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Dated: May 11, 2000.

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[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

manufacturers may need to establish the sterility of their products.

Section 200.51(b) states that manufacturers must comply with the requirements of 21 CFR 211.113(b) of FDA's current good manufacturing practice (CGMP) regulations. This section requires that manufacturers establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile. Such procedures must include validation of any sterilization process.

In addition to the above highlights, the agency notes that persons holding an approved new drug application (NDA) or abbreviated application for a nonsterile aqueous-based drug product for oral inhalation must submit to FDA a supplemental application describing the new manufacturing process under § 314.70(b) or § 314.97 (21 CFR 314.70(b) or 314.97). The proposed rule stated that if a manufacturer intended to sterilize a product by terminal sterilization, the manufacturer must obtain prior FDA approval for such change under § 314.70(b)(2), but if a manufacturer intended to sterilize a product by aseptic processing they may make the change at the time a supplemental application is submitted under § 314.70(c)(1). The agency has now determined that the technological complexity of aseptic processing warrants prior approval of any changes in the manufacturing process. Accordingly, the agency concludes that all manufacturing changes related to sterility requirements require supplemental applications to be submitted and approved under § 314.70(b)(2) prior to making any changes. In November 1999, a guidance related to this topic, entitled ''Changes to an Approved NDA or ANDA,'' became available. This guidance states that the agency considers a change in the sterilization process, e.g. from aseptic processing to terminal sterilization or vice versa, a major change to any approved application for which the manufacturer should submit a prior approval supplement. The agency notes that a proposed rule entitled ''Supplements and Other Changes to an Approved Application,'' published in the **Federal Register** of June 28, 1999 (64 FR 34608). This proposed rule is currently being finalized and may further affect the filing of supplemental applications related to this rule.

The following information should be included in a supplemental application related to this rule:

- Complete validation data for the aseptic process (see November 1994 guidance document entitled ''Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products'');
- For abbreviated applications, an executed batch record for a production batch of the product using the approved formulation;
- In-process and release control data;
- Updated release specifications that include sterility;
- Three months accelerated stability data;
- An updated stability protocol to include either sterility or container/closure integrity testing initially and at expiry; and
- A commitment to place the first three commercial batches into the routine stability program and submit the data in annual reports.

III. Comments on the Proposed Rule

The agency received a total of 61 comments on the September 23, 1997, proposed rule. Forty-nine of those comments were from consumers of an OTC aqueous solution of epinephrine sold in a kit with an atomizer. Of the remaining 12 comments, 8 were from industry, 2 were from associations of health care professionals, 1 was from academia, and 1 was from a Federal Government agency. The majority of comments requested clarification of the scope of the rule and the drug products intended to be covered, and also discussed the economic impacts of the proposed rule.

A. Covered Products

1. The proposed rule stated: ''All inhalation solutions for nebulization shall be manufactured to be sterile'' (proposed § 200.51(a)). Several comments indicated that the scope of drug products intended to be covered by the proposed rule was either unclear or overbroad. Some of the comments asked whether intranasal sprays would be subject to the rule. One comment asked whether both OTC and prescription drugs were covered. Three comments suggested clarifying that only aqueous-based drug products are subject to the rule. One comment interpreted the proposed rule to cover OTC and prescription drugs dispensed out of a manufacturer's primary packaging container into a separate, secondary and independent device prior to administration to the end user or patient, excluding nebulized or atomized sprays for inhalation. The comment stated that primary formulations should include both single-dose and multiple-use sterile products to eliminate microbial contamination during use. One comment suggested that the rule cover inhalation suspension products, stating that they contain more nutrients that contaminating microorganisms can metabolize than do inhalation solutions, and suggested that the title of the rule be modified to reflect this change.

The agency has considered these comments and agrees that further clarification of products covered by the rule is warranted. In response to these comments, the agency has revised the final rule to state: ''All aqueous-based drug products for oral inhalation must be manufactured to be sterile.'' Because the rule covers only drug products administered orally, it does not cover nasal sprays. Because the rule covers only aqueous-based drug products, pressurized metered-dose inhalers are not covered. All marketed prescription and OTC drugs are covered by the rule.

