EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Work instructions

Title: Validation of signals from the review of individual cases		
Applies to: Signal and Incident Management Service in the Inspections, Human Medicines Pharmacovigilance and Committees division		
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Lead Author	Approver	Effective Date: 29-NOV-18
Name: Gilles Touraille	Name: Peter Arlett	Review Date: 29-NOV-21
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1. Changes since last revision

Update, in line with Revision 1 of GVP Module IX, of the instructions concerning signals validation activities for Centrally Authorised medicinal Products (CAPs) and Nationally Authorised medicinal Products (NAPs) which contain the same active substance of the concerned CAPs.

2. Records

The Signal Validation Reports (SVRs) are stored in electronic format in the internal H-SD mailbox located under “Public Folders/All Public Folders/Chrono In/EMAILS/H-SD”.

All the evaluated signals are listed in the Signal Detection Tracking Table. This table is named “SDMB-IM_RM 2.xls” and is located in DREAM in “Cabinets\03. Pharmacovigilance\PhV – Human\3.3 Signal detection activities\01 Signal detection tracking tools\IM RM CAP list”.

3. Instructions

3.1. Concerned signals

This WIN refers to the SOP/H/3065 – Signal management.

The objective of this WIN is to provide recommendations and instructions regarding the evaluation and validation of signals detected and opened from:

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

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- The review of the EudraVigilance electronic Reaction Monitoring Report (eRMR)[1],
- Other data sources such as communications from Regulatory Authorities, or publications in scientific and medical literature.

When triggered from the review of the eRMR, signals are usually opened at the MedDRA Preferred Term (PT) level by the Signal Management Lead (SML). When prompted from other data sources, the SML should attempt to identify the MedDRA PT that corresponds best to the safety concern. In some instances, for example to strengthen the signal evaluation strategy, it may be more appropriate to open a signal at a broader MedDRA hierachy level (i.e. High Level Term (HLT), High Level Group Term (HLGT), System organ class (SOC), or Standardised MedDRA query (SMQ)) or by using a combination of MedDRA terms and/or non-MedDRA terms. In those situations, the use of MedDRA and non-MedDRA overarching terms by the SML can be done to open a signal. The term(s) used to open the signal should be included in the subject field of the email when sending the SVR to the H-SD mailbox.

3.2. Concerned Products

In accordance with the requirements given in Article 22(5) of the Commission Implementing Regulation (EU) No 520/212, this WIN applies to all active substances contained in CAPs.

Furthermore in line with the guidance provided in Chapter IX.C.1.2. of GVP Module IX Rev.1, the signal evaluation and validation activities covered in this document are also applicable to NAPs containing the same active substances of the concerned CAPs. This is with the exception of nationally authorised vaccines and insulins, due to the inherent variability in the manufacturing processes for those products[2], for which the monitoring of the data in the Eudravigilance database will be performed at brandname level by the concerned member states (acting as signal lead). Discussion is currently ongoing as regards the management of signal evaluation and validation activities for biosimilar medicinal products[3].

It should be noted that different products (CAPs and NAPs) containing the same active subtance may have distinct safety profiles and as a result the safety information may differ in their reference documents (e.g. product information, risk management plans). This is often observed when the medicinal products have divergent indications, mechanisms of action, routes of administration, or sites of application. Examples are presented in the table hereafter:

Active Substances	CAPs formulation & indication	NAPs formulation & indication
Brimonidine	Gel for cutaneous use in treatment of facial erythema of rosacea.	Eye drops solution for treatment of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension.
Caffeine	Infusion or oral solution in primary apnoea in newborn.	Multi-ingredient formulations with paracetamol, phenylephrine, codeine, aspirin in mild to moderate pains.
Ciclosporin	Eye drops emulsion in keratitis.	Oral capsule and IV solution for prevention of graft rejection in transplant.
Glycopyrronium	Powder or solution for inhalation (single or multi-ingredients) in	IV solution in anaesthesia; Solution in iontophoresis for idiopathic hyperhidrosis.

[1] See guidance in the WIN/H/3406 Screening electronic Reaction Monitoring Reports (eRMR) for new signals, and in the User Manual of the electronic Reaction Monitoring Report (eRMR) for National Competent Authorities and EMA (EMA/746442/2017).
[2] See Chapter P.II.B.4. of GVP Product- or Population-Specific Considerations II: Biological medicinal products EMA/168402/2014 Corr*.
[3] See EMA guidance on Biosimilar medicines.

