4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2018-D-3124]

Adaptive Designs for Clinical Trials of Drugs and Biologics; Draft Guidance for Industry; Availability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SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a draft guidance for industry entitled "Adaptive Designs for Clinical Trials of Drugs and Biologics." This document provides guidance to sponsors and applicants submitting investigational new drug applications (INDs), new drug applications (NDAs), biologics license applications (BLAs), or supplemental applications on the appropriate use of adaptive designs for clinical trials to provide evidence of the effectiveness and safety of a drug or biologic. The guidance describes the basic principles for designing, conducting, and reporting the results from an adaptive clinical trial. The draft guidance will replace the 2010 draft guidance for industry entitled "Adaptive Design Clinical Trials for Drugs and Biologics."

DATES: Submit either electronic or written comments on the draft guidance by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.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-2018-D-3124 for "Adaptive Designs for Clinical Trials of Drugs and Biologics; 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 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. 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 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; or to the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, 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: Scott Goldie, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 21, Rm. 3557, Silver Spring, MD 20993-0002, 301-794-2055; 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.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled "Adaptive Designs for Clinical Trials of Drugs and Biologics." This document provides guidance to sponsors and applicants submitting INDs, NDAs, BLAs, or supplemental applications on the

appropriate use of adaptive designs for clinical trials to provide evidence of the effectiveness and safety of a drug or biologic. The guidance describes the basic principles for designing, conducting, and reporting the results from an adaptive clinical trial. The guidance also advises sponsors on the types of information FDA needs to evaluate the results from clinical trials with adaptive designs, including Bayesian adaptive designs and complex designs that rely on computer simulations for their design. This guidance meets FDA's performance commitment under PDUFA (Prescription Drug User Fee Act) VI to publish draft guidance on complex adaptive (including Bayesian adaptive) trial designs by the end of fiscal year 2018.

The primary focus of this guidance is on adaptive designs for clinical trials intended to support the effectiveness and safety of drugs or biologics. The concepts discussed are also useful for early phase or exploratory clinical trials as well as trials conducted to satisfy postmarketing commitments or requirements. The draft guidance will replace the 2010 draft guidance for industry entitled "Adaptive Design Clinical Trials for Drugs and Biologics."

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 "Adaptive Designs for Clinical Trials of Drugs and Biologics." 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

Under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3520), Federal Agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information that they conduct or sponsor. "Collection of information" is defined in

44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal Agencies to provide a 60-day notice in the *Federal Register* for each proposed collection of information before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing this notice of the proposed collection of information set forth in this document.

With respect to the collection of information associated with this draft guidance, FDA invites comments on the following topics: (1) whether the proposed information collected is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimated burden of the proposed information collected, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information collected; and (4) ways to minimize the burden of information collected on the respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

The draft guidance discusses several collections of information that have been approved by OMB. For example, the draft guidance explains that sponsors who have questions about adaptive design elements in an early-phase exploratory trial should seek FDA feedback by either identifying specific questions in a submission containing the protocol or by requesting a meeting to discuss those questions. Discussion of the plans for an adaptive trial can be the basis for requesting a Type C meeting. Regulatory mechanisms for obtaining formal, substantive feedback from FDA on clinical trials may also include end-of-phase 2 meetings. The draft guidance also recommends that special protocol assessments (given the 45-day response timeline) are submitted for trials with complex adaptive designs only if there has been extensive

previous discussion between FDA and the sponsor regarding the proposed trial and design. The draft guidance explains that in their submissions, the sponsors should pre-specify the details of the adaptive design and provide justification that the chances of erroneous conclusions will be adequately controlled, estimation of treatment effects will be sufficiently reliable, and trial integrity will be appropriately maintained. The draft guidance notes that the sponsor should advise FDA during the course of a trial of any proposed changes to the trial design (usually through protocol amendments), and that FDA may request that the sponsor submit minutes from open sessions of a monitoring committee during an ongoing trial.

FDA has OMB approval under the PRA for the submission of INDs, including protocol amendments and information amendments, in 21 CFR part 312, subpart B, and sponsors may request comment and advice on an IND as well as request meetings with FDA under subpart C (OMB control number 0910-0014). In addition, the following collections of information that have been approved by OMB would cover other submissions discussed in the draft guidance:

- Guidance for industry on formal meetings with sponsors and applicants for PDUFA products (OMB control number 0910-0429);
- Guidance for Industry on special protocol assessment (OMB control number 0910-0470);
- Guidance for industry on clinical trial data monitoring committees (OMB control number 0910-0581);
- Guidance for industry on oversight of clinical investigations (OMB control number 0910-0733);
- International Council for Harmonization guidance for industry "E6(R2) Good Clinical Practice" (OMB control number 0910-0843)
- Protection of Human Subjects: Informed Consent; Institutional Review Boards (21 CFR parts 50 and 56) (OMB control number 0910-0755);
- Institutional Review Boards (21 CFR 56.115) (OMB control number 0910-0130); and

- Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products (OMB control number 0910-0572).

