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**Temporary Policy for
Compounding of Certain Drugs for
Hospitalized Patients by
Outsourcing Facilities During the
COVID-19 Public Health
Emergency (Revised)**

Guidance for Industry

**April 2020
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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Office of Compliance**

Preface

Public Comment

This guidance is being issued to address the Coronavirus Disease 2019 (COVID-19) public health emergency. This guidance is being implemented without prior public comment because the Food and Drug Administration (FDA or Agency) has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

Comments may be submitted at any time for Agency consideration. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <https://www.regulations.gov>. All comments should be identified with the docket number FDA-2020-D-1136 and complete title of the guidance in the request.

Additional Copies

Additional copies are available from the FDA webpage titled "COVID-19-Related Guidance Documents for Industry, FDA Staff, and Other Stakeholders," *available at* <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>, and the FDA webpage titled "Search for FDA Guidance Documents," *available at* <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>. You may also send an e-mail request to compounding@fda.hhs.gov to receive an additional copy of the guidance. Please include the document number FDA-2020-D-1136 and complete title of the guidance in the request.

Questions

For questions about this document, contact FDA's human drug compounding team at compounding@fda.hhs.gov.

Table of Contents

I. Introduction.....	1
II. Background.....	2
III. Discussion.....	3
Appendix A: Stability/Expiration Dating For Compounded Drug Products.....	6
Appendix B: Conditions Under which FDA Generally Does Not Intend to Take Regulatory Action Regarding Stability Testing and Expiration Date Requirements	10

Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Outsourcing Facilities During the COVID-19 Public Health Emergency (Revised)

Guidance for Industry

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 staff or Office responsible for this guidance as listed on the title page.

I. Introduction

FDA plays a critical role in protecting the United States from threats such as emerging infectious diseases, including the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

FDA is issuing this guidance to communicate its temporary policy for the compounding of certain human drug products for hospitalized patients by outsourcing facilities that have registered with FDA under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353b).

This policy is intended to remain in effect only for the duration of the public health emergency related to COVID-19 declared by the Department of Health and Human Services (HHS), including any renewals made by the HHS Secretary in accordance with section 319(a)(2) of the Public Health Service Act (42 U.S.C. 247d(a)(2)). As noted below, the drugs that are the subject of this policy may change during the emergency.

Given this public health emergency, and as discussed in the Notice in the *Federal Register* of March 25, 2020 (85 FR 16949), titled “Process for Making Available Guidance Documents Related to Coronavirus Disease 2019,” available at <https://www.govinfo.gov/content/pkg/FR-2020-03-25/pdf/2020-06222.pdf>, this guidance is being implemented without prior public comment because FDA has determined that prior public participation for this guidance is not feasible or appropriate (see section 701(h)(1)(C) of the FD&C Act (21 U.S.C. 371(h)(1)(C)) and 21 CFR 10.115(g)(2)).

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This guidance document is being implemented immediately, but it remains subject to comment in accordance with the Agency's good guidance practices.

In general, FDA's guidance documents, including this guidance, 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 guidance means that something is suggested or recommended, but not required.

II. Background

There is currently an outbreak of respiratory disease caused by a novel coronavirus. The virus has been named "SARS-CoV-2" and the disease it causes has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, HHS issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.¹ In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.²

FDA has received a number of reports related to increased demand and supply interruptions involving FDA-approved drug products used in the treatment of hospitalized patients with COVID-19. Many of these drug products are needed to support COVID-19 patients who have been intubated, or for other procedures involved in the care of such patients. Some reports involve drug products that appear on the drug shortage list in effect under section 506E of the FD&C Act (21 U.S.C. 356e) ("FDA's drug shortage list"). In addition, with respect to certain other drug products needed to support hospitalized COVID-19 patients but that do not appear on FDA's drug shortage list, certain hospitals have concerns about accessing them due, for example, to regional disparities in COVID-19 infection rates, or other regional conditions that may evolve quickly during the public health emergency.

FDA is working with manufacturers in the global pharmaceutical supply chain to prevent and mitigate drug shortages and access problems, using all of the Agency's authorities to restore or increase the supply of FDA-approved drug products.

