1 9 October 2017
2 EMA/827661/2011 Rev 1* - Track-change version following public consultation

# 3 Guideline on good pharmacovigilance practices (GVP)

## 4 Module IX – Signal management (Rev 1)

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|---|---|
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6 This track-change version identifies the majority of changes (revisions post-consultation marked in
7 red) introduced to the public consultation version (revisions marked in blue) of this document as the
8 Agency's response to the comments received from the public consultation. This track-change version is
9 published for transparency purposes and must not be taken or quoted as the final version.

10 * For this reason, the timetable above, and in particular the date of coming into effect, apply only the
11 clean version published as final.

12 For the final version of this module and any future updates, please see the GVP webpage of the
13 Agency's website.

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15 ** Note: The requirement for marketing authorisation holders to monitor EudraVigilance data (Sections
16 IX.C.1.1. and IX.C.3.) and inform the Agency and national competent authorities of validated signals
17 (Section IX.C.4.) will enter into force on 22 February 2018 and will only apply, for a transition period,

to active substances contained in medicinal products included in the 'List of medicinal products under additional monitoring' in force as of 22 November 2017. Please refer to dedicated communication from the Agency for more details.

* Note: Revision 1 is a major revision with modifications throughout ~~based on experience gained over the past 4 years, and guidance on signals validated by marketing authorisation holders. It~~and contains the following:

- Revised definition and process for emerging safety issues, previously addressed in GVP Module VI (IX.A.1.1. and IX.C.~~3.1~~2.);
- Streamlined information on scientific aspects of signal management (IX.B.2. to IX.B.4.), statistical aspects now addressed in Addendum I;
- Clarifications on terminology (IX.A.1.), roles and responsibilities (IX.C.1.) and processes (IX. Appendix 1);
- ~~Criteria for access by marketing authorisation holders to case narratives held in EudraVigilance, with reference to Revision 2 of the EudraVigilance Access Policy (IX.C.2.1.);~~
- Updated guidance on the ~~periodicity of~~ monitoring of EudraVigilance data (IX.C.~~2.2~~3.);
- ~~Procedural options~~Guidance ~~for~~ on signals ~~validated~~ detected by marketing authorisation holders based on the continuous monitoring of EudraVigilance data (IX.C.~~3~~4.).

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# IX.A. Introduction

Regulation (EC) No 726/2004, Directive 2001/83/EC and Commission Implementing Regulation (EU) No 520/2012 (hereinafter referred to as REG, DIR and IR, respectively) include provisions for signal management in the European Union (EU) [DIR Art 107h, REG Art 28a, IR Chapter III].

In this Module, all applicable legal requirements are referenced as explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb "shall". Guidance for the implementation of legal requirements is provided using the modal verb "should".

The objectives of this Module are to:

- ~~to~~ provide general guidance and requirements on scientific and quality aspects of signal management (IX.B.);
- ~~to~~ describe roles, responsibilities and procedural aspects in the setting of the EU ~~regulatory network~~signal management process overseen by the Pharmacovigilance Risk Assessment Committee (PRAC) (IX.C.).

This Module is applicable to medicinal products for human use authorised in the EU irrespective of the authorisation procedure (centralised or national procedure, including mutual recognition and decentralised).

Unless stated otherwise, the guidance provided in the Module applies to all organisations involved in signal management, i.e. marketing authorisation holders, national competent authorities and the European Medicines Agency (the 'Agency').

Individual organisations may follow alternative signal management processes and terminology but should encompass the general principles outlined in this Module.

An addendum to this Module, the GVP Module IX Addendum I, describes methodological aspects of signal detection from spontaneous reports of suspected adverse reactions.

The following documents provide additional guidance relevant to signal management:

- Report of CIOMS Working Group VIII on Practical Aspects of Signal Detection in Pharmacovigilance[1];
- SCOPE Work Package 5 – Signal Management - Best Practice ~~Guidance~~Guide[2];
- EMA Questions & Answers on Signal Management[3];
- Screening for Adverse ~~Drug~~ Reactions in EudraVigilance[4].

## *IX.A.1. Terminology*

### IX.A.1.1. General definitions

General d~~D~~efinitions relevant to signal management ~~applicable to this Module~~ are also included in GVP Annex I. ~~Definitions specific to the EU signal management process are also presented below.~~

***Signal***

[1] Council for International Organizations of Medical Sciences (CIOMS). Report of CIOMS Working Group VIII on Practical Aspects of Signal Detection in Pharmacovigilance. Geneva: CIOMS; 2010.
[2] See www.scopejointaction.eu ~~(will be available)~~
[3] See ~~EMA/261758/2013, available on EMA website http://~~www.ema.europa.eu~~.~~
[4] See www.ema.europa.eu ~~(available as of Q4 2016)~~

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 [IR Art 19(1)].

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 ~~event~~reaction.

~~For the purpose of monitoring data in the EudraVigilance database (also referred to as 'EudraVigilance'), only signals related to an adverse reaction shall be considered [IR Art 19(1)].~~

A signal often relates to all medicinal products containing the same active substance, including combination products. Certain signals may only be relevant for a particular medicinal product or in a specific indication, strength, pharmaceutical form or route of administration whereas some signals may apply to a whole class of medicinal products.

For the purpose of monitoring data in the EudraVigilance database (also referred to as 'EudraVigilance'), only signals related to an adverse reaction shall be considered [IR Art 19(1)].

***Signal management process***

~~The~~ A set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, scientific literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed, as well as any related recommendations, decisions, communications and tracking.

The EU signal management process includes the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment and recommendation for action [IR Art 21(1)]~~.~~ (see IX.A.1.2.).

***Signal prioritisation***

The process, continuously performed throughout signal management, which aims to identify those signals suggesting risks with a potential important patients' or public health impact or which may significantly affect the risk-benefit balance of the medicinal product and thus require urgent attention and management without delay.[5]

***Signal detection***

The ~~act~~ process of looking for and/or identifying signals using data from any source.[6]

***Signal validation***

The process of evaluating the data supporting ~~a~~ 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 ~~to justify~~ justifies further analysis of the signal [IR Art 21(1)].

This evaluation should take into account the strength of the evidence, the clinical relevance and the previous awareness of the association (see IX.B.3.).

The extent of evaluation performed during signal validation versus further assessment may vary according to the organisation's internal procedures.

[5] Based on SCOPE Work Package 5 – Signal Management - Best Practice Guide (www.scopejointaction.eu)
[6] Council for International Organizations of Medical Sciences (CIOMS). Report of CIOMS Working Group VIII on Practical Aspects of Signal Detection in Pharmacovigilance. Geneva: CIOMS; 2010.

***Validated signal***

A signal for which the signal validation process has verified 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 of the signal.

***Non-validated signal***

A signal for which the signal validation process has led to the conclusion that the available documentation at that point in time does not contain sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and that therefore further analysis of the signal is not warranted.[7]

***Signal assessment***

The process of further evaluating a validated signal taking into account all available evidence, to determine whether there are new risks causally associated with the active substance or medicinal product or whether known risks have changed. This review may include non-clinical and clinical data and should be as comprehensive as possible regarding the sources of information.

***Refuted signal***

A validated signal which, following further assessment has been determined to be "false" i.e. a causal association cannot be established at that point in time (see GVP Module VII).

***Emerging safety issue***

A safety issue considered by a marketing authorisation holder to require urgent attention by the competent authority because of the potential major impact on the risk-benefit balance of the medicinal product and/or on patients' or public health, and the potential need for prompt regulatory action and communication to patients and healthcare professionals. Examples include:

- major safety issues identified in the context of ongoing or newly completed studies, e.g. an unexpectedly increased rate of fatal or life-threatening adverse events;
- major safety issues identified through spontaneous reporting or published in the scientific literature, which may lead to considering a contra-indication, a restriction of use of the medicinal product or its withdrawal from the market;
- major safety-related regulatory actions outside the EU, e.g. a restriction of the use of the medicinal product or its suspension.

The requirements and process for emerging safety issues are outlined in IX.C.2..

## IX.A.1.2. Definitions specific to the EU signal management process with oversight of the Pharmacovigilance Risk Assessment Committee (PRAC)

***Lead Member State for signal management***

The Member State responsible for monitoring the EudraVigilance database for an active substance or combination of active substances contained in medicinal products authorised in more than one Member State through the national, mutual recognition or decentralised procedures. The lead Member State shall validate and confirm signals on behalf of the other Member States (see IX.C.1.2.).

If the active substance is authorised in only one Member State, that Member State automatically assumes the responsibilities of the Lead Member State.

[7] SCOPE Work Package 5 – Signal Management - Best Practice Guide (www.scopejointaction.eu)

***PRAC Rapporteur***

Rapporteur appointed by the PRAC in the context of the centralised procedure (see PRAC Rules of Procedure[8]). Within the EU signal management process, the PRAC Rapporteur is responsible for the confirmation of signals concerning centrally authorised medicinal products.

***Signal confirmation by the PRAC Rapporteur or (lead) Member State***

The process ~~during which the competent authority of a Member State (where the signal concerns a medicinal product authorised in accordance with DIR), or the Rapporteur appointed by the Pharmacovigilance Risk Assessment Committee (PRAC) (where the signal concerns a product authorised in accordance with REG), decides~~ of deciding whether or not a validated signal entered in the European Pharmacovigilance Issues Tracking Tool (EPITT) ~~should be~~requires further analysis~~ed~~ and prioritisation~~ed~~ by the PRAC. This should be done ~~by~~ by the PRAC Rapporteur or the (lead) Member State within 30 days from receipt of the validated signal.

