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The Opioid Epidemic and the Food and Drug Administration: Legal Authorities and Recent Agency Action

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Summary

According to the Centers for Disease Control and Prevention (CDC), the annual number of drug overdose deaths in the United States involving opioids has more than quadrupled since 1999. CDC estimates that in 2016, more than 63,000 people died from a drug overdose, and more than 42,000 of these deaths involved prescription or illicit opioids. A report issued in November 2017 by the President's Commission on Combating Drug Addiction and the Opioid Crisis also observed that "[t]he crisis in opioid overdose deaths has reached epidemic proportions in the United States ... and currently exceeds all other drug-related deaths or traffic fatalities." In combating the opioid epidemic, one central challenge for state and federal regulators is striking a balance between taking aggressive action to fight opioid misuse and addiction, while simultaneously protecting patients who experience severe pain. The Food and Drug Administration (FDA)—the executive agency tasked with protecting the public health by ensuring the nation's drug supply is safe and effective—has a pivotal role in addressing these issues.

This report focuses on FDA as a key player in federal efforts to curb the opioid epidemic. The report provides an overview of FDA's role in approving new prescription drugs, including certain challenges presented by the approval and regulation of opioid products. Next, the report addresses FDA's multifaceted approach in its response to the opioid epidemic, the agency's use of its existing legal authorities under the Federal Food, Drug, and Cosmetic Act (FD&C Act or Act), and recent agency action taken to target the misuse of opioid medications. The report concludes with a discussion of selected opioid-related legislation in the 115th Congress that would amend the FD&C Act.

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According to the Centers for Disease Control and Prevention (CDC), "115 Americans die every day from an opioid overdose," and deaths from prescription opioids have more than quadrupled since 1999.[1] The epidemic's origins are complex, with fingers pointed at pharmaceutical manufacturers and distributors, addicts and dealers, health care professionals, and insurance companies.[2] Like the causes of the opioid epidemic, any solutions to the problem will likely involve many actors, including the federal government. The Food and Drug Administration (FDA)—the executive branch agency tasked with protecting the public health by ensuring the nation's drug supply is safe and effective[3]—has a central role in addressing widespread drug abuse, including the opioid epidemic.

Given the severity of the opioid epidemic and its prominence as a matter of national concern, efforts to combat the issue will likely continue to be of significant interest to Congress. This report focuses on FDA as a key player in these efforts. The report provides a brief overview of FDA's role in approving new prescription drugs, including opioids, and also addresses selected examples of the agency's existing legal authorities under the Federal Food, Drug, and Cosmetic Act (FD&C Act or Act) and recent action taken with respect to the opioid crisis. The report concludes with a discussion of selected opioid-related legislative proposals in the 115th Congress that would amend the FD&C Act.

FDA Approval of Prescription Drugs and the Challenges of Opioids

In 1938, Congress passed the FD&C Act in an effort to bolster federal protection of public health and safety by creating new requirements designed to keep impure or dangerous products out of interstate commerce.[4] FDA is the primary federal agency responsible for the administration and enforcement of the FD&C Act.[5] With respect to prescription drugs, the FD&C Act establishes a comprehensive federal system of premarket approval for such drugs.[6] The Act generally prohibits introducing or delivering new drugs[7] in interstate commerce unless the drug is approved by

[1] CENTERS FOR DISEASE CONTROL AND PREVENTION, UNDERSTANDING THE EPIDEMIC (last visited March. 15, 2018), https://www.cdc.gov/drugoverdose/epidemic/index.html.

[2] *See* Alana Semuels, *Are Pharmaceutical Companies to Blame for the Opioid Epidemic*?, THE ATLANTIC (June 2, 2017), https://www.theatlantic.com/business/archive/2017/06/lawsuit-pharmaceutical-companies-opioids/529020/; Erica Fry, *As America's Opioid Crisis Spirals, Giant Drug Distributor McKesson is Feeling the Pain*, FORTUNE (June 13, 2017), http://fortune.com/2017/06/13/fortune-500-mckesson-opioid-epidemic/; Erica Fry, *Here's Who America Blames the Most for the Opioid Epidemic*, FORTUNE (June 21, 2017), http://fortune.com/2017/06/21/opioid-epidemic-blame-doctors/; Celine Gounder, *Who is Responsible for the Pain-Pill Epidemic*, THE NEW YORKER (Nov. 8, 2013), https://www.newyorker.com/business/currency/who-is-responsible-for-the-pain-pill-epidemic; Katie Thomas and Charles Ornstein, *Amid Opioid Crisis, Insurers Restrict Pricey, Less Addictive Painkillers*, N.Y. TIMES (Sept. 17, 2017), https://www.nytimes.com/2017/09/17/health/opioid-painkillers-insurance-companies.html?_r=0.

[3] *See* 21 U.S.C. § 393 (establishing FDA in the Department of Health and Human Services).

[4] *See, e.g.*, POM Wonderful LLC v. Coca-Cola Co., 134 S. Ct. 2228, 2234 (2014)("The FDCA statutory regime is designed primarily to protect the health and safety of the public at large."); United States v. Sullivan, 332 U.S. 689, 697 (1948); United States v. Dotterweich, 320 U.S. 277, 280 (1943)(noting that a precursor to the FD&C Act "was an exertion by Congress of its power to keep impure and adulterated food and drugs out of the channels of commerce").

[5] *See* 21 U.S.C. § 393. While many provisions of the FD&C Act authorize the Secretary of Health and Human Services (Secretary) to implement the requirements of the Act, the Secretary generally delegates this authority to the Commissioner of Food and Drugs. *See* U.S. FOOD & DRUG ADMIN., FDA STAFF MANUAL GUIDES, 1410.10 (2016) https://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm136380.htm.

[6] Id. § 355. See also generally CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*, by Agata Dabrowska and Susan Thaul.

