4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2002-D-0176 (formerly Docket No. 2002D-0350)]

Handling and Retention of Bioavailability and Bioequivalence Testing Samples; Guidance for Industry (Part Draft, Part Final); 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 guidance for industry entitled "Handling and Retention of BA and BE Testing Samples." This guidance is intended to provide recommendations for applicants of new drug applications (NDAs) and abbreviated new drug applications (ANDAs), including supplemental applications, and contract research organizations (CROs), regarding the procedures for handling reserve samples from relevant bioavailability (BA) and bioequivalence (BE) studies, and recommendations regarding responsibilities of each party involved in the study pertaining to reserve samples. Additionally, this guidance describes the conditions under which the Agency generally does not intend to take enforcement action against an applicant or CRO that retains less than the quantity of reserve samples specified in the regulation.

DATES: Submit either electronic or written comments on the draft portion of this 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60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*] to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance. Comments on the final portion of this guidance may be submitted at any time for Agency consideration.

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-2002-D-0176 (formerly Docket No. 2002D-0350) for "Handling and Retention of BA and BE Testing Samples." 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 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: Melissa Mannion, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 240-672-5296, Melissa.Mannion@fda.hhs.gov.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled "Handling and Retention of BA and BE Testing Samples." This guidance is a revision of the previously issued final guidance of the same name from May 2004 and is intended to provide recommendations for applicants of NDAs and ANDAs, including supplemental applications, and CROs, regarding the procedures for handling reserve samples from relevant BA and BE studies, as required by §§ 320.38 and 320.63 (21 CFR 320.38 and 320.63), and recommendations regarding responsibilities of each party involved in the study pertaining to reserve samples. Additionally, this guidance revises and supersedes the Agency's compliance policy related to the quantity of BA and BE samples retained under FDA regulations described in the final guidance entitled "Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c)" (August 2020) (the 2020 Compliance Policy), which is hereby withdrawn.

This guidance is issued in part as final guidance and in part as draft guidance. Specifically, section IV.B. of this guidance is issued as final guidance for immediate implementation. It revises and supersedes the Agency's compliance policy related to the quantity of BA and BE samples retained under § 320.38(c) (21 CFR 320.38(c)) described in the 2020 Compliance Policy, and describes the conditions under which the Agency generally does not intend to take enforcement action against an applicant or CRO that retains less than the quantity of reserve samples (that is, samples of the test article (T) and reference standard (RS) that were used in an in vivo BA or in vivo or in vitro BE study) specified in the regulation. It

also supersedes statements related to quantity of reserve samples in section IX. Number of Reserve Samples for BA and BE Testing of the draft guidance entitled "Nasal Aerosols and Nasal Sprays for Local Action" (April 2003).

In accordance with section 701(h)(1)(C)(i) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 371(h)(1)(C)(i)) and the good guidance practices (GGP) regulation (§ 10.115 (21 CFR 10.115)), the Agency is immediately implementing section IV.B. of the guidance on the quantity of reserve samples without prior public comment because FDA has determined that prior public participation is not feasible or appropriate as public comment would not affect the specifications of FDA's testing of retention samples (§ 10.115(g)(2)). FDA has made this determination under § 10.115(g)(2) because, with technological advances, the reduced quantity of reserve samples is sufficient for FDA testing; this reduced quantity will provide a less burdensome approach for applicants and CROs but remains consistent with the Agency's mission to ensure public health. Although this subsection of the guidance document is immediately in effect, it remains subject to comment in accordance with FDA's GGP regulation and FDA will consider all comments received and revise the guidance document as appropriate (§ 10.115(g)(3)). The remainder of the guidance is being issued in draft, consistent with the GGP regulation, to solicit public comment prior to implementation.

In the *Federal Register* on November 8, 1990 (55 FR 47034), FDA issued an interim rule that amended, in relevant part, part 320 (21 CFR part 320), by adding a requirement to retain reserve samples of certain drug products (that is, samples of the drug products that were used to conduct BA or BE studies) for a specified period and, when specifically requested, to release the reserve samples to the Agency. The interim rule was intended largely to help ensure BE between generic drugs and their reference listed drugs and to help FDA investigate possible fraud in BA and BE testing. After consideration of public comments, FDA published a final rule in the *Federal Register* on April 28, 1993 (58 FR 25918).

