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Re: Docket No. FDA-2019-P-1783

Dear Drs. Wolfe and Brown:

This letter responds to your citizen petition dated April 10, 2019 (Petition) (FDA-2019-P-1783), submitted by Public Citizen, Public Citizen's Health Research Group, Sidney Wolfe, M.D., and Raeford Brown, M.D. In the Petition, you request that the Food and Drug Administration (FDA or Agency) impose a moratorium on approval of all new drug applications (NDAs) for new opioids or new opioid formulations until FDA has implemented recommendations from the National Academies of Sciences, Engineering, and Medicine (NASEM) regarding FDA's framework for making regulatory decisions regarding opioids in NASEM's 2017 report *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use* (NASEM Report).^{1,2}

We have carefully considered the Petition and the comment submitted to the public docket for the Petition. For the reasons set forth below, your Petition is denied. However, we have recently issued draft guidance regarding the benefit-risk framework the Agency uses to evaluate candidate opioids, taking into account the NASEM Report's recommendations, and we welcome your input as we work to develop the final version of this guidance.³

I. BACKGROUND

The Petition highlights the rise in opioid abuse, addiction, and overdose deaths. We share your concern about this national crisis. The Agency has taken significant steps to

¹ NASEM's 2017 report is available online at <https://www.ncbi.nlm.nih.gov/books/NBK458654/>.

² Petition at 1.

³ We have received comments on the draft guidance from Public Citizen. These comments are under consideration.

address this crisis, such as expanding the Risk Evaluation and Mitigation Strategy (REMS) that had applied to extended-release/long-acting opioid analgesics to include immediate-release products⁴ and our efforts to curb illegal online sales of unapproved opioids.⁵ These are just two examples of the many efforts FDA has undertaken to address opioid abuse, addiction, and overdose deaths.⁶

A. NASEM Report

In early 2016, FDA asked NASEM to convene an ad hoc committee to develop a report informing FDA as to the state of the science regarding prescription opioid abuse and misuse, as well as the evolving role that opioid analgesics play in pain management. FDA further requested recommendations on the options available to FDA to address the prescription opioid epidemic, from both the individual and public health perspectives. In this regard, FDA specifically requested that the report “identify additional actions FDA and others should consider now, with a particular focus on those actions FDA can undertake, to balance the needs of pain patients and the need to address opioid misuse and abuse” (NASEM Report at 20-21). FDA specified that the report should include the following areas of focus:

FDA actions to be taken as a part of development, review and approval, and safe use of pain medicines, such as:

- Development of a formal method to incorporate the broader public health impact of opioid abuse in future FDA approval decisions regarding opioids
- The development of non-opioid pain medicines to treat severe pain
- The development of abuse-deterrent opioids
- The incorporation of prevention strategies into safe opioid prescribing, including modification of the standard opioid indication statements
- The development of medicines for medication assisted treatment for patients with opioid use disorder

⁴FDA News Release, *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*, September 30, 2018, available at <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620935.htm>.

⁵FDA News Release, *FDA takes action against 53 websites marketing unapproved opioids as part of a comprehensive effort to target illegal online sales*, June 5, 2018, available at <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm609869.htm>.

⁶ See *Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse*, available at <https://www.fda.gov/drugs/information-drug-class/timeline-selected-fda-activities-and-significant-events-addressing-opioid-misuse-and-abuse>.

- The development of medicines to treat opioid overdose
- The education of prescribers and patients about safe use of pain medications
- The education of prescribers and patients about appropriate medication storage and disposal

(NASEM Report at 21).

Following an extensive review of the relevant scientific literature, relevant FDA materials, and two public workshops, NASEM issued its report in July 2017. The report contains several recommendations regarding FDA's framework for making regulatory decisions regarding opioids. Among other things, the report recommends that FDA "incorporate public health considerations into opioid-related regulatory decisions"⁷ and "require additional studies and the collection and analysis of data needed for a thorough assessment of broad public health considerations."⁸

B. Draft Guidance on Benefit-Risk Assessment of Opioid Analgesics; Public Hearing Announcement Regarding Standards for Future Opioid Approvals

On June 20, 2019, FDA issued a new draft guidance for industry *Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework* (Draft Guidance), which describes the application of the benefit-risk assessment framework that the Agency uses in evaluating new drug applications for opioid analgesic drugs and summarizes the information that should be supplied by sponsors of opioid analgesic drug applications to facilitate the Agency's benefit-risk assessment.⁹ FDA developed the Draft Guidance based on our statutory authorities and in light of the NASEM Report's recommendations.¹⁰ The Draft Guidance devotes particular attention to those recommendations concerning the need to properly account for the public health impact of opioid analgesics within FDA's benefit-risk framework. As explained in the draft guidance:

⁷ Recommendation 6-1.

