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ICH guideline E2C (R2) - questions and answers

Step 5

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30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom

Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555

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1. Introduction

The ICH E2C (R2) Guideline: 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) Guideline¹ 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 harmonising technical requirements can only be achieved if the Guideline 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 Guideline. The ICH E2C (R2) IWG has prepared this Question and Answer (Q&A) document to support implementation of the Guideline in practice. It 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.

2. General guidance

#	Date of Approval	Questions	Answers
2.1	March 2014	How can a Marketing Authorisation Holder (MAH) manage the submission of PBRERs when the reporting interval is different across multiple countries or regions?	<p>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 fulfil the second 6-month interval of an annual cycle) (see Figure 2 below from the Guideline). 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 fulfil the shorter reporting period requirement.</p> <p>Figure 2: Submission of 6-Month and Annual PBRERs</p> <p>Region 1 requires 6-monthly PBRER, and receives PBRER A, B, C, and D (assuming agreement has been reached with pertinent regulatory authority[ies]).</p> <p>Region 2 requires annual PBRER, and receives PBRER B and D.</p>
2.2	March 2014	Can Summary Bridging Reports and Addendum Reports still be submitted?	<p>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.</p>

#	Date of Approval	Questions	Answers
2.3	March 2014	Where in the PBRER can we present information on off-label use of the product?	<p>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.</p> <p>Section 1.3 of the Guideline (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 utilisation data/studies, and published literature.</p> <p>Specific information relating to off-label use can be included in the following sections of the PBRER:</p> <p>Section 5.2 (Cumulative and Interval Patient Exposure from Marketing Experience), paragraph 3 (Other post-approval use)</p> <p>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 6.1 for points to consider in selecting the reference product information document.</p> <p>Sections 15 (Overview of Signals: New, Ongoing, or Closed) and 16 (Signal and Risk Evaluation)</p> <p>The MAH should include in this section the signals and risks arising from all uses of the</p>

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			product. Section 18.2 (Benefit-Risk Analysis Evaluation) Although the evaluation of benefit should be limited to approved use (see Section 17 of the Guideline), the overall benefit-risk evaluation should take into account the risks associated with all uses of the product.
2.4	March 2014	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 Guideline).

3. Modular format

#	Date of Approval	Questions	Answers
3.1	March 2014	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 re-use 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 Guideline lists the PBRER sections that can be shared with other regulatory documents.
3.2	March 2014	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.

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			<p>The MAH should assess the extent to which other recently submitted reports (e.g., DSUR) can be used as a data source.</p> <p>The MAH can facilitate the planning and production of PBRERs in association with other documents by synchronising the DLPs for the various documents based on the International Birth Date (IBD). The MAH must obtain approval from the relevant regulatory authorities to synchronise the DLPs, and this can make it possible for the MAH to re-use information from other documents.</p> <p>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.</p> <p>The reader can also refer to Section 2.8.1 (IBD and DLP) and Appendix D of the Guideline. Table 1 provides further clarification.</p>

Table 1 - Sharing Content between PBRER and DSUR

This table is intended to supplement Appendix D (List of PBRER Sections that May 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 (E2F)	Section #s in PBRER	Section Headings in PBRER (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

Section #s in DSUR	Section Headings in DSUR (E2F)	Section #s in PBRER	Section Headings in PBRER (E2C(R2))
6.1*	Cumulative Subject Exposure in the Development Programme	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*	Non-Clinical Data	10*	Non-Clinical 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

Section #s in DSUR	Section Headings in DSUR (E2F)	Section #s in PBRER	Section Headings in PBRER (E2C(R2))
18.1	Evaluation of the Risks	16.2**	Signal Evaluation
		16.3**	Evaluation of Risks and New Information
		16.4**	Characterisation 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.

4. International birth dates

#	Date of Approval	Questions	Answers
4.1	March 2014	When transitioning to the PBRER, how should the MAH handle medicinal products whose current DLP is not synchronised to the new definition of the IBD?	The definition of IBD in the Guideline 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 synchronise 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 harmonisation.
4.2	March 2014	How can the MAH determine the IBD for products based on the definition of IBD in the Guideline?	The definition of IBD in the Guideline 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	March 2014	How can the Development International Birth Date used for DSURs be harmonised with the IBD used for PBRERs?	As indicated in the ICH E2F Guideline (DSUR - Section 2.2), the MAH can, if desired, submit a DSUR based on the PBRER IBD. In synchronising the DLPs for the DSUR and PBRER, the period covered by the next DSUR should be no longer than one year. The MAH must obtain approval from the relevant regulatory authorities to synchronise the DLPs.

