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# Temporary Policies for Compounding Certain Starter Parenteral Nutrition Drug Products for Neonates 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 (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)**

**September 2026  
Compounding**

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# **Temporary Policies for Compounding Certain Starter Parenteral Nutrition Drug Products for Neonates**

## **Guidance for Industry<sup>1</sup>**

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**

The Food and Drug Administration (FDA or the Agency) has received reports of potential serious supply disruptions resulting from the market exit of the predominant source of certain starter parenteral nutrition drug products for neonates. Starter parenteral nutrition provides vital early nutrition, including dextrose, amino acids (protein), and sometimes calcium, while custom, patient-specific formulas can be prepared.<sup>2</sup> These products are pre-mixed intravenous solutions given to newborns immediately after birth and are especially critical for neonates who are born prematurely. The potential supply disruption is particularly important because at this time there are no FDA-approved starter parenteral nutrition drug products for neonates. FDA is working with industry and alternative suppliers to increase supply and reduce the risk of new supply disruptions.

This guidance describes FDA's regulatory and enforcement priorities regarding certain starter parenteral nutrition drug products for neonates compounded by outsourcing facilities and by State-licensed pharmacies and Federal facilities that are not registered with FDA as outsourcing facilities. The enforcement policies in this guidance are intended to provide temporary flexibility for 180 days after the publication date of this guidance, until March 8, 2027, to help ensure that these products remain available to hospitals and health systems while alternative sources increase supplies. 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.

FDA is implementing this guidance without prior public comment because the Agency has determined that prior public participation is not feasible or appropriate (see section 701(h)(1)(C)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C.

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<sup>1</sup> This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research at the Food and Drug Administration.

<sup>2</sup> See Robinson DT, Calkins KL, Chen Y, et al. Guidelines for parenteral nutrition in preterm infants: the American Society for Parenteral and Enteral Nutrition. J Parenter Enteral Nutr. 2023; 47: 830-858. doi:10.1002/jpen.2550.

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371(h)(1)(C)(i)) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately to help ensure patient access to certain starter parenteral nutrition drug products for neonates, which are essential to the care of this vulnerable patient population. While this guidance is being implemented immediately due to the urgent 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.<sup>3</sup> 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.

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

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<sup>3</sup> 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>.

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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 using bulk drug substances. 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).<sup>4</sup> 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.<sup>5</sup>

### **III. TEMPORARY POLICY FOR CERTAIN STARTER PARENTERAL NUTRITION DRUG PRODUCTS FOR NEONATES COMPOUNDED BY COMPOUNDERS NOT REGISTERED AS OUTSOURCING FACILITIES**

Although FDA is monitoring the supply chain for these products and working, within its authorities, to explore various options to bolster supply, temporary flexibility is needed to help ensure that treatment options for neonates remain available to hospitals and health systems.

Generally, 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, at this time there are no FDA-approved starter parenteral nutrition drug products for neonates and hospitals and health systems may have difficulty obtaining adequate supplies of certain starter parenteral nutrition drug products for neonates made by an outsourcing facility.

Therefore, as a temporary measure for 180 days after the publication date of this guidance, until March 8, 2027,<sup>6</sup> FDA does not intend to take action against a State-licensed pharmacy or Federal facility that is not registered as an outsourcing facility, including a hospital or health system pharmacy,<sup>7</sup> for providing a compounded drug to a hospital or health system without obtaining a

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<sup>4</sup> See section 503B(a)(2)(A) of the FD&C Act.

<sup>5</sup> 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.

<sup>6</sup> FDA will continue to carefully monitor the supply of starter parenteral nutrition drug products for neonates in the United States and may extend the duration of some or all of the temporary policies in this guidance or take other steps to help ensure that treatment options remain available, as necessary.

<sup>7</sup> 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.

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patient-specific prescription,<sup>8</sup> if all of the following circumstances are present.<sup>9</sup>

- (1) The compounded drug product appears on the list of drugs in Appendix A of this guidance.
- (2) The compounded drug product is labeled with a default beyond use date (BUD) in accordance with the table in Appendix B.<sup>10</sup>
- (3) The compounded drug product is for single-use only and does not contain antimicrobial preservatives, due to safety concerns with the use of antimicrobial preservatives in drug products for neonates.<sup>11</sup>
- (4) The State authorities that regulate pharmacy compounding in the State where the pharmacy is located (and, if different, the state where the hospital or health system is located) are aware that the pharmacy is compounding these products for the hospital or health system before the compounded drug product is provided to the hospital or health system, and the State authority(ies) do not object to the pharmacy providing the compounded drug product to the hospital or health system without first obtaining a patient-specific prescription.<sup>12</sup>
- (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.”<sup>13</sup> Drug products prepared, packed, or held under insanitary conditions could become contaminated and cause serious adverse events, including death.<sup>14</sup>

