Compounding Certain Ibuprofen Oral Suspension Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act

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)

February 2023
Compounding
Revision 1

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Compounding Certain Ibuprofen Oral Suspension Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act Immediately in Effect Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes the Food and Drug Administration's (FDA or the Agency) regulatory and enforcement priorities regarding the compounding of certain ibuprofen oral suspension products by outsourcing facilities to provide to: 1) hospitals and health systems for administration within the hospital or health system and/or 2) State-licensed pharmacies (including those within hospitals and health systems[2]), and applicable Federal facilities, to dispense to patients for use at home after receiving a valid, patient-specific prescription. The United States is currently experiencing a significant number of infections involving three viruses: Coronavirus Disease 2019 (COVID-19), respiratory syncytial virus (RSV), and influenza. Each of these viruses may produce fever in young children. FDA has received reports related to increased demand for pediatric fever-reducing medications, including ibuprofen oral suspension products. Further, FDA has received a number of reports related to hospitals, health systems, and State-licensed pharmacies experiencing challenges with obtaining these medications to use for fever and pain treatment of pediatric patients as well as for adults who are unable to swallow solid oral dosage forms (e.g., persons with feeding tubes) due, for example, to regional disparities in infection rates, distribution of resources, or other regional conditions that may evolve quickly during the winter months when the incidence of respiratory infections is expected to peak. This guidance revises and replaces the guidance for industry called *Compounding Certain Ibuprofen Oral Suspension Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act* that was issued on January 20, 2023. FDA is continually assessing the needs and circumstances related to the temporary policy set forth in this guidance, and as relevant

[1] This guidance has been prepared by multiple offices in the Center for Drug Evaluation and Research, in consultation with the Office of Regulatory Affairs, at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *health system* means an organization that includes at least one hospital and at least one group of physicians that provides comprehensive care (including primary and specialty care) who are connected with each other and with the hospital through common ownership or joint management. See the Agency for Healthcare Research and Quality's web page "Compendium of U.S. Health Systems, 2021," available at https://www.ahrq.gov/chsp/data-resources/compendium.html.

needs and circumstances evolve, FDA intends to update, modify, or withdraw this policy as appropriate.[3]

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) and 21 CFR 10.115(g)(2)). This guidance document is being implemented immediately to bolster access to ibuprofen oral suspension products compounded by outsourcing facilities and provided to hospitals, health systems, State-licensed pharmacies, and applicable Federal facilities during the current surge in respiratory infections, but 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

FDA is aware of reports from hospitals, health systems, and State-licensed pharmacies that they have experienced difficulties obtaining certain FDA-approved ibuprofen oral suspension drug products used for fever and pain treatment of pediatric patients and adults who are unable to swallow solid oral dosage forms.[4] FDA is closely monitoring this situation and using all of its applicable authorities to work with the manufacturers of approved ibuprofen oral suspension drug products to increase supply. However, we recognize that hospitals, health systems, State-licensed pharmacies, and applicable Federal facilities have concerns about assuring access to these drug products to use for fever and pain treatment of pediatric patients, and adults who are unable to swallow solid oral dosage form products, during the winter months when respiratory illnesses are likely to be elevated. Therefore, FDA is issuing this policy to provide temporary flexibility to help ensure that treatment options are available when hospitals, health systems, State-licensed pharmacies, and applicable Federal facilities are unable to obtain ibuprofen oral suspension drug products to use for fever and pain treatment of pediatric patients and adults who are unable to swallow solid oral dosage form products. This guidance addresses ibuprofen oral suspension products compounded by outsourcing facilities and provided to: 1) hospitals and health systems for administration within the hospital or health-system; 2) State-licensed pharmacies (including those within hospitals and health systems), and applicable Federal facilities to dispense to patients for use at home after receiving a valid, patient-specific prescription. Fever and pain reducing oral suspension products are needed in the hospital and

[3] FDA understands that outsourcing facilities that compound ibuprofen oral suspension products under the temporary policy in this guidance, in response to the urgent public health need, will do so without being able to fully anticipate when circumstances related to this temporary policy may evolve to a point where the temporary policy is no longer appropriate. Therefore, FDA intends to publish a *Federal Register* notice that provides at least 60-days' notice before the withdrawal of this guidance takes effect.