Signal confirmation is not intended to be a full assessment of the signal. The fact that a signal is confirmed does not imply that a causal relationship has been established, but that the signal should be discussed at EU level and further investigated by the PRAC (see IX.C.~~4~~5.).

***Confirmed signal***

A validated signal entered in EPITT that requires further analysis and prioritisation by the PRAC, according to the PRAC Rapporteur or (lead) Member State.

***Non-confirmed signal***

A validated signal entered in EPITT that does not require further analysis and prioritisation by the PRAC at that point in time, according to the PRAC Rapporteur or (lead) Member State.

***Signal analysis and prioritisation by the ~~Pharmacovigilance Risk Assessment Committee (~~PRAC~~)~~***

The process by which the PRAC determines whether a confirmed signal requires further ~~evaluation~~assessment, and if required, to what timeframe and in which procedural framework. This is based on an initial analysis of the potential impact of the signal on patients' ~~and~~ or public health and the risk-benefit balance of the concerned medicinal product(s) (see IX.C.~~5~~6.).

***Signal assessment by the ~~Pharmacovigilance Risk Assessment Committee (~~PRAC~~)~~***

Following PRAC initial signal analysis and prioritisation, the process of evaluating all available data relevant to a signal to determine the need for any regulatory action (see IX.C.~~5~~6.). This is led by the Rapporteur appointed by the PRAC following analysis and prioritisation.

***~~Lead Member State for signal management~~***

~~The Member State appointed to monitor the EudraVigilance database for an active substance contained in medicinal products authorised in accordance with DIR in more than one Member State through the national, mutual recognition or decentralised procedures. The Lead Member State shall validate and confirm signals on behalf of the other Member States.~~

~~If the active substance is authorised in only one Member State, that Member State automatically assumes the responsibilities of the Lead Member State.~~

***~~Emerging safety issue~~***

[8] See www.ema.europa.eu

- ~~A safety issue considered by a marketing authorisation holder in relation to an authorised medicinal product under its responsibility to require urgent attention of the competent authority because of the potential major impact on the risk-benefit balance of the product and/or on patient or public health, that could warrant prompt regulatory action and communication to patients and healthcare professionals (see also GVP Module VI and IX.C.3.1.).~~

# IX.B. Structures and processes

## *IX.B.1. Sources of data and information*

Signals can arise from a wide variety of ~~The~~ data sources ~~for identifying new signals are diverse~~. ~~They~~ This potentially includes all scientific information concerning the use of medicinal products and the outcome of the use, i.e. quality, non-clinical and clinical data (including pharmacovigilance and pharmacoepidemiological data).

Common sources for signals include spontaneous reporting systems ~~(see GVP Module VI)~~, active surveillance systems, studies (see The Rules Governing Medicinal Products in the European Union, Volume 10[9], GVP Module VIII) and the scientific literature reporting such data. Guidance on the collection, data management and reporting of suspected adverse reactions associated with medicinal products for human use authorised in the EU can be found in GVP Module VI.

~~Signals from spontaneous reports may be detected from monitoring of ICSRs, suspected adverse reaction databases, articles from the scientific literature or review of information provided by marketing authorisation holders in the context of regulatory procedures (e.g. risk management plan (RMP) updates (see GVP Module V), periodic safety update reports (PSURs) (see GVP Module VII), post-authorisation commitments, variations, renewals, or from other activities related to the continuous monitoring of the risk-benefit balance of medicinal products).~~

~~Suspected adverse reactions may be reported to and/or collected by other local, regional or national data collection systems allowing patients and healthcare professionals to report suspected adverse reactions, e.g. pharmacovigilance centres, poison centres, teratology information services, vaccine surveillance programmes and disease registries. Competent authorities and marketing authorisation holders should liaise, as appropriate, with other organisations managing such reporting systems so as to be informed of these suspected adverse reactions.~~

Signal detection is often based on the periodic monitoring of ~~large~~ databases of suspected adverse reactions, which can vary in size or remit, e.g. marketing authorisation holder databases, national databases, ~~such as~~ EudraVigilance~~, the US FDA Adverse Event Reporting System (FAERS) or~~ , the database of the WHO Programme for International Drug Monitoring (VigiBase).

This module focusses mainly on signals originating from the monitoring of data from spontaneous reporting systems, however all relevant sources should be considered during signal management.

## *IX.B.2. Signal detection*

Signal detection ~~shall be based on a multidisciplinary approach [IR Art 19(2)]. It~~ should follow a~~n appropriate~~ methodology~~,~~ which ~~may vary depending~~takes into account ~~on~~ the nature of data and ~~on~~ the characteristics (e.g. time on market, patient exposure, target population) as well as the type of medicinal product concerned (e.g. vaccines and biological medicinal products may for example require specific methodological strategies (see GVP P.I. and GVP P.II.)). Data from all appropriate sources should be considered (see IX.B.1.). Clinical judgement should always be applied.

[9] See http://ec.europa.eu/health/documents/eudralex/vol-10/

Signal detection may involve a review of ICSRs, statistical analyses, or a combination of both, depending on the size of the data set. When it is not relevant or feasible to assess each individual case (e.g. signals detected from published studies, healthcare record data), assessment of aggregated data should be considered.

Guidance on statistical aspects of signal detection may be found in GVP Module IX Add I.

The signal detection process should be adequately documented by each organisation (see IX.B.5.).

### *IX.B.3. Evaluation during signal validation and further ~~Eassessment~~~~valuation of the evidence supporting a signal~~*

The following elements should be considered when performing signal validation~~evaluating the evidence supporting a detected signal~~ based on the review of ICSR data:

- Previous awareness, e.g.:
  - the extent to which information on the adverse reaction is already included in the product information (summary of product characteristics (SmPC) and package leaflet);
  - whether the signal relates to an adverse reaction already included in the SmPC for other medicinal products containing the active substance of interest, bearing in mind that some signals may only be relevant to a specific medicinal product and/or a specific formulation (see IX.A.1.1.);
  - whether the association has already been assessed in the initial application for marketing authorisation, the risk management plan (RMP), the periodic safety update report (PSUR) or any other regulatory procedure, based on information held or known by each organisation;
- Strength of the evidence ~~from ICSRs~~, taking into account, ~~for example~~e.g.:
  - the total number of cases (after exclusion of duplicates), and amongst those, the number of supportive cases, e.g. cases showing a compatible temporal association, positive de- or rechallenge, lack of potential alternative causes, assessed as possibly related by the reporting healthcare professional, with supportive results of relevant investigations;
  - number of cases in the context of patient exposure;
  - additional cases reported with related terms (e.g. other MedDRA terms indicating clinical complications or different stages of the same reaction);
  - consistency of the evidence across cases (e.g. consistent time to onset, pattern with repeated observations of an association);
  - quality of the data and their documentation;
  - cases matching internationally agreed case definitions if applicable (e.g. Brighton collaboration case definitions for vaccines (see GVP P.I.), RegiSCAR criteria for ~~DRESS syndrome~~severe cutaneous adverse reactions[10]);
  - dose-reaction relationship;
  - possible mechanism based on a biological and pharmacological plausibility~~ of a biological and pharmacological relationship / possible mechanism~~;
  - ~~number of cases in the context of patient exposure;~~

[10] See http://www.regiscar.org/

- ~~measures of~~ disproportionality of reporting, if applicable (see GVP Module IX Add I).

- Clinical relevance and context, ~~for example~~e.g.:
  - seriousness and severity of the reaction;
  - outcome and reversibility of the reaction;
  - additional insight on a known adverse reaction, e.g. in terms of its severity, duration, outcome, incidence or management;
  - reactions occurring in the context of drug-drug interactions;
  - reactions occurring in vulnerable populations (e.g. pregnant women (see GVP P.III.), children (see ~~Guideline on Conduct of Pharmacovigilance for Medicines used by the Paediatric Population~~GVP P.IV.[11]) or the older population (see GVP P.~~I~~V.)) or in patients with pre-existing risk factors;
  - ~~-~~reactions occurring in different patterns of use (e.g. overdose, abuse, misuse, off-label use, medication errors, falsified products);
  - ~~whether the signal may provide additional insight on an expected reaction in terms of e.g. its severity, outcome, incidence or management;~~

~~Previous awareness, for example:~~

~~the extent to which information is already included in the product information (i.e. the summary of product characteristics (SmPC), the patient leaflet and the labelling);~~

~~whether the reaction is already included in the SmPC for other products including the same substance, bearing in mind that some signals may only be relevant to a specific medicinal product (see IX.A);~~

- ~~whether the association has already been assessed in the initial application for marketing authorisation, the RMP, the PSUR or any other regulatory procedure;~~

Additional sources of information may provide further evidence ~~on~~ for or against ~~the~~ a causal association, or a new aspect of a known association, and may be considered during further assessment of the signal, depending on their relevance for the signal and availability to each organisation. These may include ~~for example~~:

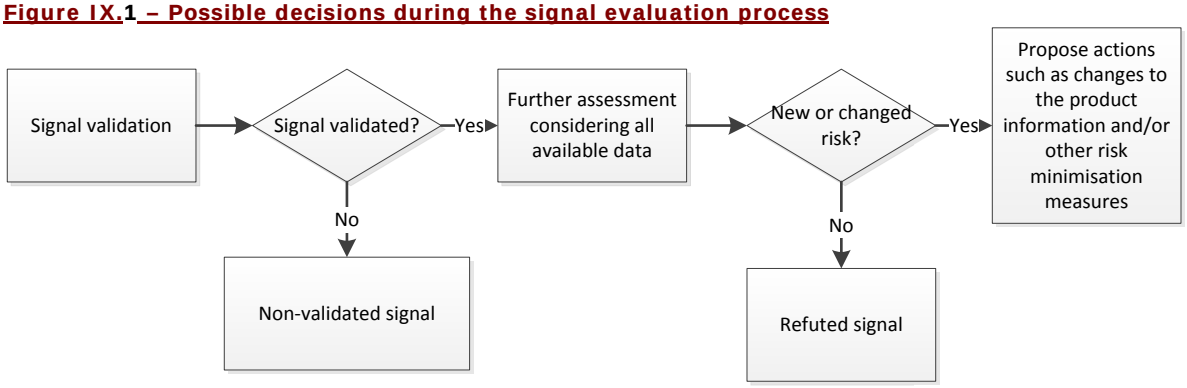
- clinical trial data;
- findings regarding similar cases in the scientific literature, including information on substances of the same class of medicinal products;
- information on the epidemiology of the adverse reaction or the underlying disease;
- experimental and/or non-clinical findings;
- databases with larger datasets (see IX.B.1.), when the signal was detected from national or ~~company~~marketing authorisation holder-specific databases~~)~~;
- healthcare databases that may provide information on characteristics of exposed patients and medicines utilisation patterns;
- information from other regulatory authorities worldwide.

Within individual organisations, the signal management process ~~The evaluation of the evidence supporting a signal~~ may involve several rounds of expert discussions and different levels of decision-

[11] ~~See www.ema.europa.eu (revision will be available in 2016/2017)~~

making~~, within individual organisations~~. This may result in various decisions, ~~such as~~as shown in the example in Figure IX.1. (see also IX.C.4.).~~:~~ Any such decision tree should be documented as part of the description of the signal management process (see IX.B.5.).

**Figure IX.1 – Possible decisions during the signal evaluation process**




~~• closing the signal, when the available data do not support a causal relationship (the signal may be re-opened at a later stage if new evidence arises) or when there is sufficient information on the association in the product information;~~

~~• monitoring the signal by reviewing new information from ICSRs or the scientific literature at appropriate time intervals to determine whether the new data are supportive of a causal relationship;~~

~~proposing actions such as changes to the product information by means of a variation, if there is sufficient evidence of a causal relationship.~~

## *IX.B.4. Signal prioritisation*

Every organisation should ~~A key and continuous~~ consider~~ation of~~ throughout the signal management process ~~is to promptly identify~~whether signals ~~that may~~suggest risks with ~~have~~ an important impact on ~~patient~~ patients' or public health and/or on the risk-benefit balance of the medicinal product (see IX.A.1.1.).

The following should be considered when evaluating this impact:

- the severity, seriousness, outcome and reversibility of the adverse reaction and the potential for prevention;
- the patient exposure and the estimated frequency of the adverse reaction;
- the patient exposure in vulnerable populations and/or in populations with different patterns of use, where appropriate;
- the consequences of treatment discontinuation on the disease under treatment and the availability of other therapeutic options;
- the expected extent of the regulatory intervention (e.g. addition of adverse reactions, warnings, contraindications, additional risk minimisation measures, suspension, revocation);
- whether the signal is likely to apply to other substances of the same class of medicinal products.

In some circumstances, ~~special consideration may be given to~~ signals that ~~may~~ could cause media attention and/or public concerns (e.g. adverse events following mass immunisation) may deserve special attention.

~~How the signal is further managed including timelines~~The timeframe for further management of the signal will depend on the prioritisation. ~~Because prioritisation is a continuous process, a~~Appropriate measures should be considered at any stage if the information available ~~supports the conclusion~~suggests that there ~~is a~~could be a risk that requires prevention or minimisation in a timely manner (see GVP Module XVI). Such measures may be required before a formal assessment of the signal is concluded. ~~Professional~~ Clinical judgement and flexibility should be applied throughout the process.

## *IX.B.5. Quality requirements*

Signal management is considered a critical process (see GVP Module I). ~~As such, a~~Any signal management system should be clearly documented to ensure that the system functions properly and effectively, that the roles, responsibilities and required tasks are clear and standardised, that these tasks are conducted by staff with appropriate qualifications and expertise and that there are provisions for appropriate control and, when needed, improvement of the system. ~~This includes the rationale for the method and periodicity of signal detection activities. Therefore, a~~A system of quality management (see GVP Module I) should be applied to all signal management processes. Detailed procedures for this quality system should be developed, documented and implemented. This includes the rationale for the method and periodicity of signal detection activities.

~~The performance of the system should be controlled and, when used, performance indicators should be presented in the pharmacovigilance system master file [IR Art 3, 9(1)] (see GVP Module I).~~

Through a tracking system, all organisations should keep an audit trail of signal management activities, allowing traceability (i.e. recording of dates and confirmation of timeliness) and process control of the details of all steps of signal management, including analyses, decisions and rationale.

The organisational roles and responsibilities for the activities including maintenance of documentation, quality control and review, and for ensuring corrective and preventive action should be assigned and recorded. Each organisation should ensure that staff members are specifically trained in signal management activities in accordance with their roles and responsibilities (see GVP Module I).

Marketing authorisation holders should include the description of the signal management process in the pharmacovigilance system master file (see GVP Module II). The performance of the system should be controlled and, when used, performance indicators should be presented in the annex to the pharmacovigilance system master file [IR Art 3, 9(1)] (see GVP Module II). Marketing authorisation holders shall put in place a record management system for all documents used for pharmacovigilance activities that ensures the retrievability of those documents as well as the traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process [IR Art 12(1)].

As for any critical process, signal management activities should be audited at regular intervals, including tasks performed by any service providers and contractors (see GVP Module IV). Data and document confidentiality (per the applicable laws and regulations), security and validity (including data integrity when transferred between organisations) should be guaranteed.

~~Through a tracking system, all parties should keep an audit trail of signal management activities, allowing traceability (i.e. recording of dates and confirmation of timeliness) and process control of the details of all steps of signal management, including analyses, decisions and rationale.~~

Documentation ~~may be requested from marketing authorisation holders to~~ demonstrate~~e~~ing compliance with these requirements should be available at any time, including justification / evidence for the steps taken and decisions made.

~~Staff members should be specifically trained in signal management activities in accordance with their roles and responsibilities (see GVP Module I).~~

# IX.C. Operation of the EU network

## *IX.C.1. Roles and responsibilities ~~of the marketing authorisation holder in the EU, the competent authorities of Member States, the Pharmacovigilance Risk Assessment Committee (PRAC) and the Agency~~*

### IX.C.1.1. Responsibilities of the marketing authorisation holder in the EU

The ~~M~~marketing authorisation holder in the EU~~s~~ 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 [DIR Art 23(2), REG Art 16(2)]. This includes information that meets the definition of an emerging safety issue (see IX.A.1.1. and IX.C.2.)

The continuous monitoring of EudraVigilance is a legal requirement in the EU [IR Art 18]. Signals detected through the continuous monitoring of EudraVigilance data should be handled according to the principles outlined in IX.C.3. and IX.C.4..

Signals detected through other sources should be handled according to the marketing authorisation holder's own signal management process, taking into account the general principles outlined in IX.B.. Such signals should be reported to the competent authorities in the EU as appropriate, taking into account the general obligations of the marketing authorisation holder to keep their product information up-to-date throughout the product's lifecycle by variation applications and to present comprehensive signal information in PSURs (see GVP Module VII). The options and timelines outlined in IX.C.4. solely apply to signals detected through the continuous monitoring of EudraVigilance data.

Signals, from any source, that meet the definition of emerging safety issues (see IX.A.1.1.) should be notified to the Agency and the competent authorities in Member States in accordance with the process outlined in IX.C.2..

The marketing authorisation holder should collaborate with the PRAC for the assessment of the signals by providing the additional information requested [DIR Art 23(4) and REG Art 16(3a)] (see IX.C.6.).

Marketing authorisation holders shall keep their product information up-to-date in the light of scientific knowledge, including the assessments and recommendations made public via the European medicines web-portal [IR Art 11(1)(f), DIR Art 23(3), REG Art 16(3)] (see IX.C.~~8~~9.).

### IX.C.1.2. Responsibilities within the EU regulatory network

The competent authority of each Member State shall be responsible for monitoring the data originating in the territory of that Member State [IR Art 18(4)].

Member States and the Agency should validate and prioritise signals they have detected or that have been brought to their attention from any source, including EudraVigilance (see IX.B.3. and IX.B.4.).

