

# **CMDh STANDARD OPERATING PROCEDURE ON THE PROCESSING OF PSUR SINGLE ASSESSMENT PROCEDURES FOR NATIONALLY AUTHORISED PRODUCTS**

*CMDh/322/2014/Rev.0  
November 2014*

## **1. INTRODUCTION**

This Standard Operating Procedure covers the processing of the Periodic Safety Assessment Report (PSUR) single assessment procedures (PSUSAs) from the pre-submission phase to the CMDh decision making process, which concerns only nationally authorised products (NAPs). In this paper, the term ‘nationally authorised product’ encompasses medicines authorised through Mutual Recognition and Decentralised procedures and purely nationally authorised products that are subject to the single assessment as per the EURD list.

## **2. LEGAL FRAMEWORK**

The legal requirements for submission of PSURs are established in Regulation (EC) No 726/2004, Directive 2001/83/EC and in the Commission Implementing Regulation in respect of format and content of electronic PSURs. The Good Vigilance Practice (GVP) Module VII provides guidance on the preparation, submission and assessment of PSURs.

In accordance with Article 107b of Directive 2001/83/EC, marketing authorisation holders (MAHs) are obliged to submit PSURs. The legislation waives the obligation to submit PSURs for generic products (authorised under Article 10(1)), well established use products (Article 10a), homeopathics (Article 14) and traditional herbal medicines (Article 16a) of Directive 2001/83/EC, unless there is a condition in the marketing authorisation for PSURs to be submitted or PSURs have been requested by member states on grounds of pharmacovigilance.

Where medicinal products containing the same active ingredient or combination of actives are subject to different authorisations across the member states, it is desirable that these have the same frequency for submission of PSURs and the same data lock point (DLP) to facilitate their single assessment. Article 107c(4) of Directive 2001/83 provides for the establishment of the Union reference date from which submission dates are calculated and these are included in a published list, the European Union Reference Date (EURD) list.

Article 107e establishes the single assessment procedure for medicinal products containing the same active substance or same combination of active substances authorised in more than one Member State and for which a Union reference date and frequency of periodic safety update reports has been established. Where a single assessment procedure as established in the EURD list does not include any centrally authorised products, the single assessment shall be conducted by a Member State

appointed by CMDh (“lead MS”).

The Member State conducting the assessment will send the report to the Pharmacovigilance Risk Assessment Committee (PRAC) who will adopt the report, with or without changes and will issue a recommendation on the maintenance, variation, suspension or revocation of the authorisation.

In the case where the assessment of the PSUSA, concerning only nationally authorised products results in a recommendation for regulatory action, CMDh shall within 30 days of receipt of the report reach a position on the maintenance, variation, suspension or revocation of the MAs concerned, including a timetable for implementation of the agreed position. If a consensus agreement cannot be reached, the position of the majority of Member States represented in the coordination group shall be forwarded to the Commission who will make the final binding decision.

### **3. PRINCIPLES OF SUBMISSION AND EVALUATION**

#### **3.1 EURD list**

The EURD list consists of a list of active substances and combinations of actives that are subject to PSUR single assessment procedures.

The EURD list contains the following information for each substance or combination:

- The EU reference dates, which usually corresponds to the date of the first authorisation in the EU;
- The frequencies of submission of PSURs;
- The data lock points (DLPs) of the next submissions of PSURs;
- The submission date;
- The PSUSA procedure number;
- The date of publication (on the European Medicines web-portal) of the frequency for PSUR submissions and data lock point. Any change to the dates of submission and frequency of PSURs specified in the marketing authorisation shall take effect 6 months after the date of such publication in the EURD list.

In addition to the above, the following is also highlighted in the list where relevant:

- Whether different PSURs should be submitted for medicinal products containing the same active substance and authorised for one MAH depending on different indications, routes of administration, dosage forms and dosing regimens. In the case where different PSURs are required, the active substance or combination of active substances appears several times in the list including in brackets the scope that should be covered by the PSUR (e.g. PSUR for “topical formulations” versus PSUR for “oral formulation”);
- Whether PSURs for products authorised under Articles 10(1), 10a, 14 and 16a of Directive 2001/83/EC have been requested by competent authority (ies) on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs relating to an active substance.

