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Dated: May 11, 2000.

**L. Robert Lake,***Director of Regulations and Policy, Center for Food Safety and Applied Nutrition.*

[FR Doc. 00-13209 Filed 5-25-00; 8:45 am]

BILLING CODE 4160-01-F

**DEPARTMENT OF HEALTH AND HUMAN SERVICES****Food and Drug Administration****21 CFR Part 200**

[Docket No. 96N-0048]

RIN 0910-AA88

**Sterility Requirement for Aqueous-Based Drug Products for Oral Inhalation****AGENCY:** Food and Drug Administration, HHS.**ACTION:** Final rule.

**SUMMARY:** The Food and Drug Administration (FDA) is amending its regulations to require that all prescription and over-the-counter (OTC) aqueous-based drug products for oral inhalation be manufactured sterile. This rule applies to aqueous-based oral inhalation drug products in both single-dose and multiple-use primary packaging. Pressurized metered-dose inhalers are not subject to this rule. Based on reports of adverse drug experiences from contaminated nonsterile inhalation drug products and recalls of these products, FDA is taking this action to help ensure the safety and effectiveness of these products.

**DATES:** This rule is effective May 27, 2002.**FOR FURTHER INFORMATION CONTACT:**

Peter H. Cooney, Center for Drug Evaluation and Research (HFD-160), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-5818.

**SUPPLEMENTARY INFORMATION:****I. Background**

In the *Federal Register* of September 23, 1997 (62 FR 49638), FDA proposed to amend its regulations to require that all inhalation solutions for nebulization be manufactured sterile. This action was proposed to help ensure the safety and effectiveness of these drug products.

Drug products for oral inhalation are used to treat a variety of breathing disorders and are frequently administered to patients who are immunocompromised, have cystic fibrosis, or have chronic obstructive

airway disease. Aqueous-based oral inhalation drug products either in single-dose or multiple-use packaging are administered by oral inhalation into the lungs as a mist or spray created by a nebulizer device. The majority of inhalation drug products on the market are manufactured to be sterile. Those products not manufactured to be sterile are often manufactured under assigned microbial count limits, but current manufacturing methods and safeguards have not prevented dangerous microbial contamination.

Inhalation drug products contaminated with microorganisms are likely to cause lung infections because the contaminating organisms are introduced with the drug product directly into the lungs through the mouth. Thus, microbial contamination of these products may result in serious health consequences. Microbial contamination of these products may also cause degradation of the drug product.

Because of contamination problems with several different aqueous-based drug products for oral inhalation and for the reasons explained in the proposed rule, FDA has determined that current manufacturing methods and safeguards against contamination, including microbial limits tests, have not prevented dangerous microbial contamination of nonsterile aqueous-based drug products for oral inhalation.

The final rule reflects FDA's determination that all aqueous-based drug products for oral inhalation be manufactured sterile. Once the final rule becomes effective, failure to comply with the sterility requirement will result in a finding that the drug product is 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)). Failure to comply with the sterility requirement will also result in the agency's refusal to approve a new or abbreviated application for a product, 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)).

**II. Highlights of the Final Rule**

This final rule amends the regulations governing requirements for specific classes of drugs to include new § 200.51 for aqueous-based drug products for oral inhalation. Section 200.51(a) requires that all prescription and OTC aqueous-based drug products for oral inhalation be manufactured sterile. FDA is taking this action to prevent the public health consequences of the distribution of contaminated aqueous-based drug

products for oral inhalation and to help ensure the safety and effectiveness of these products.

In the *Federal Register* of October 11, 1991 (56 FR 51354), FDA proposed to require that manufacturers use a terminal sterilization process when preparing a sterile drug unless the process adversely affects the drug product. The October 11, 1991, proposed rule would require that manufacturers include in their applications a written justification for not using terminal sterilization if such process is not appropriate. The agency plans to issue a final rule regarding terminal sterilization. When the proposed requirement for terminal sterilization becomes final, manufacturers of aqueous-based drug products for oral inhalation will be subject to its requirements.

The agency has revised the proposed regulation in response to comments received on the proposed rule. The comments and responses are discussed in section III of this document, "Comments on the Proposed Rule." The agency is revising the title of proposed § 200.51 from "Sterility Requirements for Inhalation Solution Drug Products" to "Aqueous-Based Drug Products for Oral Inhalation." The new title names the specific class of drugs subject to the rule in conformance with the established format of part 200 (21 CFR part 200), subpart C of the regulations. The agency is removing the phrases "inhalation solution drug products" and "inhalation solutions for nebulization" from proposed § 200.51. These phrases are replaced by the phrase "aqueous-based drug products for oral inhalation." The agency has added the phrase "for oral inhalation" to clarify that the rule applies to orally administered inhalation drug products and not nasal sprays. The agency has added the modifier "aqueous-based" to the type of drug products covered to exclude metered-dose inhalers from coverage. In addition, the agency has made minor edits to the final rule in response to the President's June 1, 1998, memorandum on plain language in government writing. The agency has increased the amount of time for manufacturers to comply with the sterility requirement from 1 year to 2 years. All manufacturers of nonsterile aqueous-based drug products for oral inhalation will have until 2 years after the date of publication of the final rule to comply with the sterility requirement. As discussed in section IV of this document, "Effective Date," the agency believes this effective date more realistically reflects the time