The agency agrees with the comment that inhalation suspension products pose contamination risks at least as great as those of inhalation solution products. Aqueous-based suspension drug products for oral inhalation would also bypass many of a patient's natural defense mechanisms and, if contaminated, pose similar risks. However, all currently marketed inhalation suspension drug products are metered-dose inhalers and, because they are metered-dose inhalers, are not subject to this final rule. Any aqueous-based oral inhalation suspension drug products approved in the future that are not metered-dose inhalers are subject to this rule.

B. Pharmacy Compounding

2. One comment asked whether the proposed rule would cover solutions for oral inhalation compounded under applicable practice of pharmacy provisions and regulations. Another comment stated that a large fraction of nebulizer solutions sold in the United States are compounded in pharmacies and suggested that such facilities use chemicals of dubious quality, that such solutions are dispensed in unsafe vials, and that preservatives used are contraindicated in anti-asthma products. This comment supported the rule and suggested that the rule would resolve issues of compounding in pharmacies which, the comment stated, results in millions of dollars in Medicare fraud.

Compounding occurs when a pharmacist or physician mixes, combines, or alters ingredients to create a customized drug product for an individual patient. The issue of pharmacy compounding is addressed in section 127 of the Food and Drug

Administration Modernization Act of 1997 (Pub. L. 105–115). Section 127 adds section 503A to the act (21 U.S.C. 353a). Section 503A(b)(3)(A) of the act provides that a drug product may qualify for exemptions from certain provisions of the act, including CGMP requirements (section 501(a)(2)(B) of the act) if, among other conditions, the drug product is not identified by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product. FDA intends to issue regulations to implement section 503A(b)(3)(A) of the act. During the course of that rulemaking, the agency intends to consider, among other issues, whether aqueous-based drug products for oral inhalation present demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product. Compounded aqueous-based drug products for oral inhalation that fail to meet any of the conditions of section 503A of the act are subject to the statutory CGMP provision (section 501(A)(2)(B) of the act) and, therefore, are subject to the requirements of this final rule.

C. Packaging

3. Several comments asked whether the proposed rule addresses maintaining the sterility of multiple-use containers after the container is opened and closed for later use. These comments stated that there is a high risk of contamination of inhalation drug products when multiple-use containers, e.g., bottles with droppers, are opened and used in a nonsterile environment. One comment asked whether the rule would require single-dose containers for one-time use. Two comments noted that new packaging is either on the market or in development that would eliminate the need to transfer aqueous-based drugs into separate secondary receptacles, thus reducing the potential for microbial contamination.

The agency recognizes that multiple-use containers raise issues of microbial contamination when aseptic handling procedures are not used either by a patient at home or in a hospital setting. However, the intent of this rule is to ensure sterility from the point of manufacture. The rule is intended to prevent contaminated products from being distributed by manufacturers. While the agency encourages the use of single-dose containers, the agency is not requiring their use at this time. The agency supports innovations in new packaging that would reduce the likelihood of microbial contamination. The agency has no current plans, however, to require the use of such packaging by manufacturers.

D. Antimicrobial Preservatives

4. One comment suggested that the proposed rule was a ''simplistic fix'' for a series of complex problems including inadequate antimicrobial preservation systems for in-use contamination control, inadequate U.S. Pharmacopeia (USP) microbiological testing methods, and defective hospital infection control procedures. The comment questioned the adequacy of microbial limits testing, in particular USP procedure <61>, to reliably detect the prevalent contaminants of inhalation drug products. The comment also suggested that there is no evidence for the assumption underlying the proposed rule that contaminating organisms have developed resistance to the antimicrobial preservative systems used. The comment stated that organisms historically known to be resistant to benzalkonium chloride have been noted and that mistakes have occurred when companies have made errors designing a product's antimicrobial preservative system. The comment also noted the inadvisability of using a single preservative in the manufacturing process and suggested that the proposed rule shows that the agency now believes preservatives are to be used to address inadequate manufacturing contamination controls that were previously considered to be serious CGMP violations.

Another comment acknowledged that some antimicrobial preservatives are no longer effective because resistance to them in certain bacterial strains has developed, and expressed concern as to whether this problem would be addressed by the rule. Similarly, a different comment noted microbial contamination in spite of preservatives. This comment indicated support for sterile, additive-free solutions, noting that one disadvantage of preservatives is that they may be contraindicated in anti-asthmatic products. This comment stated that benzalkonium chloride is a known bronchoconstrictor contraindicated in anti-asthmatic products and that edetic acid, while not as potent as benzalkonium chloride, causes bronchospasm and would not be present in an ideal nebulizer solution.

