Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c)

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact Melissa Mannion, 301-796-2747.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2020
Procedural

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Contains Nonbinding Recommendations

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Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38(c) Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. 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. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes FDA's compliance policy related to the retention of reserve samples of the test article and reference standard[2] used in an in vivo bioavailability (BA) and in vivo or in vitro bioequivalence (BE) study. Specifically, this guidance:

- Addresses the requirement at 21 CFR 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

- Describes the conditions under which the Agency does not generally intend to take enforcement action against an applicant or contract research organization (CRO) for retaining less than the quantity of reserve samples of the test article and reference standard that were used in the BA or BE study as specified in 21 CFR 320.38(c).

This guidance applies only to the requirements for retention of reserve samples contained in 21 CFR 320.38(c). This guidance does not apply to the other requirements for retention of reserve samples contained in 21 CFR 320.38, such as how testing facilities must select samples for testing, how the reserve samples must be retained, and whether reserve samples are in fact representative of the test article and reference standard used in the BA or BE study. Additionally, this guidance does not apply to the requirement in 21 CFR 211.170 to retain samples under current good manufacturing practices.

[1] This guidance has been prepared by the Office of Generic Drugs, Office of Compliance, and Office of Translational Sciences in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] A *reference standard* is the drug product selected by FDA that an applicant seeking approval of an abbreviated new drug application must use in conducting an in vivo bioequivalence study required for approval. 21 CFR 314.3(b).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

On November 8, 1990, FDA issued an interim rule that amended, in relevant part, 21 CFR 320 to require applicants to (1) retain, for a specified period, reserve samples of drug products used to conduct BA or BE studies and (2) release the reserve samples to FDA when specifically requested.[3] The interim rule was intended to help ensure BE between generic drugs and their reference listed drug[4] and to help FDA investigate possible fraud in BA and BE testing. After consideration of public comments, a final rule was published in the *Federal Register* on April 28, 1993.[5]

This final rule requires a new drug application (NDA) or abbreviated new drug application (ANDA) applicant to retain a quantity of the test article and reference standard used in BA or BE testing that is at least five times the amount of product required for release testing.[6] Specifically, 21 CFR 320.38 and 320.63 require the applicant (or its CRO) to retain reserve samples of the test article and reference standard used in conducting any in vivo BA and in vivo or in vitro BE study that support the approval of its application or supplemental application.

21 CFR 320.38(c) requires that applicants retain reserve samples of the test product and reference standard used in a BA or BE study that consist of a sufficient quantity to perform five times all the release tests required in the application or supplemental application.[7] Under the regulations, for solid oral dosage forms (e.g., tablets, capsules), applicants may be required to retain as many as 300 units each of the test article and reference standard to meet this requirement.

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[3] 55 FR 47034 (Nov. 8, 1990).

[4] A *reference listed drug* is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA. 21 CFR 314.3(b). Generally, the reference listed drug will be the drug product selected by the Agency as the reference standard for conducting in vivo BE testing.

[5] 58 FR 25918 (Apr. 28, 1993).

[6] 21 CFR 320.38(c) and 320.63.

[7] See also guidance for industry *Handling and Retention of BA and BE Testing Sample*, which discusses recommendations for applicants and/or drug manufacturers, CROs, site management organizations, clinical investigators, and independent third parties regarding the procedure for handling reserve samples from relevant BA and BE studies, as required by 21 CFR 320.38 and 320.63. We update guidances periodically. For the most updated version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

Since the final rule was issued in 1993, technological advances in FDA's ability to test these products have led to test methods that are less destructive and more sensitive, allowing FDA to detect the identity and composition of the test article and reference standard with smaller volumes of samples. As such, under current physicochemical testing, the Agency generally needs, for products manufactured in single-dose units, 30 units each of the test article and reference standard from each shipment or, for products manufactured in multi-dose units, 3 units each of the test article and reference standard from each shipment, to conduct the necessary testing of the samples. Consistent with these developments, FDA has received communications from applicants and CROs requesting to retain a lower quantity of the reserve samples.

In light of these technological advances, FDA finds it appropriate for applicants (or their CROs) to retain a quantity of samples less than what is specified in 21 CFR 320.38(c) when FDA has determined that the lower quantity of reserve samples is sufficient for FDA to conduct the necessary "chemical and physical examination of the samples to assure the identity and composition of the test article and reference standard" intended by the regulation.[8] Accordingly, at this time and based on our current understanding of the risks involved, FDA 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 identified lower quantities are retained.

