Synchronisation of periodic safety update report (PSUR) submission schemes for veterinary medicinal products (VMPs) authorised through national, mutual recognition (MR) and decentralized (DC) procedures

Questions and Answers document for Marketing Authorisation Holders (MAHs)

Version 8, March 2017

The Heads of Medicines Agencies have taken on an initiative to synchronise the PSUR submission schemes for veterinary medicinal products (VMPs) authorised through national, mutual recognition and decentralised procedures (MRP/DCP). The aim is for all VMPs with the same active substance to follow the same PSUR submission calendar, i.e. the same EU Harmonised Data Lock Point (EU-HDLP), in all European Union (EU) and European Economic Area (EEA) Member States. This concept is NOT applicable to veterinary immunological products.

The list of active substances for which EU-HDLPs have been agreed between industry and CAs, can be found on the HMA website. These harmonised dates shall be taken into account for the preparation and submission of synchronised and harmonised PSURs, these are the Workshare PSURs (WS PSURs). The list further provides information on the Member States (MSs) nominated 'PSUR-Reference Member State' (P-RMS), the MS responsible for preparing the initial and final assessment report for a certain active substance).

The list of Q&A given overleaf aims to provide guidance to industry for proposing active substances and EU-HDLPs, and for preparing and submitting PSURs in the framework of the PSUR Workshare (PSUR WS). Furthermore information on the outcome of the PSUR WS procedure is provided.

This is version 8 of the industry Q&A.

List of Questions

Establishing the list of active substances and EU-HDLPs

Applying the EU Harmonised Data Lock Points

Content and format of WS PSURs

Assessment and outcome of the WS procedure

Vaccines

Miscellaneous

For additional questions/queries you may have, please contact your industry association or local competent authority.

Establishing the list of active substances and EU HDLPs

Q. 1: How was the list of active substances first established?

A list of active substances for VMPs authorised nationally (including mutually recognised and decentralised authorised products) was first established in 2007 for the running of the pilot phase (as from January 2008) and is being updated as the project continues. Changes to the list can be proposed at two points during the year: 1 March & 1 September (see also Q.3).
Return to 'List of questions'

Q. 2: Where is the list of active substances and EU-HDLPs available from?

The list that is in application is available from the heads of medicines agencies (HMA) website at:
http://www.hma.eu/442.html
Return to 'List of questions'

Q. 3: How can I add an active substance, an EU-HDLP and an originator MAH to the list?

You may propose additions to the list published on the HMA website (http://www.hma.eu/422.html) provided that you have at least one relevant product for that active substance registered in at least three member states (MSs), with the exception of acids, vitamins, trace elements and minerals, which are currently excluded from the scope of the PSUR WS.

When putting an active substance forward, you will propose an EU-HDLP; you will then be regarded as the 'originator MAH'. A new 'originator MAH' or a new EU-HDLP for active substances already listed can be proposed like all other changes to the list by Mar 1st for use in the first six months of the following year, or September 1st for use in the second six months of the following year. Updated version of the list will be published on May 1st and November 1st, accordingly.
Your written proposal should be submitted to your national competent authority (NCA) (contact details see: Annex 1 to the EMA Standard Operating Procedure (SOP) on management of PSURs[1]), who is responsible for bringing it to the 'Regulators' Group on PSUR work-sharing. Your proposal for an EU-HDLP should include the list of all MSs in which your concerned product(s) is/are registered.