FDA generally expects 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 compounded drug products. FDA also expects that hospitals and health systems provide pharmacies, to the extent allowed by applicable laws, records that identify the patients to whom the compounded drug products were administered. Where such records exist, they may be useful for follow-up if there are adverse events or product quality issues associated with compounded drug products the pharmacy has provided.

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<sup>8</sup> Section 503A(a) of the FD&C Act.

<sup>9</sup> Drug products compounded and labeled in compliance with this guidance during the enforcement discretion period may continue to be administered through the labeled BUD after the policy expires, provided the product was distributed prior to the expiration of the 180-day period.

<sup>10</sup> When preparing these drug products, it is important that pharmacies consider storage and handling conditions per United States Pharmacopeia standards.

<sup>11</sup> Careful assessment of excipient safety should also be undertaken for neonatal populations.

<sup>12</sup> FDA recommends that State-licensed pharmacies consult with State authorities regarding local requirements.

<sup>13</sup> Section 501(a)(2)(A) of the FD&C Act (21 U.S.C. 351(a)(2)(A)).

<sup>14</sup> For more information, see the guidance for industry *Insanitary Conditions at Compounding Facilities* (November 2020).

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FDA encourages health care professionals to report adverse 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 STARTER PARENTERAL NUTRITION DRUG PRODUCTS FOR NEONATES COMPOUNDED BY OUTSOURCING FACILITIES**

As a temporary measure, for 180 days after the publication date of this guidance, until March 8, 2027, FDA does not intend to take action against an outsourcing facility for using a bulk drug substance that is not otherwise permitted under section 503B(a)(2)(A) of the FD&C Act or for not meeting CGMP requirements with regard to product stability testing and the establishment of an expiration date, as described below, when all of the following circumstances are present.<sup>15</sup>

- (1) The compounded drug product appears on the list of drugs in Appendix A of this guidance.
- (2) The outsourcing facility's practices regarding stability testing and expiration dates meet the conditions for enforcement discretion described in Appendix C (Stability/Expiration Dating for Drug Products Compounded by Outsourcing Facilities) and Appendix D (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).<sup>16</sup> These conditions include:
  - a. The outsourcing facility uses a default beyond use date of not more than 30 hours at room temperature and not more than 9 days refrigerated when a stability study and sterility test have not been completed before release;

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<sup>15</sup> Drug products compounded and labeled in compliance with this guidance during the enforcement discretion period may continue to be administered through the labeled BUD after the policy expires, provided the product was distributed prior to the expiration of the 180-day period.

<sup>16</sup> Except for provisions related to batch sizes, the policy described in Appendix C and Appendix D 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.

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- b. The outsourcing facility initiates limited stability testing<sup>17</sup> once the aggregate batch<sup>18</sup> size of the product is expected to exceed 5,000 units;<sup>19</sup> and
- (3) The compounded drug product is for single-use only and does not contain antimicrobial preservatives, due to safety concerns with the use of antimicrobial preservatives in drug products for neonates. Careful assessment of excipient safety should be undertaken for neonatal populations.
- (4) The outsourcing facility initiates container-closure integrity testing<sup>20</sup> with the first batch.<sup>21</sup>
- (5) 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.

As outsourcing facilities are required to report adverse events, 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 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.

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<sup>17</sup> As described in Appendix C. While stability testing is being conducted, the outsourcing facility can continue to use the default BUD and continue production until stability testing is complete.

<sup>18</sup> As used here, consistent with Appendix C, *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).

<sup>19</sup> As used here, consistent with Appendix C, *units* are immediate containers (e.g., vial, syringe, IV bag, tube).

<sup>20</sup> As described in Appendix C.

<sup>21</sup> When preparing these compounded drug products, it is important that outsourcing facilities consider known storage and handling conditions per USP standards.

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| <b>Guidance History[*]</b>                    | <b>Date</b> | <b>Description</b>                                 |
|-----------------------------------------------|-------------|----------------------------------------------------|
| Level 1 Guidance for Immediate Implementation | August 2026 | See notice of availability for more information.** |
|                                               |             |                                                    |
|                                               |             |                                                    |

\* This table was implemented beginning August 2026, and previous guidance history may not be captured in totality.