III. COMPLIANCE POLICY FOR THE QUANTITY OF SAMPLES RETAINED UNDER 21 CFR 320.38(c)

In light of the technological advances in FDA's ability to test retention samples, FDA does not intend to take action for violations of 21 CFR 320.38(c) against an NDA or ANDA applicant (or its CRO) if the quantity of samples retained is sufficient for all Agency testing.[9] Appendix 1 of this guidance provides a list of the minimum sample retention quantities that FDA currently considers sufficient for all Agency testing for certain products. If a product is included on this list, FDA does not intend to take action against an applicant for a violation of 21 CFR 320.38(c) if the applicant retains a quantity of samples consistent with what is indicated on this list. For products not included in Appendix 1, NDA and ANDA applicants or CROs should submit requests that FDA not take action if they wish to retain less than the quantity of reserve samples of the test article and reference standard used in BA or BE testing set forth in 21 CFR 320.38(c).

Requests that are specific to an element of generic drug product development, such as the retention of BA/BE samples, should be submitted to the Agency as a controlled correspondence. The guidance for industry *Controlled Correspondence Related to Generic Drug Development* discusses the types of requests that would be considered a controlled correspondence, what

[8] 58 FR 25918, 25923 (Apr. 28, 1993).

[9] *Agency testing* refers to FDA's "chemical and physical examination of the [reserve] samples to assure the identity and composition of the test article and reference standard" used in a BA or BE study. See 58 FR 25918, 25923 (Apr. 28, 1993).

information requestors can include in a controlled correspondence to facilitate FDA's consideration of and response to a controlled correspondence, and how to submit a controlled correspondence to FDA.[10]

[10] We update guidances periodically. For the most updated version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

APPENDIX 1

Minimum Sample Retention Quantities Sufficient for All Agency Testing[11]

For drug products that are manufactured in single-dose units (i.e., a single unit[12] is designed to provide a single dose of the drug product), FDA 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 minimum quantity of drug product for sample retention is 30 units each of the test article and reference standard from each shipment is retained.[13] The drug products listed in Table 1 are generally manufactured in single-dose units.

Table 1. Drug Products Manufactured in Single-Dose Units

Route of Administration	Dosage Form
Buccal	Film
Oral	Capsule
Oral	Granule
Oral	Solution (Single-Dose Container)
Oral	Tablet
Oral	Troche/Lozenge
Transdermal	Film
Sublingual	Tablet
Transdermal	Patch
Urethral	Suppository
Vaginal	Insert
Vaginal	Ring
Vaginal	Suppository
Vaginal	Tablet
Intramuscular	Injectable
Subcutaneous	Injection

For drug products that are manufactured in multi-dose units (i.e., a single unit is designed to provide more than a single dose of the drug product), FDA 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 minimum quantity of drug product for sample retention is 3 units each of the test article and reference standard from each shipment is retained.[14] The drug products listed in Table 2 are generally manufactured in multi-dose units.

[11] This is a list of common drug products of interest and not designed to be an exhaustive list.

[12] The term *unit* refers to the individual drug product to be dispensed or administered to study subjects. For example, *30 units of an oral tablet* means 30 oral tablets.

[13] Requests for a reduction in the quantity of reserve samples for studies involving multiple shipments and study sites (e.g., comparative clinical endpoint studies), including any unusual circumstances that may prevent a particular study from retaining samples from each shipment, will be addressed on a case-by-case basis.

[14] See footnote 13.

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Route of Administration	Dosage Form
Dental	Powder
Endocervical	Gel
Inhalation	Aerosol
Inhalation	Powder
Inhalation	Spray
Intramuscular	Injectable
Nasal	Aerosol
Nasal	Spray
Ophthalmic	Emulsion
Ophthalmic	Ointment
Ophthalmic	Solution
Ophthalmic	Suspension
Oral	Solution (Multi-Dose Container)
Oral	Suspension
Otic	Suspension
Rectal	Aerosol
Rectal	Enema
Rectal	Foam
Rectal	Gel
Subcutaneous	Implant
Subcutaneous	Injection
Sublingual	Spray
Topical	Cream
Topical	Foam
Topical	Gel
Topical	Lotion
Topical	Ointment
Topical	Shampoo
Topical	Solution
Topical	Spray
Topical	Swab
Topical	Suspension
Vaginal	Cream
Vaginal	Gel
Vaginal	Ointment

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