

CARA and the FDA: The Call to Convene and the Charge to Clarify

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I. INTRODUCTION

I pledge allegiance to the Opioid of the United States of Addiction, and to the Painkiller for which it plagues, one Nation under the influence, incapacitated, with naloxone and syringes for all.

One American dies every 13 minutes in the United States from an opioid overdose,¹ and almost half of all opioid overdose deaths result from a prescription opioid.² In 1971, President Nixon declared a “War on Drugs,” advocating that “America’s public enemy number one . . . is drug abuse.”³ Yet, almost half a century later, drug abuse and addiction continue to relentlessly ravage the American people in the form of an “opioid overdose epidemic” that the Centers for Disease Control and Prevention declared a “public health emergency nationwide” in October 2017.⁴ The number of deaths resulting from

1. See *Understanding the Epidemic*, CTRS. FOR DISEASE CONTROL & PREVENTION, <https://www.cdc.gov/drugoverdose/epidemic/index.html> (last visited Mar. 12, 2018) [hereinafter CDC, *Understanding the Epidemic*] (reporting that “115 Americans die every day from an opioid overdose,” equaling one American death every 13 minutes and 28 seconds).

2. See *Injury Prevention & Control: Opioid Overdose, Prescription Opioid Overdose Data*, CTRS. FOR DISEASE CONTROL & PREVENTION, <http://www.cdc.gov/drugoverdose/data/overdose.html> (last updated Aug. 1, 2017) [hereinafter CDC, *Injury Preventions & Control*] (reporting that “40% of all U.S. opioid overdose deaths involve a prescription opioid”). Additionally, the populations with the highest overdose rates include individuals aged 25 to 54 years and non-Hispanic whites, American Indian, or Alaskan Natives. *Id.*

3. Richard M. Nixon, President of the United States, Remarks About an Intensified Program for Drug Abuse Prevention and Control (June 17, 1971), <http://www.presidency.ucsb.edu/ws/?pid=3047>.

4. *Opioid Overdose*, CTRS. FOR DISEASE CONTROL & PREVENTION, <https://www.cdc.gov/drugoverdose/index.html> (last updated Oct. 23, 2017) [hereinafter CDC, *Opioid Overdose*] (“The United States is in the midst of an opioid overdose epidemic.”). Former President Barack Obama, when asked why he attended

prescription opioid drug overdoses continues to rise and is a reflection of the persisting drug abuse problem in America, costing the ultimate price for too many—their life.⁵

In response to this epidemic, the U.S. Food and Drug Administration (“FDA”) and Congress took action. In February 2016, the FDA published an “Opioids Action Plan,” indicating its intent to use an advisory committee to review New Drug Applications (“NDAs”)⁶ for opioid drugs that do not contain abuse-deterrent

a conference on prescription drugs, responded, “[b]ecause it’s important, and it’s costing lives, and it’s devastating communities.” Press Release, The White House, Remarks by the President in Panel Discussion at the National Prescription Drug Abuse and Heroin Summit (Mar. 29, 2016), <https://obamawhitehouse.archives.gov/the-press-office/2016/03/29/remarks-president-panel-discussion-national-prescription-drug-abuse-and-heroin-summit>. Former Surgeon General Vivek Murthy echoed President Obama when he called on his fellow colleagues to take the pledge “to turn the tide on the opioid crisis” because he, too, recognized that “communities [are] devastated by opioid overdoses.” *The Surgeon General’s Call to End the Opioid Crisis*, TURN THE TIDE, <http://turnthetidex.org> (last visited Jan. 22, 2018). On October 26, 2017, then-Acting Secretary of the U.S. Department of Health and Human Services Eric Hargan determined that the opioid crisis in the United States rose to the level of a “public health emergency . . . nationwide.” U.S. DEP’T OF HEALTH & HUMAN SERVS., DETERMINATION THAT A PUBLIC HEALTH EMERGENCY EXISTS 1 (2017), <https://www.hhs.gov/sites/default/files/opioid%20PHE%20Declaration-no-sig.pdf>.

5. In the United States, the number of prescription opioid deaths since 1999 parallels the increasing amount of opioids dispensed by prescription without a corresponding increase in the amount of pain that patients report perceiving during a similar span of years. CDC, *Understanding the Epidemic*, *supra* note 1 (citing, *inter alia*, Hsien-Yen Chang et al., *Prevalence and Treatment of Pain in Emergency Departments in the United States, 2000–2010*, 32 AM. J. OF EMERGENCY MED. 421 (2014); Matthew Daubresse et al., *Ambulatory Diagnosis and Treatment of Nonmalignant Pain in the United States, 2000–2010*, 5 MED. CARE 870 (2013)).

6. The Food, Drug, and Cosmetic Act (“FDCA”) prohibits the introduction of any new drug into interstate commerce without an effective application. 21 U.S.C. § 355(a) (2012). Thus, the FDA promulgated regulations to provide guidance to the industry to navigate completing and filing NDAs. *See generally* 21 C.F.R. § 314 (2017). Essentially, these NDAs are “supposed to tell the drug’s whole story, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug behaves in the body, and how it is manufactured, processed and packaged.” *New Drug Application (NDA)*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedand>

properties⁷ and only those abuse-deterrent formulations that “raise novel issues.”⁸ Then, in June 2016, Congress passed the Comprehensive Addiction and Recovery Act (“CARA”).⁹ CARA mandates that the FDA utilize an advisory committee to provide an independent review and recommendation on whether to approve the new opioid drug.¹⁰ The FDA’s intent to convene an advisory committee to review only new opioid drugs that do not contain abuse-deterrent properties, or those abuse-deterrent formulations that “raise novel issues,” likely conflicts directly with CARA because of CARA’s plain language, the unsatisfied public health exemptions of CARA, and the resulting misalignment of the missions between the FDA and CARA.¹¹

Additionally, because CARA likely mandates use of the FDA advisory committee for every new opioid drug, regardless of the inclusion of abuse-deterrent properties, the FDA has an opportunity to optimize the advisory committee’s charge of questions to review new opioid drug applications. The concept of using agency advisory committees is not new,¹² but the effective optimization for the new drug approval process is. The approval of Zohydro ER is one

approved/approvalapplications/newdrugapplicationnda/default.htm (last updated Mar. 29, 2016).

7. Press Release, U.S. Food & Drug Admin., Calif, FDA Top Officials Call for Sweeping Review of Agency Opioids Policy (Feb. 4, 2016) [hereinafter Press Release, Calif], <https://bit.ly/2osW4Iv>.

8. *FDA Opioids Action Plan*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm484714.htm> (last updated July 11, 2017). The FDA defines abuse-deterrent formulation as those products with “properties shown to meaningfully deter abuse, even if they do not fully prevent abuse.” U.S. FOOD & DRUG ADMIN., ABUSE-DETERRENT OPIOIDS—EVALUATION AND LABELING GUIDANCE FOR INDUSTRY 2 (2015) [hereinafter ABUSE-DETERRENT OPIOIDS], <https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf> (emphasis omitted). Additionally, the FDA does not provide any further guidance on what a “novel issue” would be for the purposes of deciding whether to subject an NDA to advisory committee review.

9. Comprehensive Addiction and Recovery Act, Pub. L. No. 114-198, 130 Stat. 695 (2016).

10. Comprehensive Addiction and Recovery Act § 106, 130 Stat. at 702–03.

11. *FDA Opioids Action Plan*, *supra* note 8. See *infra* Section V.A.

12. See *infra* Section IV.A (discussing the statutory authority and purpose of agency advisory committees).

illustrative example of a substandard exercise of an advisory committee's capability.¹³ The FDA charged the advisory committee with questions that failed to elicit necessary information to support its reasoning for a recommendation against approval, evidenced by the public outrage after the FDA's approval of the drug.¹⁴ Thus, reformulating the charge of questions to the advisory committee will help elicit informative and sound reasoning to support its recommendations regarding the drug approval process, and CARA presents a crucial opportunity to optimize an existing resource.

This Note advocates for both the use of the FDA advisory committee for *every* new opioid drug and the optimization of the FDA's charge of questions to the advisory committee through a new, proposed framework.¹⁵ Together, the use of the advisory committee and the optimization of the charge of questions may mitigate the introduction of dangerous and duplicative opioids into the marketplace, potentially curbing the opioid overdose epidemic resulting from prescription opioids. Part II follows the rise of regulation that governs the approval of new drugs, particularly opioids. Part III analyzes the evolution of opioids and the genesis of the twenty-first century opioid epidemic. Part IV critiques the approval of Zohydro ER as a case study. Part V advocates for using the advisory committee for *every* new opioid drug by interpreting pertinent provisions of CARA and proposes a framework for future FDA charges to the advisory committee.

13. Zohydro ER is an opioid drug that contains hydrocodone, which the FDA approved in October 2013. CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., SUMMARY REVIEW FOR REGULATORY ACTION: ZOGENIX, INC. (2013), https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202880Orig1s000SumR.pdf.

14. *See infra* Sections IV.B–IV.C (discussing the advisory committee's findings and concerns, subsequent FDA approval, and the aftermath addressed by Congress, health care professionals, and patient advocacy groups).

15. A "charge of questions" is a list of questions, varying in number, that a member of the FDA essentially directs the FDA's advisory committee to answer by making a recommendation regarding whether to approve the new drug. *See, e.g., infra* notes 65–78 and accompanying text.