Under the FD&C Act, outsourcing facilities may legally compound drug products that are identical or nearly identical to FDA-approved products that appear on FDA's drug shortage list.³

¹ Secretary of Health and Human Services Alex M. Azar, Determination that a Public Health Emergency Exists. (Jan. 31, 2020, renewed April 21, 2020), available at <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>.

² Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19) Outbreak (Mar. 13, 2020), available at <https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/>.

³ A human drug product compounded by or under the direct supervision of a licensed pharmacist in an outsourcing facility can qualify for exemptions from requirements under three sections of the FD&C Act: labeling with adequate directions for use (section 502(f)(1) (21 U.S.C. 352(f)(1)); new drug approval requirements (section 505 (21 U.S.C. 355)); and drug supply chain security requirements (section 582 (21 U.S.C. 360eee-1)) if all of the conditions in section 503B of the FD&C Act (21 U.S.C. 353b) are met. Although an outsourcing facility may not compound a drug product that is essentially a copy of one or more approved drugs (section 503B(a)(5) of the FD&C Act), a compounded drug product does not violate this condition if it is identical or nearly identical to an approved drug that appears on shortage list in effect under section 506E of the FD&C Act (FDA's "drug shortage list") at the time of compounding, distribution, and dispensing (section 503B(d)(2)(B)(i) of the FD&C Act). Further, if an outsourcing facility uses a bulk drug substance

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Outsourcing facilities are required to register with FDA, are inspected by FDA according to a risk-based schedule, and are subject to current good manufacturing process (CGMP) requirements, among other conditions and requirements.⁴ However, the drug products made by outsourcing facilities do not receive premarket review to ensure safety, efficacy, and quality, and outsourcing facilities are restricted in their ability to compound drugs that are not on FDA's drug shortage list.⁵ Further, CGMP requirements include a requirement to conduct stability studies to support the assignment of a product expiration date, which the facilities may not yet have completed for drugs in critical need.⁶

III. Discussion

Many hospitals are currently experiencing difficulties accessing FDA-approved drug products used for patients with COVID-19. In addition, due to the large number of persons infected with COVID-19 and subsequent hospitalizations, it is possible that other FDA-approved drug products may become unavailable in the future.

As noted above, FDA generally tries to address potential and actual drug shortages by working through the global pharmaceutical supply chain rather than relying on compounded drugs and focuses on restoring supplies of FDA-approved drugs. However, in light of unprecedented disruptions to, and demands on, the global pharmaceutical supply chain as a result of the COVID-19 pandemic, and in order to respond to evolving regional conditions, additional flexibility is temporarily needed to ensure that treatment options are available when hospitals are unable to obtain FDA-approved drugs used for hospitalized patients with COVID-19.

Therefore, as a temporary measure during the public health emergency related to COVID-19, or until FDA otherwise withdraws or revises this guidance, FDA does not intend to take action against an outsourcing facility for compounding a drug product that is essentially a copy of an approved drug,⁷ for using a bulk drug substance that is not on FDA's 503B Bulks List,⁸ or for not

to compound a drug that appears on FDA's drug shortage list at the time of compounding, distribution, and dispensing, it meets the condition in Section 503B(a)(2)(A)(ii) of the FD&C Act.

⁴ See, generally, section 503B of the FD&C Act.

⁵ See section 503B(a)(2)(A) of the FD&C Act (bulk drug substances not used to compound a drug on FDA's drug shortage list must be on a list of substances established by the Secretary for which there is a clinical need) and section 503B(a)(5) and (d)(2) (establishing conditions for compounding drugs that contain the active ingredient in approved drugs or certain OTC drugs).

⁶ See section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)). CGMP requirements for the preparation of drug products are set forth in parts 210 and 211 (21 CFR parts 210 and 211) and are addressed in FDA's draft guidance for industry *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (January 2020). This draft guidance, when final, will represent FDA's current thinking on the topics covered. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

⁷ A compounded drug product that is essentially a copy of one or more approved drugs would not meet the condition in section 503B(a)(5) of the FD&C Act. See also section 503B(d)(2) (defining the term "essentially a copy of an approved drug"). At this time, FDA does not intend to take action against an outsourcing facility for filling orders for a drug product that is essentially a copy of an approved drug product, provided the drug appeared on the list of drugs used for hospitalized patients with COVID-19 maintained on FDA's website at <https://www.fda.gov/media/138276/download> within 90 days of the outsourcing facility compounding, distributing, or dispensing the drug.