[7] Under the FD&C Act, a "new drug" is defined as a drug that, among other things, is not "generally recognized,

FDA.[8] Under current law, in order to market a new brand-name drug, a manufacturer must file a new drug application (NDA) with FDA, which must include, among other things, "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."[9] FDA may approve an NDA only if the sponsor of the application (e.g., a drug manufacturer or marketer) demonstrates, among several other things, that the drug is safe and effective under the conditions prescribed, recommended, or suggested in the product's labeling.[10] The FD&C Act generally authorizes FDA to refuse to approve an NDA if the agency finds the labeling is false or misleading in any particular.[11] Additionally, many drugs—including a majority of opioid products approved in recent decades—are reformulations of existing products.[12] Reformulated drugs may also be approved through an NDA under the FD&C Act, and drug sponsors may rely on safety and efficacy data of previously approved products as part of their applications.[13]

In addition to premarket authority, FDA also possesses postmarket authority to monitor drugs that have entered interstate commerce and ensure that the benefits of a drug continue to overbalance the risks.[14] For example, FDA may require postmarket drug labeling changes if the agency becomes aware of new safety information that the Secretary of Health and Human Services (Secretary) believes should be included in the labeling of the drug, as well as postapproval studies, clinical trials, and risk evaluation mitigation strategies (REMS) under certain circumstances.[15] Additionally, the agency may also monitor safety data related to approved drugs through an active postmarket risk assessment system.[16]

In general, FDA has broad authority with respect to the implementation of the FD&C Act.[17] The agency is empowered to promulgate regulations to efficiently enforce the Act's broad mandates and develop guidance documents that set forth the agency's interpretation of the Act or accompanying regulations.[18] The FD&C Act also authorizes FDA to "conduct examinations and investigations" to administer the Act and to disseminate information about regulated products involving "imminent danger to health" or "gross deception to the consumer."[19]

While new opioids are generally subject to the same approval requirements as most other drugs, FDA's task to ensure the safety and efficacy of opioids is particularly difficult. Throughout recorded history, societies have struggled with balancing the medicinal use of opioids in pain

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among experts . . . as safe and effective for use under the conditions prescribed . . . in the labeling." 21 U.S.C. § 321(p)(1).

[8] *See id*. §355(a).

[9] *Id*. § 355(b)(1).

[10] *Id*. § 355(d).

[11] *Id*.

[12] *See* NATIONAL ACADEMIES OF SCIENCES, ENGINEERING AND MEDICINE, PAIN MANAGEMENT AND THE OPIOID EPIDEMIC: BALANCING SOCIETAL AND INDIVIDUAL BENEFITS AND RISKS OF PRESCRIPTION OPIOID USE, 364 (2017).

[13] *See* 21 U.S.C. § 355(b)(2); *id*.

[14] *See generally* U.S. FOOD & DRUG ADMIN., STEP 5: FDA POST-MARKET DRUG SAFETY MONITORING (last visited Apr. 8, 2018), https://www.fda.gov/ForPatients/Approvals/Drugs/ucm405579.htm; Patricia J. Zettler, *The Indirect Consequences of Expanded Off-Label Promotion*, 78 Ohio St. L.J. 1053, 1077 (2017).

[15] *See, e.g.*, 21 U.S.C. §§ 355(o)(3)–(4), 355-1. For additional discussion of REMS, *see* footnote 37 through footnote 56 *infra* and accompanying text.

[16] *See, e.g.*, 21 U.S.C. § 355(k)(3).

[17] *See, e.g.*, Nutraceutical Corp. v. Von Eschenbach, 459 F.3d 1033, 1035 (10th Cir. 2006).

[18] *See* 21 U.S.C. § 371.

[19] *Id*. § 375.

management with the concomitant euphoric effects that have induced the substance's abuse.[20] Sixty years ago, the head of surgery at the University of Illinois noted, "we must appreciate that severe constant pain will destroy the morale of the sturdiest individual. . . [b]ut. . . we are often loathe to give liberal amounts of narcotics because the drug addiction itself may become a hideous spectacle."[21] As a result of these difficulties, for nearly a century, opioid pain medications were used in the United States primarily to treat acute and cancer-related pain.[22]

However, studies from the 1970s revealing inadequate management of chronic pain, followed by influential articles published in the 1980s reporting a low incidence of addictive behavior in small groups of cancer and noncancer patients, led to a trend toward more liberal prescribing of opioids within the medical community.[23] The shifting views on the safety and efficacy of opioids culminated in FDA's 1995 approval[24] of Purdue Pharma's controlled-release opioid pain medication, OxyContin, the product some point to as the catalyst for the current opioid epidemic.[25] Between 2000 and 2009, the medical community established new standards for pain management, which included pain as a new vital sign, and prescriptions for opioids increased.[26] By 2016, an estimated 11.5 million Americans were abusing prescription painkillers.[27]

FDA's legal authorities and recent actions taken in response to the opioid epidemic may be considered against the backdrop of challenging legal and policy questions about the role FDA can or should play with respect to regulation of products that have public health consequences.[28] As part of these questions, FDA officials have discussed the importance of striking the right balance between taking aggressive action to fight opioid misuse and addiction, while simultaneously protecting patients who experience severe pain.[29] Additionally, given that the agency's approach to evaluating and approving drugs is based on "the conditions prescribed, recommended, or suggested" in FDA-approved labeling,[30] questions may arise about the extent to which the agency has legal authority to consider drug misuse in carrying out its regulatory actions.[31] Under a

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[20] *See generally A Brief History of Opioids: Pain, Opioids, and Medicinal Use*, THE ATLANTIC (Jan. 7, 2015) http://www.theatlantic.com/sponsored/purdue-health/a-brief-history-of-opioids/184/.

[21] *See* Marcia L. Meldrum, *The Ongoing Prescription Epidemic: Historical Context*, 106(8) AM. J. PUB. HEALTH 1365, 1365 (Aug. 2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4940677/.

[22] *See* U.S. FOOD & DRUG ADMIN., TIMELINE OF SELECTED FDA ACTIVITIES AND SIGNIFICANT EVENTS ADDRESSING OPIOID MISUSE AND ABUSE (last visited Mar. 19, 2018), https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm338566.htm.

[23] *See* Meldrum, *supra* footnote 21.

[24] *Id*.

[25] *See* Harriet Ryan, *Senator Calls for Investigation of Purdue Pharma following Times Story on OxyContin*, L.A. TIMES (May 27, 2016), http://www.latimes.com/projects/la-me-oxycontin-full-coverage/.

[26] *See A Brief History of Opioids: Pain, Opioids, and Medicinal Use*, THE ATLANTIC (Jan.7, 2015) http://www.theatlantic.com/sponsored/purdue-health/a-brief-history-of-opioids/184/.

