4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2009-D-0283]

Postmarketing Studies and Clinical Trials--Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act; Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled "Postmarketing Studies and Clinical Trials--Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act." This draft guidance revises the guidance for industry of the same name issued April 1, 2011. The draft guidance is being revised to describe the multiple factors that FDA considers, before requiring a postmarketing study or clinical trial for the purposes described in the Federal Food, Drug, and Cosmetic Act (FD&C Act), when determining the sufficiency of the reports under the FD&C Act and the active postmarket risk identification and analysis (ARIA) system available under the FD&C Act to meet these purposes. The draft guidance is also being revised to reflect certain provisions enacted under the Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act as they relate to postmarketing studies and clinical trials.

DATES: Submit either electronic or written comments on the draft guidance by **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]** to

ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

ADDRESSES: You may submit comments on any guidance at any time 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-2009-D-0283 for "Postmarketing Studies and Clinical Trials--Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act; Draft Guidance for Industry; Availability." 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.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.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002 or Office of Communication, Outreach, and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Ayanna Augustus, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6426, Silver Spring, MD 20993-0002, 301-796-3980; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled, "Postmarketing Studies and Clinical Trials--Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act."

Section 505(o)(3) of the FD&C Act[1] (21 U.S.C. 355(o)) authorizes FDA to require certain postmarketing studies or clinical trials for prescription drugs to obtain more information about a serious risk that may be associated with a drug. In some cases, FDA may be concerned about a serious risk that is potentially or known to be associated with a drug but may not know enough about the risk to determine if or how to address it, such as by describing the risk in labeling. Section 505(o)(3)(B) of the FD&C Act states that postmarketing studies and clinical trials may be required for any or all of the following purposes: (1) to assess a known serious risk related to the use of the drug; (2) to assess signals of serious risk related to the use of the drug; or (3) to identify an unexpected serious risk when available data indicates the potential for a serious risk.

Prior to requiring a postmarketing study or clinical trial, FDA must find that the reports under section 505(k)(1) of the FD&C Act and the ARIA system[2] made available under section 505(k)(3) of the FD&C Act will not be sufficient to meet the purposes described in section 505(o)(3)(B) of the FD&C Act.[3] Similarly, before requiring a postmarketing clinical trial, FDA

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[1] Section 901 of Title IX of the Food and Drug Administration Amendments Act of 2007 (Pub. L. 110-85) amended the FD&C Act by adding section 505(o).

[2] Section 505(k)(3) of the FD&C Act mandates that FDA establish an active surveillance system for monitoring drugs, using electronic data from healthcare information holders. The Sentinel System draws on existing healthcare data from multiple sources to actively monitor the safety of medical products. The ARIA system is a subcomponent of the Sentinel System.

[3] Section 505(o)(3)(D)(i) of the FD&C Act.

must find that a postmarketing study will not be sufficient to meet the purposes described in section 505(o)(3)(B) of the FD&C Act.[4]

In April 2011, FDA issued a guidance describing how it would implement section 505(o) of the FD&C Act. At that time, the ARIA system was still in early development. The ARIA system is now officially launched, and FDA must consider the system's sufficiency to meet the purposes of section 505(o)(3)(B) of the FD&C Act to determine if a postmarketing study or clinical trial is necessary. This draft guidance revises the guidance for industry of the same name issued on April 1, 2011 (76 FR 18226). Significant changes from the 2011 version include explaining how FDA considers the reporting under section 505(k)(1) of the FD&C Act and the ARIA system when determining their sufficiency for the purposes under section 505(o)(3)(B) of the FD&C Act. The guidance is also being revised to provide examples of postmarketing requirements under section 505(o)(3) of the FD&C Act to assess a potential reduction in the expected effectiveness of a drug under certain circumstances. FDA's authority to require these types of studies or trials was clarified by a modification to the definition of *adverse drug experience* at section 505-1(b)(1)(E) of the FD&C Act (21 U.S.C. 505-1(b)(1)(E)) enacted under section 3041 of the SUPPORT Act (Pub. L. 115-271).

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the current thinking on implementation of section 505(o)(3)(B) of the FD&C Act. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations.

[4] Section 505(o)(3)(D)(ii) of the FD&C Act.

II. Paperwork Reduction Act of 1995

This draft guidance refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

The following collections of information for postmarketing reports and clinical data in 21 CFR 314.50, 314.80, 314.81, 314.98, 314.430, and 314.610(b), subpart I have been approved under OMB control number 0910-0001: (1) preparing and submitting reports pertaining to safety, postmarketing commitments and preparing and submitting spontaneous and periodic reports, including active postmarket risk identification (using electronic health care data) and any milestones or submissions for which projected dates were specified as part of the postmarketing commitment; (2) submitting a proposed timetable of the postmarketing commitments; (3) preparing registries and submitting them when appropriate; (4) designing meta-analyses to evaluate statistical analyses of data; (5) preparing assay procedures; and (6) prepare a plan or approach for approval an NDA when human efficacy studies are not ethical or feasible.

The following collections of information for postmarketing studies and clinical trials (including various patient populations) in 21 CFR 312.23 have been approved under OMB control number 0910-0014: (1) conducting in vitro laboratory tests and studies to compare pregnancy incidence an pregnancy outcomes and/or child outcomes for patients exposed to a drug; (2) submitting an introductory statement and general investigational plan, including a drug's pharmacological class; and (3) submitting protocols for drug safety and pharmacology and toxicology information.

The collections of information in 21 CFR 310.305, 314.80, and 314.98 for submitting adverse event information to the FDA Adverse Event Reporting System have been approved under OMB control numbers 0910-0230 and 0910-0291; the collections of information in 21 CFR 312.47 and 312.82 for submitting a meeting request to appeal the conduct of a postmarketing study or clinical trial have been approved under OMB control number 0910-0430 (and guidance for industry and review staff entitled "Formal Dispute Resolutions: Appeals Above the Division Level" (available at https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm343101.pdf).

The following collection of information in § 314.510 has been approved under OMB control number 0910-0765: requests for serious or life-threatening diseases or conditions that may be granted accelerated approval if FDA determines the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality or other clinical benefit.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at either https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs, https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances, or https://www.regulations.gov.

Dated: October 21, 2019.

Lowell J. Schiller,

Principal Associate Commissioner for Policy.

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