The EURD list requirement is without prejudice to the right of a NCA to request the submission of PSURs at any time, as provided for in Article 107c(2).

### **3.2 General information and pre-submission phase**

The PSUSA procedure is coordinated by the EMA PSUR Service. A Procedure Manager (PM) will oversee all aspects of the management of the procedure and will be the main contact for both MAHs and Member States. The PM will be assisted by a Procedure Assistant (PA). The PM and PA for the procedure will be allocated at least 5 months before the PSUR submission date.

Two months before the procedure start date, EMA will send an advice note for each procedure to all the MAHs (qualified person for pharmacovigilance, QPPV) whose products are included in the procedure with the following information:

- Procedure number
- Line listing of authorised products (medicinal product name, MAH name and address, Country of authorisation, active substance name etc.)

MAHs shall fully reconcile the listing in accordance with EURD list. MAHs should complete for each product in the line listing additional information regarding small and medium enterprise status, MAH contact e-mail, financial and regulatory contact e-mails. MAHs shall submit the updated line listing to the EMA no later than 10 days prior to the submission deadline. The EMA will use this updated list to calculate the fees and issue an invoice to the MAHs at the start date of the procedure.

A second reconciliation will be undertaken after submission – see 3.6 below.

### **3.3 Appointment of Lead Member State**

Where a PSUSA does not include any centrally authorised products the assessment is undertaken by a lead Member State appointed by CMDh. The identification of a lead Member State (MS) will be initiated in advance by means of a line listing and the lead Member State is appointed by the CMDh at least 6 months prior to the start date of the PSUSA procedure. The appointment will be published in the EURD list.

On monthly basis, the EMA will provide an extract from the EURD list to the CMDh (via [list-h-CMD-Pharmacovigilance@eudra.org](mailto:list-h-CMD-Pharmacovigilance@eudra.org)) for identification of lead Member States. The list will be updated to reflect the outcome of Lead Member State appointment, as per below procedure, and be circulated at the subsequent CMDh meeting for formal adoption. A discussion at the CMDh plenary is only envisaged in case no biddings have been received and/or if there are multiple biddings without clear priority. The CMDh secretariat will keep an overview of appointed lead MS in order to inform such discussion. In case there are no biddings a lead MS will be appointed from a list with potential member states ensuring equitable distribution, in so far as is possible. The final appointment is at the discretion of the CMDh Chair. The aim is, however, to always adopt a Lead MS within a month.

Note: Once a Lead Member State has been identified for first the PSUSA for a particular substance or combination, this will remain the same for all subsequent submissions to make the system more robust from a scientific point of view, unless the Lead Member State requests a replacement.

The following criteria will be considered when appointing the lead Member State based on the received expressions of interest:

- Whether the Member State is the Reference Member State in MRP/DCP procedures for medicinal products containing the substance, in accordance with Art. 107e(1). Priority will be given to the RMS of the originator product, unless they inform the CMDh secretariat in writing that they would not wish to be the Lead MS. This does not prevent RMS for other medicinal products from being appointed.
- Whether the Member State was the lead Member State (P-RMS) in the previous EU informal PSUR work sharing project or in evaluation of safety signals (as identified in the [List of active substances subject to worksharing for signal management](#)), unless they inform the CMDh secretariat in writing that they would not wish to be the Lead MS.
- The medicinal product containing the active substance, which is subject to PSUSA assessment is authorised/marketed in the Member State

The representative of the lead Member State for discussions at the PRAC plenary will be from the same Member State as appointed by CMDh. When CMDh delegates are invited to bid, there will be an optional cell in the line listing to specify who they propose as PRAC representative. If this is left blank, it would go automatically with the PRAC member of their delegation following assessment of potential conflict of interest (CoI). In line with the EMA policy on the handling of conflicts of interests of scientific committee members and experts, the PRAC secretariat can check any potential Conflict of Interest of the proposed representative.

