Permanent Discontinuance or Interruption in Manufacturing of
Certain Drug or Biological Products; Final Rule

RIN 0910-AG88

SUPPORTING STATEMENT

Terms of Clearance: None.

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 (FD&C Act). FDA is requesting OMB approval of the information collection activities resulting from this final 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 FD&C Act.

Under the final rule, applicants with an approved NDA or ANDA for a covered drug product, manufacturers of a covered drug product marketed without an approved application, and applicants with an approved BLA for a covered biological product (including certain applications of blood or blood components) must notify FDA in writing of a permanent discontinuance of the manufacture of the drug or biological product or an interruption in manufacturing of the drug or biological product that is likely to lead to a meaningful disruption in the applicant's supply (or a significant disruption for blood or blood components) of that product. The notification is required if the drug or biological product is life supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including use in emergency medical care or during surgery, and if the drug or

biological product is not a radiopharmaceutical drug product.

The final rule requires that the notification include the following information: (1) The name of the drug or biological product subject to the notification, including the NDC (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); (2) the name of each applicant of the drug or biological product; (3) whether the notification relates to a permanent discontinuance of the drug or biological product or an interruption in manufacturing of the product; (4) a description of the reason for the permanent discontinuance or interruption in manufacturing; and (5) the estimated duration of the interruption in manufacturing.

Under the final rule, the notification must be submitted to FDA electronically at least 6 months prior to the date of the permanent discontinuance or interruption in manufacturing. If 6 months' advance notice is not possible because the permanent discontinuance or interruption in manufacturing was unanticipated 6 months in advance, the applicant must notify FDA as soon as practicable, but in no case later than 5 business days after the permanent discontinuance or interruption in manufacturing occurs.

If an applicant fails to submit the required notification, FDA will issue a letter informing the applicant or manufacturer of its noncompliance. The applicant must submit to FDA, not later than 30 calendar days after FDA issues the letter, a written response setting forth the basis for noncompliance and providing the required notification.

These information collection requirements apply to: Applicants of prescription drugs and biological products subject to an approved NDA, ANDA, or BLA, and manufacturers of prescription drug products marketed without an approved ANDA or NDA, if the product is life

supporting, life sustaining, or intended for use in the prevention or treatment of a debilitating disease or condition, including use in emergency medical care or during surgery, and is not a radiopharmaceutical product. If the BLA applicant is a manufacturer of blood or blood components, it is only subject to this rule if it manufactures a significant percentage of the nation's blood supply. The final rule applies 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.

2. Purpose and Use of the Information Collection

The final rule requires all applicants of covered approved drugs or biological products and all manufacturers of covered drugs marketed without an approved application to notify FDA electronically of a permanent discontinuance or an interruption in manufacturing of the product that is likely to lead to a meaningful disruption in supply of the product in the United States. Covered drugs include those 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. The requirements in §§ 310.306, 314.81(b)(3)(iii), and 600.82 as added or amended by the final rule are designed to implement sections 506C and 506E of the FD&C Act as required by Congress in FDASIA.

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 §§ 310.306, 314.81(b)(3)(iii), and 600.82, as added or amended by the final 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 §§ 310.306, 314.81(b)(3)(iii), and 600.82, as added or amended by the final 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, §§ 310.306, 314.81(b)(3)(iii), and 600.82, as added or amended by the final 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 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

As required by section 3506(c)(2)(B) of the Paperwork Reduction Act of 1995 (PRA), FDA provided an opportunity for public comment on the information collection requirements of the proposed rule that published in the FEDERAL REGISTER of November 4, 2013 (78 FR 65904). FDA received 34 comments, however, they did not pertain to the information collection. The comments are summarized and responded to in the preamble to in section V the final rule.

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 under §§ 310.306, 314.81(b)(3)(iii), and 600.82, as added or amended by the final 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 final 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

The final rule requires 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.

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," this final rule eliminates § 314.91 in its entirety.

The final rule requires 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

final rule also requires 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 must comply with certain confidentiality protections when providing the information on these public lists of shortages.

The final rule requires FDA to issue a non-compliance letter to any person who fails to submit a section 506C notification as required under §§ 314.81(b)(iii)(3)(a) and 600.82(a) within the timeframe stated in §§ 314.81(b)(iii)(3)(b) and 600.82(b). The final rule provides that the recipient of the letter must respond to FDA within 30 days from the date of issuance of the non-compliance letter, setting forth the basis for non-compliance and providing the required notification with the required information. Under the final rule, not later than 45 days after the date of issuance of the letter, FDA must make the letter and the recipient's response public, appropriately redacted to protect any trade secret or confidential commercial information. FDA will 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.

Based 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) will 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 in the respondent's supply of that product under the final rule. We estimate that these respondents will submit annually a

total of approximately 305 notifications as required under §§ 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 IFR, thus we expect to receive approximately 225 new notifications under the final rule ("Total Annual Responses" in Table 1).[1] We estimate three notifications per respondent, because a respondent may experience multiple discontinuances or interruptions in manufacturing in a year that require notification ("No. of Responses per Respondent" in Table 1). We also estimate that preparing and submitting these notifications to FDA will take approximately 2 hours per respondent ("Hours per Response" in Table 1).

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 (Ref. 1), and under the interim final rule entitled "Applications for Food and Drug Administration Approval To Market a New Drug; Revision of Postmarketing Reporting Requirements--Permanent" (76 FR 78530; December 19, 2011), 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, February 27, 2012).

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

1 This estimate is based on the number of new notifications we anticipate receiving under the final 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, but that are not required under the IFR (e.g., as requested in the draft guidance for industry on Notification to the 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 analysis of impacts of the final rule estimates the costs and benefits 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.

Table 1.--Estimated Reporting Burden

Permanent Discontinuance or Interruption in Manufacturing Certain Drug or Biological Products; Final Rule	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
Notifications required under §§ 310.306 (unapproved drugs), 314.81(b)(3)(iii) (products approved under an NDA or ANDA), and 600.82 (products approved under a BLA)	75	3	225	2	450

12b. Annualized Cost Burden Estimate

FDA's Economics Staff ("Analysis of Impacts" section of preamble) estimates that the final rule imposes annual reporting costs of up to $16,827 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 capital costs, start-up, operating or maintenance costs associated with this information collection.

14. Annualized Cost to the Federal Government

FDA Economics Staff estimates that the final rule would impose up to $441,000 on FDA in review costs.

15. Explanation for Program Changes or Adjustments

This is a new approval request. The total burden hours for the final rule is unchanged

from the November 4, 2013, proposed rule.

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.