The 'Regulators' Group will then ensure that the proposed EU-HDLP does not create an unequal spread of work over the three years period, in which case a close by alternative will be suggested. If the proposal concerns a new formulation or species of an existing active substance, an EU-HDLP within two months of the current EU-HDLP for the active substance should be proposed. If multiple formulations of a new active substance are proposed; a single EU-HDLP should be proposed or all the DLPs should be within two months. In the next step the Regulator's Group will appoint a P-RMS.
Finally, the active substance, the originator MAH, the agreed EU-HDLP, the P-RMS, and the EU Harmonised Birth Date (EU-HBD) where relevant, i.e. for 'new' active substances, will be added to the list.
Return to 'List of questions'

1 http://www.ema.europa.eu/docs/en_GB/document_library/Standard_Operating_Procedure_-_SOP/2009/09/WC500003101.pdf

Q. 4: How is the ‘originator MAH’ defined?

A MAH can put himself forward as the originator MAH (or “Originator”) for a given active substance (or combination of active substances) on the condition that he has at least one relevant product for that active substance registered in at least three MSs; he will then be able to propose the EU-HDLP in agreement with the CAs. Generally the Originator is the first MAH to register/market a VMP with an active substance (or combination of active substances) in the EU and/or EEA. Also a MAH with a generic VMP can act as Originator for an active substance (or combination of active substances).
The CAs have the possibility to ask MAHs to act as Originator for active substances on the list which not yet have one (excluding acids, vitamins, trace elements and minerals, see Q. 3). The EU-HDLP can be set by the Originator in agreement with the ‘Regulators’ Group on PSUR WS.
Return to 'List of questions'

Q. 5: How to handle substances with VMPs authorised in less than three countries?

WS cannot be followed when there is a substance with VMPs authorised in less than three countries. However, this substance can continue to use the existing EU-HDLP. Substances already in the list will remain but will not be assessed in the PSUR WS. As this substance is not involved in the WS, no CSDS applies. However, the SPC should be provided.
Return to 'List of questions'

Q. 6: Can EU-HDLPs be changed?

No, once harmonised dates have been proposed by the ‘originator MAH’ and have been agreed and published on the HMA website, these dates can no longer be changed.
Certain exceptional circumstances, i.e. serious safety concerns during assessment, may lead to a more frequent submission of PSURs (but a more frequent submission of PSURs does not necessarily change the original EU-HDLP, it may add intermediate ones), see also Q. 3.
Return to 'List of questions'

Applying the EU Harmonised Data Lock Points

Q. 7: From what date can I start submitting WS PSURs?

Once an EU-HDLP for an active substance contained in your product(s) is published on the list available from the HMA website (see: http://www.hma.eu/442.html), you can submit WS PSURs based on this EU-HDLP (ensure that you take the formulations or species split into account, where applicable – see also Q. 15). The CAs should always be informed of your intention to change the previously established cycle of submission of PSUR to send the PSUR based on the EU-HDLP.
Your product may contain either one single active substance, a fixed combination of active substances to be regarded as ‘one active substance’ or other combinations, for which the ‘originator MAH’ may have proposed a different EU-HDLP; thus make sure you search the list for all the combinations it may contain, to ensure you use the correct EU-HDLP.
Return to 'List of questions'

Q. 8: Which date of the month shall I use for the EU-HDLP?

The agreed EU-HDLP is given in month/year. You should choose the last day of the respective month.
Return to 'List of questions'

Q. 9: How do I switch to the EU Harmonised calendar for existing products?

The most important point is that all adverse events are communicated to the authorities, i.e. gaps between the reported periods are not acceptable. In the beginning there will be overlaps, which will be accepted, since it is almost inevitable that the first harmonised PSUR will overlap with one or more PSURs submitted previously. For any VMP, submission of PSURs at a lower frequency than once every three years is not possible.
Return to 'List of questions'

Q. 10: Can I apply the EU-HDLP to a new product?

For a newly authorised product containing active substance(s) for which an EU-HDLP has been set, you may switch to the three yearly calendar unless there is a specific concern, or a MS cannot agree to the cycle based on its national legislation, or in case the product includes a new indication or species requiring a more frequent PSUR submission. For any VMP, submission of PSURs at a lower frequency than once every three years is not possible.
For newly authorised products, the MAH should seek agreement to follow the synchronised scheme during the authorisation procedure (the MAH should apply for a PSUR waiver within the authorisation application).
Return to 'List of questions'

