Providing Postmarketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report)

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Drug Safety

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Contains Nonbinding Recommendations

Providing Postmarketing Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report) Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes the conditions under which applicants[2] can use an alternative reporting format, the International Council for Harmonisation (ICH)[3] E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER), in place of the U.S. periodic adverse drug experience report (PADER), U.S. periodic adverse experience report (PAER), or ICH E2C Periodic Safety Update Report (PSUR), to satisfy the periodic postmarketing safety reporting requirements in §§ 314.80(c)(2) and 600.80(c)(2) (21 CFR 314.80(c)(2) and 600.80(c)(2)). This guidance also describes the procedures applicants should follow if they wish to submit a PBRER in place of a PADER, PAER, or PSUR.[4] The steps will differ, depending on whether or not the applicant has an approved waiver in place to substitute the PSUR for the PADER/PAER.

[1] This guidance has been prepared by the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] This guidance uses the term *applicant* to mean the holder of an approved new drug application (NDA), abbreviated new drug application (ANDA), or biologics license application (BLA), which are referred to collectively in this guidance as *applications*.

[3] Formerly the International Conference on Harmonisation. The ICH was organized to provide an opportunity for 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 for human use among regulators around the world (for more information about the ICH and the procedures for adopting harmonized guidelines, see http://www.ich.org/). Guidelines that have been formally endorsed by the ICH are implemented by the FDA in the form of FDA guidance documents whose development follows the procedures outlined in FDA's good guidance practices regulation (21 CFR 10.115).

[4] FDA accepts all three formats, the PADER/PAER, PSUR, and PBRER, to fulfill the postmarketing periodic safety reporting requirements under §§ 314.80(c)(2) and 600.80(c)(2). Each format must be submitted according to the content and timelines specified in the regulations (PADER/PAER) or by ICH (PSUR and PBRER).

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Postmarketing Periodic Safety Reporting Regulations

FDA regulations in §§ 314.80(c)(2) and 600.80(c)(2) require applicants to submit postmarketing periodic safety reports in the PADER/PAER format for each approved application. The reports must be submitted quarterly for the first 3 years following the U.S. approval date and annually thereafter (see §§ 314.80(c)(2)(i) and 600.80(c)(2)(i)), and must contain the information described in §§ 314.80(c)(2)(ii) and 600.80(c)(2)(ii).

B. The PSUR and the PBRER

In November 1996, the ICH endorsed the ICH E2C Periodic Safety Update Report Guideline (ICH E2C(R1) guideline), which established the PSUR as a harmonized format for postmarketing periodic safety reports for approved drugs and biologic products, and described the format, content, and timing of PSUR submissions. FDA adopted that guideline and, in May 1997, published it as FDA guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs*.[5] In February 2003, ICH endorsed and made final an addendum that further clarified some aspects of the ICH E2C(R1) guideline. In February 2004, FDA published the addendum as FDA guidance for industry *Addendum to E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs*.[6]

On April 11, 2012, FDA announced the availability of a draft guidance for industry entitled *E2C (R2) Periodic Benefit-Risk Evaluation Report*,[7] which reflected revisions by ICH and described the format, content, and timing of the updated version, the PBRER, as presented in the ICH EC2(R2)[8] step 2 guideline.[9] ICH subsequently endorsed a final version of that guideline on

[5] 62 FR 27470 (May 19, 1997). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[6] 69 FR 5551 (Feb. 5, 2004). When final, this guidance will represent FDA's current thinking on this topic.

[7] 77 FR 21782 (April 11, 2012).

[8] The terms *R1* and *R2* refer to successive revisions in ICH E2C.

[9] The term *step 2* refers to the point in the ICH process where the draft guideline is agreed and signed by the Expert Working Group and the ICH Assembly, which signifies acceptance for consultation by the Members of the ICH Association.

November 15, 2012, and published the ICH guideline *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2)*[10] (ICH E2C(R2) step 4 guideline).[11] The step 4 guideline updates and combines the E2C(R1) guideline and the addendum to the E2C(R1) guideline. The step 4 guideline replaces the PSUR with the PBRER for postmarketing periodic safety reporting, and describes the recommended format, content, and timing of PBRER submissions. Like the PSUR, the harmonized PBRER is intended to promote a consistent approach to periodic postmarketing safety reporting among the ICH regions and to enhance efficiency by reducing the number of reports generated for submission to regulatory authorities. FDA adopted the step 4 guideline and, on July 19, 2016, published it as FDA guidance for industry *E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER)* (ICH E2C(R2) PBRER guidance).[12]

In addition to adopting ICH guidelines as described above, on April 28, 2013, FDA made available a draft guidance for industry *Providing Postmarket Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report)*,[13] which FDA is now finalizing in this current guidance. This current guidance describes the procedures that applicants should follow to submit a PBRER in place of a PADER, PAER, or PSUR.