### 3.4 Submission requirements

Medicinal products that contain active substances or combination of active substances with a harmonised DLP in the EURD list follow the single assessment of PSURs.

In line with the EURD list, MAHs should submit their respective PSUR for their medicinal product within a PSUR single assessment procedure for an active substance or combination of active substances included in the EURD list, even if their product is authorised in only one Member State. In some procedures PSURs may have been submitted for products covered by the derogation and authorised under Article 10.1 or 10a, 14 or 16, if indicated in the published EURD.

The Marketing Authorisation Holder (MAH) should prepare a PSUR, based on the adopted EU harmonised Data Lock Point (EU DLP) for the active substance or combination of active substances according to the current [EURD list](#).

PSURs should be submitted to all Member States where the MAH holds a marketing authorisation for the medicinal product with the same active, according to the following time lines:

- Within 70 calendar days of the DLP for PSURs covering intervals up to 12 months (including intervals of exactly 12 months); and
- Within 90 calendar days of the DLP for PSURs covering intervals in excess of 12 months;

Specifically, the submission should be made in accordance to the document [Requirements for submissions for Periodic Safety Update Reports \(PSUR\) for MRP, DCP and National Products \(NAPs\)](#);

In addition to submission to the Member States where the product is authorised, the PSUR should be submitted to the EMA and to the lead Member State for the procedure (even if the product is not authorised in that Member State). Detailed guidance on how to submit to the EMA and all other procedural aspects of the EU single assessment are available on the [EMA website](#).

### 3.5 Documentation to Submit

The dossier format and content for PSURs is given in GVP Module VII and a [cover letter \(see Q&A No 3\)](#) should accompany the PSUR submission

This letter should include:

- (i) The **PSUSA Procedure Number** ( this can be retrieved from the EURD );
- (ii) **Confirmation** that the PSUR is being submitted in all Member States where products containing the active substance (or combination) are authorised, the appointed lead MS in case and the EMA;
- (iii) **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;
- (iv) **For PSURs covering more than one MA**, include a list of the medicinal products affected, including the national MA-Number and, if applicable, MRP-Number and, if the dossier is in eCTD format, the relevant eCTD sequence number should be stated for each separate authorisation (see Annex I of the above mentioned cover letter).

It is to be noted that Risk Management Plans (RMPs) cannot be submitted within a PSUSA procedure for NAPs only and will not be subject to assessment. Updates to RMPs should be submitted by the appropriate variation.

### 3.6 Submission Date and Start of the Procedure

The submission deadline and procedure start date are published in the EURD list on the EMA website. The MAHs should submit the PSUR within 70 or 90 days of the DLP, as per the EURD list.

After the submission deadline stated in the [published timetable \(see Q&A No 15\)](#) the EMA will undertake reconciliation with NCAs to confirm that all the relevant PSURs for different MAs containing the same active substance or combination of substances have been submitted to the EMA before start of procedure.

In the exceptional circumstances that the PSUR has been submitted to an MS only, the RMS will be responsible for sending these to the EMA via Eudralink. Alternatively, the RMS can request the MAH to provide the PSUR to the EMA via Eudralink. Both Eudralinks should be provided to the procedure assistant that requested the particular reconciliation.

The MAHs that have not submitted PSURs will be excluded from the evaluation procedure. It is the responsibility of MAHs to ensure that they submit the necessary PSUR by the deadline and that they

are not in breach of their legal obligations with respect to PSUR submission. The PSUSA procedure will start as per the published timetable.

### **3.7 Assessment Procedures**

#### **3.7.1 Assessment Report Format**

The assessment report should be based on the data provided in the PSUR and include an overall benefit - risk evaluation of the medicinal product. The template for the assessment report will be provided on the [EMA website](#) dedicated to assessor's templates, once available.

#### **3.7.2 Assessment Procedure**

The lead Member State is responsible for producing one preliminary Assessment Report (pAR) on the PSUR(s) submitted in the PSUSA procedure.

