GUIDANCE DOCUMENT FOR MARKETING AUTHORISATION HOLDERS ON SUBMISSIONS of PSURs UNDER THE EU PSUR WORK SHARING SCHEME

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This document sets out the responsibilities of the Marketing Authorisation Holders with respect to the submission of PSURs under the work sharing scheme. The responsibilities of the National Competent Authorities are set out in a separate guidance document.

The Marketing Authorisation Holder (MAH) should prepare a Periodic Safety Update Report (PSUR), based on the adopted EU harmonised Data Lock Point[1] (EU DLP) for an active substance. Either single report or multiple reports (e.g. three annual reports) with the summary bridging report, will be submitted. The PSUR should be prepared according to Volume 9A (Chapter I.6 based on the ICH-E2C Guideline) and submitted to all Member States where the company holds a marketing authorisation for a medicinal product with the same active substance within 60 days of the EU DLP.

It is the responsibility of the MAH to ensure that there are no gaps in the timeframe in the data sent to National Competent Authorities (NCAs). With the first harmonised PSUR there is likely to be some overlap of data which is acceptable. If the harmonised DLP falls after the date the next PSUR (or PSUR to support a renewal application) is due, the MAH should submit the PSUR according to the original DLP. To avoid any time gaps in data, the MAH should then submit an addendum report, from the last DLP to the harmonised DLP. Addendum reports under the PSUR work sharing scheme should follow the PSUR format and the data does not need to be represented in the next PSUR.

Documents to be submitted with the PSUR:

1. A cover letter should accompany the PSUR submission and should include:

(i) A **statement** that the PSUR is being submitted under the EU PSUR work sharing scheme

(ii) The **Procedure Number** (can be retrieved from the PSUR Work Sharing list, that can be found on the HMA website),

(iii) **Confirmation** that the PSUR will be submitted in all Member States where products containing the active substance are authorised,

(iv) **A single contact point** (including an email address) for communications (regarding submissions under the scheme). This email address should be valid for at least a year.

A template for the cover letter can be found on the Heads of Medicines Agencies website - www.hma.eu/80.html)

[1] The EU harmonised DLP can be any day of a certain month in a certain year.

In accordance with the template for the cover letter for the submission of PSURs for any product, the cover letter should highlight the differences between the SmPC and the Reference Safety Information (RSI), i.e. the CCDS/CCSI). For innovator PSURs submitted under the work sharing scheme the cover letter should however highlight differences between the Reference Safety Information and the proposed Core Safety Profile (CSP - see below). For this purpose a tabulation should be added to the cover letter.

The Reference Safety Information used for preparation of the PSUR usually is the Company Core Data Sheet (CCDS) or the Company Core Safety Information (CCSI). For companies who do not have a CCSI or CCDS, the Reference Safety Information (RSI) for the PSUR should be the common safety information that is included in **all** current SmPCs of the product (common denominator), as authorised in Member States at the time of data lock point.

2. A table[2] in a format with document file settings that allow editing using word processor software should be annexed to the cover letter which contains information on:

a. in which Member States the relevant product is authorised,
b. name of the marketing authorisation holder,
c. under which name of the medicinal product in accordance with Article 1(20) of Directive 2001/83/EC, pharmaceutical form and strength,
d. the marketing authorisation number along with MRP/DCP procedure numbers where applicable and the date of authorisation.

If the relevant product is not authorised in the P-RMS (PSUR Reference Member State), the MAH should submit a copy of the table to the P-RMS with **a specific cover letter** (see also template for this cover letter on the HMA website). The P-RMS will only send communications regarding the work sharing procedure to MAHs who have provided the required contact details in the cover letter.

3. A table[2] summarising adverse drug reactions from the period covered by the current PSUR should be submitted by all MAHs (a template can be found at the end of this document).