II. THE RISE OF REGULATION

An evident theme prompting drug regulation exists: when a drug results in death or severe impairment, regulation quickly follows to mitigate the drug's adverse effects. To understand CARA's purpose in the grand scheme of drug regulation, it is imperative to review the rise of drug regulation in the United States. In 1906, Congress passed the Federal Food and Drugs Act ("FFDA") to stop the transit of "misbranded and adulterated foods, drinks and drugs" between States.¹⁶ A culmination of drug failures rendered the FFDA obsolete by the 1930s.¹⁷ Congress undertook an extensive overhaul on the legislation between 1933 and 1938, ultimately resulting in the Federal Food, Drug, and Cosmetic Act ("FFDCA"), which most notably required a drug to demonstrate its *safety*.¹⁸ The overhaul sped to completion in 1937 after a Tennessee drug company produced an elixir of sulfanilamide that killed 107 people—many of whom were children—because it contained a poisonous solvent akin to antifreeze.¹⁹ Another disaster occurred globally in the 1950s with use

16. *Milestones in U.S. Food and Drug Law History*, U.S. FOOD & DRUG ADMIN. (Dec. 19, 2014), <http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm> [hereinafter *Milestones*]. Subsequent revisions of the FFDA continue to recognize the illegality of adulterating and misbranding drugs. *See, e.g.*, 21 U.S.C. § 351 (2012) (defining adulterated drugs and devices); 21 U.S.C. § 352 (2012) (defining misbranded drugs and devices).

17. *See Part II: 1938, Food, Drug, Cosmetic Act*, U.S. FOOD & DRUG ADMIN. (Aug. 24, 2012), <http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm054826.htm> (explaining that drug failures, known as the "American Chamber of Horrors," against which the 1906 FFDA did not protect, included (1) Banbar, an alleged cure for diabetes; (2) Lash-Lure, an eyelash dye resulting in permanent blindness in at minimum one patient; (3) Radithor, a radium-containing tonic that killed multiple users; and (4) Wilhide Elixir, an alleged cure for tuberculosis and other pulmonary ailments).

18. This safety requirement expanded the FDA's power, allowing it to require preclinical and clinical trials and permitting rejection of NDAs based on safety concerns. *Id.*; *Milestones*, *supra* note 16.

19. Donna Young, *Documentary Examines Sulfanilamide Deaths of 1937*, AM. SOC'Y OF HEALTH-SYSTEMS PHARMACY (Dec. 5, 2003), https://www.ashp.org/news/2003/12/05/documentary_examines_sulfanilamide_deaths_of_1937. Sulfanilamide, a drug used for the treatment of bacterial infections, was

of the drug thalidomide, a sleeping pill that physicians gave to pregnant women that caused horrendous birth defects, including phocomelia, congenital heart disease, and ocular malformations, in thousands of infants.²⁰ The Kefauver-Harris Drug Amendments were moving through the Congressional pipeline when the thalidomide tragedy occurred, causing Congress to shift the focus of the legislation from lowering drug prices to heightening drug safety requirements and, for the first time, requiring manufacturers to demonstrate drugs' efficacy.²¹

In the midst of increasing safety and mandating efficacy requirements, prescription drug abuse gained national attention.²² Congress passed the Drug Abuse Control Amendments of 1965 in response to the rising abuse of antidepressants, stimulants, and hallucinogens.²³ The Drug Abuse Control Amendments represent the beginning of a broad reorganization and consolidation of drug task forces coupled with extensive legislation in the area of drug abuse and

compounded as an elixir, using the solvent diethylene glycol to turn tablets into liquid, and sweetened with a raspberry flavoring to make the antibiotic more palatable for children. *Id.* The safety profile of the sulfanilamide elixir was not evaluated prior to its marketing, but the FDA did not require it to be at the time this elixir was marketed. *Id.* Ultimately, the elixir proved to be lethal because it often resulted in kidney failure. *Id.* The FDA exercised its regulatory authority to remove the elixir from the market, not because it was killing patients, but rather because it was misbranded. *Id.* For a product to be labeled an elixir, the product must contain alcohol, and the sulfanilamide elixir did not contain any alcohol; thus, the FDA deemed it misbranded. *Id.*

20. James H. Kim & Anthony R. Scialli, *Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease*, 122 TOXICOLOGY SCIENCES 1, 1 (2011), <http://scialliconsulting.com/publications/07%20Kim-Scialli%20thalidomide2011.pdf>.

21. Sam Peltzman, *An Evaluation of Consumer Protection Legislation: The 1962 Drug Amendments*, 81 J. OF POL. ECON. 1049, 1049–51 (1973).

22. Nixon, *supra* note 3.

23. While signing the Drug Abuse Control Amendments of 1965, President Lyndon B. Johnson stated that the law's purpose was "to prevent both the misuse and the illicit traffic[ing] of potentially dangerous drugs, especially the sedatives and the stimulants . . . [because there were] [e]nough 'goof balls' and 'pep pills' . . . manufactured this year to provide 2 dozen pills to every man, woman, and child in the United States." Lyndon B. Johnson, President of the United States, Remarks at the Signing of the Drug Abuse Control Amendments Bill (July 15, 1965), <http://www.presidency.ucsb.edu/ws/index.php?pid=27087>.

misuse to come.²⁴ In 1970, Congress passed the Comprehensive Drug Abuse Prevention and Control Act (“CDACA”) in response to America’s escalating drug problem, which effectively replaced over fifty pieces of drug legislation.²⁵ As drug abuse and addiction persisted and continued to claim the lives of thousands of Americans annually,²⁶ Congress passed CARA, the most expansive piece of federal regulation that addresses drug abuse in the 21st century.²⁷ CARA encompasses prevention, education, treatment, recovery, enforcement, and reform in order to more diligently and exhaustively address the opioid epidemic.²⁸ More specifically, CARA requires submission of

24. See generally U.S. DRUG ENF’T ADMIN., *THE DEA YEARS: 1970–1975*, at 30, 30–39 [hereinafter *DEA YEARS*], <http://bit.ly/2rvajQF>.

25. *Id.* at 31. See also Comprehensive Drug Abuse Prevention and Control Act, Pub. L. No. 91-513, 84 Stat. 1236 (1970). Title II of the CDACA, commonly known as the Controlled Substances Act (“CSA”), created five schedules of drugs based on the drugs’ (1) potential for abuse, (2) status of an accepted medical use in the United States, and (3) safety and likelihood of dependence. See generally 21 U.S.C. § 812(b) (2012). CSA contains schedules I through V. *Id.* Schedule I drugs have a high potential for abuse, no accepted medical use in the United States, and a lack of accepted safety data to be administered under the supervision of medical care. § 812(b)(1). Examples of schedule I drugs include heroin and marihuana. *Id.* Schedule V drugs have a low abuse potential relative to schedule IV drugs, currently accepted medical use in the United States, and may lead to limited dependence as compared to schedule IV drugs. § 812(b)(5).

26. Rose A. Rudd et al., *Increases in Drug and Opioid-Involved Overdose Deaths—United States, 2010–2015*, 65 *MORBIDITY MORTALITY WKLY. REP.* 1445, 1445 (2016).

27. CARA was first introduced on February 12, 2015, and President Obama ultimately signed it into law on July 22, 2016. *S.524 - Comprehensive Addiction and Recovery Act of 2016*, CONGRESS.GOV, <https://www.congress.gov/bill/114th-congress/senate-bill/524/actions> (last visited Mar. 10, 2018). CARA’s purpose of combating the epidemic has bipartisan support as evidenced by an overwhelming majority vote in both the House of Representatives and the Senate: the House of Representatives vote yielded 407 yeas, 5 nays, and 21 not voting, 114 CONG. REC. H4554 (daily ed. July 8, 2016); the Senate vote yielded 92 yeas, 2 nays, and 6 nays voting, *Roll Call Vote 114th. Congress- 2nd Session*, SENATE.GOV, http://www.senate.gov/legislative/LIS/roll_call_lists/roll_call_vote_cfm.cfm?congress=114&session=2&vote=00129 (last visited Mar. 10, 2018). Thus, concern for remedying the epidemic is not rooted in partisan politics but rather in the hearts of the American people.

28. Comprehensive Addiction and Recovery Act of 2016, Pub. L. No. 114-198, § 106, 130 Stat. 695, 695–96 (2016).

new opioid NDAs to an FDA advisory committee for review and recommendation regarding whether the drug should be approved.²⁹ Thus, the theme of drug regulation in response to drug-related deaths is still evident nearly a century later.

III. THE OPIOID

To appreciate the necessity of the expansive prescription drug regulation and the gravity of the opioid epidemic, it is imperative to understand the derivation and evolution of opioid use and abuse. Without a thorough understanding of this baseline information, the word “opioid” becomes a triviality that does not realize the drug’s potential for both relieving extraordinary pain and causing devastating deaths. Additionally, awareness of the evolution of opioid drugs and subsequent opioid abuse is critical to recognizing that this opioid epidemic is not the first of its kind. Together, this information will provide a cursory explanation for the importance of improving the opioid drug approval process.

A. The Poppy Plant

Opium, produced by the poppy plant *Papaver somniferum*, is one of the oldest drugs identified by humankind, with nearly every culture embracing it and regulating it at some point.³⁰ In 1803, a pharmacist named Friedrich Sertürner isolated the first alkaloid morphine from the juice of opium poppies.³¹ Opium and other similar

29. *Id.* at 702–03.

