EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2017
EMA/102307/2017
Human Medicines Evaluation Division

Explanatory Note to GVP Module VII

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

The following explanatory note to Good Pharmacovigilance Practices (GVP) Module VII aims at addressing the challenges encountered during the two years of running the PSUSA process. Ultimately, the explanatory note will serve as the basis for the update of GVP Module VII, which will eventually replace it. It should be noted that, as appropriate, points highlighted in this document may also apply to the assessment of centrally authorised products. This note should be read in conjunction with GVP Module VII; where appropriate, references to ICH E2C (R2) are made; it should be used for the preparation of PSURs subject to single assessment.

In order to preserve the content that is agreed by international consensus, all European Union (EU) specific information should be provided in the EU regional appendix of the PSUR (GVP Module VII section VII.C.5.).

The document is divided into sections identifying the key issues for the development of further guidance.

Throughout the explanatory note, the product information (PI) refers to the EU PI.

Recommendations made in this paper are aimed at limiting the number of issues and requests for clarification, which are raised during the assessment period, given the time constraints of the procedure.

Marketing authorisation holders (MAHs) may consider training on ICH E2C (R2) guideline and the ICH E2C Questions and Answers (Q&A) developed by the ICH-E2C (R2) Implementation Working Group (IWG).

1. Principles for the evaluation of the risk-benefit balance within PSURs and scope of the information to be included

1.1. General principles

As detailed in GVP Module VII, 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.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

The Qualified Person responsible for Pharmacovigilance (QPPV) should ensure that the PSURs are prepared and written in a way that facilitates the understanding of the data, the conclusions and the subsequent actions, i.e. the logic flow needs to be clear and understandable.

Providing the adequate level and quality of information within a PSUR and throughout the assessment procedure is key to substantiate the MAH's conclusions and any actions taken or proposed. The MAH should tailor the level of detail it provides for both the presentation of the findings (sections 6 through 14) and the subsequent evaluation (sections 15 and 16) based on the clinical significance of the presented findings. It is important to understand that this assessment involves medical and scientific judgement that should be clearly presented by the MAH, allowing the re-evaluation in full of the benefit/risk balance of a medicinal product and appropriate characterisation and management of the safety profile, focusing on real improvements for patients in terms of risk minimisation. Please also refer to guidance provided in the ICH E2C (R2) IWG Q&A.

A PSUR is generally not intended for the 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 instead. In addition, urgent safety information should be reported through the appropriate mechanism.

1.2. Changes to the Therapeutic Indication

The principle is that at the beginning of the PSUR cycle, the benefit/risk balance of the medicinal product is positive, based on the data evaluated at the time of marketing authorisation (MA) and subsequent assessments of its benefit/risk balance, such as within renewal, PSURs, etc..

As PSURs are focused on safety and whether new safety concerns affect the overall benefit/risk balance of the medicinal product, only changes to an indication, which are justified based on safety and efficacy concerns (i.e. deletion or restriction of an existing indication), can be implemented as an outcome of a PSUR assessment procedure.

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 VII.B.5.17.3).

It is important to highlight that a Pharmacovigilance Risk Assessment Committee (PRAC) recommendation stating that the benefit/risk balance for certain indications authorised only in some Member States (MSs) is unchanged cannot be used as the basis for an extension of indication in other MSs, where the indication is not authorised. Applications for new indications need to be submitted via the appropriate regulatory procedure to the relevant national competent authority (NCA) including a comprehensive data package.

1.3. PSURs for Generic medicinal products

A PSUR prepared for a generic product should follow the same format and content as outlined in GVP Module VII. The adequate level and quality of information is to be provided allowing the re-evaluation in full of the benefit/risk balance of a medicinal product and appropriate characterisation and management of the safety profile, focusing on real improvements for patients in terms of risk minimisation.

Sources of available information for the active substance are those that the MAH might reasonably have access to, and that are relevant to the evaluation of the safety or benefit/risk balance [see also

Appendix E, Examples of Possible Sources of Information that May Be Used in the Preparation of the PBRER]. Refer also to ICH E2C (R2) section 1.3 (Scope of the PBRER).

2. Actions taken in the reporting interval for safety reasons

If significant actions have been taken in any country of the world for safety reasons in the reporting interval of a PSUR, they should be described in sufficient detail to allow the assessor to understand whether or not the safety reasons for the action(s) have any impact on the benefit/risk profile of the medicinal product.

