

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration****21 CFR Part 15**

[Docket No. FDA-2019-N-2514]

Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics To Treat Pain and Addiction; Public Hearing**AGENCY:** Food and Drug Administration, HHS.**ACTION:** Notification of public hearing; request for comments.

SUMMARY: The Food and Drug Administration (FDA, Agency, we) is holding a public hearing on September 17, 2019, entitled “Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction.” The Agency today is issuing a draft guidance on the application of FDA’s existing benefit-risk assessment framework to applications for approval of opioid analgesic drugs. This public hearing is intended to receive stakeholder input on the approval process for new opioids and how FDA might best consider the existing armamentarium of therapies, among other factors, in reviewing applications for new opioids to treat pain. FDA also seeks input on potential new preapproval incentives aimed at fostering the development of new therapeutics to treat pain, as well as new treatments for addiction.

DATES: The public hearing will be held on September 17, 2019, from 9 a.m. to 5 p.m. The public hearing may be extended or may end early depending on the level of public participation. Persons can attend the event in person or via webcast. In-person attendees can also request to give a formal presentation or to speak during the open public comment portion of the hearing. Section II provides attendance and registration information. Electronic or written comments will be accepted after the public hearing until November 18, 2019.

ADDRESSES: The public hearing will be held at the FDA White Oak Campus, 10903 New Hampshire Ave., Building 31 Conference Center, the Great Room (Rm. 1503 B/C), Silver Spring, MD 20993-0002. Entrance for public hearing participants (non-FDA employees) is through Building 1, where routine security check procedures will be performed. For parking and security information, please refer to <https://www.fda.gov>AboutFDA/>

WorkingatFDA/BuildingsandFacilities/WhiteOakCampusInformation/ucm241740.htm.

You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before November 18, 2019. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of November 18, 2019. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date. You may submit comments as follows:

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal:* <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else’s Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see “Written/Paper Submissions” and “Instructions”).

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked, and identified as confidential if submitted as detailed in “Instructions.”

Instructions: All submissions received must include the Docket No. FDA-

2019-N-2514 for “Standards for Future Opioid Analgesic Approvals and Incentives for New Therapeutics to Treat Pain and Addiction; Public Hearing.” Received comments will be placed in the docket and, except for those submitted as “Confidential Submissions,” publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- **Confidential Submissions**—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.fda.gov/regulatoryinformation/dockets/default.htm>.

Docket: For access to the docket to read background documents or the received electronic and written/paper comments, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Nicole Zelenak, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6249, Silver Spring, MD 20993, 301-796-9030; nicole.zelenak@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

The Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act (or SUPPORT for Patients and Communities Act)¹ was signed into law on October 24, 2018. One provision of this law requires FDA to hold not less than one public meeting to address the challenges and barriers of developing non-addictive medical products intended to treat acute or chronic pain or addiction, which may include the manner in which the risks of abuse or misuse of a controlled substance may be incorporated into the benefit-risk assessment for new drug approvals under section 505(d) and (e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(d) and (e)).²

All opioids approved to treat pain are controlled substances. They are a crucial component of the armamentarium available for treatment of pain, but they carry serious risks of addiction, overdose, and death. Potent novel analgesics that do not carry these risks could significantly reduce or even obviate the need for opioid analgesics, but development of such drugs has remained elusive. FDA is optimistic that the enormous societal need, and the efforts of all stakeholders to meet that need, will drive scientific advances in the development of novel, safer analgesics. In the meantime, however, opioid analgesics are likely to remain a necessary part of medical practice despite their risks. FDA's goal is to regulate opioid analgesics in such a way as to reduce their serious risks to the greatest extent possible, while ensuring their continued availability to the patients who need them.

Under our existing authorities, FDA determines whether each new drug application—including each new opioid drug application—meets applicable standards for safety and effectiveness. In applying these standards, FDA evaluates whether the benefits of the drug outweigh its risks. Benefit-risk assessment is the foundation of FDA's regulatory review of human drugs and biologics. It reflects the Agency's consideration of the evidence, identification of uncertainties, and the reasoning the Agency uses to make specific regulatory decisions, including product approvals. Additionally, the benefit-risk assessment for a particular medical product serves as a tool for communicating the Agency's findings about the product.

