

August 20, 2019

Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment
Framework; Draft Guidance for Industry; Availability

Docket No. FDA-2019-D-1536

We appreciate the opportunity to submit comments to the Food and Drug Administration (FDA) regarding its June 2019 Draft Guidance, “Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework” (“Draft Guidance”).

We are submitting this comment in our individual capacities as interested professors of law and medicine who study legal, regulatory, and ethical issues associated with drug and public health policy, and who worked with the Committee on Pain Management and Regulatory Strategies to Address Prescription Opioid Abuse convened by the National Academies of Sciences, Engineering, and Medicine (NASEM). Professor Bonnie served as chair of the Committee and Dr. Kesselheim served as a member of the Committee.¹ Professors Riley and Zettler served as consultants to the Committee.²

A key task for the NASEM Committee was to make recommendations to help FDA further develop “a framework for opioid review, approval, and monitoring that balances individual need for pain control with considerations of the broader public health consequences of opioid abuse and misuse.”³ The central advice in the NASEM Committee’s 2017 report was that FDA consider a broad range of evidence and apply a “comprehensive systems approach” in its regulation of prescription opioids.⁴

We applaud the agency for developing the Draft Guidance with the recommendations of

¹ The NASEM Committee was active from June 2016 to July 2017. Dr. Kesselheim reports joining in May 2018 as an expert witness on behalf of the class of plaintiffs in the National Prescription Opiate Litigation MDL and on behalf of Baltimore, MD in lawsuits against certain opioid manufacturers and distributors.

² Prof. Zettler reports serving as expert witness retained by the Direct Purchaser Class Plaintiffs in *In re Suboxone Antitrust Litigation*, No. 2:13-MD-2445 (E.D. Pa.) and the End Payor Class, Direct Purchaser Class, and Retailer Plaintiffs in *In re Opana Antitrust Litigation*, No. 14cv-10150 (N.D. Ill.), since July 2018 and January 2019, respectively.

³ National Academies of Sciences, Engineering and Medicine, Committee on Pain Management and Regulatory Strategies to Address Prescription Opioids Abuse, Activity Description, <http://nationalacademies.org/hmd/Activities/PublicHealth/AddressPrescriptionOpioidAbuse.aspx>.

⁴ NATIONAL ACADEMIES OF SCIENCES, ENGINEERING AND MEDICINE, PAIN MANAGEMENT AND THE OPIOID EPIDEMIC: BALANCING SOCIETAL AND INDIVIDUAL BENEFITS AND RISKS OF PRESCRIPTION OPIOID USE (2017) (hereinafter “NASEM REPORT”); see also Richard J. Bonnie, Aaron S. Kesselheim & David J. Clark, *Both Urgency and Balance Needed in Addressing Opioid Epidemic: A Report From the National Academics of Sciences, Engineering, and Medicine*, 318 J. AM. MED. ASS’N 423 (2017).

the NASEM Committee’s 2017 report “in mind.”⁵ We write to emphasize that the Draft Guidance—and in particular, the agency’s proposal to consider “broader public health effects” in its overall benefit-risk assessment of opioid analgesic drugs—is an important first step in implementing the 2017 report’s recommendations that will lead to benefits for the public health. That said, as explained below, there remain critical actions for the agency to take using existing authorities to help address the opioid crisis in a balanced way and to fully implement the “comprehensive systems approach” recommended in the 2017 report.

Incorporating “Broader Public Health Effects” into FDA’s Benefit-Risk Assessment Is an Important First Step

One key recommendation in the NASEM Committee’s 2017 report was that FDA incorporate certain public health considerations into opioid-related regulatory decisions.⁶ The report recommended that, in assessing opioids, the agency should seek important systems data in addition to data about a particular drug’s benefits and risks for individual patients emerging from traditional forms of evidence, such as the pivotal clinical trials. Such evidence could include patients’ potential transition to illicit opioids or anticipated risks and benefits for patients’ families and communities, specific subpopulations or geographic areas in which a drug may have a different benefit-risk profile, and a drug’s potential for diversion and other derivative effects on the overall market for opioids.

