Guidance for Industry: Safety Labeling Changes- Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act

0910-0734

SUPPORTING STATEMENT

Terms of Clearance: None.

A. Justification

1. Circumstances Making the Collection of Information Necessary

This guidance provides information on the implementation of section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(o)(4)), which was added by section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Section 505(o)(4) authorizes FDA to require certain drug and biological product application holders to make safety-related labeling changes based on safety information that becomes available after approval of the drug or biological product.

Section 505(o)(4) of the Act authorizes FDA to require safety labeling changes for the following products:

- Prescription drug products with an approved new drug application (NDA) under section 505(b) of the Act
- Biological products with an approved biologics license application (BLA) under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262)
- Prescription drug products with an approved abbreviated new drug application (ANDA) under section 505(j) of the FD&C Act, if the NDA reference listed drug (RLD) is not currently marketed

FDA has always had the ability to request safety-related changes to the labeling of approved medical products. However, until Congress passed and the President signed the Food and Drug Administration Amendments Act of 2007 (FDAAA), FDA's authority was relatively limited.

In the past, FDA has requested that holders of applications for approved products make labeling changes related to safety to address serious risks. FDA typically learned of the potential for such serious risks from a variety of sources, including FDA's adverse events reporting systems. In most cases, application holders responded to these requests for labeling changes by negotiating appropriate language with FDA staff to address the concerns and then submitting a supplement or amended supplement to obtain approval of the changes. Negotiations were often protracted, and FDA had few tools at its disposal to end negotiations and require the changes. Before FDAAA, if the application holder did not respond to FDA's request or did not agree with the requested labeling changes, FDA could take the following actions:

- FDA could initiate proceedings to withdraw approval of the drug — an action not normally desirable if some patients were benefitting from the drug despite its risks.
- FDA could notify the public about the safety information through mechanisms like Public Health Advisories or notification on the FDA web site describing the safety information and the need for labeling changes.

- If in FDA's judgment the absence of the new safety information from the drug's label rendered the product misbranded, FDA could take appropriate enforcement action.

Congress recognized the limitations of FDA's authority in this area and, in FDAAA, gave FDA new authorities to require safety labeling changes in certain circumstances. Section 505(o)(4) of the FD&C Act authorizes FDA to require and, if necessary, order labeling changes if FDA becomes aware of new safety information that FDA believes should be included in the labeling of the drug. Section 505(o)(4) imposes time frames for application holders to submit and for FDA staff to review such changes and gives FDA new enforcement tools to bring about timely and appropriate safety labeling changes.

2. Purpose and Use of the Information Collection

The final guidance provides information on the implementation of the statutory provisions described above and in the final guidance, including a description of the types of safety labeling changes that ordinarily might be required under the new legislation; how FDA plans to determine what constitutes new safety information; the procedures involved in requiring safety labeling changes; and enforcement of the requirements for safety labeling changes.

3. Use of Improved Information Technology and Burden Reduction

To improve the use of information technology in the submission of marketing applications for human drugs and related reports, including safety-related labeling changes, FDA has developed and issued guidances for industry on electronic submissions. These guidance documents are available on FDA's Internet site at http://www.fda.gov/drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

4. Efforts to Identify Duplication and Use of Similar Information

This information collection does not duplicate other FDA initiatives.

5. Impact on Small Businesses or Other Small Entities

FDA's authority and responsibility to ensure the safe use of human drugs applies to small as well as to large businesses involved in marketing human drugs. FDA's responsibility requires the equal application of the regulations to all businesses. 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 business with help in dealing with FDA regulatory requirements.

6. Consequences of Collecting the Information Less Frequently

Less frequent information collection would reduce the statutorily-mandated requirement that holders of applications for approved products make labeling changes related to safety to address serious risks.

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

There are no special circumstances relating to these guidelines.

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 in the Federal Register of September 2, 2015, (80 FR 53161). No comments were received.

9. Explanation of Any Payment or Gift to Respondents

No payment or gift was provided to respondents.

10. Assurance of Confidentiality Provided to Respondents

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

11. Justification for Sensitive Questions

Questions of a sensitive nature are not applicable to this information collection.

12. Estimates of Annualized Burden Hours and Costs

12a. Annualized Hour Burden Estimate

This guidance provides information on the implementation of section 901 of FDAAA, which authorizes FDA to require certain drug and biological product application holders to make safety related labeling changes based upon new safety information that becomes available after the drug or biological product is approved under the FD&C Act or the PHS Act. FDA requests safety labeling changes by sending a notification letter to the application holder. Under section 505(o)(4)(B), the application holder must respond to FDA's notification by submitting a labeling supplement or notifying FDA that the applicant does not believe the labeling change is warranted and submitting a statement detailing the reasons why the application holder does not believe a change is warranted (a rebuttal statement).

The submission of rebuttal statements may result in the collection of information that is not already approved by OMB. Based on FDA's experience thus far with safety labeling changes requirements under section 505(o)(4), FDA estimates that approximately forty-two application holders will elect to submit approximately one rebuttal statement each year and that each rebuttal statement will take approximately 6 hours to prepare.

In addition, in the guidance, the agency states that new labeling prepared in response to a safety labeling change notification should be available on the application holder's Web site within 10 calendar days of approval, which may result in the collection of information that is not already approved by OMB. FDA estimates that approximately 407 application holders will post new labeling one time each year in

response to a safety labeling change notification and that the posting of the labeling will take approximately 4 hours to prepare.

The guidance also refers to previously approved collections of information. Specifically, the guidance describes: Labeling supplements for NDAs, ANDAs, and BLAs submitted under 21 CFR 314.70, 314.71, 314.97 and 601.12; and the content and format of prescription drug labeling submitted under 21 CFR 201.56 and 201.57. These collections of information are subject to review by OMB under the PRA act and are approved under OMB control numbers 0910-0001, 0910-0338, and 0910-0572. Section V of the guidance refers to the guidance entitled "Formal Dispute Resolution: Appeals Above the Division Level," which describes collections of information approved under OMB control number 0910-0430.

FDA estimates the burden of the collections of information that have not already been approved by OMB, is as follows:

Table 1.--Estimated Annual Reporting Burden[1]

	Number of Respondents	Number of Responses per Respondent	Total Responses	Hours per Response	Total Hours
Rebuttal statement	42	1	42	6	252

Table 2.--Estimated Annual Third Party Disclosure Burden

Type of Submission	Number of Respondents	Annual Frequency per Disclosure	Total Annual Disclosures	Hours per Disclosure	Total Hours
Posting approved labeling on application holder's Web site	407	1	407	4	1628

[1]

12b. Annualized Cost Burden Estimate

There are labor costs associated with the estimated 1880 annual reporting hours described above. Assuming an industry loaded wage rate of approximately $75 per hour, we estimate these costs to be approximately $141,000.

Type of Respondent	Total Burden Hours	Hourly Wage Rate	Total Respondent Costs
Pharmaceutical industry average wage grade for preparing and submitting this information collection	1880	$75	$141,000

13. Estimates of Other Total Annual Costs 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

There are no notable additional costs to FDA as a result of this information collection. The number of hours needed to review these submissions would already be included under the approximately 835 FTEs devoted annually to reviewing submissions under 21 CFR 314. If each FTE equals approximately $170,000 for these review activities, the total cost burden to the Federal Government to review submissions under 21 CFR 314 would be approximately $141,950,000.

15. Explanation for Program Changes or Adjustments

The adjustments to the currently approved burden hours of 824 are based on the latest data. The new burden hours are 1,880 total hours. This is a renewal of information collection without any program changes.

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.