



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 April 2026

EMA/518909/2016 Rev 1

Questions & Answers on Periodic Safety Update Report (PSUR) Single-Assessment (PSUSA): Guidance document for assessors

This document, structured in a questions and answers format, aims to provide practical guidance to assessors, Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteurs, alternates, members and European Medicines Agency (EMA) staff involved in the PSUSA procedure, and should be read in conjunction with Guidelines on good pharmacovigilance practices (GVP) Module VII, Explanatory Note to GVP Module VII and PSUSA Assessment Report (AR) Templates.

Please note at the end of the document some definitions have been provided with an aim of having a common understanding of some concepts such as monitor via routine pharmacovigilance, monitor/follow up in the PSUR (following a signal assessment), cumulative review, update of the summary of the safety concerns in the PSUR etc.



Table of contents

1. General principles	4
1.1. Aim of the PSUR/PSUSA and data to be reviewed	4
1.1.1. What is the purpose of a PSUR and its (single) assessment?	4
1.1.2. What should drive the assessment of a PSUSA?.....	4
1.1.3. Significant concerns about the quality of the PSUR data and pharmacovigilance inspections.....	5
1.2. Strength of evidence in the context of the stage in the product lifecycle	5
1.2.1. What is the strength and nature of the evidence that is needed to support regulatory action? Does this differ depending on the stage in a medicinal product's lifecycle?	5
1.3. Link between PSUSA and outcomes of other regulatory procedures	6
1.3.1. Should the PRAC Rapporteur/LMS reflect their ongoing or recently concluded assessments in the PSUR assessment report?.....	6
1.3.2. How to deal with inconsistency or non-compliance with previous regulatory procedure outcomes (e.g. recommendations after a referral procedure)?	7
1.4. Scope of conclusions: impact on products outside the PSUSA.....	7
1.4.1. How should conclusions on a drug-drug interaction (DDI) with the product(s) covered by the PSUSA, which may affect other products, be reflected in the AR?	7
1.4.2. How should conclusions on PSUSAs for fixed-dose combinations (FDCs) and/or mono substances be reflected in the AR and under which circumstances should findings be extrapolated and in which way?	8
1.4.3. How will information about new DDI or extrapolation related to NAPs be communicated to CMDh?	8
2. Specific assessment aspects with related sections of the PSUR AR template	8
2.1. Dealing with inconsistencies of PI	8
2.1.1. Can/should the PSUSAs be used as a tool for harmonisation of the PI?.....	8
2.1.2. Where there is sufficient cumulative evidence regarding a safety issue which needs to be reflected in the PI, is it acceptable to request an updated/new wording across all PIs, even if some of them already have the issue well reflected?.....	9
2.2. Overview of exposure and safety data (section 1.3.4 on data in summary tabulations).....	10
2.2.1 Can the tables of cumulative safety data from clinical trials and post-marketing surveillance, presented by the MAH be used as a tool for signal detection?	10
2.3. Safety concerns:	10
2.3.1. Should the PSUSAs be used as a tool for harmonisation of the safety concerns?	10
2.3.2. Safety concerns with a long latency	11
2.4. Signals and topics under monitoring (PSUR AR template: annex LMS assessment comments on PSUR, section 2.2. on signal evaluation)	12
2.4.1. If a signal is refuted should the assessment as a precautionary principle still request that this be followed up in future PSURs? If yes, based on what evidence should this be requested?.....	12
2.4.2. Topics for monitoring (i.e. beyond the safety concerns proposed by the MAH)	12
2.4.3. How to deal with a discrepancy between number of events presented by the MAH and number of Individual Case Safety Reports (ICSRs) retrieved by the LMS?	13

2.4.4. Monitoring of EudraVigilance by MAHs	13
2.4.5. How to deal with a discrepancy between number of events presented by the MAH in the body text of the PSUR and in summary tabulations or discrepancies in consecutive PSURs?.....	14
2.5. Benefit evaluation (PSUR AR template: Annex PRAC Rapporteur/LMS assessment comments on PSUR, section 3. on benefit evaluation)	14
2.5.1. How to deal with new data/studies on efficacy provided by the MAH considering that the focus of the PSUR assessment is whether there are new risks or whether risks have changed or whether there are changes to the B/R balance of medicinal products?.....	14
2.6. B/R balance (PSUR AR template: annex LMS assessment comments on PSUR, section 4. on benefit-risk balance)	15
2.6.1. How to regard the B/R balance for old established products especially when different indications are authorised in different MSs and how to achieve a common position on the B/R balance when different indications are authorised in different MS and the level of information included in the SmPC may be different as well?	15
2.6.2. Should a conclusion of "B/R balance remains unchanged" be understood as an endorsement by the PRAC of all existing indications?.....	16
2.6.3. Can a PSUR procedure add a new indication to approved medicinal products in a MS?	16
2.7. RfSI within or at next PSUR	16
2.7.1. How to deal with requests for cumulative reviews and how to differentiate between those to be answered within the 30 days and those which are for the next PSUR?.....	16
2.7.2. What to do when an issue cannot be finalised within the PSUSA?.....	17
2.8. PSUR frequency and EURD list (PSUR AR template: section 4/5. on PSUR frequency)..	18
2.8.1. Under which scenarios should the PRAC Rapporteur/LMS consider (or not) to change the PSUR frequency?	18
2.8.2. Should separate entries in the EURD list be considered for active substances, where there are major differences depending on the indication or route of administration, to allow for a more tailored PSUR assessment?.....	20
2.8.3. When should products referred to in Articles 10(1) (generics) and 10a (well established use) of Directive 2001/83/EC, as amended, (not) be requested for inclusion in a PSUSA?	21
2.9. Section 1-4 of the <PRAC> <Lead Member State> PSUR AR	22
2.9.1. How to achieve consistency in the summary sections 1-4 across different PSUSA and which elements should be reflected in each section and how detailed should it be?	22
2.9.2. Section 2: Assessment conclusions and actions	22
2.9.3. Section 4.1: Issues to be addressed in the next PSUR	22
2.10. Evaluating the effectiveness of aRMMs	23
3. Pregnancy and Breastfeeding	23
4. Use of Real World Evidence (RWE) including DARWIN EU, Real World Data (RWD) studies.....	23
5. DEFINITIONS	25

1. General principles

The PSUR is a global document and therefore the relevant European Union (EU) information, e.g. EU product information (PI), description of ongoing procedures to update the EU PI (variations) and EU risk minimisation activities and the assessment of their effectiveness, is expected to be provided within the regional appendix of the PSUR.

1.1. Aim of the PSUR/PSUSA and data to be reviewed

1.1.1. What is the purpose of a PSUR and its (single) assessment?

As laid down in the current legislation, the purpose of the PSUR is to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit/risk (B/R) balance of the medicinal products (DIR Art 107d).

