

SUPPORTING STATEMENT

Sterility Requirement for Aqueous-Based Drug Products for Oral Inhalation; Reporting and Recordkeeping Requirements - 21 CFR 200.51

A. Justification

1. Circumstances of Information Collection

The Food and Drug Administration (FDA) is requesting OMB approval of the information collection requirements contained in 21 CFR 200.51 that are listed below.

REPORTING REQUIREMENTS

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| 21 CFR 314.97 | Requires submission of a supplement to an abbreviated application for certain changes, listed in section 314.70, made to achieve sterility as required under proposed section 200.51(a). |
| 21 CFR 314.70 (b)(2) | Requires submission of a supplement to an approved application for certain changes, listed in section 314.70(b)(2), made to achieve sterility as required under proposed section 200.51(a). |
| 21 CFR 314.70(c) | Requires submission of a supplement to an approved application for certain changes, listed in |

section 314.70(c), made to achieve sterility as required under proposed section 200.51(a).

RECORDKEEPING REQUIREMENTS

21 CFR 211.113(b)

Requires that appropriate written procedures be established and followed to prevent microbiological contamination of drug products purporting to be sterile, including validation of the sterilization process.

FDA relies primarily on section 301(a) of the Federal Food, Drug, and Cosmetic Act for authority to require sterility of inhalation solutions for nebulization and on section 505(b)(1) and (j)(2)(A) to impose related reporting requirements.

Under section 301(a), the introduction or delivery for introduction into interstate commerce of an adulterated or misbranded drug is prohibited. Under the sterility requirement for inhalation solutions, an inhalation solution not manufactured as sterile would be considered injurious to health and lacking adequate directions for use, and thus would violate section 301(a).

Under section 505(b) and (j), persons applying for approval of a drug must submit to FDA as a part of the application, among other things, a full description of the methods used in, and the facilities and controls used for, the manufacture, processing,

and packing of the drug. The methods, facilities, and controls used to achieve sterility must be described pursuant to this section.

Also, 21 CFR 211.113(b) requires that appropriate written procedures be established and followed to prevent microbiological contamination of drug products purporting to be sterile.

2. Purpose and Use of Information

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. FDA needs this information to determine compliance with this new regulation and will use the information collected to make decisions on approval of supplemental applications. Applicants will have 2 years to comply with the sterility requirement.

FDA uses information about the methods, facilities, and controls used for the manufacture, processing, and packaging of drugs, including the methods used to achieve sterility, to evaluate the safety of a drug.

The sterility requirement for inhalation solutions serves a

compelling Federal interest in that it prevents dangerous microbial contamination that can lead to serious adverse health consequences. Contaminated inhalation solutions for nebulization are likely to cause lung infections because the drug product is introduced directly into the lungs in a manner which at least partially bypasses the patient's natural defense mechanisms. Many patients using inhalation solution products for nebulization have chronic obstructive airway disease or cystic fibrosis, or are immunocompromised. Microbial contamination of these products may result in serious health consequences due to opportunistic pathogens entering the lungs or the possible inactivation of the drug product by these microorganisms.

3. Use of Improved Information Technology

It is hoped that all submissions relating to the sterility issues involved in this rule could be made electronically in the future. As explained below, FDA is working toward more widespread use of electronic submissions of drug applications.

Electronic Regulatory Submissions for Archive - The Food and Drug Administration Modernization Act of 1997 (FDAMA), along with the Prescription Drug User Fee Act (PDUFA) II reauthorization, mandate that the agency shall develop and update its information management infrastructure to allow, by fiscal

year 2002, the paperless receipt and processing of INDs and human drug applications, as defined in PDUFA, and related submissions. Moving an information-intensive activity, such as drug regulatory review, from a paper-based to an electronic environment will provide a number of benefits. This is true simply from the perspective of generating, handling, and storing the huge volumes of paper commonly associated with applications. In general, these paper applications (often containing hundreds of volumes) are submitted with several copies, a process that can take several days longer than preparation of a corresponding electronic submission, which the agency can easily reproduce. Preparation of applications in electronic form results in direct cost savings related to materials, supplies, and paper handling logistics (i.e., labor, facilities). However, this is expected to be only a small portion of the potential savings. The most substantial burden reduction may not be in information recording, reporting, and recordkeeping, but in the flexibility, efficiency, speed, and ease of filing required information that will result in cost savings to regulated industry, as well as FDA.

In September 1997, FDA published the Guidance for Industry on "Archiving Submissions in Electronic Format -- NDAs." This guidance provided for the receipt and archive of electronic Case Report Forms (CRF) and Case Report Tabulations (CRT) without an

accompanying paper copy. In FY 1998, the agency established an Electronic Document Room (EDR) to manage the receipt and handling of all electronic submissions. In January 1999, FDA published the Guidance for Industry on "Providing Regulatory Submissions in Electronic Format - NDAs." This guidance document covers the full NDA and is not limited to CRTs and CRFs. Approximately 40% of original NDAs now include guidance-compliant electronic submissions (i.e., submissions for archive). Out of 86 original NDAs received since January 1999, 36 included electronic components and 9 were full electronic NDAs. The agency also received 43 electronic NDA supplements. Out of 6,978 NDA amendments, supplements, and amendments to supplements, 100 were electronic.

