PhVWP and CMD(h) BEST PRACTICE GUIDE FOR WORK SHARING CONCERNING THE ASSESSMENT OF PSURs OF PRODUCTS FOR WHICH AN EU HARMONISED VIRTUAL BIRTH DATE AND RELATED HARMONISED DATA LOCK POINT HAVE BEEN AGREED

Version, 10 November 2009.

This document sets outs the responsibilities of the P-RMS and P-CMS with respect to work sharing in the assessment of PSURs. The responsibilities of the MAHs are set out in a separate guidance document and assessors should ensure they are also familiar with this document.

Due to differences in SmPCs across Europe a document against which PSURs can be assessed is required. For the purpose of work sharing the reference safety information will be the Core Safety Profile (CSP) (see annex 1). This document will be used to determine if new safety information should be added to all SmPCs in the EU.

1 The P-RMS is responsible for producing an Assessment Report (AR) on the PSUR of the innovator product and including any safety information from PSURs of relevant products authorised in the P-RMS which has not been addressed in the innovator PSUR. The P-RMS should also assess the proposed CSP provided by the innovator. Before assessing the CSP the P-RMS should check whether there are any ongoing or proposed Article 30 referrals (http://www.hma.eu/242.html). In these cases the P-RMS should not agree a CSP. Any safety related changes considered necessary as a result of the PSUR assessment should be forwarded to the Rapporteur for inclusion in the harmonised SmPC. 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.

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.

2 The cover letters provided by MA holders should be used to create the cover sheet so it is clear which PSURs are covered by the report. The single contact point should be used for all communications with MAHs. The P-RMS will send communications to all MAHs who have sent the required information in the cover letter.

3 A PSUR in the work sharing project is based on an EU harmonised DLP which is any day of a certain month in a certain year. PSURs will be submitted within two months of the EU harmonised DLP. The P-RMS is responsible for ensuring that the innovator PSUR has been submitted to their NCA. Once received the P-RMS should validate the dossiers and start the assessment within one month. If the P-RMS requires additional data or information in order to complete its validation, Innovator MAHs will be given a maximum 14 days to submit the missing documents.
The date of starting the assessment is Day 0 of the PSUR assessment procedure. The P-RMS has 40 days after Day 0 for preparation of the preliminary assessment report.

4 The P-RMS will inform Member States (MSs) that the PSUR(s) has(have) been received by circulating the timetable to all MSs and the MAHs participating in the scheme using the single contact points provided by MAHs. Until a tracking system is in place this should be done by email using the PSUR mailbox. Templates for the subject heading and content of the email are to be used so that it is easy for competent authorities to identify the timetables – these can be found in Annex 3.

5 The AR should be generated using the template that can be found at Annex 1. The assessment should focus on the information provided in the PSUR and provide a full assessment of any signals which have arisen during the period covered by the PSUR. If as a result of this assessment changes are required to the safety information in the CSP these should be clearly stated along with the reasoning for adding the information. The proposed CSP should be appended to the WS-PSUR AR.
The P-RMS should state if any changes to the CSP are required as a result of the PSUR assessment.

The AR should be completed in line with the PhVWP guidelines for assessment of PSURs. The P-RMS should consider whether for newer products the AR template provided with the PhVWP guideline is more appropriate than the abbreviated AR in Annex 1.

For active substances where different formulations/indications exist which are not included separately on the list of harmonised birth dates, the MAH may propose more than one CSP. In these instances the MAH should clearly define these by using the appropriate ATC code and/or indications/formulation at the start of the document. The P-RMS may also prefer to produce separate assessment reports and CSPs. This should be done with the agreement of the P-CMSs during the procedure.

For details of what the CSP entails see Annex 2.

Where a RMP is submitted with the PSUR the assessment of the RMP will not be assessed as part of the PSUR work sharing procedure. It should however be clearly stated in the assessment report that an RMP was submitted.

6 Patient exposure data from the innovator PSUR (and generic PSURs where the information is informative at the discretion of the P-RMS) are to be given in an annex to the AR.. The innovator will receive the entire assessment report with all the annexes including the patient exposure data for their product. The other MAHs will receive ARs without the annexes concerning patient exposure information.

7 By Day 40 the P-RMS will distribute a work sharing preliminary PSUR AR (WS-PSUR AR) to all other MSs through the PSUR mailbox (see Figure 2 for Flowchart). A copy will also be sent for information to the MAHs using the contact details supplied in the annex to the cover letter.