⁸ The "503B Bulks List" refers to the list of bulk drug substances referenced in Section 503B(a)(2)(A)(i) of the FD&C Act. When an outsourcing facility compounds a drug product using a bulk drug substance that is not on the 503B Bulks

Contains Nonbinding Recommendations

meeting CGMP requirements with regard to product stability testing and the establishment of an expiration date,⁹ as described below, when all of the following circumstances are present¹⁰:

- a. The compounded drug product appears on the list of drugs used for hospitalized patients with COVID-19 maintained on FDA's website at <https://www.fda.gov/media/138276/download>¹¹ and contains only one active ingredient.
- b. The compounded drug product is provided directly to a hospital that informs the outsourcing facility it (i) is treating patients with COVID-19, and (ii) has made reasonable attempts to obtain adequate supplies of an FDA-approved drug product containing the same active ingredient for the same route of administration and has been unable to do so.
- c. Bulk drug substances that the outsourcing facility uses to compound the drug product are in compliance with section 503B(a)(2)(B) through (D) of the FD&C Act (21 U.S.C. 353b(a)(2)(B) through (D)), regarding conformance with applicable United States Pharmacopeia (USP) monograph standards, sourcing from facilities registered with FDA under section 510 of the FD&C Act (21 U.S.C. 360), and certificates of analysis.
- d. The outsourcing facility's practices regarding stability testing and expiration dates meet the conditions for enforcement discretion described in Appendix A to this guidance (Stability/Expiration Dating For Compounded Drug Products) and Appendix B to this guidance (Conditions Under which FDA Generally Does Not Intend to Take Regulatory Action Regarding Stability Testing and Expiration Date Requirements),¹² except that:
 - i. If the compounded drug product is an aqueous sterile solution for injection and all ingredients are readily soluble in water:
 1. The outsourcing facility uses a default beyond-use date (BUD) of not more than 28 days at room temperature and not more than 42 days refrigerated when a sterility test has not been completed before release;

List or used to compound a drug on FDA's drug shortage list, the compounded drug product does not meet the condition in section 503B(a)(2)(A) of the FD&C Act.

⁹ Section 501(a)(2)(B) of the FD&C Act and §§ 211.137 and 211.166, require outsourcing facilities to conduct stability studies to support the assignment of a product expiration date when they begin making a compounded product.

¹⁰ FDA recognizes that a registered outsourcing facility may be able to prepare a drug product that complies with the conditions in section 503B(a)(5) and (a)(2)(A) of the FD&C Act and the CGMP requirements relating to stability studies and expiration dates discussed in this guidance. The temporary policy in this guidance provides regulatory flexibility, under the circumstances described herein, when an outsourcing facility is unable to meet one or more of these conditions or requirements.

¹¹ We recommend checking this list periodically for updates.

¹² The policy described in Appendix A and Appendix B of this guidance is consistent with FDA's previously issued draft guidance for industry, *Current Good Manufacturing Practice—Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act* (January 2020). When finalized, the draft guidance will represent FDA's current thinking on the CGMP topics it addresses. FDA has adopted the policies in this guidance for immediate implementation as a temporary measure, with respect to the circumstances described herein, to respond to the public health emergency posed by COVID-19.

Contains Nonbinding Recommendations

2. The outsourcing facility initiates limited stability testing¹³ once the aggregate batch¹⁴ size of the product is expected to exceed 1,000 units;¹⁵ and
 3. The outsourcing facility utilizes a container-closure system for which it has previous experience and supporting data demonstrating suitability in maintaining sterility in another product, and it initiates container-closure integrity testing¹⁶ with the first batch.¹⁷
- ii. If the compounded, finished drug product is not intended or expected to be sterile:
1. The outsourcing facility uses the default BUDs in Table B of Appendix B of this guidance.¹⁸
 2. The outsourcing facility initiates limited stability testing¹⁹ once the aggregate batch size²⁰ is expected to exceed 5,000 units.²¹
- iii. The outsourcing facility uses a shorter BUD than those described or referenced above if literature or other scientific information, including relevant commercially available product labeling for a similar drug (e.g., components, dosage form, route of administration, primary container-closure type), indicates that the drug product may not be physicochemically stable for the duration of the default BUD period.
- e. Beginning June 1, 2020, for any drug product compounded by the outsourcing facility as described above, the outsourcing facility reports weekly to FDA the information typically reported in its biannual product reports to FDA, except that the outsourcing facility provides the cumulative number of individual units of the drug product produced during the current reporting period (December 1 through May 31 or June 1 through November 30).²²

¹³ As described in Appendix B.