For instance, simply stating "interruption of the placing on the market" would not be considered as sufficiently informative.

Examples of significant actions taken in the reporting interval for safety reasons are listed in ICH E2C (R2) and GVP Module VII (section VII.B.5.2) and include: significant safety related changes in labelling documents including restrictions on use and population treated, withdrawal or suspension of a MA, actions taken for product defects and quality issues, risk management activities such as Direct Healthcare Professional Communications (DHPCs), inspections prompted by safety concerns and other significant actions taken by both EU and non-EU Health Authorities for reasons listed in GVP Module VII (section VII.B.5.3).

3. Reference information

The reference product information should be provided in English. Where appropriate, a brief description of ongoing procedures (e.g. variations) to update the PI is a requirement of the EU regional appendix and should be included in section "proposed PI" of GVP Module VII section VII.C.5.1. Variations to update the PI expected to be included would normally be those where changes are made to safety relevant information in the PI.

Whilst the reference product information can be provided in any format as per the ICH-E2C (R2) guidelines, the QPPV must have the full oversight of the authorised PI, as this document is the key routine risk minimisation tool in pharmacovigilance.

It is essential that any discussions and considerations with regards to proposed changes to the reference safety information (RSI) in the PSUR are always also put into the context of the PIs that are authorised in the EU. For example, if a well-known adverse drug reaction (ADR) is effectively managed by a contraindication, and is either already included in the RSI or is being proposed for the RSI, the expectation is that the contraindication and ADR are not only included in the RSI, but that this is also the case for the relevant PI. As this expectation is EU specific, any discussion on the impact of RSI changes to the PI should be provided in the EU regional appendix (section VII.C.5.1) together with a statement, in which the MAH confirms that it has considered the impact of the PSUR data on the PI. If the assessor identifies an issue that is not adequately reflected in the impact statement from the MAH (e.g. the MAH concludes that no further changes to the PI are warranted based on the PSUR data while the data show a relevant reporting rate of an ADR included in the RSI but not in the PI), further data may be requested from the MAH during the assessment.

The European legislation states that based on the evaluation of the cumulative safety data and the benefit/risk balance analysis, the MAH shall draw conclusions regarding the need for changes and/or actions, including any implications for the approved PI for the medicinal product(s) for which the PSUR has been submitted [Implementing Regulation 520/2012 Art 34(5)].

Product information amendments not related to the information presented in the PSUR should not be proposed in this framework.

If changes are necessary to only some of the authorised texts, e.g. if important safety information is missing in the PI of some products but not all, the MAH should nevertheless propose a relevant wording, based on the data submitted and assessed within the PSUR. The PRAC will in principle adopt one relevant wording to describe the adverse reaction/warning/contraindication/etc., which will be applicable to all products subject to the single assessment procedure, without distinction between individual MAHs.

Marketing authorisation holders of authorisations granted under Article 10 of the Directive 2001/83/EC should ensure that they have aligned their PI in full to their reference medicinal product prior to the PSUR submission date, as the PSUR will not be used as a tool to introduce changes into the PI which are solely due to non-compliance with such alignment.

4. Patient exposure

Although it is recognised that it is often difficult to obtain and validate exposure data, the number of patients exposed should preferably be provided alongside the exposure length (preferably number of patients or patient/year). The method should be explained. Where a discrepancy exists (e.g. information provided per trial, when added together, does not match with the total provided) this should be explained.

Discrepancies of the patient exposure reported from one PSUR to another (e.g. discrepancies between previous and current cumulative exposure, different units used or data missing) should be justified and elaborated upon with an adequate level of detail.

5. Data in summary tabulations

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. 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 that may potentially alter the conclusions of an evaluation, such differences should be explained and justified.

6. Provision of study reports

It should be noted that the PSUR is not the tool to assess final clinical study reports (CSRs). The appropriate procedure should be followed and the full CSR will not be assessed during the PSUSA but in the relevant regulatory procedure, as appropriate. The type of variation for the submission of the CSR will depend of the type of PI changes targeted as per the Commission Guidelines on the details of the various categories of variations, on the operation of the procedures[1].

[1] See Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, and on the documentation to be submitted pursuant to those procedures.

However, where the study report contains safety data, the full or relevant sections of the report should also be submitted as an appendix to the PSUR. Relevant information should be cross-referred to and/or included in section 7.1 "Completed clinical trials" and section 8 "Findings from non-interventional studies" of the PSUR and should be assessed by the MAH in the PSUR accordingly.

