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IX.A. Introduction

The Report of CIOMS Working Group VIII on Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010) defines a signal as information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action [IM Art 23(1)].

For the purpose of this Module, only new information related to an adverse reaction, and not to potential beneficial effects, will be considered.

In order to suggest a new potentially causal association or a new aspect of a known association, any signal should be validated taking into account other relevant sources of information.

The signal management process can be defined as the 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, literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether risks have changed. The signal management process shall cover all steps from detecting signals (signal detection), through their validation and confirmation, analysis, prioritisation and assessment to recommending action, as well as the tracking of the steps taken and of any recommendations made [IM Art 25(1)]. Whereas the EudraVigilance database will be a major source of pharmacovigilance information, the signal management process covers signals arising from outside the EudraVigilance database or not directly supported by the EudraVigilance database. For the purpose of the EudraVigilance database, only signals related to an adverse reaction shall be considered [IM Art 23(2)].

Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004, Directive 2010/84/EU amending Directive 2001/83/EC and Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC include provisions for signal management in the European Union (EU).

In this Module, all applicable legal requirements are referenced in the way 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”.

In the EU, the main stakeholders in the signal management process include patients, healthcare professionals, marketing authorisation holders, regulatory authorities, scientific committees and decision-making bodies (such as competent authorities in the Member States and the European Commission (EC)).

The objectives of this Module are:

- to provide general guidance and requirements on structures and processes involved in signal management (section IX.B.);
- to describe how these structures and processes are applied in the setting of the EU pharmacovigilance and regulatory network in order to detect whether there are new risks or whether risks have changed (section IX.C.).

IX.B. Structures and processes

IX.B.1. Data sources for signal management

The sources for identifying new signals are diverse. They potentially include all scientific information concerning the use of authorised medicinal products including quality, non-clinical, clinical and pharmacovigilance data. Sources for signals include spontaneous reporting systems, active surveillance systems, non-interventional studies, clinical trials and other sources of information.

Spontaneous reports of adverse reactions may be notified to pharmacovigilance systems, poison centres, teratology information services, vaccine surveillance programmes, reporting systems established by marketing authorisation holders, and any other structured and organised data collection schemes allowing patients and healthcare professionals to report suspected adverse reactions related to medicinal products. Competent authorities should ensure they are informed in a timely manner of adverse reactions notified to reporting systems managed by other institutions or organisations. Due to the increase in volume of spontaneous reports, the introduction of electronic safety reporting by patients and healthcare professionals, and the mandatory electronic transmission of case reports from marketing authorisation holders to competent authorities, the signal detection is now increasingly based of periodic monitoring of large databases such as the EudraVigilance database. Spontaneous reports contained in EudraVigilance are an essential data source supporting signal management in the EU.

Signals from spontaneous reports may be detected from individual case safety reports (ICSRs), included in adverse reaction databases, articles from the scientific literature, periodic safety update reports (PSURs) or other information provided by marketing authorisation holders in the context of regulatory procedures (e.g. variations, renewals, post-authorisation commitments) or the on-going benefit-risk monitoring of medicinal products.

Active surveillance aims to stimulate the reporting of adverse reactions by healthcare professionals through specially designed systems such as prescription event monitoring or sentinel networks based on general practitioners or hospitals. They may be used to facilitate reporting of particular adverse reactions or adverse events for specific drugs.

Signals may arise from a wide range of different study types, including quality, non-clinical, interventional and non-interventional studies, systematic reviews and meta-analyses. Interventional trials and observational studies may, by design, recruit and follow-up a defined population of subjects who may experience adverse reactions. Aggregated data and statistical analyses may also point to an elevated risk of an adverse event to be further investigated.

Results of registries or studies initiated or sponsored by the marketing authorisation holder should be reported to the relevant national competent authority(ies) and/or the Agency according to their obligations (see Module VI). Published results of relevant studies should be identified by marketing authorisation holders by screening the scientific and medical literature for those journals/active substances not included in the list screened by the Agency. For general guidance on performing literature searches, refer to Module VI.

National competent authorities should put in place a system encouraging the early reporting, as soon as possible after the acceptance of the manuscript; of the results of post-authorisation safety studies (PASS) conducted on their territory (see Module VIII).

Other sources of information include the internet, digital media (such as public websites, social networks, blogs) or other systems through which patients and consumers may communicate adverse experiences with medicinal products (see Module VI). Marketing authorisation holders and competent

authorities should try to gain further information related to reactions they become aware of from such sources. If the available information is limited, suspected serious adverse reactions should be confirmed if possible in other data sources such as EudraVigilance.

IX.B.2. Methodology for signal management

As a general principle, signal detection should follow a structured and recognised methodology, which may vary depending on the type of medicinal product it is intended to cover. Vaccines, which are normally administered on a large scale to healthy individuals for anticipated benefits, may for example require other methodological strategies that other medicinal products.