Active Substances	CAPs formulation & indication	NAPs formulation & indication
	chronic obstructive pulmonary disease; Oral solution in sialorrhoea.	

In this context, particular attention should be applied when performing signal detection, evaluation and validation activities.

Signal Management Leads should be aware of the NAPs which contain the same active substances than those included in the composition of the CAPs they are monitoring. This can be achieved by querying the Article 57 database to identify all NAPs (if any) authorised in the European Union (EU) with the same active substances of the CAPs under their supervision.

For those active substances, the signal detection activities in the eRMR should be performed in ways which enable the identification of the different types of products (CAPs and NAPs) under a SML's supervision. The filtering of the eRMR on the route of administration, the product indication, or on the product name can assist/enable the detection of the specific signals for the concerned products.

For mixed NAP/CAPs characterised by different safety profiles, the relevant national product information should be considered as reference documents to ascertain the listedness of the reactions. The choice of the appropriate national reference document is at the discretion of the SML. If available in DREAM for the active substance concerned, the Periodic Safety Update Report (PSUR) Single Assessment report may also contain information on the most recent product information.

3.3. Signal validation

In line with Article 21(1) of the Commission Implementing Regulation (EU) No 520/212, the validation of signals is based on the evaluation of the data supporting the detected signal. The objective of this assessment is to verify whether the reviewed documentation contains sufficient evidence demonstrating the potential existence of a new causal association (or of a new aspect of a known association) between the suspected medicinal product and the adverse reaction and therefore justifies further analysis of the signal. The product information, PSUR and Risk Management Plan (RMP) should be considered to verify the novelty of the association.

This evaluation is mainly founded on the review of line listings or of Individual Case Safety Report (ICSR) forms but it can be complemented by the analysis of evidences provided in the scientific and medical literature.

It should be emphasised that the review of line listings and ICSR forms aims to determine if, based on their overall evaluation, the signal is validated and needs to be communicated to the PRAC Rapporteur. This evaluation should be based on clinical judgment and may require some degree of causality assessment of the cases.

This WIN contains five chapters:

1. Reviewing line listings and Individual Case Safety Report forms
2. Signal validation
3. Signal validation report
4. Sending the report to the H-SD mailbox.
5. List of acronyms

1. Reviewing line listings and Individual Case Safety Report forms

Line listings and ICSR forms for a drug-event pair are retrieved in accordance with the guidance provided in the EudraVigilance data analysis system (EVDAS) user manual (EMA/243244/2016).

1.1. Review of line listings

Although line listings contain as well free text information (first 3000 characters) on the narrative and on the reporter's and sender's comments, their reviews presented hereafter should be understood as focusing only on the structured data.

Line listings can provide an overview of a signal in terms of cases identification, regions of origin, reports type (spontaneous or solicited), demographics, literature cases, seriousness, reporters type, suspected/co-administered medicinal products/active substances, co-reported adverse reactions, patient's medical history and concurrent conditions/comorbidities. They are helpful for the initial screening of the cases, the detection of duplicates and the filtering for the most suggestive cases that may support the subsequent steps of the signal validation.

Line listings may be used to identify in the reported cases:

- The route of administration, or the indication of the concerned medicinal product; for example to distinguish cases related to CAPs and NAPs containing the same active substance but having different safety profiles due to their specific routes of administration and mechanisms of action;
- Other co-administered medicinal products/active substances that are known to be associated with the reviewed suspected adverse reaction; for example a signal of rhabdomyolysis may be explained by the concomitant intake of statins or by the occurrence of a drug-drug interaction;
- Other co-reported adverse reactions in order to estimate whether the signal could be associated to or caused by one of these reactions; for example if convulsion is a signal detected for a vaccine administered in children, the simultaneous reporting of fever in the majority of the cases may suggest that the reports may correspond to febrile convulsions and may not represent a signal (if fever is a listed reaction for the vaccine);
- Potential diagnoses based on the combination of the reported adverse reactions;
- The indications of the suspected/co-administered medicinal products in order to verify whether these conditions could be considered as confounder or risk factor for the reviewed signal. This may be important for the evaluated concerned product when it is authorised within or outside the EU with multiple indications in different therapeutic areas or if it is used off-label;
- The patients' medical history and concurrent conditions which could be considered as risk factors or provide alternative explanations for the reviewed signal;
- Demographic information that can highlight potential risk factors in specific population age groups;
- Cases confirmed by healthcare professionals from those only notified by non-healthcare professionals;
- Cases submitted to EudraVigilance as spontaneous from those sent as solicited; for example to determine if they may have occurred in the frame of patient support programmes or other organised data collection schemes (e.g. non-interventional post-authorisation studies) and may contain non-related events instead of suspected adverse reactions[4];