¹⁴ As used here, consistent with Appendix A, *aggregate batch* refers to the sum of all units produced from any number of batches over the 6-month period for which a drug product report is submitted. For more information about product reports, see the guidance for industry *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

¹⁵ As used here, consistent with Appendix A, *units* are individual tablets or capsules for solid oral dosage forms and suppositories, inserts, or immediate containers (e.g., vial, syringe, IV bag, tube) for other dosage forms.

¹⁶ As described in Appendix A.

¹⁷ When preparing these products, it is important that outsourcing facilities consider known storage and handling conditions per USP standards and approved labeling for the comparable FDA-approved product. In addition, as a general matter, outsourcing facilities should be aware of communications related to certain syringes and rubber stoppers associated with loss of potency in certain products: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-notifies-health-care-professionals-becton-dickinson-replaced-problematic-rubber-stoppers-its>.

¹⁸ See Table C in Appendix B: “Default BUDs for Nonsterile Drug Products with Aggregate Batch Size ≤ 5,000 Units.”

¹⁹ See footnote 13.

²⁰ See footnote 14.

²¹ See footnote 15.

²² For more information on electronic reporting by registered outsourcing facilities, including information outsourcing facilities must provide for each compounded drug, see the FDA webpage titled “Human Drug Compounding Registration

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Appendix A: Stability/Expiration Dating For Compounded Drug Products

I. Stability Program and Beyond-Use Dating

A stability program must be established to assess the stability characteristics of finished drug products, and the results of stability testing must be used to determine appropriate storage conditions and expiration dates (21 CFR 211.166). Stability testing is used to ensure that a drug product will retain its quality (e.g., strength) and remain sterile, if applicable, through the labeled expiration date. A stability program for compounded drug products should use past experiences, available literature, and fundamental scientific principles to establish the parameters for the program. An expiration date is established through the conduct of a stability program that includes testing to assess the product's performance against specifications after aging to the desired expiration date (21 CFR 211.137); the conditions outlined in ICH guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* are recommended.

FDA understands that a compounded drug's batch size may be small and the frequency of batch production may vary considerably. The policies regarding stability testing and expiration dating in this guidance recognize these potential aspects of compounded drug production while addressing concerns regarding the quality of these products using a risk-based approach.

FDA generally does not intend to take regulatory action against an outsourcing facility regarding stability testing requirements if all of the following apply:

- The drug product is compounded solely by combining two or more drug products approved under section 505 of the FD&C Act.
- The approved drug product labeling of at least one of the components specifies how to assign an *in-use time*.
- The compounded drug product has been prepared and labeled with an in-use time in accordance with the approved product labeling.
- The in-use time is used as the expiration date, provided the in-use time does not exceed the expiration date of any of the approved drug products used to compound the drug. If two or more approved drug products with in-use times are used in the compounded drug product, the shortest in-use time is used as the expiration date for the compounded drug product.

In addition, taking into account the unique aspects of compounding, FDA generally does not intend to take regulatory action against an outsourcing facility under the conditions described in the remainder of this section and in Appendix C, such as using a BUD established through limited stability testing or, for certain lower risk situations, using a default BUD as the expiration date, in

And Product Reporting Procedures," <https://www.fda.gov/drugs/drug-registration-and-listing-system-drls-and-edrls/human-drug-compounding-registration-and-product-reporting-procedures>. When FDA receives these reports, the Agency intends to publish on its website: the name of the outsourcing facility, name of the active ingredient, strength of the active ingredient per unit, dosage form, package description, and NDC of the final product (if assigned). These are the categories of information that FDA makes publicly available when outsourcing facilities report drugs they have produced under section 503B(b)(2).

