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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.

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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-

use primary packaging administered orally via a secondary device or other ancillary hardware (e.g., an atomizer, nebulizer, or pump), be manufactured to be sterile. This does not include inhalation solutions administered by pressurized metered dose inhalers. FDA believes this action is necessary to help ensure the safety and efficacy of these products, due to reports of adverse drug experiences from contaminated nonsterile inhalation solutions and recalls of these products.

In the preamble to the proposed rule published September 23, 1997, 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 to the proposed rule addressed aspects of FDA's original analysis of economic impacts. These comments are addressed in section III of this document and below.

FDA has reviewed its original compliance cost estimates in light of the comments to the proposed rule, and has determined that it underestimated compliance costs to industry. The agency's revised estimates are fully described in the ERG report on compliance costs (available in the docket).

In the proposed rule, FDA estimated that up to five firms may still be using a nonsterile manufacturing process for inhalation solutions. ERG found that eight firms would be affected by the final rule because they use nonsterile manufacturing processes. The ERG estimate assumes that some products with an uncertain classification were actually nonsterile.

ERG concluded that the final rule would impose a total annual cost of $10.1 million (after amortization of capital costs over 10 years at a 7 percent interest rate). The majority of these annual costs ($8 million) are attributed to the increase in annual operating costs for two large manufacturers. This estimate was derived from the comment of one of the large companies, which indicated that its operating costs would increase by $4 million, primarily due to the lower labor productivity that results from the extra activities necessary when operating in a sterile environment. One-time capital and related costs are estimated at about $8.3 million for converting to the sterile production process, including the planning, constructing and equipping of clean rooms, training of employees, and revalidation of production processes. On an annualized basis (after amortizing over 10 years at a 7 percent discount rate), these costs are projected at $600,000 per year for each of these two large manufacturers.

The other six manufacturers, which produce nonsterile inhalation products with much lower annual revenues (about $1 million or less), are not expected to convert their production processes, due to the relatively high compliance costs compared to the revenues from these products. Instead, ERG projected that one-half of these firms would transfer production of these products to a contract manufacturer, with an estimated increase in manufacturing costs of about 30 percent, resulting in an additional $900,000 per year in costs. The other one-half of these small volume manufacturers, those with the smallest revenues, are expected to discontinue these products altogether. Consumers of the discontinued products are expected to switch to alternative products. FDA believes, based on the small volume of affected sales, the wide availability of competing products, and the probable low elasticity of product demand, that the loss of consumer and producer value due to this regulation would be extremely small.

After further review, FDA also decided to require inhalation suspension products, other than suspensions in pressurized metered dose inhalers, to be sterile although they had not been included in the proposal. There are currently five approved inhalation suspension products. Because they are all metered-dose inhalers, however, they are not covered under the final rule. Further, FDA does not expect to receive any new applications for inhalation suspensions that are nonsterile, as the current procedures for new products are likely to include a sterilization process. Thus, FDA has not raised its compliance cost estimates due to the addition of inhalation suspension products for oral inhalation in the final rule.

C. Affected Entities

As stated above, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities, unless the rule is not expected to have a significant economic impact on a substantial number of small entities.

SBA limits the definition of small businesses in the pharmaceutical industry to those with less than 750 employees. ERG estimated that five small manufacturers with a total of eight products will be affected by this rule, although the data necessary to make this determination are scarce and often rely on sales volume rather than number of employees. About one-half of these manufacturers (two or three) are expected to transfer production to a contract manufacturer, which is estimated to increase operating costs by about $180,000 each per year per product. In addition, these companies may experience a loss of jobs as these products are transferred to the contract manufacturers. The other two or three companies are expected to cease production of their product completely, thereby incurring the loss of profits on those products. While neither ERG nor FDA has quantified these impacts, it expects them to be low due to the low product sales volume.

Affected firms will need to acquire some new professional skills, because this rule deals with a new manufacturing process that will require technicians to have a knowledge of sterility procedures. Any other skills necessary for implementation of this rule (e.g., skills associated with preparing the supplemental application) should already exist within the firms and should not need to be newly acquired. No other compliance costs are estimated for these manufacturers.