[4] In line with GVP VI and ICH-E2D for solicited cases, only those where the causal role of the suspected medicinal product is considered possibly related by the reporter or MAH/sponsor should be submitted to EudraVigilance. This is in contrast to

- Cases originating from published scientific and medical literature;
- Cases with a compatible temporal relationship between the start of the concerned medicinal product and the occurrence of the adverse reaction;
- Cases showing evidence of recovery of the adverse reaction after withdrawal of the concerned medicinal product (positive dechallenge) and eventually recurrence of the adverse reaction after the product reintroduction (positive rechallenge) if applicable.
- The time period of reporting of the cases and their regions of origin;
- Duplicate cases;
- Cases containing very limited information that does not allow for further assessment.

Signal Management Leads should exercise caution when making decisions based only on the review of the structured data in line listings. In some occasions, the review of these data may be sufficient to refute and close a signal when clear elements can be identified which provide alternative explanations; in other circumstances it may allow to focus the detailed review of all structured and free text data elements on a subset of selected individual cases of interest, for examples:

- Those with no identified confounders or risk factors among the co-administered medications or patients' concurrent conditions/comorbidities, or medical histories;
- Those with compatible temporal relationships between the start of the concerned medicinal product and the occurrence of the adverse reaction;
- Those showing evidence of positive dechallenge and, if applicable, positive rechallenge.

1.2. Review of Individual Case Safety Report (ICSR) forms

The review of ICSR forms may be relevant for

- The confirmation of duplicate reports,
- The validation of the signal based on the evaluation of the available clinical data, the information on temporal association, the evidence on dechallenge and rechallenge and the assessment of the causal relationship between the suspected medicinal product and the adverse reaction.

The ICSR form user manual (EMA/249220/2016) should be consulted to obtain explanations on the information provided in the different sections of the form, including the differences between the cases submitted in the ICH-E2B(R2) format and those in the ICH-E2B(R3) format.

a. Identification of duplicate reports

When evaluating a signal, it is important to exclude the duplicate cases reported more than once to EudraVigilance. These reports can be identified by using information about the patient (e.g. initials, age and/or date of birth), the country of origin of the case, the reported adverse reactions (nature and date of occurrence), the suspected and co-administered medicinal products and the information contained in other fields of the form (e.g. narrative, medical history, lab values).

The reporting of duplicate ICSRs may occur for multiple reasons for examples when:

- Several reports of suspected adverse reactions referring to the same patient have been submitted to EudraVigilance by several Marketing Authorisation Holders (MAHs) and a National Competent

spontaneous cases for which the reporter's suspicion in the association between the medicinal product and the reaction is considered assumed even if it is unstated. Companies often omit these causality assessment requirements for solicited reports and may incorrectly submit to EudraVigilance cases of non-related events.

Authority (NCA).This situation may occur when the patient was exposed to several suspected medicinal products with different MAHs and the case was notified by one or several reporters to the NCA of the country where the suspected adverse reaction occurred and to the MAHs of the suspected products; all of them having the obligation to submit the case to EudraVigilance. Each duplicate report should be checked for additional information and possible divergent causality assessments.

- The case was described in the scientific and medical literature and it concerns a generic active substance or multiple medicinal products for which several MAHs have obligation to submit the case to EudraVigilance. This would happen mainly for active substances and literatures which are not monitored by EMA as part of the Medical Literature Monitoring (MLM) services. Each duplicate report should be checked, since additional follow-up information on the case may have been obtained by one of the MAHs directly with the article author.

