FOR MEDICAL DEVICES (Aug. 31, 2017), <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf> [<https://perma.cc/9XL5-Q8JM>]; FOOD & DRUG ADMIN., *Enhancing Benefit-Risk Assessment in Regulatory Decision-Making* (2017), <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm> [<https://perma.cc/P29M-52L6>]; Evans, *supra* note 133; Jonathan P. Jarow et al., *MultiDimensional Evidence Generation and FDA Regulatory Decision*

To gain a full picture, FDA may also need to develop new sources of data and information designed to address questions about the population health impacts of drugs.<sup>201</sup> Such an effort would be consistent with FDA's ongoing regulatory science initiative, which aims to encourage the development of new approaches to understanding the safety and effectiveness of drugs and other FDA-regulated products.<sup>202</sup> Particularly relevant to understanding the public health impact of certain drug products and classes may be the agency's aim of "harness[ing] diverse data" to assess products, which includes the goal of developing new data sources and innovative approaches for monitoring drugs and other medical products throughout their lifecycles.<sup>203</sup> In addition to encouraging better methods for understanding the public health impacts of certain drugs through its regulatory science initiative, the agency also may be able to draw on its evolving experience with studying and evaluation the population health impacts of new tobacco products, to inform how the methods used to undertake a similar evaluation of drug products and classes.<sup>204</sup>

### C. Limits on Implementation

Although FDA must consider evidence about public health implications to adequately assess certain drugs and drug classes, expressly expanding the kinds of evidence that the agency considers in evaluating drugs may raise concerns about enabling the government to advance social or political positions under the guise of public health.<sup>205</sup> Indeed, there is a history of the government using public health authorities and rationales to achieve other ends,<sup>206</sup> which, arguably, includes FDA.

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*Making: Defining and Using "Real-World" Data*, 318 JAMA 703 (2017); Rachel E. Sherman et al., *Real-World Evidence—What Is It and What Can It Tell Us?* 375 NEW ENG. J. MED. 2293 (2016).

<sup>201</sup>Apart from concerns about population health impacts of drugs, scholars have suggested additional ways that, for all drugs, RCT data might be improved or supplemented, such as through designing RCTs to be more inclusive or crowdsourcing postmarket research. See, e.g., Jonathan J. Darrow, *Crowdsourcing Clinical Trials*, 98 MINN. L. REV. 805, 807 (2014); Melissa Fazzari et al., *The Phase II/III Transition: Toward the Proof of Efficacy in Cancer Clinical Trials*, 21 CONTROLLED CLINICAL TRIALS 360, 361 (2000); see also W. Nicholson Price II, *Drug Approval in a Learning Health System*, 102 MINN. L. REV. (forthcoming 2018) ("[I]f FDA learns more about drugs based on how they work in the real world, that information should be used to address how drugs are labeled, sold, and used."); Riley, *supra* note 8, at 290 ("The FDCA structure does little to incentivize clinical trial design that is designed to expose variation rather than minimize it."); Ameet Sarpatwari et al., *Crowdsourcing Public Health Experiments: A Response to Jonathan Darrow's Crowdsourcing Clinical Trials*, 98 MINN. L. REV. 2326 (2014) (describing some of the limits of crowdsourcing data).

<sup>202</sup>See FOOD & DRUG ADMIN., *Strategic Plan for Regulatory Science* (2016), <https://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm268095.htm> [<https://perma.cc/83WE-6RGB>].

<sup>203</sup>See *id.*

<sup>204</sup>The agency's experience with applying the approval standard for new tobacco products is relatively limited at this time—thus far, the agency has only approved eight new tobacco products. See FOOD & DRUG ADMIN., *Tobacco Product Marketing Orders* (2018), <http://www.fda.gov/TobaccoProducts/Labeling/TobaccoProductReviewEvaluation/ucm339928.htm>. [<https://perma.cc/4SD3-YSQL>]. But the Center for Tobacco Products may have helpful expertise from which CDER could draw.

<sup>205</sup>*Cf.* Matt Lamkin, *Regulating Identity: Medical Regulation as Social Control*, B.Y.U. L. REV. 501, 504 (2016) ("[T]he United States' considerable experience in restricting biomedical interventions on moral grounds provides ample reason to be skeptical of such proposals.")