[4] FDA has received reports related to hospitals, health systems, and State-licensed pharmacies also experiencing challenges with obtaining acetaminophen oral suspension products, which also reduce fever and treat pain. FDA is not addressing acetaminophen oral suspensions at this time to allow time for the review of additional considerations.

health system setting to treat patients with acute needs and also in the home setting for appropriate treatment of children as well as for adults who are unable to swallow solid oral dosage forms.[5] The availability of ibuprofen oral suspensions for use in homes may help to prevent patients from seeking care in hospitals and health systems when such care is not otherwise needed, which could cause unnecessary strain on hospitals and health systems.

Fever and pain reducing oral suspensions, such as ibuprofen oral suspensions, are important in the management of pediatric patients who may require more specific weight-based dosing and adult patients who cannot swallow solid oral dosage form products. Fever can make patients uncomfortable and is associated with increased metabolic rate, oxygen consumption, carbon dioxide production, and demands on the cardiovascular and pulmonary systems. In certain vulnerable populations, untreated high fever could lead to potentially serious or life-threatening situations.

Although compounded drugs can serve an important patient need, they can also pose a higher risk to patients than FDA-approved drugs. Compounded drug products are not FDA-approved, which means they have not undergone FDA premarket review for safety, effectiveness, and quality. Because compounded drug products are subject to a lower regulatory standard, the agency recommends FDA-approved drugs be used to treat patients whenever possible.

Additionally, in 2022 and 2023, FDA received reports of pediatric medication contaminated with diethylene glycol (DEG) and ethylene glycol (EG) in several countries.[6] DEG and EG are toxic

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[5] Unlike the version of this guidance that was issued in January 2023, which was limited to administration of compounded ibuprofen oral suspension products within hospitals and health systems, this guidance also addresses the use of compounded ibuprofen oral suspension products in home settings. In home settings, special packaging, such as child-resistant packaging, is generally required for ibuprofen products intended for oral administration. See 16 CFR 1700.14(a)(20). The Poison Prevention Packaging Act (PPPA) was enacted in 1970 to protect children (under 5 years of age) from unintentional exposure to household substances including food, drugs, and cosmetics in order to prevent poisonings and deaths that can occur when children access the contents of containers with hazardous products. The regulations implementing the PPPA list "special packaging standards" (e.g., child-resistant packaging) for a wide range of household products, including most oral prescription drug products and many nonprescription drug products. See Poison Prevention Packaging Act of 1970 (PPPA), (Pub. L. 91-601, 84 Stat. 1670-74), enacted December 30, 1970.

[6] FDA has received and continues to receive reports about fatal DEG poisoning of consumers who ingested medicinal syrups, such as cough syrup or acetaminophen syrup, that were manufactured with DEG-contaminated glycerin. Recently (January 23, 2023), the WHO announced that countries have reported several incidents of over-the-counter cough syrups for children with confirmed or suspected contamination with high levels DEG and EG. According to the WHO, the cases are from at least seven countries, are associated with more than 300 fatalities, and most involve children under the age of five. See *WHO urges action to protect children from contaminated medicines*, World Health Organization, Jan. 23, 2023, available at https://www.who.int/news/item/23-01-2023-who-urges-action-to-protect-children-from-contaminated-medicines. The WHO has issued three global medical alerts addressing these incidents focused on the outbreak in the Gambia (Oct. 5, 2023), Indonesia (Nov. 6, 2023), and Uzbekistan (Jan. 11, 2023). See *Medical Product Alert N°6/2022: Substandard (contaminated) paediatric medicines*, World Health Organization, Oct. 5, 2022, available at https://www.who.int/news/item/05-10-2022-medical-product-alert-n-6-2022-substandard-(contaminated)-paediatric-medicines; *Medical Product Alert N°7/2022: Substandard (contaminated) paediatric liquid dosage medicines*, World Health Organization, Nov. 2, 2022, available at https://www.who.int/news/item/02-11-2022-medical-product-alert-n-7-2022-substandard-(contaminated)-paediatric-liquid-dosage-medicines; and *Medical Product Alert N°1/2023: Substandard (contaminated) liquid dosage medicines*, World Health Organization, Jan. 11, 2023, available at

