Guidance for Industry

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

DRAFT GUIDANCE

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For questions regarding this draft document contact CDER's Division of Drug Information at 301-796-3400, or CBER's Office of Communications, Outreach and Development at 301-827-1800.

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)

April 2013
Drug Safety

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance describes the conditions under which applicants can use an alternative reporting format, the International Conference on Harmonisation (ICH) 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 safety reporting requirements at 21 CFR 314.80(c)(2) and 600.80(c)(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*. This guidance describes the procedures applicants should follow if they wish to submit a PBRER in place of a PADER, PAER, or PSUR. 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.

FDA's guidance documents, including this guidance, 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.

[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 Office of Biostatistics and Epidemiology in the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

II. BACKGROUND

A. Postmarket Periodic Safety Reporting Regulations

FDA regulations in §§ 314.80(c)(2) and 600.80(c)(2) require applicants to submit postmarket 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 (ICH E2C) and the PBRER (ICH E2C(R2))

In November 1996, the ICH[2] endorsed the ICH E2C Periodic Safety Update Report Guideline (E2C guideline), which established the PSUR as a harmonized format for postmarket periodic safety reporting 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* (ICH E2C guidance).[3] In February 2003, ICH endorsed and made final an addendum that further clarified some aspects of the ICH E2C guidance. 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* (addendum to the E2C guidance).[4]

On April 11, 2012, FDA announced the availability of a draft guidance for industry entitled *E2C (R2) Periodic Benefit-Risk Evaluation Report*,[5] which describes the format, content, and timing of the PBRER as presented in the ICH step 2 guideline.[6] ICH subsequently endorsed a final version of that guideline on November 15, 2012, and published the ICH harmonized tripartite

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[2] 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 (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 that follow the procedures outlined in FDA's good guidance practices regulation (21 CFR 10.115).

[3] 62 FR 27470 (May 19, 1997). We update guidance documents 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 or the FDA Vaccines, Blood & Biologics Web at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[4] 69 FR 5551 (Feb. 5, 2004).

[5] 77 FR 21782.

[6] 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 Steering Committee, which signifies acceptance for consultation by the six ICH cosponsors.

guideline *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2)*[7] (the ICH E2C(R2) step 4 guideline).[8] This new ICH guideline updates and combines the E2C guideline and the addendum to the E2C guideline. In particular, it replaces the PSUR with the PBRER for postmarket periodic safety reporting, and describes the recommended format, content, and timing of PBRER submissions. Like its predecessor, the PSUR, 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. FDA has initiated the process to adopt the ICH E2C(R2) step 4 guideline as final FDA guidance. We anticipate that some applicants will wish to begin using the PBRER format in the United States before the necessary administrative procedures are completed. This draft guidance describes the procedures applicants should follow to submit a PBRER.

C. PSUR Waivers

FDA regulations at 21 CFR 314.90(a) and 600.90(a) allow applicants to request a waiver of any of the postmarket adverse experience reporting requirements in §§ 314.80 and 600.80, respectively, including requests to submit postmarket periodic safety reports in the PSUR format rather than in the PADER/PAER format (PSUR waiver). PSUR waiver requests also can include proposed timing changes, such as a change of the data lock point that marks the end of the reporting interval and/or reporting frequency.

1. Waiver of the PADER/PAER Format Requirements

FDA has routinely granted PSUR waivers on the condition that applicants also submit the following information as U.S. appendices to the PSUR:

- Copies of all non-expedited individual case safety reports (ICSRs) received during the PSUR reporting interval, as required under §§ 314.80(c)(2)(ii)(*b*) and 600.80(c)(2)(ii)(B). However, copies of ICSRs that were received during the PSUR reporting interval and previously submitted should not also be submitted at the time of PSUR submission. In these instances, the PSUR should include a list, but not copies, of any ICSRs that were previously submitted 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)(*c*) and 600.80(c)(2)(ii)(C), along with a copy of the most recent U.S. labeling.

2. Waiver of the Timing Requirements for the PADER/PAER

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

[8] 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 bodies of the three regions.

a. Data lock point

FDA has routinely granted waivers of the requirement to base the data lock point for the postmarket periodic safety report on the U.S. approval date (§§ 314.80(c)(2)(i) and 600.80(c)(2)(i)). FDA has permitted applicants to change the data lock point from the U.S. approval date to a different date for harmonization purposes. These waivers have been granted on the condition that the applicant takes measures to ensure there are no gaps in reporting resulting from the date change.

b. Reporting frequency

Generally, FDA has not waived the reporting frequencies required under our regulations. However, we have permitted applicants to submit PSURs at longer intervals consistent with the ICH guidelines (e.g., 3-year PSURs), on the condition that the applicant submit a PSUR Addendum Report (as described in the addendum to the E2C guidance) or PADER/PAER as needed to fulfill the reporting frequency requirements under our regulations. These reports cover the period of time for which a periodic safety report would normally be required to be submitted. For example, we have granted waivers permitting an applicant to submit a PSUR every 3 years on the condition that the applicant also submit an annual PADER/PAER during each of the first 2 years of the 3-year PSUR cycle to fulfill the annual reporting requirement in §§ 314.80(c)(2)(i) and 600.80(c)(2)(i). We have also granted waivers permitting an applicant to submit a PSUR every 6 months on the condition that the applicant also submit a quarterly PADER/PAER in the intervening quarters to fulfill the quarterly reporting requirement in §§ 314.80(c)(2)(i) and 600.80(c)(2)(i).

