



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2019-N-2012]

New Drugs Regulatory Program Modernization: Improving Approval Package Documentation and Communication

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for comments.

SUMMARY: The Food and Drug Administration (FDA or Agency) is seeking public comment on the Clinical Data Summary Report Pilot program as part of the Agency's continuous assessment of the efficiency and transparency of the clinical data used in the regulatory decision-making process. The Agency is also seeking public feedback on a new integrated review template for the documentation of new drug marketing applications developed as part of the New Drugs Regulatory Program Modernization. The Agency hopes to receive public feedback on both of these efforts and on how FDA might continue supporting our stakeholders' needs related to the clarity and transparency of drug approval decisions.

DATES: Submit either electronic or written comments on the notice by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: 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 [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The <https://www.regulations.gov> electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. 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.

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-2012 for “New Drugs Regulatory Program Modernization: Improving Approval Package Documentation and Communication.” Received comments, those filed in a timely manner (see ADDRESSES), 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 docket, see 80 FR 56469,

September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, 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: *Regarding the Clinical Data Summary Pilot Program:* Patrick Zhou, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 1148, Silver Spring, MD 20993-0002, 301-348-1817, Patrick.Zhou@fda.hhs.gov, with the subject line “Collecting Public Feedback on the Clinical Data Summary Pilot Program.”

Regarding the Integrated Review: Kevin Bugin, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 5128, Silver Spring, MD 20993-0002, 301-796-2302, Kevin.Bugin@fda.hhs.gov, with the subject line “Collecting Public Feedback on the Integrated Review.”

SUPPLEMENTARY INFORMATION:

I. Background

Currently, FDA’s Center for Drug Evaluation and Research (CDER) provides access to action packages, which include all discipline reviews, for newly approved original new drug applications (NDAs) and biologics license applications (BLAs) by posting these action packages on the FDA website at www.fda.gov/drugs@FDA. FDA posts them regardless of whether there has been a request under the Freedom of Information Act (FOIA), 5 U.S.C. 552.

Other approval-related information such as review documents for abbreviated new drug applications (ANDAs) or NDA efficacy supplements are posted on www.fda.gov/drugs@FDA after they have been redacted and disclosed in response to a FOIA request, but they are not routinely posted proactively by the Agency. While the action packages include a significant amount of information from the sponsor's application, they can reach up to hundreds of pages and include administrative and/or correspondence-related documentation. As a result, some stakeholders have difficulty navigating the documents and using them to gain an understanding of the basis for FDA drug approvals. To address this, two efforts have been launched: (1) a pilot program referred to as the Clinical Data Summary Pilot Program (Pilot), launched in January 2018, through which parts of a sponsor's clinical study reports (CSRs) were to be posted and (2) a new integrated template that will be used to document FDA's review of new drug applications and efficacy supplements. This document seeks public comment on both of these efforts.

On January 16, 2018, then-FDA Commissioner Scott Gottlieb announced several efforts to enhance the transparency of the Agency's drug approval decisions as part of an overall approach to enhance the efficiency and transparency of the Agency's drug approval decisions. One of those efforts included the Pilot program to evaluate whether publicly disclosing certain summary information included within sponsor-submitted CSRs improves public understanding of the basis of FDA's approval decisions.

The Pilot's goals included enhancing the understanding of information about drug approvals to improve the accuracy of discussions about drug approvals in scientific publications, increasing stakeholders' understanding of the basis for FDA's approval decisions, and informing physicians and other healthcare providers about the clinical trial results on which regulatory decisions are based.

For this Pilot, FDA sought voluntary participation from the sponsors of fewer than ten marketing applications selected on the basis of novelty and clinical importance (e.g., products that are novel including drugs that are new molecular entities, products across a range of disease areas, and products of scientific interest). For any approved application whose sponsor agreed to participate, FDA would post, along with the traditional action package, summary portions of the sponsor's CSRs for the pivotal trials establishing the safety and effectiveness of the drug. One sponsor voluntarily agreed to participate. The subsequent posting can be found on FDA's Clinical Data Summary Pilot Program web page at <https://www.fda.gov/drugs/developmentapprovalprocess/ucm589210.htm>. All other contacted sponsors declined to participate in the Pilot. The recruitment phase of the Pilot is now concluded.

FDA recognizes that the needs and expectations of different stakeholders regarding transparency of information relating to drug approval decisions may vary. By opening a public docket, FDA hopes to learn from its stakeholders more about the potential benefits or risks, resource requirements, and challenges of FDA publicly releasing a limited number of sections from certain CSRs at the time of marketing approval.

In addition to the Pilot, FDA has other efforts that also seek to provide greater clarity on FDA's application review and decision-making process. One of those efforts is the new integrated review process and template developed under the New Drugs Regulatory Program Modernization, which is part of a multiyear, multiphase effort to enhance the new drugs regulatory program. The new integrated review process and template are intended to promote more integrated and interdisciplinary assessments, enhance clarity of our assessments regarding the benefits and risks for new drug products, and improve our communication about the basis for

new drug approvals. For more information, please see CDER Director Janet Woodcock's notes of June 4, 2018, available at <https://www.fda.gov/news-events/fda-voices-perspectives-fda-experts/fda-proposes-process-modernization-support-new-drug-development>.

