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May 11, 2012

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2012-D-0315: E2C(R2) Periodic Benefit-Risk Evaluation Report

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the International Conference on Harmonisation proposed guideline on *E2C(R2) Periodic Benefit-Risk Evaluation Report*.

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS:

A. Indication Specific Benefit/Risk Evaluation

The guidelines suggest that the benefit-risk profile is specific to an indication and population. Thus, a separate benefit-risk is required for each indication. We request clarification on the type of documents that need to be submitted – is a separate report required for each indication or one single report with separate benefit-risk assessments?

It should be noted that a separate report for each indication represents significant challenges and potentially increased burden for industry to prepare and submit separate reports for each indication.

B. Methodologies for Benefit/Risk Evaluation

Additionally, the only advice on what constitutes a "benefit-risk assessment" in the guidelines is to "provide a clear explanation of the methodology and reasoning used to develop the benefit-risk evaluation." For a guideline purporting to provide the structure for a report on benefit-risk assessment there is a noticeable lack of discussion regarding the methods of benefit-risk assessment. We request further clarification and discussion of benefit/risk methodologies in the context of this guidance.

We believe that methodology can change based on standard of care, indication, and jurisdiction. In regard to jurisdiction, should the detail of the PBRER also be dependent on the approval status in a given region/country? It seems that writing the same benefit-risk assessment for a product recently marketed in one region would be inappropriate for a region where it is not yet approved.

It is unclear how a MAH/sponsor should prepare a benefit-risk assessment common to all ICH regions when the benefits may vary by region as a function of the indications/uses approved by that region. The benefit-risk varies for population corresponding with each approved indication. To this end, should the sponsor include information on all indications approved regardless, or only those approved in all ICH regions, etc.? We ask that this be identified in the E2C guidance.

Furthermore, what may be considered "off-label" in one region could be on-label by another region, steps needed to take for risk-minimization activities could vary by region, affecting the conclusions and recommendations in the benefit-risk assessment.

CONCLUSION:

BIO appreciates this opportunity to comment on "*E2C(R2) Periodic Benefit-Risk Evaluation Report*." Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
1. Introduction		
1st Paragraph, 2nd Sentence	"Regulators from EU, Japan, and the US believe that the PBRER may be used to meet prevailing national and regional requirements for periodic safety and/or benefit-risk reports for approved medicinal products." This suggests that the PBRER may replace the FDA Periodic (Q3 months for first 3 years post-approval).	Please clarify how the FDA will treat the PBRER relative to the FDA's current periodic reporting requirements.
3rd Paragraph	"…included in a glossary (Appendix A)…" Appendix C explanatory terms are also demarcated with "*", and this should be included here.	Please edit statement to read: "…included in ~~**a glossary**~~ **glossaries** (Appendi~~x~~**ces** A **and C**)…"
1.1 Background		
1st Paragraph, 4th Sentence	"In clinical practice, monitoring is less intensive … and **events too rare to occur in clinical trials** may be observed…" It's not that events are too rare to occur in clinical trials, but that the time on-study might be inadequate to observe a rare event.	Please edit statement to read: "In clinical practice, monitoring is less intensive … and **rare events** ~~**too rare to occur in clinical trials**~~ may be observed…"
1st Paragraph, 5th Sentence	"… – promptly, as important findings **occur –** and periodically, to allow an overall assessment of the accumulating data." Remove the second hyphen, and replace with a comma to continue the thought, as	Please edit statement to read: "… – promptly, as important findings occur**,** ~~–~~and periodically, to allow an overall assessment of the accumulating data."

