Guidance for Industry on CMC Postapproval Manufacturing Changes
To Be Documented in Annual Reports

OMB Control Number 0910-NEW

SUPPORTING STATEMENT

Terms of Clearance: None.

## A. Justification

1. Circumstances Making the Collection of Information Necessary

The number of chemistry, manufacturing, and controls (CMC) manufacturing supplements for new drug applications (NDAs) and abbreviated new drug applications (ANDAs) has continued to increase over the last several years. In connection with FDA's Pharmaceutical Product Quality Initiative and our risk-based approach to CMC review, we have evaluated the types of changes that have been submitted in CMC postapproval manufacturing supplements and determined that many of the changes being reported present low risk to the quality of the product and do not need to be submitted in supplements.

Based on our risk-based evaluation, we developed recommendations to companies regarding some postapproval manufacturing changes for NDAs and ANDAs that may be considered to have a minimal potential to have an adverse effect on product quality, and, therefore, may be classified as a change to be documented in the next annual report (i.e., notification of a change after implementation) rather than in a supplement. We expect NDA and ANDA holders to evaluate the specific change that they are planning to make in the context of their particular circumstances to determine whether the proposed change would present a minimal potential to have an adverse effect on product quality. When a risk-based evaluation

shows that the proposed change would have a minimal potential to have an adverse effect on product quality, the change can be documented in the next annual report.

2. Purpose and Use of the Information Collection

The information collection pertains to the types of CMC postapproval manufacturing changes that FDA has determined will likely have a minimal potential to have an adverse effect on product quality (i.e., drug product identity, strength, quality, purity, or potency), and therefore, should be documented by applicants in an annual report under 21 CFR 314.70(d).

3. Use of Improved Information Technology and Burden Reduction

Applicants may use automated, electronic, mechanical, or other technological collection techniques or other forms of information technology to comply with these recommendations. FDA has issued guidance documents to assist applicants in submitting information to the agency in electronic format. These guidance documents are available at FDA's web site. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

4. Efforts to Identify Duplication and Use of Similar Information

There is no duplication in this information collection.

5. Impact on Small Businesses or Other Small Entities

Although new drug development, including the submission of supplemental applications and annual reports, is typically an activity completed by large multinational drug firms, this information collection would apply to small as well as large companies that have approved marketing applications. Under the Regulatory Flexibility Act, FDA regularly analyzes regulatory options that would minimize any significant impact on small entities. FDA also assists small businesses in complying with regulatory requirements

6. Consequences of Collecting the Information Less Frequently

The submission of supplemental applications and annual reports is required by FDA regulation, as described in the guidance, and less frequent submissions would hinder FDA's ability to approve and monitor changes to approved applications in a timely manner.

7. Special Circumstances Relating to the Guidelines in 5 CFR 1320.5

There are no special circumstances for this collection of information.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

In accordance with 5 CFR 1320.8(d), FDA published a 60 day notice for public comment in the FEDERAL REGISTER of June 25, 2010 (75 FR 36421). We received the following comments that pertained to the collection of information resulting from the guidance.

Comments on Issue One: Several comments noted that, in addition to FDA regulations on postapproval changes at §§ 314.70 and 314.71, FDA has issued multiple guidances that provide recommendations on how the Agency wishes to be notified of postapproval changes. These guidances include the "Guidance for Industry on Changes to an Approved NDA or ANDA," the "Guidance for Industry on Changes to an Approved NDA or ANDA – Questions and Answers," the "Guidance for Industry on Scale-Up and PostApproval Changes (SUPAC)," the "Guidance for Industry on Bulk Active Chemicals – Postapproval Changes II (BACPAC)," the "Draft Guidance for Industry on CMC Postapproval Manufacturing Changes Reportable in Annual Reports" (the guidance that is the subject of this Federal Register notice), and others.

The comments said that this adds duplication, complexity, redundancy, and the potential for confusion to the postapproval CMC regulatory environment. For example, the comments noted that while some of the changes described in the "Draft Guidance for Industry on CMC Postapproval Manufacturing Changes Reportable in Annual Reports" are already included in the

existing “Guidance for Industry on Changes to an Approved NDA or ANDA,” other changes to be documented in annual reports such as a move to a different manufacturing site for secondary packaging and labeling described in the “Guidance for Industry on Changes to an Approved NDA or ANDA” are not contained in the “Draft Guidance for Industry on CMC Postapproval Manufacturing Changes Reportable in Annual Reports.”

The comments recommended that all CMC changes to be documented in annual reports be consolidated into a single, updated guidance document to help ensure consistency, avoid confusion, and simplify the process for assessing change. The comments also recommended that the “Draft Guidance for Industry on CMC Postapproval Manufacturing Changes Reportable in Annual Reports” be withdrawn and that its recommendations be incorporated into an updated version of the “Guidance for Industry on Changes to an Approved NDA or ANDA.”

FDA Response on Issue One: The “Final Guidance for Industry on CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports” now includes Appendices A and B, which provides examples of chemistry, manufacturing, and control-related postapproval changes to be documented in annual reports. Section V. “Resources” of the guidance lists other previously published CMC guidances in which CMC changes to be documented in annual reports also are mentioned, along with changes that are required to be documented according to § 314.70 (b) and (c).