III. PROCEDURES APPLICANTS SHOULD FOLLOW TO SUBMIT A PBRER

A. Applicants Who Have a PSUR Waiver in Place for Their Approved Application

If you already have a PSUR waiver in place for an approved application, FDA will consider the existing PSUR waiver to permit you to submit a PBRER instead of a PSUR under the conditions described below, because the PBRER replaces the PSUR for postmarket periodic safety reporting. Thus, you do not need to submit a new waiver request. However, you should submit notification in certain instances described below.

1. Format Change Only

If you wish to submit a PBRER in place of a PSUR, with no changes in the data lock point or frequency of reporting, you can do so without submitting a new waiver request or notification to the FDA.

If your PSUR waiver permits you to submit the PSUR less frequently than required under our regulations, it is dependent on the conditional submission of a PSUR Addendum Report or

PADER/PAER to fulfill the frequency requirement. The substitution of the PBRER for the PSUR will continue to be dependent on the conditional submission of such reports. The PADER or PAER is an appropriate format for these reports.[9]

2. Format Change and a Change to the Data Lock Point and/or Frequency of Reporting

If you wish to submit a PBRER in place of the PSUR and also wish to use a different data lock point and/or submit the PBRER at a different frequency than your PSUR waiver permits, you can substitute the PBRER for the PSUR as described below:

a. Change in data lock point for the PBRER

If you wish to use a different data lock for the PBRER than you were using for the PSUR, you should do one of the following to ensure there are no gaps in reporting intervals:

- Submit overlapping reports
- Submit a one-time PADER/PAER to cover the gap in reporting intervals

You should submit notification to the application, indicating the change made to the data lock point and a description of the measures taken to ensure that there are no resulting gaps in reporting.

b. Change in reporting frequency for the PBRER

If you wish to use a different reporting frequency for the PBRER than you were using for the PSUR for harmonization purposes, you should follow the recommendations in section 2.8.2, Managing Different Frequencies of PBRER Submission, in the ICH E2C(R2) step 4 guideline.

Please note that if you wish to submit the PBRER less frequently than is permitted under your waiver, the continued validity of your waiver will be conditioned on your submission of a PADER/PAER as needed to fulfill the reporting frequency requirement under our regulations (see section II.C.2.b of this guidance for additional information). You should submit notification to the application, indicating this change. This notification should describe the measures taken to ensure that the periodicity requirements are being met.

Please also note that if you are on a quarterly reporting schedule but wish to report every 6 months without submitting a quarterly PADER/PAER in the intervening quarters, you may request a waiver of the quarterly reporting requirement (see section IV.C of this guidance for additional information).

[9] Addendum Reports are not part of the ICH E2C(R2) guideline. Therefore, FDA does not expect the reports provided between the PBRER submissions to be Addendum Reports, but rather PADERs or PAERs.

B. Applicants Who Do Not Have a PSUR Waiver for Their Approved Application

If you do not already have a PSUR waiver, you may submit a waiver request under § 314.90(a) or 600.90(a) to submit a PBRER instead of the PADER/PAER (PBRER waiver). You should submit a request to FDA for each approved application for which you are requesting the waiver. A single waiver request can include multiple applications. Each PBRER waiver request should include the following information:

- The product name(s) and application number(s).
- A brief description of the justification for the request.
- The U.S. approval date for the product(s) and current reporting interval used.
- The reporting interval of the last PADER/PAER submitted for the product(s).
- The data lock point you intend to use for each PBRER. If you propose a data lock point other than one aligned to the U.S. approval date, you should describe how you will ensure there are no gaps in reporting intervals. Examples of appropriate alternatives include:

  - Submitting overlapping reports;
  - Submitting a one-time PADER to cover the gap period; or
  - If the gap is less than 2 months, extending the reporting interval of your final PADER/PAER to close the gap.

- The frequency with which you intend to submit reports. The reporting frequency should be in accordance with section IV.C below.
- Email address and telephone number for the individual we may contact should we need additional information regarding the waiver request.

Waiver requests should be submitted to each of the application(s) in the request. Requests submitted electronically should be sent via FDA's Electronic Submissions Gateway (ESG). 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
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

For CBER-regulated biological products:

Director, Division of Epidemiology
Office of Biostatistics and Epidemiology
CBER/FDA
1401 Rockville Pike, HFM-220
Rockville, MD 20852-1448

IV. FORMAT, CONTENT, AND TIMING OF THE PBRER

A. Format and Content

You should follow the format and content recommendations described in the ICH E2C(R2) step 4 guideline. As part of your PBRER submission to the FDA, you should submit the U.S.-specific appendices listed in section II.C.1 of this guidance document.

B. Submission Deadlines

You can submit the PBRER within the 70/90-day timelines described in the ICH E2C(R2) step 4 guideline. That is, you can submit 6-month and 12-month PBRERs within 70 calendar days following the data lock point, and you can submit PBRERs covering a longer reporting interval within 90 calendar days following the data lock point.

C. Reporting Frequency

For products that are within the first 3 years post-approval in the United States, you can submit a request to waive the quarterly reporting required under §§ 314.80(c)(2)(i) and 600.80(c)(2)(i) and instead, to submit a PBRER every 6 months during the initial 3 years post-approval.

For products that have been approved for more than 3 years in the United States, you must submit a postmarket periodic safety report annually, required under §§ 314.80(c)(2)(i) and 600.80(c)(2)(i). If you wish to use the PBRER to meet this requirement, you can submit a PBRER annually. Alternatively, you can submit a PBRER less frequently than annually on the condition you also submit an annual PADER/PAER as needed to fulfill the reporting frequency requirements in our regulations.