The current GVP module VII (EMA/816292/2011 Rev 1) states that the purpose of a PSUR is to present a comprehensive, concise and critical analysis of the B/R balance of the medicinal product taking into account new or emerging information, in the context of the cumulative information on the risks and benefits. A critical appraisal is expected to consider the maturity and utilisation data of the product and its place in therapeutics. The PRAC Rapporteur/Lead Member State (LMS) should conclude on the data assessed and in case any regulatory action is recommended, present and justify the Rapporteur's/LMS' position in the assessment report and to the PRAC at the time of plenary discussion. The assessment should conclude with either maintenance, variation, suspension, or revocation.

A PSUR is generally not intended, for notification of urgent new safety or efficacy information which may have a public health impact. Other processes which are under the scope of GVP module IX (signal management) should be considered. In addition, urgent safety information should be reported to the agencies via the appropriate mechanism.

It should be noted that detailed listings of individual cases should not be systematically included as per Implementing Regulation (IR) 520/2012 [Art 34(4)]. The PSUR should focus on summary information, scientific safety assessment and integrated B/R evaluation. It should also be noted that the PSUSA is not intended for harmonising the PI or the risk management plan (RMP).

1.1.2. What should drive the assessment of a PSUSA?

The review of the PSUR should focus primarily on the data provided by the Marketing Authorisation Holder (MAH). As laid down in the current legislation (DIR Art 107b), it is the MAH's legal obligation to submit PSURs containing summaries of data relevant to the benefits and risks of the medicinal product and a scientific evaluation of the B/R balance of the medicinal product considering all available data.

To allow for an adequate assessment of the PSUR, it is critical that the information provided by the MAH is of sufficiently good quality. The data and information submitted by the MAH should enable the analysis and assessment by the regulatory authorities. An Explanatory note to GVP Module VII for MAH

has been developed to raise awareness and clarify the expectations in the different sections of the PSUR.

PRAC Rapporteurs/LMSs are expected to familiarise themselves with the therapeutic role of the product and be aware of current scientific issues of importance or major questions under debate. The assessment could identify a possible concern, which merits further action by the MAH as part of the responses to the Request for Supplementary Information (RfSI) or in the next PSUR (e.g. literature search and/or additional analyses such as cumulative reviews). The PRAC Rapporteur/LMS is not expected to routinely do searches/investigations on the products under assessment e.g. by literature searches or searches in EudraVigilance. New findings are expected to be provided and discussed by the MAH. This includes the need for further action such as update of the PI. However, if any relevant source, which contains data that can support regulatory action was not provided/discussed by the MAH but identified by the PRAC Rapporteur/LMS, it can be asked to be discussed by the MAH as part of the RfSI. If significant concerns regarding the B/R balance of the product are identified within a PSUSA (i.e. they may warrant a recommendation for an important variation of marketing authorisation, suspension or revocation), it is recommended to initiate discussions at PRAC at an earlier stage (i.e. at the time of the Preliminary AR). Consideration should also be given as to the need of consultation with a Scientific Advisory Group/Ad-hoc expert group, and whether the assessment would need to be moved into another procedure for a comprehensive evaluation of the B/R balance.

1.1.3. Significant concerns about the quality of the PSUR data and pharmacovigilance inspections.

Significant concerns about the quality of the PSUR data may also be flagged in section 2 of the assessment report as a Quality and Compliance issue which needs to be improved in the next PSUR submission. In certain circumstances, such issues may be a reason for a triggered Pharmacovigilance Inspection or be considered for an already planned inspection. Information regarding the template for pharmacovigilance inspection can be found at Pharmacovigilance inspection procedures EMA webpage: [Pharmacovigilance inspection procedures: human | European Medicines Agency \(EMA\)](#)

Template for pharmacovigilance assessment information sharing can be found here: [template](#). This template can be used to highlight quality issues identified during the PSUSA to the Supervising Authority.

1.2. Strength of evidence in the context of the stage in the product lifecycle

1.2.1. What is the strength and nature of the evidence that is needed to support regulatory action? Does this differ depending on the stage in a medicinal product's lifecycle?

The strength and nature of the evidence needed to support regulatory action may differ depending on the stage in a medicinal product's lifecycle. Uncertainty in relation to a medicine's safety profile should

be a key driver of risk proportionality. Accordingly, uncertainty is normally reduced with increased exposure. The general principle applies that the higher the patient exposure for a particular medicinal product is, more evidence (e.g. cases with a suspected causal relationship) is needed to justify an amendment of the PI.

However, independent of the stage of the medicinal product's lifecycle, and depending on the nature of the event, one single well-documented case with a definite causal relationship of an adverse event with a medicine, may be sufficient to justify regulatory action.

Any variation of the marketing authorisation needs to be well justified. This is particularly important when clinical trials do not show differences in incidence between the medicinal product and the comparator, making the causal association of an adverse reaction more uncertain. In case uncertainty on the causal association of an Adverse Event (AE) with a medicinal product prohibits concluding on a variation of the marketing authorisation within a PSUSA further evaluation taking additional evidence into account in the next one may be warranted.

New safety information should be carefully reviewed in terms of type and severity of the cases, including the nature of all available data. Assessment should not focus only on suspected adverse reaction reports but have a broader view and include information available from clinical trials, spontaneous reports, epidemiological studies and meta-analysis etc.

In addition, mechanistic plausibility, the extent of patient exposure and how long the product has been on the market, as well as the clinical context and relevance for patients and the place of the medicine in therapeutics should be considered.

1.3. Link between PSUSA and outcomes of other regulatory procedures

1.3.1. Should the PRAC Rapporteur/LMS reflect their ongoing or recently concluded assessments in the PSUR assessment report?

The PSUR assessment should specifically focus on the data provided in the PSUR. Ongoing procedures at EU or national level, regardless of the data presented in the PSUR, should generally not impact on the assessment.

If new data become available in the PSUR that concern an issue already assessed in a recently finalized procedure, and if this is considered important from a safety perspective, the PRAC Rapporteur/LMS may request the MAH to address this issue during the PSUR procedure for PRAC to conclude upon. In some cases, products included in the PSUR may have had their PI updated following another regulatory procedure completed during the PSUR reporting interval, but the update has not been applied to all products in the PSUR. Such finalised procedure may be considered, provided that the data supporting the PI update are included.

1.3.2. How to deal with inconsistency or non-compliance with previous regulatory procedure outcomes (e.g. recommendations after a referral procedure)?

Although the PRAC Rapporteur/LMS are not expected to proactively search for non-compliance with previous regulatory procedures, if such non-compliance is detected, it may be highlighted in the PSUR AR, section 2. If needed a more comprehensive overview of the situation might be requested from the MAH(s). However, there should be no reiteration of previous outcomes of other procedures in the recommendations section of the AR (section 3 of the PSUR AR template).

In cases of significant non-compliance with previously recommended actions (e.g. suspensions or deletion of indications that have not yet been implemented), follow-up should not wait until the end of the PSUSA procedure. The PRAC Rapp/LMS should inform the EMA.

PSUSAs containing nationally authorised products (NAPs):

Once the LMS has informed the EMA, the EMA will inform the Member States (MSs) concerned in order to clarify the situation and enable them to start implementing the previous recommendations before the PSUSA is finalised. A short overview of the steps taken should be included by the LMS. The LMS should play a key role to report/highlight the issue at the Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh) plenary to ensure alignment with previous outcomes.