Comments on Issue Two: Several comments said that some of the examples given in the draft guidance for changes previously submitted under manufacturing supplements that should now be documented in an annual report (because the Agency has determined those change to be of generally low risk to product quality) are problematic because some of these changes are current good manufacturing practice changes (CGMPs) and would not have previously been

reported at all but kept on file for FDA inspection. The comments said that changes that do not have an adverse effect on product quality data can be made available to FDA on request or during an inspection and do not need to be documented in the annual report. The comment said that the recommendations of the draft guidance to document these changes in the annual report will increase, not reduce, industry's regulatory reporting burden.

In addition, the comments noted that the draft guidance's recommendation that CMC changes to be documented in annual reports be supported by, among other things, a reference to affected validation protocols, standard operating procedures, and policies also would increase industry's regulatory reporting burden because these documents are frequently updated and revised, and FDA's CGMP regulations require this information to be kept on file and presented to FDA on request or during an inspection.

FDA Response on Issue Two: The guidance clarifies that executed batch records, standard operating procedures (SOPs), and data from studies and tests performed to assess the effects of each change listed in Appendix A should be kept on file and made available to the Agency on request (e.g., during an inspection). Section IV. "Contents of Annual Report Notification" of the guidance has been revised from the draft guidance to address many of industry's comments stated in the above paragraph. Summary of data, cross references to change control and change validation protocols, and SOPs that were used to assess or demonstrate the effect of the change are recommended for inclusion in the annual report. These are expected to allow the Agency to efficiently determine whether the appropriate reporting category has been used.

Comments on Issue Three: One comment said that many of the recommendations found in Appendix A, Sections 1-3 of the draft guidance (Components and Composition,

Manufacturing Sites, and Manufacturing Process) reference information that FDA regulations do not require. The comment said that this may result in an overly conservative approach to annual reports and the submission of a large amount of unnecessary information. As an example, the comment said that Appendix A, Section 1.2 (lines 147-149) of the draft guidance states that the following can be documented in an annual report: "New supplier of inactive ingredients that have a minimal effect on product performance in the drug product, providing that acceptance criteria remain unchanged." The comment noted that if the inactive ingredient meets compendial standards, the supplier need not be specified in the original application, and if the supplier of that inactive ingredient is later changed, that information does not need to be submitted to FDA if the inactive ingredient also is a compendial standard. As another example, the comment said that Appendix A, Section 2.2 (lines 161-162) of the draft guidance states that: "Addition of barriers to prevent routine in-process human intervention in a filling or compounding area that is qualified and validated by established procedures." The comment said that this is not routinely required to be documented in an annual report.

FDA Response on Issue Three: In response to the comments received on the draft guidance, the Agency has clarified the applicable circumstance when information on the new supplier(s) of inactive ingredient should be documented in the annual report. It is clarified that documenting the "addition of barriers within a conventional fill area" in an annual report would apply to the manufacturing of sterile products.

9. Explanation of Any Payment or Gift to Respondents

FDA has not provided and has no intention to provide any payment or gift to respondents.

10. Assurance of Confidentiality Provided to Respondents

The confidentiality of the information received by FDA under this guidance and the regulations is consistent with the Freedom of Information Act, the Agency's regulations under 21 CFR Part 20, and 21 CFR 314.430.

11. Justification for Sensitive Questions

There are no questions of a sensitive nature.

12. Estimates of Annualized Burden Hours and Costs

12a. Annualized Hour Burden Estimate

The number of CMC manufacturing supplements for NDAs and ANDAs has continued to increase over the last several years. In connection with FDA's Pharmaceutical Product Quality Initiative and its risk-based approach to CMC review, FDA has evaluated the types of changes that have been submitted in CMC postapproval manufacturing supplements and determined that many of the changes being reported present low risk to the quality of the product and do not need to be submitted in supplements. Based on the risk-based evaluation, FDA developed a list (attached as Appendix in the "Guidance for Industry on CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports") to provide additional current recommendations to companies regarding some postapproval manufacturing changes for NDAs and ANDAs that may be considered to have a minimal potential to have an adverse effect on product quality, and, therefore, may be classified as a change to be documented in the next annual report (i.e., notification of a change after implementation) rather than in a supplement.

FDA is requesting OMB approval for the information collection reduction resulting from the annual submissions, as required by §§ 314.70, 314.71, 314.81(b)(2), and 314.97 (21 CFR 314.70, 314.71, 314.81(b)(2), and 314.97), described below. Sections 314.70 and 314.71 require that supplements be submitted to FDA for certain changes to an approved application. Section

314.81(b)(2) requires that annual reports be submitted to FDA (Form FDA 2252). Section 314.97 sets forth requirements for submitting supplements to an approved ANDA for changes that require FDA approval. In addition, § 314.98(c) requires annual reports and other post-marketing reports for ANDAs. The estimate for annual reports for ANDAs is included under § 314.81(b)(2). Other post-marketing reports under § 314.98 are not affected by this notice.