The procedure follows the timetable given in Annex 1:

- The lead Member State has 60 days to prepare a preliminary AR. The lead Member State may request additional information from the MAH(s), which is stated in section 6 of the Assessment Report ('Lead Member State's Request for supplementary information').
- The preliminary AR is circulated to Member States for comments (via [list-H-PSUR@eudra.org](mailto:list-H-PSUR@eudra.org)) and to PRAC (via [list-H-Pharmacovigilance@eudra.org](mailto:list-H-Pharmacovigilance@eudra.org)), in order to facilitate the commenting phase as outlined in the next bullet point. The EMA PM also provides a copy to each of the contact points of the MAHs.
- Member States and MAH(s) have 30 days to provide any comments and respond to the Request for supplementary information, if applicable. PRAC members should include their comments in the MS comments of their delegation, i.e. only one (set of) comment(s) should be sent by each delegation..
- The lead Member State then has 15 days to update the assessment report based on comments received, and provide the final/updated lead MS AR. The updated lead MS AR is made available to the Member States and PRAC via the above mentioned mailboxes.
- The EMA will ensure that the procedure is included in the PRAC Agenda for adoption of the PRAC recommendation at the next available PRAC meeting.
- An oral explanation to the PRAC can be held in accordance with the PRAC Rules of Procedures at the same meeting.
- The PRAC shall adopt the updated lead MS assessment report with or without further changes at its next meeting together with a recommendation on the maintenance of the marketing authorisation or the need to vary, suspend or revoke the marketing authorisation. The PRAC recommendation may also highlight the need to conduct a post-authorisation safety study, review of safety issues and/or close monitoring of events of interest.
- Once adopted, the PRAC AR and recommendation will be forwarded to the MAHs contact points by the EMA.
- Divergent positions of PRAC members and the grounds on which they are based shall be reflected in the recommendation issued by the PRAC.

The PRAC recommendation and assessment report are made available via MMD under the relevant Agenda point of the corresponding PRAC meeting.

CMDh members will be systematically informed via email using the CMDh Pharmacovigilance mailbox (list-h-CMD-Pharmacovigilance@eudra.org) about the PRAC recommendation irrespective of the outcome. The adopted AR and recommendation will be attached to the email.

PSUR single assessment procedures will only be tabled in MMD for the next CMDh meeting if the PRAC recommended regulatory action, such as variation, suspension or revocation of the marketing authorisation(s). If the PRAC recommended maintenance of the authorisation without any amendment of the MA, this will not require a CMDh position.

### **3.8 Decision Making Process**

Within 30 days from receipt of a PRAC recommendation for any regulatory action, the CMDh shall consider the PRAC recommendation and assessment report and reach a position on the maintenance, variation, suspension, revocation of the MA(s) concerned.

An oral explanation to the CMDh may be held in accordance with the CMDh rules of procedure.

The position will contain the following:

- the final assessment report and recommendation adopted by the PRAC;
- detailed explanation of the scientific grounds for differences from the PRAC recommendation, if applicable;
- in the case of a CMDh position to vary the marketing authorisation(s), the scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation and an annex indicating the new safety warnings and key risk minimisation recommendations to be included in the relevant sections of the product information, as applicable; this annex will rely on the relevant section of the AR adopted by the PRAC, unless the CMDh diverges in their final outcome;
- in the case of a CMDh position to suspend the marketing authorisation(s), the scientific conclusions together with the grounds for suspension and conditions for lifting the suspension;
- in the case of a CMDh position to revoke the marketing authorisation(s), the scientific conclusions together with the grounds for revocation;
- Divergent position(s) for the CMDh members, where applicable.
- In case of CMDh position by consensus, a timetable for implementation in case of variation.

The final assessment conclusions and recommendations shall be published by the Agency in the European medicines web-portal. Until the web portal is fully established and into operation, the Agency's website will be acting as an interim platform, within a dedicated indent of NAPs PSUSAs in the EPAR section.

