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.

If you have a question on signal management that is not addressed in this document, please send it to p-pv-helpdesk@ema.europa.eu.

Note:

This document has been produced 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.
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1. **What is the legal basis for signal management in the European Union (EU)?**


2. **What is a safety signal?**

In the Report of the Council for International Organisations of Medical Sciences Working group VIII Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010) a signal is defined as information that arises 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. For the purpose of monitoring data in EudraVigilance, only signals related to an adverse reaction shall be considered.

Signals may originate from several sources such as 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, and therefore one source of signals.

3. **What are the steps of the signal management process?**

The signal management process consists of detection, validation, confirmation, analysis and prioritisation, assessment and recommendation for action.

*Signal detection* usually involves a combination of statistical methods and review of individual case safety reports, as well as any relevant source of information (e.g. scientific literature).

*Signal validation* is the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further analysis. The clinical significance of the signal, its previous awareness, the biological and temporal plausibility and any relevant sources of information supporting the association are taken into consideration. Signals validated by the European MedicinesAgency (EMA) or Member States are entered in the European Pharmacovigilance Issues Tracking Tool (EPITT). EPITT is a database developed by the EMA to promote the communication of pharmacovigilance and risk management issues between the EMA and Member States. Signals for which the validation process was not suggestive of a new potentially causal association, or a new aspect of a known association, will not be entered in EPITT.

*Signal confirmation* means communication via EPITT, within 30 days of its receipt by the PRAC Rapporteur or the lead Member State, that the validated signal should be analysed and prioritised by the PRAC.

*Signal analysis and prioritisation* are performed by taking into account the potential impact of the signal on the benefit-risk profile of the involved medicine(s). The prioritisation dictates the time frame for submission and assessment of data (please also refer to question 8).

*Signal assessment* is the scientific evaluation of all the evidence available, including additional data from MAHs, where applicable.

The steps of analysis, prioritisation and assessment result in a **PRAC recommendation**.
4. Who is involved in the 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 and decentralised 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 active substances subject to worksharing for signal management). For medicinal 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.

MAHs shall perform signal detection for their medicinal products using any data sources available to them (e.g. corporate database, scientific literature).

Signal validation is performed by the stakeholder that detected or first became aware of the signal. Only regulatory authorities can enter signals in EPITT. The regulatory authority that validated the signal should also 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 an evaluation, the PRAC appoints a Rapporteur who will take the lead for the assessment of all collected data.

5. What should MAHs do if they detect a signal?

If a MAH detects a signal for one of their medicinal products, they should validate it.

If the MAH considers that the validated signal may qualify as an Emerging Safety Issue (see also Module VI – Management and reporting of adverse reactions to medicinal products of the GVP), they should notify it immediately 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). MAHs should provide a precise description of the safety issue, including the available evidence and the proposed regulatory action(s).

All other validated signals should be handled according to available guidelines (see Module IX – Signal management of the GVP) 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.

Validated signals should also be presented in the relevant sections of the periodic safety update report (PSUR) (see also Module VII - Periodic safety update report (Rev 1) of the GVP).

MAHs should keep an audit trail of their signal management activities.
6. Which medicinal products can be concerned by a signal?

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.

7. When and how will MAHs know that a signal for their medicinal product is being investigated by the PRAC?

The draft agenda of the PRAC lists all confirmed signals scheduled for discussion at each plenary meeting. It is published on the EMA website, usually on the Monday of the meeting.

8. How does the PRAC prioritise signals?

When prioritising signals, the PRAC may take into account several factors, including any potential impact on the benefit-risk profile of the product, the strength of evidence supporting a causal association, the severity and seriousness of the reaction, its estimated frequency of occurrence, its preventability, the consequences of discontinuing treatment and the availability of alternative therapeutic options, the extent of utilisation of the medicinal product in the general population or in particular patient groups, the complexity of the issue and the nature of the available information.

9. 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;
- need for additional information:
  - the MAH, Member States and/or the EMA, where relevant, should monitor any relevant emerging information on the signal as it becomes available;
  - the MAH should address the signal in the following PSUR or submit an ad-hoc PSUR;
  - the MAH should submit additional data;
  - 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;
  - the MAH(s) should conduct a post-authorisation safety study;
- need for regulatory action:
  - the product information and/or risk management plan (RMP) should be updated through a variation;
  - the Member States or the Commission, as appropriate, should initiate a referral procedure;
  - urgent safety restrictions should be imposed.
When appropriate, these actions may be accompanied by additional communication measures, e.g. a Direct Healthcare Professional Communication (DHPC).