In order to determine the evidence supporting a signal, a structured and recognised methodology shall be applied taking into account the clinical relevance, quantitative strength of the association, consistency of the data, the exposure-response relationship, the biological plausibility, experimental findings, possible analogies and the nature and quality of the data [IM Art 24(1)].

Different factors may be taken into account for the prioritisation of signals, namely the fact whether the association or medicinal product is new, factors related to the strength of the association, factors related to the seriousness of the reaction involved and factors related to the documentation of the reports in the EudraVigilance database [IM Art 24(2)].

IX.B.3. The signal management process

IX.B.3.1. Introduction

The signal management process covers all steps from detecting signals to recommending action(s). It concerns all stakeholders involved in the safety monitoring of authorised medicinal products.

The signal management process includes the following steps:

- signal detection;
- signal validation;
- signal analysis and prioritisation;
- signal assessment;
- recommendation for action;
- exchange of information.

Although these steps generally follow a logical sequence, the wide range of sources of information available for signal detection may require some flexibility in the conduct of signal management, for example:

- when signal detection is primarily based on a review of individual case safety reports (ICSRs), this activity may include validation and preliminary prioritisation of any detected signal;
- when a signal is detected from aggregated results of a study, it is generally not possible or practical to assess each individual case, and validation may require collection of additional data;
- recommendation for action (followed by decision in accordance with the applicable legislation) and exchange of information are components to be considered at every step of the process.

For the purpose of this guidance, signals originating from the monitoring of data from spontaneous reporting systems are considered as the starting point of the signal management process. The same principles should apply for data originating from other sources.

IX.B.3.2. Signal detection

Detailed guidance on methods of signal detection may be found in the Report of CIOMS Working Group VIII on Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010) and in the Guideline on the Use of Statistical Signal Detection Methods in the EudraVigilance Data Analysis System (EMEA/106464/2006 rev. 1).

Whichever methods are employed for the detection of signals, the same principles should apply, namely:

- the method used should be appropriate for the data set; for example, the use of complex statistical tools may not be appropriate for small data sets;
- data from all appropriate sources should be considered;
- systems should be in place to ensure the quality of the signal detection activity;
- any outputs from a review of cumulative data should be assessed by an appropriately qualified person in a timely manner;
- urgent and appropriate action should be taken whenever a potential safety issue with major public health impact is detected;
- the process should be adequately documented, including the rationale for the method and periodicity of the signal detection activity.

Detection of safety signals may be performed based on a review of ICSRs, from statistical analyses in large databases, or from a combination of both.

IX.B.3.2.1. Review of individual case safety reports

ICSRs may originate from a spontaneous reporting system, adverse event reports from active surveillance or studies, or cases published in the literature. Even a single report of a serious or severe adverse reaction (for example, one case of anaphylactic shock) may be sufficient for raising a signal and taking further action. The information to be reviewed should include the number of cases (after exclusion of duplicates and inadequately documented cases), the patient's demographics (e.g. age and sex), the suspected medicinal product (e.g. dose administered) and adverse reaction (e.g. signs and symptoms), the temporal association, the clinical outcome in relation to drug continuation or discontinuation, the presence of potential alternative causes for the adverse event, the reporter's evaluation of causality and the plausibility of a biological and pharmacological relationship. See Module VI for guidance on ICSRs validation.

IX.B.3.2.2. Statistical analyses in large databases

Signal detection is now increasingly based on a periodic monitoring of large databases of spontaneous reports of adverse drug reactions. This has resulted from a number of factors, including an increase in volume of spontaneous reports, the introduction of electronic safety reporting by patients and healthcare professionals and the mandatory electronic transmission of case reports from marketing authorisation holders to competent authorities. Such databases allow generation of statistical reports presenting information on adverse reactions received over a defined time period for defined active substances or medicinal products. Various statistical methods have been developed to automatically

identify signals of disproportionate reporting, i.e. higher reporting than expected of an suspected adverse reaction for an active substance/medicinal product of interest compared to all other active substances/medicinal products in the database, (expressed, for example, as a lower bound of the proportionate reporting ratio $\geq$1). Given the limitations of these methods, a signal of disproportionate reporting does not necessarily indicate that there is a signal to be further investigated or that a causal association is present.

Use of statistical tools may not be appropriate in all situations. The size of the data set, the completeness of the available information and the seriousness of the adverse events should be taken into account when considering the use of statistical methods and the selection of criteria for the identification of signals.

The periodicity at which statistical reports should be generated and reviewed may vary according to the active substance/medicinal product, its indication and potential or identified risks. Some active substances/medicinal products may also be subject to an increased frequency of data monitoring (see IX.C.2.). The duration for this increased frequency of monitoring may also vary and be flexible with the accumulation of data associated with the use of concerned active substance/medicinal product.

