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3 Guideline on good pharmacovigilance practices (GVP)

4 Module IX – Signal management (Rev 1)

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

9 - Revised definition and process for emerging safety issues, previously addressed in GVP Module VI
10 (IX.C.3.1.);

11 - Streamlined information on scientific aspects of signal management (IX.B.2. to 4.), statistical aspects
12 now addressed in Addendum I;

13 - Clarifications on terminology (IX.A.1.), roles and responsibilities (IX.C.1.) and processes (IX.
14 Appendix 1);

15 - Criteria for access by marketing authorisation holders to case narratives held in EudraVigilance, with
16 reference to Revision 2 of the EudraVigilance Access Policy (IX.C.2.1.);

17 - Updated guidance on the periodicity of monitoring of EudraVigilance data (IX.C.2.2.);

18 - Procedural options for signals validated by marketing authorisation holders (IX.C.3.).

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See websites for contact details

European Medicines Agency www.ema.europa.eu
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Questions on which the Agency seeks specific feedback by means of the public consultation:

1. Are the proposed criteria for access to case narratives held in EudraVigilance by marketing authorisation holders acceptable (see IX.C.2.1.)?

These criteria have been developed to prevent unjustified download of case narratives, in relation to Annex C (Confidentiality Undertaking for Marketing Authorisation Holders) of the EudraVigilance Access Policy[1] which aims at ensuring the protection of personal data.

2. Are the recommendations regarding the frequency of monitoring of EudraVigilance data acceptable (see IX.C.2.2.)?

3. Are the proposed timelines and modalities for communication of emerging safety issues and validated signals by marketing authorisation holders clear and acceptable (see IX.C.3.)?

Comments should be provided using this template. The completed comments form should be sent to gvp@ema.europa.eu

[1] See www.ema.europa.eu

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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 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 (IX.C.).

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[2]
- SCOPE Work Package 5 – Signal Management - Best Practice Guidance[3]
- EMA Questions & Answers on Signal Management[4]
- Screening for Adverse Drug Reactions in EudraVigilance[5]

IX.A.1. Terminology

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

Signal

Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [IR Art 19(1)].

New aspects of a known association may include changes in the frequency, duration, severity or outcome of the adverse event.

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

[2] 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.
[3] See www.scopejointaction.eu (will be available)
[4] EMA/261758/2013, available on EMA website http://www.ema.europa.eu.
[5] See www.ema.europa.eu (available as of Q4 2016)

specific indication, strength, pharmaceutical form or route of administration whereas some signals may apply to a whole class of medicinal products.

Signal management process

The set of activities performed to determine whether there are new risks associated with an active substance or a medicinal product or whether known risks have changed, 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)].

Signal detection

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

Signal validation

The process of evaluating the data supporting a detected signal in order to verify that the available documentation contains sufficient evidence to justify 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.).

Signal confirmation

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 whether or not a validated signal should be analysed and prioritised by the PRAC. This should be done 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 PRAC (see IX.C.4.).

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, 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 patient and public health and the risk-benefit balance of the concerned medicinal product(s) (see IX.C.5.).

Signal assessment by the Pharmacovigilance Risk Assessment Committee (PRAC)

Following PRAC initial 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.).

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.

[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.

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

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

The data sources for identifying new signals are diverse. They potentially include 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[7], GVP Module VIII) and the scientific literature reporting such data.

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 such as EudraVigilance, the US FDA Adverse Event Reporting System (FAERS) or the database of the WHO Programme for International Drug Monitoring (VigiBase).

IX.B.2. Signal detection

Signal detection shall be based on a multidisciplinary approach [IR Art 19(2)]. It should follow an appropriate methodology, which may vary depending on the nature of data and on the type of medicinal product concerned (vaccines may for example require specific methodological strategies (see GVP P.I.)). Data from all appropriate sources should be considered (see IX.B.1.). Clinical judgement should always be applied.

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

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

(e.g. signals detected from published studies, healthcare record data), 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 (see IX.B.5.).