Antimicrobial preservatives are added to dosage forms to protect them from microbial contamination. The USP states that antimicrobial agents should not be used solely to reduce the viable microbial count as a substitute for good manufacturing practices. The USP sets forth tests for estimating the presence, or absence, of microorganisms. USP procedure <61> sets forth tests for the estimation of the number of viable aerobic microorganisms present and the absence of designated microbial species in both raw materials and finished form drug products. FDA recognizes that both sterile and nonsterile drug products may contain preservative systems to control bacteria and fungi that may be inadvertently introduced during manufacturing or use.

Concerning the comment that the proposed rule represents an inappropriate policy change in allowing preservatives to be used to address inadequate manufacturing contamination controls, this rule does not change the agency's policy of considering such use of preservatives a serious CGMP violation. To the extent agency policy is reflected in the USP, the USP clearly states that while situations may arise where the use of an antimicrobial preservative may be necessary to minimize the proliferation of microorganisms, all useful antimicrobial agents are toxic substances.

The agency agrees with the comment acknowledging that some antimicrobial preservatives are no longer fully effective because certain bacterial strains have developed resistance. The agency disagrees with the comment that suggests there is no evidence that contaminating organisms have developed resistance to antimicrobial preservatives. Bacteria best identified as belonging to the *Pseudomonas* family have been known for many years to survive and grow in commercial preparations of quanternary ammonium compounds such as benzalkonium chloride. (See, for example, Adair, F.W., S.G. Geftic, and J. Gelzer, ''Resistance of *Pseudomonas* to Quaternary Ammonium Compounds: I. Growth in Benzalkonium Chloride Solution,'' *Applied Microbiology*, vol. 18, pp. 299–302, 1969. See also, Dixon, R.E., et al., ''Aqueous Quaternary Ammonium Antiseptics and Disinfectants,'' *Journal of the American Medical Association*, vol. 236, pp. 2415–2417, 1976.) In fact, the albuterol sulfate product recalled in January 1994, discussed in the proposed rule, contained benzalkonium chloride, an antimicrobial preservative, yet the preservative failed to prevent microbial contamination of the product. As of October 28, 1997, the agency's Spontaneous Reporting System (SRS) reported that this albuterol sulfate incident was associated with a total of 2,846 cases including 1,498 serious cases, 1,163 hospitalizations, and 441 deaths.

The agency acknowledges the public health need for sterile, additive-free, aqueous-based drug products for oral inhalation for the segment of the population for whom antimicrobial products are contraindicated (e.g., sensitive patients with asthma and other pulmonary diseases). To this end, the agency encourages the manufacture of sterile, additive-free, single-dose drug products for oral inhalation. However, the agency is not at this time requiring that all aqueous-based drug products for oral inhalation be manufactured in single-dose containers.

The agency recognizes that microbial limits tests have not prevented serious microbial contamination of nonsterile inhalation drug products in the past. Endproduct microbial limits tests performed prior to distribution may not be capable of detecting low levels of contamination. Products that initially pass the microbial limits test may support the growth of contaminating organisms that could later increase to unacceptable levels. The agency believes that requiring the sterility of such products from the point of manufacture will reduce the likelihood of microbial contamination.

The agency recognizes that contamination of these products may occur during usage. Such contamination may occur because of inadequate handling procedures, including defective hospital infection control procedures, or patient handling errors. The agency notes that the National Center for Infectious Diseases of the Centers for Disease Control and Prevention is sponsoring initiatives on preventing nosocomial transmission of antimicrobial-resistant microorganisms and directs those interested to their Internet at www.cdc.gov/ncidod/ for related information. The agency encourages hospital personnel and patients to follow instructions in the labeling for such products, including any precautions for use. The agency emphasizes the importance of following proper handling technique when transferring these products from their original container into an atomizer or nebulizer. FDA has determined that the best way for it to prevent future public health problems associated with contaminated aqueous-based drug products for oral inhalation is to require sterility at the point of manufacture.

E. Costs of Compliance

In the proposed rule, FDA estimated that the affected industry would incur total annual compliance costs of $192,000 to $1,210,000 (after amortization over 10 years at a 7 percent interest rate), mostly for constructing clean rooms in the five manufacturing facilities believed to be using a nonsterile production process. Several of the comments addressed aspects of FDA's original analysis of economic impacts.

