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Comments on the Food and Drug Administration’s June 2019 Draft Guidance for Industry Entitled “Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework,” Docket No. FDA-2019-D-1536

Public Citizen, a consumer advocacy organization with more than 500,000 members and supporters nationwide, submits these comments with regard to the June 2019 draft guidance for industry entitled “Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework,” the availability of which was announced by the Food and Drug Administration (FDA) in the *Federal Register* on June 21, 2019 (Docket No. FDA-2019-D-1536).¹

This promisingly titled draft guidance purports to “[summarize] the information that should be included in a new drug application [NDA] for an opioid analgesic drug to facilitate the Agency’s benefit-risk assessment” (see page 1, lines 19-21). As is typical for its guidance documents, the FDA specifies that “*should* in Agency guidances means that something is suggested or recommended, but not required” (see page 1, lines 26-27).

We find the draft guidance overall to be woefully inadequate because its cursory content is far more focused on the nonspecific, generalized factors that the FDA itself will consider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 an 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. This deferral toward generalized factors for the FDA to consider instead of specific guidance recommendations for what industry should provide is foreshadowed in the following statement from the background section of the draft guidance:

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** (emphasis added; see page 2, lines 50-52).

These glaring omissions from the draft guidance occurred despite very specific recommendations on these same topics provided to the FDA more than two years ago by the National Academies of Science, Engineering and Medicine 2017 report, *Pain Management and the Opioid Epidemic*:

¹ 84 FR 29211.

Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use (hereafter referred to as the National Academies report),² which was commissioned by the FDA in 2016 to review the current status of FDA opioid regulation and to suggest improvements in it.

Two Specific Serious Deficiencies in the Draft Guidance

1. Failure to specify the need for sponsors to conduct comparative safety and efficacy studies on all new opioids

Section III. C. of the draft guidance, **Effectiveness and Safety Relative to Approved Analgesic Drugs**, states the following:

FDA will consider the questions including the following in assessing 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)?
- What is the anticipated benefit-risk balance relative to available approved analgesic drugs for each indication? (see page 4, lines 129-157)

Merely “encouraging applicants to provide information relevant to these factors” is an unacceptable replacement for a more specific recommendation that phase 2 and phase 3 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.

A much more robust, detailed February 2014 FDA draft guidance entitled “Guidance for Industry: Analgesic Indications: Developing Drug and Biological Products”³ was withdrawn by the agency on June 20, 2019, the day before this newly proposed draft guidance was announced.⁴ That draft guidance provided much more specific details for recommended clinical trials

² 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>.

³ Food and Drug Administration. Guidance for industry: Analgesic indications: developing drug and biological products. February 2014. <https://www.regulations.gov/document?D=FDA-2014-D-0091-0002>. Accessed August 17, 2019.

⁴ Food and Drug Administration. Withdrawn guidances (drugs). <https://www.fda.gov/drugs/guidances-drugs/withdrawn-guidances-drugs>. Accessed August 17, 2019.

evaluating new analgesics, including opioids. In particular, in the section “**Specific Efficacy Trial Considerations**,” under the subheading “*Choice of Comparators*,” the 2014 draft guidance proposed the following:

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.⁵

Thus, in the context of the FDA’s stated preference for the use of a superiority trial design for evaluating new opioids and other analgesics, the FDA in 2014 clearly and appropriately recommended the inclusion of an active comparator for such clinical trials. This same specific recommendation should have been included in the FDA’s June 21, 2019, draft guidance.