to humans when consumed and can be fatal. Toxic effects can include abdominal pain, vomiting, diarrhea, inability to pass urine, headache, altered mental state, and acute kidney injury which may lead to death. Although none of the 2022 reports were regarding products in the United States, DEG and EG contamination has been identified in past reports in the United States and remains a significant quality consideration for oral suspensions compounded using components at higher risk of contamination with DEG and EG.

The policies in this guidance are intended to balance access concerns with risks associated with compounded drug products and particularly with compounded oral suspension products.

III. DISCUSSION

Although FDA is monitoring the global pharmaceutical supply chain and working, within its authorities, with manufacturers of approved ibuprofen oral suspension products to bolster supply, temporary flexibility is needed to help ensure that treatment options are available to hospitals and health systems and children and adults being treated at home during this period of increased demand.

Therefore, as a temporary measure, until FDA withdraws or revises this guidance, FDA intends to prioritize its regulatory or enforcement action for compounding by outsourcing facilities of an ibuprofen oral suspension product (100 mg/5 mL) that is essentially a copy of an FDA-approved drug product;[7] or that uses a bulk drug substance that does not comply with section 503B(a)(2)(A) of the FD&C Act;[8] or that does not meet specific Current Good Manufacturing Practice (CGMP) requirements with regard to the establishment of an initial expiration date through product stability testing,[9] to focus on the potential for harm to the public health. In doing so, FDA is taking into consideration the need to help ensure that hospitals, health systems, State-licensed pharmacies, and applicable Federal facilities have access to certain ibuprofen oral suspension products to treat pediatric patients and adults who are unable to swallow solid oral dosage forms.

Based on FDA's current understanding of the potential risks associated with compounded ibuprofen oral suspensions, outsourcing facilities should take at least the following minimum steps to reduce the risks associated with the compounded products. FDA generally intends to prioritize its regulatory and enforcement actions if the following steps are not all followed when outsourcing facilities compound ibuprofen oral suspension products:

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https://www.who.int/news/item/11-01-2023-medical-product-alert-n-1-2023-substandard-(contaminated)-liquid-dosage-medicines.

[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. The term "essentially a copy" is defined for purposes of this provision by section 503B(d)(2).

[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 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 appropriate product expiration dates when they begin making a compounded product and to ensure the dates are appropriate throughout product expiration.

1. The ibuprofen oral suspension meets the United States Pharmacopeia (USP) ibuprofen oral suspension drug product monograph standard for identity, strength, quality, and purity, and is packaged and labeled in accordance with the provisions in the monograph.[10] One of the critical attributes in the monograph standard is Uniformity of Dosage Units.[11]

2. The ibuprofen oral suspension product has a concentration of 100 mg/5 mL.

3. 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) or National Formulary (NF) 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.

4. Ingredients other than bulk drug substances (i.e., inactive ingredients) that the outsourcing facility uses to compound drug products are in compliance with section 503B(a)(3) of the FD&C Act, regarding conformance with applicable USP or NF monograph standards.

5. Each shipment of each lot of components is tested for identity and evaluated for conformity with appropriate specifications before use in compounding (see § 211.84). The outsourcing facility only uses components that meet appropriate specifications.[12]

6. The outsourcing facility performs a limit test for DEG and EG on all containers of all lots of components at higher risk of DEG and EG contamination, due to the serious hazard associated with DEG and EG contamination, and only uses components that meet appropriate specifications. Components at higher risk of DEG and EG contamination

[10] See sections 501(b) and 502(g) of the FD&C Act.

