E2C(R2) Periodic Benefit-Risk Evaluation Report

Questions and Answers

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)

July 2016
ICH

E2C(R2) Periodic Benefit-Risk Evaluation Report

Questions and Answers

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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)

July 2016
ICH

Contains Nonbinding Recommendations

TABLE OF CONTENTS

Contains Nonbinding Recommendations

E2C(R2) Periodic Benefit-Risk Evaluation Report — Questions and Answers

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 (1)[2]

The ICH guidance *E2C(R2) Periodic Benefit-Risk Evaluation Report (PBRER)* is intended to be a common standard for periodic benefit-risk evaluation reporting on marketed products among the ICH regions. The ICH E2C(R2) guidance[3] introduced new concepts linked to an evolution of the traditional Periodic Safety Update Report (PSUR) from an interval safety report to a cumulative benefit-risk report. It changed the focus from individual case safety reports to aggregate data evaluation. In addition, the broadened scope increased the need for integrating information within the report.

The benefits of harmonizing technical requirements can only be achieved if the guidance is implemented and interpreted in a consistent way across the ICH regions. In November 2012, the ICH Steering Committee endorsed the establishment of an Implementation Working Group (IWG) on E2C(R2) to assist with the implementation of the guidance. The ICH E2C(R2) IWG has prepared this question and answer (Q&A) document to support implementation of the guidance in practice. The Q&A document is intended to facilitate practical implementation of the PBRER, including points to consider in addressing some of the more novel aspects of the new periodic safety report.

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.

---

[1] This guidance was developed within the Efficacy Implementation Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. The Q&As in this document have been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, March 2014. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and North America.

[2] Arabic numbers reflect the organizational breakdown of the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, March 2014.

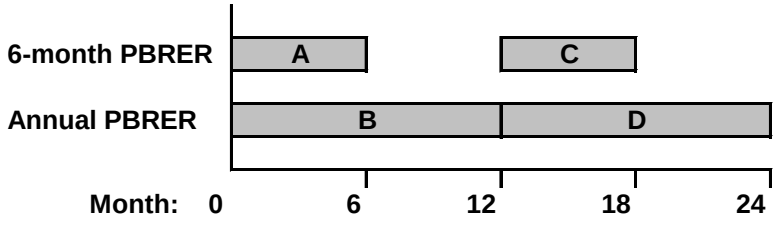
[3] The ICH E2C(R2) guidance is available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

II. GENERAL GUIDANCE (2)

2.1: How can a Marketing Authorization Holder (MAH) manage the submission of PBRERs when the reporting interval is different across multiple countries or regions?

In situations where the MAH is preparing PBRERs on both a 6-month and an annual basis for different regulatory authorities, it is possible that a PBRER on a 6-month cycle could be submitted as an up-to-date PBRER containing 12-month interval data (to fulfill the second 6-month interval of an annual cycle) (see Figure 2 below from the E2C(R2) guidance). The same may be true if a product is on a 6-month cycle in one region and a 3-year cycle in another region. However, the MAH should always discuss the acceptability of this approach with the relevant regulatory authority or authorities, noting that this approach is not an attempt to amend local reporting periodicity, but rather an opportunity to use the 12-month document to fulfill the shorter reporting period requirement.

Figure 1: Submission of 6-Month and Annual PBRERs



Region 1 requests 6-month PBRER, and receives PBRER A, B, C, and D (assuming agreement has been reached with pertinent regulatory authority or authorities).

Region 2 requests annual PBRER, and receives PBRER B and D.

2.2: Can Summary Bridging Reports and Addendum Reports still be submitted?

Summary Bridging Reports and Addendum Reports should no longer be submitted when following ICH E2C(R2). Independent of the time interval covered by the report, each PBRER should stand alone and reflect new and cumulative information currently available to the MAH.

2.3: Where in the PBRER can we present information on off-label use of the product?

The PBRER should report the evaluation of safety information based on all uses of the medicinal product, including uses outside the terms of the reference product information (more commonly known as *off-label use*). Although the benefit-risk evaluation should be conducted across approved indications, it is critical that the risk

assessment take into account all uses of the product.

Section I.C (1.3) of the E2C(R2) guidance (Scope of the PBRER) indicates that knowledge of a medicinal product's safety that is derived from data associated with uses other than the approved indication(s) should be reflected in the discussion of risk evaluation when it is available, relevant, and appropriate. Examples of potential sources of information on use outside the approved indication include, but are not limited to, spontaneous adverse event reports, investigator-initiated clinical trials, drug utilization data/studies, and published literature.

Specific information relating to off-label use can be included in the following sections of the PBRER:

- Section III.E.2 (3.5.2) (Cumulative and Interval Patient Exposure from Marketing Experience), paragraph c (Other post-approval use)

  The MAH should provide a brief description of patterns of use considered relevant for interpretation of safety data. This can include information on off-label use, including whether or not such use is supported by clinical guidelines, clinical trial evidence, or an absence of approved alternative treatments. For purposes of identifying patterns of use outside the terms of the reference product information, the MAH should use the appropriate sections (e.g., approved indication(s), contraindication(s)) of the reference product information that was in effect at the Data Lock Point (DLP) of the PBRER. See question 6.1of this Q&A document for points to consider in selecting the reference product information document.