Where the PSUR has been submitted as part of a renewal application the assessment of the PSUR should be supplied as an annex to the preliminary renewal assessment report. The PSUR assessment should also be circulated separately to all Member States through the PSUR mailbox.

8 By Day 70 the Concerned Member States should send comments through the PSUR mailbox using the template in Annex 4 to the P-RMS, including any additional information not already covered in the WS-PSUR AR from PSURs which are not authorised in the P-RMS. The NCAs are responsible for screening PSURs for products not authorised in the P-RMS and alerting the P-RMS to any new issues (see scheme in **Figure 1**).

With regard to Mutual Recognition procedures for generic products the RMS should take the responsibility of reviewing the PSUR and sending comments.

P-CMSs can send proposed amendments to the CSP as a result of safety information currently in SmPCs in their NCA. This information should be scientifically justified.

9 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 assessment report (WS-Final PSUR AR). The WS-Final PSUR AR and the agreed CSP should be sent directly to all MSs and MAHs 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), is to be sent to the MAHs as above by day 74 with a copy to MSs for information and the clock stopped. The LoQ should consist of a compilation of all MS comments in table form and request a response within 30 days. Responses

to LoQs should be sent to the P-RMS and all MSs where the MAH holds a marketing authorisation for the active substance.

iii. Where the preliminary assessment report 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 the 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 should send a request to the CMD(h) for the product/active substance to be considered for harmonisation. The CMD(h) guidelines on requests for SmPC harmonisation should be taken into account (http://www.hma.eu/242.html). The P-RMS should use the template provided in the CSP paper in Annex 2 for requesting the product is considered for SmPC harmonisation. If these divergences concern safety information this should be referred to the PhVWP in the first instance. The PSUR assessment can then continue without final agreement of the CSP.

10 Once a satisfactory response has been received the P-RMS will prepare and circulate the 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 using the PhVWP AR template provided in the CSP paper (Annex 2) for discussion at the next meeting of the PhVWP in order to reach a consensus.

11 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.

12. After finalisation of the PSUR assessment the P-RMS will send the WS-Final PSUR AR (without the annex on patient exposure) with the agreed CSP to the contact point of the MAHs and all MS. These documents must be clearly

labelled as final and agreed so that it is clear that the procedure has been finalised.

MAHs should submit variations to update SmPCs with information from the CSP within 4 months of receiving the final assessment report and agreed CSP.

Between PSUR assessments

If any NCA wishes to propose a different PSUR cycle this should be discussed with the P-RMS and EMEA before implementing. The reasoning why a different PSUR cycle is needed should be given as it maybe appropriate to alter all PSUR cycles in the EU for that particular active.

The CSP is not a living document and is not updated between work sharing assessments. Changes to national SmPCs can be made in accordance with current practices. Issues should still be raised with the PhVWP as normal.

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 stating the countries in which these updates have been submitted.

Figure 1: Scheme for Screening Generic PSURs for New Safety Information

The following is a scheme for assisting Member States in screening generic PSURs for new safety information .The Reference PSUR AR for the original product should be referred to when using this scheme.

- **What is the Company perspective**

Review overall safety evaluation/information received after data-lock point

1. Have new safety issues been identified or has the company proposed any action?

- **What has happened since the last review**

Review update on actions taken for safety reasons

2. Have there been any significant actions, for example, product withdrawal in any country or any major safety studies?

- **What is the Regulators perspective**

3. Are there any outstanding safety issues regarding the active substance?

If the answer to <u>any of</u> questions 1 –3 is Yes:

- Does the new information in the generic PSUR change or add anything to the Reference PSUR AR for the original product?

If Yes - the issue (and where appropriate the PSUR) should be referred to the P-RMS.

Figure 2: Flowchart

Day	Event
-30 - 0	PSUR received and P-RMS circulates the timetable
0	Start of procedure – circulation of timetable
40	Circulation of 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	Final assessment report (in case of consensus that there are no issues and no additional information required) OR Clock Stop 1. LoQ 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 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 draft final assessment report taking into account answers from MAHs
90	Members States send comments
95 110	Close of procedure circulation of WS-Final PSUR AR and agreed CSP **OR** 15 more days to reach a mutual agreement in case of opposing views either between

110-120	Member States and/or the MAHs, If resolved procedure closes at day 110. In case of disagreement, the P-RMS refers the matter to the PhVWP

