Permanent Discontinuation or Interruption in Manufacturing of Certain Drug and Biological Products; Proposed Rule

RIN 0910-AG88

SUPPORTING STATEMENT

A. Justification

1. Circumstances Making the Collection of Information Necessary

The Food and Drug Administration Safety and Innovation Act (FDASIA), Public Law 112-144, made significant changes to sections 506C and 506E of the Federal Food, Drug, and Cosmetic Act. As a result of these changes and as required by FDASIA, FDA is issuing a proposed rule. FDA is requesting OMB approval of the information collection activities resulting from the proposed rule, which adds FDA regulations at 21 CFR §§ 310.306 and 600.82, amends the regulation at 21 CFR § 314.81(b)(3)(iii), and deletes the regulation at 21 CFR § 314.91, all implementing sections 506C and 506E of the Federal Food, Drug and Cosmetic Act. The proposed rule would require all applicants of covered, approved prescription drug or biological products, certain applicants of blood or blood components for transfusion, and all manufacturers of covered prescription drugs marketed without an approved application, to notify FDA electronically of a permanent discontinuance or an interruption in manufacturing of the product. The proposed rule would also eliminate § 314.91 related to reductions in the notification period for "good cause." Finally, the proposed rule would require FDA to maintain a list of products in shortage, and would require FDA to issue a non-compliance letter to entities that fail to comply with the notification requirements included in the proposed rule, and would require the recipient of such a letter to respond to FDA.

Products Subject to the Proposed Rule

The proposed rule would apply to all prescription drugs, including marketed unapproved prescription drugs, and all prescription biologic drugs that are life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including any such drug used in emergency medical care or during surgery; and that are not radiopharmaceutical products.

Persons Subject to the Proposed Rule

The following persons would be subject to the proposed rule:

- All applicants with an approved new drug application (NDA) or abbreviated new drug application (ANDA) for a covered prescription drug product (proposed § 314.81(b)(3)(iii)).
- All applicants with an approved biologics license application (BLA) for a covered prescription biological drug, except blood or blood components for transfusion (proposed § 600.82(a)(1)).
- Applicants with an approved BLA for blood or blood components, if the applicant is a manufacturer of a significant percentage of the United States blood supply (proposed § 600.82(a)(2)).
- All manufacturers of a prescription drug product marketed without an approved NDA or ANDA (proposed § 310.306, which applies § 314.81(b)(3)(iii) in its entirety to covered prescription drug products marketed without an approved NDA or ANDA).

Notification Requirements

The proposed rule would require reporting to FDA of all permanent discontinuances of covered drugs and biological products, and all interruptions in manufacturing of covered drugs

and biological products that are likely to result in in either: 1) a meaningful disruption in supply of the product in the U.S. (for all covered drugs and biological products other than blood or blood components); or 2) a significant disruption in supply of the product in the U.S. (for all covered products that are blood or blood components). These notifications must be submitted to FDA at least 6 months in advance of the permanent discontinuance or interruption in manufacturing, or, if that is not possible, as soon as practicable thereafter. The notifications must be submitted electronically, in a format FDA can process, review, and archive, and must contain the following information:

- The name of the drug or biological product subject to the notification, including the National Drug Code (NDC) number for the drug or biological product (or, for a biological product that does not have an NDC, an alternative standard for identification and labeling that has been recognized as acceptable by the Center Director);
- The name of the applicant of the drug or biological product;
- Whether the notification relates to a permanent discontinuance of the drug or biological product or an interruption in manufacturing of the drug or biological product, and a description of the reason for the permanent discontinuance or interruption in manufacturing; and
- The estimated duration of the interruption in manufacturing.

Elimination of § 314.91

Under the pre-FDASIA section 506C(b) a manufacturer could seek and FDA could grant a reduction in the required 6-month advance notification period for "good cause." The statute

listed several reasons that would constitute "good cause," including when continuing to manufacture the product for the full six-month notification period could cause a public health problem or result in substantial economic or legal hardship for the manufacturer. The regulation at § 314.91 implemented the pre-FDASIA section 506C(b). Because section 506C as amended by FDASIA does not include an option for formally seeking a reduction in the 6-month advance notification period based on "good cause," the proposed rule would eliminate section § 314.91 in its entirety, and thus eliminates the information collection activities associated with § 314.91.

Drug and Biological Product Lists

The proposed rule would require FDA to maintain a publicly available list of drug and biological products that are determined by FDA to be in shortage, including providing the name and NDC of the drug or biological product (or, for a biological product that does not have an NDC, an alternative standard for identification and labeling that has been recognized as acceptable by the Center Director), the name of the applicant of the drug or biological product, the reason(s) for shortage, and the estimated duration of the shortage. The proposed rule would further require FDA to include on the drug and biological product shortages lists the reason for the shortage, choosing from a list of eight categories listed in the proposed rule. FDA would comply with certain confidentiality protections when providing the information on these public lists of shortages.

Failure to Notify

The proposed rule would require FDA to issue a non-compliance letter to any person who fails to submit a section 506C notification as required

under proposed §§ 314.81(b)(iii)(3)(a) and 600.82(a) within the timeframe stated in proposed §§ 314.81(b)(iii)(3)(b) and 600.82(b). The proposed rule would provide the recipient of the letter with 30 days from the date of issuance of the non-compliance letter to respond to the letter, setting forth the basis for non-compliance and providing the required notification with the required information. Under the proposed rule, not later than 45 days after the date of issuance of the letter, FDA would make the letter and the recipient's response public, appropriately redacted to protect any trade secret or confidential commercial information. FDA would not make the letter and the response public if FDA determines, based on the response, that the recipient of the letter had a reasonable basis for not notifying FDA as required.