	continuing analysis can be reported both promptly and periodically.	
2nd Paragraph, 2nd Sentence	"At that time, the focus of the Periodic Safety Update Report (PSUR) was on relevant new safety information in the context of patient exposure, to determine if changes were needed to the product information in order to optimise the use of the product." Product information (PI) is referred to by various names in regions and is also used in various sections throughout the document.	Suggest adding a definition to the glossary and include examples of PIs (*e.g.*, EU SmPC, US PI).
2nd Paragraph, 2nd Sentence	"…product information in order to optimize **the use** of the product." The PSUR is not only for optimal use of the product, but to monitor safe use.	Recommend stating that the PSUR is also to monitor safe use. "…product information in order to optimize the **continued safe** use of the product."
4th Paragraph, 2nd Sentence	"With recognition that the assessment of the risk of a medicinal product is most meaningful when considered in light of its benefits, the proposed report would provide greater emphasis on benefit than the PSUR, particularly when risk estimates change **importantly**." Does the use of the word "importantly" actually mean "significantly" as used in the following paragraph?	Please clarify the meaning of "importantly."
5th Paragraph, 2nd Sentence	"Thus, the level of detail provided in certain sections of the PBRER (e.g., evaluation of safety and efficacy data, evaluation of safety signals,* and benefit-risk evaluation) should be proportional to the medicinal product's	Suggest clarification in this section and suggest adding more clarification in other sections as well, particularly in the risk sections. This is mentioned in section 2.1, but recommend adding to this section as this is a key concept. Also suggest adding to section 2.8.2 as an introductory

	known or emerging important risks and to evidence of emerging important benefits." Should the evaluation be considered by approved indications? Are the risks evaluated by indication? There is some indication of this in Section 1.2; however, it is not clear throughout the document.	paragraph.
7th Paragraph	"The PBRER has been developed in such a way that the content of particular sections of the report could be identical to that of corresponding sections of other regulatory documents, specifically the safety specification described in the ICH guideline E2E and the DSUR described in ICH guideline E2F. Thus, the content of these sections of the PBRER is envisioned to be suitable for use in the other reports. This "modular approach*" would allow sections or modules to be submitted at different times to multiple authorities, across separate documents (i.e., the PBRER, DSUR, and safety specification). Only modules that include new information would need to be updated when submitting the PBRER. This approach is expected to improve efficiency for marketing authorization holders (MAHs) and regulatory authorities in their preparation and review of the these documents, respectively." It is not clear from the description and in section 1.4 as to whether the PBRER is a replacement of the PSUR, or a component, and if a component, which components should be used, etc.	It should be specifically stated early on that the PBRER is a replacement document, and recommend a transition plan between types of documents for submission to HAs (a lesson learned from the DSUR where HAs did not seem uniform in their adoption of the new report). The modular approach that is often cited in the ICH E2C as a resourcing sparing approach does not recognize that the format is largely consistent wit the existing PSUR format, which is very resource intensive document to produce. Other aspects of the Document should be cited that are genuinely new and resource sparing.

1.2 Objectives		
1st Paragraph, 1st Sentence	"The main objective of a PBRER is to present a comprehensive and critical analysis of new or emerging information on the risks of the medicinal product, and, where pertinent, on its benefit in approved indications, to enable an appraisal of the product's overall benefit-risk profile." Risk may also be different by indication and patient population.	Since the risk may be different by indication as well, which is mentioned in section 2.1, suggest adding to this section as this is a key concept.
2nd Paragraph, 1st Sentence	"A PBRER should be concise and provide sufficient information…" Some PSURs now approach 11,000 pages, and we continue to get requests for more information from health authorities for those PSURs, so this statement seems contradictory.	We request clarification and guidance on how we can move away from the lengthiness of current PSURs to produce a more concise PBRER.
1.3 Scope of the PBRER		
1st Paragraph, 1st Sentence	"The main focus of each PBRER is the evaluation of relevant new safety information from the available data sources, placed within the context of any pertinent efficacy/effectiveness information that may have become available since **the International Birth Date (IBD), the date of the first marketing approval in any country in the world, or the Development International Birth Date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country.**" It is not clear which date should be the trigger for the PBRER: the information since the	Please clarify which date should be used to determine the reporting period for the PBRER: the information since the IBD, the date of approval, the DIBD, or some other date.