4. Core Safety Profile (CSP) to be provided by the innovator only:
Vol. 9A, I.6 requires that with the PSUR the EU or national SmPC should be submitted. For the EU work sharing procedure, this may cause difficulties due to the differences in national SmPCs. Therefore, to help with the assessment, the MAH of the innovator product should prepare and submit a proposal for a Core Safety Profile. This document should be generated according to the latest

[2] These tables should always be provided electronically to the P-RMS.

SmPC guidelines and include common information **from sections 4.3 - 4.9 present** in all SmPCs within the EU and any relevant safety information from section 4.2.
The CSP will be used to indicate new information from the PSUR which should be included in all current SmPCs for the product as part of the risk management for the substance. In the cover letter the MAH should state if any changes to the CSP are required on the basis of the data included in the PSUR.

Due to differences in SmPCs for the purpose of the CSP, common information is considered information which is similar. Exact wording across all Member States is therefore not required as long as the meaning is the same. Where a condition is contraindicated in some SmPCs but is present as a warning in other SmPCs, for the purpose of the CSP this will be considered common information. This information should be included in the section which best reflects the CCSI. The MAH should highlight to the P-RMS and P-CMS where there is disharmony for certain statements/warnings in SmPCs across the EU. Likewise, for ADRs in section 4.8 similar terms will be considered common information. For the preparation of the CSP, the MedDRA preferred term should be used in line with the SmPC guidelines.

Where an SmPC has been recently harmonised through a referral procedure, this SmPC should be used to create the CSP regardless of whether the harmonised SmPC has been implemented in all NCAs at the time of preparation of the CSP.

Rarely, where a PSUR covers different indications or formulations which result in significantly different safety profiles the MAH and/or the P-RMS may consider that more than one CSP is appropriate. In these cases the documents must be clearly defined using the appropriate ATC code and/or by stating the indication/formulation at the start of the document. Early communication with the P-RMS regarding the need for more than one CSP is advisable.

5. Additional documents to be submitted by the MAHs of generics

Generic companies who hold an EU SmPC of a product containing the active substance (i.e. authorised through MRP/DCP/CP) should submit the EU SmPC along with the cover letter and the table to the P-RMS of the active substance. This is also the case if the product is not authorised in the P-RMS country. This step is to aid the P-RMS in obtaining the best possible safety information of the substance.

Procedural aspects

1. After submission of the PSUR by the MAHs to the respective MSs, the P-RMS for the active substance should validate the dossiers and start the assessment within one month. The P-RMS will circulate a timetable to all Member States and MAHs under the procedure. This information will reach the MAHs via the “single contact point” email address given in the cover letter. If the P-

RMS requires additional data or information in order to complete its validation, MAHs will be given maximum 14 days to submit the missing documents.

The P-RMS will assess the PSUR of the innovator and any other PSURs submitted to them under the work sharing scheme for products which are authorised in the P-RMS. The work sharing preliminary PSUR AR (WS-PSUR AR) including the proposed assessor commented CSP will be sent on day 40 to all Member States for comments and to all MAHs who have provided contact details to the P-RMS (innovator and generics) for information. The WS-PSUR AR will include any changes that are required to the proposed CSP. By day 70 in the procedure, MSs will send comments and any additional safety information which has not been addressed in the WS-PSUR AR, arising from the assessment of PSURs for products which are not authorised in the P-RMS.

2. After receiving comments from MSs, the P-RMS will take one of the following actions:

i) In case of consensus and if no changes to the proposed CSP are required, the WS-PSUR AR will become the work sharing final PSUR AR (WS-Final PSUR AR). The WS-Fina PSUR AR and the agreed CSP will be sent directly to all MSs and MAHs under the procedure on day 74/75.

ii) Where the preliminary assessment report and/or comments from MSs have raised minor changes to the proposed CSP, a List of Questions (LoQ) will be sent to the MAHs as above by day 74 with a copy to MSs for information and the clock will be stopped. A response will be requested within 30 days.