Q. 11: Which calendar shall I follow for recently or newly authorised generic products?

When a generic is still in its six-monthly or yearly submission cycle, a switch to the EU-HDLP can be made, unless there is a specific safety concern or in case the product includes a new indication or species requiring a more frequent PSUR submission. MAHs are encouraged to first consult the RMS or national CA before switching to the EU-HDLP.
Return to 'List of questions'

The same applies to newly authorised generic products, for which the EU-HDLP for the relevant active substance may be used from the start, if agreed with the CA at the time of granting the authorisation. For this purpose, the applicant is encouraged to inform the CA that it wishes to take part in the work-sharing initiative and apply for the first PSUR submission according to the EU-HDLP, before the end of a registration procedure. The agreement will include whether an immediate start with a three year PSUR calendar is acceptable. For any VMP, submission of PSURs at a lower frequency than once every three years is not possible.
Return to 'List of questions'

Q. 12: What is the EU-HDLP following the originally agreed EU-HDLP?

Normally, it is the originally agreed EU-HDLP plus three years.
In exceptional cases, where specific serious safety concerns emerge related to the active substance, a different PSUR time schedule may be applicable; this will be notified by the national CA and indicated in the PSUR assessment report. If the

frequency for the active substance is different from three years, this information will also be included in the list of EU-HDLPs on the HMA website.
Return to 'List of questions'

Q. 13: Are the EU Harmonised Birth Dates (EU-HBDs) and related EU-HDLPs directly linked?

For 'established products', i.e. marketed for over 5 years, the EU-HDLP is not necessarily related to the EU-HBD.
For newly or recently authorised products containing a new active substance, the EU-HDLP for this particular active substance automatically relates to the date of the product's first EU marketing authorisation, which is also the EU-HBD, unless an international birth date has already been set.
Return to 'List of questions'

Content and format of WS PSURs

Q. 14: What documents shall be prepared to accompany a WS PSUR?

You should prepare one synchronised and harmonised WS PSUR per active substance accompanied by the following documents:

a. Notification/cover letter: the MAH shall notify in its cover letter that a PSUR is submitted as part of the PSUR WS and refer to the reference number for WS PSUR as follows:
   - Coding: WS PSUR <substance> <year (DLP)> <P-RMS>
     eg. WS PSUR Ampicillin 2017 BE,
     or WS PSUR Bromhexine + Doxycycline 2016 NL
     (this reference number was agreed by Industry and NCAs. It will be also included in the WS PSUR Preliminary Assment Report and Final Assessment Report.
     This coding should appear in your cover letter and in the e-mail subject when sending the WS PSUR (see Q. 21).

b. Annex to the cover letter: the MAH shall provide sufficient information to help MSs identifying PSURs of identical products between one and another country, despite different brand names. This should be presented in an annex to the cover letter or in the PSUR itself in the format given below and with the following information:

<MAH Contact point>
<Active Substance>
<Product name for a given formulation>
<Target species>
<Concentration>
<Presentation per MS>

Country	Brand Name in the local language	Registration Number(s)	Procedure type

c. Core Safety Data Sheet (CSDS):
For more information on the CSDS see Q. 16 and 21).

d. Letter of attorney: such letter should be attached in case the MAH for the same product differs amongst MSs

Return to 'List of questions'

Q. 15: Should discussion and evolution of Antimicrobial Resistance and related literature searches be provided with the documents for the WS PSUR?

Data on resistance would only be expected to be addressed in the PSUR, in cases where lack of efficacy concerns due to resistance have been identified. Otherwise, it is not expected that the discussion and evolution of Antimicrobial Resistance is part of the PSUR. Other channels are used (e.g. resistance monitoring program) to ensure that this information will be captured and communicated to NCAs.
Return to 'List of questions'

