SCOPE Work Package 8
Lifecycle Pharmacovigilance

Practical Guide on PSUR / PSUSA Assessment

2016

SCOPE

SCOPE Work Package 8
Lifecycle Pharmacovigilance
Practical Guide on PSUR / PSUSA Assessment

Contents

Acknowledgments

Main authors

Eleanor Carey (IE), Almath Spooner (IE), Niamh Buckley (IE), Jane Woolley (UK), Alison Shaw (UK), Jelena Ivanovic (IT), Elena Marotta (IT), Leonor Chambel (PT), Yvette Escudero (ES)

WP8 active participants

This document is developed and adopted with participation of all WP8 contributors:

Ingebjorg Buajordet, Niamh Buckley, Eleanor Carey, Leonor Chambel, Maria Consuelo Cicalese, Virginia Cuconato, Marco Di Girolamo, Yvette Escudero, Rolf Gedeborg, Margarida Guimaraes, Rimul Gunnar, Jelena Ivanovic, Karl Mikael Kälkner, Miguel Ángel Macia, Elena Marotta, Ana Martins, Dolores Montero, Anja Schiel, Eva Segovia, Alison Shaw, Almath Spooner, Annika Wennberg, Jane Woolley, Qun-Ying Yue

1. Introduction

1.1 Purpose of the document

The purpose of this document is to provide practical guidance for National Competent Authority (NCA) assessors arising from WP8 – Lifecycle Pharmacovigilance, Benefit/Risk (B/R) assessment in the context of Periodic Safety Update Report (PSUR) / Single assessment of Periodic Safety Update Reports (PSUSA) and Referral procedures. WP8 lead IT, Topic Lead IT in collaboration with ES, IE, PT, SE, NO and UK.

This document is not intended as a guideline, but written to share experience within the European Union (EU) Pharmacovigilance (PV) network and to offer some practical guidance on some aspects of PSUR / PSUSA assessment and the drafting of assessment reports (ARs) for assessors. It is derived from the experience and advice of assessors working in NCAs at both junior and senior level. It is acknowledged that there are different structures in place for pharmacovigilance assessment across the Member States (MSs). The focus of the paper is on the actual assessment process and not the procedural aspects of the process, for which guidance is readily available elsewhere. Assessors need to be familiar with the relevant legislation and guidelines and refer to these, as appropriate, throughout the assessment process. This is a living document, subject to updates whenever new elements to be considered require integration.

1.2 Relevant guidelines

- Available on the EMA website (www.ema.europa.eu)
  - Guideline on Good Pharmacovigilance Practices (GVP) Module VII – PSUR
  - PSURs: Questions and answers
  - List of EURDs and frequency of submission of PSURs
  - List of EURDs and frequency of submission of PSURs: Introductory cover note
  - European Medicines Agency (EMA) post-authorisation procedural advice for users of the centralised procedure
- Available on the HMA website (www.hma.eu)
  - Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) Standard Operating Procedure (SOP) on the processing of PSUR single assessment procedures for nationally authorised products
- Available on the ICH website (www.ich.org)
  - E2C(R2) Implementation Working Group ICH E2C(R2) Guideline: Periodic Benefit-Risk Evaluation Report

1.3 Definitions and abbreviations

Terminology	Description
AR	Assessment Report
ADR	Adverse Drug Reaction
ADS	Alternative Data Source
B/R	Benefit/risk
CCDS	Company Core Data Sheet
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
DLP	Data Lock Point
DSUR	Development Safety Updated Report
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPITT	European Pharmacovigilance Issues Tracking Tool
eRMR	Electronic Reaction Monitoring Reports
EU	European Union
EURD	European Union Reference Dates
EV	EudraVigilance
GVP	Guideline on Good Pharmacovigilance Practices
HCP	Healthcare Professional
LoQ	List of Questions
MAH	Marketing Authorisation Holder
MMD	Managing Meeting Documents
MS	Member State
NCA	National Competent Authority
PAES	Post-Authorisation Efficacy Study
PASS	Post-Authorisation Safety Study
PI	Product Information
PL	Patient Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report

Terminology	Description
PSUSA	Single assessment of Periodic Safety Update Reports
PV	Pharmacovigilance
RMP	Risk Management Plan
RSI	Request for Supplementary Information
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
WHO	World Health Organization
WP	Work Package

2. Background

One of the recommendations that arose from analysis of the benefit/risk assessment topic survey results and internal discussion among contributors to WP8 was the proposal to develop a practical guidance paper on PSUR / PSUSA assessment.