1.4. Scope of conclusions: impact on products outside the PSUSA

1.4.1. How should conclusions on a drug-drug interaction (DDI) with the product(s) covered by the PSUSA, which may affect other products, be reflected in the AR?

New DDIs, when the interacting product is a NAP, will be highlighted to CMDh for further processing. No recommendations about extrapolation to products outside the scope of the PSUSA should be included in the AR. CMDh will then notify the concerned MAHs of the NAPs containing the interacting substance, via their published CMDh minutes, so that the MAHs of the relevant NAPs can take the most appropriate action at the national level.

In practice:

- when the interacting product is a NAP, an update of the PI on a DDI within a PSUSA will be flagged to CMDh by the EMA Product Manager (PM).
- when the interacting product is a Centrally authorised product(s) (CAPs), the concerned MAH(s) will be informed by the EMA Product Lead (PL).

1.4.2. How should conclusions on PSUSAs for fixed-dose combinations (FDCs) and/or mono substances be reflected in the AR and under which circumstances should findings be extrapolated and in which way?

First, it needs to be considered from a scientific point of view whether the evidence presented in the PSUR is sufficient to support extrapolation. This may involve extrapolating from a mono-component product to FDCs that contain the same active substance but are outside the scope of the PSUSA. Conversely, it may involve extrapolating from FDCs assessed in the PSUSA to mono-component products that are outside the scope of the PSUSA. A summary of the assessment of the available evidence should be included in section 2 of the AR. This information should reflect that the PSUSA outcome is relevant to other FDC/mono-component products including scientific rationale to support this extrapolation. No PI wording for products outside the scope of the PSUSA is to be included.

The information on the extrapolation will be flagged to the CMDh by the EMA PM when NAPs are affected and by the EMA PL to the MAH when CAPs are affected.

For NAPs, the information on extrapolation will to be published in the CMDh minutes to enable NAP MAHs to act at the national level.

When there is insufficient evidence reviewed in the PSUSA to conclude on the need to extrapolate, but the PRAC concludes that there might be a need to further investigate (e.g. a class effect), the PRAC Rapporteur/LMS should liaise with EMA to discuss the best regulatory framework (case-by-case basis) to formally assess this issue, and involve the concerned MAHs. In case NAPs are concerned, EMA will approach CMDh if relevant.

1.4.3. How will information about new DDI or extrapolation related to NAPs be communicated to CMDh?

Please see above and refer to the relevant information in section 2 'Assessment conclusions and actions' of the AR template where detailed instructions on this is provided as part of *green guidance text*.

2. Specific assessment aspects with related sections of the PSUR AR template

2.1. Dealing with inconsistencies of PI

2.1.1. Can/should the PSUSAs be used as a tool for harmonisation of the PI?

The PSUSA procedure is not an appropriate tool for harmonisation of the existing PI across products, even if it is acknowledged that it would be appreciated to have consistent EU PI. PI updates should be based on evidence provided in the PSUR, not just for the purpose of harmonisation. As such, recommendations to include/remove certain information from the PI should always be driven by PSUR data and be based on a review of safety. In such cases, important aspects supported by PSUR data

would be reflected in all respective national versions of the PI, as an outcome of the PSUR assessment. These recommendations are considered regulatory decisions to update the PI on the basis of the available data but should not be seen as an exercise of harmonisation of the PI across all products included in the review. However, if changes based on data submitted in the PSUR are proposed, it is acceptable to propose a wording that is already present in some of the PIs of the active substance (see section 2.1.2).

PSUSAs containing NAPs:

The LMSs can check with their CMDh counterpart on how to resolve topics related to pure PI harmonisation. However, no information is expected to be found in the PSUSA procedure regarding this matter.

2.1.2. Where there is sufficient cumulative evidence regarding a safety issue which needs to be reflected in the PI, is it acceptable to request an updated/new wording across all PIs, even if some of them already have the issue well reflected?

In case the PRAC Rapporteur/LMS conclude that there is a need for an update of the PI, the PRAC Rapporteur/LMS should recommend in the final AR a definitive wording to be applied across all products covered by the PSUSA. The PI proposal should generally not be differentiated per product or MAH. However, in some instances different wording may be justified, and should in such case be clearly described in section 2 and 3 of the AR. Indication and/or formulation differences of medicines should be considered if applicable.

Normally, the PI wording to be adopted by PRAC should be included in full, even if some wording already exists in the PI for certain products.

Implementation of the outcome for NAPs:

To support implementation of the update to the PI, the PRAC recommendation may, to the extent possible, indicate how the PI wording should be implemented. However, it is recognised that the PRAC does not have full visibility of all PIs for the products concerned across the MSs within the scope of the procedure, nor of how the new text would be best fit within each existing PI. The actual implementation lies within the remit of the National Competent Authority (NCA). Consequently, there may be a need for the NCA to discuss with the MAH how best to incorporate the PRAC recommendation into the respective national PI. In cases where a MAH has a more extensive wording than the one provided in the PRAC recommendation (section 3 of the PSUR AR template), they can discuss with the NCA whether the wording should be retained and if so how. In principle, the same implementing approach applies as for referrals. The CMDh may wish to agree on the implementing approach to avoid different approaches in the MSs.

Implementation of the outcome for CAPs:

No further national implementation steps are required, as the revised PI is varied as part of the Commission Decision to the MAH.

2.2. Overview of exposure and safety data (section 1.3.4 on data in summary tabulations)

2.2.1 Can the tables of cumulative safety data from clinical trials and post-marketing surveillance, presented by the MAH be used as a tool for signal detection?

The data presented by the MAH as cumulative summary tabulations of serious AEs from clinical trials and cumulative and interval summary tabulations from post-marketing data sources is not intended to be used as a tool for signal detection purposes. Summary tables with number of events or cases lack sufficient detail to allow for meaningful assessment of a causal association. For signal detection, other processes are in place, which are more adequate.

2.3. Safety concerns:

2.3.1. Should the PSUSAs be used as a tool for harmonisation of the safety concerns?

The PSUR is not a tool for harmonisation of the safety concerns. This principle applies both to the summary of safety concerns in the PSUR and to the RMP, where applicable.

However, should the PSUR assessment identify a new important risk, the PRAC Rapporteur/LMS can recommend to the PRAC that all MAHs are requested to include that particular risk as a safety concern. Any such requests need to be implemented by all MAHs to ensure relevant assessment of key safety concerns across all products in the next single assessment. This does not entail that the whole safety profile should be amended or harmonised.

The MAHs should be reminded that they are (in line with the legislation) obliged to review and discuss all issues identified during the interval period, whether or not the issue is included as a safety concern.

For those products where an RMP is in place, and where an update to the RMP safety concerns is recommended as an outcome of the PSUSA based on the data assessed in the PSUSA, the relevant changes to the RMP will be introduced via a subsequent variation as an outcome of the PSUSA procedure. The specific safety concern needs to be addressed, with a common terminology for all products affected by the PSUSA procedure.