IX.B.3. Evaluation of the evidence supporting a signal

The following elements should be considered when evaluating the evidence supporting a detected signal:

- Strength of the evidence from ICSRs, taking into account, for example:
  - 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, supportive results of relevant investigations;
  - 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. 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);
  - plausibility of a biological and pharmacological relationship / possible mechanism;
  - number of cases in the context of patient exposure;
  - measures of disproportionality, if applicable (see GVP Module IX Add I).
- Clinical relevance, for example:
  - seriousness and severity of the reaction;
  - 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[8]) or the older population (see GVP P.IV.)) or in patients with pre-existing risk factors;
  - reactions occurring in different patterns of use (e.g. overdose, misuse, off-label use, medication errors);
  - 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);

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

- 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 the association, for example:

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

The evaluation of the evidence supporting a signal may involve several rounds of expert discussions and different levels of decision-making, within individual organisations. This may result in various decisions, such as:

- 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

A key and continuous consideration of the signal management process is to promptly identify signals that may have an important impact on patient or public health and/or on the risk-benefit balance of the medicinal product.

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 cause media attention and/or public concerns (e.g. adverse events following mass immunisation).

How the signal is further managed including timelines will depend on the prioritisation. Because prioritisation is a continuous process, appropriate measures should be considered at any stage if the information available supports the conclusion that there is 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 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, 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 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. 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).

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.

As a critical process, signal management activities should be audited at regular intervals, including tasks performed by any service providers and contractors. 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 compliance with these requirements 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

Marketing authorisation holders 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)]. 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.).

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)].

Within the EU regulatory network, the Agency takes the lead for EudraVigilance monitoring of active substances contained in at least one centrally authorised product (CAP). 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. For these substances, a worksharing is foreseen whereby Member States may agree within the Coordination Group for Mutual recognition and Decentralised procedures – human (CMDh) to appoint a lead Member State to monitor EudraVigilance data 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)].

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..

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	✓	✓	✓		✓	

	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)
Signal confirmation			✓	✓	✓	
Signal analysis and prioritisation, assessment, recommendation						✓

IX.C.2. 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)]. 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.2.1. 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[9].

For marketing authorisation holders, the policy provides the option to request access to case narratives held in EudraVigilance ('ICSR data set level 2B'). 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.

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[10].

Relevant staff members within national competent authorities and marketing authorisation holders should familiarise themselves with the training materials made available online by the Agency on

[9] See www.ema.europa.eu
[10] Documents under development; references will be provided in the final GVP M IX Rev 1

EVDAS and the training should be documented in line with the organisation's internal procedures (see IX.B.5.).

IX.C.2.2. 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:

- time since first authorisation;
- patient exposure;
- potential risks and missing information documented in the RMP;
- PSUR submission frequency;
- any safety concern of interest in specific situations (e.g. vaccination campaigns).

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 Art 23 (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 document the frequency of their monitoring of EudraVigilance data (see also IX.B.5.).

IX.C.3. Notifications and procedural options for signals validated by the marketing authorisation holder in the EU

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.

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 "P-PV-emerging-safety-issue@ema.europa.eu". 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[11]).

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.3.2. Variation of the terms of marketing authorisation

When, as a result of signal validation, a marketing authorisation holder considers the evidence sufficient to propose changes to the product information and/or the RMP, they should submit an appropriate 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 the signal is validated.

In such instances, a standalone signal notification (see IX.C.3.4.) is not required, as the proposed changes and supportive evidence will be assessed by the relevant competent authorities within the variation procedure.

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.

Marketing authorisation holders should follow the relevant guidance on variations when preparing their variation application[12].

IX.C.3.3. Periodic safety update report

For active substances included in the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)[13], 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).

For active substances not included in the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs)[14], 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.).

[11] See www.ema.europa.eu
[12] 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.
[13] See www.ema.europa.eu
[14] See www.ema.europa.eu

Regardless of 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 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. Standalone signal notification

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[15] available on the European medicines web-portal and send it via [functional e-mail address tbc][16] 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. Signal confirmation by Member States

Within 30 days of receipt of a validated signal, 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.).

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

- it is already 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 adverse reaction is already included in the product information of other products authorised in the EU with the same active substance;
- the signal has recently 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.

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.

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

[15] See www.ema.europa.eu (will be made available later)
[16] E-mail address to be confirmed later

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

When the Agency or the national competent authority validating or confirming a signal considers that urgent action is required before the subsequent PRAC meeting, it should use the rapid alert system to inform the 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[17]).

