

Questions and Answers on the EU Synchronisation of PSUR submission schemes of medicinal products authorised through national, mutual recognition and decentralised procedures Revision March 2011

Under the auspices of the “Heads of Medicines Agencies” an initiative has been taken to ensure that medicinal products with the same active substance follow the same Periodic Safety Update Report (PSUR) submission scheme in all EU Member States. The latest version of the PSUR Work Sharing (WS) list including the adopted EU Harmonised “virtual” Birth Dates (EU HBD), related Data Lock Points (DLPs) for the forthcoming PSURs and allocated PSUR Reference Member State (P-RMS = Member State in charge of making the PSUR assessment report) and of the Synchronisation list can be found on the Heads of Medicines Agencies (HMA) webpage [<http://www.hma.eu/80.html>].

1. Why are there two distinct lists containing both active substances?

The first list is the “Work sharing list” (that includes substances with allocated P-RMS and procedure number) and the second is the “Synchronisation list” (where active substances have not an allocated P-RMS). Only the “Work sharing list” is under the work sharing scheme.

However, the active substances on the “Synchronisation list” have their DLP synchronised for their future inclusion in the Work sharing scheme, once a P-RMS is allocated.

Hence, MAHs are encouraged to adjust the PSUR cycle according to the EU-HBD whether their product is on the “Work sharing” or the “Synchronisation” list, in order to be able to join the work sharing scheme, once a P-RMS is appointed.

2. My active substance is not on any lists and my Company is the Innovator, where should I send a request for my active to be included in the work sharing scheme?

Innovator companies can submit proposals in order to have their substances or combinations added to the “Synchronisation list”. Requests should be addressed to:

- the EMA: P-PV-Helpdesk@ema.europa.eu
- With copy to EFPIA: HBDSComments@efpia.org

3. My product is not authorised in the P-RMS but my Company is taking part in the Work sharing project. Should the PSUR be sent to the P-RMS?

No. The PSUR should only be sent to the EU Member States where your medicinal product is authorised. However, you should send a cover letter to the P-RMS including an overview table of your PSURs (with the full list of marketing authorisations covered by the PSUR submitted under the ongoing WS procedure) so the P-RMS knows that your product is to be included in the WS procedure.

The MAH should also provide a contact point for correspondence in the cover letter. A general e-mail address can be provided but the Company should ensure that it will remain valid for an extended period of time. The template to be used can be found at the following link: <http://www.hma.eu/80.html>

4. How would my Company receive the Assessment Reports (AR) if its medicinal product taking part in the Work sharing procedure?

The P-RMS is responsible for the preparation of the AR and will send it to all MAHs that are taking part in the WS procedure and that have sent a cover letter to the P-RMS with the requested contact point.

The PSUR Worksharing List is updated every three months to include information regarding the progress of the procedure (Day 0, PAR-date and FAR date) so that MAHs can follow the procedural steps of their substance assessment.

5. Are there any plans to move some active substances from the Synchronisation to the Work sharing list?

Yes, but no timelines are currently defined. However, Member States will have to accept soon new P-RMS-ships, as the single assessment of PSURs will become mandatory with the implementation of the new EU pharmacovigilance legislation.

6. As MA holder for an innovator product, my Company already submitted its proposal for harmonised birth date and DLP but would like to modify them. Can my Company do so?

No, once the lists are published other MAHs for the same active substance plan their PSUR submissions based on the published DLP. Therefore the dates cannot be changed once communicated to the Competent Authorities and published on the HMA website. MAHs are requested to respect the DLPs and to submit complete PSUR applications in order to prevent any delay in the WS procedures.

7. How are managed the DLP updates ?

Once agreed at EU level, updates of DLPs are communicated via mail-boxes to pharmacovigilance department of Competent Authorities and published on the HMA website. The lists are updated every 3 months.

8. When a new work sharing procedure is due and there is already an agreed CSP from a previous work sharing procedure, how should be made the update of the CSP?

Companies should submit the previous agreed CSP together with a separate document listing what happened in which country during the intervening period.

9. In the Core Safety Profile (CSP) principle paper, it is mentioned that *“the MAH should highlight to the P-RMS and P-CMS where there is disharmony for certain statements/warnings in SmPCs across the EU”*. What does it mean?

It means that the same safety information can be included in different sections of the SmPCs (ex: contraindications in a SmPC may be warnings in another SmPCs). Therefore the MAH should indicate to P-RMS and to P-CMS these discrepancies. In the proposed CSP, the information should be included in the section which best reflects the Company Core Safety Information (CCSI).

10. How should be presented the reference safety information (RSI) for PSURs based on EU HBD?

The RSI (usually CCDS¹ or CCSI²) should still be used for preparation of the PSUR. For companies who do not have a CCSI or CCDS, the RSI should be the common safety information that is included in all current Summary of Product Characteristics (SmPCs) of the product, as authorised in Member States at the time of data lock point together with a summary of the other safety information that is not included in the RSI.

11. There are differences between our national SmPCs. Which SmPC/RSI will be used as part of the PSUR WS assessment?

Due to differences in national SmPCs, assessment based on SmPCs will not be possible. The assessment of PSURs under the WS agreement is based on the Core Safety Profile (CSP) (cf. CSP paper).

12. Where a medicinal product has several indications which cover different populations, is it possible to produce several CSPs?