For CAPs, if an RMP has been submitted with the PSUR, the RMP can be updated directly as part of the PSUSA procedure.

It should be noted that the definitions of important identified and potential risks and missing information in GVP Module V Rev.2 apply in the context of risk management planning, i.e. safety concerns in the RMP are judged based on B/R impact and the need for further risk minimisation activities and/or further evaluation as part of a pharmacovigilance plan. GVP Module VII is applicable for the purpose of risk classification in the PSUR. Therefore, the definitions in GVP Module V should generally not be used for the purpose of risk reclassification in the PSUR. Consequently, the lists of safety concerns in the RMP and PSUR might differ. Please refer to [E2C \(R2\) Step 5 Periodic benefit-risk evaluation report \(PBRER\)](#) section 3.16.1 Summary of safety concerns for further information.

It is also possible that the justification to remove a risk from the list of safety concerns in the RMP may not be applicable for reclassifying a risk in the PSUR. This might lead to an important risk being removed from the RMP, e.g. when the risk is characterised and appropriately managed with existing risk minimisation activities, but that it may still be warranted to monitor it, and thereby not remove it from the list in the PSUR. Although section 16.4 of GVP Module VII currently mentions the modules should be the same, this is no longer a requirement since the publication of GVP Module V Rev.2. This aspect will be further clarified in the next revision of GVP Module VII.

If during the assessment there are important differences identified in the safety specifications between products covered by the PSUSA, they can be noted in section 2. of the AR. This does not entail that the whole safety specification should be amended or harmonised. For each request a justification should be provided to explain the reasons for inclusion or removal and a request for revision in the next PSUR and/or RMP should be included in section 4.1 and/or section 4.3, as applicable. The same process would apply for CAPs and NAPs if there is a request for amendment of the safety specifications.

In case where there is diversity in safety concerns between NAPs, an alternative approach is for the LMS to highlight the safety concerns of the PSUR that they consider should be included for the purposes of future PSUR monitoring e.g., this may occur when no RMP is in place.

If an RMP update is requested, this will be flagged to the CMDh for NAPs via inclusion of the request for RMP update in section 4.3 of the AR and via the EMA PM who will record this information in internal tracking database so that the CMDh could make the RMP update request public via their plenary minutes. Similarly, it may be important to make CMDh aware of cases where there are substantial differences between products with regards to additional risk minimisation measures (aRMMs).

Beyond the regulatory framework of the PSUSA procedure, it is important that MAHs continue to be encouraged to strive for consistent PI across the EU, and the efforts of both CMDh and individual MSs are instrumental in this respect. However, recommendations tend to work better if they are addressed specifically to MAHs, rather than as general recommendations in guidance.

2.3.2. Safety concerns with a long latency

For safety concerns with long latency (e.g., malignancies, cardiovascular events such as myocardial infarction, chronic kidney disease, neurological disorders such as dementia, or autoimmune disorders), individual spontaneous case review rarely allows robust conclusions on causality due to the long latency, multifactorial etiology, and high background incidence. Causality assessment typically requires comparative safety studies with appropriate comparators. In this respect, the PRAC Rapporteur/LMS may consider requesting that, for such safety concerns, the MAH:

- Focus on ongoing Post Authorisation Safety Studies (PASSs), if available.
- Review relevant published pharmacoepidemiologic and clinical data.

This approach would ensure that the assessment is evidence-based and proportionate, for situations where extensive review of individual cases is not expected to provide meaningful conclusions.

In addition, the use of data from DARWIN EU studies may be considered for such safety concerns (please see section 4).

2.4. Signals and topics under monitoring (PSUR AR template: annex LMS assessment comments on PSUR, section 2.2. on signal evaluation)

2.4.1. If a signal is refuted should the assessment as a precautionary principle still request that this be followed up in future PSURs? If yes, based on what evidence should this be requested?

MAHs ultimately retain responsibility for their internal signal management processes and progress signal evaluations according to appropriately judged timelines on a continuous basis.

In principle, a refuted signal should not lead to continued monitoring in the coming PSURs for precautionary reasons, provided that the PRAC Rapporteur/LMS and ultimately PRAC agree with refuting the signal. The assessment of the data is the basis for any subsequent decision and will lead to agreement on closure of the signal or maintaining it open.

Thus, in general, if a signal is refuted it should be closed, and routine pharmacovigilance will apply. If the signal cannot be refuted, it should be kept open and be further evaluated in the next PSUR, or in a different procedure based on the signal seriousness or urgency, and available data. This should be clearly explained in the AR under the signal evaluation section.

2.4.2. Topics for monitoring (i.e. beyond the safety concerns proposed by the MAH)

As specified in GVP VII section B.5.15, when a competent authority has requested that a specific topic (not considered a signal) be monitored and reported in the PSUR, the MAH should summarise the result of the analysis in section 15 of the PSUR if it is negative. If the specific topic becomes a signal, it should be included in the signal tabulation and discussed in sub-section 16.2 ("Signal evaluation").

With the current PSUR format, the assessment should focus on signals and aggregate data in the context of the B/R assessment. It is not appropriate to routinely request line listings (LL), as the PSUR is not to be used for signal detection. Requests for review, e.g. cumulative reviews, either within an ongoing PSUR or in the next PSUR, need to be justified, and be clear on exactly what further data need to be submitted. This in turn will lead to improved response data from the MAH. A particular safety concern can motivate a request for case series review with narratives, but again, this request should be justified.

When a topic is repeatedly requested to be monitored in forthcoming PSURs, it should be considered whether the topic should be added as a safety concern in the PSUR or if the topic can be handled through routine pharmacovigilance.

A fixed time limit for keeping signals open could be restrictive in those cases where there is low exposure or the cases have been poorly documented. Therefore, the request for keeping a signal open will be assessed on a case-by-case basis in the next PSUR.

2.4.3. How to deal with a discrepancy between number of events presented by the MAH and number of Individual Case Safety Reports (ICSRs) retrieved by the LMS?

The LMS is not expected to cross check the number of events presented by the MAH from their safety database with the number of events in EudraVigilance or national databases. Any discrepancy is not surprising because the data presented by the MAHs and the LMS come from different databases. Also, the cut-off date used to query the databases may not be the same. From 22 November 2017, MAHs have access to EV at the level of the active substance and for cases submitted to the EudraVigilance post-authorisation module (EVPM), but this does not mean that both the MAHs' safety databases and EudraVigilance will be fully harmonised. MAHs nevertheless will be able to access the information in EudraVigilance for signal detection, validation and assessment purposes and, if relevant they may be able to consider whether there are discrepancies between EudraVigilance and their safety databases.

When EudraVigilance data is included in the AR, the source of the data together with the EudraVigilance search parameters used to retrieve the cases should be made clear by the LMS so that this information can be put in the appropriate context.