iii) Where the WS-PSUR AR identifies a safety concern that significantly alters the risk: benefit of the active substance, the clock will be stopped and the P-RMS will prepare a report for the PhVWP setting out the issue including any information received from P-CMSs. Depending on the preliminary advice from PhVWP the PSUR work sharing procedure may continue to finalisation.

iv) In cases where comments from the P-CMSs indicate that there is significant divergence in the SmPCs approved in different MS, the innovator may be a suitable candidate for SmPC harmonisation. The P-RMS will send a request to the CMD(h) for the product/active substance to be considered for harmonisation. If these divergences concern safety issues, these will be referred to the PhVWP in the first instance. The PSUR assessment can then continue without agreement of the CSP.

3. MAHs will have 30 days to respond to the LoQ. Responses should be sent to the P-RMS and all MSs where the MAH holds a marketing authorisation for the active substance.

4. Once a satisfactory response has been received, the P-RMS will prepare and circulate a draft WS-Final PSUR AR and the CSP within 30 days. When the draft WS-Final PSUR AR is sent the

clock will restart (day 75). The draft WS-Final PSUR AR will state when the next PSUR is expected. Member states will have 15 days to comment on the draft WS-Final PSUR AR.

i) In case of consensus and when there are no outstanding issues the WS-Final PSUR AR and agreed CSP is sent directly to all MSs and MAHs on day 95 of the procedure.
ii) In case of opposing views either between Member States and/or the MAHs, Member States and the MAHs will have an additional 15 days to comment further and reach a mutual agreement. Where agreement cannot be reached by day 110, the P-RMS will refer the matter to the PhVWP.

5. The procedure will be finalised on day 75, day 95 or day 110. If no agreement can be reached by day 110 the issue will be referred to the PhVWP for discussion.

After finalisation of the PSUR assessment the P-RMS will send the WS-Final PSUR AR with the agreed CSP to the MAHs who have provided contact details to the P-RMS and all MS.

Where the PSUR is part of a renewal application for the originator product the WS-Final PSUR AR will be circulated at the same time as the final renewal assessment report to avoid duplication.

Where a RMP is submitted with the PSUR, the RMP will not be assessed as part of the PSUR worksharing but under the relevant procedure.

Implementation

After finalisation of the PSUR assessment, the P-RMS will send the WS-Final PSUR AR with the agreed CSP to the contact point of the MAHs. The agreed CSP will include the common information identified at the start of the procedure, together with any new information identified as necessary during the work sharing procedure and will be considered the agreed minimum safety information which should be included in SmPCs across the EU.

All MAHs should compare their currently approved SmPC with the agreed CSP. In case information from the CSP is missing, this should be included in the SmPC by a type II variation within 4 months of finalisation of the work sharing procedure. Individual NCAs may also send requests for updates to SmPCs as a result of the agreed CSP at their discretion. For MRP/DCP products the RMS will take the lead in agreeing updates to the EU SmPC.

Any variations should be supported by the WS-Final PSUR AR and agreed CSP. As the information in the agreed CSP represents the agreed minimum information plus any new safety concerns resulting from the work sharing assessment, no contraindications, warnings or any other information should be deleted from SmPCs as a result of them not being included in the CSP. An exception is if it has been explicitly agreed during the work sharing procedure that some information in the CSP is

erroneous or redundant and should be deleted for the correct handling of safety for the active substance in question

Where there is a proposed or ongoing referral procedure, the work sharing will be completed, although a CSP will not be agreed during the work sharing procedure. Usually variations should not be submitted to update product information until completion of the referral and publication of the Commission Decision. The P-RMS will communicate the outcome of the work sharing procedure to the Rapporteur for the referral. The variation following the referral procedure should include any additions required as a result of the PSUR assessment, which have not been addressed in the referral procedure.
In some cases however, an issue may be identified during the work sharing procedure and a new safety update will need to be implemented before the completion of the referral. This will be where an immediate update is considered necessary for the safe use of the product.