Secure E-Mail - During a drug's development cycle, communications between FDA's CDER review divisions and the company developing the drug is sensitive and proprietary. Prior to using secure E-mail, CDER methods of "secure" communication included U.S. mail, courier, telephone, and facsimile. These methods, some of which are not entirely secure, can be inefficient or time consuming, and can significantly contribute to the overall length of time involved in the drug review process. The widespread use of E-mail across the Internet offers a more efficient and scaleable means of information exchange.

However, security risks of communicating over the Internet are well known. The information technology industry is answering security concerns by developing new standards of cryptographic techniques, E-mail formats, authentication algorithms, and other related aspects of secure communications. In 1998, CDER conducted a formal requirements study for secure E-mail which led to the selection of Worldtalk Corporation's WorldSecure Server as the base pilot platform. CDER began testing WorldSecure Server in late 1998. A pilot system was put into place in January 1999. After the pilot's run, the production system's requirements were developed from the pilot's requirements and new information gathered from the pilot results. The design for a production system was based on these requirements. CDER recently installed a production system and additional firms are being given secure E-mail accounts.

ICH M2 - The International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use was formed to minimize waste in the discovery, development, regulation, manufacture, marketing, and use of human therapeutic products worldwide. The regulatory authorities of Europe, Japan, and the United States joined with their respective pharmaceutical trade associations in an agreement to take action on harmonization by participating in the ICH.

The ICH Multi-disciplinary Group 2 (M2) Expert Working Group (EWG) was established to determine electronic standards and provide solutions to facilitate international electronic communication in the three ICH regions. The first effort of the M2 EWG was to establish a series of recommendations that would form the basis for standardized electronic communication in each of the three regions. These recommendations included physical media formats, secure communications, and structured data formats. Building on these standards, the EWG then began work on a detailed specification for the secure, electronic transmission of individual case safety reports (adverse event reports). The specification is intended to support transmission between industry partners, industry and regulatory authorities and between regulatory authorities in all three regions. The production of a specification for an electronic common technical document (CTD) was the next major effort assigned to the M2 EWG. The ICH steering committee agreed in March 1999 that this effort should be undertaken by the M2 EWG in cooperation with the subject matter expert working groups for each section of the CTD. The CTD working groups are charged with harmonizing the format and content of the application documents for new product applications. The resulting ICH guidances, when implemented,

will change the content and format of NDA submissions to the FDA. The M2 specification will define the nature of an electronic submission for CTD submissions and could have a major impact on the way electronic submissions are received, archived, and reviewed.

4. Efforts to Identify Duplication

Section 200.51 does not conflict with or duplicate other regulations. All inhalation solutions for nebulization will be required to be sterile for the first time under this rule.

Many companies already manufacture their inhalation solutions for nebulization as sterile. Of these companies, those that make a sterility claim for their products should have submitted to FDA data to establish the sterility of these products. This rule imposes no additional obligations on these companies. Other companies that manufacture their inhalation solutions for nebulization as sterile do not make a sterility claim in their labeling. These companies should incur a minimal burden under this rule to put their sterility records into an appropriate format for inclusion in a supplement to FDA.

5. Involvement of Small Entities

FDA's assurance of the safety of drug products applies to small as well as to large businesses involved in the manufacture of drugs. FDA believes that its duty requires the equal application of the regulations to all enterprises. While FDA does not believe it can apply different standards with respect to statutory requirements, FDA does provide special help to small businesses. A small business coordinator has been assigned to the Commissioner's staff to ensure that small businesses have an adequate opportunity to express their concerns and to keep FDA management apprised of how regulatory decisions might impact the small business community. To provide additional assistance to small businesses, FDA has established an office whose exclusive concern is to provide small businesses with help in dealing with FDA regulatory requirements.

Exempting small businesses from this rule is not a feasible alternative, since most firms believed to be using nonsterile manufacturing for these products meet the Small Business Administration (SBA) definition of a small business. Some small companies will choose to minimize the cost burden by contracting out the manufacture and packaging of these products to facilities that already have the capability to manufacture the products to be sterile. The rule would permit two years for the

manufacturing conversion to sterility to take place in order to prevent any disruptions and hardships to these firms.

6. Consequences if Information Collected Less Frequently

The rule imposes a one-time reporting requirement unless changes are made subsequent to submission to FDA of sterility-related documentation.

Failure to collect the information would be inconsistent with statutory requirements because the information about methods and controls used to achieve sterility is essential to the evaluation of the safety of inhalation solutions.

