



31 October 2017  
EMA/518909/2016  
Human Medicines Evaluation Division

## Q & A on PSUSA: Guidance document for assessors

Since the start of the Periodic Safety Update Report (PSUR) single assessment (PSUSA), this procedure has posed a certain number of challenges that are specific to the EU single assessment of PSURs of medicinal products approved nationally.

This document is written in a questions and answers format and aims at providing further guidance to assessors, based on the experience gained since the start of the PSUSA procedure for NAPs in January 2015. It should be noted that in some instances, the issues addressed may also apply to the assessment of PSURs of centrally authorised products.

This Q & A document should be read in conjunction with the GVP VII.

### 1. General principles

It is acknowledged that the PSUR is a global document therefore the relevant EU information, e.g. EU product information, 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 (PSUR Single Assessment) 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 balance of the medicinal products (DIR Art 107d).

In line with this, 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 benefit/risk 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 take into account the maturity and utilisation data of the product and its place in therapeutics. The assessment should focus on real improvements for patients. The Lead Member State (LMS) should come to a conclusion on the data assessed and at the time of PRAC be in a position to present and justify the LMS' position to the committee. The assessment should not be left open ended without a conclusion.

A PSUR is generally not intended, in the first instance, for notification of urgent new safety or efficacy information which may have an important 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 via the appropriate mechanism.

It should be noted that detailed listings of individual cases should not be systematically included [Art 34(4)]. The PSUR should focus on summary information, scientific safety assessment and integrated benefit/risk evaluation. It should also be noted that the PSUR single assessment is not intended for harmonising product information or the risk management plan (see also below).

**1.1.2. What should drive the assessment of a PSUSA? The data provided, additional data available to the LMS? Should the LMS pro-actively do searches/investigations on the products under assessment?**

The review of the PSUR should focus primarily on the data provided by the 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 benefit/risk balance of the medicinal product taking into account 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. 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.

The LMS should not proactively compensate for deficiencies encountered in the PSURs. MAHs should be requested to provide the adequate level/quality of information and analysis during the procedure when necessary (i.e. in the preliminary Assessment Report as Request for Supplementary Information).

Significant concerns about the quality of the PSUR data may also be flagged as a Quality and Compliance issue which has to be improved in the next PSUR submission and can be the reason for a Pharmacovigilance Inspection.

Preparation for the PSUR assessment is key. In general, 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 LMS (e.g. Eudravigilance or literature search, PV inspection request) or by the MAH as part of the responses to the RSI or in the next PSUR (e.g. literature search and/or additional analyses such as cumulative reviews). Further scientific knowledge might be incorporated into the assessment if available. However, the LMS is not expected to routinely, and proactively do searches/investigations on the products under assessment e.g. by literature searches or searches in EudraVigilance, beyond the LMS' responsibility for routine signal detection. New findings from articles are expected to be provided and discussed by the MAH. This includes the need for further action such as SmPC update. When significant changes to the benefit risk balance of the product are identified within a PSUSA assessment (i.e. they would warrant a recommendation of 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 Assessment Report). Consideration should also be given as to the need of consultation with a Scientific Advisory Group/Ad-hoc expert group.

## **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 the more evidence (e.g. cases with a suspected causal relationship) are needed to justify a change of marketing authorisation.

However, independent of the stage of the medicinal product's lifecycle, one single well-documented case with a definite causal relationship of an adverse event with a drug, or clear differences in comparative incidences in clinical studies without further evidence, may be sufficient to justify regulatory action.

Any variation of MA authorisation needs to be well justified especially if no differences in comparative incidence were found. In case uncertainty on the causal association of an AE with a medicinal product prohibits concluding on a variation of the marketing authorisation, further investigation may be considered to ascertain whether the AE can be identified as an important identified/potential risk in which case further pharmacovigilance activities can be undertaken.

General guidance on the strength of the evidence needed to support regulatory action cannot be given and this can only be addressed on a case by case basis.

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 all 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 taken into account and be the driver of change to the MA when necessary.

## **1.3. Link between PSUSA and outcomes of other regulatory procedures**

### **1.3.1. *Should the LMS reflect their ongoing or recently concluded assessments in their role of reference member state (or concerned member state) in the PSUR assessment report?***

No, the PSUR assessment should specifically look at the data provided in the PSUR and ongoing procedures at EU or national level based on data that is not presented in the PSUR should generally not impact on the assessment.