[27] See CRS Report R44987, *The Opioid Epidemic and Federal Efforts to Address It: Frequently Asked Questions*, by Lisa N. Sacco and Erin Bagalman, at 2.

[28] *See generally* National Academy of Sciences, *supra* footnote 12 at 380-87.

[29] *See, e.g.*, Scott Gottlieb, Commissioner of Food and Drugs, Remarks by Dr. Gottlieb at the Workshop "Packaging, Storage, and Disposal Options to Enhance Opioid Safety - Exploring the Path Forward" (Dec. 11, 2017). Robert M. Califf, M.D., Janet Woodcock, M.D., and Stephen Ostroff, M.D., *A Proactive Response to Prescription Opioid Abuse*, 374 (15) NEW ENGL. J. MED., 1480, 1480 (2016).

[30] 21 U.S.C. § 355(d).

[31] *See* Anthony Kakoyannis, *How Can FDA Address the Opioid Addiction Crisis? FDLI's Journal Symposium Panel Considers a Public Health Approach to Regulation*, FOOD AND DRUG LAW INSTITUTE, https://www.fdli.org/2017/10/432362362-can-fda-address-opioid-addiction-crisis/.

number of FD&C Act provisions, FDA has considerable discretion in determining the information that is relevant to its regulatory decisions.[32] The following sections of this report illustrate how FDA has exercised its discretion, particularly in its response to prescription opioid misuse and abuse.

FDA Authority and Recent Agency Action Related to the Opioid Epidemic

FDA is taking a multifaceted approach in its response to the opioid epidemic. FDA officials have indicated that the agency is focusing its efforts in four areas:

1. decreasing exposure and preventing new addiction;
2. supporting the treatment of those with opioid use disorder;
3. fostering the development of novel pain treatment therapies; and
4. improving enforcement and assessing benefit risk.[33]

Using these four categories as a framework, the following sections highlight some of FDA's recent strategies for addressing the opioid epidemic and the agency's existing authority to pursue such strategies.

Decreasing Exposure and Preventing New Addiction

FDA Commissioner Scott Gottlieb has stated that the agency is concentrating on ways to lower overall exposure to opioid drugs and, consequently, reduce the number of new cases of addiction.[34] The Commissioner has also averred that one contributing factor to the opioid epidemic is inappropriate prescribing practices, in which clinicians are writing unnecessary prescriptions for opioid products or prescribing a dose that is beyond the patient's needs.[35] FDA has recently explored various measures to influence prescriber behavior, particularly through its Risk Evaluation and Mitigation Strategy (REMS) authorities.[36]

A REMS is essentially a mandatory risk management plan for drug sponsors (commonly drug manufacturers) that is subject to FDA approval and must include a timetable for the submission of periodic assessments of the strategy.[37] For example, as part of a REMS, drug manufacturers may be required to provide certain information to patients and/or health providers (such as a medication guide or patient package insert) or impose limitations on a product's distribution.[38]

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[32] *See* 21 U.S.C. § 371.

[33] U.S. FOOD & DRUG ADMIN., OPIOID POLICY STEERING COMMITTEE (last visited Apr.8, 2018), https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/ucm587929.htm.

[34] Federal Efforts to Combat the Opioid Crisis: A Status Updated on CARA and Other Initiatives, Before the H. Energy and Commerce Comm., 115th Cong., (2017) (statement of Scott Gottlieb and others).

[35] Scott Gottlieb, M.D., Commissioner of Food and Drugs, Address at the National Rx Drug Abuse and Heroin Summit: In Search of More Rational Prescribing (Apr. 4, 2018).

[36] *See* Press Release, U.S. Food & Drug Admin., Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to help prevent new addiction, curb abuse and overdose related to opioid products (Jan. 30, 2018), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm594443.htm.

[37] *Id.* § 355-1(c)-(d). *See also*, U.S. FOOD & DRUG ADMIN. FDA BASICS WEBINAR: A BRIEF OVERVIEW OF RISK EVALUATION AND MITIGATION STRATEGIES (REMS) (last visited March 17, 2018), https://www.fda.gov/AboutFDA/Transparency/Basics/ucm325201.htm.

[38] *See id*.

FDA may require a REMS as a condition of a product's approval, or the agency may impose a REMS on a product it has already approved when new safety information arises.[39] The FD&C Act generally allows FDA to require submission of a proposed REMS if the agency determines that this strategy is necessary to ensure that the benefits of a drug outweigh its risks.[40] FDA officials, various industry stakeholders, and others have recently discussed the possibility of modifying the existing opioid REMS requirements with respect to prescriber education, including the possibility of requiring some new form of mandatory health care provider training on proper opioid prescribing and other issues related to opioid use.[41]

Questions may be raised about the scope of FDA's authority under the FD&C Act to compel physicians and other drug prescribers, through a REMS, to obtain certain training or education in order to prescribe opioid drug products. Such questions may arise in light of the fact that the regulation of health care providers and their prescribing practices has traditionally been a state function.[42] As part of a REMS, FDA may require that it contain additional, potentially more restrictive safety precautions, referred to as "elements to assure safe use" (ETASU), because of a drug's "inherent toxicity or potential harmfulness."[43] In order to require ETASU, FDA must determine that the drug has been shown to be effective, but is associated with a "serious adverse drug experience"[44] and can be only marketed if (1) such elements are required as part of the REMS, and (2) other components of the REMS are not sufficient to mitigate the risk.[45] The ETASUs must include one or more goals to mitigate a risk listed on the drug's label, and may require, among other things, that

> health care providers who prescribe the drug have particular training or experience, or are specially certified (the opportunity to obtain such training or certification with respect to the drug shall be available to any willing provider from a frontier area in a widely available training or certification method (including an on-line course or via mail) as approved by the Secretary at reasonable cost to the provider)...[46]

[39] 21 U.S.C. § 355-1(a).

[40] 21 U.S.C. § 355-1(a)(1). A list of currently approved REMS may be found at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm.

