label to assist that office in processing your requests. The guidance may also be obtained by mail by calling CBER at 1–800–835–4709 or 240–402–8010. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT:

Regarding the guidance: Scott Goldie, Center for Drug Evaluation and Research, Food and Drug Administration, Bldg. 21, Rm. 3557, Silver Spring, MD 20993–0002, 301–796–2055, *scott.goldie@fda.hhs.gov*; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, Bldg. 71, Rm. 7301, Silver Spring, MD 20993–0002, 240–402–7911.

Regarding the ICH: Jill Adleberg, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6364, Silver Spring, MD 20993–0002, 301–796–5259.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled ''E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials.'' The guidance was prepared under the auspices of ICH. ICH has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, high-quality medicines are developed, registered, and maintained in the most resource-efficient manner.

By harmonizing the regulatory requirements in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized the reporting of important safety information, standardized marketing application submissions, and made many other improvements in the quality of global drug development and manufacturing and the products available to patients.

The six Founding Members of the ICH are FDA; the Pharmaceutical Research and Manufacturers of America; the European Commission; the European Federation of Pharmaceutical Industries Associations; the Japanese Ministry of Health, Labour, and Welfare; and the Japanese Pharmaceutical Manufacturers Association. The Standing Members of the ICH Association include Health Canada and Swissmedic. Additionally, the Membership of ICH has expanded to include other regulatory authorities and industry associations from around the world (refer to *https://www.ich.org/*).

ICH works by involving technical experts from both regulators and industry parties in detailed technical harmonization work and the application of a science-based approach to harmonization through a consensus-driven process that results in the development of ICH guidelines. The regulators around the world are committed to consistently adopting these consensus-based guidelines, realizing the benefits for patients and for industry.

As a Founding Regulatory Member of ICH, FDA plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance for industry. FDA's guidance documents do not establish legally enforceable responsibilities. Instead, they describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

In the **Federal Register** of October 31, 2017 (82 FR 50433), FDA published a notice announcing the availability of a draft guidance entitled ''E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials.'' The notice gave interested persons an opportunity to submit comments by April 30, 2018.

After consideration of the comments received and revisions to the guideline, a final draft of the guideline was submitted to the ICH Assembly and endorsed by the regulatory agencies in November 2019.

This guidance finalizes the draft guidance issued on October 31, 2017. The guidance provides clarification on statistical principles for clinical trials and an update on the choice of estimand to describe a framework for planning, conducting, and interpreting sensitivity analyses of clinical trial data. The focus of the guidance is on statistical principles related to estimands and sensitivity analysis for confirmatory clinical trials. The guidance provides recommendations for aligning the choice of statistical methods with the goals of a clinical trial; on communicating the rationale for such choices to FDA; and on using sensitivity analysis to characterize the robustness of the conclusions to plausible deviations from the assumptions of the main analysis. Revisions made following the public comment period are intended to clarify content within the guidance; however, no new concepts are presented in the revised version.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on ''E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials.'' 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. Electronic Access

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

Dated: May 7, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

[FR Doc. 2021–10066 Filed 5–11–21; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2017–D–5138]

S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals; International Council for Harmonisation; 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 final guidance for industry entitled ''S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals.'' The guidance was prepared under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), formerly the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. The guidance provides key considerations for developing a testing strategy to identify hazard and characterize reproductive risk for human pharmaceuticals. The guidance is intended to align with other ICH guidances, elaborate on concepts to

consider when designing studies, and identify potential circumstances in which a risk assessment can be made based on preliminary studies. It also clarifies the qualification and potential use of alternative assays. This guidance finalizes the draft guidance issued on November 13, 2017.

DATES: The announcement of the guidance is published in the **Federal Register** on May 12, 2021.

ADDRESSES: You may submit either electronic or written comments on Agency guidances 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–2017–D–5138 for ''S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals.'' 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 this 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 the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research (CBER), 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. The guidance may also be obtained by mail by calling CBER at 1–800–835–4709 or 240–402–8010. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: *Regarding the guidance:* Ronald Wange, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 3342, Silver Spring, MD 20993–0002, 301–796–1304; 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.

Regarding the ICH: Jill Adleberg, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6364, Silver Spring, MD 20993–0002, 301–796–5259, *Jill.Adleberg@fda.hhs.gov*.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled ''S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals.'' The guidance was prepared under the auspices of ICH. ICH has the mission of achieving greater regulatory harmonization worldwide to ensure that safe, effective, high-quality medicines are developed, registered, and maintained in the most resource-efficient manner.

By harmonizing the regulatory requirements in regions around the world, ICH guidelines have substantially reduced duplicative clinical studies, prevented unnecessary animal studies, standardized the reporting of important safety information, standardized marketing application submissions, and made many other improvements in the quality of global drug development and manufacturing and the products available to patients.