#### **3.8.1 CMDh position reached by consensus:**

- The position agreed including the action to be taken is recorded by the chairperson in the minutes of the CMDh meeting where agreed.
- The final CMDh position and all related adopted documents will be tabled in MMD



- The EMA shall send the agreed CMDh position and its annexes and appendices to the MAH(s) and to MSs via [list-h-CMD-Pharmacovigilance@eudra.org](mailto:list-h-CMD-Pharmacovigilance@eudra.org).
- Moreover, the EMA will also send all the compiled translations to CMDh via [list-h-CMD-Pharmacovigilance@eudra.org](mailto:list-h-CMD-Pharmacovigilance@eudra.org) (again at the same time as sending this package to the MAHs).
- Further to receipt of the CMDh position stating that regulatory action to the concerned marketing authorisation is necessary, the NCAs shall adopt necessary measures to vary, suspend or revoke the marketing authorisation(s) concerned in accordance with the timetable for implementation determined in the agreed position.
- In cases where the agreed position of the CMDh was that variation to the terms of marketing authorisation is required, the MAH(s) shall submit the relevant variation to that effect within the timetable for implementation as appended to the agreed position.

### **3.8.2 CMDh position reached by majority vote:**

- The majority position on the action to be taken is recorded by the chairperson in the minutes of the CMDh meeting where agreed.
- The divergent views are included in the CMDh position.
- The majority position of the CMDh together with its annexes and its appendices, including translations in all EU official languages where applicable, shall be forwarded to the European Commission.
- The EMA shall send the agreed CMDh position and its appendices to the MAH(s)
- The final CMDh position and all related adopted documents will be tabled in MMD
- Further to receipt of a CMDh position stating that regulatory action to the concerned marketing authorisation is necessary, the European Commission shall adopt decision(s) addressed to the competent authorities in Member States in order for them to vary, suspend or revoke the marketing authorisation(s) of nationally authorised product(s) which is addressed to marketing authorisation holders.
- Further to receipt of the decision from the European Commission, the competent authorities in Member States shall take the necessary measures to maintain, vary, suspend or revoke the marketing authorisation(s) within 30 days.

## **4. IMPLEMENTATION**

A type IA variation C.I.3a is envisaged for NAPs which have been included in the PSUSA procedure where product information changes result from the PSUSA assessment. However, if the wording from the published PSUSA decision has to be adapted when implemented, this should be submitted as a type IB variation under category C.I.3.z.

For products, which were not part of the single PSUSA procedure (see section 3.6), the update of the product information to implement the outcome of the PSUSA should be a type IB variation C.I.3.z, unless the MAH submits additional data for assessment, in which case it would be a type II variation.

The implementation of CMDh consensus positions, or European Commission decisions, is to be monitored by the Member States, to ensure appropriate progression. When the implementation of variations following a European Commission decision is complete, the Member States are required to inform the European Commission via the permanent representative at the CMDh.



## References

- EMA post-authorisation procedure guidance on PSUR
- Cover note for the EURD list (see Q&A No 3)
- GVP VII (PSUR)
- E2C(R2) Implementation Working Group ICH E2C(R2) Guideline: Periodic Benefit-Risk Evaluation Report Questions & Answers

## ANNEX 1

### PSUR TIMETABLE

<b>Day</b>	<b>Event</b>
<b>Submission Deadline Date</b> (= DLP + 70 or 90 days)	PSUR received
<b>1</b>	Start of procedure; EMA provides pre-filled AR template and TT to the lead MS
<b>60</b>	Circulation of Preliminary AR to Member States and PRAC Members and EMA procedure management. EMA to provide AR to MAHs contact points.
<b>90</b>	Member States (only consolidated comments per delegation) and MAHs send comments on the preliminary report.
<b>105</b>	Updated lead MS assessment report sent to Members States and PRAC members
<b>120 (next PRAC meeting)</b>	PRAC recommendation and adoption of AR  If PRAC recommends maintenance – procedure finalised here  If PRAC recommends variation, suspension, revocation - PRAC recommendation sent to CMDh
<b>Within 30 days of receipt by CMDh</b>	CMDh position on recommendations for regulatory action Consensus position – binding, procedure finalised here Majority position – sent to EC for Decision making process