<sup>206</sup>See, e.g., PAUL A. LOMBARDO, THREE GENERATIONS, NO IMBECILES: EUGENICS, THE SUPREME COURT, AND BUCK V. BELL ix–xiv (2008) (describing laws permitting or requiring the sterilization of persons with mental illness in the early and mid-twentieth century); see also Hickox v. Christie, 205 F. Supp. 3d 579, 585 (D.N.J. 2016) (raising concerns about curtailing civil liberties through quarantine

FDA's "bungl[ed]" handling of access to levonorgestrel (Plan B), an emergency contraceptive, provides one example.<sup>207</sup> In 1999 FDA initially approved Plan B for prescription use. In 2001 the Center for Reproductive Rights filed a Citizen Petition requesting that FDA move the drug to over-the-counter status, and the manufacturer also submitted a supplement requesting the switch to over-the-counter status.<sup>208</sup> Despite robust data, an advisory committee recommendation that the drug be switched to over-the-counter status, and career agency staff's assessment that the evidence supported the switch, it took over 10 years, and protracted litigation, before the drug became widely available over-the-counter without proof of a purchaser's age because of political interference from two different administrations.<sup>209</sup> As another example, a recently filed lawsuit argues that certain REMS requirements for mifepristone (Mifeprex), a drug used for pregnancy termination, are not merited by the benefit-risk profile of the drug.<sup>210</sup> Although at the time of writing the outcome of that litigation remains to be seen, as in the Plan B context, the plaintiffs argue that there are ample data supporting the conclusion that mifepristone is safe for use without the REMS requirements and that FDA staff have concluded as much—implying that the REMS requirements instead reflect the political controversy around abortion.<sup>211</sup>

It is not difficult to imagine how social or political considerations similarly could commingle with FDA's regulatory decision-making on other drugs and drug classes in the process of implementing a public health regulatory perspective. Apart from opioids, other drugs for which this regulatory approach is relevant are also connected to controversial political and social topics. These include other drugs of misuse<sup>212</sup> and drugs for pre-exposure prophylaxis for HIV,<sup>213</sup> which both are associated with stigma, and drugs that can be used for cognitive enhancement, which are associated

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authority); Polly J. Price, *Epidemics, Outsiders, and Local Protection: Federalism Theater in the Era of the Shotgun Quarantine*, 19 U. PA. J. CONST. L. 369, 424 (2016) (raising the same concerns); Rob Stein, *CDC Seeks Controversial New Quarantine Powers to Stop Outbreaks*, NPR (Feb. 2, 2017), <http://www.npr.org/sections/health-shots/2017/02/02/512678115/cdc-seeks-controversial-new-quarantine-powers-to-stop-outbreaks> [<https://perma.cc/GA8H-56RA>] (describing concerns about new rules that would significantly broaden federal quarantine authority).

<sup>207</sup>Lisa Heinzerling, *The FDA's Plan B Fiasco: Lessons for Administrative Law*, 102 GEO. L.J. 927, 928 (2014).

<sup>208</sup>*See, e.g., id.* at 939.

<sup>209</sup>*See, e.g., id.*; *Tummino v. Hamburg*, 936 F. Supp. 2d 162, 164 (E.D.N.Y. 2013); *Tummino v. Torti*, 603 F. Supp. 2d 519, 522 (E.D.N.Y. 2009); *see also* Lars Noah, *State Affronts to Federal Primacy in the Licensure of Pharmaceutical Products*, 2016 MICH. ST. L. REV. 1, 17 (2016) ("[F]ederal officials grudgingly expanded nonprescription availability of [Plan B]."); Julie Rovner, *FDA to Increase Access to Generic Morning-After Pills*, NPR (Mar. 2, 2014), <https://www.npr.org/sections/health-shots/2014/03/02/284397995/fda-to-increase-access-to-generic-morning-after-pills> [<https://perma.cc/8NBA-V4KP>] (describing FDA as "removing age restrictions" on levonorgestrel products).

<sup>210</sup>Complaint, *Chelius v. Wright*, No. 17-CV-00493 (D. Hawai'i 2017), <https://www.aclu.org/legal-document/chelius-v-wright-complaint> [<https://perma.cc/X32A-S4AY>].

<sup>211</sup>*Id.*

<sup>212</sup>*See, e.g.,* Yngvild Olsen & Joshua M. Sharfstein, *Confronting the Stigma of Opioid Use Disorder—And Its Treatment*, 311 JAMA 1393, 1393 (2014).

