

The challenges of producing periodic benefit–risk evaluation reports

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Keywords

Periodic benefit–risk evaluation report (PBRER); Periodic safety update report (PSUR); Medicines and Healthcare products Regulatory Agency (MHRA); Assessor; Compliance; Regulatory documents; EU.

Abstract

This article discusses the challenges of producing a periodic benefit–risk evaluation report (PBRER) from a writing perspective. It explains that by taking into consideration the most common pitfalls encountered by regulatory assessors, companies can improve the quality of their PBRERs and reduce regulatory requests in the future.

Periodic benefit–risk evaluation reports (PBRERs) were introduced in the EU in 2012 as part of the pharmacovigilance legislation Regulation (EU) No 1235/2010 and Directive 2010/84/EU. The introduction of PBRERs answered the call for increased transparency and a clearer focus on the benefit–risk profile of medicines compared with the previously produced Periodic Safety Update Report (PSUR). Since their inception, the guidance has been clarified and PBRERs have evolved through changes introduced at the International Council for Harmonisation (ICH) level in ICH E2C(R2),¹ which have been adopted in the European Medicines Agency and Heads of Medicines Agencies' guideline on good pharmacovigilance practices (GVP) module VII² and its explanatory note.³ Although the PBRER is termed the PSUR in the EU, this article will use the ICH nomenclature of PBRER for clarity.

PBRERs are complex documents. Describing the overall benefit–risk of a medicine in the context of clinical trials and real-world evidence, while also weighing the relative merits of different sources of data in a way that is transparent and easily translatable to modular documents, such as the development safety update report (DSUR) and risk management plan (RMP), is not an easy task. Add to this the need for compliance with the legislation and guidance, consistency across the suite of pharmacovigilance (PV) documents, the need for cross-functional teams to work together within one or more global companies, and strict deadlines, and it is clear that the challenges can seem insurmountable. Although the quality of PBRERs submitted to regulatory authorities has improved in recent years,⁴ major findings in the PBRER still accounted for almost 5% of all the major findings in PV inspections by the UK's Medicines and Healthcare products

Regulatory Agency (MHRA) in 2017.⁴ These findings trigger questions and requests for information from the marketing authorisation holder (MAH). Much of this time and effort could be alleviated if MAHs took into account what an assessor is looking for and prepared PBRERs in a way that not only complied with the guidance but also made assessment of them much simpler and easier.

Regulatory authority assessors are looking for a rational description of the benefit–risk of the medicine, followed by a presentation of the evidence that led the MAH to come to the conclusions that are presented in the PBRER. If the data are not presented or there are discrepancies in the data or its evaluation, an assessor is likely to ask the MAH for more information or for new analyses. This is a common occurrence. In the first four months of 2018, 18 of the 38 recommendations on signals that the Pharmacovigilance Risk Assessment Committee (PRAC) made were for more information, comment or actions (Table 1).

Responding to additional information requests or queries takes time and effort. It is the responsibility of the Qualified Person for Pharmacovigilance (QPPV) to ensure the quality of the PBRER and this includes provision of sufficient information or evaluation to perform a thorough assessment of the safety information. By taking into consideration what an assessor requires and providing the correct data in the correct presentation, the number of queries and requests for information can be vastly reduced and the process of producing and evaluating a PBRER becomes far less fraught for both the MAH and the regulatory authority.

The PBRER must include a comprehensive, concise, critical analysis of new or emerging information on the benefit–risk of a medicine in its approved indications to enable an appraisal of overall benefit–risk. To do this, a thorough understanding of the medicine is needed, plus its place in the therapeutic armamentarium and how it is viewed by patients and healthcare providers must be considered. This calls into question the assessment of 'risks' posed by the medicine and how they are categorised – the same risk can be viewed differently depending on the context of the therapeutic indication and other available options, and this must be communicated effectively to an assessor through the PBRER.

As with many regulatory documents, the PBRER template is not restrictive. Within the sections, transparency and clarity is paramount, and assessors look for data that not only explain but support the points being made about the benefit–risk balance of the medicine and its impact on patients. PBRERs provide a valuable opportunity to evaluate the available benefit–risk data at defined points in a medicine's lifecycle, and so it is critical that the discussion in the PBRER considers not only the information that has become available during the time period of the PBRER, but also evaluates these data in the context of cumulative information. The PBRER should outline evidence of proactive and documented risk management procedures and processes, and should describe the effectiveness of specific risk minimisation measures. An assessor will look for evidence of all of these aspects.