- Sections III.O (3.15) (Overview of Signals: New, Ongoing, or Closed) and III.P (3.16) (Signal and Risk Evaluation)

  The MAH should include in these sections the signals and risks arising from all uses of the product.

- Section III.R.2 (3.18.2) (Benefit-Risk Analysis Evaluation)

Although the evaluation of benefit should be limited to approved use (see section III.Q (3.17) of the E2C(R2) guidance), the overall benefit-risk evaluation should take into account the risks associated with all uses of the product.

2.4: What information sources could be used in preparing a PBRER?

The MAH should prepare the PBRER on the active substance(s) using data that the MAH might reasonably have access to and that are relevant to the evaluation of the safety or benefit-risk profile. Compared to the product for which the MAH is the innovator, there may be less information available to the MAH on a generic product. For example, only a published report may be accessible for a clinical trial not sponsored by the MAH. The MAH can consider providing as an appendix to the report a list of the information sources used to prepare the PBRER (see Appendix E of the E2C(R2) guidance).

III. MODULAR FORMAT (3)

3.1: The modular format of the PBRER facilitates using information from other regulatory documents. How can information be reused when the other documents do not share the same DLP?

If the regulatory documents are written at different times, it may not always be possible to reuse sections, because the information may change from one period to another. For example, this can occur when the PBRER is on a 6-month cycle and the Development Safety Update Report (DSUR) is on an annual cycle. Some of the information from the 6-month PBRER could be used as a basis for populating some of the sections covering interval information in the annual DSUR. Appendix D of the E2C(R2) guidance lists the PBRER sections that can be shared with other regulatory documents.

3.2: What practical points should the MAH consider to coordinate preparing DSURs and PBRERs?

Depending on the nature of information available at the time of writing, the MAH may be able to use information across multiple documents. The MAH should first determine the interval and periodicity for each type of report the MAH is planning to produce.

The MAH should assess the extent to which other recently submitted reports (e.g., DSUR) can be used as a data source.

The MAH can facilitate the planning and production of PBRERs in association with other documents by synchronizing the DLPs for the various documents based on the International Birth Date (IBD). The MAH must obtain approval from the relevant regulatory authorities to synchronize the DLPs, and this can make it possible for the MAH to reuse information from other documents.

Where it has been established that there is no new and significant information, the MAH can consider reusing some sections from recently submitted documents with little modification.

If there is new and significant information, the MAH should review sections from recently submitted documents and provide updates of the source information, minor revisions, or a complete revision.

The reader can also refer to section II.H.1 (2.8.1) (IBD and DLP) and Appendix D of the E2C(R2) guidance. Table 1 provides further clarification.

Table 1 - Sharing Content between PBRER and DSUR

This table is intended to supplement Appendix D (List of PBRER Sections that Can Be Shared With Other Regulatory Documents) and sets out the sections that were proposed to be common. The information to be included in these sections is intended to enable sharing of content between the PBRER and DSUR when the birth dates and DLPs are aligned. In addition, this table identifies additional DSUR sections that can be considered information sources for corresponding sections in the PBRER, or vice versa. The sharing of content facilitates the modular approach, ensuring consistency across documents and avoiding duplicated effort when possible. The MAH should review information being shared or used as a data source to ensure that it is current and accurate and reflects the regulatory needs of the report in which it is being used.

Section #s in DSUR	**Section Headings in DSUR (ICH E2F)**	**Section #s in PBRER**	**Section Headings in PBRER (ICH E2C(R2))**
2*	Worldwide Marketing Approval Status	2*	Worldwide Marketing Approval Status
3*	Actions Taken in the Reporting Period for Safety Reasons	3*	Actions Taken in the Reporting Interval for Safety Reasons
6.1*	Cumulative Subject Exposure in the Development Program	5.1*	Cumulative Subject Exposure in Clinical Trials
6.2*	Patient Exposure From Marketing Experience	5.2*	Cumulative and Interval Patient Exposure From Marketing Experience (N.B.,Cumulative exposure from PBRER could be considered for the DSUR Section 6.2)
7.1	Reference Information	6.1**	Reference Information
7.3*	Cumulative Summary Tabulations of Serious Adverse Events	6.2*	Cumulative Summary Tabulations of Serious Adverse Events From Clinical Trials
8.1*	Completed Clinical Trials	7.1*	Completed Clinical Trials
8.2*	Ongoing Clinical Trials	7.2*	Ongoing Clinical Trials
8.3*	Long-Term Follow-up	7.3*	Long-Term Follow-up
8.4*	Other Therapeutic Use of Investigational Drug	7.4*	Other Therapeutic Use of Medicinal Product