30. DANIEL M. PERRINE, *THE CHEMISTRY OF MIND-ALTERING DRUGS* 43–44 (1996). “The power of opium to relive pain and induce sleep was probably know by the Sumerians” as early as 4000 B.C. *Id.* at 45. Other estimates suggest the Sumerian cultures used opium as early as 3500 B.C. FOYE’S *PRINCIPLES OF MEDICINAL CHEMISTRY* 662 (Thomas L. Lemke et al. eds., 7th ed. 2013). President Thomas Jefferson even planted opium poppies in his garden at Monticello, which were ultimately destroyed during a drug bust unrelated to planting the poppies. PERRINE, *supra*, at 44.

31. After the opium poppy flower blooms, and the unripened seeds are sliced open, a milky latex or juice oozes out to be collected and dried, “resulting [in a] yellow- to brown-colored paste [that] is raw opium.” PERRINE, *supra* note 30, at 45. Sertürner named morphine “after Morpheus, the Greek God of dreams.” Lemke et al., *supra* note 30, at 662. In 1898, the first synthetic derivative of morphine, named

isolated alkaloids, such as morphine, are named “opioids”³² because they share similar pharmacologic action—pain relief and euphoria—at the opioid receptors.³³ Because of the desirable effects that opioids induce, consumers often abuse this class of drugs by injecting, snorting, or smoking the drugs,³⁴ which often results in a faster onset of action, and ultimately a faster high, as compared to when the patient takes the drug as prescribed.³⁵ Extended-release (“ER”) and long-acting (“LA”) formulations, designed with more active drug per dose to decrease the dosing frequency, are more frequently abused because more active drug per dose often results in a greater high when abused.³⁶

diacetylmorphine, was synthesized and promoted as a “nonaddicting analgesic, antidiarrheal, and antitussive agent”; it is now widely known as heroin. *Id.* at 663.

32. See Lemke et al., *supra* note 30, at 663. The term “opiate” described only natural and synthetic opioids until the 1980s because they were structurally similar. *Id.* After scientific advancements that rendered drugs not structurally similar, but their pharmacologic mechanisms similar, the distinction between “opioid” and “opiate” became irrelevant. *Id.* Thus, the term “opioid” is a broad and all-encompassing term for drugs that act on the major opioid receptors. Daniel J. Coughlin et al., *The Opioid Abuse and Misuse Epidemic: Implications for Pharmacists in Hospitals and Health Systems*, 71 AM. J. HEALTH-SYSTEM PHARMACY 1539, 1539 (2014).

33. Generally, a “receptor” is the biological target where a drug exerts its effect. See Lemke et al., *supra* note 30, at 31. Here, an opioid receptor is the biological target where an opioid drug exerts its effect.

34. See *Commonly Abused Drug Charts, Prescription Opioids*, NAT’L INST. ON DRUG ABUSE, <https://www.drugabuse.gov/drugs-abuse/commonly-abused-drugs-charts#heroin> (last updated Jan. 2018).

35. Gwen Hughes, *A Simple Introduction to Pharmacokinetics: Part 1*, 12 NURSE PRESCRIBING 497, 497 (2014) (“Dependent on many variables, the rate of absorption according to delivery route is generally intravenous > intraosseous > endotracheal > inhalation > sublingual > intramuscular > subcutaneous > rectal > ingested.”).

36. Jeffrey Fudin, *Abuse-Deterrent Opioid Formulations: Purpose, Practicality, and Paradigms*, PHARMACY TIMES (Jan. 27, 2015, 4:36AM), <http://www.pharmacytimes.com/contributor/jeffrey-fudin/2015/01/abuse-deterrent-opioid-formulations-purpose-practicality-and-paradigms> (“Abusers often manipulate ER [extended release] opioid formulations by crushing, chewing, snorting, vaping, or injecting the total dose. Drug seekers are particularly interested in the ER formulations because tampering with these products provides them with a higher maximum concentration of the drug in a small volume of powder, which is easily snorted with minimal discomfort compared to the large amount of powder (and excipients) required of standard immediate-release (IR) dosage formulations.”).

One ongoing effort to combat the non-intended routes for administration is to manufacture the drug with abuse-deterrent properties.³⁷ The scientific data supporting the efficacy of abuse-deterrent formulations remains in its infancy,³⁸ and the opioid drug must eventually be delivered to the body by its releasing mechanism. Ultimately, these abuse-deterrent properties can only deter, not prevent, abuse.³⁹ Because the efficacy data are still unknown, the FDA intends to remain flexible and encourage further research in this area.⁴⁰ Thus, even if an opioid contains abuse-deterrent properties, the high risk for abuse remains, especially in ER/LA opioid formulations.

B. A Dose of Déjà Vu

The opioid epidemic ravaging America is not the first of its kind. During the second half of the nineteenth century, the consumption of opioids increased by 538%.⁴¹ Iatrogenic morphine addiction proved to be the primary source of the 19th century epidemic because cures were rare, and the etiology of many painful diseases was unknown.⁴² The decline of this opioid epidemic likely resulted from a combination of advancements in public health initiatives and infection control, the discovery of aspirin, the passage of the FFDA, warnings about the effects of morphine, and decreased opioid overprescribing.⁴³

37. ABUSE-DETERRENT OPIOIDS, *supra* note 8, at 2.

38. *Id.* at 25–26.

39. *Id.* at 2.

40. This type of formulation preference is not binding on future opioid drug manufacturers, and the current thinking of the FDA is that abuse-deterrent formulations are a “step towards the goal of creating safer opioid analgesics” and “a high public health priority.” ABUSE-DETERRENT OPIOIDS, *supra* note 8, at 1–2.

41. Andrew Kolodny et al., *The Prescription Opioid and Heroin Crisis: A Public Health Approach to an Epidemic of Addiction*, 36 ANN. REV. PUBLIC HEALTH 559, 561 (2015). The increase began with 0.72 opioid-addicted individuals per 1,000 persons in the 1840s, peaked at approximately 4.59 opioid-addicted individuals per 1,000 persons in the 1890s, and stabilized at 1.97 opioid-addicted individuals per 1,000 persons by 1920. *Id.*

42. *Id.* Other contributors to the 1800s opioid epidemic included (1) mothers self-medicating themselves and their children, (2) soldiers using it to “treat diarrhea and painful injuries,” (3) alcoholics using it as a hangover cure, and (4) Chinese immigrants smoking it. *Id.*

43. *See id.* at 561–62.

In the 1980s, opioid use began to rise again steadily, regaining favor with the physician's prescription pad.⁴⁴ Shortly thereafter, the FDA approved OxyContin, an ER formulation of oxycodone manufactured by Purdue Pharma L.P.⁴⁵ Within a year of approval, Dr. James Campbell, then-president of the American Pain Society, campaigned for evaluating pain as the "fifth vital sign" in addition to blood pressure, heart rate, respiratory rate, and temperature.⁴⁶ A revolution

44. *Id.* at 562. In 1986, a published study of patients taking different opioids or a combination of them found that "opioid maintenance therapy can be a safe, salutary and more humane alternative to the options of surgery or no treatment in those patients with intractable non-malignant pain and no history of drug abuse." Russell K. Portenoy & Kathleen M. Foley, *Chronic Use of Opioid Analgesics in Non-Malignant Pain: Report of 38 Cases*, 25 PAIN 171, 171 (1986). This study, consisting of only 38 patients, was commonly cited for support in expanding the use of opioids in treating chronic non-cancer pain. Kolodny et al., *supra* note 41, at 562.

45. *Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm338566.htm> (last updated Feb. 15, 2018). Lingering physician concerns remained regarding the potential for dependence and abuse because of OxyContin's nature as an ER opioid, and Purdue Pharma L.P. attempted to remedy reluctance about prescribing opioids by claiming that the medical community had been confusing addiction with "physical dependence," and that the prevalence of addiction is "rare":

The rare occurrence of euphoria in patients without a history of abuse suggests that fundamental processes may predispose to addiction and are uncommon among patients who have not previously demonstrated abuse behaviors. It can be speculated that the lack of prior substance abuse, combined with the lack of a euphorogenic response to a therapeutic opioid, signals a particularly low risk of addiction.

Russell K. Portenoy, *Opioid Therapy for Chronic Nonmalignant Pain: Clinician's Perspective*, 24 J.L., MED. & ETHICS 296, 301-02 (1996). Subsequently, Purdue Pharma L.P. sponsored over "20,000 pain-related educational programs" and "provided financial support to the American Pain Society, American Academy of Pain Medicine, the Federation of State Medical Boards, [and] the Joint Commission" to induce each organization to use its clout to influence and advocate for the more aggressive diagnosis and management of pain with opioids. Kolodny et al., *supra* note 41, at 562.

46. James N. Campbell, *APS 1995 Presidential Address*, 5 PAIN F. 85, 86 (1996). This new approach to pain management infiltrated influential health systems, including the Veterans Affairs health system and the Joint Commission on Accreditation of Healthcare Organizations ("Joint Commission"). Natalia E. Morone

in opioid treatment and prescribing habits followed because physicians evaluated a patient's subjective level of pain as routinely as evaluating the four other objective indicators of organ and body function, overcoming a history of reluctance regarding prescribing opioids to treat chronic, non-cancer pain.⁴⁷ Both advocating for pain as the fifth vital sign and the FDA's approval of OxyContin contribute to the birth of the 21st century opioid epidemic.⁴⁸

IV. ZOHYDRO ER: AN ADVISORY COMMITTEE CASE STUDY

Zohydro ER is one controversial opioid that entered the market in the midst of the 21st century opioid overdose epidemic.⁴⁹ Zohydro

& Debra K. Weiner, *Pain as the Fifth Vital Sign: Exposing the Vital Need for Pain Education*, 35 CLINICAL THERAPEUTICS 1728, 1728 (2013).