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lieu of establishing an expiration date through the conduct of a full stability program required under part 211 (21 CFR part 211),²³ if all of the following apply:

- The compounded drug's BUD does not exceed appropriately established expiration or retest-by dates for any of the components used to compound the drug.
- If the drug is compounded from an approved drug product, and the approved product labeling recommends one type of storage (e.g., refrigeration through the expiry date, such as 18 months), but also provides for storage at another condition (e.g., stable at room temperature for a time frame shorter than the expiry date, such as up to 14 days), the compounded drug product is not labeled with a BUD that is longer than the relevant storage time frame in the approved product labeling (e.g., the BUD of the compounded drug does not exceed 14 days for room temperature).

In addition, for repackaged products, FDA generally does not intend to take regulatory action against an outsourcing facility under the conditions described in the remainder of this section and in Appendix B, in lieu of establishing an expiration date through the conduct of a full stability program, if (1) the BUD does not exceed the expiration date of the drug product that is being repackaged; and (2) if the approved product labeling for the drug product being repackaged recommends one type of storage (e.g., refrigeration through the expiry date, such as 18 months) but also provides for storage at another condition (e.g., stable at room temperature for a time frame shorter than the expiry date, such as up to 14 days), the repackaged product is not labeled with a BUD that is longer than the relevant storage time frame in the approved product labeling (e.g., the BUD does not exceed 14 days for room temperature). For more information on repackaging, see the guidance for industry *Repackaging of Certain Human Drug Products by Pharmacies and Outsourcing Facilities*.

Whether you use an expiration date or BUD to be used as an expiration date according to the provisions outlined below and in Appendix C, the two studies below are required to be completed before a batch is released (see §§ 211.166 and 211.167). Each study only needs to be conducted once for each formulation and container-closure system, and a bracketing or matrixing approach can be considered to minimize the amount of testing. See Appendix C for more information regarding bracketing approaches.

- **Container-closure integrity testing** is conducted on samples aged to or beyond the desired BUD or expiration date to ensure that sterility is maintained over that time period.²⁴
- **Antimicrobial effectiveness testing** for drug products labeled or intended to be multiple dose is conducted on samples aged to the proposed BUD or expiration date. (Note that antimicrobial effectiveness testing is container-closure specific.)²⁵

Tables 2 and 3 highlight the conditions under which FDA generally does not intend to take regulatory action against an outsourcing facility for assigning a BUD to be used as an expiration date

²³ To meet the conditions under section 503B of the FD&C Act, the compounded drug product must be labeled with an expiration date (see section 503B(a)(10)(A)(iii)(VI)).

²⁴ See USP General Chapter <1207> *Package Integrity Evaluation—Sterile Products* for more information on container-closure integrity testing.

²⁵ See USP General Chapter <51> *Antimicrobial Effectiveness Testing* for more information.

Contains Nonbinding Recommendations

in lieu of conducting full stability studies required under part 211.

a. Non-sterile limited stability testing

For small batches ($\leq 5,000$ units²⁶ in an aggregate batch²⁷), FDA generally does not intend to take regulatory action if the relevant default BUDs provided in Appendix C are used for the expiration date and the conditions set forth in Appendix C are met. Alternatively, for small batches, FDA generally does not intend to take regulatory action if limited stability testing is conducted to support a BUD longer than the relevant default BUDs in accordance with Appendix C, and that BUD is used as an expiration date in lieu of conducting full stability studies required under part 211. For larger batches ($> 5,000$ units in an aggregate batch), FDA generally does not intend to take regulatory action regarding stability testing if the relevant conditions for the limited stability testing outlined in Appendix C are met. If, at any time during a 6-month reporting period, the total number of units compounded exceeds the 5,000-unit limit, the conditions applicable to small batches (i.e., $\leq 5,000$ units) do not apply.