	IBD, the date of approval, or the DIBD.	
1st Paragraph, 3rd & 4th Sentences	"Because clinical development of a drug frequently continues following marketing approval, relevant information from post-marketing studies or clinical trials in unapproved indications or populations should also be included in the PBRER. Similarly, as knowledge of the safety of a medicinal product may be derived from evaluation of data associated with uses other than the approved indication(s), such knowledge would be reflected in the risk evaluation, where relevant and appropriate." We agree that unapproved indications / populations should be included, but they should have their own section within. There doesn't appear to be clarity on how to differentiate in the risk assessment sections.	Recommend adding information that is mentioned in section 2.1, to this section (1.3) and mentioning again within the format sections (2.8).
2. General Principles		
2.1 Single PBRER for an Active Substance		
1st Paragraph, 3rd & 4th Sentences	"In exceptional cases, **submission of separate PBRERs might be appropriate, for example, an active substance used in two formulations for systemic and topical administration in entirely different indications**. In these cases, the regulatory authorities should be notified and their agreement obtained, preferably at the time of approval." In E2C (R1) for one report for one active substance, it mentioned "Cross-referencing all relevant PSURs is considered important." In subsequent sections 2.2 and 2.3 it does	If it is important to cross-reference in this case, the guideline should specify as such.

	mention the importance to cross reference.	
2.2 PBRERs for Fixed Dose Combination Product		
General Comment for the Section	We request further clarification and examples on this section.	
2.3 Products Manufactured and /or Marketed by More than One Company		
1st Paragraph	"Each MAH is responsible for submitting PBRERs for its own products."	Guideline should clarify whether co-marketers of a product can submit a single PBRER even if the responsibility falls on each MAH is responsible for the submission. For instance, can a sponsor cross-reference the PBRER submitted by a co-marketer for a product, to avoid redundancies.
2.4 Reference Information		
General Comment for this Section	The guideline recommends that a Core Data Sheet be included as a reference document for how the benefit-risk may have changed. Since the content and format of the CDS can vary by MAH, the quality and informativeness of the CDS for the benefit risk evaluation and corresponding conclusions may vary between MAH as a result.	Instead, the PBRER should specify what information specifically is needed as reference information.
1st Paragraph, 1st Sentence	"An objective of a PBRER is to evaluate whether information obtained during the reporting interval is in accord with previous knowledge on the product's benefit and risk, and to indicate whether changes should be made to product information." Product information is sometimes referred to as prescribing or physician information.	Describe "product information" as a parenthetical and add to glossary, so as to avoid confusion.
2nd Paragraph	"It is a common practice for MAHs to prepare their own 'Company Core Data Sheet*'	Suggest including this information in this section as well. Should also include labeledness/expectedness and

	(CCDS), which covers material relating to safety, indications, dosing, pharmacology, and other information concerning the medicinal product. The core safety information contained within the CCDS is referred to as the 'Company Core Safety Information*' (CCSI). The latest CCDS in effect at the end of the reporting interval should be used as the reference for both the benefit and risk sections of the PBRER. The national or regional approved product information, which can differ from the CCDS, continues to be the reference document upon which labeledness/expectedness is based for the purpose of national or regional expedited post-marketing safety reporting." The glossary indicates that the CCSI is the Reference Safety Information.	listedness to the terms defined in the glossary as there can be confusion regarding these terms.
2nd Paragraph, 2nd and 3rd Sentences	"The core safety information contained within the CCDS is referred to as the 'Company Core Safety Information,*' CCSI. The latest CCDS in effect at the end of the reporting interval **should** be used as the reference for both the benefit and risk sections of the PBRER." ICH E2C requests that the CCDS in effect at the end of the reporting period be used as the RSI for the PBRER which contradicts what is in ICH E2F, which recommends the RSI in effect at the start of the reporting period be utilised. ICH E2C (R1) recommends the use of the RSI in effect at the beginning of the reporting period.	For consistency, it is proposed that this recommendation remains the same within this revision of the guidance.