2.4.4. Monitoring of EudraVigilance by MAHs

From 22 November 2017, MAHs whose products are authorised in the EEA have access to EudraVigilance data to comply with their pharmacovigilance obligations. The access to EudraVigilance data and the EU Signal Management process do not modify the format of the PSUR which should follow the Commission IR 520/2012 and GVP Module VII. The PSUR should contain all validated signals for which the evaluation is completed or ongoing at the PSUR Data Lock Point (DLP). This is regardless of the source of the signal, or the actions taken with the signal.

As stated in the Commission IR 520/2012 and GVP Module VII, PSURs 'shall be based on all available data' and therefore EudraVigilance should be used as another source of information.

The amended Commission IR 520/2012 (Commission IR 2025/1466 of 22 July 2025) establishes that 'MAHs shall monitor the data available in the EudraVigilance database and use it together with data from other available sources' [IR, Art 18(2)]. MAHs should incorporate in the PSUR, the findings from monitoring the EudraVigilance database when applicable and in the relevant PSUR sections.

Whenever there are signal evaluations in the PSUR or there are issues under monitoring, or requests for cumulative reviews, it is expected that the data from EudraVigilance is fully considered in order to complement and enhance the MAH's assessment and the conclusions for these issues and to ensure that all available cases for the active substance are covered and reported in the PSURs as applicable.

2.4.5. How to deal with a discrepancy between number of events presented by the MAH in the body text of the PSUR and in summary tabulations or discrepancies in consecutive PSURs?

The number of events that are mentioned in the body text of the PSUR e.g. for the summary evaluation of a signal presented in section 15 or 16, may not be the same as the numbers of events with the corresponding Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) in the summary tabulations. This may be due to the DLP for the signal evaluation being different than the DLP for the PSUR and will be apparent from the dates included in the tabular summary of signals. Smaller differences can be noted in the AR but are generally not a reason to raise as a RfSI or as an issue to be clarified in the next PSUR. However, in exceptional cases, if the number of events/reactions in the PSUR text differ substantially from the number reported in the corresponding summary tabulations, and to such an extent to potentially alter the conclusions of an evaluation, further clarification can be asked to the MAH.

Safety databases are inherently dynamic as for example duplicate case reports might be corrected, and cases are updated with follow up information. When follow-up cases are included in summary tabulations of the PSUR because the reported information is considered of significance, numbers would not add up over consecutive PSURs. Integrity of the MAH's database will be verified at the time of a pharmacovigilance inspection.

2.5. Benefit evaluation (PSUR AR template: Annex PRAC Rapporteur/LMS assessment comments on PSUR, section 3. on benefit evaluation)

2.5.1. How to deal with new data/studies on efficacy provided by the MAH considering that the focus of the PSUR assessment is whether there are new risks or whether risks have changed or whether there are changes to the B/R balance of medicinal products?

This paragraph of the PSUSA AR can generally be short, referring to approved PI(s). There is no need to repeat results from clinical trials supporting previous approvals.

When there is new positive benefit information and no significant change in the risk profile in the reporting interval, the integration of baseline and new information should be succinct (GVP Module VII, Section 3.17.3). In this situation, no re-evaluation of the baseline efficacy data is warranted, only changes in the reporting interval should be considered.

Lack of efficacy or studies challenging the established efficacy profile should be discussed within the PSUR. When there is important new information indicating lack of efficacy, a detailed B/R balance analysis can be warranted or be raised for another procedure. However, in the PSUR, evidence of efficacy from a study(ies) in a non-approved indication should not be assessed.

As a reminder, the PSUR is not the appropriate procedure for submitting final or interim study reports to the EU regulatory authorities. These reports should be submitted and assessed via the appropriate

(variation) procedure. However, in case a study report can further support either the discussion by the MAH or the LMS' assessment of the PSUR sections dealing with data from clinical trials, findings from non-interventional studies, or other clinical trials and sources, the MAH may provide the study report (or relevant parts thereof) as an appendix to the PSUR.

In case a final study report has been submitted by the MAH in the PSUR, the LMS should include a reminder to the MAH in the section 2 (Assessment conclusions and actions section) that the final study report should have been submitted according to the Commission regulation (EU) 2024/1701 amending Regulation (EC) 1234/2008 via an appropriate procedure. In contrast, interim study reports may be submitted within PSURs if recommended in the Pharmacovigilance Plan of the RMP (see section 2.8.1).

Although PSURs have the appropriate regulatory scope to restrict/suspend/revoke a marketing authorisation based on safety grounds, when there is need for a wider engagement in a rigorous scientific analysis, then an alternative procedure (e.g. referral) might be more appropriate.

2.6. B/R balance (PSUR AR template: annex LMS assessment comments on PSUR, section 4. on benefit-risk balance)

2.6.1. How to regard the B/R balance for old established products especially when different indications are authorised in different MSs and how to achieve a common position on the B/R balance when different indications are authorised in different MS and the level of information included in the SmPC may be different as well?

The general principle is that at the beginning of the PSUR reporting interval, the B/R balance of a medicinal product with a valid marketing authorisation is positive, based on the data evaluated at the time of initial marketing authorisation and subsequent assessments of its B/R profile such as renewal, and previous PSURs. PSURs are focused on the evaluation of new data on safety and efficacy that has been received during the period under review in the context of the cumulative experience with the use of the medicine and whether any new information affects the overall B/R balance of the medicinal product.

The LMS should not question the B/R balance only because an indication is not authorised in their member state. Also, decisions from new Marketing Authorisation (MA) and/or re-registration procedures, where the evidence of efficacy was found to not be up to modern standards should not be taken as grounds to question the medicine's B/R balance in certain indications without new relevant data in the PSUR.

Harmonisation of the PI is not within the scope of PSURs, as more appropriate procedures are available when necessary (e.g. work-sharing variations, reminders for generics to align with their reference product). In this regard, the conclusion on the B/R balance cannot be linked to individual Adverse Reactions (ADRs) being listed or not in individual PIs. However, if a review within the PSUR of a particular safety concern, which relies on data from the current PSUR reporting interval, results in a recommendation to update the PI, common wording will be introduced.

2.6.2. Should a conclusion of “B/R balance remains unchanged” be understood as an endorsement by the PRAC of all existing indications?

No, a conclusion of “B/R balance remains unchanged” should not be understood as an endorsement by the PRAC of all existing indications. The assessment of a PSUR is focused on new safety concerns, or whether knowledge about risks have changed or whether there are changes to the benefit-risk balance of medicinal products, identified during the PSUR reporting interval.

Currently approved indications or populations may be restricted if there is enough evidence in the PSUR justifying a change in the B/R balance for those. However, any claim for a new indication needs to be submitted via the appropriate regulatory procedure (variation) including a comprehensive data package. PSURs cannot be used as a basis for extensions of indications.

2.6.3. Can a PSUR procedure add a new indication to approved medicinal products in a MS?

No, PSURs are focused on safety and whether new safety concerns affect the overall B/R balance of the medicinal product. Hence, only changes to an indication which are justified based on safety concerns (i.e. deletion or restriction of an existing indication) can be implemented as an outcome of a PSUR.