IX.B.3.2.3. Combination of statistical methods and review of individual case safety reports

Statistical reports may be designed to provide a tool for identifying suspected adverse reactions that meet pre-defined criteria of frequency, severity, clinical importance, novelty or statistical reporting association. Such filtering tools may facilitate the selection of the most important ICSRs to be reviewed as a first step. The thresholds used in this filtering process (for example, at least 3 cases reported) may vary according to the public health impact of reactions and the extent of usage of medicinal products.

Where signal detection used an automated screening of a database, the corresponding ICSRs should be individually reviewed (see IX.B.3.2.1.).

Irrespective of the statistical method used, the identification of signals should always involve clinical judgment, considering its clinical relevance. The statistical method should be a supporting tool in the whole process of signal detection and validation.

IX.B.3.3. Signal validation

When a signal has been detected, an evaluation of the data supporting the signal should be performed to verify that the available documentation is strong enough to suggest a new potentially causal association, or a new aspect of a known association, and therefore to justify further assessment of the signal [IM Art 25(1)].

For this signal validation process, independently from the source of signals, the following should be taken account:

- Clinical relevance including, for example:
  - strength of evidence for a causal effect (e.g. number of reports, taking into account exposure, temporal association, plausible mechanism, de/re-challenge, alternative explanation/confounders);
  - severity of the reaction and its outcome;
  - novelty of the reaction (e.g. new and serious adverse reactions);
  - clinical context (e.g. suspicion of a clinical syndrome including other reactions);

- possible drug-drug interactions and reactions occurring in special populations.

- Previous awareness:
  - information is already included in the summary of product characteristics (SmPC) or patient leaflet;
  - the signal has already been assessed by a competent authority in the PSUR or risk management plan (RMP), or was discussed at the level of a scientific committee or has been subject to a regulatory procedure.

In principle only signals not falling under the above categories should be validated. However, an already known signal may require validation if its apparent frequency of reporting, its temporal persistence, its severity or a change in the previously reported outcome (such as fatality) suggests new information as compared to the data included in the SmPC or previously assessed by the competent authority.

- Availability of other relevant sources of information providing a richer set of data on the same adverse reaction:
  - literature findings regarding similar cases;
  - experimental findings or biological mechanisms;
  - screening of databases with larger datasets (e.g. EudraVigilance when the signal was sourced initially by data from national or company-specific database).

Signal becomes a validated signal if the verification process of all relevant documentation is suggestive of a new potentially causal association, or a new aspect of a known association, and therefore justifies further assessment.

The magnitude and clinical significance of a signal may also be examined by descriptive analyses in other available data sources or by analysis of the characteristics of exposed patients and their medicinal product utilisation patterns (such analyses are also sometimes referred to as signal refinement, signal strengthening or signal substantiation).

Signals for which the verification process is not suggestive of a new potentially causal association or a new aspect of a known association are not-confirmed but may deserve special attention in subsequent analyses. For example, there might be an inadequate case documentation or a suspicion of a causal association only in a fraction of the ICSRs. In such scenarios, new cases of the same adverse reaction or follow-up reports of previously received cases should be reviewed at adequate time intervals to ensure that all relevant cases are considered.

Marketing authorisation holders and competent authorities should establish tracking systems to capture the outcome of the validation of signals including the reasons why signals did not suggest a new potentially causal association, or a new aspect of a known association as well as information that would facilitate further retrieval of the cases and assessment of the signal.

IX.B.3.4. Signal analysis and prioritisation

A key element of the signal management process is to promptly identify signals with important public health impact or that may affect the benefit-risk balance of the medicinal product in treated patients. These signals require urgent attention and need to be evaluated without delay. This prioritisation process should consider:

- the strength and consistency of the evidence, e.g., biological plausibility, a high number of valid cases reported in a short period of time, high values for the measure of reporting disproportionality and rapid increase of that measure over time and identification of the signal in different settings (e.g. general practice and hospital settings), data sources or countries;
- the impact on patients, depending on the severity, reversibility, potential for prevention and clinical outcome of the safety issue, and the consequences of treatment discontinuation on the disease and other therapeutic options;
- the public health impact, depending on the extent of utilisation of the product in the general population and in a vulnerable population (e.g. medicinal products used in pregnant women, children or the elderly) and the patterns of medicinal product utilisation (e.g. off-label use or misuse); the public health impact may include an estimation of the number of patients that may be affected by a serious adverse reaction, and this number could be considered in relation to the size of the general population, the population with the target disease and the treated population;
- increased frequency or severity of a known adverse effect;
- novelty of the suspected adverse reaction, e.g. when an unknown suspected adverse reaction occurs shortly after the marketing of a new medicinal product;
- if the marketing authorisation application for a new active substance is still under evaluation by a national competent authority and a safety signal is reported from a third country where the substance is already authorised, or a severe adverse reaction arising from that third country is detected in EudraVigilance, this signal should also be prioritised.

In some circumstances, priority for evaluation can also be given to signals identified for medicinal products or events with potential high media and pharmacovigilance stakeholder interest in order to communicate the result of this evaluation to the public and healthcare professionals as early as possible.