	In E2C (R1) section 1.4.5 it was referred as "a practical option." "Should" is stronger than "a practical option."	Is this required or expected? Clarification is needed.
4th Paragraph, 3rd Sentence	"The MAH **should** provide a copy of the current version of the CCDS(s) referred to in the PBRER as an appendix to the report." In E2C (R1) section 1.4.5 it was referred as "a practical option." "Should" is stronger than "a practical option." Is this expected or required? Isn't CCDS(s) an internal document?	Clarification is needed.
2.7 Periodicity and PBRER Data Lock Point		
2.7.1 International Birth Date and Data Lock Point		
3rd Paragraph	"When clinical development of a medicinal product continues following marketing approval, the starting point of the DSUR reporting interval can be synchronized with the IBD-based cycle, so that both the DSUR and PBRER can be prepared at the same time." There could be substantial resource burdens/bottlenecks if the DSUR and PBRER have to be synchronized to the same reporting timeframe as the authors are typically the same for both reports.	We request that timeframes not be synchronized for DSUR and PBRER, to allow sufficient time for the authors to draft both reports.
2.7.3.2 Ad hoc ("for cause") PBRERs		
General Comment for Section	For "ad-hoc PBRERs," more specifics should be provided on how the MAH will be notified, and the time-frames for preparing, since the preparation of a PBRER cannot be anticipated in such instances.	

2.7.2 Managing Different Frequencies of PBRER Submission		
4th Paragraph, 2nd Bullet	"For newly approved products, a 6-monthly periodicity applies in many regions, for at least the first 2 years after an NME is approved." Should re-phrase this in terms of the IBD.	Add language stating that the periods are based on the IBD, such that the PBRER for marketed products would cover the 6-month period from IBD. Please edit statement to read: "For newly approved products, a 6-monthly periodicity applies in many regions**, with the period start based on the IBD,** for at least the first 2 years after an NME is approved."
2.7.3 PBRERs When Periodicity Differs Across Regions		
1st Paragraph	GVP Module VII does not indicate that the Bridging Report (BR) or Addendum Report (AR) will be eliminated, will there be alignment later? If the EU requires the submission of BR, this can cause inconsistency between regions and will increase unnecessary workload for MAHs.	Keep the option of using PSUR Summary Bridging Report and Addendum Report in place. Removal of the option will put extra burden on the MAHs to prepare simultaneously PSURs that cover different reporting periods for multiple regions/countries.
2.7.3.1 PBRERs with Data Lock Points Based on the International Birth Date		
Entire section	This is somewhat nonsensical. If the documents all have the same data lock point (DLP), wouldn't it be best to create a document that covers the largest reporting interval and leave it at that? Otherwise it becomes significantly confusing to keep track of which PBRER is which.	Suggest again to keep the use of Summary Bridging Report to avoid preparing PSUR with identical DLP with different reporting periods
2.7.3.2 Ad hoc ("for cause") PBRERs		
1st Paragraph, 1st Sentence	"Ad hoc ("for cause") PBRERs, i.e., reports outside the specified reporting requirements, are required by some regulatory authorities, generally when there are new risks, when risks have changed, when	Suggest replacing "required" with "requested."

	efficacy/effectiveness has changed, or when there are changes to the benefit-risk profile of a medicinal product." These are requests, not regulatory requirements.	
2nd Paragraph, 2nd Sentence	"The overall benefit-risk evaluation and conclusion sections from the most recently submitted PBRER will need to be carefully reviewed and may require revision **(Scenario D in Figure 1)**." Figure states "Region," not "Scenario."	Please edit statement to read: "…may require revision (~~Scenario~~ **Region** D in Figure 1)."
Figure 1	"Region C: longer" This is not precise. This should be changed to 36 months, since the cumulative data are deemed identical for Regions A, B, and C.	Please edit statement to read: "Region C: ~~longer~~**36 months**"
2.7.4 Time Interval between Data Lock Point and the Submission		
1st Bullet	"PBRERs covering intervals of 6 or 12 months: within 70 calendar days" Section 2.7.2 states that "more frequent PBRERs may continue to be required in other regions." This needs to be accounted for.	Please edit statement to read: "PBRERs covering intervals of 6 or 12 months **(or shorter intervals)**: within 70 calendar days"
2.8 Format and Presentation of PBRER		
2.8.2 Presentation		
Item 6.1	"Reference Information" It is confusing to call this 'reference information' since earlier the Guidance referred to as the whole of the CCDS, but the	Suggest renaming "RSI" or "coding dictionary used for analyses of ARs" to more accurately reflect the content of the section.