[11] See USP General Chapter <905> *Uniformity of Dosage Units*. We note that in recent years, there was a recall due to superpotency of liquid ibuprofen suspension drug products. See *Tris Pharma, Inc Expands Its Voluntary Nationwide Retail Recall of Ibuprofen Oral Suspension Drops, USP, 50 mg per 1.25 mL, Due to Higher Concentration of Ibuprofen*, FDA, January 29, 2019, https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/tris-pharma-inc-expands-its-voluntary-nationwide-retail-recall-ibuprofen-oral-suspension-drops-usp. Ensuring uniformity of dose is more difficult in suspensions compared to liquid solutions. For example, there was another recall of children's liquid products in 2010 due to superpotency. See "McNeil Consumer Healthcare Announces Voluntary Recall of Certain OTC Infants' and Children's Products," FDA, April 30, 2010, http://wayback.archive-it.org/7993/20170112155136/http://www.fda.gov/Safety/Recalls/ArchiveRecalls/2010/ucm210443.htm. An associated Form FDA-483, Inspectional Observations, from an April 2010 inspection at McNeil further describes the inspectional issues related to superpotency, https://www.fda.gov/files/about%20fda/published/McNeil-Consumer-Healthcare--Ft.-Washington--PA-483-issued-4-30-10.pdf. Process validation is a critical CGMP element to ensure that the drug production process consistently produces quality drug product. See §211.100.

[12] CGMP regulations require the use of validated methods when performing routine testing of components, in-process material, and finished products (see 21 CFR 211.160, 211.165(e), and 211.194).

include, but are not limited to, propylene glycol, glycerin, polyethylene glycol, sorbitol solution, maltitol solution, and hydrogenated starch hydrolysate.[13, 14, 15]

7. The ibuprofen oral suspension formulation contains a level of an antimicrobial preservative, based upon scientifically valid literature, that is below a level that may be toxic to humans based on the recommended dosage and provides effective microbial protection for the duration of the labeled shelf-life.[16] Antimicrobial effectiveness testing (AET) is conducted once for each formulation and container-closure system on samples aged to the proposed beyond-use-date (BUD) or expiration date. The AET study is conducted before the first batch is released. For the purposes of this guidance, when an outsourcing facility uses containers of different sizes, and the materials for the container and cap liner are the same, FDA does not expect the outsourcing facility to conduct AET studies on more than one container size, provided preservative content testing is conducted prior to the release of each batch of drug product, regardless of the container size.

8. The ibuprofen oral suspension formulation is compounded using sterile water that complies with a USP sterile water monograph or the outsourcing facility conducts specific testing for Burkholderia cepacia complex (BCC) in accordance with USP <60> as part of batch release testing.[17]

9. The outsourcing facility's practices regarding stability testing and expiration dates at least meet the conditions 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), except that:

    a. The outsourcing facility uses a default BUD of not more than 30 days at room temperature when limited stability testing has not been completed before release;[18] and

[13] For additional information, see FDA guidance for industry *Testing of Glycerin for Diethylene Glycol* (May 2007). 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.

[14] Reliance on a certificate of analysis from a component supplier, alone, is insufficient to meet CGMP requirements, including with regard to component testing under 21 CFR 211.84.

[15] FDA's regulation at 21 CFR 211.84(a) requires testing of each lot of components; 21 CFR 211.84(b) requires that a representative sample of each shipment of each lot be collected for testing and describes that the number of containers to be sampled shall be based upon appropriate criteria. Because DEG and EG contamination presents a serious hazard, the Agency recommends that the representative sample collected for testing is of each container of each lot.

[16] See USP General Chapter <51> *Antimicrobial Effectiveness Testing*.