[41] *See, e.g.*, U.S. FOOD & DRUG ADMIN., FDA TAKES IMPORTANT STEPS TO STEM THE TIDE OF OPIOID MISUSE AND ABUSE (last visited Apr. 12, 2018), https://blogs.fda.gov/fdavoice/index.php/2017/09/fda-takes-important-steps-to-stem-the-tide-of-opioid-misuse-and-abuse/; Kate Traynor, *Advisers Say FDA's Opioid REMS Program Needs Improvement*, 73 AMER. J. HEALTH-SYSTEM PHARMACY 940 (2016), http://www.ajhp.org/content/73/13/940?sso-checked=true.

[42] Retail Indus. Leaders Ass'n v. Fielder, 475 F.3d 180, 191 (4th Cir. 2007) (noting that states "continue to enjoy wide latitude to regulate health care providers") (citations omitted); *see generally* Patricia J. Zettler, *Toward Coherent Federal Oversight of Medicine*, 52 SAN DIEGO L. REV. 427, 435-38 (2015).

[43] 21 U.S.C. § 355-1(f). Examples of ETASUs include a requirement that the drug only be dispensed to patients in certain health care settings, such as hospitals, or that each patient using the drug must be enrolled in a registry. *Id.* § 355-1(f)(3).

[44] The term "serious adverse drug experience" is defined as an adverse drug experience that, among other things, results in death or places a patient at immediate risk of death. *Id.* § 355-1(b)(4). An "adverse drug experience" means "any adverse event associated with the use of a drug in humans, whether or not considered drug related, including—(A) an adverse event occurring in the course of the use of the drug in professional practice; (B) an adverse event occurring from an overdose of the drug, whether accidental or intentional; (C) an adverse event occurring from abuse of the drug; (D) an adverse event occurring from withdrawal of the drug; and (E) any failure of expected pharmacological action of the drug." *Id.* § 355-1(b)(1).

[45] *Id.*

[46] *Id.* § 355-1(f)(3)(A).

Accordingly, assuming FDA has made the requisite determinations concerning the need for a REMS and the need for it to contain elements to assure safe use, then it appears that the agency may potentially compel a "responsible person," such as a drug manufacturer, through a REMS, to require that a health care provider obtain certain training in order to prescribe a particular drug.[47] While the FD&C Act does not expressly provide details on how a prescriber training requirement must be implemented,[48] the responsible person is generally obligated to carry out the requirements of the REMS and must provide assessments as to whether each element of the approved REMS is meeting the goals of the strategy.[49]

In 2012, FDA approved a REMS for extended-release and long-acting (ER/LA) opioid analgesics.[50] As part of this REMS, drug manufacturers must make voluntary training available at low or no cost to health care providers who prescribe these drugs, but currently there is no mandatory requirement that prescribers receive this training as a precondition to dispensing the applicable drugs to patients.[51] This REMS is now undergoing modification, and, following FDA approval, it is to also apply to all immediate release (IR) opioid analgesics intended for use in an outpatient setting.[52] Additionally, Congress, as part of the Comprehensive Addiction and Recovery Act of 2016, directed FDA to consult with stakeholders and develop recommendations regarding education programs for opioid prescribers pursuant to FDA's REMS authorities.[53] In January 2018, the agency issued a revised blueprint that contains a high-level outline of core educational messages that is to be included in the modified REMS.[54] Additionally, FDA officials are currently examining whether the modified REMS should include some type of mandatory prescriber training, and, if so, under what circumstances.[55]

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[47] *Id*. § 333(f)(4).The term "responsible person" means the person submitting a covered drug application or the holder of the approved application. *See id*. § 355-1(b)(7).

[48] However, it may be noted that the FD&C Act directs FDA to seek input from patients and health care providers about ETASUs and conduct certain evaluations. Considering the input and evaluations, FDA must "issue or modify agency guidance about how to implement the requirements [related to ETASUs]" and modify these elements as appropriate. 21 U.S.C. § 355-1(f)(5).

[49] *Id*. § 355-1(g).

[50] *See* U.S. FOOD & DRUG ADMIN., EXTENDED-RELEASE (ER) AND LONG-ACTING (ER/LA) OPIOID ANALGESICS RISK EVALUATION AND MITIGATION STRATEGY (updated 2015), http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf.

[51] *See* U.S. FOOD & DRUG ADMIN., BLUEPRINT FOR PRESCRIBER EDUCATION FOR EXTENDED-RELEASE AND LONG-ACTING OPIOID ANALGESICS (updated May 2017), http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM515636.pdf.

[52] *See* U.S. FOOD & DRUG ADMIN., FDA'S OPIOID ANALGESIC REMS EDUCATION BLUEPRINT FOR HEALTH CARE PROVIDERS INVOLVED IN THE TREATMENT AND MONITORING OF PATIENTS WITH PAIN (2018), https://www.regulations.gov/contentStreamer?documentId=FDA-2017-D-2497-0683&attachmentNumber=1&contentType=pdf.

[53] P.L. 114-198, § 106, 130 Stat. 695 (2016).

[54] *See* U.S. FOOD & DRUG ADMIN., FDA'S OPIOID ANALGESIC REMS EDUCATION BLUEPRINT FOR HEALTH CARE PROVIDERS INVOLVED IN THE TREATMENT AND MONITORING OF PATIENTS WITH PAIN (2018), https://www.regulations.gov/contentStreamer?documentId=FDA-2017-D-2497-0683&attachmentNumber=1&contentType=pdf.

[55] *See* U.S. FOOD & DRUG ADMIN., RISK EVALUATION AND MITIGATION STRATEGY (REMS) FOR OPIOID ANALGESICS (Feb. 4, 2016) (last visited Apr. 9, 2018), https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm. *See also generally* Sandee LaMotte, *FDA head calls for mandatory education, internet policing to fight opioid crisis*, CNN (Apr. 5, 2018, 11:16AM), https://www.cnn.com/2018/04/04/health/fda-gottlieb-gupta-opioids/index.html.