8.5*	New Safety Data Related to Combination Therapies	7.5*	New Safety Data Related to Fixed Combination Therapies
9*	Safety Findings From Non-interventional Studies	8*	Findings from Non-Interventional Studies
10*	Other Clinical Trial/Study Safety Information	9.1*	Other Clinical Trials
11	Safety Findings From Marketing Experience	15**	Overview of Signals: New, Ongoing, or Closed
		9.2**	Medication Errors
		5.2 (para.3)**	Other post-approval use
12*	Nonclinical Data	10*	Nonclinical Data
13*	Literature	11*	Literature
14***	Other DSURs	12	Other Periodic Reports
15*	Lack of Efficacy	13*	Lack of Efficacy in Controlled Clinical Trials
17*	Late-Breaking Information	14*	Late-Breaking Information
18.1	Evaluation of the Risks	16.2**	Signal Evaluation
		16.3**	Evaluation of Risks and New Information
		16.4**	Characterization of Risks
18.2	Benefit-Risk Considerations	18.2**	Benefit-Risk Analysis Evaluation
19	Summary of Important Risks	16.1**	Summary of Safety Concerns
20*	Conclusions	19*	Conclusions and Actions

* Sections listed in Appendix D of ICH E2C(R2) as sections that can be shared with other regulatory documents.

** PBRER sections that could be used as an information source for the DSUR.

*** DSUR sections that could be used as a data source for the PBRER.

IV. INTERNATIONAL BIRTHDATES (4)

4.1: When transitioning to the PBRER, how should the MAH handle medicinal products whose current DLP is not synchronized to the new definition of the IBD?

The definition of IBD in the E2C(R2) guidance refers to the date of the first marketing approval for any product containing the active substance granted to any company in any country in the world. Provisions are available in many countries, whether through formal regulation or informal guidance, for the MAH to synchronize the PBRER DLP with the IBD. The MAH should consult the relevant local/regional regulations for further information. It should also contact the appropriate regulatory authority and request adjustment of the PBRER DLP to the IBD, as necessary. Granting these requests is at the discretion of each regulatory authority; experience has shown that most regulatory authorities are willing to do so, in the interest of international harmonization.

4.2: How can the MAH determine the IBD for products based on the definition of IBD in the E2C(R2) guidance?

The definition of IBD in the guidance refers to the date of the first marketing approval for any product containing the active substance granted to any company in any country in the world. If the MAH has no information on the actual IBD for a product, the MAH should first refer to listings of birth dates that some regions develop and make publicly available. If the product is not included in any listing, the MAH should propose to the regulatory authority a birth date that is based on the earliest known marketing approval of the substance and then obtain the regulatory authority's agreement.

4.3: How can the Development International Birth Date used for DSURs be harmonized with the IBD used for PBRERs?

As indicated in the ICH E2F guidance (DSUR - Section II.B (2.2)), the MAH can, if desired, submit a DSUR based on the PBRER IBD. In synchronizing the DLPs for the DSUR and PBRER, the period covered by the next DSUR should be no longer than one year. The MAH should obtain approval from the relevant regulatory authorities to synchronize the DLPs.

V. MATURE PRODUCTS (5)

5.1: There can be challenges related to lack of availability of historical information for some products. How should the MAH prepare sections that should include cumulative information when preparing PBRERs for these products?

The MAH should provide all information that is available at the time they prepare the PBRER. The MAH should specify what information is not available and fully explain why it is not available. For example, if it is not feasible to obtain precise cumulative clinical trial exposure data, the MAH should explain any omission of data from the

cumulative data. When the original clinical study report for a product marketed for many years is not accessible, the MAH is advised to base its presentation of efficacy/effectiveness on information obtained from publicly available data sources, such as the published literature.

5.2: Should the PBRER for a generic product include information regarding the active substance?

The E2C(R2) guidance is applicable to generic products for which a PBRER for a generic product is required by national/regional laws and regulations. A PBRER prepared for a generic product should follow the same format and content as outlined in the guidance. Sources of information can include information available for the active substance (sources of available information are those that the MAH might reasonably have access to, and that are relevant to evaluating the safety or benefit-risk profile (see also Appendix E of the guidance, Examples of Possible Sources of Information That Can Be Used in the Preparation of the PBRER)). Refer also to ICH E2C(R2), section I.C (1.3) (Scope of the PBRER).

VI. REFERENCE INFORMATION (6)

6.1: Which reference product information should the MAH choose to prepare a PBRER for different products with different indications that are based on the same active substance?

Section II.D (2.4) of the E2C(R2) guidance provides guidance on reference information, including when indications vary across countries or regions. The PBRER should address aspects common to all products containing the active substance, with subsections that address specific formulations and indications. For example, consider an MAH that is preparing a PBRER for a corticosteroid that can be used to manage asthma and chronic obstructive airway disease (inhaler), rhinitis (intranasal spray), Crohn's Disease (oral) and ulcerative colitis (suppository) — in this situation, the MAH should specify a single reference product information document, which in practice is often the Company Core Data Sheet (CCDS). However, if the product does not have a CCDS, then the MAH should use the most comprehensive local prescribing text.