5. Mature products

#	Date of Approval	Questions	Answers
5.1	March 2014	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	March 2014	Should the PBRER for a generic product include information regarding the active substance?	The Guideline 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 Guideline. 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, Examples of Possible Sources of Information that May Be Used in the Preparation of the PBRER]). Refer also to ICH E2C(R2) Section 1.3 (Scope of the PBRER).

6. Reference information

#	Date of Approval	Questions	Answers
6.1	March 2014	Which reference product information should the MAH choose to prepare a PBRER for different products with different indications that are based on	Section 2.4 of the Guideline 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.

#	Date of Approval	Questions	Answers
		the same active substance?	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	March 2014	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.

7. Exposure data

#	Date of Approval	Questions	Answers
7.1	March 2014	What exposure data from historical clinical trials should the MAH provide for products that have been on the market for several years?	Section 3.5.1 of the Guideline 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	March 2014	According to the Guideline, Section 5.2 of the PBRER should include patient exposure from marketing experience that is presented by various parameters	The MAH should make reasonable efforts to obtain accurate and complete post-marketing 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

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		(e.g., indication, sex, age, dose, formulation and region). The Guideline 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?	describe any limitations regarding the data accuracy. If data are not available, the MAH should state this and indicate why.

8. Summary tabulations

#	Date of Approval	Questions	Answers
8.1	March 2014	Should the tabulation referred to in Section 3.6.2 of the Guideline 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?	<p>The PBRER tabulation referred to in Section 3.6.2 of the Guideline 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, characterising 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.</p> <p>Any safety signals or other significant safety information arising from clinical trials utilising the active substance contained in the product(s) represented in the PBRER should be summarised in the applicable sections of the PBRER in order to fully characterise the ongoing safety profile of the marketed product. Any findings from clinical trials that study unapproved indications, new formulations, unstudied populations</p>

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			or doses should be included if relevant to the marketed product(s).
8.2	March 2014	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 summarise 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 programme giving rise to the information). The term comparator in Section 3.6.2 of the Guideline, refers to other drugs used as comparators in the clinical development programme 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 Guideline, which provides an example of a cumulative tabulation of SAEs from clinical trials.
8.3	March 2014	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). The MAH should summarise 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	March 2014	Regarding the summary tabulations from post-marketing data sources, should the MAH list all events or all case reports,	The MAH should include both the non-serious and serious Adverse Drug Reactions (ADRs) from the case reports in the tabulation of ADRs from post-marketing sources, as exemplified by Table 7 of the Guideline.

#	Date of Approval	Questions	Answers
		which can include more than one event? And should seriousness be reflected at the case level or the event level?	The seriousness reflected in the summary tabulations should be at the event level.

9. Clinical trials

#	Date of Approval	Questions	Answers
9.1	March 2014	What level of detail should be included on findings from randomised 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 summarised 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	March 2014	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 programmes 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 programmes conducted by the MAH that follow a specific protocol (e.g., expanded access programmes, compassionate use programmes, particular patient use, single-patient Investigational New Drug applications [INDs], treatment INDs, and other organised data collection). The MAH should summarise 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 programme for a new indication). The information should be summarised 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 programme giving rise to the information.

10. Non-clinical data

#	Date of Approval	Questions	Answers
10.1	March 2014	Does Section 10 of the PBRER only refer to non-clinical 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 summarise or reference major safety findings arising from all non-clinical studies conducted and/or reported during the reporting interval, regardless of who sponsored and/or conducted the study. If such findings arise from non-clinical studies conducted by other organisations and published in the literature, the MAH should summarise them in Section 11 (Literature) and provide a suitable cross-reference in Section 10 (Non-Clinical Data) back to Section 11. In this way, unnecessary duplication of information can be avoided.

11. Literature

#	Date of Approval	Questions	Answers
11.1	March 2014	Section 3.11 of the Guideline states, "This section should summarise 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 became 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 summarise 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 Guideline 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	March 2014	Section 3.11 of the Guideline states, "Literature searches for PBRERs should	Section 11 of the PBRER should summarise all new and significant safety findings that are relevant to the product represented in the PBRER. This may include safety findings

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		be wider than those for individual adverse reaction cases.” What should the MAH include in the wider search?	related to the same active substance of the product, but not necessarily the brand sold by the MAH. Hence, the Guideline 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.

12. Lack of efficacy

#	Date of Approval	Questions	Answers
12.1	March 2014	Does the scope of Section 13 of the PBRER only include controlled clinical trials?	No. Although Section 13 of the Guideline 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	March 2014	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 judgement. The primary consideration relates to the degree of morbidity and mortality that is a potential consequence of the disease. Section 3.13 of the Guideline 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.