Table 2. BUDs for Non-Sterile Compounded Drug Products, by Aggregate Batch Size

Aggregate Batch Size (over 6-month reporting period)	Default BUD (no testing)	BUD Based on Limited Stability Testing
$\leq 5,000$ units	Default BUD, which may be further limited by literature or other scientific information. See Appendix C for the conditions that must be met.	Data-driven stability program. See Appendix C for the conditions that must be met.
$> 5,000$ units	N/A. Default BUDs are not applicable to large aggregate batch sizes.	Data-driven stability program. See Appendix C for the conditions that must be met.

b. Sterile limited stability testing

For small batches ($\leq 1,000$ units in an aggregate batch), FDA generally does not intend to take regulatory action if the relevant default BUDs provided in Appendix C are used for the expiration date and the conditions set forth in Appendix C are met. Alternatively, for small batches, FDA generally does not intend to take regulatory action if limited stability testing is conducted to support a BUD longer than the relevant default BUDs in accordance with Appendix C, and that BUD is used as an expiration date in lieu of conducting full stability studies required under part 211. For larger batches ($> 1,000$ units in an aggregate batch), FDA generally does not intend to take regulatory action regarding stability testing if the relevant conditions for the limited stability testing outlined in Appendix C are met. If, at any time during a 6-month reporting period, the total number of units compounded exceeds the 1,000-unit limit, the conditions applicable to small batches (i.e., $\leq 1,000$

²⁶ *Units* are individual tablets or capsules for solid oral dosage forms and suppositories, inserts, or immediate containers (e.g., vial, syringe, IV bag, tube) for other dosage forms.

²⁷ For the purposes of this guidance, batch size has been considered by defining *aggregate batch* as the sum of all units produced from any number of batches over the 6-month period for which a drug product report is submitted. For more information about product reports, see the guidance for industry *Electronic Drug Product Reporting for Human Drug Compounding Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act*.

Contains Nonbinding Recommendations

units) do not apply.

Table 3. BUDs for Sterile Compounded Drug Products, by Aggregate Batch Size

Aggregate Batch Size (over 6-month reporting period)	Default BUD (no testing)	BUD Based on Limited Stability Testing
$\leq 1,000$ units	Default BUD, which may be further limited by literature or other scientific information. See Appendix C for the conditions that must be met.	Data-driven stability program. See Appendix C for the conditions that must be met.
$> 1,000$ units	N/A. Default BUDs are not applicable to large aggregate batch sizes.	Data-driven stability program. See Appendix C for the conditions that must be met.

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Appendix B: Conditions Under which FDA Generally Does Not Intend to Take Regulatory Action Regarding Stability Testing and Expiration Date Requirements

A. Default BUD (No Testing) for Non-Sterile Drug Products: Aggregate Batch Size ≤5,000 Units

FDA generally does not intend to take regulatory action against an outsourcing facility regarding the requirements for stability studies and expiration dates for non-sterile drug products under §§ 211.166 and 211.137 if (1) a BUD has been assigned according to Table A; (2) water activity testing is conducted as described below, if applicable, to determine the type of product for assigning the BUD; (3) literature or other scientific information, including relevant commercially available product labeling for a similar drug (e.g., components, dosage form, route of administration, primary container-closure type), does not indicate that the drug product may not be physicochemically stable over the time period listed; and (4) the BUD is used as the expiration date.²⁸

The default BUDs in Table A are based on the likelihood of microbial proliferation as determined by water activity testing. Products with a water activity >0.6 are of greater concern microbiologically because there is potential for proliferation of microorganisms in the product. Use of a validated preservative strategy²⁹ can greatly reduce the likelihood of microbial proliferation in finished drug products.

Water activity testing is conducted as follows to determine the type of product for assigning the default BUD:

- Solid dosage forms (i.e., tablets and capsules): No water activity testing is necessary.
- Products with water activity >0.6: No water activity testing is necessary if the product is known or assumed to have a high water activity (e.g., liquid oral solution) and the applicable default BUD for products with water activity >0.6 is used.
- Products with suspected low water activity (other than solid dosage forms) (e.g., suppository): Water activity testing is conducted once for each non-sterile drug product formulation according to validated test procedures such as those described in USP General Chapter <1112>. Depending on the results of the water activity test, the BUD should be set according to Table A.

