



4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2017-D-5138]

S5(R3) Detection of Toxicity to Reproduction for Human Pharmaceuticals; International Council for Harmonisation; Draft Guidance for Industry; Availability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SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance entitled “S5(R3) Detection of Toxicity to Reproduction for Human Pharmaceuticals.” The draft guidance was prepared under the auspices of the International Council for Harmonisation (ICH), formerly the International Conference on Harmonisation. The draft guidance replaces the existing guidance entitled “S5(R2) Detection of Toxicity to Reproduction for Human Pharmaceuticals.” The draft guidance is intended to align with other ICH guidances, elaborate on concepts to consider when designing studies, and identify potential circumstances in which a risk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.

DATES: Although you can comment on any guidance at any time (see 21 CFR 10.115 (g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: 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 Office, 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 Toxicity to Reproduction 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 Office 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 Office. 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.

Submit written requests for single copies of this draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research (CDER), 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 draft guidance document.

FOR FURTHER INFORMATION CONTACT: *Regarding the guidance:* Abigail Jacobs, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 6474, Silver Spring, MD 20993-0002, 301-796-0174; or Martin (Dave) Green, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3270, Silver Spring, MD 20993-0002, 301-796-2640. *Regarding the ICH:* Amanda Roache, Center for Drug Evaluation and Research, Food

and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 1176, Silver Spring, MD 20993-0002, 301-796-4548.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled “S5(R3) Detection of Toxicity to Reproduction for Human Pharmaceuticals.” In recent years, regulatory authorities and industry associations have participated in many important initiatives to promote international harmonization of regulatory requirements. FDA has participated in several meetings designed to enhance harmonization and is committed to seeking scientifically based, harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products for human use among regulators around the world. The six founding members of the ICH are the European Commission; the European Federation of Pharmaceutical Industries Associations; the Japanese Ministry of Health, Labour, and Welfare; the Japanese Pharmaceutical Manufacturers Association; CDER and CBER, FDA; and the Pharmaceutical Research and Manufacturers of America. The Standing Members of the ICH Association include Health Canada and Swissmedic. Any party eligible to become a member in accordance with the ICH Articles of Association can apply for membership in writing to the ICH Secretariat. The ICH Secretariat, which coordinates the preparation of

documentation, operates as an international nonprofit organization and is funded by the members of the ICH Association.

The ICH Assembly is the overarching body of the Association and includes representatives from each of the ICH members and observers.

In August 2017, the ICH Assembly endorsed the draft guidance titled “S5(R3) Detection of Toxicity to Reproduction for Human Pharmaceuticals” and agreed that the guidance should be made available for public comment. The draft guidance is the product of the S5(R3) Safety Expert Working Group of the ICH. Comments about this draft will be considered by FDA and the S5(R3) Safety Expert Working Group.

The draft guidance replaces the existing guidance entitled “S5(R2) Detection of Toxicity to Reproduction for Human Pharmaceuticals.” The guidance has undergone major 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.

To support using alternative assays, compounds that are either positive or negative in their ability to induce embryoletality or malformations are used in the process of qualifying the assays. Although a number of compounds have been identified in the draft guidance’s Annex, section 11.3.4, Tables 9-6 and 9-7, with the type of information for the compounds, the list is not complete; therefore, FDA is requesting data in the form of public comments to the docket for additional positive and negative reference compounds for potential inclusion into the list. These compounds can be either pharmaceuticals or non-pharmaceuticals and should be commercially available. For additional guidance, please refer to Endnote 3 in the S5(R3) guidance. This is not

a request for data for the compounds already listed in Table 9-6, nor is this a request for examples of assays that could be used.

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 "S5(R3) Detection of Toxicity to Reproduction 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. This guidance is not subject to Executive Order 12866.

II. Electronic Access

Persons with access to the internet may obtain the draft guidance at

<https://www.regulations.gov>,

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>,

or

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

Dated: November 2, 2017.

Anna K. Abram,

Deputy Commissioner for Policy, Planning, Legislation, and Analysis.

[FR Doc. 2017-24483 Filed: 11/9/2017 8:45 am; Publication Date: 11/13/2017]