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Questions & answers on signal management

This document addresses a number of questions which stakeholders, in particular marketing authorisation holders (MAHs), may have on the management of safety signals.

Any questions on signal management that are not addressed in this document should be sent to the European Medicines Agency (EMA) using the general [enquiry](#) form (subject: "Signal Management").

Notes:

This document is for guidance only and should be read in conjunction with [Directive 2001/83/EC](#), [Regulation \(EC\) No 726/2004](#) and [Commission Implementing Regulation \(EU\) No 520/2012](#), as well as [Module IX – Signal management](#) of the guideline on good pharmacovigilance practices (GVP). The guidance published as GVP is the principal guidance supporting implementation of and compliance with legal requirements.

Concerning the pilot on signal detection in EudraVigilance, MAHs should monitor EMA targeted communications and the [EMA signal management webpage](#) for announcements and updates.

* This revision includes:

- Update of the requirements for the submission of additional data (question 11).



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1. What is the legal basis for signal management in the European Union (EU)?

Signal management is defined in article 107h of [Directive 2001/83/EC](#), article 28a of [Regulation \(EC\) No 726/2004](#) and chapter III of [Commission Implementing Regulation \(EU\) No 520/2012](#).

2. What is a safety signal?

Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.

Sources may include spontaneous reports, clinical studies and the scientific literature. The EudraVigilance database is an important source of information on suspected adverse reactions reported in association with medicinal products authorised in the European Economic Area. For the purpose of monitoring data in EudraVigilance, only signals related to an adverse reaction shall be considered.

New aspects of a known association may include changes in the frequency, distribution (e.g. gender, age and country), duration, severity or outcome of the adverse reaction.

A signal may concern any medicinal product with a valid marketing authorisation in the EU, irrespective of the authorisation procedure, i.e. national (including mutual recognition and decentralised) or centralised.

A signal generally involves an active substance regardless of its indication, strength or route of administration and applies to all brand names / medicinal products containing the active substance, including fixed combinations. However, in some instances a signal may be relevant only to a particular indication, strength or route of administration. On the other hand, a signal may encompass all active substances of a therapeutic class.

3. What does a signal management process entail?

A signal management process is a set of activities performed to determine whether there are new risks associated with an active substance or a medicinal product or whether known risks have changed, and includes any related recommendations, decisions, communications and tracking.

The EU signal management process includes the following steps: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment and recommendation for action. These steps are defined in [GVP Module IX](#).

4. Who is involved in the EU signal management process?

Signal detection is performed by the EMA, Member States and MAHs. For centrally authorised medicinal products (CAPs), the EMA is responsible for EudraVigilance data monitoring in collaboration with PRAC Rapporteurs. Member States, in collaboration with the EMA are responsible for EudraVigilance data monitoring for medicinal products authorised nationally (NAPs), including those approved via mutual recognition (MRP) and decentralised (DCP) procedures. For NAPs approved in more than one Member State, a worksharing has been organised whereby lead Member States have been appointed to monitor EudraVigilance data on behalf of the other Member States (see [List of substances and products subject to worksharing for signal management](#)). For substances or products for which a lead Member State has not yet been allocated, all Member States are responsible for monitoring EudraVigilance data, until such time as a lead Member State has been allocated.

Signal validation is performed by the stakeholder that detected or first became aware of the signal. Only regulatory authorities can enter signals in the European Pharmacovigilance Issues Tracking Tool (EPITT). The regulatory authority that validated the signal should enter it in EPITT.

Signal confirmation is the responsibility of the PRAC Rapporteur for CAPs, and the lead Member State, if appointed, for NAPs. For NAPs that have not yet been allocated to a lead Member State, the authority that validated the signal should also confirm it.

Signal analysis and prioritisation, assessment and subsequent recommendation(s) for action are the responsibility of the PRAC. At the start of the evaluation of a signal, the PRAC appoints a Rapporteur who takes the lead for the assessment of all collected data.