⁸ Recommendation 6-2. See NASEM Report at 393 and 397.

⁹ See the June 2019 draft guidance for industry *Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework*, available on the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page.

¹⁰ See FDA's *Statement on the FDA's benefit-risk framework for evaluating opioid analgesics* (June 20, 2019), available at <https://www.fda.gov/news-events/press-announcements/statement-fdas-benefit-risk-framework-evaluating-opioid-analgesics>.

FDA assesses risks and benefits of all drugs in the context of the use indicated in the labeling. However, because of the widespread misuse and abuse of prescription opioid analgesic drugs, for this class of drugs, FDA also considers the broader public health effect of opioid analgesic drugs; this involves consideration of the risks related to misuse, abuse, opioid use disorder, accidental exposure, and overdose, for both patients and others. Likewise, FDA considers any properties of a drug expected to mitigate these risks.¹¹

Accordingly, the draft guidance contains a section explaining in detail what data and information we recommend that sponsors submit related to the expected public health impact of candidate opioid analgesics, including impacts associated with anticipated inappropriate use, as well as how FDA intends to consider such data and information within the context of its overall benefit-risk assessment.¹² FDA has requested comments on the Draft Guidance, which it will consider as it develops the final version of the guidance.¹³

Also on June 20, 2019, FDA announced that it will hold a public hearing on September 17, 2019, to further discuss the Agency's benefit-risk assessment of opioid analgesics, including the manner in which risks of misuse and abuse of these products factor into the benefit-risk assessment.¹⁴ Among topics for discussion, FDA is seeking input on whether the current statutory and regulatory framework, including the benefit-risk assessment described in the Draft Guidance, allows for an adequate evaluation of applications for new opioid analgesics.¹⁵ FDA is also soliciting comments on whether new authorities are needed for FDA to fully assess candidate opioid analgesics given their serious risks and societal impact.¹⁶ FDA is specifically interested in stakeholder input on whether an applicant for a new opioid analgesic should be required to demonstrate that its product has an advantage over existing drugs as a condition of approval, and, if so, what new authorities FDA would need to impose such a requirement.¹⁷ In addition, the Agency will discuss whether new preapproval incentives (in addition to existing incentives, such as breakthrough designation) are needed to better support and encourage development of

¹¹ Draft Guidance at 2.

¹² Draft Guidance at 5-6.

¹³ See *Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework; Draft Guidance for Industry; Availability*, 84 FR 29211 (June 21, 2019). Comments on this draft guidance should be submitted to the Docket Number FDA-2019-D-1436.

¹⁴ See *Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction; Public Hearing* (84 FR 29112, June 21, 2019). Comments will be accepted after the public hearing until November 18, 2019.

¹⁵ Id. at 29113.

¹⁶ Id.

¹⁷ Id.

all therapeutics — opioid or non-opioid drugs, biological products, or devices — intended to treat pain or addiction.¹⁸

C. Section 505(q) of the Federal Food, Drug, and Cosmetic Act

Section 505(q) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) was added by section 914 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85, 121 Stat. 823) and was amended by the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144, 126 Stat. 993). Section 505(q), as originally added by FDAAA, applies to certain citizen petitions and petitions for stay of Agency action that request that FDA take any form of action relating to a pending application submitted under section 505(b)(2) or (j) of the FD&C Act (21 U.S.C. 355(b)(2) or (j)) and governs how these petitions are treated. Among other things, section 505(q)(1)(F) of the FD&C Act governs the time frame for final Agency action on a petition subject to section 505(q). Under this provision, FDA must take final Agency action on such a petition no later than 150 days after the date on which the petition is submitted. The 150-day period is not to be extended for any reason. In this case, that date is September 7, 2019, which is 150 days following the date your Petition was submitted (April 10, 2019).

II. DISCUSSION

In your Petition, you contend that “more than 19 months after the [NASEM Report], the FDA...has failed to implement the National Academies’ recommendations for creating and implementing a new opioid regulatory framework.”¹⁹ You claim that, until improvements to FDA’s regulatory framework are made, “FDA does not have a framework to effectively evaluate NDAs for new opioids and new opioid formulations to determine whether the legal standards for establishing safety and effectiveness are met” (Petition at 4). You conclude that “an immediate moratorium on opioid approvals is needed,” which “will allow the Agency time and resources to use the information and recommendations from the National Academies’ report to...creat[e] an opioid regulatory framework that is based first and foremost on protection of the public health” (Petition at 4).