However, important information relevant for the B/R balance of the product or for the product information should not be ignored. If the LMS is aware of ongoing/past safety issues that a MAH has not adequately addressed, the LMS can request the MAH to provide the supporting data during the PSUR assessment, which can then be assessed and concluded upon by the PRAC. There may also be cases where some products included in the PSUR have had their product information updated further to the completion of another regulatory procedure during the PSUR reporting interval, but the update to the PI has not been carried out across all products included in the PSUR. These finalised procedures

may be taken into account, providing the data to support the product information update is included in the PSUR.

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

If non-compliance is detected, it should be highlighted in the PSUR assessment report. 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).

The non-compliance should be flagged in the new section 'other considerations', with a reminder to the MAH of their obligation to implement previous outcomes. The non-compliance should systematically be highlighted to the CMDh by the LMS, even in case no regulatory action is recommended as a direct outcome of the PSUSA (i.e. maintenance of the MA).

Although the LMS should highlight non-compliances/divergences that are noticed, there is no expectation that the LMS should proactively find/search for non-compliance, but the PSUSA assessment can allow for detection of non-compliance.

In case of non-compliance such as in the case of a previously recommended suspension or deletion of an indication, which has not been implemented, follow-up should not await the end of the procedure and after being informed by the LMS, the EMA will inform the Member State(s) concerned in order to clarify the situation and allow for the Member State(s) to start proceeding with implementation of these previous procedures, before the PSUSA procedure is finalised. A short overview of the steps taken and the status at the time of circulating the Updated AR should be included by the LMS in the 'other considerations' section of the assessment report. The LMS should play a key role to report/highlight the issue at CMDh plenary for the CMDh 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 with the product(s) covered by the PSUSA, which may affect other products, be reflected in the assessment report?**

If a new drug-drug interaction or contraindication for concomitant use is added, due consideration should be given as to whether the change should be extended to the other impacted product(s) (i.e. the interacting substance(s) that are not within the scope of the PSUSA procedure), and to this effect there should be a comment or proposal in the assessment report to prompt further discussion at PRAC level and conclude on the implementation across other products. This should be included in the new "other considerations" section of the assessment report.

### **1.4.2. How should conclusions on combination PSUSAs and/or mono substances be reflected in the assessment report and under which circumstances should findings be extrapolated and in which way? Should a new section in the AR be dedicated to such discussion?**

First, it needs to be considered from a scientific point of view how far the conclusion on the mono product or on the combination can also be extrapolated to the other combinations/mono products. It is

acknowledged that establishing which component in a fixed dose combination (FDC) is associated with a certain ADR may not always be possible and therefore complicate any extrapolation, however, if it is considered possible, this should always be justified in the assessment report. In case it is not possible to conclude, this should also be reflected in the assessment report.

As a next step, the EURD list should be checked to identify existing active ingredient/combinations of products not subject to the procedure. If the PSUSA covers both mono products and combination products, the conclusion and recommendation can be reflected in the assessment report as usual. If other combinations/mono products exist that are not covered by the PSUSA, any conclusion on extrapolation should be included in the new "other considerations" section of the PSUR assessment report.

In PSUSA procedures, regardless whether they cover mono products only or combination products or both, if it is not possible to extrapolate, this should be clearly stated (e.g. different dosing in the combination, different route of administration) in the 'other considerations' section of the AR.

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

### **2.1. Dealing with inconsistencies of product information**

#### ***2.1.1. Can/should the PSUSAs be used as a tool for harmonisation of the SmPC/PL?***

The PSUSA procedure is not the appropriate tool for harmonisation of the existing product information across products, even if it is acknowledged that it would be appreciated to have consistent EU product information. Product information updates should be based on evidence provide in the PSUR, not on the purpose of harmonisation. As such recommendations to include/remove certain information from the SmPC and/or PL 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 product information, as an outcome of the PSUR assessment. These recommendations are considered regulatory decisions to update the product information on the basis of the available data, but should not be seen as an exercise of harmonisation of the product information 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).

