Temporary Policies for Compounding Certain Parenteral Drug Products

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). Comments may be submitted at any time for Agency consideration. 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. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact (CDER) Office of Compounding Quality and Compliance, 301-796-3400.

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

October 2024
Compounding

Temporary Policies for Compounding Certain Parenteral Drug Products

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

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

October 2024
Compounding

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Temporary Policies for Compounding Certain Parenteral Drug Products 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

As of October 10, 2024, pursuant to section 319(a) of the Public Health Service Act (PHS Act) (42 U.S.C. 247d(a)), Department of Health and Human Services (HHS) Secretary Becerra has determined that public health emergencies (PHEs) exist as a result of the consequences of Hurricane Helene in the States of North Carolina, Florida, Georgia, Tennessee, and South Carolina, and as a result of the consequences of Hurricane Milton in the State of Florida.[2] In late September 2024, Hurricane Helene had a devastating impact on one of the largest manufacturers of certain intravenous and peritoneal dialysis solutions in the United States. The Food and Drug Administration (FDA or the Agency) is working with the manufacturer and alternative suppliers to increase supply and reduce the risk of new shortages of critical drug products.

This guidance describes the FDA's regulatory and enforcement priorities regarding the compounding of certain parenteral drug products by outsourcing facilities and by State-licensed pharmacies and Federal facilities that are not registered with FDA as outsourcing facilities. This policy is intended to remain in effect only for the duration of the supply disruption related to the above referenced PHEs, or for another period of time as FDA may announce. As relevant needs and circumstances evolve, FDA intends to update, modify, or withdraw the policies in this guidance and the drug products that are the subject of this policy.

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 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 to help ensure patient access to certain parenteral drug products, such as intravenous fluids, which are essential in the care of patients, including those who are critically ill and those undergoing surgery. While this guidance is being implemented immediately due to the urgent

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research at the Food and Drug Administration.
[2] A list of HHS PHE declarations is located at: https://aspr.hhs.gov/legal/PHE/pages/default.aspx.

public health need, it remains subject to comment in accordance with the Agency's good guidance practices.

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

Although compounded drug products can serve an important patient need, they can also pose a higher risk to patients than FDA-approved drug products. Compounded drug products are not FDA-approved, which means they are not reviewed by FDA for safety, effectiveness, or quality before they reach patients. The Agency recommends FDA-approved drug products be used to treat patients whenever possible.

Section 503A of the FD&C Act (21 U.S.C. 353a) describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed pharmacy or Federal facility, or by a licensed physician, to be exempt from the following three sections of the FD&C Act: (1) section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications); (2) section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice (CGMP) requirements).

One of the conditions in section 503A of the FD&C Act is that each drug product must be compounded for an identified individual patient based on the receipt of a valid prescription order, or a notation, approved by the prescribing practitioner, on the prescription order that a compounded drug product is necessary for the identified patient.[3] The prescription requirement is a critical mechanism to distinguish compounding under section 503A of the FD&C Act from conventional manufacturing, or compounding by outsourcing facilities, and helps ensure that drug products that pharmacies compound under section 503A of the FD&C Act are provided to a patient only based on individual patient need. Another condition in section 503A of the FD&C Act is that a licensed pharmacist or licensed physician does not compound regularly or in inordinate amounts any drug products that are essentially copies of commercially available drug products.[4]

---

[3] See section 503A(a) of the FD&C Act. See also the guidance for industry *Prescription Requirement Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (December 2016). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[4] See section 503A(b)(1)(D) of the FD&C Act. FDA does not consider products on FDA's drug shortage list to be commercially available. See section 503A(b)(1)(D) of the FD&C Act, and the guidance for industry *Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (January 2018).

Section 503B of the FD&C Act (21 U.S.C. 353b) describes the conditions that must be satisfied for human drug products compounded by an outsourcing facility to be exempt from the following three sections of the FD&C Act: (1) section 505 (21 U.S.C. 355) (concerning the approval of drugs under new drug applications or abbreviated new drug applications); (2) section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) section 582 (21 U.S.C. 360eee-1) (concerning drug supply chain security requirements). Section 503B of the FD&C Act restricts outsourcing facilities from compounding drugs that are not on FDA's drug shortage list. In particular, bulk drug substances used to compound a drug that is not on FDA's drug shortage list must be on a list of substances established by the Secretary for which there is a clinical need (the 503B Bulks List),[5] and outsourcing facilities may not compound a drug that is essentially a copy of one or more approved drugs.[6] Additionally, outsourcing facilities are required to register with FDA, are inspected by FDA according to a risk-based schedule, and are subject to CGMP requirements. CGMP requirements include a requirement to conduct stability studies to support the assignment of a product expiration date.[7]

III. TEMPORARY POLICY FOR CERTAIN PARENTERAL DRUG PRODUCTS COMPOUNDED BY PHARMACY COMPOUNDERS NOT REGISTERED AS OUTSOURCING FACILITIES

Although FDA is monitoring the global pharmaceutical supply chain and working, within its authorities, with manufacturers of approved parenteral drug products to bolster supply, temporary flexibility is needed to help ensure that treatment options remain available to hospitals and health systems during this period.