6.2: When preparing the PBRER, where should the MAH include information on patterns of use that extend beyond the approved indications in a local label, including situations in which the reference product information covers all approved indications?

If patterns of use suggest that a product is being used beyond the local label in one or more countries or regions where the PBRER is being submitted, the MAH should indicate in Section 5 of the PBRER those countries or regions where the use is considered off-label. If patterns of use give rise to a safety signal, the MAH should include it in the signal tabulation (Section 15) and also address it in other relevant sections of the PBRER.

VII. EXPOSURE DATA (7)

7.1: What exposure data from historical clinical trials should the MAH provide for products that have been on the market for several years?

Section III.E.1 (3.5.1) of the E2C(R2) guidance describes the information the MAH should provide. If precise exposure data is not available, the MAH should provide its best estimate, indicating the basis and the underlying assumptions for this estimate.

7.2: According to the E2C(R2) guidance, section 5.2 of the PBRER should include patient exposure from marketing experience that is presented by various parameters (e.g., indication, sex, age, dose, formulation, and region). The guidance also states that detailed information should be provided on use in special populations. How should the MAH comply with this request when it cannot obtain the data in these groupings?

The MAH should make reasonable efforts to obtain accurate and complete postmarketing exposure data. Potential sources include, but are not limited to, sales data, registries, and healthcare databases.

When available, the MAH should provide these data in section 5.2 of the PBRER and describe any limitations regarding the data accuracy. If data are not available, the MAH should state this and indicate why.

VIII. SUMMARY TABULATIONS (8)

8.1: Should the tabulation referred to in section III.F.2 (3.6.2) of the E2C(R2) guidance contain only Serious Adverse Events (SAEs) collected during interventional clinical trials in which the investigational drug contains the same active substance as that contained in the product(s) represented in the PBRER?

The PBRER tabulation referred to in Section 3.6.2 of the guidance should include only the SAEs collected during interventional clinical trials sponsored by the MAH in which the investigational drug contains the same active substance as the product or products represented in the PBRER. This tabulation should include data from all such clinical trials sponsored by the MAH and is not limited to data from clinical trials that study the approved indication(s), approved dose(s), approved population(s), and approved formulation(s). The tabulations should also include data from clinical trials with the primary aim of identifying, characterizing, or quantifying a safety hazard, or confirming the safety profile. In addition, the tabulations should include SAEs from clinical trials that test unapproved doses or that test the investigational drug in unapproved indications or unstudied populations, if relevant and/or appropriate.

Any safety signals or other significant safety information arising from clinical trials using the active substance contained in the product(s) represented in the PBRER should be

summarized in the applicable sections of the PBRER in order to fully characterize the ongoing safety profile of the marketed product. Any findings from clinical trials that study unapproved indications, new formulations, unstudied populations or doses should be included if relevant to the marketed product(s).

8.2: In some instances, the product that is the subject of a PBRER (product A) might have been used as a comparator product for a clinical trial regarding another product (product B). Should SAEs related to product A from the clinical trial undertaken for product B be included in the comparator column of the Cumulative Tabulation of SAEs in the product A PBRER?

No. The MAH should summarize any clinically important safety findings for product A that arise from the clinical trial with product B in sections 7.1, 7.2, or 9.1 of the PBRER, as most appropriate (depending on whether or not the MAH was the sponsor of the trial program giving rise to the information). The term *comparator* in section III.F.2 (3.6.2) of the E2C(R2) guidance refers to other drugs used as comparators in the clinical development program for the product that is the subject of the PBRER.

Likewise, the MAH for product B, in preparing a PBRER for product B, should include the SAEs for product A in the comparator column when it is used as a comparator in clinical trials for product B. See Appendix B, Table 6, of the guidance, which provides an example of a cumulative tabulation of SAEs from clinical trials.

8.3: Should the MAH include in the summary tabulation SAEs that were collected in studies not sponsored by the MAH (e.g., investigator-initiated trials)?

In general, the MAH should include in the summary tabulations only those SAEs that were reported during clinical trials sponsored by the MAH, for which the drug is used as the investigational medicinal product or active comparator (see also question 8.1 of this Q&A document).

The MAH should summarize in section 9.1 of the PBRER the important safety information from clinical trials that the MAH has not sponsored. If applicable, the MAH should provide further information and evaluation in sections 15 through 18 of the PBRER.

In the interest of transparency, the MAH should provide a statement in section 6.2 of the PBRER if the MAH receives SAE case reports from a clinical trial it has not sponsored, but the MAH should not include these reports in the SAE summary tabulation.