The PRAC prioritises signals taking into account the information provided by the Member State that confirmed the signal (see IX.B.4. and IX.C.4.). 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 appoints a rapporteur and defines a timeframe taking into account the prioritisation of the signal. The appointed rapporteur should transmit to the PRAC an assessment report which should include a proposed recommendation. Marketing authorisation holders 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)]. 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. 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.

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

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

- no action is required at this point in time, other than routine pharmacovigilance;
- the marketing authorisation holder should review 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 be requested to submit an RMP or an updated RMP (see GVP Module V);
- the marketing authorisation should be varied;
- additional risk minimisation measures should be put in place (see GVP Module XVI), 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);

[17] See www.ema.europa.eu

- 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 Art 31 or 107i, or REG Art 20, as appropriate[18];
- 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;
- any other appropriate action that is not listed above.

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, and to the Coordination Group for Mutual recognition and Decentralised procedures – human (CMDh) for information in the case of nationally authorised products. The national competent authorities of Member States should take the appropriate measures at national level subsequently.

IX.C.7. Record management in 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.).

IX.C.8. Transparency

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

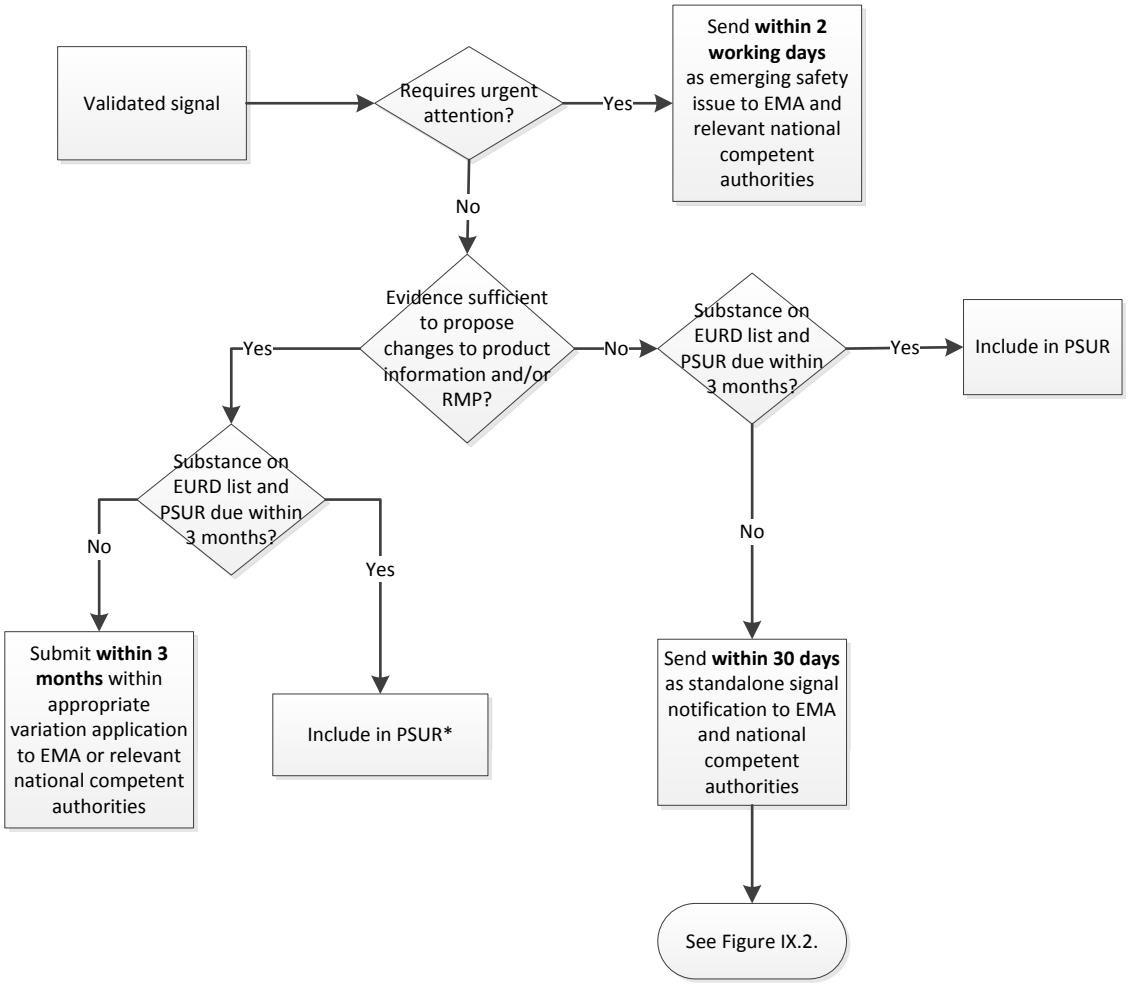
- PRAC agendas;
- PRAC recommendations (for recommendations to update the product information, the agreed wording for the product information is published in all EU official languages, as well as Norwegian and Icelandic. Marketing authorisation holders can use these translations to update the product 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;
- 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[19].