To the extent that hospitals and health systems have a need for compounded drug products, FDA encourages them to obtain such products from outsourcing facilities. As noted above, outsourcing facilities register with FDA, are subject to CGMP requirements, and are inspected by FDA according to a risk-based schedule. This helps to mitigate the risk that their drug products will be contaminated or otherwise made under substandard conditions.

However, hospitals and health systems may have difficulty obtaining adequate supplies of certain FDA-approved parenteral drug products or adequate supplies of comparable drug products made by an outsourcing facility.

[5] See section 503B(a)(2)(A) of the FD&C Act.
[6] See section 503B(a)(5) and (d)(2) of the FD&C Act.
[7] 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 21 CFR parts 210 and 211.

Therefore, as a temporary measure, FDA does not intend to take action against a State-licensed pharmacy that is not registered as an outsourcing facility, including a hospital or health system pharmacy,[8] for providing a compounded drug to a hospital or health system without obtaining a patient-specific prescription,[9] or for compounding a drug that is essentially a copy of a commercially available drug,[10] if all of the following circumstances are present.

1. The drug product appears on the list of drugs on FDA's website at https://www.fda.gov/media/182634/download?attachment.[11]

2. The compounded drug product is labeled with a default beyond use date (BUD) in accordance with the table in Appendix A.[12]

3. If the pharmacy and the hospital or health system are not owned and controlled by the same entity, the pharmacy requests that the hospital or health system provide, to the extent allowed by applicable laws, the records that identify the patients to whom the drugs were administered and document such request within 1 month of sending the compounded drug to the hospital or health system.

4. Before providing the drug product to the hospital or health system, a State-licensed pharmacy notifies the following State authorities, and the State authorities inform the pharmacy that they do not object to the pharmacy providing the drug product to the hospital or health system without first obtaining a patient-specific prescription:

    a. The State authority that regulates pharmacy compounding in the State where the pharmacy is located, and,

    b. If different, the State authority that regulates pharmacy compounding in the State where the hospital or health system is located.[13]

5. Other conditions of section 503A and other requirements in the FD&C Act are met. In particular, a drug is deemed to be adulterated "if it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health."[14] Drug products prepared, packed, or held under insanitary conditions could become contaminated and cause serious

[8] The policy in this guidance is separate from FDA's previously issued draft guidance for industry *Hospital and Health System Compounding Under Section 503A of the Federal Food, Drug, and Cosmetic Act* (October 2021) (when final, this guidance will represent the FDA's current thinking on this topic) and does not include a condition for use within 24 hours. FDA has adopted the policies in this guidance for immediate implementation as a temporary measure.
[9] Section 503A(a) of the FD&C Act.
[10] Section 503A(b)(1)(D) of the FD&C Act. FDA does not consider a drug to be commercially available if it is currently on FDA's drug shortage list.
[11] We recommend checking this list periodically for updates.
[12] When preparing these drug products, it is important that pharmacies consider storage and handling conditions per United States Pharmacopeia standards and approved labeling for the comparable FDA-approved drug product.
[13] FDA recommends that State-licensed pharmacies consult with State authorities regarding local requirements.
[14] Section 501(a)(2)(A) of the FD&C Act (21 U.S.C. 351(a)(2)(A)).

adverse events, including death.[15] Additionally, section 501(b) of the FD&C Act requires a drug recognized in the United States Pharmacopeia (USP) to meet the standards of strength, quality, and purity in the official monograph or to be clearly labeled to designate how it differs from USP standards.

FDA recommends that hospitals and health systems maintain records of both the entity supplying the hospitals and health systems with such drugs and the patients who receive the drugs. FDA also encourages hospitals and health systems to provide to the pharmacy, to the extent allowed by applicable laws, records that identify the patients to whom the drugs were administered. Such records may be important to allow follow-up if there are adverse drug events or product quality issues associated with drugs the pharmacy has provided.