It is important to note, however, that in some situations the MAH can assume the responsibilities of a sponsor on behalf of third parties that conduct clinical trials on the MAH's marketed product. In that case, any SAEs arising from those trials should be included in the SAE summary tabulations of the applicable PBRERs and described in the background to the tabulations (section 6.2 of the PBRER).

8.4: Regarding the summary tabulations from postmarketing data sources, should the MAH list all events or all case reports, which can include more than one event? And should seriousness be reflected at the case level or the event level?

The MAH should include both the nonserious and serious Adverse Drug Reactions (ADRs) from the case reports in the tabulation of ADRs from postmarketing sources, as exemplified by Table 7 in Appendix B of the E2C(R2) guidance.

The seriousness reflected in the summary tabulations should be at the event level.

IX. CLINICAL TRIALS (9)

9.1: What level of detail should be included on findings from randomized clinical trials and other safety information provided by co-development partners or from investigator-initiated trials?

Information from sources other than MAH-sponsored clinical trials should be briefly summarized in section 9.1 (Other Clinical Trials). If there are new significant safety or efficacy findings from such sources, more detail might be appropriate, for example, to support a more comprehensive evaluation later in the report.

9.2: Is section 7.4 of the PBRER intended to capture clinically important safety information from clinical trials conducted on other therapeutic uses, or is it meant to capture safety information from "other programs conducted by the MAH that follow a specific protocol, with solicited reporting"?

Section 7.4 of the PBRER should include clinically important safety information from other programs conducted by the MAH that follow a specific protocol (e.g., expanded access programs, compassionate use programs, particular patient use, single-patient investigational new drug applications (INDs), treatment INDs, and other organized data collection). The MAH should summarize important safety information arising from clinical trials conducted on other therapeutic uses of the product represented in the PBRER (e.g., a phase IIIb clinical development program for a new indication). The information should be summarized in sections 7.1, 7.2, and 9.1 of the PBRER, as applicable, depending on whether or not the MAH was the sponsor of the trial program giving rise to the information.

X. NONCLINICAL DATA (10)

10.1: Does section 10 of the PBRER only refer to nonclinical studies that are sponsored by the MAH, or does it also refer to other studies, including those found in the literature?

The intention is that section 10 of the PBRER should summarize or reference major safety findings arising from all nonclinical studies conducted and/or reported during the

reporting interval, regardless of who sponsored and/or conducted the study. If such findings arise from nonclinical studies conducted by other organizations and published in the literature, the MAH should summarize them in section 11 (Literature) and provide a suitable cross-reference in section 10 (Nonclinical Data) back to section 11. In this way, unnecessary duplication of information can be avoided.

XI. LITERATURE (11)

11.1: Section III.K (3.11) of the E2C(R2) guidance states, this section "should summarize new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts, relevant to the approved medicinal product that the MAH has become aware of during the reporting interval." Does the phrase "relevant to the approved medicinal product" refer to the active substance or to a specific brand name?

Section 11 of the PBRER should summarize all new and significant safety findings that are relevant to the product represented in the PBRER. This may include safety findings related to the same active substance of the product, but not necessarily the brand sold by the MAH. Hence, the guidance indicates that literature searches conducted for PBRERs should be wider than those for individual adverse reaction cases (i.e., for expedited reporting purposes), and if relevant, the PBRER should address information on active substances of the same class.

11.2: Section III.K (3.11) of the E2C(R2) guidance states, "Literature searches for PBRERs should be wider than those for individual adverse reaction cases." What should the MAH include in the wider search?

Section 11 of the PBRER should summarize all new and significant safety findings that are relevant to the product represented in the PBRER. This may include safety findings related to the same active substance of the product, but not necessarily the brand sold by the MAH. Hence, the guidance indicates that literature searches conducted for PBRERs should be wider than those for individual adverse reaction cases (i.e., for expedited reporting purposes), and if relevant, the PBRER should address information on active substances of the same class.

XII. LACK OF EFFICACY (12)

12.1: Does the scope of section 13 of the PBRER only include controlled clinical trials?

No. Although Section 13 of the E2C(R2) guidance is titled "Lack of Efficacy in Controlled Clinical Trials," the intent of this section is that it should include lack of efficacy data arising from all types of clinical trials conducted or completed during the reporting interval.

12.2: Lack of efficacy in clinical trials should be addressed in section 13 of the PBRER for "products intended to treat or prevent serious or life-threatening illnesses" and in section 7 for non-life-threatening diseases. What parameters should be used to define whether the drug is treating a life-threatening or a non-life-threatening condition?

The determination of what is and is not a life-threatening disease or illness is a matter of medical judgment. The primary consideration relates to the degree of morbidity and mortality that is a potential consequence of the disease. Section III.M (3.13) of the E2C(R2) guidance provides an example, namely, acute coronary syndrome, to illustrate what might be considered a serious or life-threatening illness, and here the key consideration is that lack of efficacy could present a significant risk to the population treated by the product.