If there is an important lack of consistency across products of the same active substance that cannot be addressed within the procedure this should be included in the new "other consideration" section in the AR template and highlighted to the CMDh, who will consider how to take the situation forward.

#### ***2.1.2. Where there is sufficient cumulative evidence regarding a safety issue which needs to be reflected in the SmPC/PL, 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 LMS concludes that there is a need for an update of the product information, the LMS should recommend in the final assessment report a definitive wording to be applied across all products covered by the PSUSA. The PI proposal should not be differentiated per product or MAH. However, indication and/or formulation differences of medicines should be taken into account if applicable.

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

Thereafter, the actual implementation lies within the remit of the NCA. However, 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.

***2.1.3. If major differences between SmPCs/PLs are identified in PSUSA procedures, which could potentially affect the benefit risk balance (e.g. different indications), should the initiation of Article 30/31 procedures be considered?***

In exceptional situations, the trigger of an Article 30 or 31 referral could be considered provided this is driven by important differences in safety aspects and not only by different indications.

Furthermore, as per current legislation, the moment a Member State (MS) intends to withdraw an indication, the MS should use the appropriate pathway to address the issue, i.e. informing the CMDh in case urgent measures do not need to be taken or triggering a referral at that point in time (see [NtA Volume 2A Chapter 3](#), the internal CMDh document CMDh/344/2013, and [referral webpage](#)).

**2.2. Overview of exposure and safety data (PSUR AR template: annex LMS assessment comments on PSUR, 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 adverse events 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. Dealing with inconsistencies of safety specification/RMP (PSUR AR template: annex LMS assessment comments on PSUR, section 2.1 on summary of safety concerns)**

***2.3.1. Can/should the PSUSAs be used as a tool for harmonisation of the safety specification?***

The PSUR is not a tool for harmonisation of the safety specification per se; neither the section in the PSUR which summarises the safety concerns, nor in the RMP for those products that have an RMP.

However, should the PSUR assessment identify a new important risk, the LMS can recommend to the PRAC that all MAHs are requested to include that particular risk in the safety specification. 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 specification should be amended or harmonised.

The LMS should be aware that independent of a safety issue being included in the safety specification, MAHs 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 in the safety specification.

If based on the assessment of the data, important new risks should be included or updated in the safety specification then all MAHs will have to include these risks in the safety specification (section 16.1) in the next PSUR. For those products where a RMP is in place, the relevant changes to the RMP will be introduced via a variation as an outcome of the PSUSA procedure, in line with the Variations Classification guideline of Commission Regulation 1234/2008. Only the specific safety concern needs to be addressed, with a common terminology for all products affected by the PSUSA procedure.

It should however 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 risk-benefit 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. As a consequence, the lists of safety concerns in the RMP and PSUR might differ.

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 fully characterised and appropriately managed with existing risk minimisation activities, but that it may still be warranted to follow up on 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 upcoming 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 the new 'other considerations' section of the assessment report, to make the CMDh aware, and allow for consideration to take the issue forward for further action outside of the PSUSA procedure. 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.

Beyond the regulatory framework of the PSUSA procedure, it is important that MAHs continue to be encouraged to strive for consistent product information across the EU, and the efforts of both CMDh and individual Member States 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.

#### **2.4. Signals and issues under close 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 additional follow up for precautionary reasons, provided the LMS and ultimately PRAC agrees with this assessment. 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.

If a signal is refuted it should be closed and routine pharmacovigilance will apply from this time on. If on the other hand the signal cannot be refuted, then it should be kept open and discussed in the next PSUR, or in a different procedure based on the signal seriousness or urgency, but this should be clearly explained in the assessment report under the signal evaluation section.

#### ***2.4.2. Where would additional topics for close monitoring (i.e. beyond the safety concerns proposed by the MAH) be expected to be presented and how?***

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 new PSUR format, there is agreement that in the assessment of PSURs there should be a shift from the review of line listings (LLs) to focus on signals and aggregate data in the context of the benefit-risk assessment. In light of this change of approach, it is not appropriate to routinely request Line Listings, as the PSUR is not to be used for signal detection. Requests for follow-up 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 closely monitored, it should be considered whether the topic should be added as an important identified/potential risk in the RMP or if the topic can be handled through routine pharmacovigilance.

