

## OMB INFORMATION COLLECTION

### Supporting Statement

#### Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices

##### A. Justification

##### 1. Circumstances Necessitating Information Collection

Sections 551 through 557 of the Federal Food, Drug and Cosmetic Act (the act), as created by section 401 of the Food and Drug Administration Modernization Act of 1997 (Pub. L. 105-115) (tab A) permit drug, biologic, and device manufacturers to disseminate certain written information concerning the safety, effectiveness, or benefits of a use that is not described in the product's approved labeling provided that the manufacturer has: (1) Submitted a supplemental application for the new use; (2) completed the studies needed for a supplemental application for the new use and certified that such studies are completed and that a supplemental application will be submitted within 6 months of the initial dissemination; (3) provided a proposed protocol and schedule for conducting the studies needed for a supplemental application for the new use which FDA finds to be adequate and reasonable, and certified that such application will be submitted not later than 36 months after the initial dissemination; or (4) received an exemption from the requirement to file a supplemental application on the grounds that conducting the studies needed for a supplemental application would be unethical or economically prohibitive.

The Food and Drug Administration (FDA) issued regulations, now codified at 21 CFR part 99, to implement sections 551 through 557 of the act. The regulations describe the new use information that a manufacturer may disseminate and describe the manufacturer's submissions to FDA before the manufacturer begins disseminating information on the new use. They also describe the manufacturer's certifications (either that the manufacturer will submit a supplemental application for approval of the new use within 6 months of the initial dissemination or that the manufacturer will submit a supplemental application within 36 months after the initial dissemination). The regulations describe requests to extend the time period for submitting a supplemental application for a new use and applications for an exemption from the requirement to submit a supplemental application. The regulations discuss FDA actions in response to a manufacturer's submissions, corrective actions that FDA may take (including orders to cease disseminating information), and a manufacturer's recordkeeping and reporting requirements.

FDA is requesting a renewal of OMB approval for the following information collection requirements:

## REPORTING REQUIREMENTS

- 21 CFR 99.201(a)(1)** Section 551(b)(4)(A) of the act requires each manufacturer to include, as part of its submission, a copy of the information to be disseminated. This provision of the rule requires the manufacturer to provide an identical copy of the information to be disseminated.
- 21 CFR 99.201(a)(2)** Section 551(b)(4)(B) of the act requires each manufacturer to include, as part of its submission, any clinical trial information that it has relating to the safety or effectiveness of the new use, any reports of clinical experience pertinent to the safety of the new use, and a summary of the information. This provision of the rule requires the submission of the information specified in section 551(b)(4)(B) of the act.
- 21 CFR 99.201(a)(3)** Section 551(b)(6)(B) of the act requires each submission to include a bibliography of scientific literature that has been previously published about the new use. This provision in the rule requires a manufacturer to explain its search strategy in selecting the articles for the bibliography.
- 21 CFR 99.201(a)(4)(i)(A)** If a manufacturer has completed studies needed for the submission of a supplemental application for a new use, the rule requires the manufacturer to submit the protocol(s) for the completed studies, or, if the manufacturer has submitted the protocol to an investigational new drug application (IND) or an investigational device exemption (IDE) covering the new use, to provide the IND or IDE number(s), the date of submission of the protocol(s), the protocol number(s), and the date of any protocol amendments.
- 21 CFR 99.201(a)(4)(ii)(A)** Section 554(c)(1)(A) of the act requires a manufacturer to submit a proposed protocol and schedule for conducting the studies needed for the submission of a supplemental application for the new use if the manufacturer has planned (rather than completed) studies that will be needed for the submission of a supplemental application for a new use. The rule requires the manufacturer to include, as part of the schedule, the projected dates on the principal study events will occur.
- 21 CFR 99.201(a)(5)** If a manufacturer has submitted a supplemental application for a new use, this provision requires the manufacturer to include a cross-reference to that supplemental application.
- 21 CFR 99.201(b)** This provision simply requires a manufacturer's attorney, agent, or other authorized official to sign its submissions, certifications, and requests for an exemption.
- 21 CFR 99.201(c)** Sections 551(b) and 554 of the act require a manufacturer to provide a submission and certification statement or an application for exemption to FDA. This provision requires the manufacturer to send 2 additional copies of the submission and certification statement or application for