C. Precedence for Granting PSUR Waivers

Since the introduction of the PSUR reporting format, FDA has granted waivers under §§ 314.90(b) and 600.90(b) (21 CFR 314.90(b) and 600.90(b)) to allow applicants to substitute the PSUR for the PADER/PAER (PSUR waiver). FDA has routinely granted PSUR waivers on the condition that applicants provide the following information:

- The nonexpedited individual case safety reports (ICSRs) received during the reporting interval, as required under §§ 314.80(c)(2)(ii)(B) and 600.80(c)(2)(ii)(B), excluding any previously submitted nonexpedited ICSRs. All ICSRs must be submitted electronically in a format FDA can process, review, and archive as described §§ 314.80(g) and 600.80(h) .

- A list of all ICSRs submitted during the reporting interval and their submission dates.

- A narrative that identifies any changes made to the approved U.S. labeling based on new information in the PSUR, as required under §§ 314.80(c)(2)(ii)(A)(3) and

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[10] Available at http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html.

[11] The term *step 4* refers to the point in the ICH process at which consensus is reached and the guideline is recommended for adoption by the regulatory agencies.

[12] 81 FR 17009

[13] 78 FR 20926 (April 8, 2013).

600.80(c)(2)(ii)(A)(3), along with a copy of the U.S. labeling in effect on the data lock point (DLP)[14] date.

FDA has routinely granted waivers to permit applicants to change the date of the DLP from the U.S. approval date, as required under §§ 314.80(c)(2)(i) and 600.80(c)(2)(i), to a different date for harmonization purposes. These waivers have been granted on the condition that the applicant ensures that there are no gaps in reporting resulting from the date change. FDA has also permitted applicants to include multiple products with the same active moiety or active ingredient in a single report as recommended in the ICH E2C(R1) guidance.

Generally, FDA has *not* waived the reporting frequencies required under §§ 314.80(c)(2)(i) and 600.80(c)(2)(i). However, FDA has permitted applicants to submit PSURs at longer intervals, consistent with the ICH guidelines, on the condition that the applicant submit a periodic safety report as needed to fulfill the reporting frequency requirements.

> *Example: FDA granted an applicant a waiver to submit a PSUR for its drug product every 3 years. FDA granted this waiver on the condition that the applicant also submit an annual PADER for years 1 and 2 of the 3-year PSUR cycle.*

III. PROCEDURES APPLICANTS SHOULD FOLLOW TO SUBMIT A PBRER

A. Applicants With a PSUR Waiver

If applicants already have a PSUR waiver for an approved application, FDA will consider the existing PSUR waiver to permit applicants to submit a PBRER instead of a PSUR under the conditions described below, because the PBRER replaces the PSUR for postmarketing periodic safety reporting. If applicants wish to substitute the PBRER for the PSUR with no changes in the DLP or frequency of reporting, applicants can do so without submitting a new waiver request. However, if applicants wish to change any conditions of their PSUR waiver other than the format, applicants should submit either a notification or new waiver request, depending on the circumstances described below.

1. Change in the Date of the DLP for the PBRER – Submit Notification

If applicants wish to use a DLP date for the PBRER that is different than the DLP date used for the PSUR, applicants should ensure there are no gaps in reporting intervals resulting from the change in DLP. Examples of appropriate alternatives include the following:

- Submit overlapping reports to cover the gap.
- Submit a one-time PADER/PAER to cover the gap.
- Extend the reporting interval of the applicant's upcoming PADER/PAER by up to 3 months to cover the gap.

[14] The term *data lock point* refers to the date designated as the cut-off for data to be included in the PSUR or PBRER.

Applicants should submit written notification to the application(s), indicating the change in DLP date and describing the measures taken to ensure that there are no resulting gaps in reporting.

2. Longer PBRER Reporting Intervals But No Change in Frequency – Submit Notification

If applicants wish to submit the PBRER less frequently than is permitted under their PSUR waiver, the continued validity of the applicant's waiver will be conditioned on the applicant's submission of a PADER/PAER as needed to fulfill the reporting frequency requirement under our regulations.

Applicants should submit written notification to the application, indicating this change and describing the measures taken to ensure that the periodicity requirements are being met.