In the final rule, §§ 320.38 and 320.63 require an NDA or ANDA applicant (or, if testing is performed under contract, its CRO) to retain reserve samples of the T and RS that were used to conduct certain in vivo BA studies or an in vivo or in vitro BE study submitted in support of the approval of an application or supplemental application. In the preamble to the final rule, the Agency stated that the study sponsor and/or drug manufacturer should not separate out the reserve samples of the T and RS before sending the drug product to the testing site, to ensure that the reserve samples are in fact representative of the drug product provided by the study sponsor and/or drug manufacturer for the testing. The Agency also noted that the organization that conducts the BA or BE study is responsible for retaining the reserve samples to eliminate potential sample substitution by the study sponsor and/or drug manufacturer and alteration of any reserve samples from a study before release of drug product samples to FDA.

FDA has observed a number of concerning handling and retention practices upon inspections of clinical and analytical sites that perform BA and BE studies for study sponsors and/or drug manufacturers seeking approval of drug products under NDAs and ANDAs. Based on this experience, FDA is updating and clarifying our recommendations for applicants of NDAs and ANDAs, including supplemental applications, and CROs regarding the procedures related to the handling and retention of reserve samples from relevant BA and BE studies, as required by §§ 320.38 and 320.63. In the context of §§ 320.38 and 320.63, the term applicant includes, as appropriate, study sponsor and/or drug manufacturer and the term CRO refers to any party contracted to help conduct BA or BE testing, including, as appropriate, site management organizations, investigators, and testing sites. Specifically, the guidance highlights: (1) how the T and RS for BA and BE studies should be distributed to the testing sites, (2) how testing sites should randomly select samples for testing and material to maintain as reserve samples, and (3) how the reserve samples should be retained. Examples of typical roles of each stakeholder for the handling and retention of reserve samples in various study settings are also discussed in the guidance.

In response to comments received to the August 2020 Compliance Policy, the Agency has updated its policy on the conditions under which FDA generally does not intend to enforce the quantity requirement at § 320.38(c) (to retain reserve samples of sufficient quantity to permit FDA to perform five times all the release tests required in an application or supplemental application) to reduce further the recommended minimum quantity of reserve samples to be retained. The additional reduction in the recommended minimum quantity described in this guidance relative to what was described in the August 2020 Compliance Policy is reflective of adjustments made to the Agency's procedures to accommodate continued concerns from industry, particularly for studies involving multiple shipments to multiple testing sites, regarding the ability to retain a sufficient quantity of reserve samples.

FDA has determined that, using the Agency's current testing methodology, the updated recommended minimum quantities of reserve samples described in this guidance are sufficient for FDA to conduct the necessary testing of the T and RS samples used in a BA or BE study as intended by the regulation. Accordingly, at this time and based on FDA's current understanding of the risks involved, FDA generally does not intend to enforce the requirement to retain a sufficient quantity to perform five times all the release tests required in the application or supplemental application, so long as the recommended lower quantities in this guidance are retained. This compliance policy is applicable to all reserve samples for BA and BE studies held to date, including reserve samples from previously completed BA or BE studies.

This guidance is being issued consistent with FDA's GGP regulation (§ 10.115). The draft portion of the guidance, when finalized, will represent the current thinking of FDA on "Handling and Retention of BA and BE Testing Samples." A guidance 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 for investigational new drug products have been approved under OMB control number 0910-0014. The collections of information in 21 CFR part 314 for new drug applications and abbreviated new drug applications have been approved under OMB control number 0910-0001. The collections of information in part 320 for "Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans" have been approved under OMB control number 0910-0672. The recordkeeping requirement for current good manufacturing practice sample retention in 21 CFR 211.170 has been approved under OMB control number 0910-0139.

III. Electronic Access

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

Dated: March 22, 2024.

Lauren K. Roth,

Associate Commissioner for Policy.

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