An automatic duplicate detection algorithm is in place in EudraVigilance and should limit the number of duplicate ICSRs available in the database. However, when potential duplicate ICSRs are identified in the frame of the signal detection activities, SMLs should submit their Case Reference IDs to the Data Standardisation and Analytics service via email (duplicates@ema.europa.eu) to allow for their manual management in EudraVigilance. Each cluster of reports referring to the same case should be distinguished in the notification email if it concerns multiple separate cases with duplicates.

b. Evaluation of ICSR forms

A number of information provided in the ICSR forms should be considered when evaluating the causal association between the suspected medicinal product and the adverse reaction:

i. Report:

1. Is the report appropriately documented?
2. Does the narrative include sufficient information for an evaluation?
3. Is the report originating from scientific and medical literature?
4. If the report is solicited, is a causality assessment available from the reporter or MAH/sponsor[5]?

ii. Reporter:

1. Does the information originate from a healthcare professional?
2. If this is a consumer report, was the adverse reaction confirmed by a healthcare professional?
3. Is a specific causality assessment between the adverse reaction and the suspected medicinal product emphasised by the reporter[6] with reasoning? Cases where the reporter's causality assessment is substantiated may be of particular interest in the evaluation of the signal.

iii. Suspected active substance/medicinal product:

1. Is the medicinal product name available?

[5] In line with GVP VI and ICH-E2D, only solicited cases where the causal role of the suspected medicinal product is considered possibly related should be submitted to EudraVigilance. Companies often omit this requirement and submit also cases of non-related events.
[6] For spontaneous cases, in line with GVP VI and ICH-E2D, the reporter's suspicion in the association between the medicinal product and the reaction is considered assumed. The reporter may sometime emphasise in the case the suspicion for a specific product, for example when multiple products are received by the patient.

2. Is the suspected medicinal product a CAP (or NAP) with a different safety profile than the medicinal product concerned by the signal[7]?
3. Are the dates of administration specified?
4. Is the dosage sufficiently described, e.g. doses, route of administration, duration, frequency?
5. Are the dosage and administration route in line with the marketing authorisation and adapted in accordance with the patient's age (e.g. paediatric) or concurrent medical conditions (e.g. renal, cardiac or hepatic disorder)?
6. Is there any potential evidence of overdose?
7. Is the indication specified and in line with the marketing authorisation?
8. Is there any evidence of off-label use, abuse, misuse?
9. Could the adverse reaction be linked to the reason of utilisation of the suspected medicinal product (e.g. hypoglycaemia with injectable antidiabetics by incorrect use of device)?

iv. Suspected adverse reaction:

1. Is the MedDRA term used to code the adverse reaction compatible with the available clinical descriptions?
2. Are the reported signs and symptoms compatible with the medical definition of the reported diagnosis (if any)?
3. Does the report describe how the diagnosis was made? Was it performed in line with the standard medical practices?
4. Could other cases of adverse reactions relevant to the signal be retrieved with a broadened search in EudraVigilance by filtering on higher MedDRA grouping terms (e.g. HLTs, HLGTs, SOCs, SMQs). This may need to be balanced against the risk of retrieving too many non-relevant cases.
5. Is there evidence that the reported adverse reaction started after the initiation of the suspected medicinal product?
6. Were differential diagnoses investigated? For example, for hepatitis, were viral tests performed?
7. How was the suspected adverse reaction treated? Can the corrective treatment and the adverse reaction favourable outcome contribute to confirming the diagnosis? For example, a medical event cured by antibiotics is more likely to be of infectious origin rather than drug-induced unless the suspected medicinal product induces immunosuppression.
8. Is the suspected adverse reaction the consequence of a medication error, lack of efficacy, occupational exposure, quality issue, counterfeit medicine, or interaction?

v. Patient's age and gender:

1. Is demographic information available? If so, are both patient's age and gender compatible with the suspected adverse reaction?
2. Could the age or gender of the patient be considered as risk factor?