The proposal in the Draft Guidance to “consider the positive and negative public health effects of the drug” including “the drug’s potential effect on risks to both patients and nonpatients, such as members of the patient’s household (e.g., children, teenagers, visitors, and others),” “potential safety concerns” related to abuse-deterrent formulations such as “shift(s) to more dangerous routes of abuse,” and the “potential for subpopulations where the benefit-risk balance may be unfavorable,” is both consistent with the NASEM Committee’s 2017 report’s recommendations and a necessary initial step in implementing those recommendations. We note that the Draft Guidance describes these public health effects broadly enough to include patients’ possible transition to illicit opioids, as recommended in the 2017 report,⁷ but the Final Guidance should make explicit the agency’s intent to consider information about such effects.

Indeed, we encourage the agency to move forward with finalizing its plans to consider broader public health effects in its benefit-risk assessment of opioids. Although considering such broad societal implications is not traditionally an explicit part of FDA’s approval process, it is often implicit in prescription drug approval decisions (or decisions to withdraw approval) and it is consistent with the agency’s public health mission.⁸

⁵ Statement on the FDA’s benefit-risk framework for evaluating opioid analgesics (June 20, 2019), <https://www.fda.gov/news-events/press-announcements/statement-fdas-benefit-risk-framework-evaluating-opioid-analgesics>.

⁶ See, e.g., NASEM REPORT at 409-11.

⁷ See, e.g., *id.*

⁸ For example, FDA applies its approval standards with maximal flexibility in the case of unmet medical needs. In the case of the muscular dystrophy treatment eteplirsen, the drug showed no clinically meaningful

Additionally, FDA regularly has taken broader public health effects into account in prior actions on certain drug products with clinical externalities.⁹ Such an approach is particularly necessary for evaluating opioids (and opioid derivatives) because of their special public health characteristics, including their association with nonmedical use, their association with opioid use disorder, and their potential impacts on people beyond the patients to whom they are prescribed.¹⁰ Importantly, an approach that considers broader public health effects is permitted by the agency’s existing statutory and regulatory authority (for further details, please see a recent publication by Prof. Zettler, Prof. Riley, and Dr. Kesselheim in the *Food and Drug Law Journal*¹¹).

Additional Actions Are Needed

Although the Draft Guidance begins to implement the recommendations of the NASEM Committee’s 2017 report, much remains unstated in the Draft Guidance. We encourage the agency to integrate more recommendations from the 2017 report in its Final Guidance (or additional guidance documents), with the goal of using the full reach of the agency’s existing authority to help reduce the harms associated with prescription opioids while also helping to ensure that evidence-based pain management therapies are available for patients. We are very cognizant of the fact that there has been a history of undertreatment of pain in the United States and that some attempts to address opioid use disorder may leave certain patients with inadequate treatment. Our goal is to adopt a holistic approach that balances those individual needs with broader public health needs. Here we highlight some examples of critical recommendations from the 2017 report that the agency should expressly address.

Collect New Sources of Data for a Thorough Assessment of Public Health Considerations

The NASEM Committee’s 2017 report recognized that, to utilize the systems approach recommended in the report, FDA would need data not just from well-designed clinical trials but also from other sources that also can help to inform assessment of opioids’ public health effects.¹² Accordingly, the report recommended that FDA require and collect data from both traditional (*e.g.*, clinical trials) and less traditional data sources, including non-health data, to understand the real-world impact of the availability and use of approved opioids.¹³ Examples mentioned in the report include tracking drug street price, availability, and emergence of counterfeits/fake versions; investing in a national

changes in muscle dystrophin levels but was approved, in part, according to FDA documents, because “without an approval in cases such as eteplirsen, patients would abandon all hope of approval for these types of products and would ‘lapse into a position of’ self-treatment.” Memorandum from Luciana Borio, Acting Chief Scientist to Robert Califf, Commissioner (Aug. 6, 2016), *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf.