The outcome of signal prioritisation should include a recommendation of the time frame for the evaluation of the signal.

The outcome of the signal prioritisation process should be entered in the tracking system, with the justification for the level of prioritisation attributed to the signal.

IX.B.3.5. Signal assessment

The objective of signal assessment is to examine the evidence for a causal association between an adverse reaction and a suspected medicinal product, to quantify this association (preferably in absolute terms) and to identify the need for additional data collection or for any regulatory actions. It consists of a thorough pharmacological, medical and epidemiological assessment of all the information available on the signal of interest. This review should include pharmacological, non-clinical and clinical data when available and be as complete as possible regarding the sources of information, including the application dossier, literature articles, spontaneous reports and non-published information from marketing authorisation holders and national competent authorities. Consultation with external experts should also be considered. When information is drawn from a range of data sources, the strengths and limitations of each of these should be considered in order to assess the contribution they can provide to the evaluation of the safety issue. Summarising information from different data sources also requires the choice of an internationally agreed definition of the medical issue. If no such definition exists, an operational definition should be developed.

Signals sometimes need to be assessed at the therapeutic or system organ class level or at the level of a standardised MedDRA query and the search for information may need to be extended to other products of the class and to other adverse reactions, such as to other terms linked to a complex disease (e.g. optic neuritis as a possible early sign of multiple sclerosis), to a prior stage of the reaction (e.g. QT prolongation and torsades de pointes) or to clinical complications of the adverse reaction of interest (e.g. dehydration and acute renal failure).

Gathering information from various sources may take time. A staged approach for signal assessment should therefore be considered, for example. For a new signal of a severe adverse reaction, temporary measures could be taken if the first stage of the assessment based on information already available concludes that there is a potential risk that needs to be prevented.

IX.B.3.6. Recommendation for action by competent authorities

The range of recommendations that may be taken as a result of the assessment may vary according to the applicable legislation and the conclusion of the signal assessment.

Although the recommendation for action normally takes place in a logical sequence after signal assessment based on the totality of the information, the need for action should be considered throughout the signal management process. For example, the first case of an adverse reaction indicating a manufacturing defect may require immediate recall of a product batch. The review of available information at the signal validation or signal prioritisation stages may similarly conclude that the evidence is sufficiently strong to inform healthcare professionals and patients. In such situations, it is still necessary to proceed with a formal assessment of the signal in order to confirm or not the safety issue in order to extend or lift the temporary action.

The assessment may request active monitoring of the signal or for additional information to be provided by the marketing authorisation holder in order to confirm that this conclusion is valid for all indications and patient groups. It may also conclude that the issue needs to be reviewed periodically, for example through the PSURs.

Actions may include additional investigations or risk minimisation activities if the mechanisms of occurrence of the suspected adverse reaction highlight the possibility of preventing or mitigating the adverse reaction. If the conclusion was based on limited evidence, it may be necessary to conduct a post-authorisation safety study (PASS) to investigate the potential safety issue (see Module VIII).

Whenever additional activities are requested by a competent authority to the marketing authorisation holder, the request should specify a timeframe by which they should be completed, including progress reports and interim results, proportionate to the severity and public health impact of the issue. Marketing authorisation holders and competent authorities should consider the feasibility of conducting a study within the set timelines taking into account the characteristics of the safety issue of interest, such as its incidence and the need for a prospective study design. Temporary measures to ensure the safe and effective use of the medicinal product or to eliminate the risk should be considered, including the possibility of temporarily suspending the marketing authorisation of the medicinal product.

If there is no evidence of a risk for patients, the competent authority may decide that no further assessment or action is required.

IX.B.3.7. Exchange of information

Exchange of information between competent authorities, marketing authorisation holders and other concerned parties may be needed to share information on signals, collect additional data, further evaluate the safety issue and take decisions to protect patients' health. The timing of the

communication may vary according to the safety issue, but information on signals should be communicated only if they have been validated.

Marketing authorisation holders should communicate any relevant information regarding signals to competent authorities as part of their pharmacovigilance obligations and ongoing monitoring of the benefit-risk of the medicinal products. Validated signals that may have implications for public health and the benefit-risk profile of the product in treated patients should be immediately communicated to the competent authorities, and when appropriate this should include proposals for action.

Competent authorities should communicate results of signal assessments to marketing authorisation holders.

IX.B.4. Quality requirements

IX.B.4.1. Tracking

All validation, prioritisation, assessment, timelines, decisions, actions, plans, reporting as well as all other key steps need to be recorded and tracked systematically. Tracking systems need to be documented and should include also signals, for which the verification process conducted was not suggestive of a new potentially causal association, or a new aspect of a known association, as they may merit special attention in case of subsequent analysis. All records need to be archived [IM Art 25(5), Art 28] (see Module I).