Q. 16: What is the core safety data sheet (CSDS)?

(The information sheet for the CSDS is available at: http://www.hma.eu/442.html).
The CSDS is an unofficial working document prepared by all MAHs (in an editable format, e.g. MS Word – see also Q. 14 and 21). It contains the core safety information of the product and aims to facilitate the assessment of the PSURs by the assessing CAs. Therefore, it should be prepared in English. As the CSDS is an unofficial working document prepared by the MAH, CAs cannot request changes to the CSDS after WS PSUR assessment. PSUR data/assessments are the basis for changes to the SPC which can trigger the modification of the CSDS in future.
Since it is very common to have different formulations and/or species concerned for an active substance, it is generally more appropriate to prepare a CSDS per product. It can anyhow be prepared per active substance.
In all cases, it must contain all the relevant safety information of the product(s) concerned as extracted from the relevant SPCs for that product, i.e.:
- Contra-indications
- Special precautions and warnings: user / animal / other
- Adverse reactions (frequency and seriousness)
- Use during pregnancy, lactation or lay
- Interaction with other medicinal products and other forms of interaction
- Administration route
- Overdose (symptoms, emergency procedures, antidotes), if necessary

The CSDS must be easily identifiable by its date (and its revision number where applicable). Where needed, difference related to formulations and/or species should be highlighted in the concerned sections.
Return to 'List of questions'

Q. 17: What is the WS PSUR reference number?

See also Q. 14. The WS PSUR reference number was agreed by Industry and NCAs and consists of the following coding: WS PSUR <substance> <year (DLP)> <P-RMS> (e.g. WS PSUR Ampicillin 2017 BE, or e.g. WS PSUR Bromhexine + Doxycycline 2016 NL).
This reference number should appear in MAHs cover letter and in the e-mail subject when sending the WS PSUR. It will be also included in the WS PSUR preliminary assessment report (PAR) and final assessment report (FAR) and the responding letters/emails from NCAs.
Return to 'List of questions'

Q. 18: What information shall be contained in a WS PSUR?

WS PSURs must be prepared according to the requirements given in Volume 9B of 'The Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use'[2].

The only difference is that SPCs do not need to be added to a WS PSUR, except if an SPC in English is available. The relevant information from the SPCs is already provided in the CSDS (see Q. 16) and is sufficient. For a VMP in a MRP or a DCP, a SPC instead of a CSDS could be submitted, if the VMP is authorised in all concerned member states by this MRP/DCP.

Return to 'List of questions'

Q. 19: How should the WS PSUR of a product with different formulations be prepared?

A WS PSUR may contain several parts, each part dealing individually with a given formulation and prepared individually according to the requirements of Volume 9B of 'The Rules Governing Medicinal Products in the European Union - Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use'[2]. This means that each part provides its specific sales volume, incidence calculation, line listing for each single product and with its specific benefit risk assessment.

MAHs may also choose to prepare separate PSURs for each formulation, providing they are submitted at the agreed EU-HDLP for that active substance.

In exceptional cases, e.g. products with numerous formulations or combinations, the originator may propose different EU-HBDs and EU-HDLPs for each or a group of formulations/combinations in order to spread the workload in preparing and assessing PSURs. (Usually these EU-HDLPs should be within two months see Q. 3)

Return to 'List of questions'

Q. 20: To which countries shall I send the WS PSURs?

The procedure will depend on whether you are the 'originator MAH' for the relevant active substance or not:

- If you are the 'originator MAH', you should send the WS PSUR simultaneously to all NCAs of the EEA as follows, irrespective of whether the product is registered in those countries or not:
    - Where the product is registered: according to the information provided in Annex 1 to the EMA Standard Operating Procedure (SOP) on Management of Periodic Safety Update Reports (see EMA website[3])
    - To all other countries where the product(s) is not registered: via CESP or Eudralink (see e-mail contacts in Annex I to the above mentioned EMA SOP) according to usual PSUR filing procedures with the relevant NCAs. When the product is not registered in a certain member state, a handling fee in this country should not be due
- If you are not the 'originator MAH', you should send the WS PSUR simultaneously only to MSs, where the product(s) is registered.