The guidance describes our current thinking on the interpretation of these requirements. Part of the intent for the guidance is to reduce the burden of reporting some manufacturing changes. Currently, for postapproval changes considered to be major, applicants must submit and receive FDA approval of a supplemental application to the NDA or ANDA before the product made with the manufacturing change is distributed. If a change is considered to be moderate, an applicant must submit a supplement at least 30 days before the product is distributed or, in some cases, submit a supplement at the time of distribution. If a change is considered to be minor, an applicant may proceed with the change, but must notify FDA of the change in the annual report. The guidance describes the types of postapproval changes that applicants of NDAs and ANDAs currently submit in supplements to NDAs or ANDAs but that, under the guidance, may now be documented in annual reports. As a result, applicants would no longer need to submit supplements for such changes.

FDA currently has OMB approval for the collection of information entitled "Application for Food and Drug Administration Approval to Market a New Drug" (OMB Control Number 0910-0001). This collection of information includes the requirements imposed by the regulations under 21 CFR part 314 on applicants who apply for approval of an NDA or ANDA to market or change an approved application. In particular, among other things, this collection of information includes: (1) The submission of supplements to FDA for certain changes to an

approved application in accordance with §§ 314.70 and 314.71; (2) the submission of annual reports to FDA (Form FDA 2252) in accordance with § 314.81(b)(2); (3) the submission of supplements to an approved ANDA for changes that require FDA approval; and (4) other post-marketing reports for ANDAs in accordance with § 314.98(c), of which the estimate for annual reports is included under § 314.81(b)(2). Therefore, this information collection includes the supplements to NDAs and ANDAs and the annual reports for NDAs and ANDAs that are described in the guidance.

Under the applicable regulations and the guidance, the following changes would occur to the current approval by OMB under the PRA for supplements to NDAs under §§ 314.70 and 314.71 and supplements to ANDAs under § 314.97. Although the submission of supplements to NDAs and ANDAs is approved under OMB Control Number 0910-0001, the total number of supplements submitted per year is estimated to reduce based on the recommendations in the guidance because certain changes submitted as supplements would now be documented in annual reports. Therefore, for such changes, the information collection with respect to the submission of supplements will be reduced. Because the number of supplements per year is estimated to reduce, the total number of hours for preparing supplements would correspondingly reduce.

The estimates described below are based on FDA's data of the number of supplements and annual reports submitted annually to NDAs and ANDAs, as well as the Agency's familiarity with the time needed to prepare supplements and annual reports. The total number of supplements submitted per year is estimated to reduce based on the recommendations in the guidance. Based on the number of CMC manufacturing supplements received for NDAs and ANDAs, FDA estimates that it will receive annually approximately 800 responses under §§ 314.70 and 314.71 for NDAs and approximately 2,075 responses under § 314.97 for ANDAs.

The number of annual frequencies per response is estimated to decrease. FDA estimates that approximately the same number of respondents will submit responses under §§ 314.70, 314.71, and 314.97 and each response will take approximately the same amount of time to prepare as in the information collection currently approved under OMB Control Number 0910-0001.

As set forth in the following table, the estimated annual reporting burden for this information collection is 286,000 hours. In the future, it is estimated that the Agency would reduce the currently approved burden (OMB Control Number 0910-0001) for §§ 314.70 and 314.71 for NDAs and § 314.97 for ANDAs by reducing the number of supplements for those postapproval CMC changes that can be documented in annual reports as recommended in the "Guidance for Industry on CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports."

FDA estimates the burden of this collection of information as follows:

Table 1.--Estimated Annual Reporting Burden

| Activity | No. of Respondents | No. of Responses per Respondent | Total Annual Responses | Average Burden per Response | Total Hours |
|---|---|---|---|---|---|
| Supplements and Annual Reports for NDAs | 281 (same as currently approved) | 2.85 | 800 | 150 (same as currently approved) | 120,000 |
| Supplements and Annual Reports for ANDAs | 215 (same as currently approved) | 9.65 | 2,075 | 80 (same as currently approved) | 166,000 |

| | | | | | |
|---|---|---|---|---|---|
| TOTAL | | | | | 286,000 |

12b. Annualized Cost Burden Estimate

FDA estimates an average pharmaceutical industry wage rate of $85 per hour for preparing and submitting this information collection. Thus, the total cost burden would be:

| Type of Respondent | Total Burden Hours | Hourly Wage Rate | Total Respondent Costs |
|---|---|---|---|
| Applicants | 286,000 | $85 | $24,310,000 |

13. Estimates of Other Total Annual Cost Burden to Respondents and/or Recordkeepers/Capital Costs

There are no capital, start-up, operating or maintenance costs associated with this information collection.

14. Annualized Cost to the Federal Government

Under the guidance, FDA estimates that no additional measurable burden would be required of FDA reviewers who currently review supplements and annual reports. The total burden for FDA's review of supplements and annual reports is accounted for in OMB control number 0910-0001.

15. Explanation for Program Changes or Adjustments

This is a new data collection.

16. Plans for Tabulation and Publication and Project Time Schedule

There are no tabulated results to publish for this information collection.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

FDA is not seeking approval to exempt the display of the expiration date of the OMB approval.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.