IX.B.4.2. Quality systems and documentation

An essential feature of a signal management system is that it is clearly documented to ensure that the system functions properly and effectively, that the roles, responsibilities and required tasks are standardised, that these tasks are conducted by people with appropriate expertise and are clear to all parties involved and that there is provision for appropriate control and, when needed, improvement of the system. Therefore, a system of quality assurance and quality control consistent with the quality system standards should be in place and applied to all signal management processes (see Module I). Detailed procedures for this quality system should be devised, documented and implemented. The organisational roles and responsibilities for the activities and maintenance of documentation, quality control and review, and for ensuring corrective and preventive action need to be assigned and recorded. This should include the responsibilities for quality assurance auditing of the signal management system, including auditing of sub-contractors. Data and document confidentiality (per the applicable regulations), security and validity (including integrity when transferred) should be guaranteed.

Through the tracking system, all parties should keep an audit trail of their signal management activities and of the relevant queries and their outcomes. Information received, searches, search outputs, assessments and decisions (both positive and negative) regarding potential signals should be archived. This should include the outcome of the signal validations.

Audit trail should also allow traceability of how validated signals have been investigated.

Documentation by the marketing authorisation holder demonstrating compliance with these provisions may be requested and reviewed before and after authorisation, for purposes such as assessment or inspection.

IX.B.4.3. Training

Staff should be specifically trained in signal management activities in accordance with their roles and responsibilities. This concerns not only staff within the safety departments but also staff who may become aware of potential signals or support signal management, such as staff within regulatory, non-clinical research, medical, pharmacoepidemiology and market research departments. The training should include MedDRA and available signal source databases, as applicable. The training system and location of the training records need to be documented, and curricula vitae and job descriptions need to be archived.

IX.C. Operation of the EU network

IX.C.1. Roles and responsibilities

Within the context of the operation of the EU regulatory network, the Agency and national competent authorities shall collaborate to monitor the data available in the EudraVigilance database for medicinal products authorised in the Union used within the terms of the marketing authorisation as well as outside the terms of the marketing authorisation, and for medicinal products authorised in the Union that may induce adverse reactions as a result of an occupational exposure [IM Art 22(1)].

Signal management in the EU regulatory network should be a shared responsibility of the Agency, national competent authorities, the Pharmacovigilance Risk Assessment Committee (PRAC) and the marketing authorisation holders. The detection of signals shall be based on a multidisciplinary approach and shall be supported by statistical analysis within EudraVigilance [IM Art 23(3)]. The identification of signals based on statistical analysis should be a matter of clinical judgment and subject to validation as detailed in IX.B.3.3.

Regarding medicinal products authorised in accordance with Regulation (EC) No 726/2004, the monitoring of data in EudraVigilance, signal detection and signal validation shall be performed by the Agency [REG Art 28a(1)]. The Agency shall be supported, as appropriate by the rapporteur appointed by the PRAC [IM Art 26(5)]. The Agency should also take the lead for active substances contained in several medicinal products, where at least one marketing authorisation has been granted in accordance with Regulation (EC) No 726/2004.

For medicinal products authorised in accordance with Directive 2001/83/EC, the monitoring of data in EudraVigilance, signal detection and signal validation shall be performed by the national competent authorities. For active substances and medicinal products authorised in the EU not monitored by the Agency, a work sharing may be introduced. For medicinal products authorised in accordance with Directive 2001/83/EC in more than one Member State and for active substances contained in several medicinal products where at least one marketing authorisation has been granted in accordance with Directive 2001/83/EC, Member States may agree within the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), in collaboration with the PRAC, to appoint a lead Member State for the monitoring of data in the EudraVigilance database and for validation and confirmation of signals. The lead Member State may be supported by a co-leader. Any such appointment shall be reviewed at least every four years. When appointing a lead Member State and as appropriate a co-leader, the CMDh in collaboration with the PRAC, may take into account whether any Member State is acting as reference Member State, in accordance with Article 28(1) of Directive 2001/83/EC, or as lead Member State for the assessment of periodic safety update reports in accordance with Article 107(e) of Directive 2001/83/EC [IM Art 26(1) and 26(2)].

All Member States retain however, their responsibility pursuant to Article 107h(1)(c) and (3) of Directive 2001/83/EC [IM Art 26(4)].

The national competent authorities and the Agency should validate any signal that has been detected by them in the course of their continuous monitoring of the data in EudraVigilance [IM Art 25(6)]. Signal communication to the PRAC should always be preceded by its validation.