	tabulation as described in section 3.6.1 specifies version(s) of coding dictionary used for analyses of adverse reactions.	
Item 7	"Summaries of Significant Findings from Clinical Trials during the Reporting Period" This differs from Section 3.7.	Please edit statement to read: "Summaries of Significant **Safety** Findings from Clinical Trials during the Reporting Period"
Item 16.5	"Effectiveness of Risk Minimisation (**if applicable**)" Can remove "if applicable," as instructions specify that if this section does not apply, this should be stated.	Please edit statement to read: "16.5 Effectiveness of Risk Minimisation ~~**(if applicable)**~~"
3. GUIDANCE ON CONTENTS OF THE PBRER		
1st Paragraph, 1st Sentence	"All sections should be completed; **when no information is available**, this should be stated." As an example, it's possible that data may be available for PBRER Section 16.5 Effectiveness of Risk Minimization, but the data are preliminary. The section also has "if applicable" attached to it. Stating that information is not available or is not applicable would cover most situations when data might be preliminary.	Please edit statement to read: "…when no information is **available or is not applicable**"
3.3 Actions Taken in the Reporting Interval for Safety Reasons		
"Actions related to marketed drugs" Sub-bullet #4	"new post-marketing study requirement(s) imposed by regulators."	Recommend limit this to Post market **safety** studies.

3.4 Changes to Reference Safety Information		
2nd Paragraph	"The MAH should also provide, in a regional appendix, information on any final, ongoing, or proposed changes to the national or local authorised product information based on the most recent version of the CCSI." Changes to the PI may not be based on the CCSI, but rather are regional requests and therefore are not aligned with the CCSI.	Requests from regional health authorities that are not added to the CCSI should also be included.
3.5 Estimated Exposure and Use Patterns		
3.5.1 Cumulative Subject Exposure in Clinical Trials		
1st Paragraph	"Section 5.1 of the PBRER should include the following information, if applicable…" In line with the intent to modularise the PSUR and DSUR as proposed by Appendix D i.e. re-use data for both documents, we propose that it is further clarified that the scope of Cumulative Clinical Trial Exposure and Cumulative SAEs is focused on MAH's trials that are interventional. This is in alignment with section 3.5.2 "Cumulative and interval patient exposure from marketing experience" and section 3.6.3 "Cumulative and interval summary tabulations from post-marketing data sources" which identifies non-interventional studies within scope. Of note section 3.7 makes specific reference to sponsored interventional trials.	Proposed Change in Text: "This section of the PBRER should contain the following information on the patients studied in interventional clinical trials sponsored by the MAH."
4th Bullet	"If clinical trials have been or are being performed in special populations **(e.g., pregnant women; patients with renal, hepatic, or cardiac impairment; or patients**	Add additional populations that are later called out in other document sections.

	with relevant genetic polymorphisms), exposure data should be provided, as appropriate." Include the elderly and paediatric populations here, as they are called out in other sections.	Please edit statement to read: "If clinical trials have been or are being performed in special populations (e.g., pregnant women; **the elderly; paediatric populations;** patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided, as appropriate."
3.5.2 Cumulative and Interval Patient Exposure from Marketing Experience		
1st Paragraph	To present the exposure data from post market setting by demographic and dose is impractical.	Remove or limit this to registries or other controlled distribution situations.
1st Paragraph, 2nd Sentence	"Although the difficulty of obtaining and validating exposure data is recognised, the estimated number of patients exposed should be provided when possible, along with the method(s) used to determine the estimate." Exposure data by dose and demographics is usually extrapolated from patterns observed in large healthcare databases. The generalizability of this information to the general population of the marketplace is debatable.	The document should propose how to generalize this information to the general population of the marketplace.
1st Paragraph, 3rd Sentence	"A justification should be provided if an estimate of the number of patients exposed is **impossible** to obtain." Suggest different word than "impossible." Perhaps "unavailable."	Please edit statement to read: "A justification should be provided if an estimate of the number of patients exposed is ~~**impossible to obtain**~~ **unavailable**."
Item 2, 3rd Sentence	"Populations to be considered for discussion include, but **might not be limited to**:"	Suggest strengthening as follows:

	The language in this statement is weak.	"Populations to be considered for discussion include, but ~~might not be limited to~~ **are not limited to**:"
Item 2, 8th Bullet	"Patients of different racial and/or ethnic origins." Consider substituting "specific" for "different."	Please edit statement to read: "~~Patients~~ **Populations** with ~~different~~ **specific** racial and/or ethnic origins."
3.6 Data in Summary Tabulations		
3.6.2 Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials		
1st Paragraph, 1st Sentence	"Sections 6.1-6.3 of the PBRER should present cumulative summary tabulations of SAEs from clinical trials and post-marketing sources that have been reported to the MAH since the DIBD." Please refer to issue stated in Section 3.5.1, First Paragraph.	Proposed Change to Text: "Section 6.2 of the PBRER should provide background for the appendix that provides a cumulative summary tabulation of SAEs reported in the MAH's ***interventional*** clinical trials."
2nd Bullet	"**When the Medical Dictionary for Regulatory Activities (MedDRA)** terminology is used for coding the adverse event/reaction terms, the Preferred Term level and SOC should be presented in the summary tabulations." The version of MedDRA should be specified. Any key safety results that change due to using different MedDRA versions from one PBRER to the next should be detailed.	We recommend adding language specifying that the version should be specified.
4th Bullet	"Certain adverse events in clinical trials can be excluded from the clinical trials summary tabulations, but such exclusions should be explained in the report. For example, adverse	Please elaborate further what exceptional situations may look like.

	events that have been defined in the protocol as "exempt" from special collection and entry into the safety database because they are anticipated in the patient population, and those that represent study endpoints, can be excluded (e.g., deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials)." Clarification needed in the case of such exclusion being done differently in different clinical studies under the same indication. It would be difficult to note this distinction when the same AE not being included/excluded across different studies.	
3.7 Summaries of Significant Safety Findings from Clinical Trials during the Reporting Period		
3.7.1 Completed Clinical Trials		
General Comment for Section		A definition of a "completed clinical trial" should be provided as this can vary by region or by sponsor. Is it a trial for which a CSR has been submitted, last patient follow up completed, etc.?
3rd Sentence	"It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety **signals**."	Propose to replace signals with risks to read as: It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety ~~**signals**~~ **risks**.
3.7.2 Ongoing Clinical Trials		
2nd Sentence	"It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety **signals**."	Propose to replace signals with risks to read as: It could include information that supports or refutes

		previously identified safety concerns, as well as evidence of new safety ~~signals~~ **risks**.
3.7.3 Long-Term Follow-up		
Entire Paragraph	"Where applicable, this section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly **advanced therapy products.**"	Provide the examples of advanced therapies similar to what exists in ICH E2F, otherwise it can be interpreted differently by readers.
3.7.5 New Safety Data Related to Fixed Combination Therapies		
Entire Section	It is unclear what is meant by multi drug regimen, for example most of oncology products are used in combination with other biologicals or chemotherapies, should the MAH present all the new safety data from such combinations. Does multi drug regimen refer to drugs that all are marketed or under development by a single sponsor or different sponsors	Please provide more clarification on the scope of this section.
3.8 Findings from Non-Interventional Studies		
2nd Paragraph, 2nd Sentence	"Progress or final study reports generated during the reporting period for Post-authorisation safety studies (PASS) should also be included as a regional appendix to the report." This is not previously covered in E2C (R1). Clarification is needed whether final study reports are part of the requirement or expectation.	Please clarify whether final study reports are part of the requirement or expectation. Does inclusion refer to a summary or a copy of the entire study report?