Of note, for post authorisation safety studies[2] (PASS), which were completed during the reporting interval, GVP Module VII.C.5.4. PSUR EU regional appendix, sub-section "Reporting of results from post-authorisation safety studies" requires that the final study reports should be included as an annex to the PSUR. This requirement, which could be revisited during GVP Module VII update, aims to have all the relevant information together within the same document, but as stated above, the CSR will not be assessed during the PSUSA but in the relevant regulatory procedure accordingly. GVP Module VII states in section VII.C.5.4 that PSURs should not be used as the initial communication method either for the submission of final study reports to the NCAs in Member States or for the notification of any new information that might influence the evaluation of the benefit/risk balance.

7. Late-breaking information

As stated in section VII.B.5.14 "Late-breaking information" of GVP Module VII, MAHs are reminded that any relevant safety related procedure should be mentioned in this section (e.g. the start of a referral procedure during this period should be mentioned in this section), or other important issues related to safety occurring after the data lock point (DLP)).

8. Overview of signals: new, ongoing, or closed

The MAH should provide a high level overview of signals for which the evaluation was completed during the reporting interval as well as ongoing signals that were undergoing evaluation at the end of the reporting interval. In the review of PSURs so far, a number of deficiencies have been noted including the absence of cumulative reviews requested in a previous PSUR, or a signal refuted without an appropriate explanation.

The overview should be presented in the following tabular format according to GVP Module VII Appendix 2:

Signal term	Date detected	Status (ongoing or closed)	Date closed (for closed signals)	Source of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Stroke	MMM/YYYY	Ongoing	MMM/YYYY	meta-analysis (published trials)	Statistically significant increase in frequency	Review meta -analysis and available data	Pending
SJS	MMM/YYYY	Closed	MMM/YYYY	Spontaneous case reports	Rash already an identified risk SJS not reported in pre authorisation CTs. 4 reports within 6 months of authorisation; plausible time to onset and no possible alternative causes.	Targeted follow up of reports with site visit to one hospital. Full review of cases by MAH dermatologis t and literature searches	RSI updated with a warning and precaution DHPC sent Effectiveness survey planned 6 months post DHPC. RMP updated

[2] Studies conducted with the primary aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

A NCA may request that a specific topic (not considered a signal) should be monitored and reported in the PSUR. Such requests for close monitoring by the PRAC will be duly justified. As specified in GVP Module VII section VII.B.5.15, the MAH should summarise the result of the analysis in section 15 of the PSUR, if it is negative. All the principles for signal evaluation highlighted in section 9 of this explanatory note also apply to any specific topics (not considered a signal) included in section 15 of the PSUR. If the result of the analysis is negative, MAHs may propose to discontinue specific monitoring in future PSURs. If the assessor does not endorse the MAH's position, the scientific reasons for disagreement will be clearly explained in the assessment report along with any recommendations that can inform requested evaluations in a future PSUR. If the specific topic becomes a signal, it should be included in the signal tabulation (if the signal was closed or ongoing at DLP) and discussed in sub-section 16.2 ("Signal evaluation") of the PSUR if the signal was evaluated and closed during the reporting interval. It is agreed that monitoring through routine pharmacovigilance will be appropriate once a topic has been sufficiently monitored and a safety signal has not been identified.

9. Signal evaluation

The MAHs are required to carry out pharmacovigilance on a routine basis according to the legislation. Routine pharmacovigilance is described in the pharmacovigilance system master file. There is therefore no need for the MAH to detail their routine pharmacovigilance and signal detection activities in the PSUR.

The assessment of the signal evaluation summary presented in section 16.2 of the PSUR is the basis for any decision and will lead to agreement on refuting the signal or continuing to classify the signal as ongoing, if the evaluation is inconclusive. Where the weight of evidence does not allow the signal to either be refuted or confirmed as an ADR, it should be followed-up in the next PSUR or in a different procedure based on the signal seriousness or urgency. Should the evaluation in the next PSUR prove to be inconclusive, the need to continue this assessment should be made on a case by case basis taking into account the medical importance of the signal, extent of exposure, likely impact on benefit risk balance, and the overall weight of evidence.

When safety issues (not considered a signal or important risk) are followed-up in subsequent PSURs, the interval data should be put in the context of the cumulative data (this is one of the main principles of the PSUR). When rejecting a case from a cumulative review, the MAHs are also reminded that such rejection cannot only be based on the fact that the initial reporter considered the adverse reaction not related to the drug.

