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**Presentation at the Food and Drug Administration’s September 17, 2019, Public Hearing,  
“Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to  
Treat Pain and Addiction”**

**FDA’s Response to the National Academies 2017 Recommendations for a New Opioid  
Regulatory Framework: Woefully Inadequate in Substance, Devoid of Necessary Urgency**

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The only realistic interpretation of the first part of the title of this meeting, “Standards for Future Opioid Analgesic Approvals,” is that the Food and Drug Administration (FDA) is very belatedly beginning the process of developing and seeking public input for such standards. That the title specifically refers to standards for *future* opioid approval, not to a more expansive, detailed opioid regulatory framework that already could have been in place to evaluate currently approved and future new opioid analgesics, is an admission of the dangerously preliminary progress the FDA has made thus far in developing such a framework. This meeting was announced simultaneously with the now closed public comment period for the agency’s June 2019 draft guidance for industry entitled “Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework.”

Overall, we found the draft guidance to be woefully inadequate because its cursory content is far more focused on the nonspecific, generalized factors that the FDA itself will consider when reviewing a new drug application (NDA) for an opioid, rather than providing industry with guidance as to what specific benefit and risk information *should* be sought out and included in future NDAs for opioids. The non-directive nature of the draft guidance was bluntly stated by the FDA in the document’s background section:

This guidance describes the various factors that FDA will consider in evaluating the benefits and risks of an opioid analgesic drug. **FDA encourages applicants to provide information relevant to these factors.**<sup>1</sup> [emphasis added]

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<sup>1</sup> Food and Drugs Administration. Opioid analgesic drugs: Considerations for benefit-risk assessment framework – Guidance for industry (draft guidance). June 2019. <https://www.regulations.gov/document?D=FDA-2019-D-1536-0002>. Accessed September 11, 2019.

As an example of the lack of specific, directive guidance, the draft guidance noted that the FDA will consider the following questions, among others, in assessing the effectiveness and safety of an opioid analgesic drug:

- Do any comparative efficacy data exist for the drug relative to approved opioid or nonopioid analgesic drugs? Does this analgesic drug offer any advantages relative to available approved analgesic drugs for each indication, with regard to effectiveness or duration of response?
- Do any comparative safety data exist for the drug relative to approved opioid or nonopioid analgesic drugs? Does this analgesic drug offer any other safety advantages or disadvantages relative to available approved analgesic drugs for each indication (e.g., abuse-deterrent properties, less risk of drug-drug interactions)?<sup>2</sup>

Merely “encouraging applicants to provide information relevant to these factors” is an unacceptable replacement for a more specific recommendation that clinical trials testing new opioids should include active-comparator control groups, not just placebo control groups, to get critically needed answers to the above questions.

Among the important details lacking from the guidance are recommendations that companies seeking approval for new opioids review the previous evidence for diversion of similar, earlier marketed opioids and that the companies discuss in the NDAs what intervention they plan to implement to ensure that their new opioids would be diverted less often than similar predecessor drugs, as recommended in the in the National Academies of Sciences, Engineering, and Medicine’s (National Academies) 2017 report, *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*,<sup>3</sup> which was commissioned by the FDA in 2016 to review the status of FDA opioid regulation and to suggest improvements in it.

It is noteworthy that seven of the nine questions for today’s meeting also deal with comparative assessment of the effectiveness or safety of new opioids, issues that also were specifically addressed in the recommendations made in the National Academies 2017 report.

Ironically, on June 20, 2019, the day before the FDA’s June 2019 draft guidance was posted for public comment, the FDA withdrew an earlier 2014 draft guidance that dealt with these same comparative safety and efficacy issues, but in a much more detailed and appropriately directive manner, as reflected in the following excerpt, among others:

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<sup>2</sup> *Ibid.*

<sup>3</sup> National Academies of Science, Engineering and Medicine. *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*. 2017. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/24781>.

As previously noted, efficacy trials for analgesics should be superiority trials... Even if a placebo-controlled design is used, sponsors are encouraged to include an active comparator in single-dose as well as multiple-dose trials. An active comparator may provide useful information on the relative utility of the investigational drug in that population, particularly when there is already an analgesic that is commonly used for the type of pain under evaluation.<sup>4</sup>

Including such specific recommendations in the FDA guidance would be fully consistent with the type of new opioid regulatory framework described in the National Academies report.

Given the National Academies' additional recommendation that the FDA develop a process for reviewing, and complete a review of, the safety and effectiveness of all currently approved opioids (recommendation 6-6) using the still-to-be-developed opioid regulatory framework — which would likely lead to some of these opioids being removed from the market — it is imperative that the FDA expand its focus beyond just standards for approval of *future* opioids.

In April of this year, because of the then more than 18-month FDA delay in any meaningful public response to the National Academies' 2017 recommendations, we filed a petition with the FDA to immediately impose a moratorium on approval of all NDAs for new opioids or new opioid formulations.<sup>5</sup> The petition argued that the moratorium should not be lifted until the agency has implemented the elements recommended by the National Academies for inclusion in the currently nonexistent opioid regulatory framework. The petition, which was denied on September 6, would have provided the FDA and relevant advisory committees the necessary time to construct and implement the National Academies' framework.

We agree with many of the comments submitted jointly by the chair, one member, and two consultants of the National Academies committee, expressing their own views, in response to the FDA's June 2019 draft guidance, including the following:

[T]he Draft Guidance.... is an important first step in implementing the 2017 report's recommendations that will lead to benefits for the public health... [but] 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...

Although the Draft Guidance begins to implement the recommendations of the [National Academies] 2017 report, much remains unstated in the Draft Guidance. We encourage

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<sup>4</sup> Food and Drug Administration. Guidance for industry: Analgesic indications: Developing drug and biological products (draft guidance). February 2014. <https://www.regulations.gov/document?D=FDA-2014-D-0091-0002>. Accessed September 11, 2019. PDF page 26.

<sup>5</sup> Public Citizen. Requesting an immediate moratorium on the approval of new drug applications for new Opioids or new opioid formulations. April 10, 2019. [https://www.citizen.org/wp-content/uploads/190410\\_petition\\_to\\_fda\\_new\\_opioid\\_moratorium\\_resubmitted\\_final.pdf](https://www.citizen.org/wp-content/uploads/190410_petition_to_fda_new_opioid_moratorium_resubmitted_final.pdf). Accessed September 11, 2019.

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**... [Emphasis added]

[T]he [National Academies] Committee recommended that FDA conduct a full review of currently marketed/approved opioids..., [which] 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... 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...

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...

[In announcing today's meeting,] 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 [National Academies] 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.<sup>6</sup>

Had the FDA acted with the urgency demanded by the ongoing opioid crisis and begun the important public process of developing a desperately needed improved opioid regulatory framework soon after it received the detailed, carefully considered National Academies recommendations two years ago, it is likely that the process of creating this framework would have been completed by now, rather than just beginning. The FDA now must make the development and implementation of such a framework its number one priority.

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<sup>6</sup> Bonnie RJ, Kesselheim AS, Riley MF, Zettler PJ. Comments regarding opioid analgesic drugs: Considerations for benefit-risk assessment framework; draft guidance for Industry; availability. <https://www.regulations.gov/document?D=FDA-2019-D-1536-0027>. Accessed September 11, 2019.