3.9 Information from Other Clinical Trials and Sources		
1st Paragraph	"…that is accessible by the MAH with reasonable and appropriate effort." This requirement seems open to interpretation and could encompass nearly all information considering the search capabilities of online tools.	Please clarify what information is considered accessible by the MAH. For instance, is the company expected to search for safety information in the language of each country where it is marketed, etc.?
3.11 Literature		
1st Paragraph, 1st Sentence	"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." Given that unpublished manuscripts are draft documents until accepted for publication we would propose that the need to include a summary of new and significant safety findings from an unpublished manuscript be limited to those that have been accepted for publication but not yet published.	Proposed Change to Text: "This section should summarise new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts, ***where the manuscript has been accepted for publication***, relevant to the approved medicinal product that the MAH became aware of during the reporting interval."
3.13 Lack of Efficacy in Controlled Clinical Trials		
General Comment for Section	If a test drug is compared to an established therapy in a non-inferiority trial, and fails to meet its endpoint, we would assume that this trial has shown "lack of efficacy". In other situations, there is not adequate guidance to decide whether or not to include a trial in this section:	The criteria for inclusion of a trial in this section needs to be precisely defined.

	- If a test drug is compared to an established therapy in a superiority design and fails to meet its endpoint, we would assert that no conclusion can be drawn regarding "lack of efficacy", because it is possible that the two treatments are equivalent in efficacy. Is the MAH expected to incorporate explicit statistical tests for inferiority into such trial designs in order to assess inclusion in this PSUR section? If so, what transition rules would apply to this expectation? - If a test drug is compared to an established therapy and shows an increased rate of "lack of efficacy" adverse events versus control, but overall still meets, say, a superiority endpoint, would this trial qualify for inclusion? - If a trial drug showed inferiority for a surrogate marker endpoint but equivalence (or superiority) for an outcome endpoint, is this a trial showing lack of efficacy?	
1st Paragraph	"Data from clinical trials indicating lack of efficacy, or lack of efficacy relative to **established** therapy(ies), for products intended to treat or prevent serious or life-threatening illnesses (e.g., excess cardiovascular adverse events in a trial of a new anti-platelet drug for acute coronary syndromes) could reflect a significant risk to the treated population and should be summarised in this section. When relevant to the benefit-risk evaluation, clinical trials demonstrating lack of efficacy for products not intended for treatment of life-threatening diseases in the approved indications should	If "established" is the same as "approved," then suggest changing to "approved." If not, then more clarity is needed.

	also be summarised." Is "**established** therapy(ies)" the same as "**approved** therapy(ies)"?	
1st Paragraph, 1st Sentence	It is not clear whether "lack of efficacy relative to established therapy(ies)" includes studies that demonstrate similar efficacy and/or non-inferiority, or whether this only refers to studies demonstrating inferior efficacy.	Please clarify.
3.15 Overview of Signals: New, Ongoing, or Closed		
General Comment for Section	Appendix C table has "outcome if closed" column.	Suggest mentioning "outcome" in this section.
2nd Paragraph	"**A brief description** of the method of signal detection* used, as well as the sources screened for signals, should be provided." This seems to be an excessive request. Signal detection activities are an internal process, and this report should not be expected to be a mechanism of internal process description.	Recommend removing or otherwise make clear what "a brief description" means (type and extent of specificity expected).
3.17 Benefit Evaluation		
3.17.1 Important Baseline Efficacy/Effectiveness Information		
General Comment for Section	Suggest mentioning here the sections of the CCDS that describe risks vs. those that describe benefit.	
3.17.3 Characteristics of Benefits		
General Comment for Section	Does the sources of information include meta-analyses, registry data, or limited only to interventional clinical trials?	