Supporting the Treatment of Those with Opioid Use Disorder

In responding to the opioid epidemic, FDA is also focusing on measures that would better assist individuals struggling with opioid addiction.[56] These efforts include promoting broader access to opioid antagonists that can stop or reverse an overdose, including the drug naloxone.[57] Naloxone is a medication that generally treats an overdose by quickly blocking the effects that opioids have on the brain, and it is commonly viewed as an effective and frequently life-saving intervention.[58]

One perceived legal barrier to more widespread naloxone access is its current classification as a prescription drug.[59] Under the FD&C Act, certain drugs—because of their toxicity, potential for harm, method or measures necessary for use, or a requirement of a drug's NDA—can only be dispensed upon a prescription of a licensed practitioner.[60] Similar to prescription drugs, the FD&C Act governs, among other things, the safety and efficacy of over-the-counter (OTC) medications, including the approval, manufacture, and distribution of such drugs. In general, OTC drugs, unlike prescription drugs, are those that can be adequately labeled so that they do not pose a risk of misuse or abuse and can be safely and effectively used without the supervision of a health care provider.[61] Thus, OTC drugs are publicly available for consumers to purchase for treatment of a variety of conditions. Currently, there are more 300,000 marketed OTC drug products that fall into over 80 therapeutic categories (such as analgesics or antacids).[62]

There are two main regulatory mechanisms through which a drug like naloxone may be switched from prescription to OTC status.[63] First, FDA is authorized to implement a switch through rulemaking. The FD&C Act specifies that FDA may remove drugs from the prescription requirements by regulation when such requirements "are not necessary for the protection of the public health."[64] Under current regulations, a proposal to exempt a drug from the prescription requirements may be initiated by the FDA Commissioner or any interested person.[65] The second

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[56] *See* U.S. FOOD & DRUG ADMIN., FDA OPIOIDS ACTION PLAN (Feb. 4, 2016), https://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm484714.htm.

[57] For additional information on naloxone, see CRS In Focus IF10741, *Naloxone for Opioid Overdose: Regulation and Policy Options*, by Erin Bagalman and Ada S. Cornell.

[58] *See generally* Christopher T. Creech, *Increasing Access to Naloxone: Administrative Solutions to the Opioid Overdose Crisis*, 68 ADMIN. L. REV. 517 (2016).

[59] *See* Scott Burris et al., *Stopping An Invisible Epidemic: Legal Issues in the Provision of Naloxone to Prevent Opioid Overdose*, 1 DREXEL L. REV. 273, 278 (2009).

[60] 21 U.S.C. § 353(b)(1).Typically, new drugs with new chemical entities are initially approved as prescription drugs, in case safety issues are discovered once the drug hits the market. *See* Peter Barton Hutt, Richard A. Merrill, and Lewis A. Grossman, FOOD AND DRUG LAW 806 (Foundation Press, 4th ed. 2014). It may be noted that naloxone has been on the market since the 1970s.

[61] *See* U.S. FOOD & DRUG ADMIN., OFFICE OF NONPRESCRIPTION PRODUCTS, (last visited Apr. 9, 2018), https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm093452.htm ("OTC drugs generally have these characteristics: their benefits outweigh their risks; the potential for misuse and abuse is low; consumer can use them for self-diagnosed conditions; they can be adequately labeled; health practitioners are not needed for the safe and effective use of the product"). *Id*.

[62] U.S. FOOD & DRUG ADMIN. DRUG APPLICATIONS FOR OVER-THE-COUNTER (OTC) DRUGS (last visited Apr. 8, 2018), https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/over-the-counterdrugs/default.htm.

[63] There are other regulatory pathways through which a drug may be switched from prescription to OTC status, and a discussion of these pathways is beyond the scope of this memorandum. For more information, see CRS In Focus IF10463, *Regulation of Over-the-Counter (OTC) Drugs*, by Agata Dabrowska.

[64] 21 U.S.C. § 353(b)(3). *See also* 21 C.F.R. § 310.200.

[65] *See id*. § 310.200(b).

mechanism is through the drug sponsor's submission of an NDA or a supplemental NDA, under which the sponsor, typically the manufacturer, requests that FDA approve the switch.[66] The latter approach is the more common pathway for drugs to switch to OTC status, and FDA officials have stated that it is, among other things, a much more expeditious process (as compared to FDA's notice-and-comment rulemaking).[67] With respect to both approaches, FDA takes a "fresh look" at all the safety and efficiency data used in the prescription drug's NDA.[68] Additionally, a central element necessary for FDA's determination that a product is safe for OTC use is the establishment of a label that conveys key messages about the product to a lay consumer, as well as adequate testing to ensure that consumers comprehend the label and can use the product correctly and safely in an OTC setting.[69]

FDA officials have frequently expressed support for giving naloxone OTC status.[70] The agency has also noted ways in which it is taking steps to assist naloxone manufacturers in submitting an application and pursuing approval of an OTC product.[71] For example, in 2016, FDA officials announced that the agency had developed a consumer-friendly model Drug Facts Label (DFL), a required label for OTC products, which is intended to convey the information a consumer would need to administer naloxone in the event of an emergency overdose.[72] FDA also arranged for scientific testing of this model labeling.[73] However, in early 2018, it was reported that no manufacturers of naloxone have submitted an application to FDA to make the product available over-the-counter.[74]

Despite the fact that FDA has not approved naloxone for OTC use, states have taken action to make naloxone more accessible. Although FDA has exclusive authority to approve prescription drugs, states maintain authority with respect to who may prescribe these medications and the required format for valid prescriptions.[75] Many states, for example, permit third-party prescriptions—issued to a friend, family member, or other third party who is not at risk of overdose—for use on someone else.[76] These laws provide an exception to the typical state law requirement that prescriptions be written only for the person who will actually take the

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[66] *See* 21 U.S.C. § 355.

[67] *See* Transcript, U.S. FOOD & DRUG ADMIN, *Role of Naloxone in Opioid Overdose Fatality Prevention*, 180-181 (Apr. 12, 2012) http://intranasal.net/OpiateOverdose/FDA%20naloxone%20manuscript%20April%202012%20meeting.pdf.

[68] *See id.*; 21 C.F.R. § 330.10.

[69] *See* 21 C.F.R. § 310.200(b).

[70] *See, e.g.*, U.S. FOOD & DRUG ADMIN., FDA SUPPORTS GREATER ACCESS TO NALOXONE TO HELP REDUCE OPIOID OVERDOSE DEATHS (last visited Apr. 8, 2018), https://blogs.fda.gov/fdavoice/index.php/2016/08/fda-supports-greater-access-to-naloxone-to-help-reduce-opioid-overdose-deaths/; U.S. FOOD & DRUG ADMIN., KAREN MAHONEY TRANSCRIPT (last visited Apr. 12, 2018), https://www.fda.gov/Drugs/ScienceResearch/ucm581817.htm.