All Member States shall be responsible for monitoring the data in the EudraVigilance database in accordance with Articles 107h(1)(c) and 107h(3) of Directive 2001/83/EC [IR Art 22(4)]. ~~W~~Within the EU regulatory network, the Agency takes the lead for EudraVigilance monitoring, signal detection and signal validation for ~~of~~ active substances contained in at least one centrally authorised product ~~(CAP)~~. Signals validated by the Agency should be confirmed (or not) by the PRAC rapporteur for the concerned centrally authorised product. ~~-~~For active substances only contained in nationally authorised

products ~~(NAPs)~~, ~~including those authorised through the mutual recognition and decentralised procedures,~~ Member States take the lead for EudraVigilance monitoring, signal detection, validation and confirmation. For these substances, a worksharing is foreseen whereby Member States may agree within the Co-ordination Group for Mutual Rrecognition and Decentralised ~~procedures~~ Procedures – Hhuman (CMDh) to appoint a lead Member State to monitor EudraVigilance data, detect, validate and confirm signals on behalf of the other Member States [IR Art 22(1)]. A co-leader may also be appointed to assist the lead Member State in the fulfilment of its tasks [IR Art 22(1)]. ~~All Member States shall remain responsible for monitoring the data in the EudraVigilance database in accordance with DIR Art 107h(1)(c) and Art 107h(3) [IR Art 22(4)].~~

For active substances contained in nationally authorised products authorised in more than one Member State and for which no lead Member State has been appointed, the national competent authority should perform signal validation and confirmation of the signals it has detected.

~~Each organisation should validate and prioritise signals they have detected (or that have been brought to their attention) from any source, including EudraVigilance (see IX.B.3. and IX.B.4.).~~

~~For active substances contained in NAPs authorised in more than one Member State and for which no lead Member State has been appointed, the national competent authority should validate and confirm as a single step the signals it has detected.~~

The ~~overall roles and responsibilities of the marketing authorisation holder in the EU (MAH), the competent authorities of Member States (MS) and the Pharmacovigilance Risk Assessment Committee (~~PRAC~~) and the Agency for each step of the EU signal management process are summarised in Table IX.1..~~is responsible for the prioritisation and analysis of signals that have been confirmed by the PRAC rapporteur or (lead) Member State [DIR Art 107h(2), REG Art 28a(2)]. The assessment of such confirmed signals is led by the rapporteur appointed by the PRAC at the stage of analysis and prioritisation (see IX.C.6.).

~~**Table IX.1.** Roles and responsibilities within the EU signal management process~~

| | ~~MAH (their products)~~ | ~~Agency (for CAPs)~~ | ~~Lead MS State (allocated NAPs)~~ | ~~PRAC rapporteur of CAP~~ | ~~Member States (unallocated NAPs)~~ | ~~PRAC and rapporteur appointed to assess the signal (for CAPs and NAPs)~~ |
|---|---|---|---|---|---|---|
| ~~EudraVigilance monitoring, signal detection, validation~~ | ~~✓~~ | ~~✓~~ | ~~✓~~ | | ~~✓~~ | |
| ~~Signal confirmation~~ | | | ~~✓~~ | ~~✓~~ | ~~✓~~ | |
| ~~Signal analysis and prioritisation, assessment, recommendation~~ | | | | | | ~~✓~~ |

## *IX.C.2. Emerging safety issues*

When the marketing authorisation holder in the EU becomes aware of an emerging safety issue from any source (see IX.A.1.1.), they should notify it in writing to the competent authority(ies) of Member State(s) where the medicinal product is authorised[12] and to the Agency to the mailbox "P-PV-emerging-safety-issue@ema.europa.eu". This should be done as soon as possible and no later than 3 working days after establishing that a validated signal or a safety issue from any source meets the definition of an emerging safety issue.

This is in addition to the ICSR submission requirements detailed in GVP Module VI, when the emerging safety issue refers to a single case of suspected adverse reactions.

When notifying an emerging safety issue, the marketing authorisation holder should describe the safety issue, the source(s) of information, any planned or taken actions with timelines, and should provide any relevant documentation available at the time of initial notification. Any further information relevant to the issue should be provided to the Agency and relevant national competent authorities as soon as it becomes available.

Upon being notified of an emerging safety issue, the national competent authorities and/or the Agency as appropriate should promptly assess the urgency and potential impact of the issue and agree on appropriate next steps and the potential regulatory procedure to address the matter raised. This may involve the consultation of the Incident Review Network, if warranted (see European Union Regulatory Incident Management Plan for Medicines for Human Use[13]).

For signals notified as emerging safety issues, a standalone signal notification (see IX.C.4.3.) is not required, unless the national competent authorities and/or the Agency consider it appropriate to handle the issue within the EU signal management process, in which case the marketing authorisation holder may be requested to complete and provide a standalone signal notification form.

The marketing authorisation holder should collaborate with the Agency and national competent authorities in the assessment of the emerging safety issue [DIR Art 23(4) and REG Art 16(3a)].

In order to ensure its effectiveness, the system should not be saturated by the transmission of less urgent information. Marketing authorisation holders should only communicate as emerging safety issues those safety concerns which meet the definition provided in IX.A.1.1., i.e. whose urgency and seriousness cannot permit any delay in handling.

Should the marketing authorisation holder decide as a result of the emerging safety issue to take any of the following actions: temporary or permanent cessation or suspension of marketing of a medicinal product, withdrawal of a medicinal product from the market, request for the withdrawal of a marketing authorisation or non-application for the renewal of a marketing authorisation, the notification of such action should be done in parallel to the Agency (withdrawnproducts@ema.europa.eu) and/or competent authority(ies) of the Member State(s) concerned in accordance with the requirements set out in Articles 13(4) and 14b of Regulation (EC) No 726/2004 and Articles 23a and 123(2) of Directive 2001/83/EC.

New safety information related to quality defects or suspected falsified medicinal products which might influence the evaluation of the benefits and risks of the medicinal product and which may give rise to an abnormal restriction in supply should not be notified as an emerging safety issue. These should be notified to the Agency (qdefect@ema.europa.eu) and/or to relevant competent authority(ies) of Member State(s) according to national requirements in accordance with Article 16(2) of Regulation

[12] See www.ema.europa.eu for e-mail addresses of Member States regarding emerging safety issues
[13] See www.ema.europa.eu

(EC) No 726/2004 and Article 23(2) of Directive 2001/83/EC. More detailed guidance on notifications of product withdrawals and quality defects is available on the Agency's website.

## *IX.C.~~2~~3. Monitoring of EudraVigilance data*

National competent authorities and the Agency shall cooperate in the monitoring of the data available in the EudraVigilance database [IR Art 18(1)] to determine whether there are new risks or whether risks have changed and whether those risks impact on the risk-benefit balance of medicinal products [DIR Art 107h(c) and REG Art 28a(c)]. The identification of new risks or changed risks shall be based on the detection and analysis of signals [IR Art 19(1)]. Marketing authorisation holders shall monitor the data available in the EudraVigilance database to the extent that they have access to the database [IR Art 18 (2)].

~~Such monitoring should be performed to determine whether there are new risks or whether risks have changed and whether those risks have an adverse impact on the risk-benefit balance of the medicinal product(s).~~

### IX.C.~~2~~3.1. Principles for access

The principles for providing access to ICSR data held in EudraVigilance for each stakeholder group are described in the European Medicines Agency Policy on Access to EudraVigilance data for Medicinal Products for Human Use[14].

Under the policy, national competent authorities and the Agency can access all ICSR data elements without restrictions ('ICSR Level 3').

Marketing authorisation holders can access without restrictions all data elements of those ICSRs sent by them or resulting from the medical literature monitoring activities performed by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004 ('ICSR Level 3'). For other ICSRs held in EudraVigilance, ~~For m~~marketing authorisation holders~~, the policy provides the option to~~ can request access to an extended subset of ICSR data elements including ~~to~~ case narratives~~ held in EudraVigilance~~ ('ICSR data set level 2B'), upon signature of a confidentiality undertaking and confirmation that a review of ICSR data is required due to pharmacovigilance obligations, including in the context of signal management.~~ Prior to requesting access to case narratives, the following criteria should be met:~~

- ~~The review of the electronic reaction monitoring report suggests a signal (see IX.A.);~~
- ~~To the best of the marketing authorisation holder's knowledge, the signal is not addressed in the product information of any medicinal product authorised in the EU with the concerned active substance (see also IX.C.3.4.);~~
- ~~Based on the information published on the European medicines web-portal (see IX.C.8.), the signal was not recently addressed by (a) competent authority(ies) of (a) Member State(s) or by PRAC.~~

Access to the requested data is then granted by the EudraVigilance system in a seamless way. ~~When a signal originates from EudraVigilance data, marketing authorisation holders should review the corresponding case narratives as part of the signal validation.~~

~~Guidance related to EudraVigilance outputs and the EudraVigilance Data Analysis System (EVDAS) is provided in the EVDAS Report Manual and in MAH's level 1 access via EVDAS[15].~~

[14] See www.ema.europa.eu

[15] ~~Documents under development; references will be provided in the final GVP M IX Rev 1~~

Relevant staff members within ~~national~~ competent authorities and marketing authorisation holders should familiarise themselves with the guidance and training materials on EudraVigilance outputs made available online by the Agency ~~on EVDAS~~ and the training should be documented in line with the organisation's internal procedures (see IX.B.5.).

## IX.C.~~2~~3.2. Periodicity of monitoring

Marketing authorisation holders, the national competent authorities and the Agency shall ensure the continuous monitoring of the EudraVigilance database with a frequency proportionate to the identified risk, the potential risks and the need for additional information on medicinal products or active substances [IR Art 18(3)].

The appropriate frequency of monitoring of EudraVigilance data may vary with the accumulation of knowledge on the risk profile of a given active substance or medicinal product, taking into account, ~~for example~~e.g.:

- time since first authorisation;
- extent of patient exposure;
- important potential risks and missing information documented in the RMP;
- PSUR submission frequency;
- number of ICSRs received over a given period;
- any safety concern of interest in specific situations (e.g. vaccination campaigns).