A. The Agency cannot impose a moratorium on opioid approvals.

The Agency cannot impose a moratorium on approval of new opioids or new opioid formulations because the FD&C Act and FDA regulations require us to consider each application on its merits according to a statutorily-defined process. Section 505 of the FD&C Act and FDA’s regulations in 21 CFR part 314 describe certain procedures and standards by which the Agency reviews new drug applications (NDAs). FDA is legally bound to apply this governing statutory and regulatory framework to all NDAs, including

¹⁸ Id.

¹⁹ Petition at 3.

an application for a new opioid drug product. In doing so, FDA determines whether each NDA meets applicable standards for safety and effectiveness. In applying these standards, FDA evaluates whether the benefits of the drug outweigh its risks and approves the drug if all applicable standards for approval are met. *See* FD&C Act section 505(c)(1) (“Within one hundred and eighty days after the filing of an application under subsection (b), or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall... approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies....”).

While FDA is committed to continuing its ongoing work of scrutinizing how it applies its benefit-risk framework to candidate opioids, and to exploring whether additional authority from Congress is needed, FDA must also continue to apply the existing statutory and regulatory framework to properly filed NDAs, including applications for new opioid drug products or new opioid formulations.

Furthermore, a moratorium on the approval of new opioid drug products could stifle the development and availability to patients of new opioids that could offer greater safety or other therapeutic advantages over products already on the market.²⁰

Finally, we note that a moratorium on new approvals is not necessary to guard against the possibility that a product approved today might, in the future, either under an altered regulatory framework or based upon new evidence, not be considered to have a favorable benefit-risk profile. FDA's benefit-risk evaluation does not end once a product is approved. The Agency continually monitors the safety of approved products, including opioids, based on post-market data, including adverse event reports. Based on such evidence, the Agency can take a range of actions to help ensure that approved drug products' benefits continue to outweigh their risks. In the case of opioid analgesics, over the years FDA has taken a number of actions to mitigate the serious risks associated with these products, including labeling changes to better inform prescribers and patients regarding the safe use of these products and the imposition of a REMS requiring that training be made available to health care providers involved in the management of patients with pain.²¹ Further, if the Agency concludes that a drug's benefits no longer outweigh its risks, we can withdraw its approval.

B. The Agency recently issued draft guidance regarding our opioid benefit-risk assessment framework that incorporates public health considerations.

As noted above, two months after you submitted your Petition, FDA published the Draft Guidance describing the benefit-risk assessment framework used by the Agency in evaluating applications for opioid analgesic drugs. The Agency considered the

²⁰ As noted above, one of the topics of the September 17 public hearing is whether new incentives are needed to better support and encourage development of such products.

²¹ *See Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse*, available at <https://www.fda.gov/drugs/information-drug-class/timeline-selected-fda-activities-and-significant-events-addressing-opioid-misuse-and-abuse>.

recommendations of the NASEM Report in developing this guidance. Accordingly, we disagree that FDA has not developed and articulated an opioid regulatory framework that properly incorporates public health considerations, as NASEM recommends. FDA's draft guidance describes how public health considerations factor into the benefit-risk assessment and summarizes the information that should be included in a new drug application for an opioid analgesic drug to facilitate that assessment. Also as noted above, FDA is holding a public hearing on September 17, 2019, to receive input on, among other things, whether FDA's current statutory and regulatory framework, including the benefit-risk assessment described in the Draft Guidance, allows for an adequate evaluation of applications for new opioid analgesics, or whether new authorities may be needed. We further note that the Draft Guidance and public discussion of the Draft Guidance builds on, and seeks to formalize, FDA's historic practice of considering the larger public health impact of our regulatory decisions regarding opioids.

III. CONCLUSION

For the reasons explained above, we are denying your Petition. However, given the broad overlap between the issues raised in your Petition, the subject matter of the Draft Guidance, and the topics to be discussed at the September 17, 2019, public hearing, we will continue to consider these and related issues as we receive comments on the Draft Guidance and in light of the input we receive at the public hearing as well as comments submitted to the docket associated with that hearing. We welcome your input on these related matters, either through written submission to the relevant dockets, participation at the public hearing, or both.

Sincerely,

A handwritten signature in dark ink, appearing to read "Dr. Janet L. Woodcock".

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research