5. Three comments stated that FDA had underestimated the costs of compliance and two comments provided estimates of compliance costs for their companies, although they did not provide the bases for these estimates.

FDA has considered these estimates and has revised its compliance cost estimates for the final rule, as described in section V of this document, ''Analysis of Economic Impacts.'' The agency's full cost analysis is based on a report prepared by its contractor, Eastern Research Group (ERG) (available in the docket) entitled ''Cost Impact on the Pharmaceutical Industry of Final Sterility Requirements for Inhalation Solution Products,'' and the comments mentioned above.

6. The U.S. Small Business Administration (SBA) commented that there was insufficient information on the record to evaluate the need for the regulation, as measured by the incidence of illness, against the enormous cost of compliance.

The proposed rule listed several incidents of contaminated inhalation drug products that jeopardized the public health and safety and were the subject of product recalls (62 FR 49638 at 49639). The proposed rule did not, however, provide data on adverse events associated with these recalls. The agency notes that as of October 28, 1997, FDA's SRS reported that the albuterol sulfate product recalled in January 1994, discussed in the proposed rule, was associated with 2,846 reports of adverse events including 441 deaths. FDA believes that this evidence, along with the resistance to microbial preservatives and the growth potential of the *Pseudomonas* family of bacteria, provides the public health and safety justification for this rule. Further, as the revised compliance costs of the final rule are estimated at $10.1 million per year, the agency believes that public health and safety concerns outweigh the compliance burdens.

F. Training Costs

7. SBA noted the lack of training costs for sterility procedures in the agency's original cost estimates. FDA agrees with this comment, and training costs are now included in its final estimate.

G. Enforcement of CGMP Regulations

8. One comment suggested that enforcement of CGMP regulations and monitoring of unethical repackaging operations would be more effective and less costly then requiring firms to convert to sterile processes.

The agency has determined that adherence to CGMP regulations without appropriate sterilization procedures does not provide an adequate level of assurance that aqueous-based drug products for oral inhalation will be free of contaminants. Based on past incidents of serious health risks to users, the agency has determined that enforcement of CGMP's is not enough to ensure these products are contaminant-free when they leave the manufacturer for distribution. Antimicrobial preservatives used in these products may not be effective because many bacteria, including *Pseudomonas* spp., have developed resistance to these preservatives. The albuterol sulfate product recalled in January 1994, discussed in the proposed rule, contained benzalkonium chloride, an antimicrobial preservative, yet the preservative failed to prevent microbial contamination of the product. Resistance to preservatives is not species specific; strains of many species are resistant. Furthermore, use of a single preservative in a nonsterile inhalation drug product for an extended period may actually select for preservative-resistant strains of *Pseudomonas* spp. or other bacteria. Similarly, although the agency recognizes the importance of the enforcement of repackaging regulations, this rule is intended to help ensure that products are sterile at the point of manufacture.

H. Hazard Analysis and Critical Control Point (HACCP) Program

9. SBA recommended the use of a HACCP program, like that used for the food industry. SBA stated that a HACCP program would reduce compliance costs.

HACCP is a preventive system of hazard control used primarily in the food industry. The HACCP concept is a systematic approach to the identification and assessment of the risk of biological, chemical, and physical hazards that may occur in a particular production process or practice and the control of those hazards. Under HACCP, the producer develops a plan that anticipates and identifies the points in the production process where a failure would likely result in a hazard being created or allowed to persist. These points are referred to as critical control points (CCP's). Under HACCP, identified CCP's are systematically monitored to ensure that critical limits are not exceeded, and records are kept

of that monitoring. Corrective actions are taken when control of a CCP is lost and these actions are documented. The effectiveness of HACCP is also systematically verified by the processor.

Because of the potential public health consequences of contaminated aqueous-based drug products for oral inhalation, as shown by the incidents cited earlier in this document, the agency concludes that a HACCP system is not an adequate substitute for sterilization requirements.

I. Clean Rooms

10. Another comment stated that the proposed rule would limit the use of each clean room to one product and questioned the necessity of this.

