4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2023-D-5259]

Master Protocols for Drug and Biological Product Development; Draft Guidance for Industry; Availability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SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled "Master Protocols for Drug and Biological Product Development." This draft guidance revises and replaces the previous draft guidance for industry of the same name issued on December 22, 2023. The draft guidance provides recommendations on the design and analysis of trials conducted under a master protocol as well as guidance on submissions to support regulatory review. The primary focus is on randomized trials utilizing a master protocol that are intended to contribute to a demonstration of safety and substantial evidence of effectiveness. The considerations in this guidance apply to a range of therapeutic areas. The draft guidance is intended to clarify the Agency's thinking on the use of master protocols in drug and biological product development.

DATES: Submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.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-2023-D-5259 for "Master Protocols for Drug and Biological Product 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, 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: Scott N. Goldie, Center for Drug Evaluation and Research, Office of Biostatistics, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 21, Rm. 3557, Silver Spring, MD 20993-0002, 301-796-2055, or Phillip Kurs, 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 guidance for industry entitled "Master Protocols for Drug and Biological Product Development." This draft guidance revises and replaces the previous draft guidance for industry of the same name issued on December 22, 2023, and reflects FDA's consideration of public comments on the draft guidance. The draft guidance provides recommendations on the design and analysis of trials conducted under a master protocol as well as guidance on submissions to support regulatory review. The primary focus of this guidance is on randomized trials utilizing a master protocol that are intended to contribute to a demonstration of safety and substantial evidence of effectiveness. The concepts discussed may also be useful to consider for early-phase or exploratory trials under a master protocol as well as those conducted to satisfy post-marketing commitments or requirements. The considerations in this guidance apply to a range of therapeutic areas.

Well-designed and -conducted trials using master protocols can accelerate drug development by maximizing the amount of information obtained from the research effort. Compared with stand-alone trials under separate protocols, a master protocol may offer logistical advantages by leveraging shared protocol elements (e.g., visit schedule, measurement procedures), shared infrastructure (e.g., network of clinical sites, central facilities, central randomization system, data management systems), and shared oversight (e.g., steering committee, data review committee). Some master protocols may also improve efficiency by

leveraging a shared control arm in evaluating multiple drugs or by leveraging information on drug effects across multiple related diseases, conditions, or disease subtypes. At the same time, master protocols add elements of complexity, which can increase start-up time and can lead to design challenges such as ensuring adequate blinding to treatment assignment. Additionally, master protocols involving multiple interested parties will require a high degree of coordination. The draft guidance is intended to clarify the Agency's thinking on the use of master protocols in drug and biological product development.

The guidance discusses important considerations for master protocols related to the following design and analysis topics: randomization, control group, informed consent, blinding to treatment assignment, adaptive design, comparisons between drugs, approaches for evaluating drug effects in multiple diseases, conditions, or disease subtypes, multiplicity, and safety. The guidance also discusses considerations on trial oversight, data sharing, dissemination of information, and submissions to support regulatory review.

FDA is issuing a revised draft guidance in response to public comments received on the original draft requesting that FDA provide additional recommendations on basket trials. Changes from the original draft include more detailed recommendations regarding basket trials and minor changes for clarity on topics such as randomization, choice of control, and informed consent.

FDA is issuing this revised draft guidance to satisfy, in part, a mandate under section 3607(b)(2)(C-F) of the Food and Drug Omnibus Reform Act of 2022 (FDORA) found in Title III, Subtitle F of the Consolidated Appropriations Act, 2023. Consistent with the FDORA mandate, this guidance discusses recommendations for clinical trials to streamline logistics and facilitate the efficient collection and analysis of data, as well as important principles for the evaluation of effectiveness, recommendations for communication between sponsors and the FDA, and considerations related to ensuring participant safety and data integrity in such trials.

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 "Master Protocols for Drug and Biological Product 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.

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 relating to the submission of investigational new drug applications, including protocols, protocol amendments, and information amendments, as well as the information collection in FDA's guidance for industry entitled "Establishment and Operation of Clinical Trial Data Monitoring Committees" and "Oversight of Clinical Investigations--A Risk-Based Approach to Monitoring", have been approved under OMB control number 0910-0014. The collections of information in 21 CFR part 314 pertaining to new drug applications including abbreviated new drug applications) and related guidances 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. The collections of information in 21 CFR parts 50 and 56 relating to the protection of human subjects and institutional review boards have been approved under OMB control number 0910-0130. The collections of information in 45 CFR part 46 relating to the protection of human subjects and IRB recordkeeping have been approved under OMB control number 0990-0260. The collections of information in 21 CFR part 11 relating to electronic records and signatures have been approved under OMB control number 0910-0303. The collections of information in 21 CFR part 312, subpart E relating to FDA's guidance for industry entitled "Expedited Programs for Serious Conditions--Drugs and Biologics" have been approved under OMB control number 0910-0765.

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.

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/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.

[FR Doc. 2026-12620 Filed: 6/22/2026 11:15 am; Publication Date: 6/24/2026]