The benefit/risk assessment topic survey included questions on NCAs' experiences of the assessment of PSUSAs. 10 out of 24 NCAs who responded to the specific question in the topic survey indicated that they had experience with this procedure before the closure of the survey (November 2014) and identified challenges and solutions for the assessment of PSUSAs. The survey responses also identified current practices and helpful tools used by NCAs for the evaluation of B/R. The challenges and solutions identified, in conjunction with the current practices and helpful tools used by NCAs, represented the starting point from which this practical guidance document was developed.

3. Challenges/limits

This document was developed to offer some practical guidance to assessors on some aspects of the PSUR / PSUSA assessment procedure. It is intended as a supportive tool to be used in conjunction with the relevant legislation, GVP Module VII, EMA templates including guidance text, etc. It is not intended to provide procedural guidance or scientific guidance. Furthermore, due to the complexities of the assessment process, which is hugely dependent on the quality of the submission, the characteristics of the medicinal product under assessment, the therapeutic area, the safety issues under review, etc., it is not feasible to adopt a prescriptive approach. Instead, each issue must be considered on a case-by-case basis in the context of the product lifecycle and in accordance with the available data. Consequently, this document reflects some assessment approaches adopted in different NCAs participating in the SCOPE Joint Action and is intended to provide practical guidance and advice to assist with some challenging issues, enabling reasonable scientific judgement in line with the available evidence.

.

4. Practical guidance

The main objective of the PSUR, as described in GVP Module VII, 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 cumulative information on risks and benefits. The legal requirements for PSURs are detailed in GVP Module VII and the format follows the structure described in the Commission Implementing Regulation (EU) No 520/2012. Familiarity with the legislation, the Module VII Guideline, relevant SOPs and the template guidance (provided by the EMA) are essential when drafting an AR and reference to these guidance documents is strongly recommended as you are drafting your report

This practical guidance and the associated training programme for PV assessors developed in the context of WP8, could facilitate the development of competencies to support B/R assessment among NCAs in the context of the PSUR / PSUSA procedure.

It is acknowledged that work patterns and practices vary amongst assessors, this is considered to be an advantage for the network. However, it is important that ARs are clear and consistent with the submitted data and available evidence. The introduction of the PSUSA procedure has further highlighted the importance of consistent and high-quality assessments across the network. The assessment should not rely on a standard assessment process, but should be tailored to the PSUR data and should reflect the most important findings and value judgements, including the assessor's critical analysis, and clear, justified, evidence-based conclusions and recommendations.

4.1 Planning and organisation

4.1.1 Time required for assessment

Give ample time for the assessment with organisation of your workload. While the time required can vary depending on the medicinal product under review, PSUR ARs can be very time consuming, particularly for medicinal products with complex safety profiles, or where there are safety issues arising that require detailed consideration and/or action. In situations where a considerable amount of data is submitted (e.g. a PSUSA procedure with multiple PSUR submissions), particular attention should be paid to the practical organisation of the assessment. If the PSUSA assessment involves a team of assessors, good coordination, communication and identification of the common data in different Marketing Authorisation Holder's (MAH) PSURs should be considered to optimise the assessment process and avoid duplicated evaluation of the same information (e.g. literature reports and actions taken for safety reasons). In addition, it can be useful to outline the steps in the approach taken to reach a decision in the AR, particularly in the context of complex issues and/or assessor teams. Regardless of the volume of data submitted, it may be helpful to draft 'internal' timeframes for yourself or the assessment team, including some short-term, medium-term and final milestone timeframes, within the established PSUR assessment timeframe. It is also very useful to get a draft report completed in advance of the circulation date to give adequate time for review by/discussion with peers, the PRAC member/CMDh delegate, or other relevant stakeholders, as appropriate, and to allow you to cross-check your assessment and comments with the data.