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
MSs – Member States
NCA – National Competent Authorities
PhVWP- Pharmacovigilance Working Party
P-RMS – PSUR Reference Member State
P-CMS – PSUR Concerned Member State
PSUR – Periodic Safety Update Report
RSI- Reference Safety Information
SmPC - Summary of Product Characteristics
WS-Final PSUR AR - work sharing final PSUR Assessement Report
WS-PSUR AR - work sharing preliminary PSUR Assessment Report

Annexes

1. Assessment report template
2. CSP paper
3. Email templates
4. Template for sending comments to the P-RMS

Annex 1
AR Template

P-RMS <PRELIMINARY, (DRAFT) FINAL>

ASSESSMENT REPORT

Procedure number XX/H/PSUR/XXXX/XXX

Active substance	
Innovator name of product in the P-RMS	
<for MRP products also procedure number>	
Pharmaceutical form(s)/strength	
MAH(s)	
HBD and DLP	
PSUR period	**(day Month year- day Month year)**
P-RMS	
Assessor	
Contact point	

TIME TABLE

Procedure Start Date	
Date of preliminary AR	
Deadline for comments to P-RMS	
Clock stop/ RFI / LoQ	
Procedure Restart Date	
Date of Draft Final AR	
Deadline for comments to P-RMS	
Date of Final AR	
Discussion at PhVWP	
DLP of the next PSUR submission and period of PSUR	

In addition to the innovator PSUR, the assessment report covers the following PSURs of additional products authorised in the P-RMS:

MAHs	MR procedure number (if applicable)	Period covered by the PSUR

The following PSURs of products <u>not authorised in the P-RMS</u>* have been submitted as part of the worksharing procedure.

MAHs	MR procedure number (if applicable)	Period covered by the PSUR

* An overview table has been submitted to the P-RMS.

INDICATIONS AUTHORISED IN THE P-RMS (INNOVATOR):

WORLDWIDE MARKETING AUTHORISATION STATUS AND UPDATE OF REGULATORY ACTIONS TAKEN FOR SAFETY REASONS (MAH, AUTHORITIES)

Has there been a change to the marketing authorisation status or have regulatory actions been taken for safety reasons? Yes ☐ No ☐ If yes, specify:

SUMMARY OF RELEVANT PhVWP/CHMP DISCUSSIONS *, IF ANY:

* During the period under review

CHANGES TO REFERENCE SAFETY INFORMATION

Is the CCDS the reference document? Yes ☐ No ☐ If not, please indicate which document is used as reference document: Date of the last reference document :

Which sections of the reference safety document have been changed during the period covered by the PSUR?

- ☐ posology and method of administration (4.2)
- ☐ contraindications(4.3)
- ☐ special warnings and precautions for use(4.4)
- ☐ interaction with other medicinal products and other forms of interaction(4.5)
- ☐ pregnancy and lactation (4.6)
- ☐ effects on ability to drive and use machines(4.7)
- ☐ undesirable effects(4.8)
- ☐ overdose (4.9)

Please specify the safety relevant changes:

Selected differences between RSI and proposed CSP:

SUSPECTED ADVERSE DRUG REACTIONS (INNOVATOR) DURING THE PERIOD

SERIOUS CASES AND ADRs

Total number of serious cases, incl. fatalities	
Number of fatal cases	

SUSPECTED ADVERSE DRUG REACTIONS, overview

TABLE OF ADVERSE DRUG REACTIONS (ADRs)					
	Serious		**Non-serious**		**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					

TABLE OF SELECTED* SERIOUS UNLISTED ADRs :

Serious unlisted ADRs (MedDRA PT in agreed SOC order)	Number of serious unlisted ADRs

* Selection is within the discretion of the P-RMS

VALUABLE INFORMATION FROM PSURs FOR OTHER PRODUCTS AUTHORISED IN THE P-RMS

Do any of the PSURs for other products authorised in the P-RMS contain information not addressed in the PSUR for the originator product(s)?

Yes ☐ No ☐

If yes, specify in table below:

TABLE OF SELECTED* SERIOUS UNLISTED ADRs IN OTHER PSURs AUTHORISED IN THE P-RMS

Serious unlisted ADRs (MedDRA PT in agreed SOC order)	Number of serious unlisted ADRs

* Selection is within the discretion of the P-RMS

Other information:

OVERALL ASSESSOR COMMENTS ON CASE REPORTS (INCL. LITERATURE CASES)

Describe and comment on ADRs of importance from individual case histories.