XIII. SIGNAL AND RISK EVALUATION (13)

13.1: Some sections of the E2C(R2) guidance refer to discussing "important safety information"; this could vary widely based on the interpretation of the word "important". What is the guidance's intended meaning of "important safety information" in the context of the PBRER?

Important safety information has not been defined, because it is a matter of judgment. For example, it could include information that, upon evaluation, might have an impact on the understanding of the product's safety profile or call for communication through the product label. It could include data that contribute to identifying a new signal. It could also provide information that either supports or refutes a signal.

13.2: The E2C(R2) guidance states that the PBRER should present safety-related data and findings in sections 6 through 14. How can the MAH (a) avoid repeating data in sections 15 and 16 and (b) provide sufficient detail to substantiate conclusions?

(a) Points to Consider in Avoiding Repetition in the PBRER

Although repetition of information across different sections of the PBRER is not entirely avoidable and sometimes appropriate, the MAH can consider providing instructions to its staff in its internal templates/guidance documents to minimize such repetition. These instructions could recommend cross-referencing earlier sections of the PBRER in which the data were initially presented. However, the MAH should not overuse cross-referencing, because this could prevent a clear message from being conveyed to the reader.

Sections 6 through 14 of the PBRER are intended to present only the data or findings from the various sources covered by these sections. In contrast, sections 15 and 16 are intended to present the relevant interpretation and evaluation of the significant data and findings from sections 6 through 14.

For example, if the MAH identifies a new and ongoing signal based on a literature report published during the reporting interval, the MAH should summarize the literature report in section 11 (Literature) and the identified safety signal should be included in the summary tabulation in section 15 (Overview of Signals). If the MAH refutes an ongoing safety signal based on the results of a randomized clinical trial completed during the reporting interval, then the MAH should briefly summarize the relevant study findings in section 7.1 (Completed Clinical Trials). In addition, the MAH should update the status of the signal in the section 15 signal tabulation, as well as provide a critical analysis of new and cumulative data in section 16.2 (Signal Evaluation). This integrated analysis should include the MAH's rationale and conclusions for refuting the signal. The analysis of the refuted signal discussed in section 16.2 should not completely repeat the findings included in section 7.1 but should instead provide a high-level summary that focuses on the evaluation and interpretation of these findings. Similarly, the summary analyses included in sections 16.2 and 16.3 should not be repeated in section 16.4 (Characterization of Risks) of the PBRER.

Appendix C of the E2C(R2) guidance provides a format for signal tabulation, including two examples; Appendix F provides further guidance on mapping signals and risks to the appropriate PBRER sections.

(b) Points to Consider in Providing Sufficient Detail in Sections 15 and 16 of the PBRER

General Considerations:

As described in section II.E (2.5) of the guidance, the MAH should tailor the level of detail it provides for both the presentation of findings (sections 6 through 14) and evaluation sections (sections 15 and 16) based upon the clinical significance of the presented findings; this involves medical and scientific judgment. The level of detail should be sufficient to substantiate the MAH's conclusions and any actions taken or proposed. In these sections, the MAH should discuss in greater detail any findings that have a substantial medical impact or call for a more in-depth evaluation of causality.

Considerations for Specific Sections:

Section 15: Overview of Signals

The MAH should provide in a summary table an overview of signals ongoing and closed in the reporting interval. Appendix C of the guidance provides an example summary table that contains information at a high level, as opposed to detailed data. For signals closed during the reporting interval, the MAH should supplement the information appearing in the table with a summary evaluation of available data in section 16.2. When a regulatory authority has requested that a specific topic (not considered a signal) be monitored and reported in a PBRER, the MAH should summarize the result of the analysis in this section if it is negative.

Section 16.1: Summary of Safety Concerns

For a discussion on this topic, please refer to the answer for question 13.4 of this Q&A document.

Sections 16.2 and 16.3: Signal Evaluation and Evaluation of Risks and New Information

In sections 16.2 and 16.3 of the PBRER, the MAH should include sufficient information and interpretation of the available data to enable a reviewer to understand the rationale for the MAH's conclusions and actions (if taken or proposed).

The MAH should present a clear evaluation of the available evidence for or against a possible causal relationship in section 16.2. The focus of the presented analysis should support how the MAH came to the conclusion that:

- A signal was refuted based on available evidence against a causal relationship.
- A signal became an identified risk (adequate evidence of an association).
- A signal became a potential risk (there is some basis to suspect an association, but the association has not been confirmed).

Section 16.3 should contain new information relevant to a previously recognized risk that was not already included in section 16.2, i.e., when the new information itself does not constitute a signal. This should include information on important risks and an update on important missing information, as well as updates on risks not otherwise categorized as important. The new information may be in response to a regulatory request on a previously recognized risk. Although the MAH should provide concise information, it should ensure that sufficient detail is contained in the summary to allow a regulatory authority reviewer to determine whether the information has an impact on the understanding of the risk and/or its characterization.