[17] This release testing is in addition to microbiological batch release tests such as microbial enumeration (total aerobic microbial count, total combined yeasts/molds count) and tests for specified microorganisms (for ibuprofen suspension, the specific microorganism is Escherichia coli).

[18] Compare Table 1 in Appendix A: "Default BUDs for Nonsterile Drug Products with Aggregate Batch Size ≤ 5,000 Units."

b. The outsourcing facility **initiates** limited stability testing[19] when the aggregate batch size[20] is expected to exceed 5,000 units.[21]

10. The ibuprofen oral suspension is labeled consistent with section 503B(a)(10)(A)-(B) of the FD&C Act and the label on the immediate container[22] of the ibuprofen oral suspension product, whether used for administration within a hospital or health system or for dispensing to patients for use at home, includes statements in bold type to "**Discard by [insert beyond-use-date]**" and "**Shake well before using.**"

11. The ibuprofen oral suspension product is provided:

    a. directly to a hospital or health system for administration within the hospital or health system;[23] or

    b. directly to a State-licensed pharmacy (including those within hospitals and health systems[24]), or an applicable Federal facility, to dispense to patients for use at home after receiving a valid, patient-specific prescription and without repackaging by the pharmacy or Federal facility.[25]

12. For ibuprofen oral suspension products that the outsourcing facility provides for dispensing to patients with a valid, patient-specific prescription for use at home, whether the product is provided to State-licensed pharmacies, including those within hospitals and health systems, or to Federal facilities:

    a. The outsourcing facility packages the ibuprofen oral suspension product in a container that holds no more than 120 mL of ibuprofen oral suspension.
    b. The outsourcing facility ensures that the labeling on the ibuprofen oral suspension product's immediate container includes the information in Appendix C. If the ibuprofen oral suspension is packaged in a container that is too small to

[19] As described in Appendix B.

[20] 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*.

[21] As used here, consistent with Appendix A, *units* are immediate containers (e.g., vial, bottle) for liquid dosage forms.

[22] As used in this guidance, *immediate container* means the container (e.g., bottle) that holds and is in contact with the ibuprofen oral suspension.

[23] Administration within the hospital or health system does not include providing units of ibuprofen oral suspension to a patient for use outside the hospital or health system, such as a bottle of compounded drug product for use at home.

[24] To help reduce risks including microbial contamination and accidental overdosing, FDA recommends that hospital and health system pharmacies that seek to dispense compounded ibuprofen oral suspension products to patients for use at home do so in containers procured directly from an outsourcing facility, as described in this section, that have not undergone any repackaging at the hospital or health system before such dispensing.

[25] For purposes of this guidance, *repackaging* means taking some or all of the compounded ibuprofen oral suspension product from the container in which it was distributed by the outsourcing facility and placing it into a different container or container(s) without further manipulating the product.

reasonably include all of the information in Appendix C (e.g., this may be the case for a container that holds 50 mL), the outsourcing facility provides the information in Appendix C by another means such as an outer packaging box. If an alternative means of providing the information is used, the immediate container label contains, at a minimum, the active ingredient, dosage strength, uses, and directions for use, including the dosing chart.[26]

c. The outsourcing facility ensures that the ibuprofen oral suspension product complies with applicable requirements under the PPPA, such as "special packaging standards" as applicable.[27]

13. Outsourcing facilities report adverse events associated with the products compounded under this enforcement policy consistent with the FDA guidance for industry *Adverse Event Reporting for Outsourcing Facilities Under Section 503B of the Federal Food, Drug, and Cosmetic Act* (October 2015).

FDA encourages health care professionals to report adverse events experienced with the use of compounded ibuprofen oral suspension products to the outsourcing facilities that produced the products as well as to FDA's MedWatch Adverse Event Reporting program:

- Complete and submit the report online; or
- Download and complete the form, then submit it via fax at 1-800-FDA-0178.

[26] FDA understands that State-licensed pharmacies sometimes provide dosage cups and oral syringes and outsourcing facilities may also provide these items. Because the dosing directions would be expressed in milliliters (mL), FDA notes that it is critical that any products, such as dosage cups and oral syringes, that are intended to provide calibrated units of liquid measurement are expressed in milliliters (mL) only.