47. See Marone & Weiner, *supra* note 46, at 1728 (“Given the influence of [the Veterans Health Administration and the Joint Commission], it is not surprising that clinics and hospitals across the country now assess pain routinely.”).

48. The Joint Commission also adopted “federally mandated patient satisfaction surveys asking patients to rate how often hospital staff did ‘everything they could to help you with your pain,’” Kolodny et al., *supra* note 41, at 563, which also likely contributed to the birth of the modern day opioid epidemic. In 2016, the American Medical Association (“AMA”) announced its resolution to eliminate pain as the fifth vital sign from professional standards and usage. AM. MED. ASS’N, AMA ANNUAL JUNE 11-15, 2016 REPORT 9 (2016), <https://www.aapmr.org/docs/default-source/advocacy/final-ama-annual-june-2016-meeting-report-copy.pdf>. The Association of American Medical Colleges (“AAMC”) followed suit, as evidenced in a statement it published about its continued effort to fight the opioid epidemic by equipping the future generations of physicians with the training required to effectively diagnose and treat patients. Press Release, Association of American Medical Colleges, Statement on Addressing the Opioid Epidemic (Mar. 29, 2016), <https://www.aamc.org/download/457660/data/aamcstatementonaddressingtheopioidepidemic.pdf>.

49. On May 2, 2012, Zogenix, Inc. announced that it submitted a NDA to the FDA for the drug Zohydro ER. Press Release, Zogenix, Inc., Zogenix Submits New Drug Application (NDA) to U.S. Food and Drug Administration (FDA) for Zohydro™ for Treatment of Chronic Pain (May 2, 2012) [hereinafter Zogenix Submits], <https://www.prnewswire.com/news-releases/zogenix-submits-new-drug-application-nda-to-us-food-and-drug-administration-fda-for-zohydro-for-treatment-of-chronic-pain-149799215.html>. The FDA subsequently accepted the NDA Zogenix submitted on July 16, 2012, estimating a “target action date” of March 1, 2013. Press

ER is a novel formulation of hydrocodone, indicated “for the management of moderate-to-severe pain in patients requiring continuous around-the-clock opioid therapy for an extended period of time,” that lacked an abuse-deterrent property.⁵⁰ The FDA submitted Zohydro ER to an advisory committee for evaluation,⁵¹ the advisory

Release, Zogenix Announces U.S. Food and Drug Administration (FDA) Acceptance for Review of Zohydro ER™ New Drug Application (NDA) for Treatment of Chronic Pain (July 16, 2016), <https://zogenixinc.gcs-web.com/news-releases/news-release-details/zogenix-announces-us-food-and-drug-administration-fda-acceptance>. The new formulation of hydrocodone is classified as a Schedule II controlled substance. ZOGENIX, INC., ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE, DECEMBER 7, 2012, ADVISORY COMMITTEE BRIEFING MATERIALS 1, 10 (2012) [hereinafter ZOGENIX BRIEF], <http://wayback.archive-it.org/7993/20170113234123/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM330684.pdf>. A Schedule II controlled substance indicates the drug has a “high potential for abuse.” 21 U.S.C. § 812(b)(2)(A) (2012) (indicating the risk for abuse of Schedule II substances).

50. ZOGENIX BRIEF, *supra* note 49, at 10, 93. Zogenix, Inc. advocates that “there remains a significant need for additional safe and effective ER opioid analgesic products for patients with chronic pain,” claiming novelty because no other formulation on the market contains solely hydrocodone, but rather hydrocodone in combination with another product, such as acetaminophen. *Id.* at 10; Zogenix Submits, *supra* note 49. Acetaminophen may result in hepatotoxicity when consumed in excess, and this risk is even greater in patients taking combination opioid/acetaminophen products. JOSEPH T. DiPIRO ET AL., PHARMACOTHERAPY: A PATHOPHYSIOLOGIC APPROACH 33–34 (8th ed. 2011).

51. See Memorandum, U.S. Food & Drug Admin., Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Meeting Agenda 1, 1 (Dec. 7, 2012), <http://wayback.archive-it.org/7993/20170113044149/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM333210.pdf>.

committee strongly recommended against approval,⁵² and the FDA pursued approval of it anyway.⁵³

The purpose of analyzing Zohydro ER as a case study is two-fold: first, it is important to review the genesis and influence that agency advisory committees have; and, second, the case illustrates an opportunity to optimize the charge of questions to the advisory committee seeking more clear reasoning for its recommendation, which will ultimately equip the FDA with the knowledge to make more informed decisions about whether to approve new opioid drugs. The case shows that, even when an advisory committee reviews a new opioid drug, the FDA may still reject the advisory committee's recommendation because a defective charge of questions fails to capture reasons to persuade the FDA to deny a new opioid drug application. Thus, Zohydro ER's approval case study demonstrates the need to reformulate the advisory committee's charge of questions when reviewing new opioid drugs.⁵⁴

A. Agency Authority for Advisory Committees

Agency advisory committees are not new. Congress enacted the Federal Advisory Committee Act ("FACA") in 1972, which provides the legal authority for committee operation and emphasizes public involvement and uniformity among committees.⁵⁵ The FDA tasks their committees with "furnishing expert advice, ideas, and diverse opinions to the Federal Government," and that advice is non-

52. See Memorandum, U.S. Food & Drug Admin., Summary Minutes of Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee, Questions to the Committee 1, 6 (Dec. 7, 2012) [hereinafter Questions to the Committee], <http://wayback.archive-it.org/7993/20170113044153/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM336475.pdf> (noting an 11-2-1 vote against approval).

53. Press Release, U.S. Food & Drug Admin., FDA Approves Extended-Release, Single-Entity Hydrocodone Product (Oct. 25, 2013) [hereinafter FDA Approves Hydrocodone Product], <https://wayback.archive-it.org/7993/20170111161044/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm372287.htm>.

54. See *infra* Section IV.B.

55. 5 U.S.C. app. § 2 (1972).

binding on the federal entity.⁵⁶ The FDA took initiative to implement advisory committees within its regulatory regime,⁵⁷ and the number and specificity of advisory committees continues to increase and evolve just as new drug products do, totaling thirty-three advisory committees convening on various topics.⁵⁸ Approval-recommendation data from the FDA advisory committees that review new drug products between 2001 and 2010 indicate that the FDA follows the advisory committees' advice to approve 88% of the time and to not approve 86% of the time.⁵⁹ This trend of the FDA largely following the advisory committees' recommendations suggests the strong influence the committee has over the FDA's ultimate decision.⁶⁰ In essence,

56. §§ 2(a), (b)(6). Specific to the FDA, Congress amended the FDCA in 1997 with the Food and Drug Administration Modernization Act ("FDAMA"), which included the addition of scientific advisory panels tasked with "providing expert scientific advice and recommendations to the Secretary [of Health and Human Services] regarding a clinical investigation of a drug or the approval for marketing of a drug." 21 U.S.C. § 355(n)(1) (2012). This amendment to the FDCA also details the following: delegation of authority to create the panel from the Secretary to the FDA director, ideal panel candidates, required training for panel members on regulations promulgated by the FDA and other binding law, compensation for panel members, requirement for regular panel meetings, and deadlines for the panel to make their recommendation. § 355(n). In the interim period between the enactment of FACA and FDAMA, the FDA promulgated regulations to establish general procedures for its advisory committees. *See generally* 21 C.F.R. § 14 (2016) (explaining advisory committee procedures). In 1998, the FDA issued a guidance document to ensure its compliance with FDAMA amendments, concluding the amendments merely added to the pre-existing framework FACA rather than replaced it. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY ADVISORY COMMITTEES: IMPLEMENTING SECTION 120 OF THE FOOD AND DRUG ADMINISTRATION MODERNIZATION ACT OF 1997 2 (1998) ("FDA understands the term *panels of experts* to mean advisory committees.").

57. DIV. OF HEALTH CARE POL'Y, INST. OF MED., FOOD AND DRUG ADMINISTRATION ADVISORY COMMITTEES 67 (Richard A. Rettig et al. eds., 1992).

58. *Committees & Meeting Materials*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/default.htm> (last updated May 1, 2017).

59. *See* PHILIP MA ET AL., MCKINSEY CTR. FOR GOV'T, FDA ADVISORY COMMITTEE OUTCOMES 1, 3–4 (2013), <https://mck.co/2rs4y6j> (demonstrating that the FDA approves applications and the advisory committee recommends products at a similar frequency of 75%).

60. Advisory committees "exercise great influence in agency decisions . . ." DIV. OF HEALTH CARE POL'Y, *supra* note 57, at 67.

these advisory committees not only provide an unbiased and sciences-based recommendation, but also considerably influence the FDA's final decision of approval regarding new drugs.