OVERALL ASSESSOR COMMENTS ON MAH SPONSORED STUDIES

Describe and comment on studies of relevance to safety of the product(s)

OVERALL ASSESSOR COMMENTS ON STUDIES FROM THE LITERATURE

Describe and comment on literature studies of relevance to safety of the product(s).

OVERALL ASSESSOR COMMENTS ON NEW INFORMATION REGARDING

Special populations: **Pregnancy/lactation:** **Drug interaction:** **Overdose:** **Abuse or misuse:** **Medication errors:** **Long-term treatment:** **Off label use:**

COMMENTS ON ANY CHANGE OF THE RISK BENEFIT BALANCE

MAH conclusion: **<u>Assessors conclusions and comments:</u>**

ACTION PLAN AND CONCLUSIONS

A CHANGES OF THE BENEFIT RISK BALANCE

Has the benefit risk balance changed?

No ☐

Yes ☐ , please specify:

B CHANGES REQUIRED IN THE CSP

Is the CSP acceptable?

Yes ☐ No ☐

If not, specify the necessary changes (specific wordings):

C REGULATORY ACTIONS * PROPOSED, IF ANY

* Regulatory options may include urgent safety restrictions, variations, suspension or revocation. Topics for close monitoring should be mentioned below in section E.

D SUMMARY OF COMMENTS FROM OTHER MSs

Member State	Comment	Agreed action e.g. updating CSP, close monitoring

E POINTS TO BE ADDRESSED IN THE NEXT PSUR

<E.g. agreed topic(s) for close monitoring / review to be included in next PSUR.>

F RFI / LoQ: REQUEST FOR FURTHER INFORMATION / LIST OF QUESTIONS

Questions to be addressed by the MAH: **MAH response:** **P-RMS assessment and conclusion:**

FINAL CONCLUSION (SUMMARY OF A-F)

DATE AND CONCLUSION OF PHVWP DISCUSSION CONCERNING THIS PSUR, IF ANY:

Annex I : CSP

In PAR: Proposed CSP with assessor comments, if any
In Draft FAR: Proposed CSP with assessor comments
In FAR: Agreed CSP

Annex II:

PATIENT EXPOSURE (one annex for each PSUR of products authorised in the P-RMS)

Patient exposure in this PSUR :

Methodology used for the exposure number calculation :

☐ Defined Daily Dose
☐ patients/day
☐ number of prescriptions
☐ number of doses
☐ Other (please specify)

Comparison with previous PSUR, if information is available

Change in methodology used for calculation:
Yes ☐ No ☐

Overall change in patient exposure:
Yes ☐ No ☐

Increase ☐ Decrease ☐

Annex III: COMMENTS ON THE PSUR (annex exclusively for innovator MAH)

Is the PSUR in accordance with international guidelines (CIOMS II, Volume 9A) ? Yes ☐ No ☐ If not, specify non-conformance with the guidelines

Annex 2
CSP Paper

Core Safety Profile Paper
10.07.09

Background

Volume 9A of "The Rules Governing Medicinal Products in the European Union," sets out that the objective of the PSUR is to establish whether information recorded during the reporting period is in accordance with previous knowledge of the medicinal product's safety and to indicate whether changes are required to the product information or the risk management plan. Reference safety information is needed to carry out this comparison and forms the basis for determining whether an adverse reaction is listed or unlisted.

In accordance with the ICH-E2C guidelines, the Reference Safety Information (usually the Company Core Data Sheet (CCDS) or the Company Core Safety Information (CCSI)) should be used for preparation of the work sharing PSUR.
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 document containing the safety information for the substance. This document should be generated according to the latest SmPC guidelines and only include common information in all SmPCs within the EU from sections 4.3 – 4.9 and any relevant safety information from section 4.2. The safety information in this document will be referred to as the proposed Core Safety Profile (CSP). In accordance with Vol.9A the cover letter should highlight the differences between the SmPC and the Reference Safety Information (CCDS, CCSI, RSI), however for innovator PSURs submitted under the work sharing scheme the cover letter should highlight differences between the Reference Safety Information and the proposed CSP.

Core Safety Profile

The CSP should be prepared by the innovator only. In this document 'MAH' refers to the innovator MAH with the exception of the section on implementation. 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.

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. 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.
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.

The main focus of the work sharing assessment will be to identify if there is new emerging safety information affecting the risk-benefit of the product and any changes required to SmPCs within the EU as a result of the assessment of this information. At the end of the assessment an agreed CSP will be produced, which 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. This will be the agreed CSP and will be considered the agreed minimum safety information which should be included in SmPCs across the EU.