A fixed time limit for signals under close monitoring could be restrictive in particular in those cases where there is low exposure or the cases have been poorly documented. Therefore, the request for the continuation of signals under close monitoring 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 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 (EV) or national databases. Any discrepancy is not surprising because the data presented by the MAHs and the LMS comes 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 (EVPAM), but this does not mean that both the MAHs' safety databases and EudraVigilance will be fully harmonised for all the drug event combinations. 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 EV data is included in the AR, the source of the data together with the 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. Transitional arrangements for monitoring 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 new steps in the EU Signal Management process do not modify the format of the PSUR which should follow the Commission Implementing Regulation 520/2012 and GVP Module VII. The PSUR should contain all validated signals for which the evaluation is completed or ongoing at the PSUR DLP. This is regardless of the source of the signal or the actions taken with the signal.

As stated in the Commission Implementing Regulation 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, nevertheless the transitional arrangements agreed by the EMA and the European Commission to streamline the monitoring of EudraVigilance by MAHs should apply, i.e.

- MAHs with the obligation to monitor EudraVigilance from 22 February 2018 (those whose active substances are included in the in the list of medicines under additional monitoring on 22<sup>nd</sup> Nov 2017) should incorporate in the PSUR the findings from monitoring the database when applicable and in the relevant PSUR sections;
- The rest of the MAHs with no obligation to monitor EudraVigilance for one year starting from 22 February 2018, also have access to the database and will be able to integrate the data into their own signal management process, when relevant. These MAHs will have no obligation to continuously monitor EudraVigilance for the production of PSURs, nevertheless whenever there are signal evaluations in the PSUR triggered by other sources of information or there are issues under close monitoring, it is expected that the data from EudraVigilance is considered in order to complement and enhance the signal assessment and the conclusions for these issues.

#### **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 for specific reactions that are mentioned in the body text of the PSUR e.g. for the summary evaluation of a closed signal presented in section 15, may not be the same as the numbers of events with the corresponding Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms in the summary tabulations. This may be due to the data lock point for the signal evaluation being earlier than the DLP for the PSUR and will be apparent from the dates included in the tabular summary of signals. However, should the number of events/reactions in the PSUR text differ from the number reported in the corresponding summary tabulations to such an extent to potentially alter the conclusions of an evaluation, this should be explained and justified by the MAH.

As 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 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 benefit/risk balance of medicinal products?***

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, a full re-evaluation of the baseline efficacy data is not warranted, only changes in the reporting interval should be taken into account.

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 benefit/risk balance analysis is warranted. However, the assessment of the PSUR should not conclude on evidence of efficacy in new indications, for which an application would need to be submitted by the MAH via an appropriate procedure.

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 procedure in line with the Variations Classification guideline of Commission Regulation 1234/2008. However, in case a study report is able to 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 study report has been submitted by the MAH in the PSUR, the LMS should include in the other considerations section a reminder to the MAH that the study report should also have been submitted according to the Commission regulation 1234/2008 via an appropriate procedure.

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. Benefit risk 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 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?***

As a general guide, the principle is that at the beginning of the PSUR reporting interval the benefit/risk balance profile of the medicinal product is positive, based on the data evaluated at the time of initial Marketing Authorisation (MA) and subsequent assessments of its benefit/risk profile such as renewal, and upcoming 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, its place in therapeutics and whether this information affects the overall benefit/risk balance of the medicinal product.

The LMS should not question the benefit/risk balance only because an indication is not authorised in their member state. Also, decisions from new 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 put the medicine's benefit-risk balance in certain indications in question without new relevant data in the PSUR.

Harmonisation of the SmPC is not within the scope of PSURs, as more appropriate procedures are available when necessary (i.e. worksharing variations, reminders for generics to align with their reference product, or referrals). In this regard, the conclusion on the benefit/risk balance cannot be linked to individual ADRs being listed or not in individual SmPCs. However, if a review within the PSUR of a particular safety concern, which rests on data from the current PSUR reporting interval, results in a recommendation to update the product information, common wording will be introduced.

**2.6.2. Should a conclusion of "benefit risk balance remains unchanged" be understood as an endorsement by the PRAC of all existing indications?**

No, a conclusion of "benefit risk 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 risks, or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products, identified during the PSUR reporting interval, and whether this information affects the overall benefit/risk balance of the medicinal product.