B. Advisory Committee v. Zohydro ER

In December 2012, the FDA convened the Anesthetic and Analgesic Drug Products Advisory Committee to advise the agency on whether to approve Zohydro ER.⁶¹ Zohydro ER posed particular risks for abuse because it is an ER formulation that did not contain any abuse-deterrent properties.⁶² Further, Zohydro ER contains hydrocodone, which was the most-prescribed opioid in the U.S. in 2013 when this drug came before the advisory committee,⁶³ and it was the opioid most associated with drug abuse and drug diversion compared to any other licit or illicit opioid.⁶⁴ Thus, the advisory committee's review of Zohydro ER's safety, efficacy, and risk-benefit balance was essential to adequately advise the FDA on whether to approve this new opioid drug.

Subsequent to presentations and personal testimonies, the Director of the Anesthetic and Analgesic Drug Products Advisory Committee tasked his committee to "discuss the risks and benefits" and "determine whether the benefit-risk assessment . . . favor[ed] [Zohydro

61. See generally U.S. FOOD & DRUG ADMIN., ANESTHETIC AND ANALGESIC DRUG PRODUCTS ADVISORY COMMITTEE (AADPAC) MEETING ROSTER 1, 1 (Dec. 7, 2012), <http://wayback.archive-it.org/7993/20170113044151/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM333215.pdf>.

62. ZOGENIX BRIEF, *supra* note 49, at 93.

63. Douglas C. Throckmorton, *Re-scheduling Prescription Hydrocodone Combination Drug Products: An Important Step Toward Controlling Misuse and Abuse*, FDA VOICE (Oct. 6, 2014), <https://blogs.fda.gov/fdavoices/index.php/2014/10/re-scheduling-prescription-hydrocodone-combination-drug-products-an-important-step-toward-controlling-misuse-and-abuse/>.

64. See OFFICE OF DIVERSION CONTROL, U.S. DRUG ENF'T ADMIN., HYDROCODONE (2014), https://www.dea.gov/druginfo/drug_data_sheets/Hydrocodone.pdf.

ER's] approval for marketing.”⁶⁵ To assess the risks and benefits, and to make a recommendation, the advisory committee discussed the following five questions, commonly referred to as “the charge”⁶⁶:

1. VOTE: Has the Applicant demonstrated that Zohydro ER is effective for the management of moderate to severe chronic pain when a continuous around-the-clock opioid analgesic is needed for an extended period of time?

....

2. VOTE: Has the Applicant demonstrated that Zohydro ER is safe in the intended population?

....

3. DISCUSSION: Please discuss whether the data presented or discussed suggest that the postmarketing experience concerning abuse with Zohydro ER would be expected to be different from the postmarketing experience associated with other approved Schedule II extended-release opioids.

....

4. DISCUSSION: Please discuss whether the data support the need for additional postmarketing risk mitigation requirements beyond the ER/LA

65. Agenda, U.S. Food & Drug Admin., Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Meeting 1, 1 (Dec. 7, 2012), <http://wayback.archive-it.org/7993/20170113044149/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM333210.pdf>.

66. See, e.g., CFSAN Risk Analysis Working Group, *Initiation and Conduct of All “Major” Risk Assessments Within a Risk Analysis Framework*, U.S. FOOD & DRUG ADMIN. (Mar. 2002), <https://www.fda.gov/Food/FoodScienceResearch/RiskSafetyAssessment/ucm475127.htm> (“*The charge* should include a statement of purpose, define the risk management problems, and the specific risk assessment questions to be answered. Key assumptions must also be identified in *the charge*.” (emphasis added)).

REMS [Risk Evaluation and Mitigation Strategy].⁶⁷

....

5. VOTE: Based on the data presented and discussed today, do the efficacy, safety and risk-benefit profile of Zohydro ER support the approval of this application?⁶⁸

The preceding questions are intended to foster focused discussion among the advisory committee members, calling on their experience and expertise to make a sound and evidence-based recommendation either for or against approval. A majority of the advisory committee voted that Zohydro ER was effective for its intended indication, but also that it was not safe in its intended population.⁶⁹ An overwhelming majority voted that the risk-benefit profile of Zohydro ER did not support its approval.⁷⁰ The advisory committee raised concerns regarding the potential for abuse and diversion because Zohydro ER lacked any abuse-deterrent properties.⁷¹ Additionally, in Question Four, the committee discussed the need for more extensive measures to avoid abuse, in addition to the efforts that the drug manufacturer Zogenix proposed, because of the state of the opioid epidemic, noting that these measures should apply to all ER/LA opioids.⁷² The discussion and the final voting results highlight the advisory committee's serious lingering concerns about

67. U.S. FOOD & DRUG ADMIN., A BRIEF OVERVIEW OF RISK EVALUATION & MITIGATION STRATEGIES 1, 2 (2017), <https://www.fda.gov/downloads/AboutFDA/Transparency/Basics/UCM328784.pdf> (“REMS are required risk management plans that use risk minimization strategies beyond the professional labeling to ensure that the benefits of certain prescription drugs outweigh their risks.”).

68. Questions to the Committee, *supra* note 52, at 5–6.

69. The final votes, reflecting either yes, no, or abstained, respectively, totaled 7-6-1 for Question One (regarding effectiveness) and 5-9-0 for Question Two (regarding safety). *Id.* at 5.

70. *Id.* at 6. The final votes for Question Five, reflecting either yes, no, or abstained, respectively, totaled 11-2-1. *Id.*

71. *Id.*

72. *Id.*

approving Zohydro ER.⁷³ Despite the advisory committee's nearly unanimous recommendation against approval, however, the FDA announced its approval of Zohydro ER on October 25, 2013.⁷⁴ Because the advisory committee's recommendation does not bind the FDA, and the agency may exercise its discretion to approve new drugs,⁷⁵ the question is not *how* the FDA approved Zohydro ER, but rather *why*. The FDA reasoned, "the benefits of the product outweigh its risks."⁷⁶

The advisory committee wrestled with its charge of questions, and the transcript from their meeting evidenced their challenge in their discussion.⁷⁷ Three prominent issues commandeered the advisory committee's discussion and became central to their ultimate recommendation. First, the charge did not include a separate question inquiring about the appropriateness of Zogenix's study design and methods for testing the new opioid drug. The committee members discussed this as part of the inquiry to determine whether Zohydro ER is effective for its intended indication, citing a 12-week trial period as inadequate for a drug indicated for chronic pain.⁷⁸ Data from the study demonstrating that patients taking Zohydro ER did not experience a clinically significant difference in pain relief bolstered the committee's observation that the study's length was inadequate.⁷⁹ Thus, the overarching issue of whether Zohydro ER is effective overshadowed a

73. *Id.* at 5–6.

74. *See generally* FDA Approves Hydrocodone Product, *supra* note 53.

75. *See generally* 21 U.S.C. § 355(d) (2012).

76. *FDA Provides Facts About Zohydro*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm395456.htm#correct> (last updated Mar. 14, 2016). The benefits of Zohydro ER included elimination of acetaminophen-induced liver toxicity and an alternative treatment option for patients in pain. *Id.* The risks of Zohydro ER include the inherent high potential for abuse and the lack of an abuse-deterrent formulation to deter that high risk. *Id.*

77. *See generally* Questions to the Committee, *supra* note 52, at 5–6 (demonstrating the difficulties the committee faced regarding the charge of questions).

78. *Id.* at 5 (discussing question one, questioning the length of the study). "The committee members who voted 'No' and the member who abstained agreed that the length of the 12-week study period was not sufficient to demonstrate efficacy for a chronic use indication." *Id.*

79. *Id.* (articulating evidence of "only . . . a modest change in pain score" as the basis for conflict).

more narrow but necessary inquiry into the appropriateness of the study design.

Second, the committee's discussion about Zohydro ER's safety focused more on comparing Zohydro ER to other previously approved ER/LA opioids than to the data from its own studies.⁸⁰ A majority of the committee ultimately voted against deeming Zohydro ER safe, indicating that the safety of a new opioid drug must be evaluated based on its own studies as opposed to the safety of other similarly and previously approved drugs.⁸¹ Here, Zohydro ER did not have any abuse-deterrent properties; Zogenix instead relied only on the REMS program and a "conservative plan" to market the drug.⁸² Additionally, rates of drug diversion and death that occurred during Zohydro ER's clinical trial were disturbingly high, given the controlled environment.⁸³ Therefore, the safety of a new opioid drug must not be determined based on a comparison to similarly situated and approved opioid drugs because these previously approved drugs, such as OxyContin, are in part to blame for the 21st century opioid epidemic.⁸⁴

Third, when the committee weighed the risks and benefits of approving Zohydro ER, the committee expressed concerns about the

80. *Id.* ("The committee agreed that [Zogenix] met the safety standards set forth by the Agency and stated that Zohydro ER is as safe as other long-acting and extended release opioid analgesics that have previously been approved.").

81. *Id.* (discussing Question Two). At one point during the committee discussion, Dr. Bob Rappaport, FDA Director of the Division of Anesthesia, Analgesia Products, and Addiction Products, asked, in response to one of the committee member's comments, "is it that there really is something different, or that you're holding it to a different standard[?] Because you're punishing this company and this drug because of the sins of the developers and their products. And we can't— from a regulatory standpoint, that's not something we can do." Transcript of FDA Anesthetic and Analgesic Drug Products Advisory Committee Meeting at 351:15–21 (2012) [hereinafter Zohydro Approval Meeting], <http://wayback.archive-it.org/7993/20170113044154/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM339619.pdf>.

82. ZOGENIX BRIEF, *supra* note 49, at 10.

83. Questions to the Committee, *supra* note 52, at 5 ("[C]ommittee members noted that drug diversion and deaths still occurred in clinical trials despite close monitoring, and that frequency of these adverse outcomes would likely be worse in real life clinical practice in the absence of close monitoring.").