Before beginning drafting an AR it is helpful to read the PSUR a couple of times. The first reading allows the assessor to form a general impression of the likely issues and "path" of the PSUR; while additional, more detailed, readings allow the assessor to hone in on the details and consider carefully the issues. For less experienced assessors particularly, it can also be helpful to use these readings to ensure that the MAH(s) have completed all of the relevant sections of the PSUR. It is important that if there are substantive or significant issues arising these are flagged as early as possible to senior staff or the PRAC member to allow sufficient time for considerations and proposals to be discussed with the relevant stakeholders (EMA, clinical experts etc.).

It might be helpful to use a Word copy of the body of the PSUR, which can facilitate the generation of the AR, particularly when presenting or replicating tables or diagrams. If not otherwise available, this is usually readily available from the MAH(s).

4.1.2 Inform yourself

Make sure you are aware of any relevant recent or parallel procedures for the substance/product during the timeframe of your PSUR assessment. Consulting the European Pharmacovigilance Issues Tracking Tool (EPITT) and other relevant data sources as appropriate could be useful in retrieving discussions on relevant safety issues.

It is very useful to consider previous PSUR assessments when drafting your AR and to consider whether there is consistency between the reporting intervals, or if there are any significant issues that are substantially different from previous reports or emerging issues. In addition, it is important to ensure that any requests made by the assessor in the preceding PSUR(s) have been addressed by the MAH(s). It can also be useful to learn from other ARs for other substances with regard to the approach and management of similar issues. Do keep in mind other agents in the class, if necessary, particularly when considering recommendations and outcomes.

During the assessment it is recommended that you consult available relevant clinical guidelines for particular issues under consideration. In particular, clinical and scientific associations' guidelines can be useful in relation to the use of the medicine in clinical practice and may provide an insight into the potential impact of any regulatory decisions on clinical practice across different healthcare settings.

4.1.3 Consider patients and healthcare professionals

Keep the patients, healthcare professionals (HCPs) and use of the product/active substance in clinical practice in mind when performing your assessment. This is of particular importance in situations where uncertainties relating to the B/R balance emerge from the assessment process.

If new issues arise during the assessment process that may impact on the B/R balance of the product, consider the possibility of obtaining advice from relevant experts.

4.1.4 EURD List

Make sure to check the EURD list for the active substance (or combination of active substances) to ensure that, following your assessment of the PSUR, you are in agreement with the published EURD list for that substance. In addition, if you wish to request any amendments to the EURD list, keep in mind that they will only become legally binding six months after publication.

4.1.5 Reviewers

When writing your AR, remember the other MSs' reviewers and keep your report focused. You (unlike the reviewer) may be very familiar with the issues at hand and, therefore, it is useful to summarise very briefly in assessor comments the relevant issue before providing your own comments, assessment and conclusions. This facilitates review by MSs and other reviewers. This summary can also facilitate the formulation of requests for further information arising from your conclusions.

In addition, vast copying and pasting from the MAH's PSUR makes the report very difficult to read and there is a risk that the important issues may be lost. It is more helpful and effective to include the key points and text that sufficiently illustrate the issue and exclude text that can be more succinctly summarised.

4.2 Support for overcoming challenges during evaluation of risks/risk characterisation or for benefit/risk decision making

4.2.1 Action taken in the reporting interval for safety reasons

Consider carefully if this is relevant to your PSUR assessment, e.g. product information updates in other regions – are they covered in the EU Summary of Product Characteristics (SmPC)? It is essential to consider the evidence for the action taken and whether it has been presented in the particular PSUR under review. It is also relevant to remember that labelling approaches may differ across regions. Whilst in some regions the product information will only include adverse reactions (where causality is suspected), as is the case in the EU, in other regions, the label may include events (i.e. without evidence of a causal relationship). In addition, product indications, recommended dosages and populations may differ, both within and outside the EU.

