Supplemental Applications Proposing Labeling Changes

for Approved Drugs and Biological Products;

Proposed Rule

RIN 0910-AG94

SUPPORTING STATEMENT

A. Justification

1. Circumstances Making the Collection of Information Necessary

FDA regulations at §§ 314.70 and 314.97 set forth the requirements for submitting supplements to FDA for certain changes to an approved new drug application (NDA) or abbreviated new drug application (ANDA). These regulations specify the submission of supplements at different times, depending on the change to the approved application. Under § 314.70(c)(6), an applicant may commence distribution of a drug product upon receipt by FDA of a supplement for a change to the applicant's approved application (a CBE-0 supplement). The changes for which a CBE-0 supplement may be submitted include, among other things, changes in the labeling (§ 314.70(c)(6)(iii)) to reflect newly acquired information, for example, to add or strengthen a contraindication, warning, precaution, or adverse reaction for which there is reasonable evidence of a causal association.

FDA generally has advised that an ANDA holder may use the CBE-0 supplement process only to update its product labeling to conform with approved labeling for the referenced listed drug (RLD) or to respond to FDA's specific request to submit a labeling change under this provision, and may not unilaterally change ANDA labeling in a manner that differs from the RLD. If an ANDA holder believes that newly acquired safety information should be added to its product labeling, FDA has advised that it should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic drug(s) and the RLD should

be revised. However, as the generic drug industry has matured and captured an increasing share of the market, tension has grown between the requirement that a generic drug have the same labeling as its RLD, which facilitates substitution of a generic drug for the prescribed product, and the need for an ANDA holder to be able to independently update its labeling to reflect data obtained through postmarketing surveillance and to ensure that the labeling is accurate and up-to-date.

The proposed rule would permit ANDA holders to update product labeling to reflect certain types of newly-acquired safety information using the same process now available to NDA holders when they submit a CBE-0 labeling supplement. At the time of submission, the ANDA holder would be required to send notice of the labeling change proposed in the CBE-0 supplement, including a copy of the information supporting the change, to the NDA holder for the reference listed drug (RLD), unless approval of the NDA for the RLD has been withdrawn.

2. Purpose and Use of the Information Collection

If an NDA holder, ANDA holder, or BLA holder obtains or otherwise receives newly acquired information that should be reflected in product labeling to accomplish any of the objectives specifically described in § 314.70(c)(6)(iii) or § 601.12(f)(2), the application holder must submit a CBE-0 supplement to FDA. At the time of submission of an ANDA holder's CBE-0 labeling supplement to FDA, the ANDA holder must send notice of the labeling change proposed in the supplement, including a copy of the information supporting the change, to the NDA holder for the RLD, unless approval of the NDA for the RLD has been withdrawn. ANDA holders, NDA holders, and BLA holders would be required to verify that the correct information regarding the labeling changes proposed in their CBE-0 supplement appears on the proposed FDA Web page and, if the information is incorrect, they must contact the appropriate FDA review division within 2 business days of posting on the FDA Web page.

3. Use of Improved Information Technology and Burden Reduction

FDA has developed several guidances for industry to improve the use of information

technology in the submission of marketing applications and related reports for human drugs. These guidance documents are available at FDA's web site http://www.fda.gov/cder/guidance/index.htm.

4. Efforts to Identify Duplication and Use of Similar Information

This information is not otherwise submitted to the agency, and thus, there is no duplicate reporting.

5. Impact on Small Businesses or Other Small Entities

As explained in the "Analysis of Impacts" section of the proposed rule (section IV), this rulemaking would not have a significant economic impact on a substantial number of small entities.

6. Consequences of Collecting the Information Less Frequently

Although there is no prescribed frequency to submit this information, FDA has determined that it is important for ANDA holders to be able to independently update their labeling to include important newly acquired safety-related information, for example, to add or strengthen a contraindication, warning, precaution, or adverse reaction for which there is reasonable evidence of a causal association.

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

This information collection is consistent with 5 CFR 1320.5.

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

This is a proposed rule. FDA is requesting public comment on these proposed requirements and plans to evaluate all comments and respond to the issues raised in the final rule.

9. Explanation of Any Payment or Gift to Respondents

FDA did not provide any payment or gifts to respondents.

10. Assurance of Confidentiality Provided to Respondents

Confidentiality of the information submitted under these reporting requirements is protected under 21 CFR 314.430 and under 21 CFR part 20. The unauthorized use or disclosure of certain types of trade secrets required in marketing applications is specifically prohibited under section 301(j) of the Federal Food, Drug, and Cosmetic Act. FDA expects that application holders will use available means to distribute the revised labeling proposed in the CBE-0 supplement to the public at the time of submission of the CBE-0 supplement to FDA. Accordingly, certain information contained in the CBE-0 supplement will be publicly disclosed or acknowledged. To make safety-related changes to generic drug labeling readily available to prescribing health care providers and the public while FDA is reviewing a CBE-0 supplement, FDA would promptly post information regarding the labeling changes proposed in a CBE-0 supplement on a dedicated Web page (or, alternatively, a modification of an existing FDA Web page).

11. Justification for Sensitive Questions

No questions of a sensitive nature are asked.