Section 16.4: Characterization of Risks

In characterizing the risk for section 16.4 of the PBRER, the MAH should consider whether the risk is important or not. A risk may not be important if it is infrequent, nonserious, reversible, and readily managed with no significant impact on the individual patient or public health. Even a common ADR may not constitute an important risk if it is not linked to clinically significant adverse sequelae.

Unlike sections 15, 16.2, and 16.3, which cover all signals and risks, section 16.4 only includes important risks. In section 16.4, the MAH should present more detailed information on the parameters outlined in the guidance to illustrate why the risk should be considered important.

13.3: When a regulatory authority has requested that a specific topic be monitored and reported in a PBRER, where in the PBRER should the MAH summarize the results of the analysis?

If the MAH determines that the specific topic constitutes a signal, the MAH should include it in the signal tabulation, evaluate it as such, and handle it in accordance with the usual approach for summarizing signals within the PBRER.

If the MAH does not consider the specific topic to constitute a signal, the MAH should summarize its analysis on the requested monitoring topic in section 15 of the PBRER.

13.4: Section III.P.1 (3.16.1) of the E2C(R2) guidance states that the PBRER should include a summary of important risks and missing information that are known at the beginning of the reporting interval. However, for products that have existing safety specifications submitted to different countries, it is not unusual for the particular safety concerns to differ across countries or regions.

For example, a local regulatory authority might request that certain additional safety concerns be addressed. In addition, what is considered an important "potential" risk by the regulatory authority in one region might be considered an important "identified" risk by the regulatory authority in another region.

Section 16.4 of the PBRER (Characterization of Risks) could be similarly affected. How should the MAH handle this situation?

The MAH should tailor the way it handles this situation based on the number of additional concerns or the range of different regional or national requests from the different regulatory authorities. One approach is detailed below, but it may not be optimal in every situation. If the MAH is unsure about which approach is best for its product, the MAH should seek guidance from the relevant regulatory authorities, particularly if there are substantial regional differences in the safety specifications. One approach to handling such a situation is described below:

- When a PBRER will be submitted to regulatory authorities with previously different assessment conclusions on how a risk should be classified (potential or identified) or on the scope of information that should be documented in a risk management plan as missing information, the MAH can include all risks and missing information in the summary of safety concerns and clarify, using footnotes, those that are specific to only one country or region, indicating the country or region to which this additional safety concern applies.
- If a safety concern is considered to be an important identified risk in one region and an important potential risk in another region, then the risk should appear under both categories within this section of the PBRER (see sample tabulation below).
- In addition to the categorization from the different regulatory authorities, the MAH may wish to indicate the company core position on categorizing the various risks.

- Other approaches to presentation, such as the use of individual tables for each region within this section, can be used, and the guiding principle should be to ensure a clear and transparent presentation of information.
- An example is given below:

Summary of Safety Concerns

Important Identified Risks	• Important Risk A[1] • Important Risk B • Important Risk C[2]
Important Potential Risks	• Important Risk A[1] • Important Risk D • Important Risk E • Important Risk F[3]
Important Missing Information	• Important Missing Information G[4]

[1]Important identified risk in the European Union (EU) and Switzerland; important potential risk in Canada.

[2] Important identified risk in Japan, Korea, and Switzerland.

[3] EU only.

[4] United States, Canada, and Australia only.

If this method is used, all the safety concerns listed in section 16.1 should be characterized in section 16.4 of the PBRER, including a description of the important missing information.

From a practical perspective, if this suggested approach is used, section 16.1 of the PBRER should remain common across multiple PBRERs that are submitted to different regulatory agencies at the same time. As such, this approach promotes transparency and avoids creating different sections in the main body of the PBRER to meet different regulatory requirements, which may be regional.

13.5: In section III.P.4 (3.16.4) (Characterization of Risks) of the E2C(R2) guidance, "public health impact" is listed as one of the points that can be included in characterizing an important risk. What factors should the MAH consider in providing this information for the purposes of section 16.4 of the PBRER?

It is outside the scope of the guidance and this Q&A document to provide advice on how to conduct a public health impact assessment because, in reality, this is a complex undertaking that takes into account multiple factors and considerations.

In section 16.4 of the PBRER, the MAH should present its evaluation of the public health impact of the risk as part of the characterization of important risk(s) for the purposes of the PBRER. In assessing the public health impact of individual risks, the MAH should consider the following points that are intended to be illustrative rather than

comprehensive: extent of product use (size of treated population), frequency, and health consequences (including consideration of seriousness, preventability, and reversibility).

Characterization of risk should include consideration of the impact on the individual patient, as well as on the overall population.

XIV. RISK AND BENEFIT SECTIONS (14)

14.l: Regarding section III.P.5 (3.16.5) (Effectiveness of Risk Minimization), the wording of the E2C(R2) guidance implies that the MAH should include information relevant to the effectiveness and/or limitations of specific risk minimization activities that have become available during the reporting period.