In this context, roles and responsibilities for signal management in the EU regulatory network are as follows:

IX.C.1.1. Roles and responsibilities of the Agency

The Agency:

- shall make public a list of active substances/medicinal products and the authority (lead Member State, co-lead Member State or the Agency) responsible for their monitoring in EudraVigilance [IM Art 26(3)];
- shall take the lead for EudraVigilance data monitoring, signal detection and signal validation for centrally authorised products and for active substances contained in several medicinal products, where at least one marketing authorisation has been granted in accordance with Regulation (EC) No 726/2004;
- following consultation with the PRAC may publish a list of medical events that have to be taken into account for the detection of a signal [IM Art 23(3)];
- shall support the monitoring of the data in the EudraVigilance database by providing access to:
  - data outputs and statistical reports allowing a review of new adverse reactions and of all adverse reactions reported to EudraVigilance in relation with an active substance or a medicinal product;
  - customised queries supporting the evaluation of individual case safety reports and case series;
  - customised grouping and stratification of data enabling the identification of patient groups with a higher risk of occurrence of adverse reactions or with a risk of a more severe adverse reaction;
  - statistical signal detection methods [IM Art 27(1)];
- should prepare a technical document establishing common triggers for signal detection and describing EudraVigilance data outputs and statistical reports;
- shall administer a tracking system (see IX.C.5.) for validated signals that require further assessment [IM Art 25(7)];
- shall enter validated signals in the tracking system and shall transmit signals it has validated to the PRAC with a proposal for analysis and prioritisation [IM Art 25(7)];
- shall confirm in collaboration with the Member States within 15 days (including, if appropriate, in the EudraVigilance database and taking into account other information available) any validated signal communicated by marketing authorisation holders involving a centrally authorised product or an active substance for which the EudraVigilance data monitoring is performed by the Agency; in this context, where the validity of the signal is not confirmed within 15 days, no further action shall be required [IM Art 25(5)];
- should confirm (including, if appropriate, in the EudraVigilance database) any other signal communicated by a third party (e.g. regulatory authority from outside the EU), involving a centrally authorised products or an active substance for which the EudraVigilance data monitoring is performed by the Agency;

- shall forthwith communicate to the concerned marketing authorisation holder(s) the conclusions of the assessment of the signal by the PRAC[1] [IM Art 25(9)];
- should collaborate to the signal validation performed by a national competent authority that detected a signal involving a centrally authorised products or an active substance for which the EudraVigilance data monitoring is performed by the Agency;
- shall keep an audit trail of its signal detection activities [IM Art 28].

IX.C.1.2. Roles and responsibilities of the lead/co-lead Member State

The lead/co-lead Member State:

- shall take the lead for EudraVigilance data monitoring, signal detection and signal validation for active substances/medicinal products, for which it has been appointed the lead or co-lead Member State;
- shall enter validated signals in the tracking system and shall transmit validated signals for active substances/medicinal products for which it has been appointed the lead Member State, to the PRAC with a proposal for prioritisation [IM Art 25(7)];
- shall confirm within 15 days (including, as appropriate, in the EudraVigilance database and taking into account other information available) any validated signal communicated by marketing authorisation holder involving an active substance/medicinal product for which it has been appointed the lead or a co-lead Member State; in this context, where the validity of the signal is not confirmed within 15 days, no further action shall be required [IM Art 25(5)];
- should validate (including, if appropriate, in the EudraVigilance database) any other signal communicated by a third party (e.g. regulatory authority from outside the EU) involving an active substance/medicinal product for which it has been appointed the lead or a co-lead Member State;
- should collaborate to the signal validation performed by a national competent authority that detected a signal involving an active substances/medicinal products for which it has been appointed the lead or a co-lead Member State;
- shall keep an audit trail of their signal detection activities [IM Art 28].

IX.C.1.3. Roles and responsibilities of the national competent authorities

The national competent authorities:

- shall specifically monitor data originated in their territory [IM Art 25(3)], including data arising from sources mentioned in IX.B.1.;
- if a lead/co-lead Member State or the Agency has been appointed for the monitoring of an active substance/medicinal product, the national competent authorities:
  - should validate in collaboration with the lead/co-lead Member State or the Agency any signal detected from all available sources;
  - should enter validated signals in the tracking system and shall transmit validated signals to the PRAC with a proposal for analysis and prioritisation;

[1] until pharmacovigilance contact points for all European marketing authorisation holders are established following implementation of Art 57 of Regulation (EU) No 1235/2010, the communication should be via a dedicated mailbox

- if no lead/co-lead Member State or the Agency has been appointed for the monitoring of an active substance/medicinal product authorised in their territory, the national competent authorities:
  - shall monitor the data of the EudraVigilance database for these medicinal products to determine whether there are new risks or whether risks have changed;
  - shall confirm within 15 days (including, as appropriate, in the EudraVigilance database and taking into account other information available) any validated signal communicated by marketing authorisation holder involving an active substance/medicinal product marketed in their territory; in this context, where the validity of the signal is not confirmed within 15 days, no further action shall be required [IM Art 25(5)];
  - shall validate any signal detected from EudraVigilance for these medicinal products;
  - shall enter validated signals in the tracking system and shall transmit validated signals to the PRAC with a proposal for prioritisation;
- shall keep an audit trail of their signal detection activities [IM Art 28].