3.18 Integrated Benefit-Risk Analysis for Approved Indications		
1st Paragraph, 1st Sentence	"The purpose of this section is to provide an overall appraisal of the benefit and risk of the medicinal product as used in clinical practice."	Clinical practices may vary from one region to another, both as a function of variations in the approved prescribing information (e.g., different indications) as well as variations in medical practice. Consequently, the guidance is unclear in how a sponsor should prepare a benefit-risk evaluation that is applicable to all ICH regions. For instance, a drug is approved ex-US but not in the US, so the benefit risk as a function of medical need and comparative efficacy for a new drug of this class could be considered different in part on the availability of alternative therapies. For sake of clarity, some types of uncertainties should be mentioned. E.g., methodologic uncertainties used to calculate the impact of drop-outs on key effects versus uncertainty due to sample size or uncertainty due to homogeneity of the population evaluated.
3.18.2 Benefit-Risk Analysis Evaluation		
3rd Bullet	"… (e.g., for **therapies for arthritis:** reduction of symptoms and inhibition of radiographic progression of joint damage)." Specify type of arthritis, as the indications are not necessarily typical of other arthritis diseases.	Please edit statement to read: "… (e.g., for therapies for **rheumatoid** arthritis: reduction of symptoms and inhibition of radiographic progression of joint damage)."
3.19 Conclusions and Actions		
Entire Section	It may not be feasible to present preliminary proposals to optimize or further evaluate the BR as within the PBRER preparation timeline.	Suggest including a possibility of presenting the proposals in a subsequent PBRER.

4. APPENDICES TO THIS GUIDELINE		
APPENDIX A – Glossary		
General Comment for Section	Consider adding definitions to glossary for: Product Information, Reference Information, IBD, DIBD, listedness, expectedness, labeledness.	
1st Paragraph, 1st Sentence	"Whenever possible the **Working Group has used terms in use in other ICH Guidelines**, or …" Re-phrase, repetitious wording with "use" in "…has used terms in use…"	Please edit statement to read: "Whenever possible the Working Group has used terms ~~**in use**~~ **present** in other ICH Guidelines…"
Item 3	"Company Core Safety Information (CCSI)" "All relevant safety information contained in the CCDS prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the **reference information** by which listed and unlisted are determined for the purposes of periodic reporting for marketed products, but not by which expected ad unexpected are determined for expedited reporting." "Reference information" also refers to the potential efficacy sections of the CCDS.	Suggest making the following change: "All relevant safety information contained in the CCDS prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the ~~**reference information**~~ **reference safety information** by which listed and unlisted are determined for the purposes of periodic reporting for marketed products, but not by which expected ad unexpected are determined for expedited reporting."
Item 21	**"Spontaneous report** or spontaneous notification" "An unsolicited communication to a company, regulatory authority, or other organization that describes an ADR in a patient given one or more medicinal products	Suggest modifying the verbiage to align with section 3.6.3.

	and which does not derive from a study or any organized data collection scheme." While conservatively considered an ADR for reporting purposes (see section 3.6.3), this definition is much more definitive.	
APPENDIX B – Examples of Summary Tabulations		
Table 4	"40" under Dose (mg/day) Typographical error: the "≥" symbol is missing from the example. This is also the case with Table 5.	Please edit statement to read: "≥40" under Dose (mg/day)"
Table 4, Footnote	"Table 4 includes cumulative data obtained from month/day/year through month/day/year, where available." Cumulative should include all data in the source through month/day/year, not from.	Please edit statement to read: "Table 4 includes cumulative data obtained ~~**from**~~ **through** month/day/year, where available."
APPENDIX D – List of PBRER Sections, Identified as Providing Cumulative or Interval Information, and Ability to Share Modules with Other Regulatory Documents		
Item 7	"Summaries of Significant Findings from Clinical Trials during the Reporting Period" Missing "Safety" here for the type of findings.	Please edit statement to read: "Summaries of Significant **Safety** Findings from Clinical Trials during the Reporting Period"
Other: Regional Appendix		
Lines 263-264, 812, 1003	The "regional appendix" is repeatedly referred to but then an example is not provided in the list of E2C appendices. So the regional expectation in content and format is unclear. As such, health authorities in ICH-abiding regions should publish template appendices prior to the ICH E2C guidance being finalized, so that MAHs can be assured that they will meet regional requirements at the time the E2C guidance is implemented.	