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Guideline on good pharmacovigilance practices (GVP)

Module IX – Signal management

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IX.A. Introduction

The Report of the Council for International Organisations of Medical Sciences Working group VIII 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*.

For the purpose of this Module, only new information related to adverse 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 known risks have changed. The signal management process shall include all steps from initial signal detection; through their validation and confirmation; analysis and prioritisation; and signal assessment to recommending action, as well as the tracking of the steps taken and of any recommendations made [IR Art 21(1)].

In the European Union, the signal management process concerns all stakeholders involved in the safety monitoring of medicinal products including 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)).

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 monitoring data in EudraVigilance database, only signals related to an adverse reaction shall be considered [IR Art 19(1)].

Regulation (EU) No 1235/2010 amending Regulation (EC) No 726/2004, Directive 2010/84/EU amending Directive 2001/83/EC and Commission Implementing Regulation (EU) No 520/2012 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.

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 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 (section IX.C.).

IX.B. Structures and processes

IX.B.1. Sources of data and information

The sources for identifying new signals are diverse. They potentially include all scientific information concerning the use of medicinal products including quality, non-clinical, clinical, pharmacovigilance and pharmacoepidemiological data. Specific sources for signals include spontaneous adverse drug reaction (ADR) reporting systems, active surveillance systems, non-interventional studies, clinical trials, scientific literature and other sources of information.

Signals from spontaneous reports may be detected from monitoring of individual case safety reports (ICSRs), ADR databases, articles from the scientific literature or review of information provided by marketing authorisation holders in the context of regulatory procedures (e.g. variations, renewals, post-authorisation commitments, periodic safety update reports (PSURs), Risk Management Plan (RMP) updates or from other activities related to the on-going benefit-risk monitoring of medicinal products.

Spontaneous reports of ADRs may also be notified to 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 liaise with other institutions or organisations managing such reporting system so as to be informed of these suspected adverse reactions.

Due to the increase in volume of spontaneous reports of (ADRs), 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, signal detection is now increasingly based on periodic monitoring of large databases such as the EudraVigilance database.

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 ADRs. Review of aggregated data and statistical analyses may also point to an elevated risk of an adverse event to be further investigated as a signal.

Published results of relevant studies should be identified by marketing authorisation holders by screening the scientific literature. For general guidance on performing literature searches, refer to Module VI.

Marketing authorisation holders should regularly screen internet or digital media under their management or responsibility as specified in Module VI, for potential reports of suspected ADRs, which may characterise a new signal. Marketing authorisation holders and competent authorities should seek further information related to suspected ADRs they become aware of from any source. Suspected serious ADRs should be confirmed if possible through other data sources such as EudraVigilance.

IX.B.2. Methodology for signal detection

As a general principle, signal detection should follow a recognised methodology, which may vary depending on the type of medicinal product it is intended to cover. Vaccines may for example require other methodological strategies.

The detection of signals shall be based on a multidisciplinary approach. Signal detection within the EudraVigilance database shall be complemented by statistical analysis where appropriate [IR Art 19(2)].

In order to determine the evidentiary value (i.e. the supporting evidence) of a signal a recognised methodology shall be applied taking into account the clinical relevance, quantitative strength of the association, the consistency of the data, the exposure-response relationship, the biological plausibility, experimental findings, possible analogies and the nature and quality of the data [IR Art 20(1)].

Different factors may be taken into account for the prioritisation of signals, namely whether the association or the active substance/medicinal product is new, the strength of the association, the seriousness of the reaction involved and the documentation of the reports in the EudraVigilance database [IR Art 20(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) as follows:

- 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 e.g.:

- 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 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 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 (Doc. Ref. 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 smaller 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;
- the process should be adequately documented, including the rationale for the method and periodicity of the signal detection activity.

Detection of 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

As specified in Module VI, ICSRs may originate from a spontaneous reporting system, post-authorisation studies and monitoring of literature. Even a single report of a serious or severe adverse reaction (for example, one case of toxic epidermal necrolysis, aplastic anaemia or liver transplant) may be sufficient to raise a signal and to take further action. A review of ICSRs for this purpose should consider the number of cases (after exclusion of duplicates), the patient's demographics (including age and gender), the suspected medicinal product (including dose administered, formulation) and the suspected adverse reaction (including signs and symptoms), the temporal association, the clinical outcome in relation to drug continuation or discontinuation (i.e. de-challenge / re-challenge information). An assessment of causality of a suspected association should also consider, the presence of potential alternative causes including other concomitant medications, the underlying disease, the reporter's evaluation of causality and the plausibility of a biological and pharmacological relationship.