84. Kolodny et al., *supra* note 41, at 562.

entire class of ER/LA opioid drugs.⁸⁵ The discussion that ensued culminated with the advisory committee overwhelmingly recommending against approval of Zohydro ER and a recommendation that every ER/LA opioid drug use abuse-deterrent properties.⁸⁶ The advisory committee attempted to make an example of Zohydro ER and recommend against its approval, before the FDA issued guidance about this specific issue, in hopes of requiring opioid drug manufacturers to include abuse-deterrent properties.⁸⁷ The FDA did not issue guidance recommending that ER/LA opioids include an abuse-deterrent formulation until 2015, amounting only to a recommendation—not a requirement.⁸⁸ This question diverted the advisory committee’s discussion to a commentary on FDA practices that resulted in inadequate support for the committee’s recommendation. Ultimately, the advisory committee placed more emphasis on the opioid epidemic when weighing the risks and benefits instead of on Zohydro ER’s inadequate study design, safety measures, and clinical efficacy.

C. Aftermath of Zohydro ER

The approval of Zohydro ER fueled the fire in many communities intimately involved and impacted by the FDA’s decision to approve it.⁸⁹ Lawmakers were livid.⁹⁰ Patient advocacy groups

85. Questions to the Committee, *supra* note 52 (“The committee believed these additional risk mitigation strategies should also apply to marketed ER/LA opioids in general.”).

86. *Id.* (“Although the committee agreed that [Zogenix] met the Agency standards for efficacy and safety, the majority of the committee did not support the approval of this application. . . . The committee stated that the FDA should not approve ER/LA opioids without tamper-resistant or abuse-deterrent formulations”).

87. See, e.g., David Morgan, *FDA Panel Opposes Recommending Painkiller, Cites Safety*, REUTERS (Dec. 7, 2012, 3:45 PM), <http://www.reuters.com/article/us-usa-fda-opioid/fda-panel-opposes-recommending-painkiller-cites-safety-idUSBRE8B619S20121207>.

88. ABUSE-DETERRENT OPIOIDS, *supra* note 8, at 1–3.

89. See generally Fudin, *supra* note 36.

90. See, e.g., Delia A. Stubbs, *FDA Makes Zohydro ER the First Approved Single-Entity Hydrocodone Analgesic, First ER/LA Opioid to Contain Hydrocodone, and First ER/LA Opioid With New Labeling*, FDA L. BLOG (Oct.

were outraged.⁹¹ Health care providers were perplexed.⁹² The approval of Zohydro ER illuminated the challenges with approving new opioid drugs in the midst of an opioid epidemic.

In February 2016, the FDA announced its “Opioids Action Plan,” which is a “far-reaching action plan to reassess the agency’s approach to opioid medications” that encompasses seven initiatives in

29, 2013, 4:17AM), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2013/10/fda-makes-zohydro-er-the-first-approved-single-entity-hydrocodone-analgesic-first-erla-opioid-to-con.html (“In addition to marking several firsts, Zohydro ER’s approval has received sharp criticism by lawmakers due to its apparent departure from a movement by FDA to potentially require abuse-deterrent technology for all opioids, like hydrocodone.”). In response to the FDA’s approval of Zohydro ER, Congressman William Keating explained that

[I]ast year, a FDA panel questioned the medical need to have such a strong drug on the market and today, FDA not only approves this dangerous drug, but does so without requiring any abuse-deterrent features. This is outrageous. Abuse-deterrent technologies should not be the anomaly—they must be the norm.

Id. Senators Mitch McConnell, Lamar Alexander, and Tom Coburn wrote a letter to FDA Commissioner Margaret Hamburg that approval of Zohydro ER would “undermine the important measures taken by the FDA, lawmakers, and state attorneys general to curb prescription drug abuse across the country.” Tim Devany, *Senate GOP: FDA-Approved Drug Poses “Significant Danger,”* THE HILL (Feb. 13, 2014, 6:10 PM), <http://thehill.com/regulation/healthcare/198384-senate-gop-fda-approved-drug-poses-significant-danger>. Senator Joe Manchin and Representatives Stephen Lynch and Hal Rogers introduced legislation after the FDA approved Zohydro ER in an attempt to withdraw Zohydro ER’s approval and prevent the FDA from approving similar drugs in the future. Kurt Orzeck, *Lawmakers Want to Undo FDA’s Approval Of New Painkiller,* LAW360 (Mar. 14, 2014, 6:31 PM), <https://www.law360.com/articles/518798/lawmakers-want-to-undo-fda-s-approval-of-new-painkiller>.

91. See, e.g., Letter from The FED UP! Coalition Steering Committee to Margaret A. Hamburg, Commissioner, U.S. Food & Drug Admin. (Feb. 24, 2014), <https://www.citizen.org/sites/default/files/2185.pdf> (sending a letter that forty-two leaders from various institutions and patient advocacy groups signed).

92. Frank LoVecchio, *Just Say No to Zohydro ER*, 33 AM. C. OF EMERGENCY PHYSICIANS 1, 17 (2014) (“[U]ntil further data are available—especially addressing post-marketing safety—it is best to ‘say no to Zohydro’ [sic] in the ED.”); Cara A. Young, *Controversy Surrounds FDA Approval Zohydro*, 19 PHARMACY TODAY 48, 48–50 (2013).

response to the opioid epidemic.⁹³ The most pertinent initiative is the FDA's intent to "[c]onvene an expert advisory committee before approving any New Drug Application for an opioid that does not have abuse-deterrent properties."⁹⁴ Essentially, according to its 2015 guidance to the pharmaceutical industry, the FDA prefers abuse-deterrent formulations for ER/LA opioids;⁹⁵ but the FDA only intends on convening the advisory committee to review new opioid drugs that do not contain abuse-deterrent properties or opioid drugs that do contain those properties and also "raise novel issues."⁹⁶ Yet, even when the committee convenes to review a new opioid drug without abuse-deterrent properties, such as Zohydro ER, the committee still struggles to make a sound and supported recommendation because of the inadequate charge of questions. The opportunities to use the advisory committee and to optimize its charge of questions abound.

V. THE CALL AND THE CHARGE

Convening the advisory committee for *every* new opioid and reformulating a framework for the FDA's charge of questions to the committee will better protect the public than the status quo. Making more informed decisions about approval of new drugs entering the market will hopefully combat the opioid epidemic. Without using the advisory committee and optimizing of the charge of questions, the most potent formulations of opioids—specifically ER/LA opioids that include abuse-deterrent properties—have the potential to reach the market without the review and recommendation of an expert, independent advisory committee while America is in the midst of an opioid epidemic. Aligning the FDA's opioids action plan with CARA and developing a charge of questions rooted in the statutory language that authorizes approval of new drugs will help the country avoid flooding the market with dangerous ER/LA opioids that lack abuse-deterrent properties.

93. Press Release, Califf, *supra* note 7; *FDA Opioids Action Plan*, *supra* note 8.

94. *FDA Opioids Action Plan*, *supra* note 8.

95. ABUSE-DETERRENT OPIOIDS, *supra* note 8, at 2.

96. *FDA Opioids Actions Plan*, *supra* note 8.

A. The Call: Convening the Committee for Every New Opioid

CARA supports the call to the FDA to convene the advisory committee to review every new opioid drug for the following three reasons: (1) the plain language of the statute requires it; (2) the abuse-deterrent formulations likely do not qualify for a public health exemption; and (3) the importance of aligning the mission of the FDA with that of CARA with respect to combating the epidemic demands it. The statutory language of CARA that implicates the FDA's new drug approval process, as it pertains to new opioid drugs, provides

- (A) IN GENERAL.—Subject to subparagraph (B), prior to the approval pursuant to an application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(b)) of a new drug that is an opioid, the Secretary of Health and Human Services (referred to in this section as the “Secretary”) shall refer the application to an advisory committee of the Food and Drug Administration to seek recommendations from such advisory committee.
- (B) PUBLIC HEALTH EXEMPTION.—A referral to an advisory committee under subparagraph (A) is not required with respect to a new opioid drug or drugs if the Secretary—
 - (i) finds that such a referral is not in the interest of protecting and promoting public health;
 - (ii) finds that such a referral is not necessary based on a review of the relevant scientific information; and
 - (iii) submits a notice containing the rationale for such findings to the Committee on Health, Education, Labor, and Pensions

of the Senate and the Committee on Energy and Commerce of the House of Representatives.⁹⁷

The following subsections analyze sources of support for convening the advisory committee for *every* new opioid drug prior to the FDA's discretionary determination of whether to approve the new opioid drug.

1. CARA § 106(a)(1)(A): Plain Language

Section 106(a)(1)(A) of CARA explicitly requires the FDA to convene the advisory committee to review all new opioid applications prior to granting approval. The statutory text states, “[s]ubject to subparagraph (B), prior to the approval . . . of a new drug that is an opioid, the Secretary of Health and Human Services . . . shall refer the application to an advisory committee of the Food and Drug Administration to seek recommendations from such advisory committee.”⁹⁸ Thus, if a manufacturer submits an application for a new opioid drug to the FDA for approval, then the FDA must submit that application to its appropriate reviewing advisory committee for a recommendation regarding approval. The statute requires referral as opposed to granting the agency discretion because the statute uses the term “shall.”⁹⁹ Yet the FDA's opioids action plan indicates that the “FDA will convene an expert advisory committee before approving any New Drug Application for an opioid that does not have abuse-deterrent properties.”¹⁰⁰ When mandating referral of an application to the advisory committee, CARA does not distinguish between different

97. Comprehensive Addiction and Recovery Act of 2016, Pub. L. No. 114-198, § 106(a)(1)(A)–(B), 130 Stat. 695, 702–03 (2016).