It is recommended to monitor EudraVigilance data at least every 6 months. A more frequent monitoring ~~A two weeks' interval between reviews of EudraVigilance data~~ is recommended for active substances contained in medicinal products included in the additional monitoring list in accordance with ~~REG~~ Article 23 of Regulation (EC) No 726/2004 (see GVP Module X), unless the sole reason for inclusion on the list is the request of a post-authorisation safety study (PASS). ~~A monthly monitoring of EudraVigilance data is routinely applied by the Agency for other active substances. It is recommended that the interval between reviews of EudraVigilance data should not exceed 6 months.~~

Each organisation should determine the appropriate frequency for each active substance / medicinal product they monitor in EudraVigilance, taking into account the above-mentioned elements. The monitoring frequency (including any changes) and the justification thereof should be documented in accordance with ~~–~~ the organisation's internal procedures ~~the frequency of their monitoring of EudraVigilance data~~ (see also IX.B.5.).

## IX.C.3.3. Analysis of EudraVigilance data

The selection of drug-event combinations for further review should be based on scientific judgement taking into account, e.g. the number of cases and relevant statistical measures, the known safety profile of the medicinal product, the clinical relevance (e.g. important medical events), the underlying condition, the patient population and previous assessments.

Not all signals of disproportionate reporting have to be further investigated and conversely, some drug-event combinations that do not appear as signals of disproportionate reporting may warrant further investigation. Methods of routine signal detection in EudraVigilance are further discussed in Screening for adverse reactions in EudraVigilance[16].

[16] see www.ema.europa.eu

The outputs of EudraVigilance monitoring are generally provided at the level of the active substance or combination of active substances. Scientific judgement should be applied to determine whether a particular signal may apply to all, or only some medicinal products containing an active substance. Marketing authorisation holders should consider in their analysis all ICSR data that are relevant to the safety profile of their medicinal product.

For the purpose of signal validation, a thorough analysis of EudraVigilance data should be performed taking into account any previous awareness on the signal, the strength of evidence from the cases (including narrative information) and the clinical relevance (see IX.B.3. and IX.C.4.).

Record management in relation to the monitoring and analysis of EudraVigilance data should be performed in line with the organisation's internal procedures (see IX.B.5.).

### *IX.C.~~3~~4. Notifications and procedural options for signals ~~validated~~ detected by the marketing authorisation holder in the EU based on the continuous monitoring of EudraVigilance data*

Where a marketing authorisation holder detects a new signal when monitoring the Eudravigilance database, it shall validate it and shall forthwith inform the Agency and national competent authorities [IR Art 21(2)].

For this purpose, signal validation by the marketing authorisation holder should include a thorough analysis of EudraVigilance data (see IX.B.3. and IX.C.3.3.). This analysis should be complemented, for validated signals, by the marketing authorisation holder's assessment of other relevant data available to them (e.g. own database, literature, clinical trials) (see IX.B.3.). By definition, a signal should provide new information on an association (see IX.A.1.1.) and therefore, the marketing authorisation holder should check, wherever possible, whether a risk may already be addressed in the product information of other EU medicinal products containing the active substance of interest (except for product-specific issues), in which case the product information should be aligned as appropriate through an application for variation of the terms of marketing authorisation. The marketing authorisation holder should also take into account the information published or communicated by the Agency in relation to signals (see IX.C.9. and Figures IX.3. and IX.4. in IX. Appendix 1.).

Based on their own assessment, the marketing authorisation holder 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. The conclusion that a signal represents a new or changed risk and/or that further analysis by the competent authorities is required is the starting point ('Day 0') of the timelines indicated herein.

A new or changed risk that requires a change to the terms of the marketing authorisation should in principle be the object of an application for variation of the terms of marketing authorisation (see IX.C.4.1.), unless the marketing authorisation holder considers that further analysis by the competent authorities is warranted. Further analysis by the competent authorities may be sought in the case of validated signals that cannot be refuted nor confirmed as new or changed risks by the marketing authorisation holder based on their assessment.

Signals requiring further analysis by the competent authorities may be reported only in PSURs if the conditions outlined in IX.C.4.2. are met. If not, a standalone signal notification should be submitted (see IX.C.4.3.).

Refuted signals should only be reported in PSURs (see GVP Module VII).

These options are further detailed in sections IX.C.4.1., IX.C.4.2. and IX.C.4.3., and illustrated in Figure IX.2. in IX. Appendix 1.. ~~This section outlines the options marketing authorisation holders have~~

~~to inform competent authorities of signals they have validated. These options are also illustrated in Figure IX.1. in IX. Appendix 1.~~

~~These options are without prejudice to the obligation of the marketing authorisation holder to update their marketing authorisation throughout the lifecycle of the product by variation applications.~~ All validated signals requiring urgent attention should be reported as emerging safety issues (see IX.C.2.).

### ~~IX.C.3.1. Emerging safety issue~~

~~When a marketing authorisation holder becomes aware of an emerging safety issue (see IX.A.), they should notify it in writing to the relevant competent authority(ies) of Member State(s) and to the Agency to the mailbox "". This should be done within 2 working days of becoming aware of the issue.~~

~~When notifying an emerging safety issue, the marketing authorisation holder should describe the safety concern, the source(s) of information, any planned or taken actions, and should provide any relevant documentation. In such instances, a standalone signal notification (see IX.C.3.4.) is not required.~~

~~Upon being notified of an emerging safety issue, national competent authorities and/or the Agency as appropriate should promptly assess the urgency and potential impact of the issue and agree on appropriate next steps and the potential regulatory procedure to address the matter raised (see European Union Regulatory Incident Management Plan for Medicines for Human Use[17]).~~

~~In order to ensure its effectiveness, the system should not be saturated by the transmission of less urgent information. Marketing authorisation holders should only communicate as emerging safety issues those safety concerns which meet the definition provided in IX.A, i.e. whose urgency and seriousness cannot permit any delay in handling, for instance validated signals that cannot wait up to 30 days for confirmation by Member States.~~

## IX.C.~~3~~4.~~2~~1. Variation of the terms of marketing authorisation

~~When, as a result of signal validation, a~~A marketing authorisation holder may conclude, based on their assessment of a signal detected through the monitoring of EudraVigilance data, ~~considers the evidence sufficient to propose changes to~~that the product information and/or the RMP should be updated through a variation. In such cases, the marketing authorisation holder~~, they~~ should submit ~~an appropriate~~ the variation application to the relevant competent authorities ~~(if urgent attention is required, see IX.C.3.1.). This should be done~~ as soon as possible and no later than 3 months after completing the assessment of the signal ~~is validated.~~ if it corresponds to an important risk (see GVP Annex I), or within 6 months for adverse reactions or risks not considered important.

In such instances, a separate standalone signal notification (see IX.C.~~3~~4.~~4~~3.) is not required, as the proposed changes and supportive evidence will be assessed ~~by the relevant competent authorities~~ within the variation procedure by the relevant competent authorities, which may consult the PRAC if required.

~~When the application refers to the introduction of a change not reflected in the innovator product information, marketing authorisation holders for generic products should liaise with the relevant competent authorities prior to the submission of such variation application to agree on the appropriate way to handle the potential amendment of the product information.~~

~~[17] See www.ema.europa.eu~~

Marketing authorisation holders should follow the relevant guidance on variations, including worksharing procedures, and liaise with competent authorities as appropriate when preparing their variation application[18].

## IX.C.~~3~~4.~~3~~2. Inclusion of the signal in the periodic safety update report (PSUR)

~~For active substances included in the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)[19], if by the time a marketing authorisation holder concludes that a signal is validated, a PSUR is due to be submitted in the following 3 months, the signal, together with any potentially related amendment to the product information, may be reported in the PSUR, unless the marketing authorisation holder considers that a variation application with supportive data should be submitted. In such cases, a standalone signal notification (see IX.C.3.4.) is not required as the signal will be assessed by the PRAC / Member State(s) within the PSUR procedure (see GVP Module VII).~~If an active substance is included in the List of Union Reference Dates and Frequency of Submission of Periodic Safety Update Reports (PSURs) (EURD List)[20] and a PSUR is due to be submitted within 6 months of the completion, by the marketing authorisation holder, of the assessment of a signal detected through continuous EudraVigilance monitoring, the submission of a separate standalone signal notification (see IX.C.4.3.) is not required. Indeed, the signal will be further assessed by the PRAC / competent authorities in Member States as appropriate within the PSUR procedure (see GVP Module VII). If the data-lock point of the PSUR has elapsed by the time the marketing authorisation holder has completed their assessment of the signal, it should be mentioned in the PSUR section 'Late-breaking Information' together with a proposal for further management of the signal (see GVP Module VII).

~~For active substances not included in the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)21, validated signals should be reported via one of the options described in IX.C.3.2. and IX.C.3.4.~~

~~Validated signals requiring urgent attention should be reported as emerging safety issues regardless of the submission date of the PSUR (see IX.C.3.1.).~~Based on the evaluation of the cumulative safety data and the risk-benefit balance analysis submitted in the PSUR, the marketing authorisation holder shall draw conclusions regarding the need for changes to the terms of the marketing authorisation and/or actions, including any implications for the approved product information for the medicinal product(s) for which the PSUR has been submitted [IR Art 34(5)]. This also applies to the conclusions drawn based on the evaluation of safety signals (see GVP Module VII).