It is important to bear in mind that a PRAC recommendation of unchanged B/R balance in an indication that is authorised only in some MS, cannot be automatically extended to other MSs where the indication is not authorised. New indications need to be submitted via the appropriate regulatory procedure including a comprehensive data package. PSURs and the efficacy data presented by MAHs cannot be used as a basis for extension of indications.

2.7. RfSI within or at next PSUR

2.7.1. How to deal with requests for cumulative reviews and how to differentiate between those to be answered within the 30 days and those which are for the next PSUR?

For the RfSI section, a risk-based approach should always be taken by PRAC Rapporteur/LMS to limit requests to only those which are needed to address potential recommendations for regulatory action(s) within the PSUSA, or which may affect the B/R balance. For instance, if there is an issue reviewed within the PSUSA, which may lead to a recommendation for regulatory action, but the amount of data, the quality of the data or analyses of data presented in the initial PSUR are insufficient for an adequate assessment, MAHs should be requested to provide further level of/quality of information and/or data analyses via an RfSI.

Questions which are merely nice to have, address observed discrepancies in submitted datasets, or seek small clarifications, which will not have an impact on the assessment conclusions or recommendations should be avoided in the RfSI section. However, such points may be recorded in the AR as a flag to the concerned MAHs.

Requests for cumulative reviews should always be risk-based, justified and clear. It is also important to limit the number of requested cumulative reviews in the RfSI since there is only a limited time for MAHs

to respond (30 days) and for further assessment (15 days). In several cases, it is more relevant to request a cumulative review for the next PSUR instead, especially if the PSUR cycle is on a shorter frequency, although such requests should also be well justified and as few as possible, see further below.

Considering the timetable (TT), the LMS/PRAC Rapporteur has 15 days, following receipt of the MAHs' responses and MSs' comments to update the AR. Only questions which may lead to a regulatory action as part of the PSUSA outcome or that are critical to the assessment of the B/R balance, should be considered. Other questions can be included in the recommendations to be addressed in future PSURs or via possible other regulatory alternatives when the PSUR is on a long cycle (please refer to section 2.7.2). It is also recommended to limit the number of questions for the next PSURs, as much as possible, thus many small questions which would not result in any regulatory action or any consequences to the assessment should not be raised. A comment in the AR can often be sufficient to make the MAH aware for future submissions. Please note that, while the PSUSA procedure is ongoing, the procedure should be scheduled for PRAC plenary discussion (in the month preceding the adoption of the PRAC recommendation) if the evaluation in the Preliminary AR questions the B/R balance, proposes to revoke/suspend the MA, or in case of a restriction of the indication (e.g. by a new contraindication), or a reduction of the recommended dose. In such cases, the PRAC Rapporteur/LMS should consult EMA to confirm that an early plenary discussion is warranted.

Any requests that do not reflect the principles and format of the PSUR, for example requests aimed at using the PSUR summary tables for signal detection, systematic requests for LL and Council for International Organizations of Medical Sciences (CIOMS) reports should not be undertaken.

In addition, careful consideration should be given as to whether the proposed request will provide meaningful information that could be the basis for regulatory action.

2.7.2. What to do when an issue cannot be finalised within the PSUSA?

The usual approach is to raise the issue for the next PSUR. Earlier follow up requests outside the PSUR cycle should be exceptional and always be risk proportionate and scientifically justified. Moreover, in situations where the assessment of a follow up request would finalise in parallel or even later than the next PSUR, such request should be avoided. This means that follow up requests should generally not be raised when the PSUR cycle, as listed in the European Union Reference Dates (EURD) list, is under or on a yearly basis.

CAPs only

When an important safety issue has been raised during the PSUSA, but its evaluation cannot be finalised within the procedure and further evaluation is needed before the next PSUR submission, it is possible to request a Post-Authorisation Measure imposed under EU legislation (LEG procedure) as an outcome to the PSUSA. A LEG is a Post-Authorisation Measure which is defined as a statutory obligation in the pharmaceutical legislation. In a LEG procedure, the MAH will be requested to provide further data for assessment as a stand-alone submission within a short timeframe (between 2 to 6 months following PRAC recommendation on the PSUSA). If the outcome of the LEG evaluation is to recommend a PI update, such update will be addressed via an implementing variation. It is important not to request a LEG procedure when the PSUR cycle is short i.e. 1 year or less since the conclusion of the LEG procedure may overlap with the next PSUR evaluation.

NAPs only

LEG procedures do not exist for NAPs. However, other mechanisms are available, and LMS/PRAC should consider, on a case-by-case basis, which tool is most appropriate if further review is needed after the PSUSA procedure but before the next one. The procedure for handling of a continued review should be clearly defined in the AR. This procedure should be defined in consultation with the CMDh member from the respective LMS.

Amongst the various existing regulatory tools, LMS (in liaison with the CMDh member)/PRAC should consider whether: if possible (i.e. when the relevant product is authorised in the LMS and the follow up request is directed to one MAH), the assessment of the data should be performed by the LMS e.g. in case the MAH will submit this data via a WS variation, Mutual Recognition Procedure or national variation procedure (either upon the MAHs' own initiative or upon a CMDh request). For situations where multiple MAHs are involved, such follow up request will be handled via an informal WS procedure PSUR follow-up (PSUFU) procedure. PRAC should generally be consulted in the assessment of the data through a MS request for PRAC advice made by the LMS, but this is depending on the nature of the data to be assessed.

The LMS should indicate in the AR (section 4.2. <Issues to be addressed as part of a follow-up measure to the PSUSA:>) the route which should be followed for the submission of the data (e.g. PSUFU or variation procedure). As mentioned above, this process should be defined in consultation between the CMDh member and PRAC member of the respective LMS.

Other options – when the outstanding issue is compatible with the procedure - may be to:

- Trigger a signal procedure at PRAC level;
- Bring the next PSUR submission forward (i.e. to advise changing the PSUR cycle at the end of the PSUSA assessment), however this should only be done rarely;
- Trigger the appropriate referral procedure.

2.8. PSUR frequency and EURD list (PSUR AR template: section 4/5. on PSUR frequency)

2.8.1. Under which scenarios should the PRAC Rapporteur/LMS consider (or not) to change the PSUR frequency?

As per GVP Module VII, MAH for products authorised before 02 July 2012 (CAPs) and 21 July 2012 (NAPs) **and for which frequency and dates of submission are not laid down as a condition to the marketing authorisation or determined in the list of Union reference dates**, shall submit PSURs according to the following submission schedule [REG 28(2), DIR Art 107c(2)].

- at 6 month intervals once the product is authorised, even if it is not marketed;
- once a product is marketed, 6 monthly PSUR submission should be continued following initial placing on the market in the EU for 2 years, then once a year for the following 2 years and thereafter at 3-yearly intervals.

For CAPs, the QRD PI template includes the following conditions in Annex IIC (**Other conditions and requirements of the marketing authorisation holders**):

- for all authorised medicinal products:

The requirements for submission of PSURs for this medicinal product are set out in the EURD list provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

- In addition to the above paragraph, medicinal products authorised as conditional marketing authorisation (CMA) include the below condition:

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

Thus, the above conditions listed in the MA overrule the submission schedule mentioned above ([REG 28(2), DIR Art 107c(2)]). Therefore, except for CMAs, PRAC may recommend any PSUR frequency.