Table A: Default BUDs for Non-Sterile Drug Products With Aggregate Batch Size ≤5,000 Units

Type of Product	Storage Conditions	
	Controlled Room Temperature (20° to 25°C)	Refrigerator (2° to 8°C)
Solid dosage forms	180 days	N/A
Water activity >0.6	Preserved: 30 days	Preserved: 30 days

²⁸ To be eligible for the exemptions provided under section 503B of the FD&C Act, the compounded drug product must be labeled with an expiration date (see section 503B(a)(10)(A)(iii)(VI)).

²⁹ See USP General Chapter <51>.

Contains Nonbinding Recommendations

	Unpreserved: Not applicable	Unpreserved: 14 days
Water activity ≤ 0.6	90 days	N/A

B. Default BUD (No Testing) for Sterile Drug Products: Aggregate Batch Size $\leq 1,000$ Units

FDA generally does not intend to take regulatory action against an outsourcing facility regarding the requirements for stability studies and expiration dates under §§ 211.166 and 211.137 if (1) a BUD has been assigned according to the criteria based on processing conditions in Table B; (2) literature or other scientific information, including relevant commercially available product labeling for a similar drug (e.g., components, dosage form, route of administration, primary container-closure type), does not indicate that the drug product may not be physicochemically stable over the time period listed; and (3) the BUD is used as the expiration date.³⁰

Table B. Default BUDs for Aggregate Batch Size $\leq 1,000$ Units With Given Processing and Storage Conditions

Processing Conditions	Contains a Preservative?	Storage Conditions		
		Controlled Room Temperature (20° to 25°C)	Refrigerator (2° to 8°C)	Freezer (-25° to -10°C)
<ul style="list-style-type: none"> Finished drug product is aseptically processed; and A sterility test has not been completed before release 	No	6 days	9 days	45 days
	Yes	28 days	42 days	45 days
<ul style="list-style-type: none"> Finished drug product is terminally sterilized; A validated sterilization cycle that uses physical, chemical, or biological indicators is employed; and A sterility test has not been completed before release 	No	14 days	28 days	45 days
	Yes	28 days	42 days	45 days
<ul style="list-style-type: none"> Finished drug product is aseptically processed or terminally sterilized and has a completed, passing sterility test before release 	No	28 days	42 days	45 days
	Yes	42 days	42 days	45 days

³⁰ To be eligible for the exemptions provided under section 503B of the FD&C Act, the compounded drug product must be labeled with an expiration date (see section 503B(a)(10)(A)(iii)(VI)).

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C. Enforcement Policy Regarding the Use of Limited Stability Testing To Assign a BUD

Stability testing is intended to confirm the stability performance of a non-sterile or sterile compounded drug product held under the labeled storage conditions for the duration of the BUD. Procedures established for assessing the stability of drug products compounded by outsourcing facilities must achieve the following (§§ 211.122, 211.160, and 211.166):

- Incorporate stability-indicating test methods that are reliable, meaningful, and specific.
- Evaluate samples of the drug product in the same container-closure system and with the same or representative label and adhesive that will be affixed to the container in which the drug product is marketed.
- Evaluate samples for stability that are representative of the batch from which they were obtained and are stored under suitable conditions.
- Incorporate testing to evaluate antimicrobial effectiveness for drug products labeled or intended to be multiple dose. If antimicrobial effectiveness has been previously established for the formulation and container-closure system, a test for preservative content may be used in lieu of a full antimicrobial effectiveness study.

FDA generally does not intend to take regulatory action against an outsourcing facility regarding stability testing and expiration date requirements if the outsourcing facility uses the approach outlined below describing a number of lots and a set of tests—which should be conducted at lot release as part of normal operations—to be performed at the time of the desired BUD. This section C does not apply to non-sterile unpreserved aqueous drug products because of the higher risk of microbiological proliferation.

The following conditions apply:

- Samples are evaluated following aging under the long-term storage conditions (i.e., temperature and humidity) in ICH Q1A(R2).
- The data from each time point are evaluated against the established specifications for the compounded drug product.
- The BUD is not longer than 12 months.
- If the data for any test fall outside of the established specifications, the BUD is restricted to the last time point at which the data remained within specifications, or the default BUD (described above) is used.

Because of the possibility that a sample may not meet specifications at the final time point, FDA strongly recommends the inclusion of testing at least once at an interim time point. If the data at the final time point do not confirm the stability of the product at the desired BUD (e.g., some measurements fall outside of the established specifications), but the data at the interim time point are

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acceptable (i.e., measurements meet the established specifications), a BUD equal to the interim time point meets the second condition above.