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

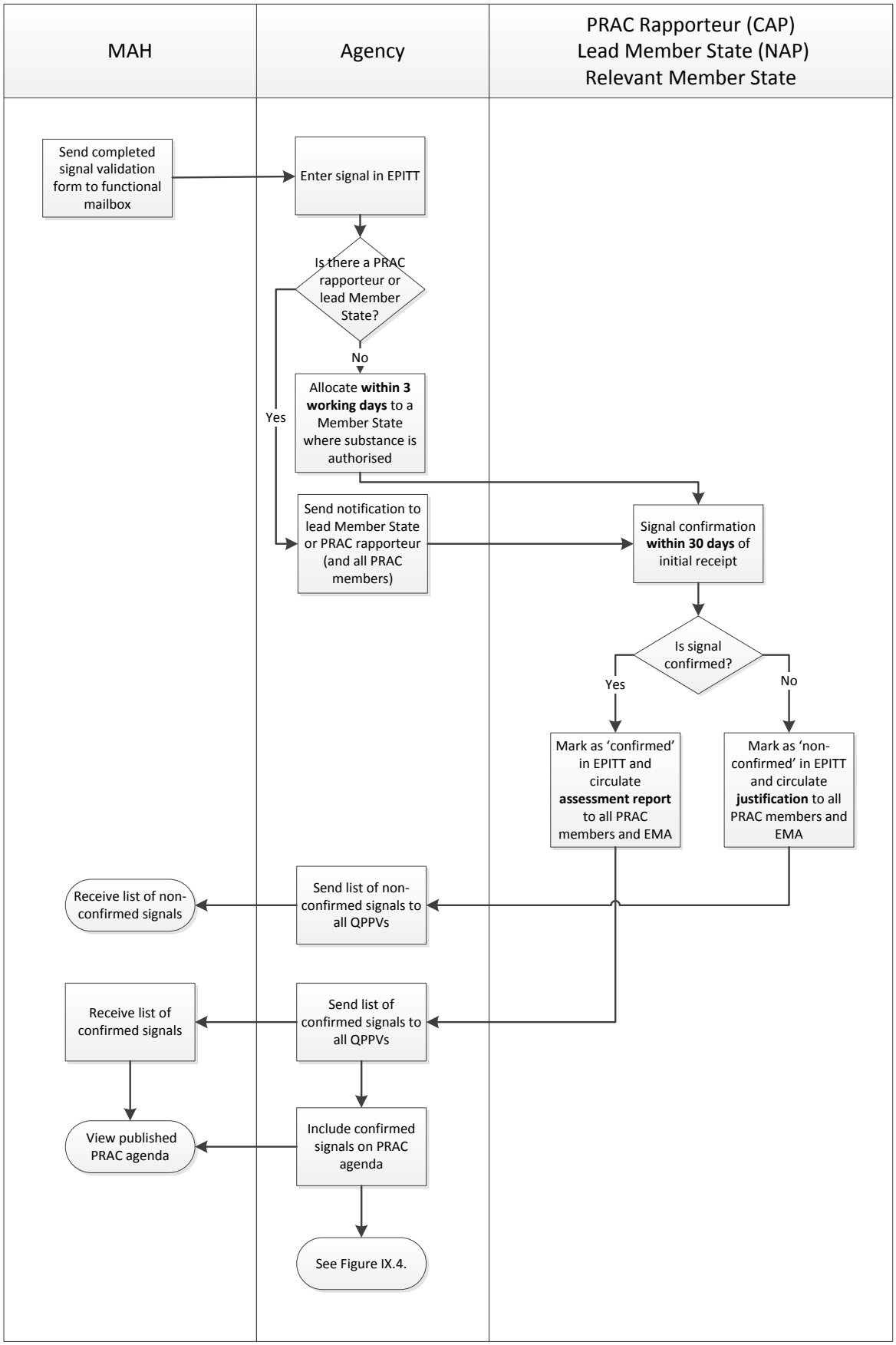
IX. Appendix 1. Figures on the EU signal management process