FDA encourages health care professionals to report adverse drug events experienced with the use of compounded drug products to the pharmacies that produced the drug products as well as to FDA's MedWatch Safety Information and Adverse Event Reporting Program (available at https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program):

- Complete and submit the report online at FDA's MedWatch Online Voluntary Reporting Form web page (at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm); or
- Download and complete the Form FDA 3500 MedWatch: The FDA Safety Information and Adverse Event Reporting Program (available at https://www.fda.gov/media/76299/download), and, then submit it via fax at 1-800-FDA-0178.

IV. TEMPORARY POLICY FOR CERTAIN PARENTERAL DRUG PRODUCTS COMPOUNDED BY OUTSOURCING FACILITIES

As a temporary measure, 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,[16] for using a bulk drug substance that is not on FDA's 503B Bulks List,[17] or for not meeting CGMP requirements

[15] For more information, see the guidance for industry *Insanitary Conditions at Compounding Facilities* (November 2020).

[16] See section 503B(a)(5) and (d)(2) of the FD&C Act. 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 on FDA's website at https://www.fda.gov/media/182633/download?attachment within 180 days of the outsourcing facility compounding, distributing, or dispensing the drug. A drug is not essentially a copy of one or more FDA approved drugs if it is identical or nearly identical to an approved drug on FDA's drug shortage list.

[17] See section 503B(a)(2)(A) of the FD&C Act. At this time, FDA does not intend to take action against an outsourcing facility for compounding a drug product using a bulk drug substance that is not on the 503B bulks list if the drug compounded from the bulk drug substance appeared on the list of drugs on FDA's website at https://www.fda.gov/media/182633/download?attachment within 180 days of the outsourcing facility compounding, distributing, or dispensing the drug.

with regard to product stability testing and the establishment of an expiration date, as described below, when all of the following circumstances are present.

1. The drug product appears on the list of drugs on FDA's website at https://www.fda.gov/media/182633/download?attachment.[18]

2. The outsourcing facility's practices regarding stability testing and expiration dates meet the conditions for enforcement discretion described in Appendix B (Stability/Expiration Dating for Drug Products Compounded by Outsourcing Facilities) and Appendix C (Conditions Under Which FDA Generally Does not Intend to Take Regulatory Action Regarding Stability Testing and Expiration Date Requirements for Drug Products Compounded by Outsourcing Facilities).[19] These conditions include:

    a. The outsourcing facility uses a default beyond use date 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;
    b. The outsourcing facility initiates limited stability testing[20] once the aggregate batch[21] size of the product is expected to exceed 5,000 units;[22] and

3. The outsourcing facility initiates container-closure integrity testing[23] with the first batch.[24]

4. Other conditions of section 503B and other requirements in the FD&C Act are met. Section 501(b) of the FD&C Act requires a drug recognized in USP to meet the standards of strength, quality, and purity in the official monograph or to be clearly labeled to designate how it differs from USP standards.

FDA encourages health care professionals to report adverse events experienced with the use of compounded drug products to the outsourcing facilities that produced the products as well as to

[18] We recommend checking this list periodically for updates.
[19] Except for provisions related to batch sizes, the policy described in Appendix B and Appendix C 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.
[20] As described in Appendix B. While stability testing is being conducted, the outsourcing facility can continue to use the default BUD and continue production until stability testing is complete.
[21] As used here, consistent with Appendix B, *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* (December 2016).
[22] As used here, consistent with Appendix B, *units* are immediate containers (e.g., vial, syringe, IV bag, tube).
[23] As described in Appendix A.
[24] When preparing these drug products, it is important that outsourcing facilities consider known storage and handling conditions per USP standards and approved labeling for the comparable FDA-approved drug product.

FDA's MedWatch Safety Information and Adverse Event Reporting Program (available at https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program):

- Complete and submit the report online at FDA's MedWatch Online Voluntary Reporting Form web page (at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm); or
- Download and complete the Form FDA 3500 MedWatch: The FDA Safety Information and Adverse Event Reporting Program (available at https://www.fda.gov/media/76299/download), and then submit it via fax at 1-800-FDA-0178.