**exemption to FDA.**

- 21 CFR 99.203(a)** This provision permits a manufacturer to request an extension of the time for completing studies and submitting a supplemental application for a new use. The extension request may be made before the manufacturer makes a submission regarding the dissemination of information under part 99.
- 21 CFR 99.203(b)** Section 554(c)(3) of the act permits manufacturers to request, in writing, an extension of the time for completing studies after it has made a submission to FDA. This provision specifies the contents of such requests for an extension. The required information includes a description of the studies, an explanation as to why the study or studies cannot be completed on time, the current status of the studies (including a summary of the work conducted), and an estimate of the additional time needed.
- 21 CFR 99.203(c)** This provision requires 2 additional copies of the information submitted under 21 CFR 99.203(a) or (b) and that the manufacturer mark the envelope to identify it as a request for an extension.
- 21 CFR 99.205(b)** Section 554(d) of the act permits manufacturers to submit an application for exemption from the requirement to file supplemental applications for a new use. This provision specifies the contents of these applications for exemption.
- 21 CFR 99.501(b)(1)** Section 553(a)(1) of the act requires each manufacturer to submit, on a biannual basis, a list containing the titles of articles and reference publications relating to the new use that it disseminated in a 6-month period. This provision requires a manufacturer to submit to FDA semiannually a list containing the articles and reference publications that were disseminated in the preceding 6-month period.
- 21 CFR 99.501(b)(2)** Section 553(a)(2) of the act requires each manufacturer who disseminates information to submit to FDA semiannually a list that identifies the categories of providers that received the articles and reference publications. This provision also requires that the list also identify which category of recipients received a particular article or reference publication.
- 21 CFR 99.501(b)(3)** Section 555(a)(2) of the act requires each manufacturer to submit additional knowledge on clinical research or other data relating to the safety or effectiveness of the new use involved and to provide the data if the manufacturer possesses it. This provision, in relation to § 99.201(a)(2) requires a manufacturer to provide, on a semiannual basis, a notice and summary of any additional clinical research or other data relating to the safety and effectiveness of the new use, and, if it possesses such research or data, to provide a copy to FDA.
- 21 CFR 99.501(b)(4)** Section 554(c)(2) of the act requires manufacturers to submit periodic progress reports on studies. If a manufacturer discontinues or

terminates a study before completing it, this provision requires the manufacturer to state the reasons for the discontinuation or termination in its periodic progress report to FDA.

**21 CFR 99.501(b)(5)** This provision requires a manufacturer to submit any new or additional information that relates to whether it continues to meet the requirements for an exemption after an exemption has been granted.

#### **RECORDKEEPING REQUIREMENT**

**21 CFR 99.501(a)(1)** Section 553(b) of the act requires manufacturers to keep records which, at FDA's discretion, may identify recipients of the disseminated information or categories of such recipients. This provision of the rule requires such records if FDA has notified the manufacturer that it must keep such records.

**21 CFR 99.501(a)(2)** Section 553(b) of the act requires manufacturers to keep records that it may use if it must take corrective action. The rule also requires each manufacturer to maintain a copy of the information disseminated.

**21 CFR 99.501(c)** This provision requires a manufacturer to maintain records for 3 years after it has ceased disseminating that information.

#### **2. Purpose and Use of Information**

The submissions, requests, and applications described in the rule are specifically required by statute, and the submissions, under law, must be sent to FDA before a manufacturer can begin disseminating the treatment information or must be sent to FDA in order to obtain an extension of time or to get an exemption from the supplemental application requirement. Information sent to FDA will be evaluated to determine whether it is objective and balanced before it is disseminated to health professionals. FDA will use the information in the records to determine whether a manufacturer has complied with the act's requirements when the manufacturer seeks to disseminate treatment information on an unapproved use for an approved human drug, biologic, or device.

#### **3. Use of Improved Information Technology**

The collection of information neither requires nor prohibits the use of automated, electronic, mechanical, or other technological collection techniques.

#### **4. Efforts to Identify Duplication and Similar Information Already Available**

FDA is the only agency responsible for the approval of human drugs, biologics, and devices for their intended uses, and the final rule implements new statutory authority concerning the dissemination of information on unapproved/new uses. Consequently, no duplication of data exists.

#### **5. Impact on Small Businesses or Other Small Entities**

The information collection under 21 CFR 99 would apply to both small and large manufacturers. FDA has drafted the rule so that the required information is the minimum amount of information necessary in order to effectively implement the act. Thus, FDA did not use any methods to minimize any impact on small businesses.