All organisations should have a robust signal management process and keep an audit trail of their signal management activities, allowing traceability and process control of all steps of signal management, including analyses, decisions and rationale.

5. What are the requirements for monitoring EudraVigilance data applicable to MAHs?

The monitoring of EudraVigilance data is a legal requirement in the EU which applies to EMA, national competent authorities of Member States and MAHs.

During a pilot period, only MAHs with active substances or combinations of active substances included in the [List of active substances involved in the pilot on signal detection in EudraVigilance by marketing authorisation holders](#) have to monitor them in EudraVigilance.

All other MAHs also have access to EudraVigilance data and can integrate the data into their own signal management processes. However, during the pilot period they have no obligation to continuously monitor EudraVigilance data.

MAHs should monitor the [EMA signal management webpage](#) for information and announcements on the EudraVigilance signal detection pilot.

Guidance on the monitoring of EudraVigilance data, including periodicity, is available in [GVP Module IX](#) and in the guideline on [Screening for adverse reactions in EudraVigilance](#).

Further information is available on the [EudraVigilance training and support webpage](#).

6. What are the responsibilities of MAHs in terms of signal management?

MAHs should continuously monitor the safety of their medicinal products and inform the authorities of any new information that might have an impact on the marketing authorisation.

If a MAH detects a signal for one of their medicinal products, they should validate it in accordance with the principles outlined in [GVP Module IX](#).

For signals detected through continuous monitoring of EV data within the scope of the pilot, signal validation should be complemented by the MAH's assessment of other relevant data available to them (e.g. own database, literature, clinical trials). Based on their assessment, the MAH may conclude that a signal is refuted, that there is a new or changed risk and/or that further analysis is required by the competent authorities. Refuted signals should only be reported in PSURs. Other validated signals should be reported as standalone notification, through submission of safety variations and/or within PSURs. These options are further detailed in [GVP Module IX](#) and illustrated in Figure 1.

Standalone notifications of signals detected in EudraVigilance within the scope of the pilot should be sent to the Agency (MAH-EV-signals@ema.europa.eu) and to the competent authorities in Member

States where the medicinal product is authorised. The standalone signal notification form and the national contact points are available on the [EMA signal management webpage](#).

All other validated signals (e.g. detected from sources other than EudraVigilance or falling outside the scope of the pilot) should be handled according to the MAH's own signal management process (see question 3) and if an update to the product information is warranted a variation should be submitted. In line with article 16(3) of [Regulation \(EC\) No 726/2004](#) and article 23(3) of [Directive 2001/83/EC](#), MAHs have a legal obligation to ensure that their product information is kept up to date with the current scientific knowledge, including published PRAC recommendations on signals.

Validated signals should also be presented in the relevant sections of the periodic safety update report (PSUR) (see also GVP [Module VII - Periodic safety update report](#)).

If the MAH considers that a validated signal from any source may qualify as an Emerging Safety Issue, they should notify it in writing to the competent authorities in Member States where the medicinal product is authorised and to the EMA via email (P-PV-emerging-safety-issue@ema.europa.eu), as per the process outlined in [GVP Module IX](#).