FDA today issued a draft guidance on the application of FDA's benefit-risk

assessment framework to applications for approval of opioid analgesic drugs entitled "Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework—Guidance for Industry." This draft guidance discusses the Agency's application of the existing benefit-risk assessment framework, which takes into account not only the benefits and risks of a proposed new opioid to patients when used as prescribed, but also the effectiveness and safety of the proposed product relative to currently available analgesics as well as the public health impact of anticipated inappropriate use. Comments on that draft guidance may be submitted to the docket number for the draft guidance, FDA-2019-D-1536. Comments are requested to be submitted by [enter DATE that is 60 days after issuance of the draft guidance] to ensure that your comments will be considered before finalization of the guidance.

The existing benefit-risk assessment process has been, and continues to be, a comprehensive and effective mechanism for evaluating all new drug approvals, including new opioid approvals. Given the current opioid crisis, however, it is critical that FDA explore every possible option for effectively responding to opioid misuse and abuse. To this end, the Agency is announcing this public hearing to gather input on additional factors the Agency could consider during the approval process for new opioid therapies. For example, should a new opioid analgesic be required to demonstrate an advantage over existing drugs to justify its addition to the market? If so, what new authorities would FDA need to impose such a requirement? What other new authorities might FDA need to fully assess candidate opioid analgesics given their serious risks and the societal impact of opioids overall?

As noted above, potent novel analgesics that do not carry the serious risks of existing opioids could greatly reduce or even eliminate the need for opioid analgesics in the armamentarium of drugs available to treat serious pain. In addition, there is an urgent need for new and better treatment options for opioid use disorder. Accordingly, FDA is also considering whether new preapproval incentives (in addition to existing incentives, such as breakthrough designation) are needed to better support and encourage development of all therapeutics (opioid or non-opioid drugs, biological products, or devices) intended to treat pain or addiction. Such new incentives could be tailored to the development of novel analgesics and could include, among other things, an FDA

commitment to hold a series of meetings and provide written feedback at various stages of product development, with a firm seeking approval of a product with the potential to offer an advantage relative to existing products indicated to treat pain or addiction. We invite comment on potential new incentives as discussed below.

II. Topics for Discussion at the Public Hearing

FDA is seeking feedback from a broad group of stakeholders, both private and public, who are working on the challenges of improving pain management and addressing the opioid crisis. Some questions for consideration at the public hearing are provided below. We welcome input on other relevant issues as well.

1. Does the current statutory and regulatory framework, including the benefit-risk assessment described in the recently issued draft guidance, allow for an adequate evaluation of applications for new opioid analgesics, or are new authorities required? If new authorities are required, please expand on what should be added to the existing statutory and regulatory paradigm.

2. Should sponsors of new opioid analgesics be required to demonstrate some comparative advantage relative to existing analgesics? If so, what new authorities would be necessary to impose a comparative advantage requirement for opioid analgesics?

3. If so, how should that comparative advantage be defined?

a. Can it be quantified?

b. Should the assessment encompass any potential comparative advantage, including, e.g., safety advantages that reduce the prevalence or consequences of abuse or misuse by non-patient populations?

c. For any given application, to which existing products should the proposed new product be required to demonstrate comparative advantage? Any other opioid approved for the same analgesic indication(s) for which approval is sought? What are the implications if the new product only offers a comparative advantage over some of the other opioid products approved for the same indication(s)?

4. If a showing of comparative advantage were made a requirement for approval of new opioid analgesics, could a proposed product meet this standard even if the product also carried additional or novel risks compared to existing products?

5. If a showing of comparative advantage were made a requirement for approval of new opioid analgesics, should there be any exceptions, for

¹ Public Law 115-271.

² *Id.*, section 3001(a).

example with regard to medically necessary drugs in shortage?

6. If a showing of comparative advantage were made a requirement for approval of new opioid analgesics, what would be the impact on development of such products?

7. If a showing of comparative advantage were made a requirement for approval of new opioid analgesics, what would be the impact on patients, providers, and on the public health generally? Please consider that the existing opioid market consists largely of relatively inexpensive generic drugs.

8. In what other ways should FDA be considering the existing armamentarium of therapies to treat pain when reviewing an application for the approval of a new opioid analgesic? To what extent would new authorities be required?

9. Please comment on whether new pre-approval incentives are needed to better support and encourage development of therapeutics intended to treat pain or addiction. If so, what new incentives would be most effective, and what new authorities might FDA need to offer them? If the new incentives are offered through a designation process (analogous to breakthrough designation), what should be the criteria for designation?