Regardless of their source~~whether they have been reported in accordance with the processes described in sections IX.C.3.1., IX.C.3.2. and IX.C.3.4.~~, all validated signals and emerging safety issues for which the evaluation was concluded during the reporting interval of a PSUR, or are ~~under evaluation~~ongoing at the time of a PSUR data lock point, should be reported in that PSUR (PSUR sections 15 and 16) (see GVP Module VII).

## IX.C.~~3.~~4.3. Standalone signal notification

When a marketing authorisation holder, based on their assessment of a signal detected through EudraVigilance monitoring, and which does not meet the conditions outlined in IX.C.4.1. and IX.C.4.2., concludes that further analysis of the signal by the competent authorities is required, they should

[18] Guidance on variations is available on the websites of the EMA (www.ema.europa.eu), Heads of Medicines Agencies (www.hma.eu) and national competent authorities of Member States.

~~[19] See www.ema.europa.eu~~

[20] See www.ema.europa.eu

~~[21] See www.ema.europa.eu~~

complete the standalone signal notification form available on the European medicines web-portal[22] and send it to the Agency using the mailbox "MAH-EV-signals@ema.europa.eu" and to the competent authorities in Member States where the medicinal product is authorised[23].

This should be done as soon as possible and no later than 30 days after the marketing authorisation holder has completed their assessment and concluded that further analysis by the competent authorities is required.

Standalone signal notifications are not required in case of signals included within PSURs or variation applications, as per the conditions outlined in IX.C.4.1. and IX.C.4.2..

Signals refuted by marketing authorisation holders should not be sent as standalone signal notifications but should be included in PSURs as applicable (see GVP Module VII).

~~When a validated signal does not meet any of the conditions outlined in IX.C.3.1., IX.C.3.2. or IX.C.3.3., the marketing authorisation holder should complete the signal validation form[24] available on the European medicines web-portal and send it via [functional e-mail address tbc][25] to the Agency and national competent authorities.~~

~~This should be done as soon as possible and no later than 30 days after the signal is validated.~~

~~In line with the definition of a signal (see IX.A.), information that does not relate to a new association, or a new aspect of a known association, should not be sent as a standalone signal notification. This may include, for example, risks that are adequately addressed in the product information of other medicinal products in the EU containing the same active substance (except for product-specific issues), in which case the product information should be aligned as appropriate through a variation application, or signals already considered by PRAC (see IX.C.8.), in which case, the PRAC recommendation should be followed or awaited, as appropriate.~~

### *IX.C.~~4~~5. Signal confirmation by the PRAC rapporteur or (lead) Member State~~s~~*

Within 30 days of receipt of a ~~validated~~ signal validated by the Agency or a Member State, or a standalone signal notification from a marketing authorisation holder~~,~~, the PRAC rapporteur or (lead) Member State, as applicable, should confirm or not the signal, i.e. decide whether or not it should undergo PRAC analysis and prioritisation ~~at the subsequent meeting~~ (see IX.A.1.2.).

Standalone signal notifications from marketing authorisation holders concerning nationally authorised products with no lead Member State are allocated by the Agency to a Member State where the substance is authorised (see Figure IX.3.).

If a validated signal involves several rapporteurs or (lead) Member States, confirmation by one of them triggers analysis and prioritisation by the PRAC.

The Member State or rapporteur confirming a signal should make a proposal for further management of the signal in preparation for the analysis and prioritisation by the PRAC.

A Member State or rapporteur may decide not to ~~bring~~ confirm a validated signal ~~for discussion at PRAC~~ if, for example:

[22] See www.ema.europa.eu
[23] See www.ema.europa.eu for e-mail addresses of Member States regarding standalone signal notifications
[24] ~~See www.ema.europa.eu (will be made available later)~~
[25] ~~E-mail address to be confirmed later~~

- it is already adequately handled through a different procedure (e.g. PSUR, variation) at the time confirmation is considered, including procedures for other medicinal products containing the same active substance (e.g. originator product);
- the validated signal involves an adverse reaction that is already ~~included~~ adequately reflected in the product information of other products authorised in the EU with the same active substance;
- the signal has ~~recently~~ already been subject of review and the data that has arisen since this review does not provide substantial new evidence;
- the available data does not warrant further analysis due to limited evidence or clinical relevance.

~~The Member State confirming a signal should make a proposal for further investigation and management of the signal in preparation for the first discussion at PRAC, based on the information provided by whoever validated the signal.~~

The justification for not confirming a signal should be communicated to the Agency and PRAC and is shared by the Agency with marketing authorisation holders (see Figures IX.3. and IX.4. in IX. Appendix 1.)

More details on the confirmation process are provided in Figures IX.~~2~~3. and IX.~~3~~4. in IX. Appendix 1.

## *IX.C.~~5~~6. Signal analysis, prioritisation and assessment by the ~~Pharmacovigilance Risk Assessment Committee (~~PRAC~~)~~*

When the Agency or the ~~national~~ competent authority in the Member State validating or confirming a signal considers that urgent action is required before the subsequent PRAC meeting, it should use the pharmacovigilance rapid alert system of the EU regulatory network to inform this ~~e EU regulatory~~ network about the issue and request discussion on any potential action (see European Union Regulatory Incident Management Plan for Medicines for Human Use[26]).

The PRAC should prioritise~~s~~ signals taking into account the information provided by the Member State or rapporteur that confirmed the signal (see IX.B.4. and IX.C.~~4~~5.). The PRAC may further amend the scope of the signal management by extending it to other active substances of the same class of medicinal products or to other related adverse reactions.

When further assessment is considered needed within the signal procedure, the PRAC should appoint~~s~~ a rapporteur and define~~s~~ a timeframe taking into account the prioritisation of the signal.

The appointed rapporteur should lead the assessment and ~~should~~ transmit to the PRAC an assessment report. The assessment report ~~which~~ should ~~should~~ include a proposed recommendation and should be updated as appropriate based on comments from other PRAC members and the marketing authorisation holder(s). A template for the signal assessment report is available on the Agency's website[27]. Guidance for competent authorities in Member States is also available in the SCOPE Best Practice Guide on Signal Management[28].

The standard timeframe is two months for the submission of additional data by marketing authorisation holders and a further two months for assessment by the PRAC. Depending on the signal multiple rounds of assessment may be needed. Timetables for signal assessment are published on the Agency's website.

Marketing authorisation holders ~~should~~ shall collaborate with the PRAC for the assessment of the signals by providing the additional information requested [DIR Art 23(4) and REG Art 16(3a)]. Such

[26] See www.ema.europa.eu
[27] See www.ema.europa.eu
[28] See www.scopejointaction.eu

requests are generally addressed to marketing authorisation holders of the reference medicinal products and usually consist of a cumulative review of relevant data (e.g. from spontaneous reports, clinical trials, scientific literature), together with a discussion and conclusion from the marketing authorisation holder. Marketing authorisation holders that provide data are also invited to comment on the rapporteur's preliminary assessment report.

~~The timeframe is agreed on a case-by-case basis. A typical timeframe is two months for submission of data and a further two months for assessment by PRAC. Timetables for signal assessment are published on the Agency's website.~~ The detailed process for PRAC assessment of confirmed signals is shown in Figure IX.~~4~~5. in IX. Appendix 1.

When the PRAC recommends assessment of the signal within another procedure (e.g. PSUR, referral, variation), the process and timelines for that procedure ~~will~~ apply and the signal procedure is closed.

## *IX.C.~~6~~7. Recommendations on signals from the ~~Pharmacovigilance Risk Assessment Committee (~~PRAC~~)~~*

PRAC recommendations are adopted after prioritisation~~,~~ and after each plenary discussion during the assessment ~~and any follow-up discussion on~~of the signal. The recommendations may include any or a combination of the following conclusions:

- the marketing authorisation holder should provide additional data for assessment within a signal procedure;
- ~~no action is required at this point in time, other than routine pharmacovigilance;~~
- the marketing authorisation holder should provide a review of additional data on the signal in the following PSUR or submit an ad-hoc PSUR (see GVP Module VII);
- ~~the marketing authorisation holder should provide additional data according to a defined timeline;~~
- ~~the Agency or Member States should collect further information (e.g. via the 'non-urgent information system of the EU regulatory network for pharmacovigilance') or perform additional analyses;~~
- ~~other EMA scientific committees or EMA expert groups should be consulted;~~
- the marketing authorisation holder should update the product information through an application for a variation to the terms of the marketing authorisation;
- the marketing authorisation holder should be requested to submit an RMP or ~~an~~ to update the~~d~~ RMP (see GVP Module V);
- ~~the marketing authorisation should be varied;~~
- the marketing authorisation holder should implement additional risk minimisation measures such as educational materials ~~should be put in place~~ (see GVP Module XVI) or~~, e.g.~~ the dissemination of a Direct Healthcare Professional Communication (DHPC) (see GVP Module XV);
- the marketing authorisation holder should sponsor a post-authorisation study according to an agreed protocol and submit the final results of that study (see GVP Module VIII);
- ~~an urgent safety restriction should be imposed in accordance with Article 22 of Regulation (EC) 1234/2008;~~

- the Member States or the European Commission should consider a referral procedure in accordance with ~~DIR~~ Articles 31 or 107i of Directive 2001/83/EC, or ~~REG~~ Article 20 of Regulation (EC) No 726/2004, as appropriate[29];
- the Agency or Member States should collect further information (e.g. via the pharmacovigilance non-urgent information system of the EU regulatory network) or perform additional analyses;
- other EMA scientific committees or EMA expert groups should be consulted;
- an inspection should take place in order to verify that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements laid down in ~~DIR~~ Titles IX and XI of Directive 2001/83/EC;
- any other appropriate action that is not listed above;~~.~~
- no action is required at this point in time, other than routine pharmacovigilance.