⁹ NASEM REPORT at 380-86; *see also* Patricia J. Zettler, Margaret Foster Riley & Aaron S. Kesselheim, *Implementing a Public Health Perspective in FDA Drug Regulation*, 73 *FOOD & DRUG L.J.* 221, 236-39 (2018).

¹⁰ NASEM REPORT at 386.

¹¹ Patricia J. Zettler, Margaret Foster Riley & Aaron S. Kesselheim, *Implementing a Public Health Perspective in FDA Drug Regulation*, 73 *FOOD & DRUG L.J.* 221 (2018).

¹² NASEM REPORT at 412

¹³ *Id.* at 412

behavioral surveillance system of people who use drugs; developing a system of agent-level surveillance of nonfatal overdose and other emergency department referred drug-related events (as was done previously with SAMHSA's DAWN); and devising a national network of key "sentinel surveillance" samples, such as through arrestee drug use monitoring (formerly ADAM). We encourage FDA to work with other agencies establish, and make public, guidelines for the collection and analysis of such data.

Conduct a Full Review of Currently Marketed/Approved Opioids

In its 2017 report, the NASEM Committee recommended that FDA conduct a full review of currently marketed/approved prescription opioids, considering the same public health effects that the Committee recommended that the agency consider when evaluating new drug applications for approval.¹⁴ The Committee envisioned an approach that it called the "Opioid Study Implementation" (OSI) process, modeled on the Drug Efficacy Study Implementation (DESI) of the 1960s, in which an expert panel "would systematically examine the current range of approved brand-name and generic opioids to determine which of these drugs remained effective and safe; which might need revised labels, formulations, or post-market requirements; and which should be withdrawn from the market entirely."

Conducting this full review of currently marketed/approved opioids is necessary to achieve maximum public health benefits of incorporating "broader public health effects" into FDA's benefit-risk assessment of opioids. There are numerous, widely-used prescription opioids currently on the market; DEA records show that 76 billion oxycodone and hydrocodone pills were distributed in the US between 2006 and 2012.¹⁵ Shifting the agency's approach to benefit-risk assessment only for novel products entering the market leaves substantial public health risks unaddressed. For example, many currently marketed extended release/long-acting opioids are indicated and used for long-term treatment. At the same time, there is evidence that the long-term use of opioids for the management of chronic non-cancer pain increases the risks of adverse outcomes, such as opioid use disorder and overdose, without strong evidence supporting the appropriateness of such uses.¹⁶ Incorporating public health considerations into the benefit-risk assessment for such products that are currently on the market is an essential element of a regulatory strategy for addressing the ongoing opioid crisis.

The NASEM Committee's 2017 report acknowledged that the OSI process might ultimately lead to the removal of some opioid formulations or doses from the U.S. market

¹⁴ *Id.* at 405-409.

¹⁵ *Drilling into the DEA's Pain Pill Database*, WASH. POST (July 21, 2019), https://www.washingtonpost.com/graphics/2019/investigations/dea-pain-pill-database/?utm_term=.e6d1d42ab48e.

¹⁶ NASEM REPORT at 51. Our focus here is on the lack of evidence and how that lack of evidence affects the benefit-risk decision. At the same time, we believe that it is crucial to find effective, evidence-based interventions for chronic pain. Patients suffering from chronic pain should not be left undertreated. It may be determined, after better data are developed and analyzed, that opioids are the only available effective option for some patients.