Registration and Requests for Oral Presentations: The FDA Conference Center at the White Oak location is a Federal facility with security procedures and limited seating. Attendees can register at <https://www.eventbrite.com/e/fda-standards-for-future-opioid-therapy-approvals-part-15-meeting-tickets-60645674846>. Attendees have the following options:

- **Presenter**—Presenters will give a timed presentation followed by a timed question and answer period by the panel. The presentation time allotted will be approximately 10 minutes, but this is subject to change based on the number of presenters who register. Presenters can opt to use a presentation slide deck. Presenters must register no later than August 9, 2019. Slide decks are due to *CDER-PublicMeeting@fda.hhs.gov* in PDF or PowerPoint format no later than August 23, 2019. If presenters choose to not use a slide deck, they are requested to submit a single slide with name of presentation and contact information by September 6, 2019.

- **Open Public Commenter**—Open public commenters will provide a timed oral testimony. The comment time allotted will be approximately 3 minutes, but this is subject to change based on the number of commenters who register. Open public commenters

shall not have presentation materials or a question and answer period with the panel. Commenters must register no later than September 10, 2019.

- **In-Person Attendee**—In-person attendees will attend the meeting at the FDA White Oak facility.

- **Webcast Attendee**—For those unable to attend in person, FDA will provide a live webcast of the hearing. Webcast attendees will be provided with a link via email to use to view the streaming webcast of the public hearing.

Attendees shall register for only one person. Those without internet or email access can register and/or request to participate as an open public hearing speaker or a formal presenter by contacting Nicole Zelenak by the above dates (see **FOR FURTHER INFORMATION CONTACT**).

FDA will try to accommodate all persons who wish to register. Registration may close early if slots are full. Individuals and organizations with common interests may consolidate or coordinate their presentations and request time for a joint presentation. Individual organizations are limited to a single presentation slot. FDA will notify registered Presenters of their scheduled presentation times no later than 1 week prior to the meeting. The time allotted for each presentation will depend on the number of individuals who wish to speak. Persons registered to present are encouraged to arrive at the hearing room early and check in at the onsite registration table to confirm their designated presentation time. Actual presentation times, however, may vary based on how the meeting progresses in real time. An agenda for the hearing and any other background materials will be made available 5 days before the hearing at <https://www.fda.gov/drugs/development-approval-process-drugs/standards-future-opioid-therapy-approvals-09172019-09172019>.

If you need special accommodations because of a disability, please contact Nicole Zelenak (see **FOR FURTHER INFORMATION CONTACT**) at least 7 days before the hearing.

Transcripts: Please be advised that as soon as a transcript is available, it will be accessible at <https://www.regulations.gov>. It may be viewed at the Dockets Management Staff (see *Comments*). A transcript will also be available in either hard copy or on CD-ROM, after submission of a Freedom of Information request. The Freedom of Information office address is available on the Agency's website at <https://www.fda.gov>.

III. Notice of Hearing Under 21 CFR Part 15

The Commissioner of Food and Drugs is announcing that the public hearing will be held in accordance with 21 CFR part 15. The hearing will be conducted by a presiding officer, who will be accompanied by FDA senior management from the Office of the Commissioner, the Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and the Center for Devices and Radiological Health. Under § 15.30(f), the hearing is informal and the rules of evidence do not apply. No participant may interrupt the presentation of another participant. Only the presiding officer and panel members can pose questions; they can question any person during or at the conclusion of each presentation. Public hearings under part 15 are subject to FDA's policy and procedures for electronic media coverage of FDA's public administrative proceedings (21 CFR part 10, subpart C). Under § 10.205, representatives of the media may be permitted, subject to certain limitations, to videotape, film, or otherwise record FDA's public administrative proceedings, including presentations by participants. Persons attending FDA's public hearings are advised that FDA is not responsible for providing access to electrical outlets. The hearing will be transcribed as stipulated in § 15.30(b) (see *Transcripts*). To the extent that the conditions for the hearing, as described in this notice, conflict with any provisions set out in part 15, this notice acts as a waiver of those provisions as specified in § 15.30(h).

Dated: June 17, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 1

[REG-101828-19]

RIN 1545-BP15

Guidance Under Section 958 (Rules for Determining Stock Ownership) and Section 951A (Global Intangible Low-Taxed Income)

AGENCY: Internal Revenue Service (IRS), Treasury.

ACTION: Notice of proposed rulemaking.