In the context of every PSUSA procedure, the PRAC Rapporteur / LMS should review the current PSUR frequency and recommend an appropriate frequency for the next PSUR based on the current characterisation of the safety profile based on cumulative data and newly presented data. PSURs frequencies should always be defined on a risk-based approach.

The below should be considered when recommending the PSUR frequency:

In general, for medicinal products containing a new active substance, a short PSUR cycle is initially anticipated (every 6 months). For substances already approved in other medicines, a longer PSUR frequency can often be adequate, in line with the PSUR frequency for the already approved medicines (e.g. a known substance included in a new fixed dose combination, or a known substance approved in a new pharmaceutical form). In principle, if an EURD list entry already exists for the substance concerned, the newly approved product should be included under that entry. A new PSUR frequency should only be defined in cases where a new EURD list entry is required, based on a clearly articulated justification.

The foreseen exposure in the post-marketing setting should also be considered. A low exposure to the medicinal product (and expectation that this will not increase significantly in the short term) should be considered as a criterion to prolong the PSUR frequency to gather meaningful data in the PSUR. On the other hand, new medicinal products such as vaccines expected to be used in extensive vaccination campaigns (e.g. during a pandemic) would generally warrant a short PSUR cycle, which may be complemented with summary of safety reports submitted with an even shorter frequency between a monthly and bimonthly cycle.

For more mature products, not all ongoing safety topics warrant keeping a short PSUR cycle. To determine whether a short PSUR frequency remains warranted, the nature of the safety concern(s) and the approved use, should be considered. Furthermore, the extent of patient exposure and whether a short PSUR cycle would allow to gather sufficient new information that could lead to regulatory action or impact public health should also be considered. In case a PSUR cycle should be kept to further characterise a specific safety concern, the PSUR frequency should generally be extended once the safety issue has been further characterised.

The availability of additional regulatory tools such as signal detection activities and risk management activities (including agreed PASS – interim reports, final reports) should also be considered. Parallel ongoing procedures (e.g. referrals or type II variations) are not a reason for not prolonging a PSUR frequency. Similarly, the fact that there are post authorisation safety studies ongoing is not an adequate justification for not prolonging the PSUR frequency. Furthermore, PSURs are not a tool to report final PASS results, other appropriate regulatory tools should be used instead. Although interim results from ongoing PASS sometimes are requested to be submitted within a PSUR, such request should not be the only reason to maintain a short frequency. In such cases, other solutions should be sought, e.g. change to less frequent submissions of interim results, or to ask for that within a separate procedure. In all other cases, regular submission of interim reports at specific milestones can be agreed with the MAH and detailed in the corresponding section of the RMP. Final results should also be presented in an appropriate procedure (see section 2.5.1. above). Any changes to the PSUR frequency should be discussed in Section 2 (Assessment conclusions and actions) and included in section 4/5 (PSUR frequency <and other changes to the EURD list) of the PSUR AR.

2.8.2. Should separate entries in the EURD list be considered for active substances, where there are major differences depending on the indication or route of administration, to allow for a more tailored PSUR assessment?

Unless otherwise specified in the EURD list or agreed with the NCAs or the EMA, as appropriate, a PSUSA shall be prepared for all medicinal products containing the same active substance and authorised for one MAH as set out in the Commission IR (EU) No 520/2012 on the performance of pharmacovigilance activities. Therefore, careful consideration should be given before splitting entries which should only be done in exceptional cases when significantly different safety profiles are expected. It must be taken into account that splitting entries should not create more complexity in managing PI updates as the safety outcome for one indication will mostly be relevant for the other indication of products containing the same active substance.

The decision to merge or split entries in the EURD list might be made as part of the regulatory procedure (e.g. PSUSA, initial procedure, extension of indication). In the context of PSUSA procedure, the proposal should be discussed in section 2 (Assessment conclusions and actions) and included in section 4/5 (PSUR frequency <and other changes to the EURD list) of the PSUR AR. Involvement of Granularity and Periodicity Advisory Group (GPAG) is not required, however the LMS may consider approaching GPAG for consultation (via eurdlist@ema.europa.eu).

Should the decision to merge or split an entry be taken outside of a regulatory procedure, this should be done well in advance i.e. more than 6 months before the submission date of the next PSUR. In such case, GPAG consultation is always required, and the outcome will be implemented as part of the GPAG outcomes that are adopted by PRAC and CHMP/CMDh.

2.8.3. When should products referred to in Articles 10(1) (generics) and 10a (well established use) of Directive 2001/83/EC, as amended, (not) be requested for inclusion in a PSUSA?

According to DIR Art 107b(3), the MAHs for medicinal products authorised via articles 10(1) (generics) or 10a (well established use) are exempted from submitting PSURs, except in the following circumstances:

- where such obligation has been laid down as a condition in the marketing authorisation in accordance with Article 21a or Article 22; or
- when requested by a competent authority based on concerns relating to pharmacovigilance data or due to the lack of periodic safety update reports relating to an active substance after the marketing authorisation has been granted.

The below should be considered as guidance to determine the need to request PSUR for generics/well established use:

The following criteria constitute a justification for requesting PSURs for generics / well established use products:

- when medicinal products containing the same active substance or/and combination of active substances are only authorised under legal basis 10(1) and/or 10(a) in more than 1 MS i.e., the originator no longer has a marketing authorisation.

- when medicinal products containing the same active substance or/and combination of active substances are authorised in only 1 MS via any of the following articles:

- *article 8(3)(full application)*
- *Art 10b (fixed dose application)*
- *Art10c (Informed consent application)*
- *Art 10(3) hybrid application)*

AND medicinal products containing the same active substance or/and combination of active substances are authorised in other MS(s) via Art 10(1) (generic) or 10(a) (well established use).

In these 2 previous cases, as the medicinal products are authorised in more than one MS, the PSUSA procedure can take place. These scenarios are usually managed by the EURD list Team/GPAG.

- When the WEU have indications not authorised for the originator and which are considered significantly different to those of the originator.

The following criteria do not constitute a justification for requesting PSURs for generics /well established use products:

- when a safety topic is not fully characterised.

- when the submitted PSUR contains limited data due to - e.g., low patient exposure, rare disease, low quality of data. The MAH for the reference / originator products has the responsibility to report all relevant information from all the sources in the PSUR which includes EudraVigilance cases for the substance covered by the PSUR, thereby also include cases reported for other products such as generics.

- when there are other procedures more appropriate to address the safety issue.

When the reason for the initial request for PSUR submissions for generic/WEU products has been addressed and is no longer applicable, the EURD list should be revised and no longer request PSUR submissions for such products. If the original cause is unclear e.g., decisions taken a long time ago, the PRAC Rapporteur/LMS should assess whether any of the above-mentioned criteria are still met. In the context of every PSUSA procedure, the PRAC Rapporteur/LMS should proactively review the need to maintain the request for PSUR submission for generic/WEU products switch on.