If the MAH communicated the risk with a Dear Healthcare Professional Communication (or local equivalent) during the reporting interval, should the MAH address the effectiveness of that risk communication in the PBRER?

Reporting on the effectiveness of such activities is driven by the standards of the risk management plan, or as agreed with the regulatory authorities. The MAH should include information on the effectiveness of such risk minimization activities in section 16.5 of the PBRER if the results are applicable across different regions; otherwise this information should be included in the appropriate regional appendix.

XV. BENEFIT EVALUATION (15)

15.1: What is meant by the terms "efficacy" and "effectiveness"?

Because the use of these words is not harmonized across regions, the phrase "efficacy/effectiveness" is used in the E2C(R2) guidance to clarify that information from both clinical trials and everyday medical practice is within the scope of the information on benefit that should be included in the PBRER. In some regions, *efficacy* refers to evidence of benefit from controlled clinical trials, while *effectiveness* refers to use of the product in everyday medical practice. However, in other regions this distinction is not made.

For the purposes of the PBRER, any pertinent efficacy/effectiveness information from clinical trials and from everyday medical practice should be included.

15.2: What efficacy/effectiveness information should be presented in section 17.1 (Important Baseline Efficacy/Effectiveness Information) of the PBRER?

In addition to the guidance provided in section III.Q.1 (3.17.1) of the E2C(R2) guidance, the MAH may wish to consider the following points when presenting efficacy/effectiveness information in section 17.1 of the PBRER.

The MAH should present any efficacy/effectiveness information on approved indications that is relevant and supports the characterization of benefit presented in section 17.3 of the PBRER. The content should focus on important evidence that supports the benefit of the product. The MAH can use tables, graphs, and/or narrative descriptions to communicate this information.

The following are examples of points to consider for information that might be included in section 17.1 of the PBRER:

- A statement about the intended purpose and impact of the product on the outcome(s) of each approved indication in the populations treated, including the nature of the benefit (diagnostic, preventative, symptomatic, or disease-modifying treatment).
- Evidence including (but not limited to) clinical trial data, systematic reviews, meta-analyses, clinical pharmacology, relevant outcome studies.
- Information described in Appendix E in the guidance (Examples of Possible Sources of Information that May Be Used in the Preparation of the PBRER). The MAH should also consider the following:
    - Evidence that the benefits are applicable to subpopulations, for example, pediatric, elderly, pregnant, vulnerable populations.
    - Information about multiple efficacy endpoints, where they support efficacy/effectiveness.
    - Evidence of efficacy/effectiveness from various sources (e.g., placebo-controlled trials, active controlled trials, meta-analyses, observational studies).
    - Trends, patterns, and/or evidence of benefit or lack of benefit in important subgroups.

15.3: What new information should be included in section 17.2 (newly identified information on efficacy/effectiveness) of the PBRER?

In section 17.2 of the PBRER, the MAH should present information that is data driven and scientifically based.

What constitutes new information is efficacy/effectiveness information that might alter the known benefit profile of the product in the approved indication. As such, the MAH should not include new efficacy/effectiveness information that only confirms what was already known for the product. The same principle applies to other sections of the PBRER in which the MAH provides summaries of new, clinically important efficacy/effectiveness information that became available during the interval covered by the PBRER.

15.4: Section III.Q.2 (3.17.2) of the E2C(R2) guidance states, "New information about efficacy/effectiveness in uses other than the approved indication(s) should not be included, unless relevant for the benefit-risk evaluation in the approved indication." Please provide the definition of "relevant".

It is not possible to define *relevant* because this is a matter of judgment. The MAH should consider whether or not new efficacy/effectiveness information relating to an unapproved indication may have an impact on the benefit-risk profile for the approved indication(s) and, if so, should summarize the new information accordingly.

15.5: What is meant by "key risk" and "key benefit" in the context of the PBRER?

Key risks and key benefits are those benefits and risks that contribute importantly to the overall benefit-risk evaluation and may not necessarily include all important benefits and risks included in the PBRER, as described in section III.R.2 (3.18.2) of the E2C(R2) guidance. The particular risks and benefits the MAH should consider as key is a matter of medical judgment.

15.6: Are there specific methods for performing a formal quantitative or semi-quantitative assessment of benefit-risk?

It is beyond the scope of the E2C(R2 guidance to provide definitive advice on specific methods for performing a formal quantitative or semi-quantitative analysis. If the MAH provides a formal quantitative or semi-quantitative assessment of benefit-risk, the MAH should include a summary of the analytical methods used.

15.7: Can the PBRER include a benefit-risk evaluation in the context of the local label?

In general, the MAH should perform the benefit-risk assessment within the context of the applicable reference product information for the PBRER. The E2C(R2) guidance does make provision for the MAH to use regional product information as the reference document. As such, the guidance does not exclude the possibility of a benefit-risk assessment within the context of a local label, which would most likely occur at the request of a specific regulatory authority for a specific product. The MAH could provide the assessment either within a suitable subsection of the PBRER or as an appendix.