## **6. Consequences If Information Collected Less Frequently**

The act requires manufacturers to provide the submissions, certifications, and applications described in the rule and to maintain certain records. Less frequent information collection would prevent manufacturers from disseminating information pursuant to sections 551 through 557 of the act. Moreover, less frequent information collection would adversely affect FDA's ability to ensure compliance with the act and its ability to determine that the information on unapproved or new uses being disseminated is objective and balanced.

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

The recordkeeping and reporting requirements are consistent with the guidelines in 5 CFR 1320.5(d)(2). The records that are required under the rule would be retained for 3 years after the manufacturer has ceased disseminating the information under part 99.

## **8. Consultation Outside the Agency**

In the Federal Register of March 4, 1999 (64 FR 10470) FDA invited comments on the collection of information specifically: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, (2) the accuracy of FDA's estimate of the burden of the proposed collection of information; including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology. There were no comments received.

## **9. Remuneration of Respondents**

FDA did not provide any payment or gift to respondents.

## **10. Assurance of Confidentiality**

The rule concerns submissions relating to the dissemination of treatment information on unapproved/new uses, requests for extension, and applications for exemption as required by law. Assurances of confidentiality beyond those already existing in federal law and FDA regulations are unnecessary.

## **11. Questions of a Sensitive Nature**

No questions of a sensitive nature are asked.

## **12. Estimates of Annualized Hour Burden**

This supporting statement requests a renewal of the OMB approval for the reporting and recordkeeping requirements.

FDA based its estimates of the number of submissions it would receive and the number of manufacturers who would be subject to part 99 on the number of efficacy and new use supplements for approved drugs, biologics, and devices received in fiscal year (FY) 1997 and on a projected

**increase in supplements due to FDAMA. In FY 1997, FDA received 198 efficacy and new use supplements from 115 manufacturers. The number of supplements increased 100% from FY 1995 to FY 1997 as a result of 2 new initiatives, the Prescription Drug User Fee Act and a new pediatric labeling regulation. If FDAMA results in an additional 50% increase in the number of supplements and a corresponding increase in the number of manufacturers, then the estimated number of submissions under 21 CFR part 99 is 297 ( $198 + (0.5 * 198)$ ), and the estimated number of manufacturers is 172 ( $115 + (0.5 * 115)$ ). These figures are reflected in the tables below for §§ 99.201(a)(1), 99.201(a)(2), 99.201(a)(3), 99.201(b), 99.201(c), 99.501(a)(1), 99.501(a)(2), 99.501(b)(1), 99.501(b)(3), and 99.501(c).**

The estimated burden hours for these provisions are as follows:

- \* Section 99.201(a)(1) requires the manufacturer to provide an identical copy of the information to be disseminated, including any required information. Because the manufacturer must compile this information in order to prepare its submission to FDA, FDA estimates that 40 hours would be required per submission. Because 297 annual responses are expected under § 99.201(a)(1), the total burden for this provision is 11,880 hours ( $297 \text{ responses} * 40 \text{ hours per response}$ ).
- \* Section 99.201(a)(2) requires the manufacturer to submit clinical trial information pertaining to the safety and effectiveness of the new use, clinical experience reports on the safety of the new use, and a summary of the information. FDA estimates 24 burden hours per response for this provision for assembling, reviewing, and submitting the information and assumes that the manufacturer will have already acquired some of this information in order to decide whether to disseminate information on an unapproved use under part 99. The total burden for this provision is 7,128 hours ( $297 \text{ annual responses} * 24 \text{ hours per response}$ ).
- \* Section 99.201(a)(3) requires the manufacturer to explain its search strategy when assembling its bibliography, and so FDA estimates that only 1 hour would be required for the explanation because the manufacturer would have developed and used its search strategy before preparing the bibliography. Because 297 annual responses are expected under § 99.201(a)(3), the total burden for this provision is 297 hours ( $297 \text{ annual responses} * 1 \text{ hour per response}$ ).
- \* Section 99.201(b) simply requires the manufacturer's attorney, agent, or other authorized official to sign its submissions, certifications, and requests for an exemption. FDA, therefore, estimates that only 30 minutes are necessary for such signatures. Because 297 annual responses are expected under § 99.201(b), the total burden for this provision is 148.5 hours ( $297 \text{ response} * 0.5 \text{ hours per response} = 148.5 \text{ hours}$ ).
- \* Section 99.201(c) requires the manufacturer to provide 2 copies with its original submission. Copying the submission should not be time-consuming, so FDA estimates the burden to be 30 minutes. Because 297 annual responses are expected under §

99.201(c), the total burden for this provision is 148.5 hours.