Importantly, including such a specific recommendation in the FDA guidance would be fully consistent with the type of new opioid regulatory framework described the National Academies report, as reflected in the following comments and recommendations from that report:

The FDA’s standards for new drug approval, therefore, serve a key public health function. **However, the [FDA’s] investigational drug evaluation process also has important limitations, particularly with respect to the approval of opioids.**

For example, showing that a drug has substantial evidence of efficacy **does not necessarily mean that the drug is more effective than currently available therapies, or that the efficacy demonstrated is clinically meaningful.** In the case of hydrocodone ER (see Box 6-1), the drug was tested against a placebo. Also, **while the hydrocodone ER case showed a statistically significant improvement in pain outcomes, it is not clear whether the slight numeric difference in the pain scale is clinically meaningful for patients with pain,** particularly since pain worsened overall over the course of the trial among both the subjects receiving hydrocodone ER and those receiving placebo...

However, the FDA bases its approval decision on the data provided by the manufacturer at the time of the NDA and does not require that trials of investigational drugs be conducted with particular characteristics...

Recommendation 6-2. Require additional studies and the collection and analysis of data needed for a thorough assessment of broad public health considerations. **To utilize a systems approach that adequately assesses the public health benefits and risks described in Recommendation 6-1, the U.S. Food and Drug Administration (FDA)**

⁵ Food and Drug Administration. Guidance for industry: Analgesic indications: developing drug and biological products. February 2014. <https://www.regulations.gov/document?D=FDA-2014-D-0091-0002>. Accessed August 17, 2019. PDF page 26.

should continue to require safety and efficacy evidence from well-designed clinical trials...⁶

[Emphasis added]

2. Failure to address the diversion of opioids

The failure of the draft guidance to address key recommendations from the National Academies report is not limited to the issue of providing evidence of comparative efficacy. In particular, the report included a lengthy discussion of diversion of prescription opioids and the following specific recommendations that, in part, addressed this issue:

Recommendation 4-1. Consider potential effects on illicit markets of policies and programs for prescription opioids. In designing and implementing policies and programs pertaining to prescribing of, access to, and use of prescription opioids, **the U.S. Food and Drug Administration**, other agencies within the U.S. Department of Health and Human Services, state agencies, and other stakeholders **should consider the potential effects of these interventions on illicit markets—including both the diversion of prescription opioids from lawful sources** and the effect of increased demand for illegal opioids such as heroin among users of prescription opioids—**and take appropriate steps to mitigate those effects.**⁷ [Emphasis added]

Recommendation 6-1. Incorporate public health considerations into opioid-related regulatory decisions. The U.S. Food and Drug Administration (FDA) should utilize a comprehensive, systems approach for incorporating public health considerations into its current framework for making regulatory decisions regarding opioids... **When recommending plans for opioids under investigation; making approval decisions on applications for new opioids, new opioid formulations, or new indications for approved opioids; and monitoring opioids on the U.S. market, the FDA should explicitly consider...**

- effects on the overall market for legal opioids and, to the extent possible, **impacts on illicit opioid markets;**
- **risks associated with existing and potential levels of diversion of all prescription opioids...**⁸

[Emphasis added]

Despite these specific recommendations and the related discussion concerning opioid diversion in the National Academies' report, the word diversion is entirely missing from the draft

⁶ 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>. Pages 364 and 397.

⁷ *Ibid.* Page 6

⁸ *Ibid.* Pages 7-8.

guidance. Although clearly a subset of abuse and misuse, which are referenced in the draft guidance, diversion itself is a much more specific issue.

The National Academies report also included the following discussion regarding how the FDA could ensure the gathering of more information prior to approval during the clinical development stage for a new opioid:

A more comprehensive approach to organizing pre-approval trials could encompass

- testing the drug in subpopulations at high risk of harmful outcomes, including those in locations of the country with high rates of misuse, OUD [opioid use disorder], or diversion;⁹

Although diversion of new, not-yet-marketed opioids should ideally not have occurred before approval and marketing, because most new opioids are new formulations of older ones, the draft guidance should have recommended that companies seeking approval for new opioids review the previous evidence for diversion of similar, earlier marketed opioids. Part of the NDA should then discuss what intervention the companies plan to implement to ensure that their new opioids would be diverted less often than similar predecessor drugs.