[71] *See id.*

[72] *See id.*

[73] *See id.*

[74] *See* German Lopez, *Naloxone, the medicine helping fight the opioid crisis, explained*, VOX, (FEB. 12, 2018, 11:00AM) https://www.vox.com/science-and-health/2018/2/12/16846242/naloxone-opioid-heroin-fentanyl-epidemic.

[75] As discussed *supra*, under the FD&C Act, drugs meeting certain criteria may only dispensed upon a prescription of a "licensed practitioner." 21 U.S.C. § 353(b)(1). The FD&C Act does not contain licensing requirements for these health care providers, and the Act has been interpreted as allowing state law to govern which entities may be licensed to administer prescription drugs and other prescription products. *See, e.g. generally*, United States v. Shock, 379 F.2d 29, 33 (8th Cir. 1967). *See also* Hutt et al., *supra* footnote 60.

[76] *See, e.g.*, SUBSTANCE ABUSE AND MENTAL HEALTH SERV. ADMIN, UNDERSTANDING NALOXONE ACCESS LAWS, (last visited Apr. 8, 2018), https://www.samhsa.gov/capt/sites/default/files/resources/naloxone-access-laws-tool.pdf.

medication.[77] Additionally, some states permit medical practitioners to prescribe naloxone through standing orders, through which the drug may be dispensed by a pharmacy or other entity based on certain criteria, without the prescriber's examination of a particular patient.[78] Notwithstanding these state laws, some entities still argue a need for FDA to give naloxone OTC status.[79]

Fostering the Development of Novel Pain Treatment Therapies

FDA has stated that it is working with industry and other government entities to spur the development and marketing of new pain treatments that have less potential for abuse, including generic abuse-deterrent formulations (ADFs) of opioid products.[80] ADF technologies are those intended to make abusing a drug more difficult or less rewarding, and the benefits of these technologies have been the subject of debate.[81] To date, FDA has approved 10 opioid analgesics with these characteristics.[82] However, currently, opioids with ADFs are only available as brand-name products, and there are no generic opioids with FDA-approved abuse-deterrent labeling on the market.[83] FDA Commissioner Scott Gottlieb has noted that because opioids with ADFs are only available as brand-name products, they are fundamentally more expensive than available generic versions of non-ADF opioids.[84]

In order to provide a quicker route for the approval of generic drugs, Congress passed the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, which created the abbreviated new drug application (ANDA) process.[85] Under this act, a generic drug may be approved for marketing without the same clinical studies and safety and effectiveness evidence required for brand-name drug approval if the generic drug mimics the approved brand-name drug in certain key ways.[86] For example, an ANDA generally must contain

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[77] *See id*.

[78] *See* NAT. INST. ON DRUG ABUSE, IS NALOXONE ACCESSIBLE?, (last visited Apr. 8, 2018) https://www.drugabuse.gov/publications/medications-to-treat-opioid-addiction/naloxone-accessible.

[79] *See, e.g*., Megan McLemore and Corey Davis, *The opioid commission almost got something right with their naloxone recommendation*, U.S.A. TODAY (Dec. 1, 2017), https://www.usatoday.com/story/opinion/2017/12/01/opioid-commission-almost-got-right-their-naloxone-recommendation-megan-mclemore-corey-davis-column/899812001/; Jeffrey A. Singer, *Why Doesn't the Surgeon General Seek FDA Reclassification of Naloxone to OTC?*, CATO INSTITUTE, (Apr. 5, 2018), https://www.cato.org/blog/why-doesnt-surgeon-general-seek-fda-reclassification-naloxone-otc.

[80] *See* Califf, et al., *supra* footnote 29 at 1482-83.

[81] *See* U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: ABUSE-DETERRENT OPIOIDS — EVALUATION AND LABELING (Apr. 2015) at 2, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf. *See also, e.g.*, William C. Becker, M.D., and David A. Fiellin, M.D., *Abuse-Deterrent Opioid Formulations — Putting the Potential Benefits into Perspective*, 376 NEW ENGL. J. MED. 2103, 2104 (2017); C. Bernie Good, Chronis Manolis, and William Shrank, There's little evidence abuse-deterrent opioids work. Why should we use them? Stat (Aug. 8, 2017), https://www.statnews.com/2017/08/08/abuse-deterrent-opioids-oxycontin/.

[82] *See* Press Release, U.S. Food & Drug Admin., Statement from FDA Commissioner Scott Gottlieb, M.D., on steps to promote development of generic versions of opioids formulated to deter abuse (Nov. 21, 2017), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm586117.htm.

[83] *See, e.g.*, U.S. FOOD & DRUG ADMIN., OPIOID MEDICATIONS (last visited Apr. 8, 2018), https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm337066.htm.

[84] *See* Press Release, U.S. Food & Drug Admin., Statement from FDA Commissioner Scott Gottlieb, M.D., on steps to promote development of generic versions of opioids formulated to deter abuse (Nov. 21, 2017), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm586117.htm.

[85] P.L. 98-417, 98 Stat. 1585 (1984).

[86] 21 U.S.C. § 355(j). *See also* Mut. Pharm. Co. v. Bartlett, 133 S. Ct. 2466, 2471 (2013).

information demonstrating that the route of administration, the dosage form, and the strength of the new generic are the same as those of its brand-name analog.[87] In addition, ANDA applications must contain "information to show that the labeling proposed for the new drug is the same as the labeling approved for the [brand-name] drug," subject to certain specified exceptions.[88]

In November 2017, as directed by Congress as part of the Comprehensive Addiction and Recovery Act of 2016, FDA issued a nonbinding guidance document for industry, which contains recommendations about what studies a potential ANDA applicant should conduct and submit to FDA to demonstrate that the generic drug's abuse deterrent properties are on par with its prescription counterpart.[89] Additionally, in a FY2019 budget justification document for the Department of Health and Human Services, the Trump Administration described its request for resources to address the opioid addiction crisis, including $10 million for FDA activities. According to the document, part of this funding would be devoted to accelerate the development of generic versions of opioid drug products with ADFs. The document further states that "FDA will use the resources to fund studies to identify additional tools and methodologies that can be used to evaluate whether differences in formulations impact abuse deterrence. FDA anticipates that identification of such tools and methodologies will help generic drug applicants streamline the testing necessary to support approval, resulting in increased competition."[90]