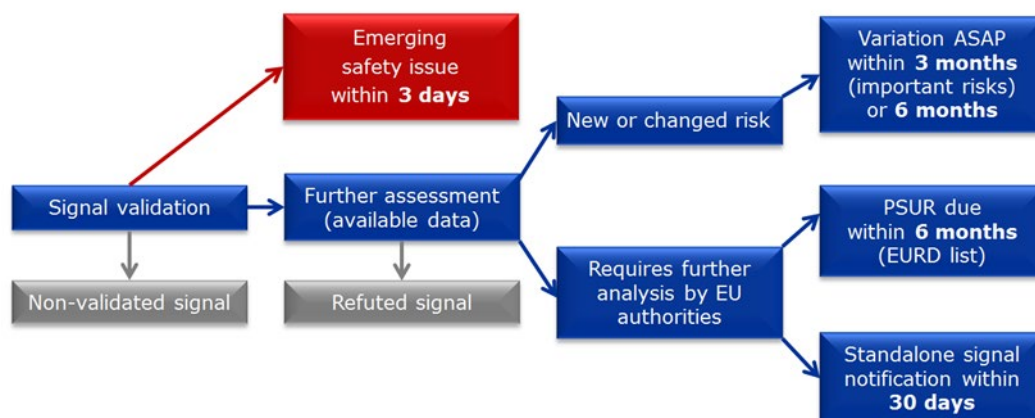


Figure 1 - Handling of signals detected by MAHs in EudraVigilance

7. What could be the PRAC recommendation?

The PRAC recommendation may include any or a combination of the following conclusions:

- no need for further evaluation or action at this point of time, other than routine pharmacovigilance;
- need for additional information:
 - the MAH should submit additional data within the signal procedure;
 - the MAH should address the signal in the following PSUR or submit an ad-hoc PSUR;
 - the EMA or Member States, as relevant, should collect further information (e.g. via a non-urgent information request) or perform additional analyses in EudraVigilance or other data sources;
 - other EMA scientific committees or expert groups should be consulted;
 - the MAH(s) should sponsor a post-authorisation safety study and submit its final results;

- need for regulatory action:
 - the product information and/or risk management plan (RMP) should be updated through a variation;
 - the MAH should implement additional risk minimisation measures such as the preparation of educational materials or the dissemination of a Direct Healthcare Professional Communication (DHPC);
 - the Member States or the Commission, as appropriate, should initiate a referral procedure.
- A pharmacovigilance inspection should take place.
- Any other appropriate action(s) not listed above.

When applicable the PRAC recommendation includes the timeline for the action(s) and a brief rationale.

PRAC recommendations to provide additional data are directly actionable by the concerned MAHs. PRAC recommendations for regulatory action (e.g. amendment of the product information) are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when the signal concerns CAPs, and to the Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh) for information in the case of NAPs, before implementation by the concerned MAHs.

A recommendation is adopted each time a signal is discussed by the PRAC, from the initial analysis and prioritisation and, subsequently, after any follow-up discussion during the different stages of the assessment.

8. When and how are MAHs informed that additional data are requested?

Shortly after the PRAC plenary meeting at which the initial analysis and prioritisation took place, the EMA sends via Eudralink to the concerned MAH(s) the adopted signal assessment report after redaction of personal data and commercially confidential information. The assessment report contains the PRAC request for additional data together with the deadline for responses.

Other MAHs are informed of the PRAC recommendations via publication on the EMA website (see also question 16).

9. Are additional data requested of all MAHs with a marketing authorisation for a medicinal product concerned by the signal?

Requests for additional data are usually addressed to the MAH(s) for the innovator products as they are expected to hold the most comprehensive safety data on the concerned substance. These MAH(s) are identified from sources such as the [Article 57 database](#). In some instances (e.g. signals involving a therapeutic class) the PRAC may request additional data from more than one MAH(s). The MAHs requested to provide data are specified in the PRAC recommendation.

Requests for additional data are sent to the Qualified Person Responsible for Pharmacovigilance (QPPV) for both CAPs and NAPs and to the contact person for MAH for CAPs. For CAPs and NAPs, QPPV details are identified based on the information provided by MAHs in the context of [Article 57\(2\) of Regulation \(EC\) No 726/2004](#).

If a MAH that is not the innovator for a substance concerned by a signal receives a request for supplementary information, they should inform the relevant signal management lead and the PRAC Rapporteur (as detailed in the request sent by EMA) and provide the details of the 'innovator MAH'.

If an 'innovator MAH' has not received any notification by the time the recommendation is published (see also question 16), they should liaise with the EMA using the general [enquiry form](#) (subject: "Signal Management").