IX.B.3.2.2. Statistical analyses

Signal detection is now increasingly based on a regular periodic monitoring of large databases of spontaneous reports of ADRs. 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 methods have been developed to identify statistics of disproportionate reporting, i.e. higher reporting than expected for an suspected adverse reaction for an active substance/medicinal product of interest compared to all other active substances/medicinal products in the database, (expressed e.g. as a lower bound of the proportionate reporting ratio ≥ 1). Given the limitations of these methods, statistics of disproportionate reporting alone do 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 severity of the adverse reaction(s) should be taken into account when considering the use of statistical methods and the selection of criteria for the detection 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 any known 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 knowledge of the risk profile associated with the use of the 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 tools for identifying suspected adverse reactions that meet pre-defined criteria of frequency, severity, clinical importance, novelty or statistical association. Such filtering tools may facilitate the selection of 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 extent of usage of medicinal products and thus the potential public health impact.

Irrespective of the statistical method used, where statistical reports are used to automate the screening of a database, signal detection should always involve clinical judgement and the corresponding ICSRs should be individually reviewed, considering their clinical relevance (IX.B.3.2.1.).

The statistical method should therefore be a supporting tool in the whole process of signal detection and subsequent validation.

IX.B.3.3. Signal validation

Signal validation is the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further analysis [IR Art 21(1)].

To validate a signal the following should be taken into account:

- Clinical relevance including, for example:
  - strength of evidence for a causal effect (e.g. number of reports, exposure, temporal association, plausible mechanism, de/re-challenge, alternative explanation/confounders);
  - seriousness and severity of the reaction and its outcome;
  - novelty of the reaction (e.g. new and serious adverse reactions);
  - drug-drug interactions;
  - reactions occurring in special populations.
- Previous awareness:
  - the extent to which information is already included in the summary of product characteristics (SmPC) or patient leaflet;
  - whether the association has already been assessed in a PSUR or RMP, or was discussed at the level of a scientific committee or has been subject to a regulatory procedure.

In principle only a new signal for which there is no previous awareness should be validated. However, an already known association may give rise to a new signal if its apparent frequency of reporting, its duration, its severity or a change in the previously reported outcome (such as new fatality) suggests new information as compared with the information 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 association:
  - 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).

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.

Signals for which the validity is not confirmed may deserve special attention in subsequent analyses i.e. it may be appropriate to continue to monitor the potential signal until there is enough evidence to confirm the signal. For example, there might be an inadequate case documentation or a supporting evidence of a causal association only in some 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 appropriate 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 were not validated as well as information that would facilitate further retrieval of ICSRs and validation of signals.

IX.B.3.4. Signal analysis and prioritisation

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

- the impact on patients depending on the severity, reversibility, potential for prevention and clinical outcome of the association;
- the consequences of treatment discontinuation on the disease and the availability other therapeutic options;
- the strength and consistency of the evidence supporting an association, e.g., biological plausibility, a high number of cases reported in a short period of time, the measure of disproportionality of reporting 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;
- clinical context (e.g. whether the association suggest a clinical syndrome that may include other reactions);
- the public health impact, including the extent of utilisation of the product in the general population and in special populations (e.g. 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 an 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 reaction;
- 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 a marketing authorisation application for a new active substance is still under evaluation.

In some circumstances, priority 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 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 management of the signal.

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

IX.B.3.5. Signal assessment

The objective of signal assessment is to further evaluate a validated signal so as to identify the need for additional data collection or for any regulatory action. It consists of an assessment of the available pharmacological, non-clinical and clinical data and information from other sources. This review should be as complete as possible regarding the sources of information, including the application dossier, literature articles, spontaneous reports, expert consultation, and information held by marketing authorisation holders and competent authorities. When information is drawn from a range of sources, the strengths and limitations of each source should be considered in order to assess the contribution they can provide to the overall evaluation of the signal in terms of a recommendation for action. Summarising information from different data sources also requires the choice of an internationally agreed case definition (e.g. Brighton collaboration case definition for vaccines). If no such definition exists, an operational definition should be developed.

