stages in tumor development. In addition, the mutagenic response may be due to exceeding a detoxification threshold or the induction of oxidative damage to which bacterial cells may be more sensitive than mammalian cells in vitro or tissues in vivo.

This guidance makes recommendations on followup testing for Ames-positive active ingredients in those rare circumstances when a sponsor decides to continue development for potential approval by FDA. These recommendations are intended to potentially address and lower certain safety concerns before proceeding with FIH trials in healthy human subjects. Followup testing cannot entirely mitigate the concerns raised by an Ames-positive finding, and some residual risk remains in the absence of an adequate carcinogenicity assessment. Thus, Ames-positive active ingredients that are further developed should be those targeting serious or life-threatening diseases with unmet medical needs.

Consideration might be given to the administration of an investigational new drug containing an Ames-positive active ingredient to healthy human subjects only if the results of extensive followup testing conducted before clinical administration lowered the concern for cancer based on a weight-of-evidence (WoE) approach evaluating the potential for mutagenicity. A WoE evaluation, for instance, might find that followup testing in an in vitro mammalian cell mutation assay and in vivo mutation assay are both negative and that other considerations do not raise any other safety concerns. Positive findings in either the in vitro mammalian cell mutation assay or in vivo mutation assay would preclude testing in healthy human subjects. The sponsor also should provide a thoroughly considered rationale for why FIH trials should enroll healthy subjects in lieu of patients with the disease or condition the investigational drug product with the Ames-positive active ingredient is intended to treat. Alternatively, consideration should be given to enrolling patients with the disease or condition of interest and designing the trial in a manner that may offer a treatment benefit in addition to the usual aims of a phase 1 trial (*e.g.,* pharmacokinetics, tolerability, etc.).

The guidance recommends that a consistent process of followup testing and evaluation should first be conducted for an Ames-positive active ingredient before FIH trials are commenced in healthy subjects. An Ames-positive metabolite observed at low levels (*e.g.,* at the threshold of toxicological concern) would generally pose minimal safety concerns and may be managed differently. The recommendations explained in the guidance for followup testing are intended to inform both review staff and industry.

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 of FDA on ''Recommended Followup Testing for an Ames-Positive Drug (Active Ingredient) or Metabolite To Support First-in-Human Clinical Trials With Healthy Subjects.'' 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.

II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. The previously approved collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501–3521). The collections of information in 21 CFR part 312 for investigational new drug applications have been approved under OMB control number 0910–0014. The collections of information found in 21 CFR parts 50 and 56 pertaining to protection of human subjects have been approved under OMB control number 0910–0130.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at *https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs, https://www.fda.gov/regulatory-information/search-fda-guidance-documents*, or *https://www.regulations.gov*.

Dated: November 21, 2024.

P. Ritu Nalubola,

Associate Commissioner for Policy.

[FR Doc. 2024–27796 Filed 11–26–24; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2024–D–4643]

Assessment of Ovarian Toxicity in Premenopausal Adults During Drug Development for Oncologic Products; 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 ''Assessment of Ovarian Toxicity in Premenopausal Adults During Drug Development for Oncologic Products.'' This draft guidance provides recommendations to sponsors regarding the measurement of ovarian toxicity using clinical measures and biomarkers of ovarian function in relevant cancer clinical trials that enroll premenopausal adults with ovaries. Assessment of ovarian toxicity in cancer trials helps ensure that patients and clinicians have information about the possible long-term impacts of treatment on ovarian function and thus facilitate informed decision-making regarding anti-cancer agents.

DATES: Submit either electronic or written comments on the draft guidance by January 27, 2025, 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–2024–D–4643 for ''Assessment of Ovarian Toxicity in Premenopausal Adults During Drug Development for Oncologic Products.'' 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, 240–402–7500.

• 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.govinfo.gov/content/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, 240–402–7500.

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. 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: Suparna Wedam, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 2112, Silver Spring, MD 20993, 301–796–1776, or James Myers, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993, 240–402–7911.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled ''Assessment of Ovarian Toxicity in Premenopausal Adults During Drug Development for Oncologic Products.'' This draft guidance provides recommendations to sponsors regarding the measurement of ovarian toxicity using clinical measures and biomarkers of ovarian function in relevant cancer clinical trials that enroll premenopausal adults with ovaries. Loss of ovarian function is a potentially irreversible toxicity associated with systemic anti-cancer agents that may result in infertility and long-term morbidities related to early-onset menopause and estrogen deficiency, including vasomotor symptoms, sexual dysfunction, osteoporosis, cardiovascular disease, and cognitive dysfunction. Routine collection of ovarian toxicity data in cancer clinical trials of investigational agents is currently lacking. Assessment of ovarian toxicity in cancer trials is essential to ensure that patients and clinicians have information about the possible long-term impacts of treatment on ovarian function and thus facilitate informed decision-making regarding anti-cancer agents.

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 of FDA on ''Assessment of Ovarian Toxicity in Premenopausal Adults During Drug Development for Oncologic Products.'' 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.

II. Paperwork Reduction Act of 1995

While this guidance contains no collection of information, it does refer to previously approved FDA collections of information. The previously approved collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501–3521). The collections of information in 21 CFR part 312 for investigational new drug applications have been approved under OMB control number 0910–0014. The collections of information in 21 CFR part 314 relating to new drug applications have been approved under OMB control number 0910–0001. The collections of information in 21 CFR part 601 relating to biologics license applications have been approved under OMB control number 0910–0338.

III. Electronic Access

Persons with access to the internet may obtain the draft guidance at *https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs, https://www.fda.gov/regulatory-information/search-fda-guidance-documents,* or *https://www.regulations.gov.*

Dated: November 19, 2024.

P. Ritu Nalubola,

Associate Commissioner for Policy.

[FR Doc. 2024–27804 Filed 11–26–24; 8:45 am]

BILLING CODE 4164–01–P