Yet, while the act requires manufacturers to provide a submission to FDA before they disseminate information on unapproved/new uses, it also permits manufacturers to: (1) Have completed studies and promise to submit a supplemental application for the new use within 6 months after the date of initial dissemination; (2) provide protocols and a schedule for completing studies and submitting a supplemental application for the new use within 36 months after the date of initial dissemination; (3) have completed studies and have submitted a supplemental application for the new use; or (4) request an exemption from the requirement to submit a supplemental application. These possible scenarios are addressed in §§ 99.201(a)(4)(i)(A), 99.201(a)(4)(ii)(A), 99.201(a)(5), and 99.205(b) respectively.

- \* To determine the number of responses in §§ 99.201(a)(4)(i)(A), 99.201(a)(4)(ii)(A), 99.201(a)(5), and 99.205(b), FDA began by estimating the number of requests for an exemption under § 99.205(b). The legislative history indicates that such exemptions are to be limited. In the final rule, FDA estimated that approximately 10% of all respondents would seek--or 10% of all submissions would contain--an “economically prohibitive” exemption (resulting in 17 total respondents and approximately 30 annual responses) and that the estimated reporting burden per response would be 82 hours. This results in a total hour burden of 2,460 hours for § 99.205(b) (30 submissions \* 82 hours per submission).

The estimated increase in the number of exemption requests results in a corresponding decrease in the remaining number of respondents and submissions under §§ 99.201(a)(4)(i)(A), 99.201(a)(4)(ii)(A), and 99.201(a)(5). FDA assumes that the remaining 267 submissions (297 total submissions - 30 submissions containing an exemption request) will be divided equally among §§ 99.201(a)(4)(i)(A), 99.201(a)(4)(ii)(A), and 99.201(a)(5), resulting in 89 responses in each provision (267 submissions/3 provisions). FDA has estimated the number of respondents in a similar fashion ((172 total respondents - 17 respondents submitting an exemption request)/3 provisions = 51.6, rounded up to 52 respondents per provision).

- \* As stated earlier, § 99.201(a)(4)(i)(A) requires the manufacturer, if the manufacturer has completed studies needed for the submission of a supplemental application for the new use, to submit the protocol(s) for the completed studies, or, if the protocol was submitted to an investigational new drug application (IND) or investigational device exemption (IDE), to submit the IND or IDE number(s), the date of submission of the protocol(s), the protocol number(s), and the date of any amendments to the protocol(s) must be submitted with the application. FDA estimates that 30 hours would be required for this response because this is information that each manufacturer already maintains for its drugs or devices. The total burden for this provision is 2,670 hours (89 annual responses \* 30 hours per response).

- \* For manufacturers who submit protocols and a schedule for conducting studies, § 99.201(a)(4)(ii)(A) requires the manufacturer to include, in its schedule, the projected dates on which the manufacturer expects the principal study events to occur. FDA estimates a manufacturer would need approximately 60 hours to include the projected dates because it would have to contact the studies' principal investigator(s) and other company officials. The total burden for this provision is 5,340 hours (89 annual responses \* 60 hours per response).
- \* If the manufacturer has submitted a supplemental application for the new use, § 99.201(a)(5) requires a cross-reference to that supplemental application. FDA estimates that only 1 hour would be needed because manufacturers already maintain this information. The total burden for this provision is 89 hours (89 annual responses \* 1 hour per response).
- \* Under § 99.203, a manufacturer who has certified that it will complete studies necessary to submit a supplemental application within 36 months after its submission to FDA, but later finds that it will be unable to complete such studies or submit a supplemental application within that time period, may request an extension of time from FDA. Such requests for extension should be limited, occurring less than 1% of the time, because manufacturers and FDA, when developing or reviewing study protocols, should be able to identify when a study will require more than 36 months to complete. Section 99.203 contemplates extension requests under two different scenarios. Under § 99.203(a), a manufacturer may make an extension request *before* it makes a submission to FDA regarding the dissemination of information under part 99. The agency expects such requests to be limited, occurring less than 1% of the time (or 1 annual response), and that such requests will result in a reporting burden of 10 hours per request. The total burden hours for this provision, therefore, is 10 hours (1 annual response \* 10 hours per response).
- \* Section 99.203(b) specifies the contents of a request to extend the time for completing planned studies *after* the manufacturer has provided its submission to FDA. The required information includes a description of the studies, the current status of the studies, reasons why the study cannot be completed on time, and an estimate of the additional time needed. FDA estimates that 10 hours for reporting the required information under § 99.203(b) because it would require consultation between the manufacturer and key individuals (such as the study's principal investigator(s)). As in the case of § 99.203(a), the expected number of responses is very small (1 annual response), and the total burden hours for this provision is 10 hours (1 annual response \* 10 hours per response).