Signals may need to be assessed at a broader level e.g. at the therapeutic or system organ class level or at the level of a Standardised MedDRA[1] Query (i.e. SMQ). The search for information to assess the significance of a signal may also 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 a 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. For a new signal of a serious or severe adverse reaction, measures should be taken at any stage in the management of a signal including detection, if the information already available supports the conclusion that there is a potential risk that needs to be prevented or minimised in a timely manner.

IX.B.3.6. Recommendation for action

Signal assessment results in a recommendation that either no further action is required at this point in time or a further action is needed. Although the recommendation for action normally takes place in a logical sequence after signal assessment based on the extent 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 introduce temporary measures. In such situations, it is still necessary to proceed with a formal assessment of the signal to confirm or not the safety issue in order to extend or lift the temporary measures.

The recommendation for action may include a request for:

- immediate measures including the possibility of suspending the marketing authorisation of the medicinal product;

[1] MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

- additional information to be provided by the marketing authorisation holder, e.g. in order to confirm if a conclusion is valid for all indications and patient groups;
- periodic review of the signal, for example through PSURs (see Module VII);
- additional investigations or risk minimisation activities;
- an update of the product information through a regulatory procedure;
- conduct of a post-authorisation safety study (see Module VIII).

Whenever actions are requested of a marketing authorisation holder, the request should specify a timeframe by which they should be completed, including provision of progress reports and interim results, proportionate to the severity and public health impact of the signal.

IX.B.3.7. Exchange of information

Information on validated signals, Emerging Safety Issues and the outcome of signal assessments should be exchanged between competent authorities and marketing authorisation holders.

Marketing authorisation holders should communicate signals that may have implications for public health and the benefit-risk profile of a product immediately to the competent authorities as an Emerging Safety Issue (see Module VI), and when appropriate this should include proposals for action.

The outcomes of signal assessment involving new or changed risks and risks that have an impact on the benefit-risk balance of the concerned active substance/medicinal products should be communicated to the public including health care professionals and patients (see IX.C.6.) as well as to the concerned 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 should be recorded and tracked systematically. Tracking systems should be used for documentation and should also include signals, for which the validation process conducted was not suggestive of a new potentially causal association, or a new aspect of a known association. All records need to be archived [IR Art 24(1)] (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 developed, 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 their tracking system, all parties should keep an audit trail of their signal management activities and of the relevant queries and their outcomes, including how signals have been detected, validated, confirmed and assessed [IR Art 24(2)].

Documentation may be requested from the marketing authorisation holders demonstrating compliance with these provisions and reviewed before and after marketing authorisation.

Staff should be specifically trained in signal management activities in accordance with their roles and responsibilities. The training system and location of the training records should be documented, and curricula vitae and job descriptions should 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 marketing authorisation holders, the Agency and national competent authorities should continuously monitor the data available in the EudraVigilance database to determine whether there are new risks or whether risks have changed and whether those risks have an impact on the benefit-risk balance. A recognised signal detection methodology should be applied and detected signals should be validated, as appropriate.

The Agency and national competent authorities shall cooperate in the monitoring of the data available in the EudraVigilance database [IR Art 18(1)].

Regarding medicinal products authorised in accordance with Regulation (EC) No 726/2004 (centrally authorised products (CAPs)) the Agency shall be assisted in the monitoring of data in EudraVigilance by the rapporteur appointed by the PRAC in accordance with Article 62(1) of that Regulation [IR Art 22(5)].

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 on behalf of the other Member States. The lead Member State may be supported by a co-leader, which shall assist the lead Member State in the fulfilment of its tasks. Any such appointment shall be reviewed at least every four years [IR Art 22(1)]. 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 a rapporteur for the assessment of periodic safety update reports in accordance with Article 107(e) of that Directive [IR Art 22(2)].

All Member States shall remain responsible for monitoring the data in the EudraVigilance database in accordance with Article 107h(1)(c) and Article 107h(3) of Directive 2001/83/EC [IR Art 22(4)].

The national competent authorities and the Agency shall validate and confirm any signal that has been detected by them in the course of their continuous monitoring of the data in EudraVigilance database [IR Art 21(4)].

For medicinal products or active substances where a rapporteur has been appointed by the PRAC, this rapporteur should confirm validated signals. For medicinal products or active substances where a lead Member State has been appointed, this lead Member State should confirm validated signals.

