Providing Waiver-Related Materials in Accordance With Draft Guidance for Industry on Providing Postmarket Periodic Safety Reports in the International Conference on Harmonisation E2C(R2) Format

0910-[NEW]

SUPPORTING STATEMENT

Terms of Clearance – None.

A. Justification

1. Circumstances Making the Collection of Information Necessary

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. In January 2012, the ICH Steering Committee agreed that the "E2C(R2) Periodic Benefit-Risk Evaluation Report" draft guidance (the draft PBRER guidance) should be made available for public comment. The PBRER is intended to provide a common standard for periodic reporting on approved drugs or biologics among the ICH regions. The harmonized PBRER is intended to promote a consistent approach to periodic postmarket safety reporting among the ICH regions and to enhance efficiency by reducing the number of reports generated for submission to the regulatory authorities.

The draft PBRER guidance revises an earlier version of this guidance issued in 1997 with an addendum issued in 2004. In the Federal Register of April 11, 2012 (77 FR 21782), FDA announced the availability of the draft PBRER guidance for public comment. FDA presented the comments received as part of the considerations by the E2C(R2) Expert Working Group for revisions of the guidance. A final version of the guidance was subsequently endorsed by the ICH

on November 15, 2012, and published as the ICH harmonized tripartite guideline "Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2)" (the PBRER guidance), available at *http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html*. FDA anticipates issuing final guidance on this topic that is consistent with the final ICH document, published November 2012, and thus is seeking PRA approval for information collections consistent with that document.

FDA currently has OMB approval for the required submission of periodic adverse drug experience reports (PADER) for drugs subject to a new drug application (NDA) or an abbreviated new drug application (ANDA) (§ 314.80(c)(2) (21 CFR 314.80(c)(2)), and for the required submission of periodic adverse experience reports (PAER) for drugs subject to a biologics license application (BLA) (§ 600.80(c)(2) (21 CFR 600.80(c)(2)). Such reports include, for the reporting interval, reports of serious, expected adverse experiences and all non-serious adverse experiences and an index of these reports, a narrative summary and analysis of adverse experiences, an analysis of the 15-day Alert reports submitted during the reporting interval, and a history of actions taken because of adverse experiences. Applicants must submit each PADER/PAER to FDA quarterly for the first 3 years after the product is approved by FDA and annually thereafter.

There is considerable overlap in the information required under §§ 314.80(c)(2) and 600.80(c)(2) and the information requested in a periodic safety report using the ICH E2C(R2) PBRER format. As a result, FDA, in the Federal Register of April 8, 2013 (78 FR 20926), announced the availability of a draft guidance to indicate its willingness to accept postmarket periodic safety reports using the ICH PBRER format in lieu of the specific reports described in FDA regulations. Companies who submit periodic reports on the same drug to multiple

regulators, including not only the United States, but, also the European Union, Japan, and regulators in other countries who have elected to adopt the ICH standards, may find it in their interest to prepare a single PBRER, rather than preparing multiple types of reports for multiple regulators. Companies who choose to submit a PBRER to FDA would include some information beyond that required by FDA regulations, including worldwide marketing approval status; estimated exposure and use patterns; information from clinical trials, non-interventional studies, non-clinical data, and literature; benefit evaluation, and benefit-risk analysis for approved indications, and should use a particular format described in the draft PBRER guidance.

FDA is not proposing to require submission of the PBRER; applicants subject to periodic safety reporting requirements under FDA regulations could choose to continue to submit the reports as specified in those regulations, and would be permitted to alternate between submission of reports in the PBRER format and submission of reports as specified in FDA regulations with an approved waiver. Based on FDA's experience with submission of periodic safety reports under previous ICH periodic reporting guidance, FDA believes that applicants would elect to submit the PBRER to FDA only in cases where they are also submitting that report to other regulatory authorities, some of which have underlying legal requirements that closely parallel the elements of the PBRER.

Because FDA regulations in §§ 314.80(c)(2) and 600.80(c)(2) include specific requirements for periodic safety reports, in order for an applicant to submit an alternative report, such as the PBRER, for a given product, FDA must grant a waiver. In the Federal Register of April 8, 2013, FDA announced the availability of a draft guidance entitled “Providing Postmarket Periodic Safety Reports in the ICH E2C(R2) Format,” which indicates that FDA will be prepared to grant waivers to enable submission of the PBRER in the United States in place of

a PADER required under § 314.80(c)(2) or in place of a PAER required under § 600.80(c)(2). The draft guidance both explains conditions under which applicants that have previously received waivers to submit reporting information in the format of the previous ICH guidance would be permitted to apply those existing waivers to the submission of PBRERs, and also advises how applicants that have not previously obtained a waiver may submit waiver requests to submit the PBRERs.

