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### *DRAFT GUIDANCE*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

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**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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1 **Guidance for Industry<sup>1</sup>**  
2 **Providing Postmarket Periodic Safety Reports in the ICH E2C(R2)**  
3 **Format (Periodic Benefit-Risk Evaluation Report)**  
4

5  
6 This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current  
7 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to  
8 bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of  
9 the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA  
10 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call  
11 the appropriate number listed on the title page of this guidance.  
12

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17 **I. INTRODUCTION**  
18

19 This guidance describes the conditions under which applicants can use an alternative reporting  
20 format, the International Conference on Harmonisation (ICH) E2C(R2) Periodic Benefit-Risk  
21 Evaluation Report (PBRER), in place of the U.S. periodic adverse drug experience report  
22 (PADER), U.S. periodic adverse experience report (PAER), or ICH E2C Periodic Safety Update  
23 Report (PSUR), to satisfy the periodic safety reporting requirements at 21 CFR 314.80(c)(2) and  
24 600.80(c)(2).  
25

26 This guidance uses the term *applicant* to mean the holder of an approved new drug application  
27 (NDA), abbreviated new drug application (ANDA), or biologics license application (BLA),  
28 which are referred to collectively in this guidance as *applications*. This guidance describes the  
29 procedures applicants should follow if they wish to submit a PBRER in place of a PADER,  
30 PAER, or PSUR. The steps will differ, depending on whether or not the applicant has an  
31 approved waiver in place to substitute the PSUR for the PADER/PAER.  
32

33 FDA's guidance documents, including this guidance, do not establish legally enforceable  
34 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should  
35 be viewed only as recommendations, unless specific regulatory or statutory requirements are  
36 cited. The use of the word *should* in Agency guidances means that something is suggested or  
37 recommended, but not required.  
38

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<sup>1</sup> 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.

## *Contains Nonbinding Recommendations*

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### 39 **II. BACKGROUND**

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#### 41 **A. Postmarket Periodic Safety Reporting Regulations**

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

48

#### 49 **B. The PSUR (ICH E2C) and the PBRER (ICH E2C(R2))**

50

51 In November 1996, the ICH<sup>2</sup> endorsed the ICH E2C Periodic Safety Update Report Guideline  
52 (E2C guideline), which established the PSUR as a harmonized format for postmarket periodic  
53 safety reporting for approved drugs and biologic products, and described the format, content, and  
54 timing of PSUR submissions. FDA adopted that guideline and, in May 1997, published it as  
55 FDA guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update*  
56 *Reports for Marketed Drugs* (ICH E2C guidance).<sup>3</sup> In February 2003, ICH endorsed and made  
57 final an addendum that further clarified some aspects of the ICH E2C guidance. In February  
58 2004, FDA published the addendum as FDA guidance for industry *Addendum to E2C Clinical*  
59 *Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* (addendum to the  
60 E2C guidance).<sup>4</sup>

61

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

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<sup>2</sup> 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).

<sup>3</sup> 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>.

<sup>4</sup> 69 FR 5551 (Feb. 5, 2004).

<sup>5</sup> 77 FR 21782.

<sup>6</sup> 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.

## ***Contains Nonbinding Recommendations***

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66 guideline *Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2)*<sup>7</sup> (the ICH E2C(R2) step 4  
67 guideline).<sup>8</sup> This new ICH guideline updates and combines the E2C guideline and the addendum  
68 to the E2C guideline. In particular, it replaces the PSUR with the PBRER for postmarket  
69 periodic safety reporting, and describes the recommended format, content, and timing of PBRER  
70 submissions. Like its predecessor, the PSUR, the harmonized PBRER is intended to promote a  
71 consistent approach to periodic postmarket safety reporting among the ICH regions and to  
72 enhance efficiency by reducing the number of reports generated for submission to the regulatory  
73 authorities. FDA has initiated the process to adopt the ICH E2C(R2) step 4 guideline as final  
74 FDA guidance. We anticipate that some applicants will wish to begin using the PBRER format  
75 in the United States before the necessary administrative procedures are completed. This draft  
76 guidance describes the procedures applicants should follow to submit a PBRER.

### **C. PSUR Waivers**

78  
79  
80 FDA regulations at 21 CFR 314.90(a) and 600.90(a) allow applicants to request a waiver of any  
81 of the postmarket adverse experience reporting requirements in §§ 314.80 and 600.80,  
82 respectively, including requests to submit postmarket periodic safety reports in the PSUR format  
83 rather than in the PADER/PAER format (PSUR waiver). PSUR waiver requests also can include  
84 proposed timing changes, such as a change of the data lock point that marks the end of the  
85 reporting interval and/or reporting frequency.