4.2.2 Changes to Reference Safety Information

Are changes to reference safety information already covered or applicable to the EU and licensed product labelling? In some instances they may reflect previous or ongoing European variations, but they are important to consider and it may be necessary to request further information on this if it is not provided. For centrally authorised products (CAPs), it can also be useful to refer to the assessment history of the product available on the EMA website. Remember changes to the Company Core Data Sheet (CCDS) will generally not be available to HCPs and patients unless reflected in product labelling, but changes to the CCDS are not automatically applicable to the product labelling without assessment of the supporting data. The assessment should not focus on the contents of the CCDS (which is the company document, distinct from the regulatory document, which is the SmPC) or consider a harmonisation of the relevant SmPCs/PILs. The driver for labelling changes (i.e. changes to the SmPC and Patient Leaflet (PL)) should be the evidence.

4.2.3 Estimated exposure and use patterns

It is useful to look at exposure carefully and compare methods of calculation and exposure levels with previous PSURs. In addition, consider exposure variations across different geographical regions and in special populations (e.g. paediatric/elderly population, pregnant/lactating women, etc.). Significant differences in exposure or trends in exposure should be highlighted in your AR and consideration should be given to the reasons for these differences, e.g. newly authorised products, significant safety issues, availability of alternatives, etc. When interpreting and extrapolating from exposure data, consider the limitations of the methodology and assumptions made in the estimations. Remember that reporting rates have a number of limitations and that caution should be exercised when interpreting or calculating these rates.

When considering patterns of use, including off-label use, critically consider whether there are particular safety concerns in any sub-population or associated with any particular pattern of use, rather than just considering off-label use *per se*.

4.2.4 Data in summary tabulations

It is useful to review carefully the interval report numbers in the context of cumulative numbers and any changes in patient exposure, and to consider those that may be of clinical significance or potentially raise a new safety concern. Reporting rates that account for changes in patient exposure, rather than numbers of reports, are important to consider when reviewing this section. This is a data presentation section rather than an evaluation section of the PSUR, and the MAH is advised not to provide analysis or conclusions in this subsection. However, the assessor may highlight potentially significant issues in the AR.

It may be useful to comment on whether the adverse drug reactions (ADRs) reported are in accordance with the known safety profile of the product and whether there are any differences in the safety profile according to the route of administration/indication, etc. It is advised that the assessor ensures that any issues arising have been followed up elsewhere in the PSUR by the MAH and, if not, it may be necessary to request or consider additional data or information if the issue is of clinical significance or potentially raises a new safety concern. It is important that questions arising do not merely follow numbers without further consideration by the assessor of clinical significance, etc. Do consider whether EudraVigilance (EV) and electronic reaction monitoring reports (eRMR) data may be helpful to provide supplementary data or insight into the reported cases when examining any issues arising here. However, one should not necessarily expect reconciliation of numbers of reports and there can be justified reasons for differences.

4.2.5 Summaries of significant findings from clinical trials during the reporting interval

Remember this section should focus on clinically important emerging efficacy and safety findings during the reporting interval.

4.2.6 Literature

Consider carefully the information provided and keep in mind that the MAH should provide their critical analysis of findings and how they impact B/R. Carefully consider the limitations and potential biases of the published papers before reaching any final conclusions. It may be useful to supplement the PSUR literature review with your own search on selected topics to gather background information, supplemental data or more recent papers.

4.2.7 Late-breaking Information

Ensure that any conclusions on significant information presented here are carried through in the PSUR and the assessment. It is important to note that GVP Module VII states that the data presented in this section should be taken into account in the evaluation of risks and new information.

4.2.8 Overview of signals

Carefully review the tabulated summary of signals and check if you agree with the MAH's classification of signals as new, on-going or closed. Signals that have been evaluated and actioned appropriately should be closed. It may be appropriate to maintain a signal as on-going if further data that will impact the signal assessment is likely or expected imminently.

In case of on-going signals, carefully consider the type and extent of additional data that should be requested and the most important aspects that should be monitored during the reporting period, in order to appropriately address the raised safety issue(s) in the next PSUR. Clear instructions on the expected presentation of this data should also be included in the request, to facilitate the assessment.

