
Guidance for Industry

Sterility Requirement for Aqueous- Based Drug Products for Oral Inhalation — Small Entity Compliance Guide

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

**November 2001
Small Entity Compliance Guides**

Guidance for Industry

Sterility Requirement for Aqueous- Based Drug Products for Oral Inhalation — Small Entity Compliance Guide

*Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
<http://www.fda.gov/cder/guidance/index.htm>*

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

**November 2001
Small Entity Compliance Guides**

Guidance for Industry¹

Sterility Requirement for Aqueous-Based Drug Products for Oral Inhalation — Small Entity Compliance Guide

This guidance document represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This small entity compliance guide is one of a series of guidance documents prepared in accordance with section 212 of the Small Business Regulatory Fairness Act (Public Law 104-121). The guidances are intended to explain the actions small entities are required to take to comply with rules for which the Agency prepared a final regulatory flexibility analysis.

This guidance restates in plain language the legal requirements set forth in the current regulation requiring that all prescription and over-the counter (OTC) aqueous-based drug products for oral inhalation be manufactured sterile. FDA issued a final rule, published in the *Federal Register* of May 26, 2000 ([65 FR 34082](#)), in response to reports of adverse drug experiences from contaminated nonsterile inhalation drug products and recalls of these products. FDA issued the final rule after considering all comments on the proposed rule, which was published in the *Federal Register* of October 11, 1991 (56 FR 51354).

II. SUMMARY OF THE REGULATION

In the final rule, FDA amended its regulations governing specific classes of drug products by adding new § [200.51](#) (21 CFR 200.51). Section 200.51 requires that all aqueous-based drug products for oral inhalation be manufactured sterile as of the effective date of the rule. Manufacturers must also comply with § [211.113\(b\)](#) (21 CFR 211.113(b)), which requires them to establish and follow appropriate written procedures designed to prevent microbiological contamination of any product manufactured sterile, including validation of any sterilization process used. Manufacturers must be in compliance with the final rule as of its effective date, May 27, 2002.

¹ This small business compliance guide was developed by the Office of Regulatory Policy in the Center for Drug Evaluation and Research, FDA.

III. QUESTIONS AND ANSWERS

Question: Is the product I manufacture subject to this rule?

Answer: If you manufacture an aqueous-based oral inhalation drug product, your drug product is subject to this rule and must be manufactured sterile. The rule applies to drug products packaged in both single-dose and multiple-use primary packaging. *Nasal spray drug products and pressurized metered-dose inhalers are not subject to this rule.*

Question: I manufacture an aqueous-based oral inhalation drug product that is packaged in single-dose primary packaging. Is my drug product subject to this rule?

Answer: Yes, drug products packaged in both single-dose and multiple-use primary packaging are subject to this rule.

Question: I manufacture an aqueous-based oral inhalation drug product that is a suspension. Is my drug product subject to this rule?

Answer: Aqueous-based suspensions for oral inhalation are subject to this rule. However, if your suspension drug product is packaged in a pressurized metered-dose inhaler, it is not subject to the rule.

Question: I currently manufacture a drug product that is subject to this rule and is not manufactured sterile. What must I do to comply with this rule?

Answer: You must submit a supplemental [new drug application](#) (NDA) or a supplemental abbreviated new drug application (ANDA) to establish the sterility of your drug product. Your supplemental application must be submitted to FDA no later than May 27, 2002.

Question: I currently have an NDA or ANDA pending for a nonsterile aqueous-based drug product for oral inhalation with FDA. What must I do to comply with this rule?

Answer: If your NDA or ANDA was under review by FDA between May 26, 2000, and May 27, 2002, your application may be approved if it is otherwise approvable and you agree to establish the sterility of the drug product in a supplemental application by May 27, 2002. On or after May 27, 2002, FDA will refuse to approve an NDA or ANDA for your drug product if you have not established the sterility of the product.

Question: I plan to manufacture a new drug product that is subject to this rule. What must I do to comply with this rule?

Answer: The NDA or ANDA you submit to FDA must establish the sterility of your drug product.

Question: When must I be in compliance with this rule?

Answer: You must be in compliance with this rule no later than May 27, 2002. On or after May 27, 2002, you are prohibited from introducing or delivering for introduction into interstate commerce any nonsterile aqueous-based drug products for oral inhalation except for those drug products marketed in pressurized metered-dose inhalers or as nasal sprays.

Question: What will happen if I fail to comply with this rule by May 27, 2002?

Answer: If you fail to comply with this rule by May 27, 2002, your drug product will be found to be adulterated under section 501(a)(2)(B) of the [Federal Food, Drug, and Cosmetic Act \(the Act\)](#) (21 U.S.C. 351 (a)(2)(B)) and misbranded under section 502(j) of the Act (21 U.S.C. 352(j)) and may be subject to regulatory action. In addition, the Agency will refuse to approve a new or abbreviated application for a drug product that fails to comply with this rule, under section 505(d)(1), (d)(2), (d)(3), and (j)(4)(A) of the Act (21 U.S.C. 355(d)(1), (d)(2), (d)(3), and (j)(4)(A)).

Question: If I have questions about whether the drug product I manufacture is subject to this rule, how to comply with the rule, or any related issues, whom should I contact at FDA?

Answer: You should contact the Assistant Director for Microbiology, Office of New Drug Chemistry, at the Center for Drug Evaluation and Research (HFD-805), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-7340.