Pharmacovigilance

SECTION EDITOR

Tiziana von Bruchhausen, PhD
tiziana.von_bruchhausen@
boehringer-ingelheim.com

Editorial

In the EMWA symposium held in May 2023, Sven Schirp, Global Head of Patient Safety (PS) Writing at Boehringer Ingelheim, gave an overview of the newly introduced requirement of the European public assessment reports risk management plan publication in the EU. For this article, I have asked him to share the experience gathered since then in his group (where I also work) and interviewed him, along with my colleagues Kerstin Prechtel, Principal Safety Writer, and Thomas Rohleder, Document Specialist.

Happy reading!

Tiziana von Bruchhausen,
Chair of EMWA's
Pharmacovigilance Special Interest
Group (PV SIG)
and Principal Safety Writer

Experience with risk management plan publication in European public assessment reports

Tiziana von Bruchhausen
Boehringer Ingelheim
Ingelheim, Germany

doi: 10.56012/tkqm7398

RMP publication in EPARs

Since October 20, 2023, for all centrally authorised products in the EU, the European Medicines Agency (EMA) has been publishing full risk management plans (RMPs) (initial evaluations and post-marketing updates) in European public assessment reports (EPARs). This process aims to further increase transparency of safety information for the public and replaces the publication of the RMP summary for the public (i.e. RMP Part VI).

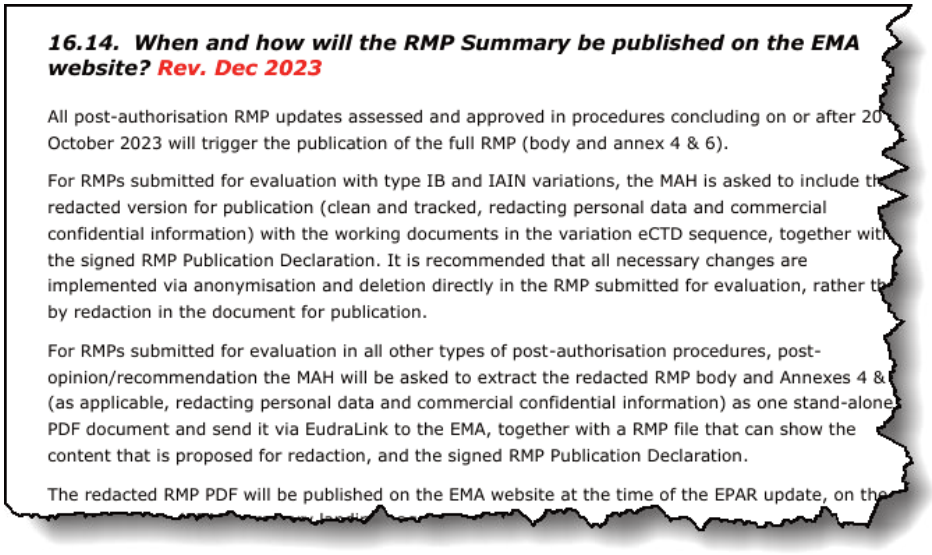
Published RMPs consist of the main body, annex 4 (specific adverse events follow-up questionnaires), and annex 6 (key messages of additional risk minimisation measures) in a single .pdf file. For the sake of publication, RMPs need to be reviewed to identify potential protected personal data (PPD) and commercially confidential information (CCI) for redaction. Marketing authorisation holders (MAH) submit their proposals for redaction of PPD and CCI. All changes are of editorial nature and are implemented in the RMP during the scientific review process preceding Opinion and adoption of the final RMP version. At the time of the EPAR update, the redacted RMP is published on the EMA website on the product's page (EPAR summary landing page). The published redacted RMP is referred to as "EPAR RMP" for the purpose of this article. Figure 1 provides the procedural advice related to RMP publication for products authorised via centralised authorisation procedure (CAP).[1]

How to address the EPAR RMP requirement – an example

The RMP publication process at the Patient Safety (PS) Writing group: An interview with Sven Schirp, Global Head of PS Writing at Boehringer Ingelheim,

Q: How did your group address the new requirement for EPAR RMPs?

Sven Schirp (SS): We had previous experience with third-party requests for RMPs, for which we used to review RMPs *ad hoc* (upon EMA request) and to create manually redacted RMP versions outside of our document management system (DMS). Since the new requirement applies to all initial evaluations and post-marketing updates of RMPs, we considered that a dedicated process covering all, from front-loading of activities up to creating redacted RMPs within the DMS, would increase our efficiency.