Indication or populations may be deleted or restricted if there is enough evidence in the PSUR justifying a change in the benefit/risk but 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 Member State?**

No, PSURs are focused on safety and whether new safety concerns affect the overall benefit/risk balance of the medicinal product. Hence, only changes to an indication which are justified on the basis of 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 benefit/risk 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. Requests for further/supplementary information 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?**

Requests for cumulative reviews should be risk-based, and both the request and its timing should be well justified in the assessment report, and, as far as possible, be part of the ongoing or next PSUR.

Please note that while the PSUSA procedure is ongoing an issue can be brought to the attention of the PRAC at the time of drafting or circulation of the preliminary assessment report if there are elevated concerns or guidance is needed from the Committee.

Generally, requests for supplementary information should be made early at D60 with the expectation to be addressed during the PSUSA procedure. If this is not possible, e.g. where the data requested cannot be gathered within the 30-day time period for comments, then such requests should only be made if there is a good scientific justification relating to a safety concern.

Any requests that are in opposition to the PSUR format and spirit, for example requests aimed at using the PSUR summary tables for signal detection, such as systematic requests for Line Listings and CIOMS reports should not be undertaken.

In addition, careful consideration should be given as to whether the proposed request will provide meaningful information, e.g. whether a request for a cumulative review for a product with an established safety profile where only spontaneous data is available, would reveal any important new information that could lead to changes in the product information.

### **2.7.2. What to do when an issue cannot be finalised within the PSUSA, as no LEGs are possible for NAPs?**

The LMS should follow a risk based approach to limit the number of follow-up requests to a PSUSA assessment. Follow-up request should be exceptional and if there are any, should always be scientifically justified; hence the LMS should consider the strength of evidence and formulate clear and relevant questions in the preliminary AR only. Moreover, in order to avoid situations where the assessment of follow-up requests to a PSUSA finalises in parallel or even later than the next PSUR, follow-up to a PSUSA assessment should not be requested when the PSUR cycle of an active substance or a combination of active substances as listed in the EURD list, is under or on a yearly basis.

The LEGs concept does not exist for NAPs. However, other mechanisms exist and Lead Member State/PRAC should consider on a case by case basis which tool is the preferred option for the submission of the requested data. The process for handling of the follow-up should be clearly defined in the AR. This process should be defined in consultation between the CMDh and PRAC member of 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 may be performed by the LMS e.g. in case the MAH will submit this data via a variation WS procedure (either upon own MAHs' initiative or CMDh advice). PRAC could be consulted in the assessment of the data through a Member State request for PRAC advice made by the LMS.
- For situations where the product(s) is (are) not authorised in the LMS or multiple MAHs are involved, another procedure is being under development by the [Working Party on Pharmacovigilance Procedures Work Sharing](#) . Until this procedure has been defined, the LMS should liaise with their CMDh member to choose the appropriate way forward.

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 to change the PSUR cycle at the end of the PSUSA assessment), however this should only be done rarely;
- Trigger the appropriate referral procedure.

The LMS should indicate in the assessment report (new section “Other considerations”) the route which should be followed for the submission of the data. As mentioned above, this process should be defined in consultation between the CMDh and PRAC member of the respective Lead MS.

## **2.8. PSUR frequency and EURD list (PSUR AR template: section 4. on PSUR frequency)**

### ***2.8.1. 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?***

The general principle as foreseen in the legislation is a single PSUR per active substance, as clearly set out in the Commission Implementing Regulation (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. It must be taken into account that splitting entries should not create more complexity in managing product information 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 should be made well in advance i.e. at least more than 6 months before the submission date of the next PSUR. If consideration is given to merging or splitting entries during the PSUSA procedure, the Granularity and Periodicity Advisory Group (GPAG) should be consulted by the LMS (via [eurdlist@ema.europa.eu](mailto:eurdlist@ema.europa.eu)) at D60.

After this consultation, changes recommended to PSUR cycle and/or EURD list should be included in section 4 of the PSUR assessment report.

## **2.9. Section 1-4 of the <PRAC> <Lead Member State> PSUR assessment report**

### ***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 assessment report template is currently under review with a particular focus on these four sections in light of the initiative on proactive publication of this executive summary which is ongoing.