Improving Enforcement and Assessing Benefit Risk

As part of its response to the opioid epidemic, FDA officials have expressed a desire to better leverage the agency's enforcement capabilities.[91] The FD&C Act contains a number of enforcement mechanisms, both civil and criminal in nature, which may apply to, among many other things, the marketing of diverted opioids, as well as drugs not approved by FDA. Persons who violate the requirements of the Act may be subject to a variety of sanctions, including civil monetary penalties, injunctions, seizures, fines, and imprisonment, depending on the particular misconduct at issue. Commonly, FDA may issue a warning letter to encourage voluntary compliance with the FD&C Act before initiating further enforcement action.[92] Under one example of recent opioid-related enforcement, in May 2018, FDA issued a number of warning letters[93] to marketers and distributors of kratom products.[94] According to FDA, these products were sold with

[87] 21 U.S.C. § 355(j)(2)(A)(iii).

[88] *Id*. § 355(j)(2)(A)(v).

[89] *See* P.L. 114-198, § 106, 130 Stat. 695 (2016); U.S. FOOD & DRUG ADMIN., GENERAL PRINCIPLES FOR EVALUATING THE ABUSE DETERRENCE OF GENERIC SOLID ORAL OPIOID DRUG PRODUCTS (Nov. 2017), https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[90] DEPT. OF HEALTH AND HUMAN SERV., FISCAL YEAR 2019 FOOD AND DRUG ADMINISTRATION, JUSTIFICATION OF ESTIMATES FOR APPROPRIATIONS COMMITTEES, https://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/BudgetReports/default.htm.

[91] *See* U.S. FOOD & DRUG ADMIN., OPIOID POLICY STEERING COMMITTEE, (last visited Apr. 8, 2018), https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/ucm587929.htm.

[92] U.S. FOOD & DRUG ADMIN., FDA REGULATORY PROCEDURES MANUAL, Ch. 4-1-1 (2017) https://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm; *see generally* CRS Report R43609, *Enforcement of the Food, Drug, and Cosmetic Act: Select Legal Issues*, by Kathryn B. Armstrong and Jennifer A. Staman.

[93] *See* Press Release, U.S. Food & Drug Admin., FDA warns companies selling illegal, unapproved kratom products marketed for opioid cessation, pain treatment and other medical uses (May 22, 2018), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm608447.htm.

[94] FDA has raised concerns about the safety of kratom, a botanical substance that the agency has found to have pharmacologic properties similar to opioids. According to FDA officials, there have been injuries and "scores of deaths" associated with its use. *See* U.S. FOOD & DRUG ADMIN., FDA AND KRATOM, (last visited June 1, 2018),

unproven claims that the products could treat opioid addiction and withdrawal. In the warning letters, the agency states, among other things, that the products are not generally recognized as safe and effective for the referenced uses and are therefore considered unapproved new drugs sold in violation of the FD&C Act.[95] The letters request the parties take immediate corrective action, and include notice of FDA's intention to take further enforcement actions if the recipients fail to comply.[96]

Additionally, with respect to the assessment of the benefits and risks of a particular drug, one question that may be raised is whether FDA can withdraw approval for certain opioid medications when it is determined that the benefits of treating pain are outweighed by the potential for abuse. The FD&C Act authorizes FDA to withdraw approval of an approved NDA when, among other things, there is new clinical evidence showing that the product is unsafe for its approved use. [97] FDA must first provide the manufacturer with notice that the agency is proposing to withdraw approval and an opportunity for a hearing on the merits.[98] However, the agency may suspend new drug approval immediately if it is determined that the product poses an immediate hazard to the public health.[99] Although it is not a common occurrence, it has been estimated that FDA has withdrawn approval of approximately 600 new drug and abbreviated new drug applications.[100]

FDA has signaled its willingness to withdraw approval of products with serious potential for abuse. In June 2017, FDA requested that Endo Pharmaceuticals recall from market Opana ER— a potent painkiller reformulated to make it difficult to crush and snort.[101] Although the product was intended to curb opioid abuse, it reportedly led to the largest HIV outbreak in Indiana history when addicts resorted to liquidizing and injecting the drug with shared needles.[102] Ultimately, the company announced in July 2017 that it would comply with FDA's request.[103]

Selected Opioid-Related Bills in the 115th Congress That Would Amend the FD&C Act

As FDA relies on its existing legal authorities to combat opioid abuse, congressional interest remains high in amending the FD&C Act to address perceived deficiencies in the federal

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https://www.fda.gov/NewsEvents/PublicHealthFocus/ucm584952.htm; Douglas C. Throckmorton, M.D., Scott Gottlieb, M.D., and Janet Woodcock, M.D., *The FDA and the Next Wave of Drug Abuse — Proactive Pharmacovigilance*, NEW ENGL. J. MED (2018), https://www.nejm.org/doi/full/10.1056/NEJMp1806486#article_supplementary_material.

[95] *See, e.g.*, Letter from U.S. Food & Drug Admin. to Augustine Hanger, Revibe, Inc., https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm607904.htm (May 18, 2018).

[96] *See id*.

[97] *See* 21 U.S.C. § 355(e).

[98] *See id*.

[99] *See id.*

[100] *See* Kurt R. Karst, *How Often Are Drugs Withdrawn For Safety or Effectiveness Reasons (and How Many)? Not Too Often in Recent Years, But There is a Tranche of Withdrawals Historically*, FDA LAW BLOG (JUNE 14, 2015), http://www.fdalawblog.net/2015/06/how-often-are-drugs-withdrawn-for-safety-or-effectiveness-reasons-and-how-many-not-too-often-in-rece/.

[101] Press Release, U.S. Food & Drug Admin., FDA Requests removal of Opana ER for risks related to abuse, https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm562401.htm (June 8, 2017).

[102] *See* Amanda Macmillan, *The Opioid Opana ER Is Being Taken Off the Market*, TIME HEALTH, July 7, 2017, http://time.com/4849361/opioid-opana-er-fda/.