PRAC recommendations to provide additional data are communicated directly to concerned marketing authorisation holders by the Agency. PRAC recommendations for regulatory action such as variation are submitted to the Committee for Medicinal Products for Human Use (CHMP) for endorsement when ~~they concern~~ centrally authorised medicinal products are involved, and to the Co-ordination Group for Mutual R~~r~~ecognition and Decentralised procedures – ~~human~~ Human (CMDh) for information in the case of nationally authorised medicinal products. The national competent authorities of Member States should take the appropriate measures at national level subsequently.

PRAC recommendations on signals are published on the Agency's website (see IX.C.9.).

## IX.C.~~7~~8. Record management in the European Pharmacovigilance Issues Tracking Tool (~~the European Pharmacovigilance Issues Tracking Tool (~~EPITT~~)~~)

The Agency should enter in the ~~European Pharmacovigilance Issues Tracking Tool (~~EPITT~~)~~ the signals it has validated and validated signals notified by marketing authorisation holders. Member States should enter in EPITT signals they have validated. The following elements should be entered:

- a description of the validated signal;
- for non-confirmed signals: justification for not confirming;
- for confirmed signals: signal assessment report, timetables, PRAC recommendations.

The Agency also enters in EPITT relevant information on emerging safety issues (see IX.C.~~3.4~~2.).

## IX.C.~~8~~9. Transparency

In relation to the EU signal management process, the following information is published by the Agency on the European medicines web-portal:

- PRAC agendas;
- PRAC recommendations (for recommendations to update the product information, the agreed wording for the product information is published in all EU official languages, as well as Norwegian and Icelandic. Marketing authorisation holders can use these translations to update the product information of the medicinal products they are responsible for);
- cumulative list of all signals discussed by the PRAC with links to the relevant PRAC minutes;

[29] See www.ema.europa.eu for EMA guidance on referral procedures

- list of active substances subject to worksharing for signal management and the lead Member State appointed for monitoring those substances in the EudraVigilance database [IR Art 22(3)].

Outcomes of safety referrals and single assessments of PSURs (see GVP Module VII), which may be relevant to signal management, are also published[30].

[30] See www.ema.europa.eu

# IX. Appendix 1. Figures on the EU signal management process

**Figure IX.2.** Notifications and procedural options for emerging safety issues and for signals ~~validated~~ detected by marketing authorisation holders based on the continuous monitoring of EudraVigilance data

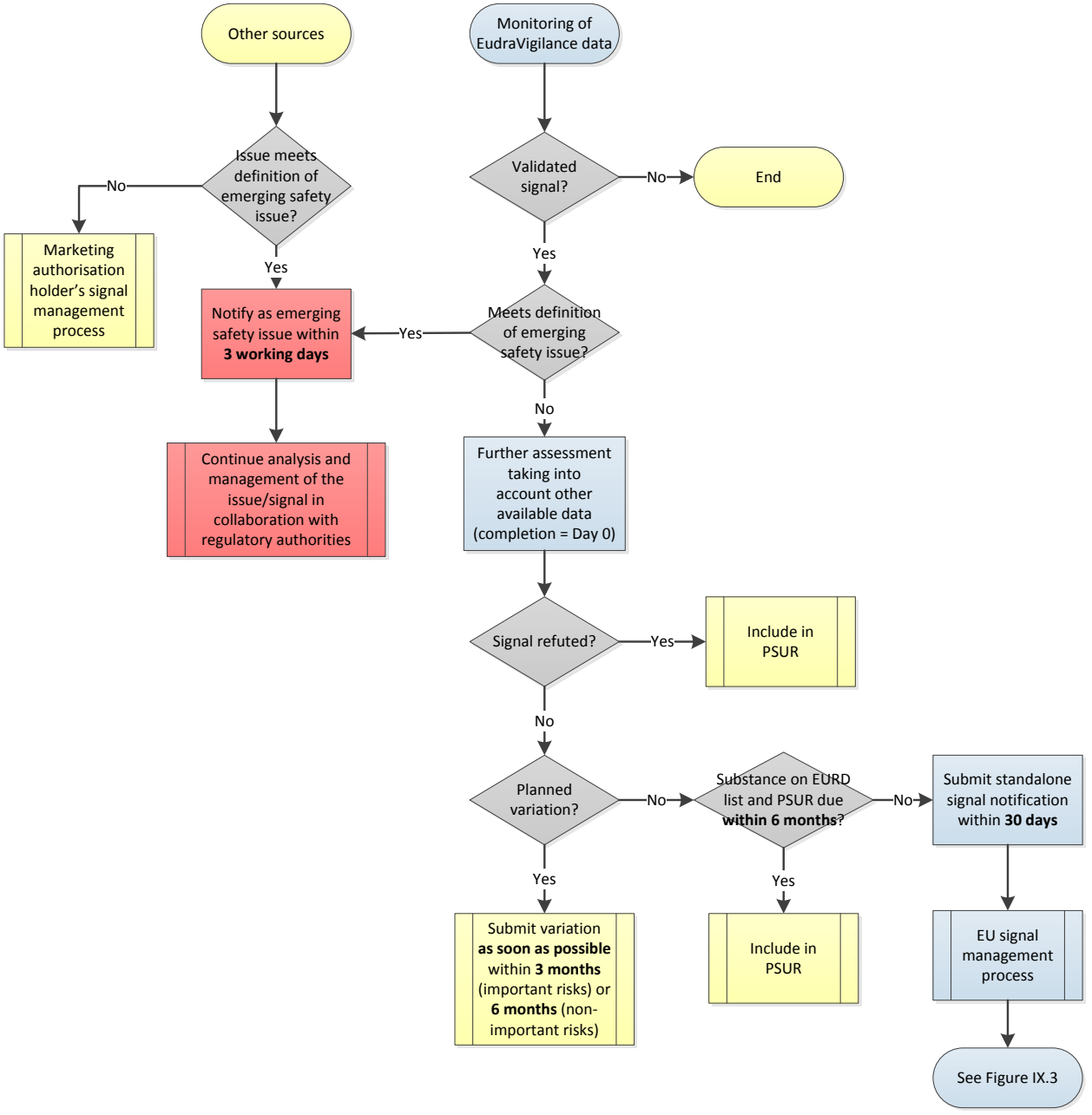
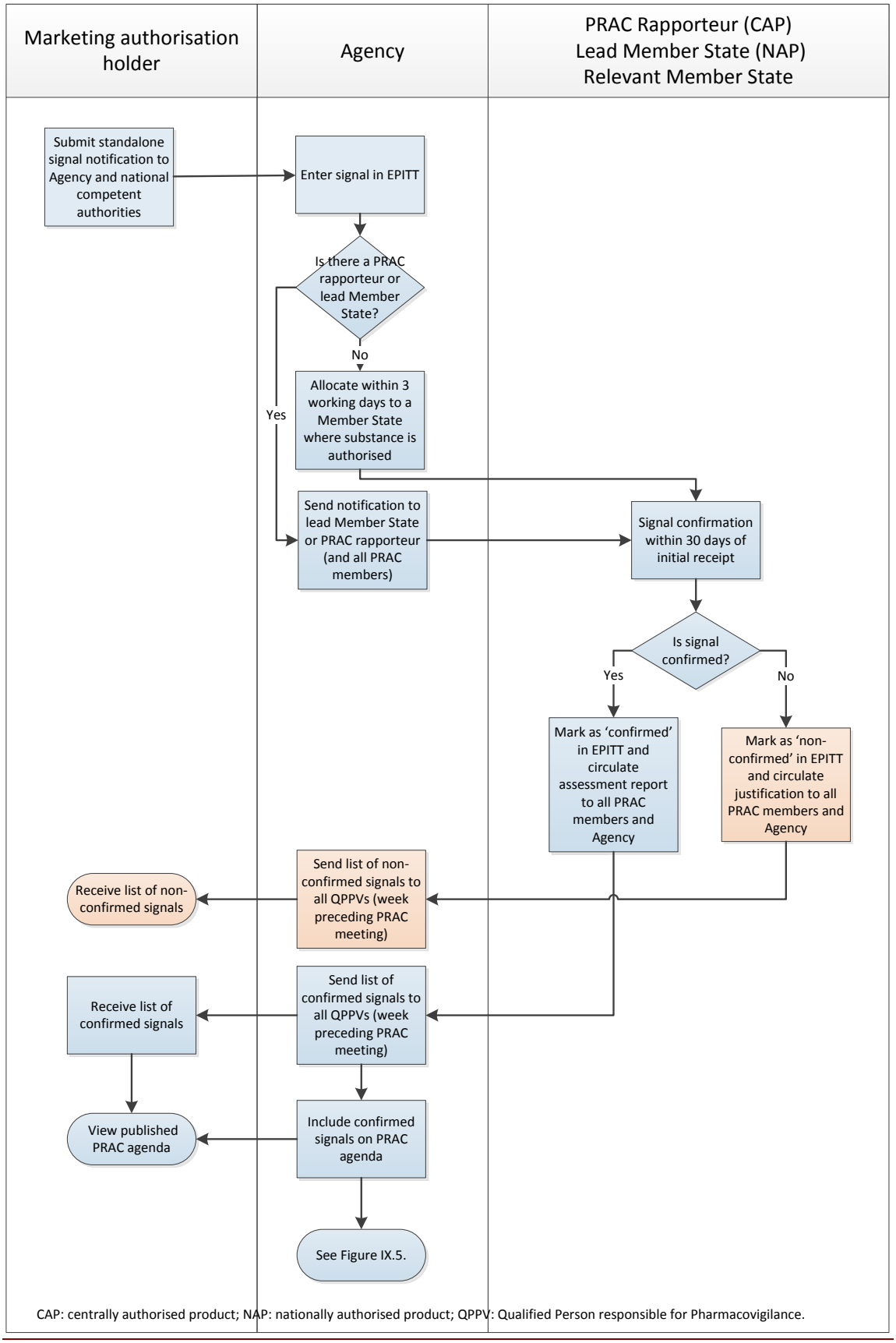
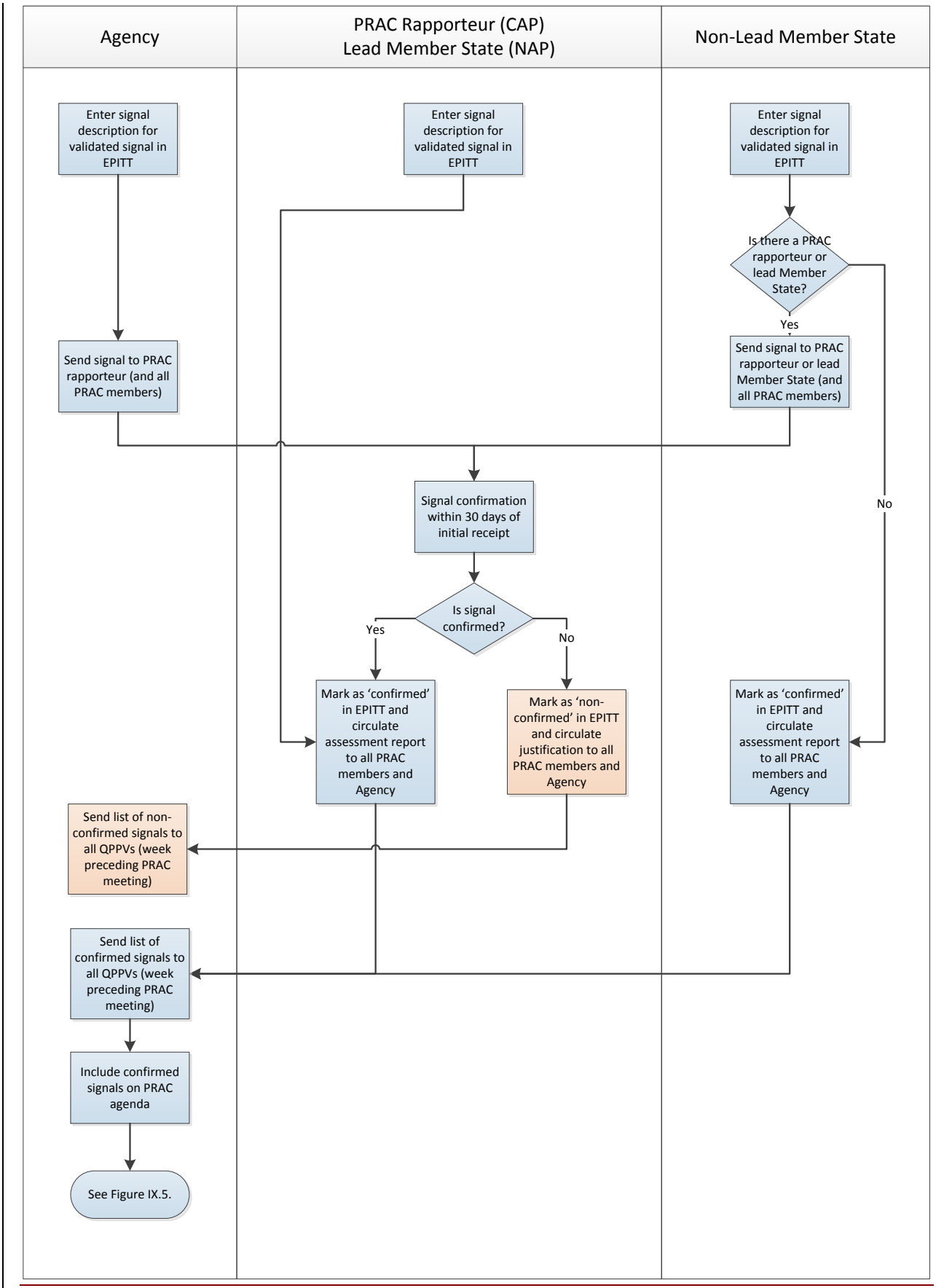