FDA has previously granted waiver requests, submitted under §§ 314.90(a) and 600.90(a), that allow applicants to prepare and submit reports using the periodic safety update report (PSUR) format described in the 1997 and 2004 ICH E2C guidance. In accordance with the recommendations of the April 8, 2013, draft guidance, if an applicant already has a PSUR waiver in place for a given approved application, FDA will consider the existing PSUR waiver to allow the applicant to submit a PBRER instead of a PSUR because the PBRER replaces the PSUR for postmarketing periodic safety reporting for that application. The applicant would not need to submit a new waiver request unless the applicant wishes to change the frequency of reporting. The FDA will consider requests to be waived of the quarterly reporting requirement but will not waive applicants of the annual reporting requirement.

If an applicant submits a PBRER in place of the PSUR and uses a different data lock point, the applicant should submit overlapping reports or submit a one-time PADER/PAER in order to cover the gap in reporting intervals. The applicant should submit notification to the application(s), indicating the change in data lock point and should include a description of the measures taken to ensure that there are no resulting gaps in reporting with the change.

If an applicant submits a PBRER in place of the PSUR and uses a different reporting frequency for the PBRER than was used for the PSUR, the continued validity of the waiver will

be conditioned on the submission of a PADER/PAER as needed to fulfill the reporting frequency requirement under FDA regulations. The applicant should submit a notification to the application(s), describing this change and the measures taken to ensure that the periodicity requirements are being met.

If an applicant does not have a PSUR waiver in place for an approved application, the applicant may submit a waiver request under § 314.90(a) or § 600.90(a) to submit a PBRER instead of the PADER/PAER. The applicant should submit a request to FDA for each approved application for which a waiver is requested, and a single waiver request letter can include multiple applications. Waiver requests should be submitted to each of the application(s) in the request, and may be submitted electronically or by mail as described in the April 8, 2013, draft guidance.

2. Purpose and Use of the Information Collection

The information collection pertains to the submission of periodic safety reports as described in the draft guidance entitled "E2C(R2) Periodic Benefit-Risk Evaluation Report ," which describes the format, content, and timing of a PBRER for an approved drug or biologic. The information collection also pertains to the submission of waiver-related materials as described in the draft guidance entitled "Providing Postmarket Periodic Safety Reports in the ICH E2C(R2) Format," which informs applicants of the conditions under which FDA will exercise its waiver authority to permit applicants to submit an ICH E2C(R2) PBRER in place of the ICH E2C(R1) Periodic Safety Update Report (PSUR), U.S. periodic adverse drug experience report (PADER), or U.S. periodic adverse experience report (PAER), to satisfy the periodic safety reporting requirements in FDA regulations.

3. Use of Improved Information Technology and Burden Reduction

FDA has issued several guidance documents explaining how to submit information to the agency in electronic format. These guidance documents and others are available at FDA's web site http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064994.htm under "electronic submissions."

4. Efforts to Identify Duplication and Use of Similar Information

This information does not duplicate any other collection.

5. Impact on Small Businesses or Other Small Entities

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 frequency of reports is determined by timeframes set in FDA regulations and ICH guidelines.

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 12/10/2013 (78 FR 74151). FDA received no comments pertaining to the information collection.

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 these requirements.

10. Assurance of Confidentiality Provided to Respondents

Confidentiality of the information submitted under this collection is protected under 21 CFR part 20 and 21 CFR §§ 314.80(h) and 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

FDA currently has OMB approval for the required submission of PADERs for drugs subject to a new drug application (NDA) or an abbreviated new drug application (ANDA) (§ 314.80(c)(2) (21 CFR 314.80(c)(2)); OMB control number 0910-0230), and for the required submission of PAERs for drugs subject to a biologics license application (BLA) (§ 600.80(c)(2) (21 CFR 600.80(c)(2)); OMB control number 0910-0308). Such reports include, for the reporting interval, reports of serious, expected adverse experiences and all non-serious adverse experiences and an index of these reports, a narrative summary and analysis of adverse experiences, an analysis of the 15-day Alert reports submitted during the reporting interval, and a history of actions taken because of adverse experiences. Applicants must submit each PADER/PAER to FDA quarterly for the first 3 years after the product is approved by FDA and annually thereafter. As described in the supporting documentation under OMB control numbers 0910-0230 and 0910-0308, FDA currently has OMB approval for approximately 60 hours for the preparation and submission of each PADER under § 314.80(c)(2) and 28 hours for the preparation and submission of each PAER under § 600.80(c)(2).