16.14. When and how will the RMP Summary be published on the EMA website? Rev. Dec 2023

All post-authorisation RMP updates assessed and approved in procedures concluding on or after 20 October 2023 will trigger the publication of the full RMP (body and annex 4 & 6).

For RMPs submitted for evaluation with type IB and IAIN variations, the MAH is asked to include th redacted version for publication (clean and tracked, redacting personal data and commercial confidential information) with the working documents in the variation eCTD sequence, together wit the signed RMP Publication Declaration. It is recommended that all necessary changes are implemented via anonymisation and deletion directly in the RMP submitted for evaluation, rather th by redaction in the document for publication.

For RMPs submitted for evaluation in all other types of post-authorisation procedures, post-opinion/recommendation the MAH will be asked to extract the redacted RMP body and Annexes 4 & (as applicable, redacting personal data and commercial confidential information) as one stand-alone PDF document and send it via EudraLink to the EMA, together with a RMP file that can show the content that is proposed for redaction, and the signed RMP Publication Declaration.

The redacted RMP PDF will be published on the EMA website at the time of the EPAR update, on th

Figure 1. Procedural advice related to RMP publication for centralised products[1]

Q: What does this process look like?

SS: At Boehringer Ingelheim, the PS Writing group has taken over the responsibility for redaction of RMPs.

- In general, for initial RMPs and RMP updates, the PS Writer front-loads activities related to the EPAR RMP requirement and advises the product team to prevent the inclusion of content that could potentially include PPD or CCI, to reduce redaction efforts at a later point in time. The RMP review should also cover the identification of PPD and CCI. This way, submitted RMPs are ideally already anonymised and there is no need to redact content later.
- At the point in time when the EMA requirement applies, the Global Regulatory Lead (GRL) requests the EPAR RMP. If there has not been a redaction-specific review during RMP preparation (which could be the case for existing RMPs with very tight timelines for the update), the PS Writer coordinates such a review within the provided timelines. Even if there is no need for content redaction, there may be standard items for redaction, e.g. post-marketing exposure by country in module SV (as this is considered CCI).
- Before redactions are applied, a copy of the submitted RMP (here referred to as pre-redacted EPAR RMP) is saved and stored in the DMS. In this pre-redacted EPAR RMP, the PS Writer includes proposals for redactions in red rectangles.
- The document specialist creates an EPAR RMP in the DMS based on the latest approved RMP according to EMA requirements of the EPAR publication. This EPAR RMP consists of main body, annex 4, and annex 6, and includes an adjusted table of contents and sequential page numbering. The redaction proposals from the pre-redacted EPAR RMP are implemented in the EPAR RMP.
- Both versions, the pre-redacted and the redacted EPAR RMP, are reviewed by the document specialist and the PS Writer, e-approved by the European Union Qualified Person for Pharmacovigilance (EU-QPPV), and submitted to EMA by the GRL.

Q: To what extent have the EPAR RMP requirement and the new process affected the workload in your group?

SS: Let me first explain how our group is structured. The safety writers take care of planning, coordination, and content-wise preparation of the pharmacovigilance documents. The technical finalisation and management of the documents in the DMS is done by our document specialists. For each CAP, initial or updated RMP being submitted to EMA, a redacted version needs to be prepared in addition. Thanks to the structure of the PS Writing group, the additional workload has been spread across two functions. Kerstin Prechtel and Thomas Rohleder can tell you more about their experience and perspective.

Content review of RMPs for EPAR publication: Interview with Kerstin Prechtel, Principal Safety Writer at Boehringer Ingelheim

Q: How are PPD and CCI identified in practice?

Kerstin Prechtel (KP): The EMA guidance[2] provides examples of PPD and CCI in RMPs, as well as rules for anonymisation. In general, the RMP is not expected to include either PPD (trial participant/patient level information) or CCI; however, for RMPs submitted before October 2023, redaction might be needed. The PS Writer reviews the RMP according to the guidance and marks any PPD and CCI for redaction. Particularly with regard to CCI, content review by specific functions may be needed, as the RMP might include detailed information on ongoing

clinical trials, unpublished data with an impact on future clinical development, manufacturing, or regulatory strategies. Therefore, the pre-reviewed draft is shared with the RMP authoring team, who has been trained about the EMA requirement by the PS Writing group.

Q: Who decides what should be redacted in case of doubt?

