EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 August 2016
EMA/261758/2013 Rev 2- Corr 2*
Inspections and Human Medicines Pharmacovigilance Division

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").

Note:

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.

* This revision includes minor procedural clarifications in questions 14.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

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?

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 is the act of looking for and/or identifying signals using data from any source. 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 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 supportive of a new potentially causal association, or a new aspect of a known association, are not entered in EPITT.

Signal confirmation means communication via EPITT, within 30 days of its receipt by the Rapporteur, the lead Member State or a national competent authority that the validated signal is confirmed or not confirmed. Any confirmed signal should be analysed and prioritised by the Pharmacovigilance Risk Assessment Committee (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 the subsequent steps of the evaluation of the signal (see also 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 (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.

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 takes 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 (Rev 1) 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 are MAHs informed that a signal for their medicinal product is being investigated by the PRAC?

All MAHs with medicinal products in the Article 57 database receive advance notice of signals that are scheduled for discussion at PRAC on Thursday of the week preceding the relevant PRAC plenary. These signals are also reflected in the draft PRAC agenda which 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 expected volume of data.

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.

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.

  These actions may be accompanied by additional communication measures, e.g. a Direct Healthcare Professional Communication (DHPC).
- A pharmacovigilance inspection should take place.
- Other 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.

10. Where are the PRAC recommendations on signals published?

All PRAC recommendations on signals are published on the EMA website[1] 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 a few days 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 National Competent Authorities (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.

[1] The EMA's website serves as the European medicines web portal for the dissemination of information on medicinal products authorised in the European Union (see Legal notice)

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

Shortly after the PRAC plenary meeting the EMA sends to the concerned MAH(s) the request for additional data via Eudralink, together with the deadline for responses. Other MAHs are informed of the PRAC recommendations via publication on the EMA website (see also question 10).

12. 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 List of substances under PSUR Work Sharing scheme and other substances contained in Nationally Authorised Products with DLP synchronised or 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 10), they should liaise with the EMA using the general enquiry form (subject: "Signal Management").

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

Although requests for additional data are usually addressed to 'innovator MAHs' (see also question 12), 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 14.

14. How and to whom should MAHs submit their responses?

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

The cover letter should mention the EPITT number specified in the request for additional data.

For *centrally authorised products*, please refer to the Dossier requirements for Centrally Authorised Products (CAPs) published on the EMA website (submission type 'PAM'). As per this guidance, the requested data should be submitted to the EMA only. In section 12 of the table template to be included in the cover letter, 'SDA', 'Pharmacovigilance' and 'Follow-up request from PRAC' should be selected as 'PAM type', 'PAM area' and 'PAM data', respectively.

For *nationally authorised products*, please refer to Dossier requirements for referral, ASMF and NAP submissions (PASS107, Workshare, Signal Detection procedures) and ancillary medicinal substances in a medical device published on the EMA website. As per this guidance, the requested data should be submitted to the EMA and to the PRAC (Rapporteur and other members' national competent authorities).

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.

15. 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").

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

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.

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

The EMA sends to all MAHs that have submitted data the preliminary AR after redaction of personal data and commercially confidential information, usually within 2 working days from circulation by the PRAC Rapporteur. 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. The final PRAC AR adopted by PRAC is sent to the relevant MAHs within a week of the following CHMP/CMDh meeting (see also question 9).

When data are requested from more than one MAH, all responses are assessed within the same AR. This AR is shared with all those MAHs that provided data (see also question 12).

18. 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 9 and 10). The implementation of the published wording and translations can generally be handled through a type IA_{IN} variation. 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 6).

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 10). For instance, recommendations for update of the product information adopted by PRAC in September 2014 were expected to be submitted within 1 or 2 months of 30 September 2014 (publication date), as applicable.

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).