There is considerable overlap in the information required under §§ 314.80(c)(2) and 600.80(c)(2) and the information requested in a periodic safety report using the ICH E2C(R2) PBRER format. As a result, FDA, in the Federal Register of April 8, 2013 (78 FR 20926), announced the availability of a draft guidance to indicate its willingness to accept postmarket periodic safety reports using the ICH PBRER format in lieu of the specific reports described in FDA regulations.

Companies who submit periodic reports on the same drug to multiple regulators, including not only the United States, but, also the European Union, Japan, and regulators in other countries who have elected to adopt the ICH standards, may find it in their interest to prepare a single PBRER, rather than preparing multiple types of reports for multiple regulators. Companies who choose to submit a PBRER to FDA would include some information beyond that required by FDA regulations, including worldwide marketing approval status; estimated exposure and use patterns; information from clinical trials, non-interventional studies, non-clinical data, and literature; benefit evaluation, and benefit-risk analysis for approved indications, and should use a particular format described in that guidance.

FDA is not proposing to require submission of the PBRER; applicants subject to periodic safety reporting requirements under FDA regulations could choose to continue to submit the reports as specified in those regulations, and would be permitted to alternate between submission of reports in the PBRER format and submission of reports as specified in FDA regulations with an approved waiver. Based on FDA's experience with submission of periodic safety reports under previous ICH periodic reporting guidance, FDA believes that applicants would elect to submit the PBRER to FDA only in cases where they are also submitting that report to other regulatory authorities, some of which have underlying legal requirements that closely parallel the

elements of the PBRER. For this reason, FDA believes that the additional burden associated with preparation of a PBRER in lieu of existing PADERs/PAERs is not attributable to the proposed collection of information by FDA, but rather is a "usual and customary" expenditure of time, effort, and financial resources that would be "incurred by persons in the normal course of their activities," and thus is excluded from the calculation of burden under the PRA (5 CFR 1320.5(b)(2).) Cf. 5 CFR 1320.5(b)(3) (permitting exclusion from Federal burden of burden incurred in complying with an information collection that is also conducted by a State or local government if the State or local requirement would be imposed even in the absence of a Federal requirement).

We therefore believe that the existing estimate of burden for submission of periodic safety reports, approved under OMB control numbers 0910-0230 and 0910-0308, would be unchanged by this proposed collection, which would permit, but not require, the substitution of a PBRER for the periodic safety report otherwise required.

Because FDA regulations in §§ 314.80(c)(2) and 600.80(c)(2) include specific requirements for periodic safety reports, in order for an applicant to submit an alternative report, such as the PBRER, for a given product, FDA must grant a waiver. Existing regulations permit applicants to request waivers of any postmarketing safety reporting requirement, and the information collections associated with such waiver requests generally are approved under existing control numbers. (See § 314.90(a), waivers for drugs subject to NDAs and ANDAs (approved under OMB control number 0910-0001); and § 600.90(a), waivers for products subject to BLAs (approved under OMB control number 0910-0308).)

In the Federal Register of April 8, 2013, FDA announced the availability of a draft guidance entitled "Providing Postmarket Periodic Safety Reports in the ICH E2C(R2) Format," which indicates that FDA will be prepared to grant waivers to enable submission of the PBRER

in the United States in place of a PADER required under § 314.80(c)(2) or in place of a PAER required under § 600.80(c)(2). The draft guidance both explains conditions under which applicants that have previously received waivers to submit reporting information in the format of the previous ICH guidance would be permitted to apply those existing waivers to the submission of PBRERs, and also advises how applicants that have not previously obtained a waiver may submit waiver requests to submit the PBRERs.

FDA has previously granted waiver requests, submitted under §§ 314.90(a) and 600.90(a), that allow applicants to prepare and submit reports using the PSUR format described in the 1997 and 2004 ICH E2C guidance. In accordance with the recommendations of the April 8, 2013, draft guidance, if an applicant already has a PSUR waiver in place for a given approved application, FDA will consider the existing PSUR waiver to allow the applicant to submit a PBRER instead of a PSUR because the PBRER replaces the PSUR for postmarketing periodic safety reporting for that application. The applicant would not need to submit a new waiver request unless the applicant wishes to change the frequency of reporting.