Example: If the applicant's PSUR waiver specifies annual PSUR submission but the applicant wishes to submit a PBRER every 3 years, the applicant can substitute the PBRER for the PSUR, provided the applicant submits a PADER/PAER for years 1 and 2 of the 3-year PBRER cycle to maintain the annual reporting frequency required under the regulations and as specified in its PSUR waiver.

3. Other Changes to the PSUR Waiver – Submit New Waiver

If applicants wish to change any other condition of their PSUR waiver beyond what is described in sections III.A.1 and III.A.2 above, then applicants should submit a new waiver request. For example, a new waiver request should be submitted to change the overall reporting frequency or to add or remove products covered by the report.

B. Applicants Without a PSUR Waiver

If applicants do not already have a PSUR waiver and wish to submit in the PBRER format, a waiver request must be submitted under § 314.90(a) or 600.90(a) in order to submit a PBRER instead of the PADER/PAER (PBRER waiver). In accordance with the ICH E2C(R2) PBRER guidance, applicants can prepare a single PBRER for multiple products with the same active moiety or ingredient.

If the applicant's waiver request is for several products, the applicant can submit a single waiver request letter that references multiple applications.

Each PBRER waiver request should include the following information:

1. The product name(s) and application number(s).
2. Email address and telephone number for the individual FDA may contact should the Agency need additional information regarding the waiver request.

3. A brief description of the justification for the request.
4. The U.S. approval date for the product(s) and current reporting interval used.
5. The reporting interval of the last PADER/PAER submitted for the product(s).
6. The date of the DLP that applicants intend to use for each PBRER. If applicants propose a DLP date other than one aligned to the U.S. approval date, applicants should describe their plan to ensure there are no gaps in reporting intervals. Examples of appropriate alternatives include:
    - Submitting overlapping reports to cover the gap;
    - Submitting a one-time PADER/PAER to cover the gap; or
    - Extending the reporting interval of the applicant's final PADER/PAER by up to 3 months to close the gap.
7. The frequency with which applicants intend to submit reports.

    The time period from the product's U.S. approval date is less than or equal to 3 years: Applicants can ask FDA to consider waiving the quarterly reporting requirement under §§ 314.80(c)(2)(i) and 600.80(c)(2)(i), and instead propose to submit the PBRER less frequently during this period (e.g., every 6 or 12 months). FDA will grant or deny the request on an application-specific basis.

    The time period from the product's U.S. approval date is greater than 3 years: Applicants must submit a postmarketing periodic safety report annually, as required under §§ 314.80(c)(2)(i) and 600.80(c)(2)(i). Alternatively, applicants can submit a PBRER less frequently on the condition that applicants also submit an annual periodic safety report in one of the other acceptable formats (i.e., PADER/PAER or PSUR) as needed to fulfill the annual requirement. See the example in section II.C.

IV. SUBMITTING WAIVER REQUESTS

The applicant's waiver request letter should be submitted to each of the applications for which a waiver is being requested. Requests submitted electronically should be sent via FDA's Electronic Submissions Gateway (ESG) to the electronic common technical document (eCTD)[15] for the applications for which a waiver is being requested.

Requests submitted on paper should be sent to the appropriate address below:

For CDER-regulated drug and biological products:

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration

[15] Guidance for industry, *Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (May 2015).

5901-B Ammendale Rd.
Beltsville, MD 20705-1266

For CBER-regulated biological products:

U.S. Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology
Document Control Center
10903 New Hampshire Ave.
Bldg. 71, Rm. G112
Silver Spring, MD 20993-0002

V. FORMAT, CONTENT, AND TIMING OF THE PBRER

When preparing and submitting the PBRER, the applicant should follow the format, content, and timing recommendations described in the ICH E2C(R2) PBRER guidance.

As part of the applicant's PBRER submission to FDA, the applicant should provide a list of all ICSRs submitted during the reporting interval, a narrative that identifies any changes made to the approved U.S. labeling, and a copy of the U.S. labeling in effect on the DLP, as specified in the bulleted list in section II.C. Applicants must also electronically submit nonexpedited ICSRs received during the reporting interval, as required under §§ 314.80(c)(2)(ii)(B) and 600.80(c)(2)(ii)(B), excluding any previously submitted nonexpedited ICSRs.[16,17]

The applicant can submit 6-month and 12-month PBRERs within 70 calendar days following the DLP, and the applicant can submit PBRERs covering a longer reporting interval within 90 calendar days following the DLP.

[16] Draft guidance for industry, *Providing Submissions in Electronic Format — Postmarketing Safety Reports* (June 2014). When final, this guidance will represent FDA's current thinking on this topic.

[17] Guidance for industry, *Providing Submissions in Electronic Format — Postmarketing Safety Reports for Vaccines* (August 2015).