Yes, this is possible. However it needs to be discussed and agreed with the P-RMS and P-CMS before the start of the PSUR WS procedure. Several CSPs can be submitted, when judged necessary.

13. If PSURs have been submitted in the past on different dates because of different national birth dates, the first PSUR based on the EU HBD and related DLP will have an overlap with some PSURs that were submitted previously. Is this acceptable?

It is acceptable only for the first PSUR to be based on the EU HBD to overlap with one or more PSURs previously submitted nationally.

14. In order to avoid duplicate submissions of a given PSUR as part of its PSUR cycle and renewal due dates, is it possible for companies to submit the renewal application without the PSUR, but refer to the PSUR submitted under the PSUR Work Sharing Scheme?

Although legislation requires different data period covered and different submission scheme for renewal and for work sharing assessment, some PSUR can be common for these two procedures. Thus, there is no need to be submitted again. However, the MAH should make a reference to this already submitted PSUR, the covered period and the submission date.

15. My medicinal product is due for renewal, can my Company use a PSUR based on the EU-HBD?

Yes, the renewal can be anticipated in order to synchronise the PSUR submission with the EU-HBD. However, guidelines on renewal procedures still apply and if several PSURs are submitted within the renewal procedure, a summary bridging report in line with Volume 9a (section 6.2.4.b) should be supplied.

¹Company Core Safety Information

²Company Core Data Sheet

It is to be noted that to support a renewal application, PSUR must cover at least one year of data. If the harmonised EU-DLP falls after the DLP of the renewal, then the submission for this renewal should be made according to the due DLP.

Then for the WS procedure, an addendum report or line listings should be submitted as appropriate (see Vol. 9A, 1.6), to cover the period from the DLP of the renewal until the harmonised EU-DLP.

It should be noted that Addendum reports should follow the PSUR format. Thus, the data does not need to be represented in the next PSUR. Addendum reports covering periods longer than 12 months will not be accepted.

16. Is it acceptable for a generic product to immediately switch to the relevant harmonised DLPs if the current PSUR submission scheme is still in the 6 monthly or yearly phase?

Yes, unless a safety concern is raised, or the innovator is not under a three years PSUR cycle, or when new indication is introduced. In these cases, a more frequent PSUR submission is required. The PSUR cycle should be agreed during the MA assessment process and MAH should establish this with the RMS/NCA.

17. How are handled PSUR WS procedures when the P-RMS is different from the RMS?

As a general rule, the RMS has been attributed the P-RMS-ship. In the rare exceptions where the P-RMS is different from the RMS, the P-RMS will do the assessment and the RMS will comment during the work sharing procedure and will communicate with the P-RMS when necessary.

18. Regarding the ADR overview table to be provided with the PSUR submission, do generic MAHs need to submit it also? Isn't there a risk of duplicating ADR information?

Although the assessment is mainly based on the originator's data, the assessor may cross-check with the generic overview table for completeness. The ideal situation would be that Companies summarize all the ADRs in the overview table including the Generic's ADRs. This would provide a comprehensive overview.

This table shall be in line with Volume 9A. It should be submitted in Word format.

19. What would happen if an Innovator did not submit its PSUR as scheduled under the WS scheme?

In this case, the work sharing procedure can not take place. However, an Innovator should not –in principle- miss the submission date, in particular, with the soon implementation of the new legislation.

20. What would happen if a generic did not submit its PSUR as scheduled under the WS scheme?

In case a generic company has missed the submission date, they can request to be included in the next WS procedure.

21. When there is more than one Innovator involved in the Work sharing procedure, how is prepared the CSP?

The innovators should prepare together a common CSP before the start of the WS procedure.

22. At the end of a work sharing procedure, how MAHs will include any new safety information reflected in the agreed CSP which is not already present in the SmPC?

With the implementation of the new regulation for variation that came into force in January 2010, simplification has been introduced and the MAH will have to submit type IB variation.

This type IB variation should be submitted within 4 months after the end of the work sharing procedure.

23. Can we submit one single PSUR for all formulations?

It is strongly recommended that, when possible, information about indications, dosage forms and regimens related to an active substance authorised with the same Marketing Authorisation Holder to be included in a single PSUR, with a single data lock point. It is important to have a consistent, broad-based examination of the safety information for an active substance in a single document. However, in exceptional cases, after consultation of the Agency and the P-RMS, MAH may consider it appropriate to have separate PSURs.

24. We would like to confirm if the first WS PSUR of an innovator with less than 3 years data can be accepted within the WS submission.

As long as there are no gaps in the safety data, PSURs of less than 3 years can be accepted for the first entry of the MAHs into the WS procedure. Indeed, NCAs are urged to be flexible to facilitate this implementation phase of the Work sharing process for both NCAs and MAHs.

25. What happens if the P-RMS pointed out significant divergences in the registered safety information across Member States?

The P-RMS will communicate these divergences to the CMD(h)³ and request to consider the product for a SmPC harmonisation. In this case, the CSP will not be agreed until the end of the harmonisation procedure.

26. What happens if there is a disagreement either between Member States or between Member State(s) and MAH (s) regarding updates of the CSP or other risk management measures?

The matter will then be raised to the PhVWP⁴ by the P-RMS.

³Coordination group for Mutual recognition and Decentralised procedure (human)

⁴Pharmacovigilance Working Party