4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2025-D-3403]

Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations; Draft Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA, the Agency, or we) is announcing the availability of a draft document entitled "Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations." The draft guidance document provides recommendations to sponsors who are planning clinical trials of cell and gene therapy (CGT) products intended for use in a disease or condition that affects a small population, generally one that meets the definition of a rare disease or condition under section 526(a)(2) of the FD&C Act (21 U.S.C. 360bb(a)(2)). It describes FDA requirements and provides considerations for the use of various clinical trial designs and endpoints to generate clinical evidence to support product licensure. The recommendations are intended for sponsors developing CGTs intended for use in small populations to leverage the use of innovative trial designs to simultaneously expedite drug development and generate data necessary to demonstrate substantial evidence of effectiveness.

DATES: Submit either electronic or written comments on the draft guidance by **[INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]** to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.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-2025-D-3403] for "Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations; Draft Guidance for Industry." 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 Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research

(CBER), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3103, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist the office in processing your requests. The draft guidance may also be obtained by mail by calling CBER at 1-800-835-4709 or 240-402-8010 or emailing industry.biologics@fda.hhs.gov. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Janet Goldberg, Center for Biologics Evaluation and Research, Food and Drug Administration, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft document entitled "Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations; Draft Guidance for Industry." The draft guidance document provides recommendations to sponsors who are planning clinical trials of CGT products intended for use in a disease or condition that affects a small population, generally one that meets the definition of a rare disease or condition under section 526(a)(2) of the FD&C Act (21 U.S.C. 360bb(a)(2)). It describes FDA requirements and provides considerations for the use of various clinical trial designs and endpoints to generate clinical evidence to support product licensure. The guidance expands on principles described in FDA's existing guidance documents related to this topic, by providing additional recommendations for the planning, design, conduct, and analysis of cell and gene therapy trials to facilitate FDA's assessment of product effectiveness. The recommendations are intended for sponsors developing CGTs intended for use in small populations to leverage the use of innovative trial designs to simultaneously expedite drug development and generate data necessary to demonstrate substantial evidence of effectiveness.

FDA is issuing this draft guidance in accordance with a commitment outlined in the reauthorization of the Prescription Drug User Fee Act (PDUFA VII) under the 2022 FDA User Fee Reauthorization Act.

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 "Innovative Designs for Clinical Trials of Cellular and Gene Therapy Products in Small Populations." 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.

As we develop final guidance on this topic, FDA will consider comments on costs or cost savings the guidance may generate, relevant for Executive Order 14192.

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 parts 50 and 56 pertaining to institutional review boards and the protection of human subjects, respectively, have been approved under OMB control number 0910-0130. The collections of information under 21 CFR part 312 pertaining to Investigational New Drug Applications, including clinical trials and formal meetings, have been approved under OMB control number 0910-0014. The collections of information in 21 CFR part 601 pertaining to the submissions of biologics license application product for development have been approved under OMB control number 0910-0338. The collections of information described in FDA's guidance entitled "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products" have been approved under OMB control number 0910-0297.

III. Electronic Access

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

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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