Any changes in the submission of PSURs for products referred to in Articles 10(1) and 10a of Directive 2001/83/EC as amended, should be detailed in section 2 (Assessment conclusions and actions), with a justification and scientific rationale, in line with the general principles agreed by GPAG and the PRAC, and reflected in section 4/5 PSUR frequency <and other changes to the EURD list>).

2.9. Section 1-4 of the <PRAC> <Lead Member State> PSUR AR

2.9.1. How to achieve consistency in the summary sections 1-4 across different PSUSA and which elements should be reflected in each section and how detailed should it be?

The LMS/PRAC Rapporteur should carefully follow the *green guidance text* in the AR template.

2.9.2. Section 2: Assessment conclusions and actions

This section aims at outlining the assessment conclusions which primarily result in specific action(s) to be taken by the MAH(s) involved in the PSUSA e.g., recommendation for PI update in section 3 of the AR, issues to be addressed in the next PSUR or as part of a follow-up measure (sections 4.1 and 4.2 of the AR) or as part of a subsequent RMP update (section 4.3 of the AR) or a change to the PSUR frequency or EURD list (section 4/5 of the AR). In section 2 of the AR, it is not expected that the LMS/PRAC Rapporteur will repeat all issues that have been assessed in the PSUSA, as those are already detailed in the Annex of the PSUSA AR, especially not for issues where no action is to be taken by the MAH(s). In general, section 2 should not be longer than approximately two pages. For PSUSA procedures where the proposed recommendation is maintenance, section 2 should be succinct (half a page to 1 page maximum).

In section 2, it is not considered necessary to include all authorised indications of the products in scope of the PSUSA in full details but rather in short. Posologies are generally not needed to be reflected at all.

2.9.3. Section 4.1: Issues to be addressed in the next PSUR

This section is optional and should only be used when there is a need to follow up on specific, important issues, beyond those listed in the summary of safety concerns, in the next PSUR. Applying the same principle as for requests raised in the RfSI (see under 2.7.1), the issues to be addressed in the next

PSUR should always be risk based and possibly affecting the B/R of the products in scope of the PSUSA. In section 4.1, questions which may be nice to know but are not relevant for a PI update or the assessment of the B/R balance of the products should be avoided. Such points may be recorded in the current PSUSA AR as a flag to the concerned MAHs in the relevant assessors' comment boxes and may, if important, be commented in section 2 of the AR.

2.10. Evaluating the effectiveness of aRMMs

Reference is made to GVP Module VII (VII.C.5.5. PSUR EU regional appendix, sub-section "Effectiveness of risk minimisation") and GVP module XVI on Risk minimisation measures. If there are aRMMs in place for a medicinal product, it is expected that the continued need of these is reevaluated within the PSUSA. Such re-evaluation should ideally take place before generics/biosimilars come to the market. The review should consider whether effectiveness of aRMMs have been evaluated in any study setting and, where applicable, consider the results of this study. Furthermore, the feasibility across MSs should be considered, particularly for more complex aRMMs, and whether the recommendations given in the aRMMs for specific clinical actions to address certain risks have become integrated into standard clinical practice, such as inclusion into treatment protocols or clinical guidelines. It is anticipated that this is usually the case when a medicinal product has been used for a certain period of time by a considerable number of healthcare professionals and patients. In light of this, particular attention should be paid to the more mature products. Based on the outcome of the review, a proposal should be made regarding whether the aRMMs should be maintained, amended or whether the aRMMs can be partially or completely discontinued. In case of proposed amendment or discontinuation of the aRMMs, the PRAC Rapporteur/LMS should also consider whether the PSUR cycle should be revised.

3. Pregnancy and Breastfeeding

Assessors are reminded that the [Guideline on good pharmacovigilance practices \(GVP\) Product- or Population-Specific Considerations III: Pregnant and breastfeeding women](#) and their children exposed in utero or via breast milk outlines specific requirements on the reporting and assessment of pregnancy and breastfeeding data in PSURs. This GVP should be consulted when evaluating PSURs that include data on pregnancy or breastfeeding exposures.

4. Use of Real World Evidence (RWE) including DARWIN EU, Real World Data (RWD) studies

EMA has access to RWD in the form of patient electronic health records from different sources including a number of existing registries, which can be used to facilitate regulatory evaluations and inform decision-making. On this basis, EMA provides a service to generate and deliver RWE to EMA's scientific committees, national competent authorities (NCAs), EMA functions and other EU decision-makers and partner organisations. More information can be found here: [Real-world evidence provided by EMA](#)

In case uncertainties in relation to a safety concern of clinical relevance concerning an active substance or therapeutic class remain following the assessment of the data provided in the PSUR, the use of DARWIN EU to generate RWE may be considered after discussion and agreement in the plenary by PRAC.

The PRAC rapporteur /LMS can reach out to: rwe@ema.europa.eu. As a first step, EMA will investigate the feasibility of conducting a study. EMA will then inform the requester accordingly, for the PRAC to decide on whether to perform the study, if feasible.

If access to data from patient registries outside DARWIN EU is required, EMA can also facilitate the identification of, and liaison with existing registries if any, to explore the possibility for collaboration (and/or the performance of the study under existing framework contracts).

5. DEFINITIONS

1. Monitor via Routine Pharmacovigilance

Defined in GVP:

- Refers to the MAH's standard signal detection and safety monitoring activities.
- No formal requirement to report on the issue in the PSUR unless new relevant data emerge.
- If nothing new is identified, the issue does not need to be mentioned at all in the PSUR.

MAH expectation: No specific action unless new relevant data have arisen in the reporting period.

2. Monitor/Follow up in the PSUR

Defined in GVP Module VII, Section 15

- Used when a competent authority requests that a particular topic (not an open signal) be **monitored and reported in the PSUR**.
- Results of the MAH analysis (even if negative) should be presented in **Section 15 of the PSUR**.
- If new data leads the MAH to consider the issue a signal, it must also be included in the **Signal Tabulation (Section 15)** and evaluated in **Section 16.2**.

MAH expectation: Review the new data (since the last time the topic was reviewed) and make a decision/proposal considering the totality of the data.

Please note that the concept of 'close monitoring' should be avoided. However, if this is used, it will be understood as this specific definition.

3. Cumulative Review in the PSUR

- This refers to a **formal PRAC request** to be provided by the MAH and assessed in the PSUSA.

MAH expectation: Conduct a structured analysis and include conclusions/recommendations e.g., PI update as necessary.

4. Update of the Summary of Safety Concerns in the PSUR

- PRAC may recommend **adding a safety concern to the Summary of safety concerns in the PSUR** (Section 16.1) **(without) updating the RMP**.
- Please see the section 2.3 of this guidance and Explanatory Note to GVP VII. It is acknowledged that the PSUR Summary of Safety Concerns may differ from the RMP.

MAH expectation: Ensure consistency with PRAC recommendations.

5. For other definitions such as **Safety concern, Important Identified/Potential Risks** and **Identified risk (including a reference to Potential risk)**. Please see [GVP Annex I Definitions](#).