Figure IX.1. Notifications and procedural options for signals validated by marketing authorisation holders



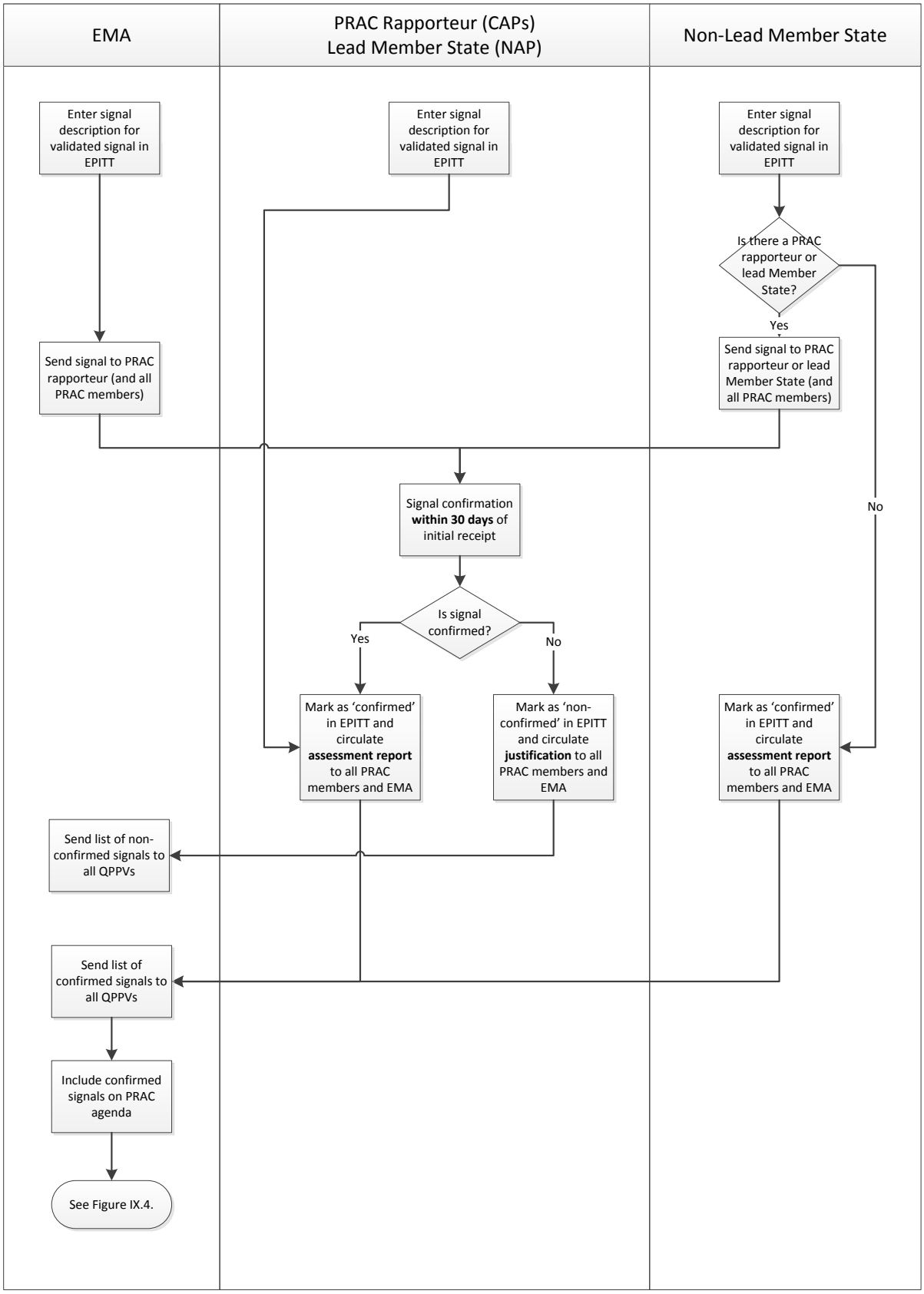
* Unless the MAH considers that a variation application should be submitted.