In addition, the submission of NDAs, including 21 CFR 314.50(d)(5) (clinical data section) and (d)(6) (statistical section), has been approved under OMB control number 0910-0001. The submission of BLAs and their supplements has been approved under OMB control number 0910-0338.

The draft guidance also requests the submission of information that has not been approved by OMB under the PRA.

In section VIII.B, the draft guidance states that the documented plan for a clinical trial with a proposed adaptive design should include the information described below. The information could be included in the clinical trial protocol and/or in separate documents, such as a statistical analysis plan, a data monitoring committee (DMC) charter, or an adaptation committee charter. Although different types of information might be included in different documents, all important information described below should be submitted to FDA during the design stage so that FDA has sufficient time to provide feedback prior to initiation of the clinical trial:

- A rationale for the selected design;
- A detailed description of the monitoring and adaptation plan, including the anticipated number and timing of interim analyses, the specific aspects of the design that may be modified, and the specific rule that will be used to make adaptation decisions;
- Information on the roles of the bodies responsible for implementing the adaptive design, such as the DMC and/or the dedicated adaptation committee;

- Pre-specification of the statistical methods that will be used to produce interim results and guide adaptation decisions, and to carry out hypothesis tests, estimate treatment effects, and estimate uncertainty in treatment effect estimates at the end of the trial;
- Evaluation and discussion of the design operating characteristics;
- When simulations are the primary or sole technique for evaluating trial operating characteristics, a detailed simulation report should be submitted, including:
    - An overall description of the trial design;
    - Example trials, in which a small number of hypothetical trials are described with different conclusions, such as a positive trial with the original sample size, a trial stopped for futility after the first interim look, a positive trial after increasing the sample size;
    - A description of the set of parameter configurations used for the simulation scenarios, including a justification of the adequacy of the choices;
    - Simulation results detailing the estimated Type I error probability and power under the various scenarios;
    - Simulation code that is readable and adequately commented and should include the random seeds used to generate the simulation results;
    - A summary providing overall conclusions.
- A comprehensive written data access plan defining how trial integrity will be maintained in the presence of the planned adaptations. This documentation should include the following information: (1) the personnel who will perform the interim analyses; (2) the personnel who will have access to interim results; (3) how that access will be controlled; (4) how adaptive decisions will be made; and (5) what type of information will be disseminated following adaptive decisions, and to whom it will be disseminated. The data access plan should describe what information, under what circumstances, is permitted to be passed to the sponsor or investigators. In addition, it is recommended that sponsors establish procedures to evaluate compliance with the data access plan and to document all interim

meetings of the committee tasked with making adaptation decisions, i.e., the DMC or other adaptation committee (e.g., with written minutes describing what was reviewed, discussed, and decided).

In section VIII.C, the draft guidance states that a marketing application to FDA that relies on a trial with an adaptive design should include, in addition to the typical content of that marketing application, sufficient information and documentation to allow FDA to thoroughly review the results, including:

- All prospective plans, any relevant committee charters (e.g., the DMC or adaptation committee charter), and any supporting documentation (e.g., literature references, programming code, simulation report);
- Information on compliance with the planned adaptation rule and with the procedures outlined in the data access plan to maintain trial integrity;
- Records of deliberations and participants for any interim discussions by any committees involved in the adaptive process;
- Results of the interim analyses used for the adaptation decisions;
- Appropriate reporting of the adaptive design and trial results in the proposed package insert. For example, the trial summary should describe the adaptive design utilized. In addition, treatment effect estimates should appropriately take the design into account, or if naïve estimates such as unadjusted sample means are used, the extent of bias should be evaluated and estimates should be presented with appropriate cautions regarding their interpretation.

Based on our review of INDs, NDAs, BLAs, and supplemental applications for the use of adaptive designs for clinical trials to provide evidence of effectiveness and safety, we estimate that approximately 40 sponsors or applicants ("number of respondents" in table 1, row 1) will prepare approximately 240 documented plans for clinical trials containing a proposed adaptive design and analysis plan and will submit this information to FDA in a clinical trial protocol and/or in separate documents such as a statistical analysis plan, a DMC charter, or an adaptation

committee charter ("total annual responses" in table 1, row 1), and that preparing and submitting this information will take approximately 50 hours per sponsor or applicant ("average burden per response" in table 1, row 1).

In addition, we estimate that approximately 15 sponsors or applicants ("number of respondents" in table 1, row 2) will prepare and submit to FDA approximately 20 marketing applications that rely on a trial with an adaptive design ("total annual responses" in table 1, row 2), and that preparing and submitting this information will take approximately 50 hours per sponsor or applicant ("average burden per response" in table 1, row 2).

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden[1]

Guidance on Adaptive Designs for Clinical Trials of Drugs and Biologics	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Clinical trial protocols and related submissions to FDA with an adaptive design and analysis plan should contain the information in section VIII.B	40	6	240	50	12,000
Marketing applications that rely on studies with an adaptive design should contain the information in section VIII.C	15	1.33	20	50	1,000
Total					13,000

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

III. Electronic Access

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

Dated: September 25, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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