An Example of Better FDA Guidance Providing Detailed Specific Recommendations: Final 2015 Guidance Limited to Abuse Deterrent Opioids

In stark contrast to the June 2019 draft guidance entitled “Opioid Benefit Risk Assessment Framework Guidance,” the FDA’s final 2015 guidance entitled “Abuse-Deterrent Opioids — Evaluation and Labeling: Guidance for Industry”¹⁰ is much more useful because it provides numerous specific, detailed recommendations that companies should follow when designing pre-approval studies to support NDAs for new abuse-deterrent opioids. The following excerpt from table of contents of the 2015 guidance reflects the range of detailed recommendations that it provided spanning 14 pages:

⁹ NASEM page 392

¹⁰ Food and Drug Administration. Abuse-deterrent opioids — evaluation and labeling: Guidance for industry. April 2015. <https://www.fda.gov/media/84819/download>. Accessed August 18, 2019.

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In contrast to the June 2019 draft guidance, this earlier 2015 guidance appropriately begins with the need for specific rigor of the design of these studies:

First and foremost, any studies designed to evaluate the abuse-deterrent characteristics of an opioid formulation should be scientifically rigorous. Important general considerations for the design of these studies include the appropriateness of positive controls ^{[footnote] 6} and comparator drugs, outcome measures, data analyses to permit a meaningful statistical analysis, and selection of subjects for the study.

^{[Footnote] 6} For purposes of this guidance, a positive control is an opioid drug product or drug substance expected to result in a predictable opioid drug liking effect and has a known potential for, or history of, abuse.¹¹

Later, referring to the recommended “Clinical Abuse Potential Studies (Category 3),” the 2015 guidance states the following:

[T]he preferred design is a randomized, double-blind, placebo-controlled and positive controlled crossover study. These studies generally are conducted in a drug-experienced, recreational user population. The use of a pre-qualification phase (see section 2 below) to identify subjects who can reproducibly distinguish active drug from placebo is a common enrichment strategy used to improve the power of the study to establish a difference between treatments.¹²

Thus, the FDA’s disabling unwillingness to be more specific in its June 2019 draft guidance addressing opioids more broadly is a striking contrast to its much more directive 2015 final guidance on abuse-deterrent opioids. Particularly glaring are the specific, detailed requests for proper designs of studies in the 2015 guidance, contrasted with the dangerous, nonspecific

¹¹ *Ibid.* PDF page 7.

¹² *Ibid.* PDF page 7.

approach in the 2019 draft guidance regarding the design of safety and efficacy clinical trials for all new opioids, the major stated topic of the draft guidance.

Conclusions

The proposed benefit-risk assessment described in the draft guidance is mainly a cursory menu of the factors the FDA will consider in evaluating the benefits and risks of new opioids, rather than a directive about the preferred study designs that the industry should follow in its future NDAs for new opioids.

It is now more than two years since the FDA received the thorough National Academies report, which contained multiple recommendations for the FDA to incorporate into a future opioid regulatory framework. The stated goal was to improve the safety and efficacy of future opioids, both for the intended users and for public health more broadly, ultimately reducing the number fatal and nonfatal opioid overdoses.

In April of this year, Public Citizen petitioned the FDA for a temporary “moratorium on approval of all NDAs [new drug applications] for new opioids or new opioid formulations,” not to be lifted until the agency “has implemented the elements recommended by the National Academies for inclusion in the currently non-existent opioid regulatory framework.”¹³

The draft guidance is a beginning, albeit a poor one, of the necessary work to design and implement this important new opioid regulatory framework. The current status of the FDA’s proposed opioid benefit-risk assessment framework fails to incorporate many of the most important recommendations of the National Academies report and is thus too weak to be relied upon for improving the current FDA regulation of opioids.

Thank you for the opportunity to comment on this critically important public health issue.



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¹³ Public Citizen. Citizen petition: 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. Accessed August 18, 2019.