547 **Figure IX.2.** Confirmation process for signals validated by marketing authorisation holders



548

549 **Figure IX.3.** Confirmation process for signals validated by the Agency or the competent authorities in
550 Member States



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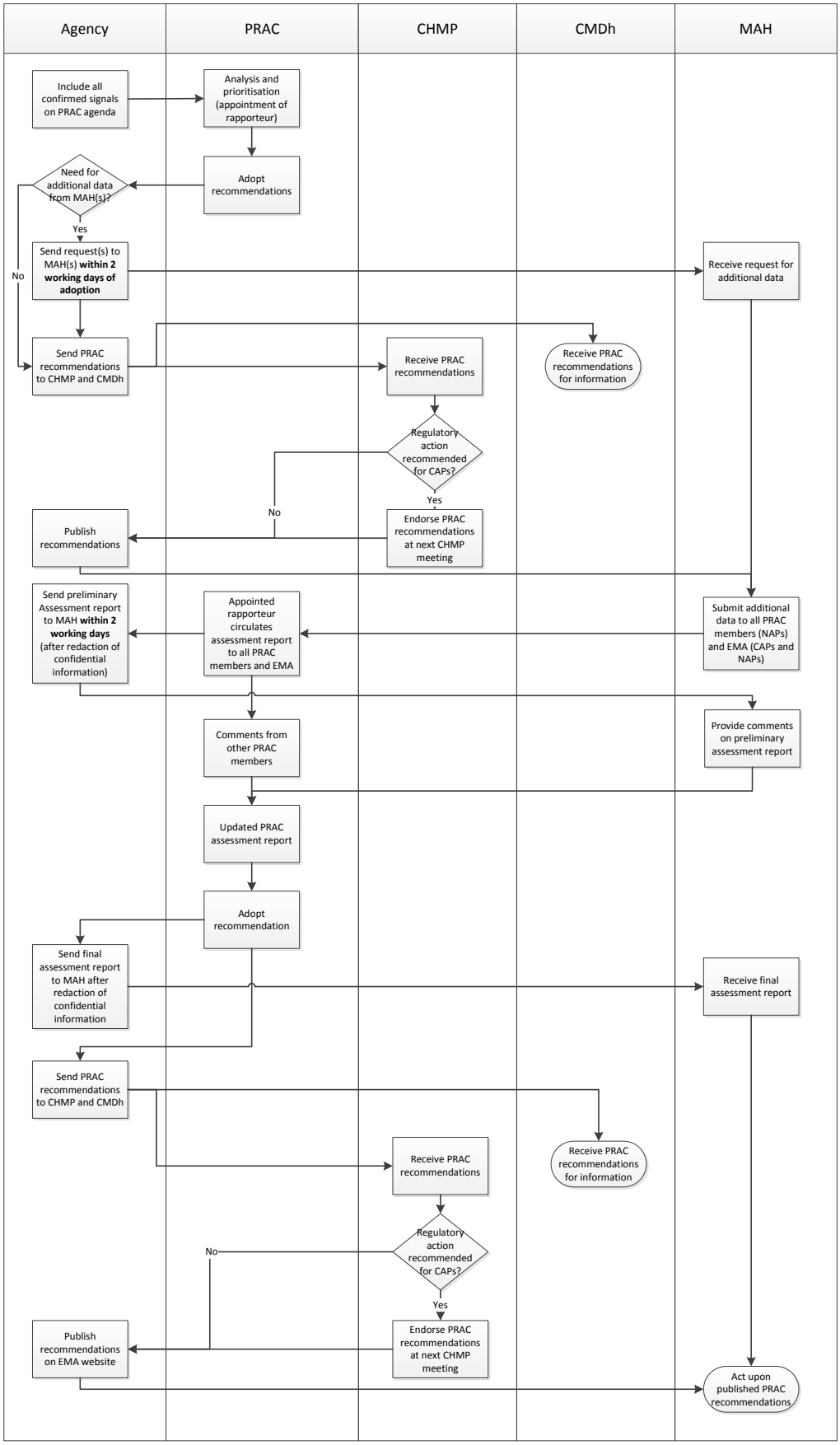
553 **Figure IX.4.** Process for analysis, prioritisation and assessment of signals by the Pharmacovigilance
554 Risk Assessment Committee



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