<sup>213</sup>*See, e.g.,* Jim Burrell, *'Truvada Whores' Stigma Endures Among Doctors and LGBTs*, ADVOCATE (Aug. 11, 2014), <http://www.advocate.com/health/2014/08/11/truvada-whore-stigma-endures-among-doctors-and-lgbts>.

with various social concerns including about “cheating,” producing “unnatural” results, and undermining individual responsibility.<sup>214</sup>

The line between political and public health concerns is not always clear. For example, one concern raised about using drugs for cognitive enhancement is that once such use becomes the norm in some groups, others, who might not have otherwise chosen to use drugs for cognitive enhancement, will feel pressured to do so.<sup>215</sup> Widespread use of cognitive enhancing drugs implicates both public health concerns—about the safety and effectiveness of the drugs for that use—but also concerns about whether such expansive use is socially desirable.<sup>216</sup>

Although the line between public health, and social or political, considerations may not always be distinct, FDA should strive to focus solely on questions of public health.<sup>217</sup> This is consistent both with the limits of the agency’s institutional competence, and its statutory authority. Tying regulatory decisions to sound data regarding the public health effects of the drugs at issue may be one way to help the agency keep an appropriate scope to its review.

## CONCLUSION

Often FDA’s drug approval and withdrawal decisions are understood to be focused on the benefits and risks as defined in the preapproval clinical trials, which generally do not capture broader, population-level considerations, such as the ways in which provider and patient behaviors—actual use of the drug—may alter a drug’s safety or effectiveness. For many drugs, this approach works well. But for some drugs with particularly problematic population health impacts, including those associated with provider and patient behaviors such as opioids, it is necessary for FDA to look beyond its traditional mode for making benefit-risk determinations, and apply a public health approach. This Article describes FDA’s authority to consider a wide range of data and information in determining whether a drug’s benefits outweigh its risks, including patient and provider behaviors, both for drugs of misuse as well as other drugs with externalities. Given this broad authority, as FDA

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<sup>214</sup>See, e.g., Henry T. Greely et al., *Towards Responsible Use of Cognitive-Enhancing Drugs by the Healthy*, 456 NATURE 702 (2008) (describing the controversy around the off-label use of ADHD and other drugs for cognitive enhancement).

<sup>215</sup>See, e.g., Nicholas S. Fitz et al., *Public Attitudes Toward Cognitive Enhancement*, 7 NEUROETHICS 173, 174 (2014).

<sup>216</sup>See, e.g., *id.*; see also Lucie Wade et al., *Generating Genius: How an Alzheimer’s Drug Became Considered a ‘Cognitive Enhancer’ for Health Individuals*, 15 BMC MEDICAL ETHICS 37 (2014) (describing the limited evidence supporting claims about donepezil’s (Aricept) effectiveness for cognitive enhancement).

<sup>217</sup>*Cf.* Lamkin, *supra* note 205, at 545–69 (making a similar argument about the regulation of enhancement technologies). *But see* Dov Fox, *Safety, Efficacy, and Authenticity: The Gap Between Ethics and Law in FDA Decisionmaking*, MICH. ST. L. REV. 1135, 1195 (2005) (arguing that, for enhancement technologies the FDCA should be amended to require FDA to consider “individual and social values” and “social consequences”); Craig Konnoth, *Drugs’ Other Side Effects* (on file with authors) (exploring whether FDA should consider certain non-health effects in its drug approval decisions); Gary Marchant et al., *Integrating Social and Ethical Concerns into Regulatory Decision-Making for Emerging Technologies*, 11 MINN. J.L. SCI. & TECH. 345, 351 (2010) (arguing that for enhancement technologies “there is a strong presumptive case for allowing agencies to give express consideration to ethical and social concerns in regulatory decisions”).

intensifies its efforts to address the risks associated with opioid misuse,<sup>218</sup> the lessons learned from regulating opioids—including the need for consistency, developing new methods for assessing drug risks and benefits, and limiting the agency to matters of safety and effectiveness—should be extended beyond opioids to other drugs with externalities.

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<sup>218</sup>See, e.g., Gottlieb, *FDA Takes Important Steps to Stem the Tide of Opioid Misuse and Abuse*, *supra* note 70.