10. Can MAHs submit additional data on a voluntary basis?

Although requests for additional data are usually addressed to 'innovator MAHs' (see also question 9), other MAHs may submit data if they consider that they would be relevant to the evaluation of the signal. Those MAHs should inform the PRAC Rapporteur appointed for the signal and the EMA (using the general [enquiry form](#), subject: "Signal Management") that they intend to provide data, as early as possible in advance of the planned submission. The deadline for submission is the same as that for the MAH(s) identified by the PRAC and is specified in the PRAC recommendation. For submission requirements, please refer to question 11.

11. How and to whom should MAHs submit the requested data?

The applications (responses) should be submitted in English and electronically to the EMA within the timeline specified in the PRAC recommendation. The requested data should be submitted following the Common Technical Document (CTD) format and within the appropriate modules (e.g. 5.3.6. Reports of post-marketing experience) of the CTD.

The relevant sections of the EMA [eSubmission web UI \(.xml delivery file\)](#) should be completed and the package sent through the eSubmission Gateway. Please see further details in the [User Guidance for submissions via eSubmission Gateway / Web Client using xml delivery files](#).

MAHs should follow the below instructions:

For Nationally Authorised Products

- Choose a submission type: "Signal detection"
- Choose a Submission-Unit: "Initial" / relevant Unit type
- EPITT number: number as provided in the request sent by EMA.

For Centrally Authorised Products

- Choose a submission type: "PAM-SDA" for Centralised Products
- Choose a Submission-Unit: "Response"

The Common Repository is in use for both CAPs and NAPs and has replaced the use of the CESP and CD/DVD for submissions to National Competent Authorities (NCAs). All submissions sent to the EMA are considered delivered to all NCAs' representatives and alternates.

The cover letter should be addressed to the PRAC rapporteur for the signal (copy PRAC members) and to the signal management lead, as detailed in the request sent by EMA. The EPITT reference number should be mentioned on the cover letter.

MAHs with both CAPs and NAPs for the same substance and wishing to carry out a combined cumulative review should list all the concerned products in the cover letter of each submission.

When the PRAC recommends that a cumulative review is submitted within the following PSUR, the signal should be included in Section 15 of the PSUR (tabulation of signals). Depending on its extent, the analysis should be included either in Section 16.2 (Signal Evaluation) or as an annex to the PSUR, with appropriate cross-references. The full evaluation report should always be submitted. Please refer to [GVP Module VII](#) for further guidance on PSURs.

If a MAH decides to submit the requested data in support of a type II variation, they should inform the relevant signal management lead, the procedure manager (for CAPs) and the PRAC Rapporteur (as detailed in the request sent by EMA) in writing. In such cases, the MAH should not provide in addition a separate standalone submission of the responses to the PRAC request, but clearly indicate in the cover letter and in the scope section of the variation application the request that is being addressed together with the EPITT number. The variation should be submitted by the time the responses to the PRAC request are due and is handled according to established procedures.

12. Who is the contact point for MAHs within the regulatory network?

Any question on a signal should be addressed to the PRAC Rapporteur appointed for the signal and the signal management lead, when known, or the EMA (using the general [enquiry form](#), subject: "Signal Management").

13. What are the timelines for assessment of additional data by the PRAC?

The timelines for evaluation are agreed at the stage of initial analysis and prioritisation by PRAC based on the potential impact of the signal on public health and/or benefit-risk balance. These elements dictate the timelines for the subsequent steps of the signal evaluation. When the PRAC requests additional data from MAHs, these timelines usually encompass 2 months for submission of responses by the MAHs and 60 days for assessment by the PRAC. However, where appropriate, shorter or longer timelines may apply.

The exact date by when data should be submitted is stated in the request for supplementary information letter sent to the concerned MAH(s) and published on the EMA website.

If a MAH is unable to provide the requested data on time, it must inform the relevant signal management lead and the PRAC Rapporteur (as detailed in the request sent by EMA) in writing as early as possible in advance of the due time of submission. A justification for the delay should be provided and a new submission date proposed.