- A pharmacovigilance inspection should take place.

Note: the above list may not be exhaustive and other actions may be recommended by the PRAC.

When applicable, the PRAC recommendation will specify the timelines for the actions. If the product information should be amended, the PRAC recommendation will include the wording to be implemented in the summary of product characteristics (SmPC) and package leaflet (PL).

10. **To whom are PRAC recommendations addressed?**

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 CHMP for endorsement when the signal concerns CAPs, and to the CMDh for information in the case of NAPs. Thereafter, MAHs are expected to take action according to the PRAC recommendations.

When appropriate, the PRAC may also recommend the conduct of additional analyses by the EMA or Member States (see also question 9).

11. **Can more than one PRAC recommendation be issued for a particular signal?**

A recommendation is issued 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.

12. **Where are the PRAC recommendations on signals published?**

PRAC recommendations – for both CAPs and NAPs – involving updates to the product information will be published on the EMA website, after the CHMP/CMDh meetings following the relevant PRAC meeting. All PRAC recommendations are reflected in the meeting minutes, which are published a few days after their adoption at the following PRAC meeting. Member States may also publish this information on their websites.

In addition, in some instances, outcomes of signals may also be made public through other communication means, such as meetings highlights or press releases.

MAHs have a legal obligation to continuously monitor the information on the European medicines web portal in line with Article 11 of Commission Implementing Regulation (EU) No 520/2012.

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

The contact points within the regulatory network for any question pertaining to a specific signal depend on the type of authorisation procedure of the concerned product.

For CAPs the contact point is the EMA product team leader (PTL).

For NAPs the contact point is the national competent authority of the PRAC Rapporteur, as reflected in the published PRAC recommendation and/or the notification letter sent to the MAHs, when applicable.

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1 The EMA’s website will serve as the European medicines web portal for the dissemination of information on medicinal products authorised in the European Union (see Legal notice)
14. When and how will MAHs be informed that additional data are requested?

If additional data from one or more MAH(s) are required, the concerned MAH(s) will receive a direct communication from the EMA (please also refer to question 16). This communication is usually sent via Eudralink within a few days of the end of the PRAC plenary meeting. Other MAHs will be informed of the PRAC conclusions via publication on the EMA website (please also refer to question 12).

15. If the signal concerns a substance contained in several medicinal products with several MAHs, to whom will the request for additional data be addressed?

Requests for additional data will be addressed to the MAHs for the innovator products.

16. How is the innovator identified?

MAHs for innovator products will primarily be identified by the EMA from the List of substances under PSUR Work Sharing scheme and other substances contained in Nationally Authorised Products with DLP synchronised.

In case the innovator MAH cannot be identified from this list, the PRAC Rapporteur will be consulted to identify the MAH(s) that will be requested to provide data.

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

Although requests for additional data are primarily addressed to the MAHs for innovator products, any other MAH may submit data on a signal if they consider that such data would be relevant to the evaluation of the signal. Those MAHs should inform the EMA (PTL in case of CAPs or p-pv-helpdesk@ema.europa.eu in case of NAPs) and PRAC members that they intend to provide data as early as possible in advance of the submission. The same timelines and requirements as for the MAHs for the innovator products apply. For submission of data, please refer to Question 20.

18. Who will be the contact person within the MAH to communicate with the EMA/Member States during the procedure?

Initial requests for additional data are sent to the qualified person responsible for pharmacovigilance (QPPV). For CAPs, the QPPV details are those provided by MAHs to the EMA in the application dossier or subsequent updates. For 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.

19. What should I do if I have not received any communication from the EMA?

If a MAH for an innovator product concerned by a signal for which the PRAC requested additional data has not been contacted by the EMA by the time the recommendations are published, they should liaise with the EMA (PTL in case of CAPs or p-pv-helpdesk@ema.europa.eu in case of NAPs).

20. How and to whom shall I submit my answers?

The responses should be submitted in English and electronically within the timeline specified in the PRAC recommendation.

Centrally authorised products

The requested data should be submitted in eCTD format within the appropriate modules (e.g. 5.3.6. Reports of post-marketing experience). The EMA strongly recommends using the eSubmission Gateway or the eSubmission Web Client as the preferred submission methods for all eCTD submissions. More information on how to register and connect to the Gateway / Web Client can be found in the
eSubmission website and detailed information on the required naming conventions and file formats can be found in the Gateway Q&A and the Web Client Q&A. Applicants must not send duplicate submissions electronically or via CD-ROM or DVD as this might lead to delays in the handling of applications.