APPENDIX A: BEYOND USE DATES FOR DRUG PRODUCTS COMPOUNDED BY PHARMACY COMPOUNDERS NOT REGISTERED AS OUTSOURCING FACILITIES

Processing Conditions	Storage Conditions	
	Controlled Room Temperature (20° to 25°C)	**Refrigerator (2° to 8°C)**
• Finished drug product is aseptically processed; and • A sterility test has not been completed before release	4 days	6 days
• Finished drug product is terminally sterilized; • A verified sterilization cycle that uses biological indicators is employed; and • A sterility test has not been completed before release	10 days	12 days
• Finished drug product is aseptically processed or terminally sterilized and has a completed, passing sterility test before release[1]	20 days	22 days

[1] The default beyond use dates in this row include the time necessary to complete a sterility test, which may include rapid sterility test methods as well as sterility testing described under United States Pharmacopeia (USP) General Chapter <71> *Sterility Tests*.

APPENDIX B: STABILITY/EXPIRATION DATING FOR DRUG PRODUCTS COMPOUNDED BY OUTSOURCING FACILITIES

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 the International Council for Harmonisation (ICH) guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003)[1] 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 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 appendix and in Appendix C, such as using a beyond use date (BUD) established through limited stability testing or, for certain lower risk situations, using a default

[1] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

BUD as the expiration date, in lieu of establishing an expiration date through the conduct of a full stability program required under part 211 (21 CFR part 211),[2] 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).

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, generally under CGMP requirements the two studies below must 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 normally conducted on samples aged to or beyond the desired BUD or expiration date to ensure that sterility is maintained over that time period prior to release of the first batch. However, for the purpose of the enforcement policy described in this guidance, an initial container-closure integrity test may be performed prior to release of the first batch using unaged samples to demonstrate ability of the container-closure system to maintain sterility at release. If using this approach, subsequent container-closure integrity tests on samples aged to or beyond the desired BUD or expiration date must be initiated upon release of the first batch.[3]

- **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.)[4] Antimicrobial effectiveness testing must be conducted before a batch is released.

The table in this appendix highlights 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 in lieu of conducting full stability studies required under part 211.

[2] 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)).
[3] See USP General Chapter <1207> *Package Integrity Evaluation—Sterile Products* for more information on container-closure integrity testing.
[4] See USP General Chapter <51> *Antimicrobial Effectiveness Testing* for more information.

a. Sterile limited stability testing

For aggregate batches ≤5,000 units, 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 batches ≤5,000 units do not apply.

Table. 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**
≤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, unless stability testing has been initiated, but not yet completed.	Data-driven stability program. See Appendix C for the conditions that must be met.

APPENDIX C: CONDITIONS UNDER WHICH FDA GENERALLY DOES NOT INTEND TO TAKE REGULATORY ACTION REGARDING STABILITY TESTING AND EXPIRATION DATE REQUIREMENTS FOR DRUG PRODUCTS COMPOUNDED BY OUTSOURCING FACILITIES

A. Default Beyond Use Date (No Testing) for Sterile Drug Products: Aggregate Batch Size ≤5,000 Units

The Food and Drug Administration (FDA) generally does not intend to take regulatory action against an outsourcing facility regarding the requirements for stability studies and expiration dates under 21 CFR 211.166 and 211.137 if (1) a beyond use date (BUD) has been assigned according to the criteria based on processing conditions in the table in this appendix; (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.[1]

Table. Default BUDs for Aggregate Batch Size ≤5,000 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)
• Finished drug product is aseptically processed; and • A sterility test has not been completed before release	No	6 days	9 days
	Yes	28 days	42 days
• 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
	Yes	28 days	42 days
• Finished drug product is aseptically processed or terminally sterilized and has a completed, passing sterility test before release	No	28 days	42 days
	Yes	42 days	42 days

[1] To be eligible for the exemptions provided under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the compounded drug product must be labeled with an expiration date (see section 503B(a)(10)(A)(iii)(VI) of the FD&C Act)).

B. 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 (21 CFR 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 B 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 the International Council for Harmonisation (ICH) guidance for industry *Q1A(R2) Stability Testing of New Drug Substances and Products* (November 2003).[2]
- 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.

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

- 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 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).

Sterile compounded drug products

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.
- Subvisible particles (10 micrometers (μm) to –100 μm).[3]

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 United States Pharmacopeia (USP) General Chapter <1207> *Package Integrity Evaluation—Sterile Products*) or a sterility test (see USP General Chapter <71>

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

Sterility Tests) is conducted. When performed, container-closure integrity testing is conducted on a number of units that is suitable for the chosen test method.

C. 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.[4] 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 bracketed formulations. Proportional formulations are not required. The same container-closure system must be used (21 CFR 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 milligrams (mg)/milliliter (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 to 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.

[4] See ICH guidance for industry *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products* (January 2003) for more information on bracketing and matrixing.