12. Estimates of Annualized Hour Burden and Costs

12a. Annualized Hour Burden Estimate

FDA currently has OMB approval under control number 0910-0001 for the submission of supplements to FDA for changes to an approved NDA or ANDA under §§ 314.70 and 314.97. The proposed rule would permit ANDA holders to submit a CBE-0 supplement to FDA for certain safety-related labeling changes based on newly acquired information. This collection of information is not currently approved under OMB control number 0910-0001. Under proposed § 314.70(c)(8), if an NDA holder or ANDA holder obtains or otherwise receives newly acquired information that should be reflected in product labeling to accomplish any of the objectives specifically described in § 314.70(c)(6)(iii), the NDA holder or ANDA holder must submit a CBE-0 supplement to FDA. Proposed § 314.70(c)(8) is intended to permit ANDA holders to update product labeling promptly, to reflect newly acquired information that meets the criteria

described in § 314.70(c)(6)(iii) irrespective of whether the revised labeling (temporarily) differs from that of the RLD.

To minimize confusion and make safety-related changes to generic drug labeling readily available to prescribing health care providers and the public while FDA is reviewing a CBE-0 supplement, FDA would establish, under proposed § 314.70(c)(8), a dedicated Web page (or, alternatively, a modification of an existing FDA Web page) on which FDA would promptly post information regarding the labeling changes proposed in a CBE-0 supplement. ANDA holders would be required to verify that the correct information regarding the labeling changes proposed in their CBE-0 supplement appears on the FDA Web page. If the information is incorrect, the ANDA holder must contact the appropriate FDA review division within 2 business days of posting on the FDA Web page.

At the time of submission of the CBE-0 labeling supplement to FDA, proposed § 314.70(c)(8)(ii) would require the ANDA holder to send notice of the labeling change proposed in the supplement, including a copy of the information supporting the change, to the NDA holder for the RLD, unless the NDA for the RLD has been withdrawn.

Based on the data summarized in section IV of the proposed rule (Analysis of Impacts), we estimate that a total of approximately 15 ANDA holders ("number of respondents" in table 1) would submit to us annually a total of approximately 20 CBE-0 labeling supplements under proposed § 314.70(c)(8) ("total annual responses" in table 1). We also estimate that preparing and submitting each CBE-0 labeling supplement under proposed § 314.70(c)(8) will take approximately 15 hours per ANDA holder ("hours per response" in table 1).

This burden hour estimate includes the time needed by an ANDA holder to verify, as required under proposed § 314.70(c)(8), that the correct information regarding the labeling change proposed in its CBE-0 supplement appears on the FDA Web page, and the time needed to contact FDA if the information is incorrect. The burden hour estimate also includes the time needed by the ANDA holder to send notice of the labeling change proposed in the supplement,

including a copy of the information supporting the change, to the NDA holder for the RLD, as required under proposed § 314.70(c)(8)(ii).

NDA holders, under proposed § 314.70(c)(8), and BLA holders, under proposed § 601.12(f)(2)(iii), would also be required to verify that the correct information regarding the labeling changes proposed in their CBE-0 supplement appears on the FDA Web page. If the information is incorrect, they must contact the appropriate FDA review division within 2 business days of posting on the FDA Web page. We estimate that approximately 173 NDA holders and BLA holders will review and verify that the correct information appears on the FDA Web page for approximately 230 CBE supplements, and that it will take approximately 30 minutes to review and verify this information. This burden hour estimate includes the time needed to contact FDA if the information is incorrect.

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

Table 1.--Estimated Annual Reporting Burden

| 21 CFR Section | No. of Respondents | No. of Responses per Respondent | Total Annual Responses | Hours per Response | Total Hours |
|---|---|---|---|---|---|
| Proposed requirements for ANDA holders under 314.70(c)(8) and 314.70(c)(8)(ii) | 15 | 1.34 | 20 | 15 | 300 |
| Proposed verification requirements for NDA and BLA holders under 314.70(c)(8) and 601.12(f)(2)(iii) | 173 | 1.33 | 230 | 0.5 (30 minutes) | 115 |
| Total | | | | | 415 |

12b. Annualized Cost Burden Estimates

Section IV of the proposed rule (Analysis of Impacts) concludes that the rulemaking would generate little cost, and estimates the net annual social costs to be between $4,237 and $25,852. The present discounted value over 20 years would be in the range of $63,040 to

$384,616 at a 3 percent discount rate, and in the range of $44,890 to $273,879 at a 7 percent discount rate.

Based on the hours estimated above, the burden hour costs for the reporting requirements would be as follows:

| Type of Respondent | Total Burden Hours | Hourly Wage Rate | Total Respondent Costs |
|---|---|---|---|
| ANDA, NDA, or BLA Holders | 415 | $75.00 | $31,125 |

13. Estimates of Other Total Annual Cost Burden to Respondents

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

14. Annualized Cost to the Federal Government

There are no additional cost burdens to FDA to review these submissions. These reviews are already accounted for in the Federal burden estimates for OMB Control Numbers 0910-0001 and 0910-0338.

15. Explanation for Program Changes or Adjustments

This is a new approval request.

16. Plans for Tabulation and Publication and Project Time Schedule

Information collected under this rulemaking will not be published in its entirety. However, to make safety-related changes to generic drug labeling readily available to prescribing health care providers and the public while FDA is reviewing a CBE-0 supplement, FDA would promptly post information regarding the labeling changes proposed in a CBE-0 supplement on a dedicated Web page (or, alternatively, a modification of an existing FDA Web page).

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

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

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.