Under this policy, samples from one lot are tested. Each unit subjected to one or more tests that compromise the integrity of the primary container-closure is only tested at a single time point (i.e., not at additional time points). If a single unit is to be used for multiple discrete tests to minimize destructive testing, the unit dosage is subdivided into multiple aliquots that are not held longer than the time to complete the testing (typically not longer than 48-72 hours) and the aliquots are placed into appropriate testing containers (e.g., high performance liquid chromatography vials or sample tubes) that protect the sample from being compromised (e.g., from exposure to air, light, evaporation).

I. Non-sterile

a. Nondestructive tests

The following test is conducted:

- Appearance.

b. Destructive chemical tests

The tests to be conducted include:

- pH, if applicable (e.g., for aqueous formulations).
- Assay.³¹
- Appropriate specifications.

³¹ If the API is known (from literature or other scientific information) to have the potential to form genotoxic degradants as discussed in ICH guidance for industry M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk, the presence of the impurity or impurities should be evaluated as part of the assay or, if the assay method is not sufficiently sensitive, using a different test.

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- c. Microbiological tests, if water activity >0.6

The tests to be conducted include:

- Antimicrobial effectiveness testing/preservative content testing at expiry.
- Microbial enumeration³² (USP General Chapter <61>).
- Test for specified organisms³³ (USP General Chapter <62>).

2. *Sterile*

- a. Nondestructive tests

The following tests are conducted:

- Appearance.
- Color and clarity.
- Visible particulates.

- b. Destructive chemical tests

The tests to be conducted include:

- pH, if applicable (e.g., for aqueous formulations).
- Assay.³⁴
- Subvisible particles (10µm–100µm).³⁵

- c. Sterility or container-closure integrity tests

To confirm that sterility is maintained over the proposed BUD, container-closure integrity testing (such as described in USP General Chapter <1207>) or a sterility test (see USP General Chapter <71>) is conducted. When performed, container-closure integrity testing is conducted on a number of units that is suitable for the chosen test method.

D. Bracketing

Use of bracketing in stability studies allows for more streamlined evaluation of drug products for which there are multiple strengths or volume presentations produced. Bracketing assumes that the stability of intermediate strengths (or intermediate fill volumes) is adequately represented by the extremes tested.³⁶ For multiple drug products to be eligible for bracketing stability studies, the candidate formulations should vary only in strength (or concentration) or fill volume. Although individual excipient amounts may vary, all excipients (in worst-case amounts) should be in all

³² See, for example, USP General Chapter <1111>.

³³ Ibid.

³⁴ See footnote 31.

³⁵ Applicable only to intrathecal, intravenous, intra-arterial, ophthalmic, intramuscular, sterile otic, and subcutaneous preparations.

³⁶ See ICH guidance for industry *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products* for more information on bracketing and matrixing.

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bracketed formulations. Proportional formulations are not required. The same container-closure system must be used (§ 211.166). If three or more strengths, concentrations, or volume presentations exist, intermediate cases for stability studies as follows may reflect an appropriate use of bracketing:

- If 3 or 4 drug product strengths, concentrations, or volume presentations are produced, test the high and low extremes (e.g., if available strengths include 2.0 mg/mL, 3.5 mg/mL, 5.0 mg/mL, and 10.0 mg/mL, test 2.0 mg/mL and 10.0 mg/mL).
- If 5-10 drug product strengths, concentrations, or volume presentations are produced, test the high and low extremes and 1 intermediate case.
- If more than 10 drug product strengths, concentrations, or volume presentations are produced, test the high and low extremes and 2 intermediate cases.

It is critical that determination of the extremes be done with care. For example, with respect to volume fill, the appropriate extremes are not necessarily always the highest and lowest fluid volume fills. Rather, the head space-to-fluid volume ratio may better represent the appropriate extreme depending on the container volume used in the various presentations.

Bracketing as described in this section does not apply to microbial testing of sterility, endotoxins, or bioburden. Bracketing may be appropriate for water activity testing and antimicrobial effectiveness testing when used in conjunction with a preservative content testing strategy.