II. The Integrated Review Process

The new integrated review process and documentation template, currently being implemented, supports reviewers in conducting a scientifically-rigorous review that efficiently documents regulatory decisions. The integrated review process includes the use and public posting, upon approval of a new drug or biologic, of an integrated review document that contains a summary, an integrated assessment, and appendices. This new review template would replace the current documentation where each discipline provides a separate application review document. The updated template would be a collaborative document with input from clinical, clinical pharmacology, biostatistics, toxicology reviewers, and other disciplines based upon the issues raised by the application. FDA believes this program will also meet the goal of effectively communicating the basis for new drug approvals. The Agency is therefore considering whether to focus its efforts to better communicate the basis for drug approvals on the development of new integrated review documents, rather than on the release of CSRs.

The guiding principles of this initiative are the importance of conducting an issue-focused assessment, enhanced communication both within the review team and with the applicant, and stronger interdisciplinary collaboration. FDA believes that the format and content of the integrated review will provide a clearer description of FDA's analysis of the scientific issues raised by the application, and will thereby more effectively communicate the basis for the approval decision.

As mentioned above, the integrated review template has three main components:

- Summary:
 - Contains an executive summary of FDA's decision and assessment of the application, including FDA's benefit-risk determination (as currently employed in marketing application reviews)
 - Provides an overall Agency assessment, including an overview of the major decisions made during the review process, and a brief discussion of the basis for the decisions
- Integrated Assessment:
 - Promotes succinct, integrated, focused analyses of the evidence of benefit-risk, and therapeutic individualization (e.g., special populations, drug interactions)
 - Highlights key issues in an interdisciplinary manner that the review team thinks are pertinent to the decision-making process
- Appendices:
 - Contains assessments and analyses that are supportive or important to key facts/data or conclusions for the overall review
 - Contains work that did not directly impact the overall assessment of benefit-risk, regulatory action, labeling, or risk mitigation plans

The target audiences for this document are diverse, and include the lay public with a specific interest in the particular application, drug sponsors, researchers and others who are seeking to understand the basis for FDA's decision. In general, the first two parts of the integrated document would be expected to provide a complete explanation of FDA's action, with the third component (the appendices) also available for those looking for additional detail on the comprehensive analyses FDA conducted in its review of the drug application.

As part of FDA's internal assessment for both of these programs, the Agency is interested in receiving responses to the following questions, in addition to any general comments the public might have. For convenience, it would be helpful if commenters refer to the numbered question and subject when submitting responses and comments to the following questions:

A. Regarding the Clinical Data Summary Pilot Program

Please see the CSR posting available on FDA's Clinical Data Summary Pilot Program web page at <https://www.fda.gov/drugs/developmentapprovalprocess/ucm589210.htm>.

1. How did the CSR posted in this Pilot affect or compare with your understanding of the CSRs submitted to FDA by drug sponsors?
2. How usable and/or accessible was the information in the CSR that was posted for the Pilot?
3. Did the required redactions/removal of certain information from the posted CSR affect your understanding or use of the posted information?
4. How might the information/content posted from this Pilot be used? What other information/content would have been helpful?
5. Given the other review documents available (e.g. FDA's action package), how did the posted CSR affect your understanding of FDA's decision-making process regarding drug applications?
6. What do you believe would be the potential advantages and disadvantages of posting this information routinely?
7. Is there any additional information you would like to provide regarding the, potential benefits or risks, resource requirements, and international challenges of publicly releasing a limited number of sections from certain CSRs at the time of marketing approval?

To illustrate the new integrated review template, the original reviews for NDA 210806 (PIFELTRO (doravirine) tablets, 100 milligrams (mg)) and NDA 210807 (DELSTRIGO

(doravirine, lamivudine, and tenofovir disoproxil fumarate) tablets, 100/300/300 milligrams) have been rewritten to provide an example. The original multidisciplinary review for the NDAs and the information provided in the new integrated review template are posted on <https://www.fda.gov/newdrugsmodernization#integrated>.

B. Regarding the Integrated Review

1. How does the new format of the integrated review inform your knowledge of FDA's basis for making decisions?
2. How does the usability and accessibility of information in the new integrated review compare to the original review posted on FDA's website?
3. How could the information provided in the new integrated review format be used, if at all?
4. What do you believe would be the potential advantages and disadvantages of posting review documents in this format?
5. Based on the integrated review, were the issues that concerned the review team clear and understandable? If so, what helped achieve this? If not, what can be improved?
6. Is there important information in the integrated review that is difficult to locate or should be added?

Dated: June 24, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

[FR Doc. 2019-13751 Filed: 6/26/2019 8:45 am; Publication Date: 6/27/2019]