13. Signal and risk evaluation

#	Date of Approval	Questions	Answers
13.1	March 2014	Some sections of the Guideline refer to discussing “important safety information”; this could vary widely based on the interpretation of the word important. What is the Guideline’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 judgement. 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	March 2014	The Guideline 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?	<p>a) Points to Consider in Avoiding Repetition in the PBRER</p> <p>Although repetition of information across different sections of the PBRER is not entirely avoidable and sometimes appropriate, the MAH can consider providing instructions to their staff in their internal templates/guidance documents to minimise 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.</p> <p>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.</p> <p>For example, if the MAH identifies a new and ongoing signal based on a literature report published during the reporting interval, the MAH should summarise 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 randomised clinical trial completed during the reporting interval, then the MAH should briefly summarise the relevant study findings in Section 7.1 (Completed Clinical Trials). In addition, the MAH should update the status of</p>

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			<p>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 (Characterisation of Risks) of the PBRER.</p> <p>Appendix C of the Guideline provides a format for signal tabulation, including two examples; Appendix F provides further guidance on mapping signals and risks to the appropriate PBRER sections.</p> <p>b) Points to Consider in Providing Sufficient Detail in Sections 15 and 16 of the PBRER</p> <p><u>General Considerations:</u></p> <p>As described in Section 2.5 of the Guideline, 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 judgement. 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.</p> <p><u>Considerations for Specific Sections:</u></p> <p>Section 15: Overview of Signals</p> <p>The MAH should provide in a summary table an overview of signals ongoing and closed in the reporting interval. Appendix C of the Guideline 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</p>

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			<p>authority has requested that a specific topic (not considered a signal) be monitored and reported in a PBRER, the MAH should summarise the result of the analysis in this section if it is negative.</p> <p>Section 16.1: Summary of Safety Concerns For a discussion on this topic, please refer to the answer for Question 13.4.</p> <p>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 recognised 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 categorised as important. The new information may be in response to a regulatory request on a previously recognised 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 characterisation.</p> <p>Section 16.4: Characterisation of Risks In characterising the risk for Section 16.4 of the PBRER, the MAH should consider</p>

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			<p>whether the risk is important or not. A risk may not be important if it is infrequent, non-serious, 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.</p> <p>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 Guideline to illustrate why the risk should be considered important.</p>
13.3	March 2014	When a regulatory authority has requested that a specific topic be monitored and reported in a PBRER, where in the PBRER should the MAH summarise the results of the analysis?	<p>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 summarising signals within the PBRER.</p> <p>If the MAH does not consider the specific topic to constitute a signal, the MAH should summarise its analysis on the requested monitoring topic in Section 15 of the PBRER.</p>
13.4	March 2014	<p>Section 3.16.1 of the Guideline 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 may request that certain additional safety concerns be addressed. In addition, what is considered an important potential risk by the</p>	<p>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.</p> <p>One approach to handling such a situation is described below:</p> <p>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 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</p>

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		<p>regulatory authority in one region may be considered an important identified risk by the regulatory authority in another region.</p> <p>Section 16.4 of the PBRER (Characterisation of Risks) could be similarly affected. How should the MAH handle this situation?</p>	<p>categories within this section of the PBRER (see sample tabulation below).</p> <p>In addition to the categorisation from the different regulatory authorities, the MAH may wish to indicate the company core position on categorising the various risks.</p> <p>Other approaches to presentation, such as the use of individual tables for each region within this section, may be used, and the guiding principle should be to ensure a clear and transparent presentation of information.</p> <p>An example is given below:</p> <table border="1"> <thead> <tr> <th colspan="2">Summary of safety concerns</th> </tr> </thead> <tbody> <tr> <td>Important Identified Risks</td> <td>Important Risk A¹ Important Risk B Important Risk C²</td> </tr> <tr> <td>Important Potential Risks</td> <td>Important Risk A¹ Important Risk D Important Risk E Important Risk F³</td> </tr> <tr> <td>Important Missing Information</td> <td>Important Missing Information G⁴</td> </tr> </tbody> </table> <p>¹ Important identified risk in EU and Switzerland; important potential risk in Canada.</p> <p>² Important identified risk in Japan, Korea and Switzerland.</p> <p>³ EU only.</p> <p>⁴ United States, Canada, and Australia only.</p> <p>If this method is used, all the safety concerns listed in Section 16.1 should be characterised in Section 16.4 of the PBRER, including a description of the important missing information.</p> <p>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 the need to create different sections in the main body of the PBRER to meet different regulatory requirements, which may be regional.</p>	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
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										