Confirmation by the PRAC rapporteur or the lead Member State means communication through the European Pharmacovigilance Issues Tracking Tool (EPITT) (see IX.C.5.) that the signal is valid. A justification should be provided when the signal is not confirmed. All confirmed signals shall be transmitted to the PRAC. For such medicinal products or active substances for which a lead Member State has been appointed, the lead Member State should validate and confirm as a single step the signals it has detected. For such medicinal products or active substances where a lead Member State has not been appointed, the national competent authority should validate and confirm as a single step the signals it has detected.

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

The Agency:

- shall make public on the European medicines web-portal 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 [IR Art 22(3)];
- 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 [IR Art 19(2)];
- shall support the monitoring of the data in the EudraVigilance database by providing national competent authorities with access to:
  - data outputs and statistical reports allowing a review 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 [IR Art 23];
- shall ensure appropriate support for the monitoring of the data in EudraVigilance by marketing authorisation holders [IR Art 23];
- should prepare a technical document establishing common requirements for signal detection and describing EudraVigilance data outputs and statistical reports;
- shall administer the European Pharmacovigilance Issues Tracking Tool (EPITT) for validated signals that require further assessment [IR Art 21(5)];
- shall take the lead for EudraVigilance data monitoring, signal detection and signal validation for CAPs and for active substances contained in several medicinal products, where at least one marketing authorisation has been granted in accordance with Regulation (EC) 726/2004;
- shall enter validated signals it has detected into EPITT;
- should validate (including, if appropriate, in the EudraVigilance database) and enter into EPITT any other signal communicated by a third party (e.g. regulatory authority from outside the EU), involving a CAP or an active substance for which the EudraVigilance data monitoring is performed by the Agency;
- shall confirm in collaboration with the Member States as soon as possible and no later than 30 days from its receipt any validated signal communicated by marketing authorisation holders involving a CAP 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, special attention shall be paid to any follow-up information which may allow for the signal's confirmation [IR Art 21(3)], see IX.B.3.3;

- shall transmit confirmed signals to the PRAC for initial analysis and prioritisation in accordance with Article 28a(2) of Regulation (EC) No 726/2004 [IR Art 21(5)];
- shall forthwith inform the concerned marketing authorisation holder(s) of the conclusions of the PRAC of the assessment of any confirmed signal [IR Art 21(6)];
- shall keep an audit trail of its signal detection activities [IR Art 24(1)].

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

The lead Member State:

- shall take the lead for EudraVigilance data monitoring, signal detection, signal validation and signal confirmation for active substances/medicinal products for which it has been appointed the lead;
- shall confirm signals that have been detected and validated by a national competent authority for these substances/medicinal products;
- shall enter into EPITT signals it has detected, validated and confirmed itself for these substances/medicinal products
- should validate (including, if appropriate, in the EudraVigilance database) and enter into EPITT any other signal communicated by a third party (e.g. regulatory authority from outside the EU) for these substances/medicinal products;
- shall confirm as soon as possible and no later than 30 days from its receipt any validated signal communicated by marketing authorisation holders for these substances/medicinal products. In this context, where the validity of the signal is not confirmed, special attention shall be paid to any follow-up information which may allow for the signal's confirmation [IR Art 21(3)], see IX.B.3.3.;
- shall keep an audit trail of their signal detection activities [IR Art 24 (1)].

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

The national competent authorities shall specifically monitor data originated in their territory [IR Art 18(4)], including data arising from sources mentioned in IX.B.1.

If a lead Member State or the Agency has been appointed for the monitoring of an active substance/medicinal product, the national competent authorities:

- should enter validated signals it has detected into EPITT for the lead Member State or the rapporteur appointed by the PRAC to confirm.

If no lead Member State or the Agency has been appointed for the monitoring of an active substance/medicinal product, the national competent authorities:

- shall monitor the data of the EudraVigilance database for substances/medicinal products authorised in their territory;
- shall validate and confirm any signal they have detected from EudraVigilance for substances/medicinal products authorised in their territory;
- shall enter validated and confirmed signal they have detected into EPITT for substances/medicinal products authorised in their territory;

– shall confirm as soon as possible and no later than 30 days from its receipt any validated signal communicated by a marketing authorisation holder for an active substance/medicinal product authorised in their territory. In this context, where the validity of the signal is not confirmed, special attention shall be paid to any follow-up information which may allow for the signal's confirmation [IR Art 21(3)], see IX.B.3.3.