Actions of all MAHs in the period between PSUR submissions

Between PSUR submissions the CSP will not be updated. However MAHs should continue their Pharmacovigilance activities and have an obligation to submit variations to update product information as required.

Update to CSP at submission of next PSUR

At the next DLP, the innovator MAH should propose an updated CSP. This proposed CSP should be formed from the previously agreed CSP together with a separate document listing new information which has been added to the CCSI or any SmPC during the intervening period. Unless these updates were a result of a PhVWP assessment, a short reasoning for these updates should also be provided, as well as the countries in which these updates have been submitted.

Abbreviations

CCDS- Company Core Data Sheet
CCSI- Company Core Safety Information
CMD(h) – Co-ordination group for mutual recognition and decentralised procedures
CP – Centralised Procedure
DCP- Decentralised Procedure
DLP- Data Lock Point
CSP –Core Safety Profile
HMA - Heads of Medicines Agencies
LoQ – List of Questions
MAH Marketing Authorisation Holder
MRP- Mutual Recognition Procedure
MS – Member States
NCA – National Competent Authorities
PhVWP- Pharmacovigilance Working Party
P-CMS – PSUR Concerned Member State
P-RMS – PSUR Reference Member State
PSUR – Periodic Safety Update Report
RSI- Reference Safety Information
SmPC - Summary of Product Characteristics
WS-Final PSUR AR - work sharing final PSUR Assessment Report
WS-PSUR AR - work sharing preliminary PSUR Assessment Report

Flow Chart

Day	Event
-30 – 0	Upon receipt of the PSUR, the P-RMS validates the dossier and circulates the timetable
0	Start of procedure
40	P-RMS circulates the WS-Preliminary Assessment Report (WS-PSUR AR) to Member states and MAHs for information
70	Member States send comments and any additional information from PSURs submitted in their Member States for consideration to the P-RMS.
74	P-RMS circulates the WS- Final assessment report (WS-Fina PSUR AR) (in case of consensus that there are no issues and no additional information required) OR Clock Stop 1. RFI issued on day 74. Clock stop for 60 days (30 days for MAH to respond and 30 days for P-RMS to prepare draft WS-Final PSUR AR. 2. Safety concern which potentially significantly affects the risk - benefit balance. P-RMS refers issue to PhVWP. 3. Significant divergence of safety information in national SmPCs. P-RMS refers to CMD(h). If the inconsistencies concern safety issues: referral to PhVWP in first instance.
75 Clock restart	Clock restart P-RMS circulates the WS-Draft Final Assessment Report taking into account answers from MAHs
90	Members States send comments
95	Close of procedure - P-RMS circulates WS-Final

	PSUR AR and agreed CSP **OR**
110	15 more days to reach a mutual agreement in case of opposing views either between Member States and/or the MAHs. If resolved, procedure closes at day 110.
110-120	In case of disagreement, the P-RMS refers the matter to the PhVWP.

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Annex to the PSUR

TABLE OF ADVERSE DRUG REACTIONS (ADRs)					
	Serious		**Nonserious**		**Total**
System Organ Class (SOC)	**Listed**	**Unlisted**	**Listed**	**Unlisted**	
Blood and lymphatic system disorders					
Cardiac disorders					
Congenital and familial and genetic disorders					
Ear and labyrinth disorders					
Endocrine disorders					
Eye disorders					
Gastrointestinal disorders					
General disorders and administration site conditions					
Hepatobiliary disorders					
Immune system disorders					
Infections and infestations					
Injury poisoning and procedural complications					
Investigations					
Metabolism and nutrition disorders					
Musculoskeletal and connective tissue disorders					
Neoplasms benign, malignant and unspecified					
Nervous system disorders					
Pregnancy, puerperium and perinatal conditions					
Psychiatric disorders					
Renal and urinary disorders					
Reproductive system and breast disorders					
Respiratory thoracic and mediastinal disorders					
Social circumstances					
Skin and subcutaneous tissue disorders					
Surgical and medical procedure					
Vascular disorders					
Total					