98. § 106(a)(1)(A), 130 Stat. at 702.

99. *Cf. Mallard v. U.S. Dist. Ct. for the S. Dist. of Iowa*, 490 U.S. 296, 301–02 (1989) (presuming that Congress knows how to require courts to require attorneys to represent litigants proceeding *in forma pauperis* by using the word “shall” in statutory text and concluding that Congress had not done so because it used the verb “request”).

100. Press Release, Califf, *supra* note 7; *FDA Opioids Action Plan*, *supra* note 8. Additionally, the FDA indicates that it will convene an advisory committee for opioids with abuse-deterrent formulations “when they raise novel issues.” *FDA Opioids Action Plan*, *supra* note 8.

opioid formulations, such as whether the new opioid drug contains abuse-deterrent properties, treatment indications, patient populations, durations of action, or doses. The FDA's distinction between opioids with and without abuse-deterrent properties directly contradicts CARA's mandatory language. Because the FDA cannot ignore Congress's plain-language mandates, the agency must submit every new opioid drug application to its advisory committee.

2. CARA § 106(a)(1)(B): Unsatisfied Public Health Exemptions

Section 106(a)(1)(B) articulates three mechanisms that allow a new opioid drug application to bypass advisory committee review.¹⁰¹ It is unlikely, however, that the FDA's carve-out for new opioid drugs with abuse-deterrent properties satisfies any of these three mechanisms. Accordingly, these drugs likely do not qualify for the public health exemption and may not bypass advisory committee review for three reasons: (1) the escalating opioid epidemic; (2) the lack of science to support abuse-deterrent formulations; and (3) the Secretary of Health and Human Sciences ("Secretary") supplanting the independent, unbiased check the advisory committee provides. Thus, the lack of a satisfactory public health exemption further supports convening the advisory committee for every new opioid drug prior to the FDA's determination of approval.

i. Section 106(a)(1)(B)(i)

Section 106(a)(1)(B)(i) articulates the first mechanism to bypass advisory committee review and recommendation, stating that "[a] referral to an advisory committee under subparagraph (A) is not required with respect to a new opioid drug or drugs if the Secretary finds that such a referral is not in the interest of protecting and promoting public health."¹⁰² If the FDA attempts to use this provision to justify exempting new opioid drugs with abuse-deterrent properties from advisory committee critique, it will bear the burden of establishing that it is somehow not in the public's interest to review new opioid drugs in the middle of an opioid overdose epidemic, which

101. § 106(a)(1)(B), 130 Stat. at 702–03.

102. § 106(a)(1)(B)(i), 130 Stat. at 702.

likely renders this exemption inoperative so long as the epidemic persists.¹⁰³

Opioids in general pose an extreme risk to public health, as evidenced by increasing numbers of opioid overdose deaths across the nation in addition to addiction and abuse potential.¹⁰⁴ ER/LA opioids pose an even greater threat because they often contain more active drugs than other formulations. Finally, ER/LA opioids without abuse-deterrent properties, such as Zohydro ER at the time of its approval and initial entry into the market, pose an even greater risk because they combine more active drugs per dose with the ease of extraction and abuse.¹⁰⁵ Because referring all new opioid drugs to the advisory committee for an independent review of the opioid's safety and efficacy, and for a recommendation regarding approval, is necessary in the midst of an escalating opioid epidemic, the FDA cannot likely satisfy this public health exemption.

ii. Section 106(a)(1)(B)(ii)

Section 106(a)(1)(B)(ii) articulates the second mechanism to bypass advisory committee review, stating that “[a] referral to an advisory committee under subparagraph (A) is not required with respect to a new opioid drug or drugs if the Secretary finds that such a referral is not necessary based on a review of the relevant scientific information.”¹⁰⁶ If the FDA attempts to use this provision to justify exempting new opioid drugs with abuse-deterrent properties from advisory committee critique, then it will likely also fail because the data regarding abuse-deterrent formulations are minimal, “indicating that the reviewers were not able to determine with high certainty that a small, moderate, or large net health benefit to abuse-deterrent opioid

103. CDC, *Opioid Overdose*, *supra* note 4.

104. CDC, *Injury Prevention & Control*, *supra* note 2.

105. In 2015, Zogenix reformulated Zohydro ER to include an abuse-deterrent mechanism, which the FDA subsequently approved. Ryan Marotta, *Abuse-Deterrent Zohydro ER Formulation Gets FDA Nod*, PHARMACY TIMES (Feb. 2, 2015), <http://www.pharmacytimes.com/product-news/fda-approves-abuse-deterrent-formulation-of-extended-release-hydrocodone-product>.

106. § 106(a)(1)(B)(ii), 130 Stat. at 703.

formulations existed.”¹⁰⁷ These data measuring the effectiveness of abuse-deterrent formulations are partly lacking because the technology used to make the formulas is in its infancy.¹⁰⁸ The FDA recognizes that it lacks robust data about abuse-deterrent formulations.¹⁰⁹ In its 2015 guidance to the industry, the FDA noted its intent to be “flexible” and that the recommendation to include abuse-deterrent properties in ER/LA opioid drugs would be non-binding.¹¹⁰ Scientific data surrounding abuse-deterrent formulations will not yield enough information to bypass the advisory committee’s critique because adequate and compelling data do not yet exist, which again suggests that the FDA cannot rely on this public health exemption.

iii. Section 106(a)(1)(B)(iii)

Section 106(a)(1)(B)(iii) articulates the third mechanism to bypass advisory committee review, stating that “[a] referral to an advisory committee under subparagraph (A) is not required with respect to a new opioid drug or drugs if the Secretary submits a notice containing the rationale for such findings to the Committee on Health, Education, Labor, and Pensions of the Senate and the Committee on Energy and Commerce of the House of Representatives.”¹¹¹ If the FDA attempts to use this provision to justify exempting new opioid drugs with abuse-deterrent properties from advisory committee critique, then its success and the ultimate outcome of whether advisory committee review will be warranted are unclear. This exemption would require the Secretary to submit notice and reasoning for the findings that allowed the new opioid drug to escape advisory committee critique to Congress, which would effectively replace the independent analysis from a panel of experts who specialize in this class of drugs. Essentially, this exemption contradicts the very purpose that the advisory committee serves: an independent, unbiased check

107. William C. Becker & David A. Fiellin, *Abuse-Deterrent Opioid Formulations—Putting the Potential Benefits into Perspective*, 376 N. ENGL. J. MED. 2103 (June 1, 2017), <http://www.nejm.org/doi/full/10.1056/NEJMp1701553#t=article>.

108. ABUSE-DETERRENT OPIOIDS, *supra* note 8, at 2.

109. *See id.* at 25–26.

110. *See generally id.*

111. § 106(a)(1)(B)(iii), 130 Stat. at 703.

on the agency. Thus, it is unclear whether a new opioid drug with abuse-deterrent properties would garner the Secretary's attention and reasoning to bypass the advisory committee's critique.

3. CARA and the FDA: Aligning Missions to Protect the Public

Convening the advisory committee to review *every* new opioid is the only way to align the statutory mission of CARA and the agency mission of the FDA. The statutory mission of CARA is to innovatively and extensively combat the opioid epidemic.¹¹² The FDA's mission is to "promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner."¹¹³ By convening the advisory committee for *every* new opioid, CARA's mission to extensively combat the epidemic and the FDA's mission to protect the public align through the advisory committee's use of the experience and expertise of its experts to provide an independent, unbiased check on the FDA. To align missions, the FDA must submit a New Drug Application to the advisory committee whether or not it follows the committee's recommendation. Additionally, the advisory committee is already chartered and operates on an estimated budget of \$245,564 annually.¹¹⁴ Even if the cost to operate the committee increases because it convenes more often, the cost of the opioid epidemic would dwarf that amount. A recent estimate of the financial burden of prescription overdoses,

112. Cf. Press Release, Drug Policy Alliance, Congress Passes Landmark Opioid Bill – the Comprehensive Addiction and Recovery Act (CARA) (July 13, 2016), <http://www.drugpolicy.org/press-release/2016/07/congress-passes-landmark-opioid-bill-comprehensive-addiction-and-recovery-act> (noting that CARA "advances a large number of treatment and prevention measures intended to reduce prescription opioid and heroin misuse, including evidence-based interventions for the treatment of opioid and heroin addiction and prevention of overdose deaths").

113. 21 U.S.C. § 393(b)(1) (2012) (stating the statutory mission of the FDA).

114. *Anesthetic and Analgesic Drug Products Advisory Committee Charter*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/ucm094127.htm> (last visited Mar. 17, 2017) (combining the operating costs for compensation and travel for members and FDA staff support).

abuse, and deaths to the American society is \$78.5 billion.¹¹⁵ Thus, both the statutory mission of CARA and the FDA align when the advisory committee is convened to review *every* new opioid—and it is feasible to do so because the committee is already fully operational.

B. The Charge

Reformulating a framework for the FDA's charge of questions to the advisory committee is not a challenge for science but rather one for the law.¹¹⁶ For the advisory committee to be most effective, and to

115. 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).