**Figure IX.3.** Confirmation process for standalone signals notifications ~~validated by~~ from marketing authorisation holders




CAP: centrally authorised product; NAP: nationally authorised product; QPPV: Qualified Person responsible for Pharmacovigilance.

902 **Figure IX.4.** Confirmation process for signals validated by the Agency or the competent authorities in
903 Member States

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905

**Figure IX.5.** Process for analysis, prioritisation and assessment of signals by the ~~Pharmacovigilance Risk Assessment Committee~~PRAC

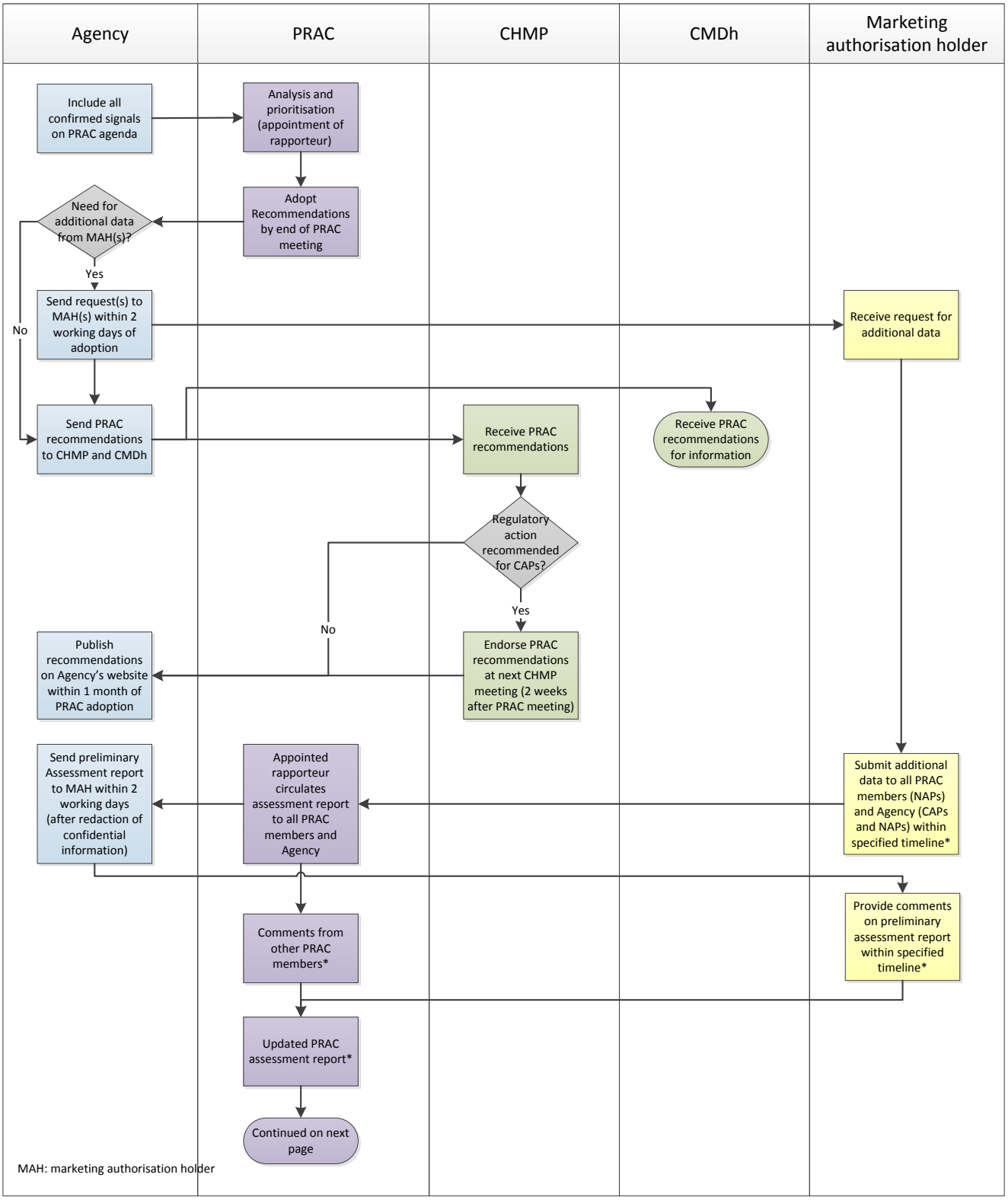

**Figure IX.5. (continued)** Process for analysis, prioritisation and assessment of signals by the PRAC