Table 1: Recommendations from the Pharmacovigilance Risk Assessment Committee January–April 2018.

Month	Recommendation on signal	
	Information requested from marketing authorisation holder	Other action needed/no action
January	5 supplementary information requests	4 no action needed 1 continue routine pharmacovigilance (PV) actions 1 assess/monitor in the next periodic safety update report (PSUR)
February	2 supplementary information requests	1 continue routine PV actions 1 assess/monitor in the next PSUR 1 submit variation 1 no action needed
March	2 supplementary information requests 1 provide comments on the signal	1 assess/monitor in the next PSUR 1 no action needed
April	6 supplementary information requests 1 assess cases of anaphylactic reaction 1 provide comments on the signal	5 assess/monitor in the next PSUR 2 no action needed 1 issue to be addressed in ongoing variation

Source: European Medicines Agency, available at:

http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2018/01/WC500242002.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2018/03/WC500245782.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2018/04/WC500247424.pdf

http://www.ema.europa.eu/docs/en_GB/document_library/PRAC_recommendation_on_signal/2018/02/WC500243854.pdf

Key points to consider

There are several key points that assessors consider when reviewing a PBRER. For any new or changing risk, they assess whether its clinical importance has been considered – the nature of the risk, its seriousness, frequency, and whether it can be prevented or minimised. If there are new data relating to the efficacy or effectiveness of the medicine, what are the implications for the existing indication or posology?

Assessment of evidence

When the evidence is being evaluated, have its strengths, weaknesses and uncertainties been factored into the impact on the benefits and risks? Any implications on the benefit–risk balance must be described and discussed, along with any measures that may be required to evaluate the benefit–risk balance further, and any changes to the product information. Once this has been discussed, the PBRER should state whether existing risk minimisation measures (RMMs) are adequate or if additional risk minimisation measures (aRMMs) are required and, if so, what these would be. If a variation is requested, this should be derived from the information presented in the PBRER, and its scientific justification should be clearly laid out and defended. Any wording changes to the summary of product characteristics (SmPC) and package leaflet should also be proposed.

Signal and risk evaluation

To allow an assessor to navigate the discussion easily, the presentation of information and assessments for each safety issue should be structured so that safety data, signals, risk evaluations, and the integrated benefit–risk analysis are mapped throughout the corresponding PBRER sections. Any cumulative information should also be presented in the appropriate sections (summary tabulations

Requests for additional information normally mean that an assessor does not have enough data to be able to agree with the conclusions given in the PBRER

from clinical trials and post-marketing data should always include cumulative data, and the characterisation of risks in Section 16.4 should present the updated cumulative information about all safety concerns). Safety concerns and ongoing signals should always be monitored in PBRERs. Each signal evaluation should have a conclusion, discussing the evidence for or against a possible causal relationship with the medicine. If the signal is refuted, the PBRER should outline the analyses supporting this conclusion. For each new risk (either identified or potential), assessors will expect a discussion about whether the benefit–risk is affected and whether the RMP needs to be updated. The PBRER should provide sufficient information for an assessor to be able to follow the ‘story’ of the medicine – the background, methods (including data sources and search criteria), results (summary and critical analysis of key data), a conclusion and any resulting actions.

Data in summary tabulations

Summary tables are not intended for signal detection but they can be useful to highlight particular areas of interest to an assessor. The PBRER should comment on these data if there are unusual or striking figures – an explanation should be provided, especially if there are

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unexpected or discrepant changes. Differences in the number of case reports in the PBRER text and the summary tabulation, or counts that do not correlate with previous PBRERs, should be explained, and all of the data should be double-checked for anomalies before being presented to an assessor.

Exposure data

The exposure data should add up; for example, the cumulative total cannot be smaller than the interval total. The pattern of use should also be described, along with any changes in this pattern. For example, if patient exposure within X years is only two times more than the interval exposure, this could be caused by changes in the exposure calculation methodology, or by a significant increase in the number of treated patients in the interval period. An assessor will expect the MAH to take a view on this and to explain how the conclusion has been drawn.

Signal detection

An assessor has the opportunity to disagree with the assessment of a signal as closed or ongoing, etc. Therefore, a full justification should be given for the decision in the PBRER. If there is an increase in the number of serious adverse events compared with placebo, this should be evaluated as a possible signal, and if signals are detected, they should also be evaluated.