If an applicant submits a PBRER in place of the PSUR and uses a different data lock point, the applicant should submit overlapping reports or submit a one-time PADER/PAER in order to cover the gap in reporting intervals. The applicant should submit notification to the application(s), indicating the change in data lock point and should include a description of the measures taken to ensure that there are no resulting gaps in reporting with the change.

If an applicant submits a PBRER in place of the PSUR and uses a different reporting frequency for the PBRER than was used for the PSUR, the continued validity of the waiver will be conditioned on the submission of a PADER/PAER as needed to fulfill the reporting frequency requirement under FDA regulations. The applicant should submit a notification to the

application(s) describing this change and the measures taken to ensure that the periodicity requirements are being met when submitting the PBRER.

FDA expects approximately 187 waiver requests and notifications to include the additional information described in this document for using a different data lock point and/or for using a different reporting frequency when submitting a PBRER. FDA expects approximately 55 applicants to make these submissions, and we estimate that the time for submitting the additional information described previously would be on average approximately 1 hour for each waiver request or notification.

If an applicant does not have a PSUR waiver in place for an approved application, the applicant may submit a waiver request under § 314.90(a) or § 600.90(a) to submit a PBRER instead of the PADER/PAER. The applicant should submit a request to FDA for each approved application for which a waiver is requested, and a single waiver request letter can include multiple applications. Waiver requests should be submitted to each of the application(s) in the request, and may be submitted electronically or by mail as described in the April 8, 2013, draft guidance. Each PBRER waiver request should include the following information:

(1) The product name(s) and application number(s);

(2) A brief description of the justification for the request;

(3) The U.S. approval date for the product(s) and current reporting interval used;

(4) The reporting interval of the last PADER/PAER submitted for the product(s);

(5) The data lock point that will be used for each PBRER. If a data lock point other than one aligned to the U.S. approval date is proposed, the applicant should describe how he/she will ensure that there are no gaps in reporting intervals (e.g., by submitting overlapping reports;

submitting a one-time PADER/PAER to cover the gap period; or, if the gap is less than 2 months, extending the reporting interval of the final PADER/PAER to close the gap).

(6) The frequency for submitting the PBRER, as described in section IV.C of the April 8, 2013, draft guidance.

(7) The email address and telephone number for the individual who can provide additional information regarding the waiver request.

As explained earlier, existing regulations at §§ 314.90(a) or 600.90(a) permit applicants to request waivers of any postmarketing safety reporting requirement, and the information collections associated with such waiver requests generally are approved under OMB control numbers 0910-0001and 0910-0308. FDA believes that the information submitted under numbers 1-4 and number 7 in the list in the previous paragraph is information that is typical of any waiver request regarding postmarketing safety reporting and is accounted for in the existing approved collections of information for waiver requests and reports. Concerning numbers 5 and 6, FDA expects approximately 67 waiver requests to include the additional information for using a different data lock point and/or for using a different reporting frequency when submitting a PBRER. FDA expects approximately 29 applicants to make these submissions, and we estimate that the time for submitting the additional information described in the previous paragraph would be on average approximately 2 hours for each waiver request.

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

Table 1.--Estimated Reporting Burden

Additional Information and/or Notifications for Using a Different Data Lock Point and/or a Different Reporting Frequency	Number of respondents	Number of responses per respondent	Total annual responses	Average burden per response	Total hours
Applicants that have a PSUR waiver for an approved application	55	3.4	187	1	187
Applicants that do not have a PSUR waiver for an approved application	29	2.3	67	2	134
Total					321

12b. Annualized Cost Burden Estimate

Type of Respondent	Total Burden Hours	Hourly Wage Rate	Total Respondent Cost
Pharmaceutical industry average wage grade for preparing and submitting this information collection	321	75.00	$ 24,075

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

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

14. Annualized Cost to the Federal Government

FDA estimates that it requires 1.6 FTEs at approximately $250,000. Therefore, the total estimated annual cost to the government for this collection of information is approximately $375,000.

15. Explanation for Program Changes or Adjustments

This is a new data collection.

16. Plans for Tabulation and Publication and Project Time Schedule

FDA does not intend to publish tabulated results of these information collection requirements.

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

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

18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.