#### *1. Waiver of the PADER/PAER Format Requirements*

86  
87  
88  
89 FDA has routinely granted PSUR waivers on the condition that applicants also submit the  
90 following information as U.S. appendices to the PSUR:

- 91  
92 • Copies of all non-expedited individual case safety reports (ICSRs) received during the  
93 PSUR reporting interval, as required under §§ 314.80(c)(2)(ii)(b) and 600.80(c)(2)(ii)(B).  
94 However, copies of ICSRs that were received during the PSUR reporting interval and  
95 previously submitted should not also be submitted at the time of PSUR submission. In  
96 these instances, the PSUR should include a list, but not copies, of any ICSRs that were  
97 previously submitted and their submission dates.
- 98  
99 • A narrative that identifies any changes made to the approved U.S. labeling based on new  
100 information in the PSUR, as required under §§ 314.80(c)(2)(ii)(c) and  
101 600.80(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*

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<sup>7</sup> Available at <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>.

<sup>8</sup> 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.

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105 a. Data lock point

106  
107 FDA has routinely granted waivers of the requirement to base the data lock point for the  
108 postmarket periodic safety report on the U.S. approval date (§§ 314.80(c)(2)(i) and  
109 600.80(c)(2)(i)). FDA has permitted applicants to change the data lock point from the U.S.  
110 approval date to a different date for harmonization purposes. These waivers have been granted  
111 on the condition that the applicant takes measures to ensure there are no gaps in reporting  
112 resulting from the date change.

113  
114 b. Reporting frequency

115  
116 Generally, FDA has not waived the reporting frequencies required under our regulations.  
117 However, we have permitted applicants to submit PSURs at longer intervals consistent with the  
118 ICH guidelines (e.g., 3-year PSURs), on the condition that the applicant submit a PSUR  
119 Addendum Report (as described in the addendum to the E2C guidance) or PADER/PAER as  
120 needed to fulfill the reporting frequency requirements under our regulations. These reports cover  
121 the period of time for which a periodic safety report would normally be required to be submitted.  
122 For example, we have granted waivers permitting an applicant to submit a PSUR every 3 years  
123 on the condition that the applicant also submit an annual PADER/PAER during each of the first  
124 2 years of the 3-year PSUR cycle to fulfill the annual reporting requirement in §§ 314.80(c)(2)(i)  
125 and 600.80(c)(2)(i). We have also granted waivers permitting an applicant to submit a PSUR  
126 every 6 months on the condition that the applicant also submit a quarterly PADER/PAER in the  
127 intervening quarters to fulfill the quarterly reporting requirement in §§ 314.80(c)(2)(i) and  
128 600.80(c)(2)(i).

129  
130 **III. PROCEDURES APPLICANTS SHOULD FOLLOW TO SUBMIT A PBRER**

131  
132 **A. Applicants Who Have a PSUR Waiver in Place for Their Approved**  
133 **Application**

134  
135 If you already have a PSUR waiver in place for an approved application, FDA will consider the  
136 existing PSUR waiver to permit you to submit a PBRER instead of a PSUR under the conditions  
137 described below, because the PBRER replaces the PSUR for postmarket periodic safety  
138 reporting. Thus, you do not need to submit a new waiver request. However, you should submit  
139 notification in certain instances described below.

140  
141 *1. Format Change Only*

142  
143 If you wish to submit a PBRER in place of a PSUR, with no changes in the data lock point or  
144 frequency of reporting, you can do so without submitting a new waiver request or notification to  
145 the FDA.

146  
147 If your PSUR waiver permits you to submit the PSUR less frequently than required under our  
148 regulations, it is dependent on the conditional submission of a PSUR Addendum Report or

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149 PADER/PAER to fulfill the frequency requirement. The substitution of the PBRER for the  
150 PSUR will continue to be dependent on the conditional submission of such reports. The PADER  
151 or PAER is an appropriate format for these reports.<sup>9</sup>

152

### 153 2. *Format Change and a Change to the Data Lock Point and/or Frequency of* 154 *Reporting*

155

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

159

#### 160 a. Change in data lock point for the PBRER

161

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

164

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

167

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

171

#### 172 b. Change in reporting frequency for the PBRER

173

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

177

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

184

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

189

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<sup>9</sup> 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.

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### **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

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### **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.