because it is “highly unlikely that all of these products would be judged safe and effective” with a benefit-risk assessment that includes consideration of broader public health effects.¹⁷ But the committee also fully expected the OSI process to assure adequate access for patients in need of pain management. The report explained that the OSI process would need to take into account advantages *and disadvantages* of removing any product from the armamentarium of pain treatment options and should also allow reasonable time periods for compliance with any decisions to remove a product to minimize treatment disruptions. Costs also should not increase so long as sufficient numbers of generic manufacturers continue to produce those opioid formulations that remain on the market.¹⁸

Additionally, conducting the full review of currently marketed/approved opioids would treat similarly all prescription opioid analgesics, whether being considered for approval for the first time or already on the market. There is no sound medical reason for using a different approach for assessing the benefits and risks of currently marketed opioids than the agency uses for evaluating applications of unapproved opioids; nor is there any medical justification for declining to take account of the broader public health effects of currently marketed products. Likewise, the agency’s authority under the Federal Food, Drug, and Cosmetic Act does not provide a basis for taking a different approach to assessing benefits and risks for currently marketed products than for unapproved products. Indeed, mirroring the approval standard in section 505(d), section 505(e) of the Federal Food, Drug, and Cosmetic Act provides that FDA “shall” withdraw approval of a new drug application if the agency finds that the drug is not safe or effective (*i.e.*, that its benefits do not outweigh its risks).¹⁹ Because, in this case the public health risks potentially extend to the whole class of drugs, to focus only on novel drugs leaves much of the market untouched.

We note that the agency issued a Draft Guidance in July 2019 to assist certain manufacturers, including opioid manufacturers, in writing the section of drug labeling that conveys information about risks of substance use disorders.²⁰ Although conveying such information accurately and informatively is important, labeling alone cannot adequately address the public health effects of opioids. Regardless of the agency’s efforts to improve opioid labeling, it remains critical that FDA conduct a review of the benefits

¹⁷ *Id.* at 407.

¹⁸ Additionally, this process for opioids should require much less time, and far fewer of the agency’s resources, than DESI did because it would be limited to a single class of drugs about which substantial information already exists.

¹⁹ 21 U.S.C. § 355(e).

²⁰ FDA, Draft Guidance: Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products—Content and Format (July 2019), <https://www.fda.gov/media/128443/download>. Although we recognize that terms such as “abuse” are used in the Federal Food, Drug, and Cosmetic Act and the Controlled Substances Act, we strongly encourage the agency to avoid such stigmatizing language whenever possible, consistent with recommendations from the Office of National Drug Control Policy and the American Society of Addiction Medicine. *See, e.g.*, NASEM REPORT at 22-23; *see also* Health in Justice Action Lab at Northeastern University School of Law, Changing the Narrative, Stigmatizing Language, <https://www.changingthenarrative.news/stigmatizing-language>.

and risks of currently marketed opioids, incorporating public health considerations into that assessment.

We encourage the agency to expressly explain that it will apply the benefit-risk assessment described in the Draft Guidance to currently marketed/approved opioids, and to move forward with structured reviews of those products in a timely fashion.

Strengthen Post-Approval Oversight Including REMS

Another recommendation in the NASEM Committee’s 2017 report was that FDA “take steps to improve post-approval monitoring of opioids” including requiring, monitoring, and enforcing Risk Evaluation and Mitigation Strategies (REMS) that “have been demonstrated to improve prescribing practices.”²¹

The report noted concerns that the Opioid Analgesic REMS was, as structured, inadequately addressing dangerous prescribing practices, and discussed research raising concerns about whether certain REMS achieve their public health goals.²² Since the report was published, additional research has raised concerns about FDA’s implementation of its REMS authority. For example, a study of the REMS for Transmucosal Immediate-Release Fentanyl (TIRF) products found that the REMS did not prevent substantial rates of inappropriate TIRF use and that, as of February 2019, FDA had not required significant modifications to the REMS to address this troubling shortcoming of the REMS.²³

Although recently the agency has taken some steps to better utilize its REMS authority to help address the opioid crisis, including requiring REMS for immediate release opioid analgesics²⁴ and taking first steps to modify the TIRF REMS,²⁵ concerns remain about continued unsafe prescribing practices and existing REMS’ ability to mitigate them. Consistent with the recommendations in the NASEM Committee’s 2017 report,²⁶ and to the extent permissible under current law, FDA should establish a practice of routinely making public information about how well opioid REMS are achieving their goals. Such information is necessary to enable the public to understand how REMS are functioning. In the meantime, one way to relatively quickly make information about particular REMS

²¹ NASEM REPORT at 413.

