4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2015-D-2306]

Testicular Toxicity: Evaluation During Drug Development; 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 "Testicular Toxicity: Evaluation During Drug Development." The guidance addresses nonclinical findings that may raise concerns of a drug-related adverse effect on the testes, clinical monitoring of adverse testicular effects early in clinical development, and the design and conduct of a safety clinical trial assessing drug-related testicular toxicity. The guidance is intended to assist sponsors developing drugs and therapeutic biologics regulated within the Center for Drug Evaluation and Research to identify nonclinical signals of testicular toxicity and to evaluate the potential for such toxicity in humans. This guidance finalizes the draft guidance of the same name issued on July 17, 2015.

DATES: The announcement of the guidance is published in the *Federal Register* on [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

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-2015-D-2306 for "Testicular Toxicity: Evaluation During Drug Development." 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 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. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: Jennifer Mercier, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave, Bldg. 22, Rm. 5390, Silver Spring, MD 20993-0002, 301-796-0957.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled "Testicular Toxicity: Evaluation During Drug Development." This guidance is intended to help sponsors identify nonclinical signals that raise concern regarding the potential for human testicular toxicity and to evaluate those signals appropriately in human studies.

The guidance describes the standard battery of nonclinical studies that are used to assess the effects of pharmaceuticals on the male reproductive system. The guidance discusses findings in nonclinical studies that may increase the level of concern for drug-related testicular toxicity. The

guidance provides a general approach on how to weigh the relevance of nonclinical findings, considering factors that can confound the interpretation of these findings. If a concerning nonclinical signal is identified, the guidance presents suggestions for clinical monitoring when the product is initially administered to humans.

If a reasonable basis for concern of human testicular toxicity exists, a trial with a primary objective of evaluating drug-related testicular toxicity may be warranted. The guidance provides recommendations for the design of such a trial, including study conduct, endpoints, and presentation of results. These are general recommendations for defining the role of drugs in testicular injury; however, the specific details of an individual trial may vary depending on the context of use of the drug product.

This guidance finalizes the draft guidance of the same name issued on July 17, 2015 (80 FR 42501). Changes made to the guidance took into consideration written and verbal comments received. In addition to editorial changes primarily for clarification, the major changes in the guidance include revision of information on nonclinical study design (including species selection, chronic study design, histopathology assessment, sperm quality, and findings that increase concern for impaired fertility) and revision of information that, to the extent possible, subjects enrolled in the dedicated clinical safety trial represent the intended population.

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 the evaluation of testicular toxicity during drug development. 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. Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information that 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 collections of information in 21 CFR part 312 have been approved under OMB control number 0910-0014. The collections of information in 21 CFR parts 50 and 56 ("Protection of Human Subjects: Informed Consent and Institutional Review Boards") have been approved under OMB control number 0910-0755.

III. Electronic Access

Persons with access to the internet may obtain the guidance at either https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm or https://www.regulations.gov.

Dated: October 19, 2018.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2018-23304 Filed: 10/24/2018 8:45 am; Publication Date: 10/25/2018]