Signal assessment should be made on the basis of an aggregate review of cumulative data available to the MAH and should evaluate the weight of evidence for and against a causal association with the medicinal product. This assessment will generally be made by evaluating data from multiple sources of information and the MAH should use the methodology most suited to the available data, taking into consideration the source of the signal. For example, when evaluating spontaneous data, important factors to take into consideration include time to onset, and evidence of positive de- and re-challenge.

Recognised methodologies such as the Bradford Hill criteria can also be useful. Whatever analysis is used, the MAH evaluation should be clearly presented and should include sufficient information and interpretation to enable an assessor to understand the rationale for the MAH's conclusions and actions (if taken or proposed).

The MAH should present clear evidence for or against a possible causal relationship in section 16.2 of the PSUR. The focus of the presented analysis should support how the MAH came to the conclusion that:

- a signal was refuted based on available evidence against a causal relationship;
- a signal became an identified risk (i.e. an undesirable clinical outcome for which there is sufficient scientific evidence that it is caused by the medicinal product);
- a signal became a potential risk (i.e. an undesirable clinical outcome for which there is scientific evidence to suspect the possibility of a causal relationship with the medicinal product but where there is currently insufficient evidence to conclude that this association is causal).

When a signal evaluation is finalised and the signal is determined to be either an identified or potential risk by the MAH, the respective rationale should be presented as to why a signal/concern will or will not impact on the benefit/risk balance. Evaluations where insufficient explanation is provided may trigger questions. For instance, there have been situations where fatal cases are mentioned in the signal assessment but no further explanation was provided, which triggered a series of questions from the Lead Member State (LMS).

In addition to the high level information already provided in the signal tabulation, the section on the evaluation (section 16.2) should provide minimum information as listed below, as appropriate. Overall, the information provided in this section of the PSUR should provide a clear rationale to support the MAH's conclusions:

- a description of the signal;
- source or trigger of the signal;
- background relevant to the evaluation;
- methods of evaluation including data sources and search criteria;
- results:
    - summary and critical analysis of the data considered to be key in the signal evaluation including an overview of the cases (where appropriate and integral to the assessment);
    - based on robust cumulative review and analysis;
- conclusion of the evaluation including the need for further evaluation and activities taken or planned.

The assessment of the data is the basis for any decision, and will lead to agreement on closure of the signal or maintaining it open. In principle, a refuted signal should not lead to additional follow up for precautionary reasons, provided the PRAC agrees with its assessment. Routine pharmacovigilance will apply from this moment on. A clear rationale for refuting the signal should be provided together with the data that supports the conclusion (e.g. cumulative review and analysis) in section "Signal evaluation". GVP Module VII in section B.5.16.2 specifies that MAHs' evaluations and conclusions for refuted signals should be supported by data and clearly presented.

The PSUR should focus on summary information, scientific safety assessment and integrated benefit/risk evaluation. Therefore, line listings or individual case narratives should in principle neither be systematically included[3] by the MAH nor requested by the LMS, unless they are integral to the scientific analysis of a signal or safety concern. In this context, the term "case narrative" refers to clinical evaluations of individual cases rather than the CIOMS[4] narratives. In such a case, a clinical evaluation of important or illustrative cases in the context of the evaluation of the safety concern/signal may be more relevant.

However, in certain situations a detailed description of pivotal or illustrative cases including a summary of the case narratives might be relevant for the MAH to provide or for the assessor to request. In such instances, the searches in the safety databases and literature should include all the relevant terms related to the signal. The search strategy and terms included should be clearly specified. Special attention should be paid to whether the signal may concern medical concepts with different, very specific terminologies. Examples are histiocytosis haematophagic and macrophage activation syndrome, juvenile idiopathic arthritis and Still's disease. Determination of the most appropriate search criteria to evaluate a signal requires medical and scientific judgement.

9.1. Summary of safety concerns

A summary of safety concerns specific to the PSUR/substance(s) at the start of the reporting interval should be provided, taking into account that the PSUR is a document submitted globally and hence may need to include additional safety concerns requested by non-EU regulatory authorities. The ICH E2C (R2) Q&A (13.4) proposes one approach to handling the situation where safety concerns differ across countries or regions.

For a product, for which there is an EU-Risk Management Plan (RMP) in place, the summary of safety concerns outlined in the EU RMP at the beginning reporting interval is expected to be included as a minimum. In the EU regional appendix in GVP Module section VII.C.5.3 the RMP version number should be provided as well as an explanation for any differences or additional safety concerns in section 16.1 of the PSUR compared to the EU RMP.