116. See generally Memorandum, Questions to the Committee, U.S. Food & Drug Admin., Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) (Apr. 22, 2014), <https://wayback.archive-it.org/7993/20170404144340/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM396866.pdf>. The following is the advisory committee's charge to review Moxduo, a combination product containing both morphine and oxycodone, which are both Schedule II controlled substances similar to hydrocodone:

- 1) DISCUSSION: Please discuss whether the data from Study 22 provide evidence of clinically meaningful differences in respiratory safety between Moxduo and morphine and/or Moxduo and oxycodone.
- 2) DISCUSSION: Please discuss whether the overall opioid-related adverse event data provide evidence of clinically meaningful differences in safety between Moxduo and morphine and/or Moxduo and oxycodone.
- 3) VOTE: Given the available safety data, has the Applicant provided evidence that Moxduo is safer than morphine and oxycodone when these drugs are used individually and at comparable doses?
- 4) VOTE: Should Moxduo be approved for the management of moderate to severe acute pain where the use of an opioid analgesic is appropriate?
 - a) DISCUSSION: If you voted "No" to question #4, please discuss whether there are any additional studies to

provide a recommendation reflective and incorporative of their knowledge and expertise, the charge of questions must intentionally elicit meaningful and pertinent dialogue among members. Thus, the charge of questions must derive from the FFDCFA, which guides new drug approval.

1. FDA Statutory Requirements for Approval of a New Drug

The theme throughout new drug regulation and approval is safety and efficacy.¹¹⁷ The specific language of the FFDCFA granting authority for new drug approval provides in pertinent part that:

If the Secretary finds . . . (1) the investigations . . . do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed,

support approval of this product in the future.

Id.

117. See *supra* Part II (discussing the rise of federal regulation regarding new drug approval).

recommended, or suggested in the proposed labeling thereof; . . . he shall issue an order refusing to approve the application. If . . . the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. . . . The Secretary shall implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks, a consistent and systematic approach to the discussion and regulatory decisionmaking, and the communication of the benefits and risks of new drugs.¹¹⁸

The preceding provisions must serve as the basis for developing a charge of questions to an advisory committee because these provisions ultimately drive new drug approval. For an advisory committee to make a recommendation that is informative and influential, the recommendation must incorporate all relevant issues. Those issues essentially are: (1) the study used to evaluate the drug in question was appropriate (“appropriate study design”); (2) the results from the study used are significant and demonstrate the drug’s safety profile (“significant study safety results”); (3) the method used in formulating and manufacturing is appropriate to preserve the product (“appropriate formulation”); (4) that there is sufficient information provided to determine the safety of the drug (“sufficient safety information”); and (5) the drug works like the manufacturer alleges it does (“sufficient efficacy results”). These five provisions must lay the foundation for the FDA’s charge of questions to its advisory committee to help make the best recommendation possible and provide the greatest insight to the FDA when it makes its decision of whether to approve a new drug. Formulating a framework for a charge of questions is not an exact science because the nature of drug approval

118. 21 U.S.C. § 355(d) (2012). *See also id.* (“[T]he term ‘substantial evidence’ means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”).

is inherently inexact: “[i]n the end, no matter how much data are available, [the FDA] often [has] to make a judgment call, weighing the known benefits against known risks and the potential—and possibly unknown—risks.”¹¹⁹ Nevertheless, optimizing the advisory committee’s capability to render the most informed recommendation to the FDA and ultimately combat the opioid epidemic is an opportunity worth pursuing.

2. Zohydro ER Charge to the Committee: Where It Went Wrong

The Zohydro ER charge to the advisory committee is an example of a charge that presents an opportunity for optimization. First, the charge did not purely address the study methods that Zogenix, Inc. employed to evaluate Zohydro ER, but rather folded it into the general determination of whether the new opioid drug was effective.¹²⁰ Second, when questioned about the safety of Zohydro ER in its intended population, the discussion resulted in a safety determination based off its similarity to other previously approved ER/LA opioids.¹²¹ After reviewing the data, however, the advisory committee found Zohydro ER to be unsafe because it lacked abuse-deterrent properties and had high rates of diversion during the clinical trial.¹²² Third, when the committee ultimately weighed the risks and benefits of approving this drug, the looming existential threat of a worsening opioid epidemic pervaded their reasoning and resulted in the committee’s advocacy for some properties to deter abuse.¹²³ The

119. *How The FDA Evaluates Regulated Products: Drugs*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm269834.htm> (last visited Dec. 31, 2016).

120. Questions to the Committee, *supra* note 52, at 5 (highlighting the advisory committee questioning the length of the study and clinical significance of the change in pain score).

121. *Id.* At one point during the committee discussion, Dr. Bob Rappaport, FDA Director of the Division of Anesthesia, Analgesia Products, and Addiction Products, asked, in response to one of the committee members’ comments, “is it that there really is something different, or that you’re holding it to a different standard[?] Because you’re punishing this company and this drug for the sins of the developers and products. And we can’t—from a regulatory standpoint, that’s not something we can do.” Zohydro Approval Meeting, *supra* note 81.

122. Questions to the Committee, *supra* note 52.

123. *Id.*

preceding three examples identify opportunities to optimize the charge of questions to the advisory committee to more explicitly and effectively evaluate new opioid drugs. Thus, there is a solution to the shortcoming of an inadequate charge of questions.

3. The Proposed Framework for Future FDA Charges

The proposed reformulated framework for the FDA's charge of questions that follows could theoretically apply to any advisory committee reviewing new drug applications; however, this framework targets the Anesthetic and Analgesic Drug Products Advisory Committee. The framework extracts provisions from the FDCA that pertain to drug approval and are within the expertise of the advisory committee members.¹²⁴ The proposed framework for future FDA charges to its advisory committee, in question format, is as follows, including the changes to the charge in italics:

1. *VOTE: Has the Applicant demonstrated an appropriate study design to produce relevant information regarding [insert name of new opioid drug here] for [insert proposed indication of new opioid drug]?*
2. *VOTE: Has the Applicant demonstrated based on only the data from the [insert Sponsor's name here] research conducted that [insert name of new opioid drug here] is safe in its intended population?*
3. VOTE: Has the Applicant demonstrated based on the data from the [insert Sponsor's name here] research conducted that [insert name of new opioid drug here] is manufactured with an *appropriate formulation?*
4. VOTE: Has the Applicant provided sufficient data pertaining to [insert name of new opioid

124. 21 U.S.C. § 355(d) (2012).

drug here] that it is safe?

5. VOTE: Has the Applicant demonstrated based on the data from the [insert Sponsor's name here] research conducted that [insert name of new opioid drug here] is efficacious?
6. VOTE: Based on the data presented and discussed today, does the risk-benefit profile of [insert name of new opioid drug here] support the approval of this application?

A table comparing the advisory committee's Zohydro ER charge of questions to this proposed charge of questions demonstrates the gaps that existed in the original charge:

Zohydro ER Advisory Committee Questions¹²⁵	Reformulated Statute-based Advisory Committee Questions¹²⁶	Statutory Authority¹²⁷
Sufficient efficacy	Sufficient efficacy results	§ 355(d)(5)
Safety in intended patient population	Sufficient safety information in intended population from all sources	§ 355(d)(4)
Postmarketing abuse potential of Zohydro ER compared to other approved Schedule II substances	Appropriate formulation	§ 355(d)(3)

125. Questions to the Committee, *supra* note 52, at 5–6.

126. 21 U.S.C. § 355(d) (2012).

127. *Id.*

Adequacy of data supporting abuse mitigation strategies		
Risk-benefit balance	Risk-benefit balance	§ 355(d)
	Appropriate study design	§ 355(d)(1)
	Sufficient safety information in intended population only from study conducted	§ 355(d)(2)

Of note, the Zohydro ER charge did not explicitly ask questions about the appropriate study design or whether researchers gathered sufficient safety information from the patient population that was the subject of the study. This proposed and optimized charge of questions directs the advisory committee's discussion on these points and will likely yield clearer reasoning to support the advisory committee's recommendation to the FDA. This, in turn, ensures that the FDA is best informed about the risks and benefits associated with the new opioid drug to aid its decision of whether to approve. Therefore, the FDA should adopt this proposed framework for a charge of questions because it promotes pertinent and adequate reasoning in the advisory committee on which the FDA can rely to deny approval of a new opioid drug.

VI. CONCLUSION

America is in the midst of a public health crisis—the opioid epidemic. An opportunity exists to use the FDA's advisory committee and optimize the committee's charge of questions to combat this opioid epidemic. Convening the advisory committee for every new opioid drug alone, or reformulating the framework for the FDA's advisory committee's charge alone, however, would be a futile effort. To mitigate the opioid epidemic, CARA supports convening the advisory committee for *every* new opioid drug because its plain statutory language requires it, abuse-deterrent formulations cannot likely qualify for any public health exemption, and the public has a strong interest in

aligning Congress's statutory purpose in enacting CARA with the FDA's mission. Reformulating the framework for a charge of questions optimizes the recommendation the advisory committee may make to the FDA regarding drug approval. Thus, CARA's mandate to convene the advisory committee for *every* new opioid, coupled with a reformulated charge of questions, is one effort to avoid duplicative and dangerous opioids from entering the marketplace, prevent further escalation of the opioid crisis, and protect the American people from paying the ultimate price of the epidemic—their lives.