IX.C.1.4. Roles and responsibilities of the Pharmacovigilance Risk Assessment Committee

The Pharmacovigilance Risk Assessment Committee (PRAC):

- shall prioritise validated signals for further assessment [IM Art 25(7)] [REG Art 28a];
- should nominate a rapporteur for the assessment of the validated signals with a time frame for the assessment;
- shall transmit to the Committee for Medicinal Products for Human Use (CHMP) or to the CMDh, as appropriate, any recommendations following the signal assessment;
- shall perform a regular review of the signal management methodology to be used and publish recommendations, as appropriate [IM Art 24(3)];
- should review the list of medical events that have to be taken into account for the detection of a signal before their publication by the Agency [IM Art 23(3)].

IX.C.1.5. Roles and responsibilities of marketing authorisation holder

The marketing authorisation holder:

- shall monitor all available data and information for signals;
- shall monitor the data in EudraVigilance to the extent of their accessibility [IM Art 22(2)]. See also EudraVigilance access rights for stakeholder group III in the EudraVigilance Access Policy for Medicines for Human Use[2]. The frequency of the monitoring should be at least once monthly and shall be proportionate to the identified risk, the potential risk and the need for additional information [IM Art 25(2)];
- shall monitor all emerging data and perform worldwide signal detection activities [IM Art 22(2)]; signal detection should include the validation of signals taking into account elements of information presented in IX.B.3.3.;

[2] EudraVigilance access policy for medicines for human use published on 8 July 2011 http://eudravigilance.ema.europa.eu/human/docs/EV%20Access%20Policy%20for%20human%20use%20doc.pdf

- shall validate any detected signal and shall forthwith inform the responsible competent authority in line with the list as published by the Agency (referred to in lines 463-464) [IM Art 25(4)];
- should notify as an Emergency Safety Issue (see Module VI) any safety issue arising from its signal detection activity;
- should collaborate with the PRAC for the assessment of the signals by providing additional information upon request;
- should keep an audit trail of their signal detection activities.

IX.C.2. Periodicity of data monitoring in EudraVigilance

National competent authorities and the Agency shall ensure the monitoring of data in the EudraVigilance database with a frequency proportionate to the identified risk, the potential risk and the need for additional information [IM Art 25(2)]. The monitoring should be based on a periodic review of statistical outputs (e.g. reaction monitoring reports) to determine whether there are new or changed risks in the safety profile of an active substance/medicinal product. The statistical outputs contain adverse drug reactions in a structured hierarchy (e.g. MedDRA hierarchy) per active substance(s)/medicinal product(s) and allow filters and thresholds to be applied on several fields as appropriate.

The baseline frequency for reviewing the statistical outputs from EudraVigilance should be once-monthly. An increase to the baseline frequency of data monitoring in EudraVigilance may be decided by the lead Member State, the national competent authority or the Agency if justified by the identified or potential risks of the product, or by the need for additional information. The PRAC should be informed of the decision and its justification.

For products subject to additional monitoring (see Module X), the frequency for reviewing the statistical outputs should be every 2 weeks until the end of additional monitoring, or its extension. A 2-week frequency for reviewing the statistical outputs may also be applied for any other product taking into account the following criteria:

- any product considered to have an identified or potential risk that could impact significantly on the risk-benefit balance or have implications for public health. This may include risks associated with an important misuse, abuse or off-label use. The product may be moved back to baseline frequency of monitoring if risks are not confirmed;
- any product for which the safety information is limited due to low patient exposure during drug development, including products authorised under conditional approval or under exceptional circumstances, or for which there are vulnerable or poorly studied patient populations or important missing information (e.g. children, pregnant women, renally impaired patients) while post-marketing exposure is likely to be significant;
- any product that contains active substances already authorised in the Union but is indicated for use in a new patient population or with a new route of administration;
- any product for which the existing marketing authorisation has been significantly varied (e.g. changes to indication, posology, pharmaceutical form or route of administration), thereby modifying the exposed patient population or the safety profile.

A signal arising from the EudraVigilance data monitoring activities does not necessarily imply that the product has to be more frequently monitored.

More frequent monitoring than every 2 weeks should be based on a proposal from the lead Member State, national competent authority or the Agency. It should be targeted to a safety concern of interest especially during public health emergencies (e.g. pandemics) and may be applied in the context of customised queries or near real time alerts[3] conducted in the EudraVigilance Data Analysis System (EVDAS).

IX.C.3. Signal analysis, prioritisation and assessment by the Pharmacovigilance Risk Assessment Committee (PRAC)

Any signal that has been detected and validated by the Agency or a national competent authority should be sent to the PRAC for consideration. The PRAC should agree on a prioritisation based on the individual patient and public health impact of the potential change to the risk-benefit-balance. Depending on the level of the prioritisation, an analysis of the need for further assessment or for immediate action should be made, taking into account the time frame proposed by the Agency or the national competent authority that detected the signal.