Applications that are sent using the eSubmission Gateway and eSubmission Web Client will receive an automated ‘acknowledgement’, confirming whether the submission has passed the relevant technical validation criteria and whether it has been uploaded to the EMA’s review tool. There is no need to send any separate paper cover letters for these submissions, as the cover letter will be in the relevant part of eCTD module 1 in PDF format.

MAHs not yet using the eSubmission Gateway or the Web Client solution should send their data as CD-ROM or DVD for the attention of the Product and Application Business Support at the following address:

Product and Application Business Support
European Medicines Agency
Loading Dock
Ontario Way
Canary Wharf
UK - London, E14 4HB

Only one CD-ROM or DVD (in eCTD format) of the data should be submitted to the EMA, together with one original, signed cover letter. The EMA PTL and signal validator (as indicated in the request for submission of data) should be indicated in copy "cc" on the cover letter (no additional copy needed).

One electronic copy of the responses and supportive documentation should be submitted to the PRAC (Co-)Rapporteurs and all the other PRAC members, after the eSubmission Gateway / web client confirmation of a technically valid submission.

It is essential that identical eCTD sequences are circulated to PRAC Committee Members. Any minor changes that affect the "md5 checksum" will lead to inconsistency and possibly result in future technical invalidity.

Any additional information/documentation requested during the evaluation should be equally provided to the EMA, PRAC (Co-)Rapporteurs and the other PRAC members. Responses to a request for supplementary information should be submitted within a new or consolidated eCTD sequence in order to maintain the eCTD life-cycle. Please refer to the TIGes Harmonised Guidance and eCTD for specific advice.

For a full overview of dossier requirements for National Competent Authorities of PRAC (Co-) Rapporteur and Committee members, including delivery addresses, please refer to the following document: Dossier requirements for Centrally Authorised Products (CAPs).

Please note that for CAPs the EMA only accepts submissions made in a mandatory eCTD format.

Nationally authorised products

The requested data should be submitted within the appropriate CTD modules (e.g. 5.3.6. Reports of post-marketing experience) and accompanied by a signed cover letter. One electronic copy of the responses and supportive documentation should be submitted to the PRAC (Co-)Rapporteurs and all the other PRAC members.

Any additional information/documentation requested during the evaluation should be equally provided to PRAC (Co-) Rapporteurs and the other PRAC members.
21. By when do I have to submit the requested data?

The timeline for submission is decided by the PRAC based on several criteria, including the seriousness and public health impact of the issue, and the expected volume of data. In general, MAHs will be requested to submit data within 60 days. However, where deemed appropriate, shorter or longer timelines may apply. The exact date by when data should be submitted will be stated in the notification letter sent to concerned MAH(s) and published on the EMA website.

22. What is the timetable for assessment of additional data by the PRAC?

The assessment starts 2 days after the submission deadline.

The standard timetable encompasses 60 days for the assessment of MAH’s responses and adoption of a recommendation.

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<td>Day 1</td>
<td>Start of procedure</td>
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<tr>
<td>Day 30</td>
<td>Preliminary PRAC Rapporteur AR</td>
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<td>Day 45</td>
<td>Comments from PRAC members</td>
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<tr>
<td>Day 50</td>
<td>Updated PRAC Rapporteur AR</td>
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<tr>
<td>Day 60</td>
<td>Adoption of PRAC recommendation</td>
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If the urgency of a signal warrants it, the PRAC may agree on a shorter timetable, as follows.

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<tr>
<td>Day 1</td>
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<td>Day 15</td>
<td>Preliminary PRAC Rapporteur AR</td>
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<td>Day 20</td>
<td>Comments from PRAC members</td>
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<td>Day 25</td>
<td>Updated PRAC Rapporteur AR</td>
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<td>Day 30</td>
<td>Adoption of PRAC recommendation</td>
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23. 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 European Medicines web portal, in line with article 16(3) of Regulation (EC) No 726/2004 and article 23(3) of Directive 2001/83/EC.

MAHs are expected to submit the variation according to the timeline specified in the PRAC recommendation. The specified timeline is usually calculated from either the date of direct communication by a regulatory authority or the date of publication of the PRAC recommendation, (i.e. after the following CHMP/CMDh meetings), whichever comes first. For CAPs, the submission dates for variations are published here.

24. How will my variation application be handled?

Variations are handled according to established procedures. Relevant guidance is available on the websites of the EMA, Heads of Medicines Agencies or relevant MSs, as applicable.