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

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)

January 2023
Compounding

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

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
Office of Policy

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

January 2023
Compounding

TABLE OF CONTENTS

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 in outsourcing facilities for administration in hospitals and health systems.[2] The United States is currently experiencing a surge in 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 and health systems experiencing challenges with obtaining these medications to use in the treatment of pediatric patients with fever 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. FDA is continually assessing the needs and circumstances related to the temporary policy set forth in this guidance, and as relevant needs and circumstances evolve FDA intends to update, modify, or withdraw this policy as appropriate.

This guidance is being implemented without prior public comment because the Agency has determined that prior public participation is not feasible or appropriate (see 21 CFR 10.115(g)(2) and (g)(3). FDA made this determination because of the urgent need to bolster access to ibuprofen oral suspension products in hospitals and health systems during the current surge in respiratory infections, as described above, but the guidance remains subject to comment in accordance with the Agency's good guidance practices.

[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.

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 and health systems that they have experienced difficulties obtaining certain FDA-approved ibuprofen oral suspension drug products used for pediatric patients with fever and adults who are unable to swallow solid oral dosage forms.[3] FDA is closely monitoring this situation and using all of its applicable authorities to work with the manufacturers of the approved ibuprofen oral suspension drug products to increase supply. However, we recognize that hospitals and health systems have concerns about assuring access to these drug products to treat pediatric patients with fever and adults who are unable to swallow solid oral dosage form products during the winter months, when respiratory illnesses may be elevated. Therefore, FDA is issuing this policy to provide temporary flexibility to help ensure that treatment options are available when hospitals and health systems are unable to obtain oral suspension drug products to use in the treatment of pediatric patients with fever and adults who are unable to swallow solid oral dosage form products. This guidance is limited to ibuprofen oral suspension products used in hospitals because hospitals treat patients with more acute needs and have better controls to assure appropriate dosing and administration than generally would be found in the household setting.

Fever-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.

Compounded drug products are not FDA-approved, which means they have not undergone FDA premarket review for safety, effectiveness, and quality.

Additionally, in 2022, FDA received reports of pediatric medication contaminated with diethylene glycol (DEG) and ethylene glycol (EG) in several countries.[4] DEG and EG are toxic

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

[4] 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 (October 5, 2022), the WHO announced that contaminated children's cough and cold syrup was

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 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;[5] or that uses a bulk drug substance that does not comply with section 503B(a)(2)(A) of the FD&C Act;[6] or that does not meet specific CGMP requirements with regard to the establishment of an initial expiration date through product stability testing,[7] 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 and health systems have access to certain ibuprofen oral suspension products to treat pediatric patients and adults who are unable to swallow solid oral dosage forms.

---

found in The Gambia, Africa, with unacceptable amounts of the DEG and EG contaminants. According to the WHO, the products may have been distributed through informal markets to other countries or regions and have been potentially linked with acute kidney injuries and deaths among children. 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. Similarly, the WHO announced that children's liquid dosage medicines containing unacceptable amounts of DEG and/or EG were identified in Indonesia. According to the WHO, the products may have been distributed, through informal markets, to other countries or regions. See *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.

[5] 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).

[6] 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.

[7] 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 an appropriate product expiration date when they begin making a compounded product and to ensure the date is appropriate throughout product expiration.

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:

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 labeled in accordance with the provisions in the monograph.[8] One of the critical attributes in the monograph standard is Uniformity of Dosage Units.[9]

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. The outsourcing facility performs required testing on all components. In addition, a specific identity test must be performed on all containers of material at higher risk of DEG and EG contamination, such as propylene glycol, glycerin, polyethylene glycol, sorbitol solution, maltitol solution, and hydrogenated starch hydrolysate, due to the serious hazard associated with DEG and EG contamination, and only uses components that meet appropriate specifications.[10, 11, 12]

---

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

[9] 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. Process validation is a critical CGMP element to ensure that the drug production process consistently produces quality drug product. See §211.100.

[10] 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.

[11] 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.

[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).

6. 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.[13] 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. In addition, preservative content testing is conducted prior to the release of each batch of drug product.

7. 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.[14]

8. 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;[15] and
    b. The outsourcing facility **initiates** limited stability testing[16] when the aggregate batch size[17] is expected to exceed 5,000 units.[18]

9. The ibuprofen oral suspension is labeled consistent with section 503B(a)(10)(A)-(B) of the FD&C Act.

10. The ibuprofen oral suspension product is provided directly to a hospital or health system for administration in the hospital or health system.[19]

---

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

[14] 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).

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

[16] As described in Appendix B.

[17] 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*.

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

[19] 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.

11. 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.

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),[20] 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 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 doses is conducted on samples aged to the proposed BUD or expiration date. (Note that antimicrobial effectiveness testing is container-closure and formulation specific.)[21]

[20] 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)).

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

2. Non-sterile limited stability testing

In lieu of conducting full stability studies required under part 211, for small batches (≤5,000 units[22] in an aggregate batch[23]), FDA generally does not intend to take regulatory action if the relevant default BUD of not more than 30 days at room temperature when limited stability testing has not been completed before release, as provided in this guidance, is used for the expiration date and the conditions set forth in Appendix B 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 30 days at room temperature in accordance with Appendix B, 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 B are met. If, at any time during a 6-month reporting period, the total number of units compounded exceeds the 5,000-unit limit, the conditions applicable to small batches (i.e., ≤5,000 units) do not apply.

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.

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

[23] 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 doses. 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 no 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.[24]
- Appropriate specifications.[25]

C. Microbiological tests

The tests to be conducted include:

- Antimicrobial effectiveness testing/preservative content testing at expiry.
- Microbial enumeration[26] (USP General Chapter <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests*).
- Test for specified organisms[27] (USP General Chapter <62> *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms*).[28]

[24] 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.
[25] 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.
[26] See, for example, USP General Chapter <1111> *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*.
[27] See, for example, USP General Chapter <1111> *Microbiological Examination of Nonsterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*.
[28] If sterile water is not used, USP General Chapters <60> *Microbiological Examination of Nonsterile Products – Tests for Burkholderia cepacia complex*.