7. Consistency with the Guidelines in 5 CFR 1320.5(d)(2)

There is no inconsistency as a result of this rulemaking. Any inconsistencies are related to regulatory requirements concerning supplement submission under 21 CFR 314.70, and are approved by OMB under Control Number 0910-0001.

8. Consultation Outside the Agency

Industry representatives and academicians were consulted

with respect to the technical elements of the sterility requirement. There was general agreement as to the availability of necessary data and the need for the minimally burdensome, one-time submission to the agency of information regarding the methods and controls used to assure sterility.

On May 26, 2000 (65 FR 34082), FDA published a final rule to be effective May 27, 2002. On September 18, 2000 (65 56314) FDA published a request for comments on the proposed information collection. There were no comments received.

9. Remuneration of Respondents

No payment or gift is provided to respondents.

10. Assurance of Confidentiality

Confidentiality of the information submitted under these requirements is protected under 21 CFR Part 20 and 21 CFR 314.430. Much information submitted to a drug application is generally regarded as trade secret or confidential commercial or financial information and is not available for public disclosure. (See also 21 U.S.C. 331(j)).

11. Questions of a Sensitive Nature

The information requirements contained in this rule do not result in the collection of sensitive information.

12. Estimates of Annualized Hour Burden

The expected burden of information collection is as follows: This rule would affect only those manufacturers of inhalation solutions for nebulization that do not already manufacture their products to be sterile or that manufacture their products to be sterile but make no labeling claims relating to sterility. For those companies manufacturing a sterile product and making sterility claims, the rule imposes no new burden because submission of sterility information would already be required.

Based on new data collected by its contractor, ERG, FDA has revised its estimate in the proposed rule of the number of respondents in the reporting and recordkeeping burden charts. 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. However, 4 of the manufacturers are estimated to cease manufacturing,

leaving 4 companies manufacturing 7 products. These companies are estimated to cease manufacturing because they may lack the inhouse 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 (§ 314.81(b)(2)(iv)), the number of annual responses for nonsterile products has increased to 7. Based on a review of FDA's past experience with applicants submitting supplemental applications under § 314.97, it is estimated that 160 hours are needed to prepare a supplemental application. Therefore, the total hours for the annual reporting burden for manufacturers of nonsterile products has increased from 800 hours in the proposal to 1120 hours in the final. The agency's review of the estimated reporting burden for manufacturers of sterile products in the proposal and its experience with the annual reporting burden for manufacturers of sterile products supported the estimate provided in the proposal. Therefore, the estimated reporting burden for manufacturers of sterile products in the final rule is the same as in the proposal. Because of the estimated increase from the proposal to the final in the number of respondents for nonsterile products, the numbers of recordkeepers in the recordkeeping burden chart

has increased by 2 from the proposal. FDA estimated a total of 7 recordkeepers in the proposal and now estimates a total of 9 recordkeepers as a result of new data collected by ERG. The proposal 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.

Estimated Annual Reporting Burden						
CFR Section	Number of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours	
314.97,	7	1	7	160	1120 ¹	
314.70	2	1	2	20	40 ²	
total					1160	

¹ Reporting burden for manufacturers of nonsterile products

² Reporting burden for manufacturers of sterile products

Estimated Annual Recordkeeping Burden						
CFR Section	Number of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours	
211.113(b)	9	1	9	2	18	
total					18	

There are no capital costs or operating and maintenance costs associated with this proposed rule.

13. Estimates of Annualized Cost Burden to Respondents

The estimated average hourly wage for program personnel involved in complying with the reporting and recordkeeping requirements is \$33.00. Multiplying the estimated average hourly wage by 1.5 to account for non-wage labor costs, an estimated hourly labor cost is \$50.00. The estimated total cost to the respondents for submitting a sterility supplement to FDA and maintaining sterility records, using \$50.00 as the hourly cost figure, is \$58,900 (1120 + 40 + 18 x \$50).

14. Estimates of Annualized Cost Burden to the Government

No additional equipment or staff will be required to undertake review of the additional information. The information is submitted in an application or supplement to the appropriate reviewing division within FDA for review by agency microbiologists with an estimated wage rate of \$26.00 per hour. Assuming an overhead rate of 60 percent, the cost to FDA is about \$42.00 per hour. A required sterility assurance review would take approximately 25 hours per application, on average. Thus, total FDA cost to review these forms is approximately \$9450.00 (25 x 9 x \$42).

15. Changes in Burden

This is a new regulation. Approval is requested for 3 years.

16. Time Schedule, Publication, and Analysis Plans

There are no publications.

17. Displaying of OMB Expiration Date

The agency is not seeking an exemption not to display the expiration date for OMB approval of the information collection.

18. Exception to the Certification Statement - Item 19

There are no exceptions to the certification statement identified in Item 19, "Certification for Paperwork Reduction Act Submission," of OMB Form 83-I.

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