²² *Id.* at 366-67.

²³ Rollman JE, Heyward J, Olson L, Lurie P, Sharfstein J, Alexander GC. Assessment of the FDA Risk Evaluation and Mitigation Strategy for Transmucosal Immediate-Release Fentanyl Products. *JAMA*. 2019;321(7):676–685.

²⁴ FDA Takes Important Steps to Encourage Appropriate and Rational Prescribing of Opioids Through Final Approval of New Safety Measures Governing the Use of Immediate-Release Opioid Analgesic Medications, <https://www.fda.gov/news-events/press-announcements/fda-takes-important-steps-encourage-appropriate-and-rational-prescribing-opioids-through-final>.

²⁵ Statement from FDA Commissioner Scott Gottlieb, MD, on New Steps to Strengthen Agency’s Safety Requirements Aimed at Mitigating Risks Associated with Transmucosal Immediate-Release Fentanyl Products, <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-steps-strengthen-agencys-safety-requirements-aimed>.

²⁶ NASEM REPORT at 399-400.

more transparent in a forum that allows for public input might be to ask the Anesthetic and Analgesic Drug Products Advisory Committee and the Drugs Safety and Risk Management Advisory Committee to consider modifications to a specific REMS, such as the Opioid Analgesic REMS.

But improving the use of REMS to mitigate the risks of opioids clearly requires more than an advisory committee meeting. We encourage FDA to follow any such meetings with agency actions and not to wait for such a meeting to take needed actions—including timely requiring any necessary modifications to opioid REMS. New components of the REMS should emphasize well-designed educational interventions, close monitoring of the messages communicated to health care providers, and careful attention to the impact of the interventions. For example, academic detailing—a process by which trained medical professionals interact directly with prescribers—has been shown to be effective at making prescribing more evidence-based.²⁷ The agency should also consider creative approaches to REMS that might prove beneficial for opioids, such as asking that independent third parties, rather than manufacturers, lead the REMS.

Conclusion

In sum, we applaud the agency for proposing to consider opioids’ “broader public health effects” in evaluating new drug applications and for taking this important step in implementing the recommendations in the NASEM Committee’s 2017 report. We encourage the agency both to move forward with finalizing the Draft Guidance and to work to implement the numerous other recommendations in the 2017 report to embed consideration of these broader public health effects throughout FDA’s regulatory framework for opioids.

Additionally, we note that, in its Federal Register Notice announcing the September 2019 meeting on opioids and soliciting comments,²⁸ FDA posed various questions about requiring that new opioid analgesics demonstrate a “comparative advantage” over existing analgesics and about the authorities that FDA would need to impose such a requirement. We believe that the recommendations in the NASEM Committee’s 2017 report would achieve much the same goals sought by a “comparative advantage” approach, would apply to both the existing market and novel drugs, and have the benefit of being grounded in the agency’s existing authority. Working to implement these recommendations, therefore, would be a way for FDA to improve its efforts to address the opioid crisis now, without waiting for Congressional action.

We appreciate your consideration of this comment. If the agency or the Advisory Committees have any questions, please do not hesitate to contact us.

Sincerely,

²⁷ See, e.g., Trotter Davis M, Bateman B, Avorn J. Educational Outreach to Opioid Prescribers: The Case for Academic Detailing, *Pain Physician*. 2017 Feb;20(2S):S147-S151.

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

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