Responsibilities of Contributors in relation to the CSP

Responsibilities of MAH
The MAH should provide the following documents:

- Information common to all SmPCs within the EU (proposed CSP)

- Tabulation of differences between the proposed CSP and the Reference Safety Information within the cover letter.

Rarely where a PSUR covers different indications or formulations which result in significantly different safety profiles the MAH 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.

Responsibilities of the P-RMS

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. If the conclusion of the PSUR assessment is that an update to the product information is required these updates will be made to the CSP.

The P-RMS should check whether there are any ongoing referral procedures before agreeing a CSP. If there are any ongoing referral procedures the P-RMS will continue with the assessment of the PSUR and communicate any safety changes considered necessary as a result of this assessment to the Rapporteur. In these cases a CSP will not be agreed during the procedure and only safety updates which NCAs consider should be implemented immediately for the safe use of the product will be made following the PSUR assessment (see paragraph below on implementation).

If the new information concerns a serious safety issue or there is a disagreement either between the Member States or with the MAH regarding updates to the CSP or other

risk management measures the matter will be referred to the PhVWP by the P-RMS using the template in Annex 1.

The P-RMS may consider that more than one CSP is appropriate for a particular active substance and can make a recommendation independently of the MAH; this should be agreed with the P-CMSs.

The P-RMS will review the CSP against information provided by P-CMSs at day 70 of the procedure. Where there is significant divergence in the registered safety information across Member States the P-RMS will communicate these to the CMD(h) using the template provided in Annex II and request that the product is considered for SmPC harmonisation. The P-RMS should take into account the CMD(h) rules for selecting active substances for harmonisation when considering referring the active substance to CMD(h). In instances where the P-RMS has recommended an active substance is considered for harmonisation only updates as a result of the PSUR assessment will be added to the CSP proposed by the MAH.

The P-RMS will make a recommendation in the assessment report to all Member States regarding the agreed minimum safety information, in form of the CSP, to be included in all SmPCs

Responsibilities of P-CMSs
P-CMSs will provide any additional data from PSURs submitted to them under the work sharing scheme which highlight issues not raised within the preliminary AR.

The P-CMSs will also review the information present in their SmPCs and provide the P-RMS with significant information which the P-CMS considers should be included in the CSP. A short scientific justification for the inclusion will also be provided.

Implementation – All MAHs

After finalisation of the PSUR work sharing procedure all MAHs should compare their currently approved SmPC with the CSP. In case information from the CSP is missing this should be included in the SmPC by a Type II variation within 120 days 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.
Any variations should be supported by the final assessment report and agreed CSP. For MRP/DCP products the RMS will take the lead in agreeing updates to the EU SmPC. As the information in the 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 to this 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 to correct the safety information for the active substance in question.

Where there is an ongoing referral procedure the work sharing will be completed but usually variations would not be submitted to update product information until completion of the referral and publication of the Commission Decision. The P-RMS should 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 Data Lock Point 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.

Annex I

Template for communication with PhVWP

<day month in words year>
Doc.Ref.:
Confidential

<RMS/MS/PhVWP/CMD(h)> Request for <CMD(h)/ PhVWP > discussion on <safety issue >

<PhVWP/CMD(h)> Representative :

[This request should be drafted by the PhVWP/CMD(h) representative of the RMS or Lead Member State and submitted to the PhVWP) no later than two weeks before the next PhVWP) meeting.]

BACKGROUND

[Description of the issue and procedural context in which the issue has arisen i.e. PSUR work sharing.

NATURE OF REQUEST

[State the questions to be addressed]

TIMETABLE

[Specify a deadline for the transmission of the PhVWP recommendations to the CMD(h)/PhVWP or a proposed time table as appropriate.]

DOCUMENTS

[Documents relevant for the discussion at the PhVWP e.g. the work sharing assessment.

Annex II

Template for requesting SmPC harmonisation by CMD(h)

Medicinal products for SmPC harmonisation under Article 30(2) of Directive 2001/83/EC, as amended

Nominating Member State:

Invented Name	**INN**	MAH	**Significant differences in 4.1-4.4 (Yes/No)**	**Exclusivity period/date patent expiry**	**Use (H = Hospital, GP = General Practice and Hospital)**	**Active substance in MRP/ referrals (Yes/No)**	**Priority (1 = top priority)**	**Other relevant information**
a.								
b.								
c.								
d.								
e.								
f.								
g.								
...								