4.2.9 Signal evaluation

The MAH should provide their evaluation of signals ongoing and closed during the reporting interval. The assessor should be able to make their assessment of the signal conclusion based on the information provided, which is dependent on sufficient information being provided by the MAH. It may be useful for the assessor to additionally consider the signal in EudraVigilance and consult the associated eRMR during their assessment of the MAH's evaluation. Consulting the signal management database published monthly in Managing Meeting Documents (MMD) can also be helpful, particularly when another MS is signal lead for the medicinal product. In some instances it may be necessary to request further information or detail from the MAH on the signal, to add clarity and understanding to the MAH's evaluation and actions. Bear in mind that GVP Module VII advises that the MAH should provide a summary of the signal evaluation with a level of detail reflecting the medical significance of the signal, and that evaluations and conclusions should be supported by the information provided and clearly presented. However, in the case of non-serious ADRs, the significance and potential impact to the patient and on medication adherence should also be considered (e.g. alopecia in women). It also may be helpful to understand the scope of the MAH Case Search Strategy. The availability and a clear presentation of the clinical trial evidence can also be very valuable in the consideration of emerging issues or safety issues under consideration.

4.2.10 Evaluation of risks and risk characterisation

This section should focus mainly on new information and how it impacts on existing knowledge. If there is no substantive new data emerging, this section in the AR can be kept brief. It is helpful to briefly summarise the Risk Management Plan (RMP) in place for safety concerns and to consider any impact of the PSUR assessment on the RMP. It is important to assess whether any new data has been presented in the PSUR in relation to areas of missing information or important potential risks included in the RMP, as these safety concerns can be reconsidered depending on the data presented in each PSUR. It is also important to be aware of any ongoing variations and those concluded after the Data Lock Point (DLP) involving the RMP. It should be remembered that the PSUR is a global retrospective evaluation document, as distinct from the EU RMP, which is a regional prospective planning document. For this reason, it is not particularly pertinent to focus on trying to align the classification of safety concerns across documents from several MAHs. The focus of the PSUR is on evaluation of the available evidence with a view to updating product information or risk management approaches, but not necessarily on advising MAHs on how to categorise safety concerns in future PSURs, unless this is particularly relevant for evaluation purposes.

4.2.11 Characterisation of benefits

As the PSUR is intended to focus on new or interval information in the context of the cumulative knowledge of a product, this section may briefly outline the benefits unless there is new benefit information that has become available during the reporting interval for authorised indications. For CAPs it may be helpful to refer to the European Public Assessment Report (EPAR), available on the EMA website, when preparing this section of the report.

4.2.12 Benefit-Risk evaluation

The purpose of the B/R evaluation is to describe if the favourable effects, with their uncertainties, outweigh the unfavourable effects, with their uncertainties.

The level of detail presented in the AR should depend on whether there are issues arising that potentially impact the B/R balance of a product, particularly when the outcome for the PSUR is one other than maintenance. The level of experience with the medicine (e.g. well-established versus subject to additional monitoring) is also likely to impact on the detail presented in this section.

If new issues arise that potentially impact the B/R balance of a product, first describe the importance of the unfavourable effects/safety issue, with the assessor's estimation of the impact on the B/R balance, followed by a concise general discussion, including the impact of the uncertainties and the regulatory options (e.g. possible risk minimisation measures, etc., where applicable). During the evaluation, consider also the place in the treatment of the medicinal product under assessment and the availability of alternative therapeutic options (with their respective safety profiles).

4.3 Different approaches to assessment according to the lifecycle of the medicine

It is recognised that at the time of authorisation information on the safety of a medicinal product is relatively limited. This is due to a number of factors, including the numbers of subjects included in clinical trials compared with the intended treatment population, restricted population with regard to age, co-morbidity, concomitant medication use, ethnicity, etc. and the relatively short duration of exposure and follow-up.