[27] See 16 CFR 1700 for substances requiring special packaging and the relevant packaging standards. See also footnote 6 of this guidance.

Appendix A: Stability/Expiration Dating for Compounded Drug Products

1. 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, appropriate microbial quality) through the labeled expiration date. A stability program for compounded drug products should use previous experience, 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 during and 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.

Taking into account the unique aspects of compounding, FDA generally does not intend to take regulatory action against an outsourcing facility for compounding ibuprofen oral suspension products according to the circumstances in this guidance, including those in the remainder of this section and in Appendix B, such as using a BUD established through limited stability testing in lieu of establishing an expiration date through the conduct of a full stability program required under part 211 (21 CFR part 211),[28] if 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.

Whether you use an expiration date or BUD to be used as an expiration date according to the provisions outlined below and in Appendix B, the studies below are required to be completed before a batch is released (see §§ 211.166 and 211.167). Each antimicrobial effectiveness testing study only needs to be conducted once for each formulation and container-closure system.

- **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 and formulation specific.)[29] As noted in number 7 in section III above, for purposes of this guidance, when an outsourcing facility uses containers of different sizes, and the materials for the container and cap liner are the same, FDA does not expect the outsourcing facility to conduct AET studies on more than one container size, provided preservative content testing is conducted prior to the release of each batch of drug product, regardless of the container size.

[28] 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)).

[29] See USP General Chapter <51> *Antimicrobial Effectiveness Testing* for more information.

286
287 *2. Non-sterile limited stability testing*
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289 In lieu of conducting full stability studies required under part 211, for small batches (≤5,000
290 units[30] in an aggregate batch[31]), FDA generally does not intend to take regulatory action if the
291 relevant default BUD of not more than 30 days at room temperature when limited stability
292 testing has not been completed before release, as provided in this guidance, is used for the
293 expiration date and the conditions set forth in Appendix B are met. Alternatively, for small
294 batches, FDA generally does not intend to take regulatory action if limited stability testing is
295 conducted to support a BUD longer than 30 days at room temperature in accordance with
296 Appendix B, and that BUD is used as an expiration date in lieu of conducting full stability
297 studies required under part 211. For larger batches (>5,000 units in an aggregate batch), FDA
298 generally does not intend to take regulatory action regarding stability testing if the relevant
299 conditions for the limited stability testing outlined in Appendix B are met. If, at any time during
300 a 6-month reporting period, the total number of units compounded exceeds the 5,000-unit limit,
301 the conditions applicable to small batches (i.e., ≤5,000 units) do not apply.
302
303 **Table 1. 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**
≤5,000 units	Default BUD, which may be further limited by literature or other scientific information. See Appendix B for the conditions that must be met.	Data-driven stability program. See Appendix B 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 B for the conditions that must be met.

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[30] *Units* are immediate containers (e.g., vial, bottle) for liquid dosage forms.
[31] 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*.

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

Enforcement Policy Regarding the Use of Limited Stability Testing to Assign a BUD

Stability testing is intended to confirm the stability performance of a 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.

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.

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).

A. Nondestructive tests

The following test is conducted:

- Appearance.

B. Destructive chemical tests

The tests to be conducted include:

- pH.
- Assay.[32]
- Appropriate specifications.[33]

C. Microbiological tests

The tests to be conducted include:

- Antimicrobial effectiveness testing/preservative content testing at expiry.
- Microbial enumeration[34] (USP General Chapter <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests*).
- Test for specified organisms[35] (USP General Chapter <62> *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms*).[36]

[32] 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.
[33] For ibuprofen oral suspension products appropriate specifications include the additional tests in the USP monograph: Identification, dissolution, uniformity of dosage units, deliverable volume, and impurities.
[34] See, for example, USP General Chapter <1111> *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*.
[35] See, for example, USP General Chapter <1111> *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*.
[36] If sterile water is not used, USP General Chapters <60> *Microbiological Examination of Nonsterile Products – Tests for Burkholderia cepacia complex*.