Once they have submitted the requested data, MAH are informed of the applicable timetable for assessment by PRAC. Procedural timetables for assessment of supplementary information on signals are available [here](#).

14. Do MAHs receive the assessment report (AR) on the data submitted?

The assessment report is shared with all MAHs requested to submit additional data (see question 9), at the following stages:

- within two working days of PRAC adoption after initial analysis and prioritisation,
- within two working days of circulation of the preliminary assessment report by the PRAC rapporteur,
- within a week of the CHMP meeting following PRAC adoption of the final assessment report.

The assessment report is shared with the MAHs after redaction of personal data and commercially confidential information.

MAHs are invited to comment on the preliminary AR by the timeline specified in the communication. This may be done by e-mail, Eudralink or in eCTD format, as appropriate. This AR is shared with all those MAHs that provided data (see also question 9).

15. What should MAHs do if the PRAC recommends a variation to their marketing authorisation?

MAHs have a legal obligation to ensure that their product information is kept up to date with the PRAC recommendations published on the EMA website, in line with article 16(3) of [Regulation \(EC\) No 726/2004](#) and article 23(3) of [Directive 2001/83/EC](#).

PRAC recommendations for update of the product information following assessment of a signal usually include the wording to be implemented in the summary of product characteristics (SmPC) and/or package leaflet (PL) as well as the timeline for submission of the variation (see also questions 7 and 16). The implementation of the published wording and translations can generally be handled through a type IA_{IN} variation, category C.I.z. If in doubt, MAHs are advised to contact the EMA or the relevant NCAs.

PRAC recommendations to update the product information are applicable to all medicinal products containing the concerned substance, unless otherwise specified (see also question 2).

MAHs are expected to submit the requested variation according to the timeline specified in the PRAC recommendation. This timeline is calculated from the date of publication of the PRAC recommendation (see also question 16). For instance, recommendations for update of the product information adopted by [PRAC in September 2018](#) were expected to be submitted within 2 or 3 months, as applicable, of 1st October 2018 (publication date).

Of note, the timeline recommended by PRAC for submission of variations following signal assessment is applicable to both innovator and generic products, unless otherwise specified.

Guidance on variations available on the websites of the [EMA](#), [Heads of Medicines Agencies](#) or relevant MSs is also applicable to variations resulting from signal assessment. For questions that are not addressed in the above guidance, MAHs should seek advice from the EMA (Iaquery@ema.europa.eu, Ibquery@ema.europa.eu or Iiquery@ema.europa.eu) for CAPs. For other products, queries should be addressed to the reference member state (MRP/DCP) or to the relevant NCAs (purely nationally authorised medicinal products).

16. How does EMA communicate on signals?

MAHs requested to submit data are contacted directly by EMA (see questions 8 and 14).

The week before each PRAC plenary meeting, all MAHs with medicinal products in the [Article 57 database](#) receive advance notice of signals that are scheduled for discussion (i.e. confirmed signals) as well as a cumulative list of non-confirmed signals. MAHs are encouraged to consider this information as a resource for their signal detection activities.

The confirmed signals are also reflected in the [draft PRAC agenda](#) which is published on the EMA website usually on the Monday of the meeting.

All PRAC recommendations on signals are published on the [EMA Signal Management webpage](#) within a month of the relevant PRAC meeting.

PRAC recommendations to update the product information are published in full; other PRAC recommendations are summarised in a tabular format. A cumulative list of signals discussed at PRAC since its establishment (September 2012) is also published. All PRAC recommendations are further reflected in the meeting [minutes](#), which are published after their adoption at the following PRAC meeting.

For PRAC recommendations to update the product information, the agreed wording is published in English and, as of January 2015, after review by NCAs of Member States, also in all EU official languages, as well as Norwegian and Icelandic. MAHs can use these translations to update their product information.

Member States may also publish information on signals discussed at PRAC on their websites.

MAHs have a legal obligation to continuously monitor the information on the EMA website in line with Article 11 of [Commission Implementing Regulation \(EU\) No 520/2012](#).