For a product for which no EU RMP is in place, the considerations below should be taken into account in order to determine what constitutes an important identified or potential risk or missing information (i.e. safety concerns). Focus should be given to those important identified/potential risks that are critical to the benefit/risk balance and may profit from further characterisation.

- This section should not be an extensive listing of all labelled adverse reactions and therefore could be very brief (e.g. for mature products where important risks are absent due to full characterisation of the safety profile). It should concentrate on important safety concerns/missing information at the start of the reporting interval.
- A justification for each inclusion should be provided for a product where there is no EU RMP available. For products without an EU RMP, GVP Module VII states that in section 16.1 the MAHs should provide information on the important identified and potential risks as well as missing information. Experience with PSUSAs shows that very old products authorised through old regulatory routes may include safety profiles which are not fully defined. The information provided

[3] Art 34(4) of Commission implementing regulation (EU) 520/2012
[4] Council for International Organizations of Medical Science

should therefore be sufficient to substantiate the safety concerns and should be based on scientific and clinical evidence.

Section 16.1 of the PSUR provides a summary of safety concerns in place at the beginning of the reporting interval and against which new information and evaluations can be made. If new safety concerns have been added to the safety specification of the EU RMP during the reporting interval covered by the PSUR, these would be characterised in section 16.4 and could be annotated as "new" in the appropriate sub-section. If a new safety concern has been identified e.g. as the result of a signal evaluation included in the PSUR but is still undergoing a variation procedure for the EU RMP, the proposal to add would be included in the conclusions of the PSUR. This approach would be consistent with both ICH E2C (R2) and GVP Module VII. If a re-classification or removal has been approved during the reporting interval of the PSUR, this can be noted in section 16.4 or in the conclusions, as appropriate.

As a general principle, the PSUR per se is not a tool for harmonisation of the list of safety concerns across products with the same active substance(s) whether or not the product has an associated EU RMP. However, should the PSUR assessment identify a new important potential or a new important identified risk, or missing information, it can be recommended that all MAHs include that particular risk in the safety specification of RMPs already in place to ensure that the newly identified safety concern is appropriately managed and addressed in future PSURs for the medicinal product(s) concerned. Any of such requests need to be implemented by all MAHs to ensure relevant assessment of the new safety concerns across all products in the next single assessment. Where no EU RMP is in place but a new RMP should be developed, a request will be made on a case by case basis. Where RMPs for such products exist, due consideration should be taken with a view to also amend the safety specification in the RMP via the appropriate variation procedure.

If important safety concerns need to be included or updated in the safety specification of the RMP for nationally authorised products, they 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.

9.2. Evaluation of risks and new information

The aim of this section is to provide new information relevant to previously known risks that has arisen during the period covered by the report (e.g. information arising from studies to further characterise an important potential risk); it is not to present all available information related to the list of safety concerns. It is not necessary to include a detailed discussion of the information arising during the period covered by the PSUR that merely confirms the established safety profile or risk characterisation of the product.

The MAH should not only discuss new data that became available during the period for which the signal threshold was reached. The MAH is also expected to discuss new data that became available during the reporting interval under review without duplication between the signal section and the risk section, which focuses on changes to the safety profile.

MAHs should consider the impact of the new information on the benefit/risk balance of their product(s), namely on the list of safety concerns and/or pharmacovigilance/risk minimisation activities and provide a level of detail proportionate to the level of risk. As such, special attention should be given to the important potential risks and whether the new data could confirm those risks. The focus

given to the analysis of new data should be in the context of known and cumulative information (i.e. the cases received during the reporting interval should be analysed in the context of cumulative numbers and previous analysis). If there is no new significant data, it may be useful to state it.

9.3. Characterisation of risks

This section should reflect a characterisation of the important identified and/or potential risks for the product based on cumulative data (i.e. not solely based on information received during the reporting interval) and also describe important missing information associated with the use of the product. As for other sections of the PSURs, this section should be prepared using data the MAH might reasonably have access to and that are relevant to the characterisation of the risks. For products without an EU RMP, the MAH may propose changes to the list of safety concerns based on information arising from the evaluation period (e.g. successful risk minimisation measures in place). When an important risk or missing information is re-classified or removed, a justification should be provided in this section.