\*\* The notice of availability is accessible via the Search for FDA Guidance Documents web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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**APPENDIX A: ELIGIBLE STARTER PARENTERAL NUTRITION DRUG PRODUCTS FOR NEONATES**

FDA has identified the following list of drugs for the purposes of the temporary policies in this guidance. FDA intends to update this list as appropriate.

| Neonatal Parenteral Nutrition Formulations <sup>1</sup> |                                                 |              |                         |                              |                   |
|---------------------------------------------------------|-------------------------------------------------|--------------|-------------------------|------------------------------|-------------------|
| <i>All formulations: 250 mL bag</i>                     |                                                 |              |                         |                              |                   |
| #                                                       | Pediatric-Specific Amino Acids <sup>2</sup> (%) | Dextrose (%) | Calcium Gluconate (mEq) | Heparin <sup>3</sup> (units) | Total Volume (mL) |
| 1                                                       | 2.0%                                            | 5%           | 3.75 mEq                | 125 units                    | 250 mL            |
| 2                                                       | 2.0%                                            | 10%          | 2.33 mEq                | 125 units                    | 250 mL            |
| 3                                                       | 2.0%                                            | 10%          | 3.75 mEq                | 125 units                    | 250 mL            |
| 4                                                       | 2.5%                                            | 10%          | 3.75 mEq                | 125 units                    | 250 mL            |
| 5                                                       | 3.0%                                            | 5%           | 2.33 mEq                | 125 units                    | 250 mL            |
| 6                                                       | 3.0%                                            | 5%           | 3.75 mEq                | —                            | 250 mL            |
| 7                                                       | 3.0%                                            | 5%           | 3.75 mEq                | 125 units                    | 250 mL            |
| 8                                                       | 3.0%                                            | 10%          | —                       | —                            | 250 mL            |
| 9                                                       | 3.0%                                            | 10%          | 2.33 mEq                | 125 units                    | 250 mL            |
| 10                                                      | 3.0%                                            | 10%          | 3.75 mEq                | —                            | 250 mL            |
| 11                                                      | 3.0%                                            | 10%          | 3.75 mEq                | 125 units                    | 250 mL            |
| 12                                                      | 3.5%                                            | 10%          | —                       | —                            | 250 mL            |
| 13                                                      | 3.5%                                            | 10%          | —                       | 125 units                    | 250 mL            |
| 14                                                      | 3.5%                                            | 10%          | 2.33 mEq                | 125 units                    | 250 mL            |
| 15                                                      | 3.5%                                            | 10%          | 3.75 mEq                | —                            | 250 mL            |

<sup>1</sup> Neonatal parenteral nutrition should not contain antimicrobial preservatives due to safety concerns in this population.

<sup>2</sup> For example, pediatric-specific amino acids include Aminosyn-PF 7% (NDA #019398) <https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=2d212e10-7e08-4aeb-b63f-dcc927897769&type=pdf>; Aminosyn-PF 10% (NDA #019492) <https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=46e74ce4-cd7e-437f-bf54-ca9b98eb2663&type=pdf>; Premasol 10% (ANDA #075880) <https://dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=9afdcc3e-0d06-47f4-86ca-40da48b2b02b&type=pdf>; TrophAmine 10% (NDA #019018) [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2020/019018Orig1s036lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/019018Orig1s036lbl.pdf).

<sup>3</sup> Heparin sodium, USP

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|    |      |     |          |           |        |
|----|------|-----|----------|-----------|--------|
| 16 | 3.5% | 10% | 3.75 mEq | 125 units | 250 mL |
| 17 | 4.0% | 10% | —        | —         | 250 mL |
| 18 | 4.0% | 10% | 3.75 mEq | 125 units | 250 mL |
| 19 | 4.5% | 10% | —        | 125 units | 250 mL |
| 20 | 6.0% | 10% | 3.75 mEq | 125 units | 250 mL |

mEq = milliequivalent, mL = milliliter

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**APPENDIX B: BEYOND USE DATES FOR CERTAIN STARTER PARENTERAL NUTRITION DRUG PRODUCTS FOR NEONATES COMPOUNDED BY COMPOUNDERS NOT REGISTERED AS OUTSOURCING FACILITIES**

| Processing Conditions                                                | Storage Conditions                        |                          |
|----------------------------------------------------------------------|-------------------------------------------|--------------------------|
|                                                                      | Controlled Room Temperature (20° to 25°C) | Refrigerator (2° to 8°C) |
| Neonatal starter parenteral nutrition that is aseptically processed. | 30 hours                                  | 9 days <sup>1</sup>      |