When it considers that immediate action is needed, the PRAC should make a recommendation on the action(s) required and appropriate procedure(s) should be initiated by the Agency and/or national competent authorities in conjunction with the marketing authorisation holder.

When it considers that further assessment is needed, the PRAC should nominate a rapporteur for the evaluation and should define a timeframe for this evaluation taking into account the prioritisation of the signal. The rapporteur for the signal assessment should transmit to the PRAC a report stating whether there may be new risks, whether risks have changed or whether there is a change in the risk-benefit balance in relation with the concerned active substance or medicinal product. The report should also include proposal for actions, if appropriate.

Following the circulation of the rapporteur's assessment report, the PRAC should make a recommendation, stating the reasons on which it is based. The recommendation should include an implementation timetable for completion of any actions requested of the marketing authorisation holder. The Agency should inform the marketing authorisation holder(s) of the recommendation made by the PRAC in the event of new risks or risks that have changed or when changes to the risk-benefit balance have been detected.

IX.C.4. Processes for EU-specific regulatory follow-up

Where the PRAC considers that follow-up action may be necessary, the signal shall be assessed and any subsequent action concerning the marketing authorisation shall be agreed within a timescale commensurate with the extent and seriousness of the matter in accordance with Article 107h(2) of Directive 2001/83/EC and Article 28a(2) of Regulation (EC) No 726/2004 [IM Art 25(8)] The recommendation of the PRAC should be sent to the CHMP in the case of an active substance that is centrally-authorised and to the CMDh in the case of an active substance that is nationally authorised including authorisation through the mutual recognition or decentralised procedure. The PRAC might consider any or a combination of the following conclusions:

- no further evaluation or action is required at EU level;
- the marketing authorisation holder should conduct further evaluation of data and provide the results of that evaluation according to a defined timeline;
- the marketing authorisation holder should submit an *ad-hoc* PSUR;

[3] EVDAS automated data processing and network transmission takes usually 1 day

- the marketing authorisation holder should sponsor a post-authorisation study according to an agreed protocol and submit the final results of that study;
- the marketing authorisation holder should be requested to submit a RMP or an updated RMP;
- the marketing authorisation holder should take any measures that are required for ensuring the safe and effective use of the medicinal product;
- the marketing authorisation should be varied, suspended, revoked or not renewed;
- the Member States or the Commission should initiate as appropriate, the procedure provided for in Article 31 or in Section 4, Urgent Union Procedure or in Article 31 where appropriate, of Directive 2001/83/EC;
- urgent safety restrictions in accordance with Article 22 of Regulation (EC) No 1234/2008;
- need for an inspection in order to verify that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements laid down in Titles IX and XI of Directive 2001/83/EC;
- inclusion in the list of medicinal products that are subject to additional monitoring where falling within the scope defined in Article 23 of Regulation (EC) No 726/2004.

Where recommended by the PRAC and agreed by the CHMP or the CMDh as appropriate, a procedure should be initiated with a timetable in which the marketing authorisation should be varied, suspended, revoked or not renewed where applicable.

IX.C.5. Record management in the EU regulatory network

The Agency and the national competent authorities shall keep an audit trail of all their signal management activities relating to EudraVigilance and of the relevant queries and their outcomes.

Any signal that has been detected and validated by the Agency or a national competent authority in line with the processes described in IX.B. and that requires further analysis by the PRAC should be entered into the web-based European Pharmacovigilance Issues Tracking Tool (EPITT) administered by the Agency. All subsequent evaluations, timelines, decisions, actions, plans, reporting and all other key steps need to be recorded and tracked systematically in EPITT by the Agency or the national competent authority in line with the guidance document Exchange of Information Relating to Signals through EPITT by the EU Regulatory Network (EMA/383041/2011).

IX.C.6. Transparency

Article 26(1) of Regulation (EC) No 726/2004 states that the Agency shall, in collaboration with the Member States and the Commission, set up and maintain a European medicines web-portal for the dissemination of information on medicinal products authorised in the EU. Article 102(d) of Directive 2001/83/EC states the Member States shall ensure that the public is given important information on pharmacovigilance concerns relating to the use of a medicinal product in a timely manner through publication on the web-portal and through other means of publicly available information as necessary; Article 26(j) of Regulation (EC) No 726/2004 states that by means of that portal, the Agency shall make public at least the following: conclusions of assessments, recommendations, opinions, approvals and decisions taken by the Committees referred to in points (a) and (aa) of Article 56(1) of this Regulation and by the CMDh, the national competent authorities and the EC in the framework of the procedures of Articles 28, 28a and 28b of this Regulation and of sections 2 and 3 of Chapter 3 and Chapter 4 of Title IX of Directive 2001/83/EC.

In this context, several key documents will be made publicly available through the Agency's web-portal. These documents will include the conclusions of the PRAC assessments and recommendations following the evaluation of signals.