KP: The ultimate responsibility is with the lead PS physician. The PS Writer provides advice based on the guidance and the experience gathered with EMA. For example, once we received extensive proposals for redaction of clinical data from the medical colleagues and a reworded sentence to replace redacted information from the pharmacovigilance colleagues. However, we knew that EMA will not accept extensive blackening and revision of text and that all changes to the RMP should be of editorial nature only. After discussion with the lead PS physician, we made the final decision and communicated it to the team.

Q: Is Patent or Legal involved in the RMP review?

KP: We included Patent review in the first RMP reviews, when the teams needed to gather experience on potential CCI. Based on this experience, most information included in RMPs is either already shared via clinical documents under policy 70 or published. Therefore, the standard process does not require involving Patent or Legal in the review. We usually ask the authoring team if they deem their involvement necessary. In our experience, it does not make sense to routinely involve legal or patent functions in the review of the complete RMP. It makes more sense to ask them specific questions on selected sections or paragraphs, if required.

Technical preparation of EPAR RMPs – interview with Thomas Rohleder, Document Specialist

Q: Do you create an EPAR RMP even if there are no redaction proposals?

Thomas Rohleder (TR): According to our process, I do. The EPAR RMP is an EMA requirement and is submitted for publication regardless of whether it contains content redactions. The minimum extent of redactions concerns the "Confidential" or confidentiality statements in the headers/footers of the document. Since we create the EPAR RMP within our DMS, the confidentiality statements in the published output for submission, as well as selected appendices, are automatically removed. In addition, the table of content and page numbering are adapted to reflect inclusion of annex 4 and annex 6, only. This is the RMP that we submit for publication.

Q: What is the advantage of establishing this process and technical solution for EPAR RMPs versus preparing EPAR RMPs manually?

TR: We could prepare EPAR RMPs manually. However, in view of the high volume of RMP updates our company submits, the new process is more efficient and less error prone. The DMS generates an RMP output ready for publication, i.e. we do not have to spend time in removing the "Confidential" manually from all headers/footers and the appendices not intended for publication, or in adapting the table of content and page numbering.

Q: Would you say that the published output you create in the DMS is of higher quality compared with a manually prepared EPAR RMP?

TR: It is not only a matter of quality. Both solutions are valid and according to our experience, both seem to be accepted by EMA. However, the timelines for submission of EPAR RMPs can be short, and we usually finalise a high number of submission documents. With our process in the DMS, we save time and resources. Nevertheless, to keep flexibility, we can still prepare EPAR RMPs manually.

Q: Can the EPAR RMP be prepared in parallel with the actual RMP?

TR: This is technically not possible. The EPAR RMP is a new version of the latest approved RMP version in the DMS. Therefore, the EPAR RMP can only be created after e-approval and archiving of the submission RMP. We had to provide the EPAR RMP shortly after RMP submission in only a couple of instances. It was challenging, but it worked! Also in this case, having a process in the DMS helped us gain time.

Real-life and lessons learnt

Not only pharmaceutical companies, but also EMA are still learning and gathering experience with the EPAR RMP requirement. These are lessons learnt so far:

- Our DMS published output is well accepted by EMA, but in the past, we observed that also scanned versions of RMPs or RMPs with no bookmarks were published.
- We believe that the best approach is to create new RMPs and RMP updates in an anonymised way and front-load redaction review, to reduce efforts later, when time is tight.
- If in doubt when applying EMA guidance, common sense will help.
- Even though we have a process and a technical solution, we keep flexibility and would prepare an EPAR RMP manually, i.e. with no adapted table of content and page numbering, if needed.
- Our process efficiently addresses the EPAR RMP requirement, independently of the timelines, which may vary according to the regulatory procedure/ variation.
- EMA also seems to be still learning. In a recent procedure, we were asked to provide a redacted version plus a version that highlights the proposed redactions.

Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by their employer or EMWA.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

References

1. European Medicines Agency post-authorisation procedural advice for users of the centralised procedure. 4 October 2024. EMEA-H-19984/03 Rev. 109 [cited 2024 Oct 14]. Available from: European Medicies Agency post-authorisation procedural advice for users of the centralised procedure (europa.eu)
2. Anonymisation of personal data and assessment of commercially confidential information during the preparation and redaction of risk management plans (body and Annexes 4 and 6). 10 April 2024. EMA/153000/2024 Rev. 2 [cited 2024 Oct 14]. Available from: Microsoft Word - Process RMP - Guidance - preparation for publication and post-approval redaction (europa.eu)