C = Celsius

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<sup>1</sup> A shorter BUD than those described or referenced in this guidance should be used 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. For example, parenteral nutrition admixtures may require a shorter BUD due to stability concerns arising from numerous formulation- and environment-specific variables, including macronutrient concentrations, electrolyte content, pH, lipid injectable emulsion composition, temperature, light, oxygen exposure, container characteristics, and storage time. *See also* the BUD recommendations from The American Society for Parenteral and Enteral Nutrition (ASPEN), *see ASPEN clinical guidelines: parenteral nutrition ordering, order review, compounding, labeling, and dispensing*. JPEN J Parenter Enteral Nutr. 2014 Mar-Apr;38(3):334-77. doi: 10.1177/0148607114521833. Epub 2014 Feb 14. PMID: 24531708.

## **APPENDIX C: 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)<sup>1</sup> 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 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 D, such as using a beyond use date (BUD) established through limited stability testing or, for certain lower risk situations, using a default 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),<sup>2</sup> if all of the following apply:

- The compounded drug's BUD does not exceed appropriately established expiration or

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<sup>1</sup> 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>.

<sup>2</sup> 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)).

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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 D, generally under CGMP requirements the study below must be completed before a batch is released (see §§ 211.166 and 211.167). The 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.<sup>3</sup>

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.

### a. Sterile limited stability testing

For aggregate batches  $\leq 5,000$  units, FDA generally does not intend to take regulatory action if the relevant default BUDs provided in Appendix D are used for the expiration date and the conditions set forth in Appendix D 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 D, 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 D 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  $\leq 5,000$  units do not apply.

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<sup>3</sup> See United States Pharmacopeia (USP) General Chapter <1207> *Package Integrity Evaluation—Sterile Products* for more information on container-closure integrity testing.

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**BUDs for Sterile Compounded Drug Products, by Aggregate Batch Size**

| <b>Aggregate Batch Size<br/>(over 6-month<br/>reporting period)</b> | <b>Default BUD (no testing)</b>                                                                                                              | <b>BUD Based on Limited<br/>Stability Testing</b>                                  |
|---------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| ≤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 D 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 D for the conditions that must be met. |

BUD = beyond use date

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**APPENDIX D: 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**

**1. Default Beyond Use Date (No Testing) for Sterile Drug Products: Aggregate  
Batch Size of 5,000 Units or Fewer**

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.<sup>1</sup>

**Default BUDs for Aggregate Batch Size of 5,000 Units or Fewer With Given Processing and Storage Conditions**

| Processing Conditions                                                                                                                                | Storage Conditions                           |                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|-----------------------------|
|                                                                                                                                                      | Controlled Room Temperature<br>(20° to 25°C) | Refrigerator<br>(2° to 8°C) |
| Neonatal starter parenteral nutrition that is aseptically processed and a stability study and sterility test have not been completed before release. | 30 hours                                     | 9 days <sup>2</sup>         |

C = Celsius

<sup>1</sup> 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)).

<sup>2</sup> A shorter BUD than those described or referenced in this guidance should be used 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. For example, parenteral nutrition admixtures may require a shorter BUD due to stability concerns arising from numerous formulation- and environment-specific variables, including macronutrient concentrations, electrolyte content, pH, lipid injectable emulsion composition, temperature, light, oxygen exposure, container characteristics, and storage time. *See also* the BUD recommendations from The American Society for Parenteral and Enteral Nutrition (ASPEN), *see ASPEN clinical guidelines: parenteral nutrition ordering, order review, compounding, labeling, and dispensing*. JPEN J Parenter Enteral Nutr. 2014 Mar-Apr;38(3):334-77. doi: 10.1177/0148607114521833. Epub 2014 Feb 14. PMID: 24531708.

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### **2. 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.

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.

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).<sup>3</sup>
- 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 acceptable (i.e., measurements meet the established specifications), a BUD equal to the interim time point meets the second condition above.

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<sup>3</sup> 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>.

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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
- Osmolarity
- Assay
- Subvisible particles (10 micrometers (µm) to 100 µm)

#### 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> *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.

### **3. 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.<sup>4</sup> 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

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<sup>4</sup> 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.

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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.