2. Purpose and Use of the Information Collection

As explained above, the requirements of sections 310.306, 314.81(b)(3)(iii), and 600.82 as added or amended by the proposed rule are designed to implement sections 506C and 506E of the FD&C Act.

3. Use of Improved Information Technology and Burden Reduction

Sections 310.306, 314.81(b)(3)(iii), and 600.82 provide that the notifications must be provided to FDA electronically, in a format that FDA can process, review, and archive. We anticipate that manufacturers will email us the submissions.

4. Efforts to Identify Duplication and Use of Similar Information

The information collection under sections 310.306, 314.81(b)(3)(iii), and 600.82, as added or amended by the proposed rule would not duplicate any other information collection.

5. Impact on Small Businesses or Other Small Entities

Although new drug and biological product development is typically an activity completed by large multinational drug firms, the information collection under sections 310.306, 314.81(b)(3)(iii), and 600.82, as added or amended by the proposed rule would apply to small as well as large companies. 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

As explained above, sections 310.306, 314.81(b)(3)(iii), and 600.82, as added or amended by the proposed rule set forth procedures for applicants or unapproved drug manufacturers of covered drug or biological products to notify us at least 6 months before a permanent discontinuance or interruption in manufacturing of the product, or, if that is not possible, as soon as practicable thereafter. The 6-month notification period is a statutory requirement; thus we cannot reduce or otherwise alter the frequency of the information collection activities.

7. Special Circumstances Relating to the Guidelines of 5 C.F.R. § 1320.5

There is no inconsistency with the guidelines.

8. Efforts to Consult Outside the Agency

We are currently seeking OMB clearance to publish the proposed rule which will include an opportunity for public comment on the information collection included in the entirety of sections 310.306, 314.81(b)(3)(iii), and 600.82 (as added or amended by the proposed rule).

9. Remuneration of Respondents

FDA has not provided and has no intention to provide any payment or gift to respondents under sections 310.306, 314.81(b)(3)(iii), and 600.82, as added or amended by the proposed rule.

10. Assurance of Confidentiality Provided to Respondents

Confidentiality of the information submitted under drug approval applications is protected under 21 CFR 314.430 and under 21 CFR part 20. The unauthorized use or disclosure of trade secrets required in applications is specifically prohibited under Section 310(j) of the FD&C Act. In addition, respondents are protected by 314.81(b)(3)(iii)(d), and 600.82(d), as added or amended by the proposed rule.

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

Notification of Permanent Discontinuance or Interruption in Manufacturing: Based on data collected by the CDER and CBER drug shortage coordinators on the number of drug and biological product shortage related notifications we have received during the past 12 months, we estimate that annually a total of approximately 75 respondents ("number of respondents" in Table 1) would notify us of a permanent discontinuance of the manufacture of a drug or biological product or an interruption in manufacturing of a drug or biological product that is likely to lead to a meaningful disruption (significant disruption for blood or blood components) in the respondent's supply of that product under the proposed rule. We estimate that these respondents would submit annually a total of approximately 305 notifications as required under

proposed §§ 310.306, 314.81(b)(3)(iii) and 600.82. Approximately 80 of these notifications are notifications that we currently receive under OMB control number 0910-0699 (for the interim final rule (IFR) entitled "Applications for Food and Drug Administration Approval To Market a New Drug; Revision of Postmarketing Reporting Requirements – Permanent discontinuance; Interim Final Rule" (76 FR 78530, Dec. 19, 2011)), thus we expect to receive approximately 225 new notifications under the proposed rule ("total annual responses" in Table 1).[1] We also estimate that preparing and submitting these notifications to FDA would take approximately 2 hours per respondent ("hours per response" in Table 2).

We base these estimates on our experience with the reporting of similar information to FDA since the issuance of the President's Executive Order 13588 of October 31, 2011, and under the IFR, and the draft guidance entitled "Draft Guidance for Industry on Notification to Food and Drug Administration of Issues That May Result in a Prescription Drug Shortage" (77 FR 11550, Feb. 27, 2012).

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN

	Number of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
Notifications required under proposed §§ 310.306, 314.81(b)(3)	75	3	225	2	450

1 This estimate is based on the number of new notifications we would receive under the proposed rule as compared to notifications we currently receive under the IFR. The IFR is our baseline for comparison for purposes of estimating the burden under the PRA, because additional notifications that we may currently receive voluntarily, but that are not required under the IFR (e.g., as requested in the Draft Guidance for Industry, on Notification to Food and Drug Administration of Issues That May Result in a Prescription Drug Shortage) are not covered under any existing OMB control number, and thus must be captured in this PRA estimate. In contrast, the preliminary analysis of impacts of the proposed rule estimates the costs and benefits of the proposed rule as compared to current practice. As a result of the use of different baselines for comparison, the estimate of new notifications under the PRA does not match the estimate of new notifications included in the preliminary analysis of impacts (see Table 2B of Ref. 3, which estimates the number of new notifications we would receive under the proposed rule, as compared to the number of notifications the Agency receives currently, including all voluntary notifications not specifically required by the IFR).

(iii) and 600.82					

12b. Annualized Cost Burden Estimate

FDA's Economics Staff estimates that the proposed rule would impose annual reporting and compliance costs of up to $9.89 million on applicants and manufacturers affected by the rule.

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

There are no other costs, including capital costs or operating and maintenance costs, associated with this information collection.

14. Annualized Cost to the Federal Government

FDA Economics Staff ("Analysis of Impacts" section of preamble) estimates that the proposed rule would impose up to $6.6 million annually on FDA in preventive compliance and enforcement costs.

15. Explanation for Program Changes or Adjustments

This is a new approval request.

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. Exception to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.