Additional information requested

Requests for additional information normally mean that an assessor does not have enough data to be able to agree with the conclusions given in the PBRER. By considering this earlier in the process, many additional information requests can be prevented.

Common additional requests include:

- “The MAH is requested to provide a cumulative analysis of reports of XXX”
- “The MAH should provide detailed information on the cases of XXX”
- “The MAH should provide the narrative of the nine cumulative spontaneous reports”
- “Stratification by indication would be useful to understand the information provided”
- “The MAH should provide an analysis explaining the high number of medication errors”
- “The MAH should provide details regarding the unlisted clinical trial cases”
- “MAH should clarify which safety concerns led to the study discontinuation”
- “The MAH should provide further information on the safety-related studies”.

Missing information

The PBRER must provide a comprehensive justification for the evaluation of the benefit–risk of the medicine and so an assessor will request information that he or she considers to be missing. For example, evidence that a search of literature has been carried out; discussion of articles that contain important safety information regarding the use of the medicine but were not included in the PBRER; or a request for a more considered conclusion if the information provided did not allow an assessor to decide if the literature reviewed did or did not affect the benefit–risk balance. Other discrepancies that can trigger assessor requests are a lack of explanation for apparent changes in the safety information (for example, an apparent increase in number of fatal cases, off-label use, medication error, overdose), a lack of information in a whole population subset (for example, no discussion at all of paediatric reports), or a lack of information or analysis of certain indications. A PBRER may also be accepted with a request for further analyses or evaluations in a subsequent PBRER. Any previous requests from assessors should be checked and completed as requested, otherwise a second request will then be made as this also constitutes missing information.

Other common pitfalls

Assessors come across common errors in PBRERs. Some of these can be avoided by considering potential mistakes when preparing the document, including:

- Lack of information provided on closed/refuted/ongoing signals. Sometimes it is helpful to include case narratives and the causality assessment based on these narratives.
- Specific topics to be monitored in the PBRER – if there are any specific topics to be monitored, either as a RMM or an aRMM from a previous PBRER, or following an RMP update, it is important that these are included and discussed in the PBRER. These should be discussed in Section 15 if they are not considered to be a signal, and in Section 16.2 if they are considered to be a signal. The MAH may propose discontinuing monitoring if the analyses justify it, but this must be clearly explained to an assessor.
- Lack of explanation for notable rises in adverse drug reactions – an explanation and analysis should be included.
- Signal assessment – a signal assessment should be made on the basis of a review of the cumulative data available, taking into account the evidence, time to onset, and rechallenge and dechallenge. Cases may be inappropriately dismissed (for example, because of a lack of information or because of concomitant medicines) and any methodology used should be clearly described so that an assessor can evaluate this as part of an assessment of the conclusion made by the MAH.
- Lack of information on pregnancy, off-label use, interactions, etc. If the MAH becomes aware of a pattern of off-label use of its product, then a brief discussion should be provided including quantitative information on use and, where possible, a comment on whether such use is supported by clinical guidelines, clinical trial evidence, or by the absence of authorised alternative treatment.
- Post-marketing exposure (cumulative and interval) – the number of patients exposed should be provided, along with the method used to determine the estimate. Any discrepancies, including any from the previous PBRER, should be explained so that an assessor does not need to query them.
- Studies completed during the reporting period – a summary of the main safety findings and the MAH’s comments should be provided.

Requests for additional information normally mean that an assessor does not have enough data to be able to agree with the conclusions given in the periodic benefit–risk evaluation report. By considering this earlier in the process, many additional information requests can be prevented

Conclusion

The trepidation that some teams feel about preparing PBRERs is understandable. A major step towards getting them right is thinking about them from an assessor's point of view. Some tips to consider are:

- Follow the GVP module and ICH guidance and template
- Consider the quality of the information being presented in the PBRER
- Do your figures add up – have you explained any anomalies?
- Are there any changes in signal patterns and, if so, have they been analysed?

- Provide a rationale for closure of signals
 - Provide details of any analysis done
 - Be proportionate
 - Include a critical assessment of the data
 - Do not be repetitive
 - Make sure that previous assessor requests have been completed.
- Adopting a slightly different mind-set and considering these top tips should make the challenges of writing a PBRER much easier to overcome, and reassure teams new to the PBRER experience. ■

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