Consequently, when conducting a PSUR assessment, it is important to consider the stage in the lifecycle of the medicine, for example, whether it is a newly authorised or well-established medicine. Uncertainty in relation to a medicine's safety profile should be the key driver of risk proportionality in PV. Accordingly, uncertainty is reduced with increased exposure, meaning that a well-established medicine with extensive exposure will have limited uncertainties in relation to its safety profile and the focus with respect to risk proportionality will likely be on the effectiveness of risk minimisation in practice.

4.4 Support for the drafting of questions to be addressed by the MAH

If the need for additional information is foreseen during the assessment, sufficient time should be allocated to drafting the List of Questions (LoQ), as this is a crucial aspect of the assessment.

Keep the questions clear and focused and avoid wording that is open to misinterpretation. It is usually useful to ask somebody else to read the draft questions before they are finalised and sent to the MAH(s). In the LoQ it helps to reference the relevant section of the PSUR/AR and add that more detailed assessor's comments are available in these sections. Make sure you specify when these questions need to be addressed by the MAH(s) Request for Supplementary Information (RSI), next PSUR, recommendation for future PSURs, or other procedure).

It is really important that the RSI is reserved for issues that need to be addressed during this PSUR procedure and are feasible for the MAH to address in the available time. The RSI should focus on issues likely to impact the conclusions and recommendations of the PSUR assessment and may impact B/R. The importance and relevance of the requested data should be explained. It is also very important to bear in mind the timeline for assessment of the MAH responses, requested/accompanying data and production of the PSUR Updated AR. Some issues may be best addressed in the next PSUR or in an alternative procedure. The timelines for the next PSUR submission should be considered (refer to the EURD list). Depending on the safety issue, requesting that it is addressed in the next PSUR may be appropriate where the periodicity of assessment is frequent, but may not be appropriate in the case of longer interval periods. In the case of the latter, issues may need to be followed up through an alternative procedure.

4.5 Support for better delivery of procedure recommendations and final outcomes

4.5.1 PSUR outcomes

Three possible outcomes result from the assessment of a PSUR: maintenance, variation, suspension or revocation.

Do make a decision – recommendations from your assessment must be logical, clearly presented and robustly justified in line with evidentiary standards in your AR. If proposing changes to section 4.8 of the SmPC, consider whether there is evidence to support a causal association considering the population exposed and other relevant factors. The appropriate frequency evaluation and estimation for proposed ADRs should also be considered. Harmonisation should not be the driver for proposing updates.

Again, carefully consider early on in the assessment process, and flag up to the relevant people as soon as possible, if the plan or recommendation is likely to be one other than maintenance of the Marketing Authorisation, so that there is adequate discussion and peer review of the scientific grounds/evidence base for any recommendations. When recommending a variation to the marketing authorisation, pay particular attention to the provision of a clearly outlined and robust scientific justification for the recommendation. In cases where the PSUSA includes different formulations of a medicinal product for which the recommendations vary, it is essential that the recommendations for each formulation are clearly distinguished in the AR.

4.5.2 Product Information updates

The MAH may propose a Product Information (PI) update as a result of the data presented in the PSUR, which should be evaluated by the assessor. Alternatively, the assessor may propose a PI update following an evaluation of the evidence presented. As far as possible, specify your proposed wording for product labelling at the stage of the Preliminary AR, as it gives both MSs and the MAH(s) time for consideration. It can be useful sometimes to request the MAH to contribute to wording for the PL, due to their in-house communication expertise/resources.

In some instances it may be necessary to reflect the uncertainties around particular issues (e.g. available evidence, causality assessment, etc.). The assessor should discuss, if relevant, risk management or other proposals/actions that are in place or that are planned to help address these uncertainties.

4.5.3 Summary paragraph

The summary paragraph should be succinct and contain the important issues to highlight and conclusions relating to these issues.

4.5.4 Updated reports

It is recommended that the changes in the updated AR are highlighted to facilitate review of the updated report when circulated, as the timeline for such review is short at this stage. In some instances the responses from the MAH(s) can be very lengthy and it may be more useful to summarise the MAH responses, rather than completely reproducing them. The assessor's overall conclusions should be clearly documented in the updated report.