D. Alternatives Considered

FDA has considered alternatives to this rule. FDA considered exempting small entities. However, as stated in the proposal, the alternative of exempting small businesses from the rule is not feasible, because most firms using a nonsterile process are small firms and thus granting small businesses an exemption would negate the purpose of the rule.

One alternative mentioned in the comments discussed in section III.H of this document was the creation of a HACCP program whereby the most critical points in the production process would be monitored for microbial safety problems, possibly resulting in lower compliance costs for small businesses. As discussed above, FDA has rejected a HACCP program for these drug products because of the potential public health consequences of contaminated products, as shown by the cited earlier incidents involving aqueous-based drug products for oral inhalation.

Another alternative to the final rule would have been to retain the 1-year effectiveness date as required by the proposed rule. Instead, FDA has responded to public comments by delaying the effectiveness date an extra year in order to give industry members additional time to adjust to the new requirements and mitigate costs as much as possible. In doing so, FDA has

eliminated compliance costs for 1 year, the present value of which is $10.1 million.

Another alternative mentioned in the comments and discussed in section III.G of this document was more uniform enforcement of CGMP's and monitoring of unethical repackaging. Based on past incidents of serious health risk 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. Similarly, one comment suggested end-testing the product in batches prior to shipment from the manufacturing facility. This comment incorrectly stated that all contaminated products to date have been caught prior to reaching or harming patients. As discussed in section III.E of this document, contaminated products have caused serious harm to patients. For this reason, the agency has determined that end-testing and/or enforcement of CGMP's are not adequate to address the serious public health and safety concerns raised by such incidents.

Due to contamination problems with several different inhalation solution drug products and adverse experience reports, 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. Based on the significant health risk to users, FDA is requiring that all aqueous-based drug products for oral inhalation be manufactured sterile.

One alternative considered was to supply consumers and providers with information related to the potential risks of aqueous-based drug products for oral inhalation that are not manufactured to be sterile, instead of mandating sterility in this market. FDA is concerned that many prescribers and consumers may not understand the potential risks of such products, given that these products are approved and therefore regarded as safe and effective when used according to the labeling. In many circumstances, additional information would assist prescribers and users in making informed choices, and if it were possible to provide correct and complete information to all prescribers and consumers in this market, they should make the optimal choice for their situation. However, FDA does not believe that such information could be developed for nonsterile aqueous-based oral inhalation drug products that would be consistent with FDA's mandate under the Federal Food, Drug, and Cosmetic Act to assure that drug products are safe and effective. Additionally, even if such information could be developed, the cost associated with providing the information to the relevant parties would be too large, and FDA believes that these costs would overshadow any expected benefits of allowing fully informed consumers to make their own choice in this market.

VI. Environmental Impact

The agency previously considered the environmental effects of this rule as announced in the proposed rule (62 FR 49638). At that time, the agency determined under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. No new information or comments have been received that would affect the agency's previous determination that there is no significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection provisions are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Sterility Requirements for Aqueous-based drug products for oral inhalation.

Description: The final rule requires that all aqueous-based drug products for oral inhalation, including those currently approved, be manufactured sterile. Respondents will be required to submit a supplemental application under § 314.70(b) or § 314.97, describing their new manufacturing process for achieving sterility of their aqueous-based drug products for oral inhalation. FDA needs this information to determine compliance with this new regulation and will use information collected to make decisions on approval of supplemental applications. Applicants will have 2 years after the date of publication of the final rule to comply with the sterility requirement.

Description of Respondents: Respondents are businesses engaged in the manufacture of aqueous-based drug products for oral inhalation.