Appendix C: Information for Inclusion on the Labeling of Ibuprofen Oral Suspension Products for Dispensing

The following is an example of partial content of the FDA-approved labeling of a children's ibuprofen oral suspension product (100mg/5mL); to label products as described in item 12.b. of this guidance, the outsourcing facility would include all of this information on the labeling of the ibuprofen oral suspension product's immediate container when dispensed to a patient for use at home.[37]

Drug Facts

Active ingredients (in each 5 mL)
Ibuprofen 100 mg

Purpose (NSAID)* …… Fever reducer/Pain reliever
*nonsteroidal anti-inflammatory drug

Uses
temporarily:

- reduces fever
- relieves minor aches and pains due to the common cold, flu, sore throat, headaches, and toothaches

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Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:

- hives
- facial swelling
- asthma (wheezing)
- shock
- skin reddening
- rash
- blisters

If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if the child:

- has had stomach ulcers or bleeding problems
- takes a blood thinning (anticoagulant) or steroid drug

[37] For containers smaller than 120 mL if the container is too small to reasonably permit the inclusion of all of this information on the immediate container, the outsourcing facility would provide the information by another means such as an outer packaging box. If an alternative means of providing the information is used, the immediate container would contain, at a minimum, the active ingredient, dosage strength, uses, and directions for use, including the dosing chart.

- takes other drugs containing prescription or nonprescription NSAIDs [aspirin, ibuprofen, naproxen, or others]
- takes more or for a longer time than directed

Heart attack and stroke warning: NSAIDs, except aspirin, increase the risk of heart attack, heart failure, and stroke. These can be fatal. The risk is higher if you use more than directed or for longer than directed.

Sore throat warning: Severe or persistent sore throat or sore throat accompanied by high fever, headache, nausea, and vomiting may be serious. Consult doctor promptly. Do not use more than 2 days or administer to children under 3 years of age unless directed by doctor.

Do not use

- if the child has ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if

- stomach bleeding warning applies to the child
- child has problems or serious side effects from taking pain relievers or fever reducers
- child has a history of stomach problems, such as heartburn
- child has high blood pressure, heart disease, liver cirrhosis, kidney disease, asthma, or had a stroke
- child has not been drinking fluids

Ask a doctor or pharmacist before use if the child is

- under a doctor's care for any serious condition
- taking any other drug

When using this product

- take with food or milk if stomach upset occurs

Stop use and ask a doctor if

- child experiences any of the following signs of stomach bleeding:
    - feels faint
    - vomits blood
    - has bloody or black stools
    - has stomach pain that does not get better
- child has symptoms of heart problems or stroke:
    - chest pain
    - trouble breathing
    - weakness in one part or side of body
    - slurred speech
    - leg swelling
- child has lost a lot of fluid due to vomiting or diarrhea

- child is taking a diuretic
- the child does not get any relief within first day (24 hours) of treatment
- fever or pain gets worse or lasts more than 3 days
- redness or swelling is present in the painful area
- any new symptoms appear

Directions

- **this product does not contain directions or complete warnings for adult use**
- **do not give more than directed**
- **shake well before using**
- **mL = milliliter**
- find right dose on chart. If possible, use weight to dose; otherwise use age.
- repeat dose every **6-8 hours**, if needed
- do not use more than **4 times a day**
- **discard after [insert beyond-use-date]**

Dosing Chart		
Weight (lb)	Age (yr)	Dose (mL)
Under 24 lb	Under 2 yr	Ask a doctor
24-25 lb	2-3 yr	5 mL
36-47 lb	4-5 yr	7.5 mL
48-59 lb	6-8 yr	10 mL
60-71 lb	9-10 yr	12.5 mL
72-95 lb	11 yr	15 mL

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