FDA is aware that the trade press has reported that the proposed rule would require one product per clean room. FDA is clarifying that this interpretation of the proposed rule is inaccurate. FDA did not intend to limit, and is not limiting, each clean room to the manufacture of only one inhalation product.

J. Specific OTC Drug Product

11. The agency received 49 comments from consumers of an OTC asthma inhalant, Breatheasy, as well as one comment from the manufacturer of the Breatheasy product, Pascal Co., Inc., of Bellevue, WA. Pascal Co., Inc., distributed a letter to consumers of its product stating the agency's new policy would require that all inhalants be manufactured in clean rooms and suggesting that overhead costs to produce clean rooms would far exceed annual sales of this product. Pascal stated that the rule would be cost prohibitive for the company and would require it to discontinue manufacture of the product. The 49 letters from consumers of this product indicated that they had been informed by Pascal Co., Inc., that the new policy would require the manufacturer to discontinue manufacture of the product. These letters testified to individual experiences with the product, stating duration of use, some for as many as 50 or 60 years, lack of any ill effects or quality problems, unique needs met by the product exclusive of any other available remedy, and the low cost of the product.

The agency has reviewed the concerns of individuals who have used this product for many years and who are understandably concerned about it being discontinued. The agency contacted Pascal, Inc., and reviewed the labeling of the product to determine if it is the type of product intended to be covered by the rule.

The Breatheasy product is a 2-percent buffered aqueous solution of epinephrine that comes in a kit that contains an atomizer. Breatheasy is the type of product that has raised serious concerns about the health and safety of individuals using such products and it is an example of the type of product intended to be covered by the final rule. The agency has determined that other, alternative OTC epinephrine inhalation products, which do not raise the safety concerns of this product, are available on the market to treat the symptoms of these individuals. Should Breatheasy become unavailable, the agency suggests that individuals consult their health care practitioners for the identity of an appropriate alternative OTC product.

IV. Effective Date

12. Two comments stated that the time for implementation was too short and impractical for conversion to sterile processes. Both comments requested up to a 2-year phase-in period to allow development time for packaging, stability data, and facility modifications. SBA stated that allowing a 1-year transition period, as proposed, was not sufficient. The comment requested a transition period of 2 years.

FDA has considered these comments and has decided to lengthen the effective date to 2 years after publication of the final rule to give each firm a longer period of time to implement the new sterility requirements.

The final rule prohibits all manufacturers of nonsterile aqueous-based drug products for oral inhalation, including those products currently approved, from introducing or delivering for introduction into interstate commerce any such products that are nonsterile beginning 2 years after the date of publication of the final rule in the **Federal Register**.

Holders of approved NDA's and abbreviated new drug applications (ANDA's) must submit supplemental applications to FDA to establish sterility of these products within 2 years after the publication of the final rule in the **Federal Register**.

Any NDA or ANDA for a nonsterile aqueous-based drug product for oral inhalation under review by FDA on or after the date of publication of the final rule, but before the effective date of the final rule may be approved if the application is otherwise approvable and the applicant agrees to establish the sterility of its drug product in a supplemental application by the effective date. On or after the effective date of the final rule, FDA will refuse to approve an NDA or ANDA for an aqueous-based drug product for oral inhalation if the applicant has not established the sterility of the product.

V. Analysis of Impacts

A. Introduction

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Pub. L. 104–121)), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104–4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). Under the Regulatory Flexibility Act, if a rule has a significant impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. The Unfunded Mandates Reform Act requires agencies to prepare an assessment of anticipated costs and benefits before enacting any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

FDA concludes that this final rule is consistent with the principles set forth in the Executive Order and in these two statutes. FDA estimates that the final rule would impose annual compliance costs on industry of about $10.1 million. In addition, the final rule is a significant regulatory action as defined by the Executive Order and was subject to review under the Executive Order. FDA has also determined, as explained later in this section, that the final rule may have a significant economic impact on a substantial number of small entities. This section, along with the report by FDA's contractor ERG, constitutes the agency's final regulatory flexibility analysis as required under the Regulatory Flexibility Act. Further, because this final rule makes no mandates on government entities and will result in expenditures of less than $100 million in any one year, FDA need not prepare additional analyses under the Unfunded Mandates Reform Act.

B. Compliance Requirements and Costs

FDA is amending its regulations to require that all prescription and OTC aqueous-based inhalation solutions or suspensions in single-dose or multiple-

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