[103] Press Release, Endo Pharmaceuticals, Endo Provides Update On OPANA® ER (Jul. 6, 2017), https://www.prnewswire.com/news-releases/endo-provides-update-on-opana-er-300484191.html.

regulatory regime governing opioids. Both the House and the Senate are currently considering legislative measures that would amend the Act and address a range of issues related to the opioid crisis. Proposals include the following:

- **Changes to FDA's REMS Authority.** In an effort to promote appropriate prescribing practices and decrease exposure to opioids, various bills have been introduced that would clarify or expand FDA's REMS authorities. For example, the Opioid Crisis Response Act (S. 2680) would explicitly permit FDA to require a REMS for certain drugs, through which the agency would be authorized under specified circumstances to compel medications to be made available with certain packaging systems (such as blister packs or other packaging that provided a set treatment duration) or dispensed with safe disposal systems.[104] Another bill, S. 2608, the Reducing Opioid Risk Act, would allow FDA to require, as a potential element of a REMS, a communication plan to health care providers that disseminates information about federal and state prescribing requirements for controlled substances.[105]
- **Additional FDA Enforcement Capabilities.** Some Members of Congress have introduced legislation intended to provide FDA with additional enforcement tools to address the opioid epidemic. For instance, multiple bills address FDA's enforcement role with respect to drug importation.[106] Under current law, FDA, in collaboration with the Customs and Border Protection Agency, is authorized to inspect, detain, and refuse entry to imported drugs, devices, food, and other products under its jurisdiction.[107] Recently, FDA Commissioner Gottlieb and others have highlighted challenges associated with diverted opioids or illegal drugs that enter the United States through international mail facilities, including issues with inspecting the high volume of items entering these facilities and procedural difficulties in determining whether a particular product violates the FD&C Act before it may be refused entry or destroyed. [108] Legislation such as the Stop Illicit Drug Importation Act of 2018 (H.R. 5752) would aim to streamline the process of refusing entry to diverted or illegal drug products by, among other things, deeming certain articles to be drugs for purposes of the importation requirements (including articles that contain an active ingredient in a drug

[104] S. 2680, 115th Cong. § 302 (as reported by S. Comm. on Health, Education, Labor and Pensions, May 7, 2018). *See also generally* Press Release, U.S. Food & Drug Admin., Statement from FDA Commissioner Scott Gottlieb, M.D., on new steps to help prevent new addiction, curb abuse and overdose related to opioid products (Jan. 30, 2018), https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm594443.htm (addressing use of FDA's REMS authorities and changes in medical product packaging).

[105] S. 2608, § 2, 115th Cong. (2018).

[106] *See, e.g.*, S. 2680, 115th Cong. § 303, 305 (as reported by S. Comm. on Health, Education, Labor and Pensions, May 7, 2018); H.R. 5228, 115th Cong. § 2-4 (as ordered to be reported by H. Energy and Commerce Comm., May 17, 2018).

[107] *See* 21 U.S.C. § 381(a).

[108] *See, e.g.*, U.S. FOOD & DRUG ADMIN., FDA IS USING INNOVATIVE METHODS TO PREVENT ILLEGAL PRODUCTS WITH HIDDEN DRUG INGREDIENTS FROM ENTERING THE UNITED STATES (last visited May 23, 2018), https://blogs.fda.gov/fdavoice/index.php/2018/03/fda-is-using-innovative-methods-to-prevent-illegal-products-with-hidden-drug-ingredients-from-entering-the-united-states/. *See also* Combatting the Opioid Crisis: Prevention and Public Health Solutions, Before the H. Energy and Commerce Comm., 115th Cong., (2018)(statement of Scott Gottlieb).

approved under the FD&C Act) and establishing new authority to refuse admission to certain "articles of concern," as defined by the legislation.[109]

- **Agency Guidance to Promote Development and Use of Nonaddictive and Nonopioid Analgesics.** In an effort to encourage the development of new therapies and limit improper use of opioid products, several bills would direct FDA to hold public meetings and issue nonbinding guidance to assist industry stakeholders and health care providers. For example, S. 2669, the Advancing Innovation in Alternative Pain and Addiction Therapies Act, would generally require FDA to issue guidance "clarifying the methods and processes by which [FDA] may provide accelerated approval for non-opioid or non-addictive drugs" for treating pain or substance use disorders, as well as guidance on breakthrough therapy status[110] for these medications.[111] H.R. 5473, the Better Pain Management Through Better Data Act of 2018; S. 2665; and other bills would instruct FDA to address opioid sparing and how to collect data on sparing in order to support drug labeling claims about the efficacy of non-opioid painkillers, or whether a reduced amount of an opioid product may be sufficient to treat pain.[112] S. 2680, the Opioid Crisis Response Act, would require FDA to hold at least one public meeting and issue guidance on various opioid-related issues, including the circumstances under which the agency considers misuse and abuse of controlled substances in determining whether to approve an NDA or withdrawal an existing application.[113]

Author Information

Jennifer A. Staman
Legislative Attorney

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[109] H.R. 5752, 115th Cong. § 2 (as ordered to be reported by H. Energy and Commerce Comm., May 17, 2018).

[110] Section 506(a) of the FD&C Act addresses the designation of a drug as a breakthrough therapy. *See* 21 U.S.C. § 356(a). Under this section, the Secretary may, upon request of an NDA sponsor, expedite development and review of a drug if the drug is intended to treat a serious or life-threatening disease or condition and evidence indicates that the drug may generally demonstrate improvement over existing therapies on a clinically significant endpoint. *Id*. The FD&C Act specifies that FDA make take certain actions to expedite the development and review of breakthrough therapies, including providing timely advice to, and interactive communication with, the sponsor regarding the drug development, as well as the involvement of higher level FDA staff as part of the review process. *Id*. § 356(a)(3)(B).

[111] S. 2669, § 2-3, 115th Cong. (2018).

[112] S. 2665, § 1, 115th Cong. (2018). S. 2665 is entitled "To require guidance on how the Food and Drug Administration will consider claims of opioid sparing and on the conditions under which the Food and Drug Administration will consider misuse and abuse of drugs in making certain determinations of safety."

[113] S. 2680, 115th Cong. § 301 (as reported by S. Comm. on Health, Education, Labor and Pensions, May 7, 2018).

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