#	Date of Approval	Questions	Answers
13.5	March 2014	In Section 3.16.4 (Characterisation of Risks) of the ICH E2C(R2) Guideline, "public health impact" is listed as one of the points that can be included in characterising an important risk. What factors should the MAH consider in providing this information for the purposes of Section 16.4 of the PBRER?	<p>It is outside the scope of the Guideline and this Q&A 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.</p> <p>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 characterisation 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). Characterisation of risk should include consideration of the impact on the individual patient, as well as on the overall population.</p>

14. Risk and benefit sections

#	Date of Approval	Questions	Answers
14.1	March 2014	<p>Regarding Section 3.16.5 (Effectiveness of Risk Minimisation), the wording of the Guideline implies that the MAH should include information relevant to the effectiveness and/or limitations of specific risk minimisation activities that has become available during the reporting period.</p> <p>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?</p>	<p>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 minimisation 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.</p>

15. Benefit evaluation

#	Date of Approval	Questions	Answers
15.1	March 2014	What is meant by the terms efficacy and effectiveness?	<p>Because the use of these words is not harmonised across regions, the phrase "efficacy/effectiveness" is used in the Guideline 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.</p> <p>For the purposes of the PBRER, any pertinent efficacy/effectiveness information from clinical trials and from everyday medical practice should be included.</p>
15.2	March 2014	What efficacy/effectiveness information should be presented in Section 17.1 (Important Baseline Efficacy/Effectiveness Information) of the PBRER?	<p>In addition to the guidance provided in Section 3.17.1 of the Guideline, the MAH may wish to consider the following points when presenting efficacy/effectiveness information in Section 17.1 of the PBRER.</p> <p>The MAH should present any efficacy/effectiveness information on approved indications that is relevant and supports the characterisation 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.</p> <p>The following are examples of points to consider for information that might be included in Section 17.1 of the PBRER:</p> <p>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).</p> <p>Evidence including (but not limited to) clinical trial data, systematic reviews, meta-analyses, clinical pharmacology, relevant outcome studies.</p> <p>Information described in Appendix E in the Guideline (Examples of Possible Sources of Information that May Be Used in the Preparation of the PBRER), the MAH should also consider the following:</p>

#	Date of Approval	Questions	Answers
			<p>Evidence that the benefits are applicable to subpopulations, for example, paediatric, elderly, pregnant, vulnerable populations.</p> <p>Information about multiple efficacy endpoints, where they support efficacy/effectiveness.</p> <p>Evidence of efficacy/effectiveness from various sources (e.g., placebo-controlled trials, active controlled trials, meta-analyses, observational studies).</p> <p>Trends, patterns, and/or evidence of benefit or lack of benefit in important subgroups.</p>
15.3	March 2014	What new information should be included in Section 17.2 (newly identified information on efficacy/effectiveness) of the PBRER?	<p>In Section 17.2 of the PBRER, the MAH should present information that is data-driven and scientifically-based.</p> <p>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.</p> <p>If new clinically important efficacy/effectiveness information from clinical trials has been included in previous sections of the PBRER, for example, in Sections 7, 9.1, or 13, the MAH should include cross-references to the relevant section(s), because it is not necessary to duplicate information presented elsewhere in the document. It is therefore likely that earlier sections will include new information from a clinical trial setting, and Section 17.2 will focus on new information on efficacy/effectiveness under conditions of actual use.</p> <p>In addition, the MAH should include in Section 17.2 concise information on new indications approved during the reporting interval. The MAH should provide a level of detail sufficient to support the characterisation of benefit in Section 17.3 of the PBRER.</p>
15.4	March 2014	Section 3.17.2 of the Guideline states, "New information about efficacy/effectiveness in uses other than the approved indication(s) should not be included, unless relevant for the	<p>It is not possible to define relevant because this is a matter of judgement. 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 summarise the new information accordingly.</p>

#	Date of Approval	Questions	Answers
		benefit-risk evaluation in the approved indication". Please provide the definition of relevant.	
15.5	March 2014	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 3.18.2 of the Guideline. The particular risks and benefits the MAH should consider as key is a matter of medical judgement.
15.6	March 2014	Are there specific methods for performing a formal quantitative or semi-quantitative assessment of benefit-risk?	It is beyond the scope of the Guideline 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	March 2014	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 Guideline does make provision for the MAH to use regional product information as the reference document. As such, the Guideline 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.