Return to 'List of questions'

---

2 http://ec.europa.eu/health/files/eudralex/vol-9/vol_9b_2011-10.pdf

3 http://www.ema.europa.eu/docs/en_GB/document_library/Standard_Operating_Procedure_-_SOP/2009/09/WC500003101.pdf

Q. 21: In which format shall I send WS PSURs?

The MAH should comply with the requirements in Annex I to the EMA Standard Operating Procedure (SOP) on Management of Periodic Safety Update Reports on the EMA website (see footnote three on previous page).
National competent authorities should accept submission in an electronic and searchable format such as pdf (with the CSDS sent separately and in an editable format, e.g. MS Word).
The use of CESP or Eudralink is also expected to become accepted by all MSs.

When sending a WS PSUR, you should add the unique reference number for the PSUR (see Q. 14 and Q. 17) in your cover letter and in the heading of all e-mails.
Return to 'List of questions'

Assessment and outcome of the WS procedure

Q. 22: Is there a procedure of the WS PSUR assessment in competent authorities (CAs)?

The CAs agreed to work in a consistent manner. The principles of the CAs' assessment and the roles of the P-RMS and the P-CMS is laid down in the "BEST PRACTICE GUIDE for Handling of Periodic Safety Update Reports (PSURs) in the context of the EU PSUR Worksharing" published on HMA website:
http://www.hma.eu/150.htm

P-RMS sends a PAR to all CAs for comments. At the end of the WS procedure the P-RMS provides all CAs with an agreed FAR as otherwise the national phase cannot start.
Return to 'List of questions'

Q. 23: What is the risk-based algorithm?

The Risk-based algorithm used by the NCAs to define the 'level of scrutiny planned for' required for the PSUR assessment is published HMA website:
http://www.hma.eu/442.html
Return to 'List of questions'

Q. 24: Is there the possibility for MAHs to comment on the WS PSUR assessment?

The assessment of the WS PSUR ends with a draft FAR six month after EU HDLP. The P-RMS sends the draft FAR only for Originator VMPs as soon as possible to the 'originator MAH' to give this MAH at least 15 days to comment.
Return to 'List of questions'

Q. 25: When is the WS procedure finalised and what is the outcome of the procedure?

The WS procedure ends when the FAR is considered accepted in case of no further comments from 'originator MAH' and P-CMSs, which is normally 205 days after the EU-HDLP.
The P-RMS will send:

- the part of the FAR concerning Originator VMPs to the Originator
- for additional PSURs authorised nationally in the MS or for VMPs authorised via MRP/DCP if the P-RMS is also RMS for the MR/DC procedure, the part of the FAR concerning the VMPs of those non-originator MAHs or at least an outcome letter to these MAHs.

The P-RMS does not circulate the part of FAR concerning the VMPs of non-originator MAHs or an outcome letter to MAHs for VMPs not authorised in P-RMS country. That will be done by the RMS/NCAs in MS where the products are authorised.
Return to 'List of questions'

Q. 26: What happens after PSUR WS assessment in national, MR or DC procedure?

The outcome of the PSUR assessment of the active substance(s) within the PSUR WS, including any requests or any requirements for the following PSUR (in line with FAR) will be provided to all MAHs by relevant NCAs depending on the procedure (national, MR/DC), see Q. 25 and Q. 27.
After the WS procedure ends it is important that MAH receives feedback from all NCAs where the product is registered in a predefined time period. All NCAs agreed on a common approach on sending their feedback on VMPs within six month after the finalised WS procedure on basis of the agreed WS FAR to the relevant MAH. This helps MAHs to plan the variation process.
NCAs may request changes to national SPCs in line with assessment outcomes. This is a national issue and concerns nationally authorised VMPs.
Return to 'List of questions'

Q. 27: How and by which CA is the outcome of the PSUR WS for VMPs in MR/DC procedure managed?

For VMPs authorised via MRP/DCP: the MRP/DCP RMS of the VMP may request changes to the SPC on the basis of the WS FAR, if applicable and ensures that the MAH carries out the agreed actions.
Return to 'List of questions'

Q. 28: Can changes of the CSDS be requested by national competent authorities (NCAs)?

NCAs cannot request changes to the CSDS as the CSDS is an unofficial working document prepared by the MAH. PSUR data/assessments are the basis for changes to the SPC of each single VMP which can trigger the modification of the CSDS in future.
Return to 'List of questions'

Q 29: What are the timelines to get feedback from all NCAs where the VMPs are registered after PSUR WS procedure was finalised?