9.4. Effectiveness of risk minimisation (if applicable)

The results of the evaluation of the effectiveness of risk minimisation activities in place should be presented in the EU regional appendix (section VII.C.5.5).

Based on this evaluation, the MAH should propose the implementation of further measures/ amendments to existing ones and/or consider the relevance of maintaining or removing the related safety concern.

10. Benefit-risk analysis evaluation

As a general guide, the principle is that at the beginning of the PSUR period the benefit/risk balance of the medicinal product is positive, based on the data evaluated at the time of initial MA and subsequent assessments of its benefit/risk balance such as renewals and 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.

It is acknowledged that the focus of the PSUR assessment should be on whether there are new important risks or whether already recognised important 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 during the reporting interval, the integration of baseline and new information should be succinct. The MAH should not include new efficacy/effectiveness information that only confirms what was already known for the product. In this situation, a full re-evaluation of the baseline efficacy data is not warranted. Only changes during the reporting interval should be taken into account.

Lack of efficacy or studies challenging the established efficacy profile should be discussed within the PSUR in section 7 or 13 as per GVP Module VII. When there is important new information indicating lack of efficacy, a detailed benefit/risk balance analysis is warranted.

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.

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

11. Assessment and outcome

The assessment of PSURs is a critical appraisal focused on the evaluation of new data on safety and efficacy that have been received during the period under review.

The level of detail provided in certain sections of the PSUR should depend on the medicinal product's known or emerging important benefits and risks. Therefore, the extent of information provided will vary among individual PSURs. For example, when there is important new safety information, a detailed presentation of that information should be included, plus the relevant benefit information, in order to facilitate a robust benefit/risk balance analysis. Conversely, when little new important safety information has become available during the reporting interval, a concise summary of baseline benefit information should be sufficient, and the benefit/risk evaluation would consist primarily of an evaluation of updated interval safety data. Requests to the MAH in the preliminary assessment report or for the next PSUR will be risk-based, and both the request and its timing will be well justified in the assessment report, and, as far as possible, be part of the ongoing or next PSUR. A negative correlation between the level and quality of information provided in the PSUR and the number and nature of requests made in the context of the assessment has been observed.

Generally, requests for supplementary information will be made at day 60 of the procedure with the expectation that they will be addressed within 30 days and concluded upon during the procedure. In exceptional cases, where this is not possible, e.g. where the data requested cannot be gathered within the 30-day time period for comments, other procedures may be followed. The process for handling the submission of follow-up data will be clearly defined in the AR.

Requests for line listings and CIOMS reports will in principle be avoided unless duly justified. Before requesting a cumulative review or line listings and CIOMS narratives, the assessor will need to carefully consider whether or not the proposed request will or is even likely to provide meaningful information (e.g. whether a request for a cumulative review for a product with an established safety profile, where only spontaneous data are available, would reveal any important new information that could lead to changes in the PI).

Harmonisation of the PI is not the scope of PSURs, as more appropriate procedures, such as worksharing variations or a referral under Article 30 of Directive 2001/83/EC, are available when necessary. MAHs should keep their PI up to date and submit variations following the appropriate regulatory route to maintain their PIs aligned. However, in the context of the PSUR single assessment procedure, a common wording applicable to all products covered by a PSUR may be introduced, when the scientific review of a particular safety concern results in a recommendation by the PRAC to update the PI. The PRAC will recommend a wording applicable to all products and there should be no differentiation per product/company unless there are specific and justifiable reasons (e.g. pharmaceutical form). However, indication and/or formulation differences of medicines should be taken into account where applicable. The wording stated in the PRAC recommendation should be included in full. If some wording already exists in the PI for certain products, it should be replaced by the new wording unless the existing wording is very similar and placement in the PI is the same as the PRAC recommendation.

12. Quality systems for PSURs at the level of the marketing authorisation holders

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.

MAHs are also requested to provide the adequate level and quality of information and analyses during the procedure in response to the request for supplementary information in the preliminary assessment report or as a follow-up to a previous PSUR.

An appropriate quality system should be in place in order to avoid failure to comply with the PSUR requirements such as the failure to provide adequate answers to competent authorities' requests.

Significant concerns about the quality of the PSUR data may also be flagged for follow up as a quality and compliance issue which has to be improved in the next PSUR submission and can be the reason for a further pharmacovigilance inspection.

The MAH should be aware that any non-compliance detected will be highlighted in the evaluation of the PSUR and further actions will be discussed at EU level.