Justification for each nomination:

I. What are the expected benefits of harmonisation?

.....

.....

II. Please provide additional information on significant differences in sections 4.1-4.4 in the SmPC.

.....

.....

Annex 3
Email templates

To: PSUR mailbox

Subject: Timetable for assessment of PSUR for ‘active’/’trade name’ covering period XX/XX/XXXX to XX/XX/XXXX under work sharing agreement. Procedure number XX/H/PSUR/XXXX/XXX

Dear colleagues,

Please find attached the timetable for the assessment for ‘active’/’trade name’ PSUR covering the period XX/XX/XXXX to XX/XX/XXXX. Procedure number XX/H/PSUR/XXXX/XXX. Please can member states send comments and any additional information from Generic PSURs by day 70 XX/XX/XXXX.

Day 0 XX/XX/XXXX
Day 40 XX/XX/XXXX
Day 70 XX/XX/XXXX
Day 75 XX/XX/XXXX

[where appropriate please also include]

This PSUR has been submitted in conjunction with MR/DP renewal procedure number XX/H/XXX/XX/RX.

To: PSUR mailbox

Subject: Preliminary PSUR AR for work sharing of ‘active’/’trade name’ covering period XX/XX/XXXX to XX/XX/XXXX under work sharing agreement. Procedure number XX/H/PSUR/XXXX/XXX.

Dear colleagues,

Please find attached preliminary AR for ‘active’/’trade name’ PSUR covering the period XX/XX/XXXX to XX/XX/XXXX. Procedure number XX/H/PSUR/XXXX/XXX. Please can member states send comments and any additional information from Generic PSURs by day 70 XX/XX/XXXX

[where appropriate please also include]

This PSUR AR has also been circulated in relation to the MR/DP renewal procedure number XX/H/XXX/XX/RX.

To: PSUR mailbox

Subject: Final PSUR AR for work sharing of ‘active’/’trade name’ covering period XX/XX/XXXX to XX/XX/XXXX under work sharing agreement. Procedure number XX/H/PSUR/XXXX/XXX.

Dear colleagues,

Please find attached final work sharing PSUR AR for ‘active’/’trade name’ PSUR covering the period XX/XX/XXXX to XX/XX/XXXX. Procedure number XX/H/PSUR/XXXX/XXX.

To: PSUR mailbox

Subject: Draft Final PSUR AR for work sharing of ‘active’/’trade name’ covering period XX/XX/XXXX to XX/XX/XXXX under work sharing agreement. Procedure number XX/H/PSUR/XXXX/XXX

Dear colleagues,

Please find attached the draft final AR for ‘active’/’trade name’ PSUR covering the period XX/XX/XXXX to XX/XX/XXXX. Procedure number XX/H/PSUR/XXXX/XXX. Please send comments by XX/XX/XXXX (30 days from circulation of report). If no agreement is reached the draft report will be sent to the PhVWP for consultation.

To: PSUR mailbox

Subject: (Country code) Comments on PSUR AR for work sharing of ‘active’/’trade name’ covering period XX/XX/XXXX to XX/XX/XXXX under work sharing agreement. Procedure number XX/H/PSUR/XXXX/XXX.

Dear colleagues,

Please find attached our comments on the AR for ‘active’/’trade name’ PSUR covering the period XX/XX/XXXX to XX/XX/XXXX. Procedure number XX/H/PSUR/XXXX/XXX

Annex 4

Template for sending comments to P-RMS

Comments on Work sharing PSUR (Preliminary/Final) assessment report
Procedure number XX/H/PSUR/XXXX/XXX

1. Comments sent by:

Member State	
Assessor(s)	Name: Email: Telephone:

2. Comments refer to report on:

Active substance	
BRANDNAME(S)	
<for MRP products also procedure number>	
Pharmaceutical form(s) and strength	
MAH(s)	
HBD	
PSUR Nº	**Covered period**
(P)RMS	
Assessor	
Contact point	

3. Comments

We fully endorse report of the P-RMS and have no additional comments ☐

We endorse the report of the P-RMS and have additional comments ☐

We endorse the report of the P-RMS and have additional information for the attention of the P-RMS. ☐

4. Additional comments

Issue	**Proposed action e.g. updating CSP, close monitoring**

5. Additional information from PSUR in NCA of member state

Issue	**Proposed action e.g. updating CSI, close monitoring**

Relevant PSUR attached Yes ☐ No ☐