After the WS procedure ends it is important that MAH receives feedback from all NCAs where the product is registered in a predefined time period after the PSUR was evaluated. All NCAs agreed on a common approach on sending their feedback on VMPs within six month after finalised WS procedure on basis of the agreed WS FAR to the relevant MAH. This helps MAHs to plan the variation process.
Return to 'List of questions'

Vaccines

Q. 30: Can I submit WS PSURs for vaccines?

No, currently vaccines are not included within the project
Previous DLPs from when vaccines were in scope can be respected for use in timing submissions outside the WS process

Rabies (monovalent) / horse	1H 2011
Avian vaccines	2H 2011
Cat vaccines	1H 2012
Swine Vaccines	2H 2012
Dog Vaccines	1H 2013
Ruminant Vaccines	2H 2013

Return to 'List of questions'

Miscellaneous

Q. 31: What is the 'PSUR Synchronisation Sub-Group' (PSSG)?

The PSSG is a joint industry and regulators sub-group of the ESS (European Surveillance Strategy Group of HMA) and consists of 6 competent authorities' representatives and 6 industry members (2 from EGGVP and 4 from IFAH-Europe[4]). It was originally set-up to initiate the running of the pilot phase (January 2008 to December 2009) and develop harmonised procedures. More recently, it also ensures the initiative is progressing well and, together with the 'Regulators' Group on PSUR WS, is responsible for maintaining the list of active substances and EU-HDLPs.
Return to 'List of questions'

Q. 32: What is the 'Regulators' Group?

The ‘Regulators’ Group is a Group where all MSs are present meeting in the margins of the CVMP Pharmacovigilance Working Party.
Return to 'List of questions’

Q. 33: Is the WS PSUR submission linked to the renewal procedure?

If the period from the granting of the MA to renewal is covered by more than one PSUR (including WS PSURs), a PSUR Summary Bridging Report should be submitted.
In cases where the gap between the last EU-HDLP and the renewal is considered too big, a PSUR Addendum Report may be submitted in agreement with the CA. A PSUR Addendum Report is an update of the most recently completed PSUR when a safety update is required outside the EU-HDLP PSUR schedule.
Return to 'List of questions’

Q. 34: Which SPC will be used to assess the WS PSUR?

The WS PSURs will be assessed based on the information contained in the CSDS and not the SPC. However, for a VMP in a MRP or a DCP, a SPC instead of a CSDS could be submitted, if the VMP is authorised in all CMS by this MRP/DCP. (see Q. 14 and Q. 18).
Return to 'List of questions’

---

[4] IFAH-Europe: International Federation for Animal Health Europe - http://www.ifaheurope.org/

EGGVP: European Group for Generic Veterinary Products - http://www.eggvp.org/

List of acronyms

CAs	Competent Authoritys
CMS	Concerned Member State
CSDS	Core Safety Data Sheet
DC(P)	Decentralised (Procedure)
EEA	European Economic Area
EU	European Union
EU-HBD	European Union Harmonised Birth Date
EU-HDLP	European Union Harmonised Data Lock Point
FAR	Final Assessment Report
HMA	Heads of Medicines Agencies
MAH	Marketing Authorisation Holder
MR(P)	Mutual Regognition (Procedure)
MSs	Member States
NCA	National Competent Authority
PAR	Preliminary Assessment Report
P-CMS	PSUR-Concerned Member State
P-RMS	PSUR-Reference Member State
PSSG	PSUR Synchronisation Sub-Group
PSUR	Periodic Safety Update Report
RMS	Reference Member State
SPC	Summary of Product Characteristics
VMP	Veterinary Medicinal Product
WS	Workshare