The six Founding Members of the ICH are FDA; the Pharmaceutical Research and Manufacturers of America; the European Commission; the European Federation of Pharmaceutical Industries Associations; the Japanese Ministry of Health, Labour, and Welfare; and the Japanese Pharmaceutical Manufacturers Association. The Standing Members of the ICH Association include Health

Canada and Swissmedic. Additionally, the Membership of ICH has expanded to include other regulatory authorities and industry associations from around the world (refer to *https://www.ich.org/*).

ICH works by involving technical experts from both regulators and industry parties in detailed technical harmonization work and the application of a science-based approach to harmonization through a consensus-driven process that results in the development of ICH guidelines. The regulators around the world are committed to consistently adopting these consensus-based guidelines, realizing the benefits for patients and for industry.

As a Founding Regulatory Member of ICH, FDA plays a major role in the development of each of the ICH guidelines, which FDA then adopts and issues as guidance for industry. FDA's guidance documents do not establish legally enforceable responsibilities. Instead, they describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.

In the **Federal Register** of November 13, 2017 (82 FR 52306), FDA published a notice announcing the availability of a draft guidance entitled ''S5(R3) Detection of Toxicity to Reproduction for Human Pharmaceuticals.'' The notice gave interested persons an opportunity to submit comments by February 12, 2018.

After consideration of the comments received and revisions to the guideline, a final draft of the guideline was submitted to the ICH Assembly and endorsed by the regulatory agency members in January 2020.

The guidance finalizes the guidance issued on November 13, 2017. The guidance has undergone revisions to align with other ICH guidances, elaborate on concepts to consider when designing studies, and identify potential circumstances in which a risk assessment can be made based on preliminary studies. It also clarifies the qualification and potential use of alternative assays.

The purpose of this guidance is to provide key considerations for developing a testing strategy to identify hazard and characterize reproductive risk for human pharmaceuticals. The guidance informs on the use of existing data and identifies potential study designs to supplement available data to identify, assess, and convey risk. General concepts and recommendations are provided that should be considered when interpreting study data and assessing reproductive risk in support of clinical development and marketing approval.

This guidance applies to pharmaceuticals, including biotechnology-derived pharmaceuticals; vaccines (and their novel constitutive ingredients) for infectious diseases; and novel excipients that are part of the final pharmaceutical product. It does not apply to cellular therapies, gene therapies, and tissue-engineered products. The methodological principles (*e.g.,* study design, dose selection, and species selection) outlined in this guidance can also apply to all compounds for which the conduct of reproductive and/or developmental toxicity studies is appropriate, including vaccines for other indications (*e.g.,* cancer). (see ICH guidance for industry ''S9 Nonclinical Evaluation for Anticancer Pharmaceuticals'' (March 2010), available at *https://www.fda.gov/media/73161/download*).

The guidance reflects revisions made in response to comments received on the draft guidance. These include reorganization of the guidance to improve readability and clarity, to introduce discussion of conventional assessment strategies earlier in the document, and to clarify which elements of the guidance are more appropriate for biotechnology-derived therapies. To accommodate the rapidly evolving nature of alternative assay development, the discussion of alternative assays was placed in an Annex, subject to a maintenance procedure, to allow for more frequent updating of this material.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on ''S5(R3) Detection of Reproductive and Developmental Toxicity for Human Pharmaceuticals.'' 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

This guidance contains no collection of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501–3521) is not required.

However, this guidance refers to previously approved FDA collections of information. These collections of information are subject to review by OMB under the PRA. The collections of information in 21 CFR part 58 have been approved under OMB control number 0910–0119; the collections of information in 21 CFR part 314 have been approved under OMB control number 0910–0001; the collections of information in 21 CFR part 312 have been approved under OMB control number 0910–0014; and the content and format requirements for pregnancy and lactation labeling of human prescription drug and biological products have been approved under OMB control number 0910–0624.

III. Electronic Access

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

Dated: May 6, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

[FR Doc. 2021–10017 Filed 5–11–21; 8:45 am]

BILLING CODE 4164–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2020–D–1370]

COVID–19: Developing Drugs and Biological Products for Treatment or Prevention; 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 final guidance for industry entitled ''COVID–19: Developing Drugs and Biological Products for Treatment or Prevention.'' This guidance describes FDA's current recommendations regarding phase 2 or phase 3 trials for drugs or biological products under development for the treatment or prevention of COVID–19. Given the public health emergency presented by COVID–19, this guidance document is being implemented without prior public comment because FDA has determined that prior public participation is not feasible or appropriate, but it remains subject to comment in accordance with the Agency's good guidance practices. This final guidance revises and replaces the final guidance of the same name issued