- \* Section 99.203(c) requires 2 copies of an extension request (in addition to the request required under section 554(c)(3) of the act), and FDA estimates that these copies would result in a minimal reporting burden of 30 minutes. However, this requirement would apply to extension requests under §§ 99.203(a) and (b), so the total number of annual responses is 2, resulting in a total burden hour for this provision of 1 hour (2 annual responses \* 0.5 hours per response).

The remaining reporting and recordkeeping burdens are as follows:

- \* Section 99.501(a)(1) requires the manufacturer to maintain records that identify recipients by category or individually. Under § 99.301(a)(3), FDA will notify the manufacturer whether it needs to maintain records identifying individual recipients due to special safety considerations associated with the new use. This means that, in most cases, the manufacturer will only have to maintain records identifying recipients by category. In either event, the manufacturer will know whether it must maintain records that identify individual recipients before it begins disseminating information. The time required to identify recipients individually should be minimal, and the time required to identify recipients by category should be even less. Therefore, FDA estimates the burden for this provision to be 10 hours, and, because 297 annual responses are expected under § 99.501(a)(1), the total burden for this provision is 2,970 hours (297 annual responses \* 10 hours per response).
- \* Section 99.501(a)(2) requires the manufacturer to maintain a copy of the information it disseminates. This task is not expected to be time-consuming, so FDA estimates the burden to be 1 hour. Because 297 annual responses are expected under § 99.501(a)(2), the total burden for this provision is 297 hours (297 annual responses \* 1 hour per response).
- \* Section 99.501(b)(1) requires the manufacturer to submit to FDA semiannually a list containing the articles and reference publications that were disseminated in the preceding 6-month period. FDA tentatively estimates a burden of 8 hours for this provision. The actual burden may be less if the manufacturer develops and updates the list while it disseminates articles and reference publications during the 6-month period (as opposed to generating a completely new list at the end of each 6-month period) and if the volume of disseminated materials is small. The total burden for this provision is 4,752 hours (297 responses submitted semiannually \* 8 hours per response = 297 \* 2 \* 8 = 4,752 hours).
- \* Section 553(a)(2) of the act requires manufacturers that disseminate information to submit to FDA semiannually a list that identifies the categories of providers who received the articles and reference publications. Section 99.501(b)(2) also requires the list to identify which category of recipients received each particular article or reference

publication. If each of the 297 submissions under part 99 results in disseminated information, § 99.501(b)(2) would result in 594 lists (297 submissions \* 2 submissions/year) identifying which category of recipients received each particular article or reference publication. The agency estimates the burden to be only 1 hour per response because this type of information is maintained as a usual and customary business practice, and the total burden for this provision is 594 hours (594 lists \* 1 hour per list).

- \* In relation to § 99.201(a)(2), § 99.501(b)(3) requires the manufacturer to provide, on a semiannual basis, a notice and summary of any additional clinical research or other data relating to the safety and effectiveness of the new use and, if it possesses such research or data, to provide a copy to FDA. This burden should not be as extensive as that in § 99.201(a)(2), so FDA estimates the burden to be 20 hours per response, for a total burden of 11,880 hours for this provision (297 annual responses submitted semiannually \* 20 hours per response =  $297 * 2 * 20 = 11,880$  hours).
- \* If a manufacturer discontinues or terminates a study before completing it, § 99.501(b)(4) requires the manufacturer to state the reasons for discontinuing or terminating the study in its next progress report. Based on FDA's regulatory experience in monitoring studies to support supplemental applications, FDA estimates this would affect only 1% of all applications ( $297 * 0.01 = 2.97$ , rounded up to 3) and only 2 manufacturers ( $172 * 0.01 = 1.72$ , rounded up to 2). FDA estimates 2 hours of reporting time for this requirement because the manufacturer should know the reasons for discontinuing or terminating the study and would only need to provide those reasons in its progress report. The total burden hours for this provision is 6 hours (3 annual responses \* 2 hours per response).
- \* Section 99.501(b)(5) requires the manufacturer to submit any new or additional information that relates to whether the manufacturer continues to meet the requirements for the exemption after an exemption has been granted. FDA cannot determine, at this time, how many exemption requests will be granted, but, for purposes of this information of collection, has estimated that 10% of all submissions will contain an exemption request (297 total submissions \* 0.10 = 29.7, rounded up to 30) and has assumed that all exemption requests will be granted, for a total of 30 annual responses. The information sought under § 99.501(b)(5) pertains solely to new or additional information and is not expected to be as extensive as the information required to obtain an exemption. Thus, FDA tentatively estimates the burden for § 99.501(b)(5) to be 41 hours per response (or half the burden associated with an exemption request), for a total burden of 1,230 hours for this provision (30 annual responses \* 41 hours per response).