The national competent authorities shall keep an audit trail of their signal detection activities [IR Art 24 (1)].

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

The Pharmacovigilance Risk Assessment Committee (PRAC):

- shall prioritise validated and confirmed signals for further assessment [REG Art 28a];
- should nominate a rapporteur for the assessment of the validated and confirmed signals with a time frame for the assessment;
- shall transmit to the CHMP or to the CMDh, as appropriate, any recommendations for action following the signal assessment;
- shall perform a regular review of the signal management methodology to be used and publish recommendations as appropriate [IR Art 20 (3)];
- should review at least every four years the lead and the co-lead Member States responsible for the monitoring of the data in EudraVigilance [IR Art 22(1)];
- 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 [IR Art 19(2)].

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

The marketing authorisation holder should continuously monitor the safety of its medicinal products and inform the authorities of any changes that might have an impact on the marketing authorisation.

The marketing authorisation holder:

- shall monitor the data in EudraVigilance to the extent of their accessibility [IR Art 18(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 18(3)];
- shall validate any signal detected from EudraVigilance and shall forthwith inform the responsible competent authority for signal detection in line with the list as published by the Agency [IR Art 21(2)]. For the validation step, the elements of information presented in IX.B.3.3. should be taken into account;
- should notify in writing as an Emerging Safety Issue to the competent authorities in Member States where the medicinal product is authorised and to the Agency via email (P-PV-emerging-safety-issue@ema.europa.eu) (see also Module VI), any safety issue arising from its signal detection

[2] EudraVigilance access policy for medicines for human use published on 23 August 2011 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/07/WC500108538.pdf

activity which could have a significant impact on the benefit-risk balance for a medicinal product and/or have implications for public health;

- should collaborate with the PRAC for the assessment of the signals by providing additional information upon request;
- should keep an audit trail of its signal detection activities.

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

National competent authorities and the Agency shall ensure the continuous monitoring of data in the EudraVigilance database with a frequency proportionate to the identified risk, the potential risk and the need for additional information [IR Art 18(3)]. 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 should contain ADRs in a structured hierarchy (e.g. MedDRA hierarchy) by 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 the 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. 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 benefit-risk balance or have implications for public health. This may include risks associated with significant 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, renal-impaired patients) while post-marketing exposure is likely to be significant;
- any product that contains active substances already authorised in the EU 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.

Confirmation of a signal arising from the EudraVigilance data monitoring activities does not necessarily imply that the product has to be more frequently monitored and a risk proportionate approach should be applied.

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)

When the Agency or national competent authority validating or confirming a signal considers urgent action is required before the next PRAC meeting it should trigger the Rapid Alert procedure (see Module XII). All other signals that have been detected, validated and confirmed by the Agency or a national competent authority should be sent to the PRAC for consideration at its next meeting. In its consideration of a signal, the PRAC should agree on a prioritisation based on the individual patient and public health impact of the potential change to the benefit-risk balance. Depending on the prioritisation, an analysis of the need for further assessment or for any immediate recommendation for action should be made, taking into account the time frame proposed by the Agency or the national competent authority that detected the signal.

When PRAC considers a signal as a high priority at a given meeting, a recommendation on the action(s) required should be made during the same meeting 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 signal assessment is needed, the PRAC should nominate a rapporteur and should define a timeframe for this assessment taking into account the prioritisation of the signal.

The rapporteur for the signal assessment should transmit to the PRAC an assessment stating whether there may be new risks, whether risks have changed or whether there is a change in the benefit-risk balance in relation to the concerned active substance or medicinal product. The assessment should also include a proposed recommendation for action(s), if appropriate. The PRAC can also conclude that no action is required at EU level at this time point.

Following review of the rapporteur's assessment report, the PRAC should make a recommendation for action(s), 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 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) 726/2004.

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

The recommendation for action 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 CHMP or CMDh may decide on any or a combination of the following actions:

- 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;
- the marketing authorisation holder should sponsor a post-authorisation study according to an agreed protocol and submit the final results of that study;

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

- 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 should be imposed in accordance with Article 22 of Regulation (EC) 1234/2008;
- 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 Titles IX and XI of Directive 2001/83/EC;
- the medicinal product should be included in the list of medicinal products that are subject to additional monitoring within the scope defined in Article 23 of Regulation (EC) 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 section IX.B. 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 should 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) 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. This information will include the conclusions of the PRAC following the assessment of signals and any recommendations.