The collection of information described in the proposed rule was approved by OMB under control number 0910–0353. However, based on new data collected by its contractor, ERG, FDA has revised its estimate of the number of respondents in the original proposal for reporting and recordkeeping burden. Because the number of respondents has changed, the estimate of the total hours has changed. The economic analysis of the proposed rule estimated 5 manufacturers, while the economic analysis of the final rule estimates 8 manufacturers with 11 nonsterile products based on new data collected by ERG (see Ref. 1). However, four of the manufacturers are estimated to cease manufacturing, leaving four companies manufacturing seven products. These companies are estimated to cease manufacturing because they may lack the in-house technical capability to convert their operations or might find the prospective investments in sterile production technologies to be unattractive. Because each nonsterile product will require an annual report (21 CFR 314.81(b)(2)(iv)), the number of annual responses for nonsterile products has increased to seven. Based on a review of FDA's past experience with applicants submitting supplemental applications under § 314.97, we estimate 160 hours to prepare a supplemental application. Therefore, due to the increased estimate of respondents, the total hours for the annual reporting burden for manufacturers of nonsterile products has increased from 800 hours in the proposed rule to 1,120 hours in the final rule. The agency's review of the estimated reporting burden for manufacturers of sterile products in the proposed rule and its experience with the annual reporting burden for manufacturers of sterile products supported the estimate provided in the proposed rule. Therefore, the estimated reporting burden for manufacturers of sterile products in the final rule is the same as in the proposed rule.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
314.97	7	1	7	160	1,120[1]
314.70	2	1	2	20	40[2]
Total					1,160

[1]Reporting burden for manufacturers of nonsterile products.
[2]Reporting burden for manufacturers of sterile products.

Because of the estimated increase from the proposed rule to the final rule in the number of respondents for nonsterile products, the number of recordkeepers in the recordkeeping burden of Table 2 has increased by two from the proposed rule. FDA estimated a total of seven recordkeepers in the proposed rule and now estimates a total of nine recordkeepers as a result of new data collected by ERG. The proposed rule estimated 2 hours per record, and FDA's review of that estimate and its experience with the control and validation of microbiological contamination supports this proposed estimate. Therefore, the total number of hours for the recordkeeping burden has increased from 14 hours to 18 hours.

TABLE 2.—ESTIMATED ANNUAL RECORDKEEPING BURDEN [1]

21 CFR Section	No. of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Record	Total Hours
211.113(b)	9	1	9	2	18
Total					18

[1]There are no capital costs or operating and maintenance costs associated with this collection of information.

Individuals and organizations may submit comments on these burden estimates or on any other aspect of these information collection provisions, including suggestions for reducing the burden, and should direct them to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

The information collection provisions of this final rule have been submitted to OMB for review. Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number.

VIII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

IX. Reference

The following reference is on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Eastern Research Group, ''Cost Impact on the Pharmaceutical Industry of Final Sterility Requirements for Inhalation Solution Products,'' 1998.

List of Subjects in 21 CFR Part 200

Drugs, Prescription drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 200 is amended as follows:

PART 200—GENERAL

1. The authority citation for 21 CFR part 200 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360e, 371, 374, 375.

2. Section 200.51 is added to subpart C to read as follows:

§ 200.51 Aqueous-based drug products for oral inhalation.

(a) All aqueous-based drug products for oral inhalation must be manufactured to be sterile.

(b) Manufacturers must also comply with the requirements in § 211.113(b) of this chapter.

Dated: February 1, 2000.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

[FR Doc. 00–13210 Filed 5–25–00; 8:45 am]

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DEPARTMENT OF STATE

22 CFR Part 123

[Public Notice 3318]

Exports of Commercial Communications Satellite Components, Systems, Parts, Accessories and Associated Technical Data

AGENCY: Bureau of Political-Military Affairs, State.

ACTION: Interim final rule.

SUMMARY: Section 1309(a) of the Foreign Relations Authorization Act for Fiscal Years 2000 and 2001 requires the Department of State to establish a regulatory regime for the export licensing to U.S. allies of commercial satellites, technologies, components, and systems, which shall include expedited approval, as appropriate, while ensuring priority to national security and U.S. commitments under the Missile Technology Control Regime.

Section 1302(a) of the same Act requires the Department to promulgate regulations in order to ensure timely reporting to the Department (within 15