\* Section 99.501(c) requires the manufacturer to maintain records for 3 years after it has ceased dissemination of the information. FDA estimates the burden hour for this provision to be 1 hour. Because 297 annual responses are expected under § 99.501(c), the total burden for this provision is 297 hours.

Description of Respondents: All manufacturers (persons and businesses, including small businesses) of drugs, biologics, and device products.

**The reporting and recordkeeping burdens discussed above are as follows:**

Table 1. -- Estimated Annual Reporting Burden<sup>1</sup>

21 CFR Section	Number of Respondents	Annual Frequency Per Response	Total Annual Responses	Hours Per Response	Total Hours
99.201(a)(1)	172	1.7	297	40	11,880
99.201(a)(2)	172	1.7	297	24	7,128
99.201(a)(3)	172	1.7	297	1	297
99.201(a)(4)(i)(A)	52	1.7	89	30	2,670
99.201(a)(4)(ii)(A)	52	1.7	89	60	5,340
99.201(a)(5)	52	1.7	89	1	89
99.201(b)	172	1.7	297	0.5	148.5
99.201(c)	172	1.7	297	0.5	148.5
99.203(a)	1	1	1	10	10
99.203(b)	1	1	1	10	10
99.203(c)	2	1	2	0.5	1
99.205(b)	17	1.8	30	82	2,460
99.501(b)(1)	172	3.4	594	8	4,752
99.501(b)(2)	172	3.4	594	1	594
99.501(b)(3)	172	3.4	594	20	11,880
99.501(b)(4)	2	1.7	3	2	6
99.501(b)(5)	17	1.8	30	41	1,230

Total Hours					48,644
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[Footnote: There are no capital costs or operating and maintenance costs associated with this collection of information]

**Estimated Annual Recordkeeping Burden<sup>1</sup>**

21 CFR Section	Number of Recordkeepers	Annual Frequency of Recordkeeping	Total Annual Records	Hours Per Recordkeeper	Total Recordkeeping Hours
99.501(a)(1)	172	1.7	297	10	2,970
99.501(a)(2)	172	1.7	297	1	297
99.501(c)	172	1.7	297	1	297
Total Hours					3,564

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

**13. Estimates of Annualized Cost Burden to Respondents**

FDA estimates an average industry wage rate of \$35.00 per hour for preparing and submitting the information collection requirements under 21 CFR 99. This figure is based on an analysis of pharmaceutical industry wages prepared for FDA for an earlier rulemaking where the average wage rates were: \$52 per hour for upper management; \$34 per hour for middle management; and \$17 per hour for clerical assistance. FDA weighted the hourly wage rates by 0.25, 0.50, and 0.25 respectively, resulting in an average industry wage rate of \$35  $((\$52 * 0.25) + (\$34 * 0.50) + (\$17 * 0.25) = \$34.75$ , rounded up to \$35). Multiplying the averaged wage rate of \$35.00 per hour by the estimated total burden hours, therefore, yields a total cost burden to respondents for the information collection requirements under the Paperwork Reduction Act of \$1,827,280  $(\$35 \text{ per hour} * 52,208 \text{ total hours})$ .

**14. Estimates of Annualized Cost Burden to the Government**

FDA estimates it would need approximately 8 full time equivalents (FTE's) to review the information submitted under 21 CFR part 99. Assuming each FTE equals approximately \$100,000, the annualized cost burden to FDA would be \$800,000.

**15. Changes in Burden**

There are no changes in the burden.

**16. Statistical Reporting**

Information collected under this requirement will not be published.

**17. Exemption for Display of Expiration Date**

The agency does not seek an exemption from displaying the expiration date.

**18. Exemption to Certification Statement**

**The agency is not requesting any exemption from the certification statement identified in item 19 of OMB Form 83-I.**