[7] E.g. for tacrolimus, Protopic (topic formulation) and Advagraf (systemic formulation) are CAPs with different safety profiles; for cyclosporine, Ikervis (CAP ophthalmic formulation) and Neoral (NAP systemic formulation) have also different safety profiles.

vi. Temporal relationship:

1. Did the first administration of the suspected medicinal product occur before the onset of the adverse reaction or its first signs/symptoms?
2. Is the time to onset (i.e. the time interval from the first intake of the suspected medicinal product to the onset of the first signs/symptoms of the adverse reaction) compatible with the patho-physiological mechanism of occurrence of the adverse reaction? For example, if the reported adverse reaction is anaphylactic reaction, did it occur shortly after the reintroduction of the suspected medicinal product?

vii. Outcome:

1. What was the outcome of the suspected adverse reaction?
2. Was the suspected adverse reaction fatal? If the reaction is already listed in the SPC, is the fatal outcome risk also specified?
3. Was the suspected medical product discontinued or was the dose reduced in response to the development of the adverse reaction?
4. If the suspected medicinal product was stopped or the dose was reduced (dechallenge), did the adverse reaction abate/resolve (positive dechallenge) or persist (negative dechallenge) without corrective treatment?
5. Is this chronology of the recovery compatible with the medical occurrence?
6. If the suspected medicinal product was not stopped, did the adverse reaction abate/resolve or persist, with or without corrective treatment?
7. If positive dechallenge was noted with the discontinuation or dose reduction of the suspected medicinal product, did the adverse reaction worsen/recur when the product was re-administered under the same conditions (positive rechallenge)?

viii. Medical history, concurrent conditions/comorbidities:

1. Are there relevant medical histories, concurrent conditions/comorbidities in the patient that may have contributed to the development of the suspected adverse reaction and that could be considered confounders or risk factors?

ix. Co-administered medicinal products:

1. Was the patient taking other medicinal products which are known to potentially induce the suspected adverse reaction and which could be considered as confounders? Were these products considered suspect or concomitants by the reporter?
2. Were these medicinal products started before the onset of the suspected adverse reaction? Is the timing of administration of those products compatible with the development of the suspected adverse reaction?
3. Were these co-administered medicinal products stopped after the adverse reaction occurrence? Were they restarted? What was the outcome of their dechallenge/ rechallenge?
4. Can the reaction be caused by an interaction between the suspected and the co-administered medicinal products? Is the occurrence of the suspected adverse reaction compatible with this interaction? Is the risk of interaction mentioned in the product information of those products? Is there a known compatible mechanism of interaction between the suspected and co-administered medicinal products?

x. Biological and patho-physiological plausibility:

1. Is there a compatible biological or patho-physiological association between the suspected medicinal product and the adverse reaction? This information may not be generated just by analysing the information reported in the cases and SMLs may need to consult scientific and medical literature and reference documents.

1.3. Causality assessment

The temporal relationship is probably the only absolute criterion that can be considered to refute a causal association, as a medicinal product could not be assumed to have caused an adverse reaction if the product first administration took place after its occurrence. For this reason, it is important to look at the date of occurrence of the first signs or symptoms of the reported adverse reaction. For example, a pulmonary hypertension is often diagnosed several weeks or months after the occurrence of dyspnoea.

Multiple methods have been proposed for assessing in a consistent, structured and standardised manner the likelihood of a causal association between the exposure to a medicinal product and the occurrence of adverse reactions. They are largely based on the following criteria:

- The time interval between the medicinal product administration and the event occurrence,
- The medical plausibility (signs and symptoms, laboratory tests, pathological findings),
- The compatible pharmacological or pharmacokinetic mechanisms,
- The response to the withdrawal of the treatment and to its readministration,
- The existence of confounders or risk factors (concurrent conditions/comorbidities, co-medications, patients' medical histories or demographics).

The following classification from the WHO-UMC[8] causality assessment system is an example of tool that may be used by SMLs for evaluating the available information in a case in order to assess the association between the suspected medicinal product and the reported adverse reaction:

- Very likely/Certain: A clinical event occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent diseases or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
- Probable/Likely: A clinical event with a reasonable time sequence to drug administration, and which is unlikely to be attributed to concurrent diseases or other drugs or chemicals. The event follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
- Possible: A clinical event with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- Unlikely: A clinical event whose time relationship to drug administration makes a causal connection improbable, but which could be explained by an underlying disease or other drugs or chemicals.

[8] https://www.who-umc.org/

- Unrelated: A clinical event with an incompatible time relationship and which could be explained by underlying disease or other drugs or chemicals.
- Unassessable/Unclassifiable: A clinical event with insufficient or contradictory information to permit assessment and identification of the cause.

For the purpose of signal validation, cases that are evaluated by the SML at least possibly related to the suspected medicinal product should be considered in support of a valid signal (see chapter 2 hereafter); among them, cases with a probable or a very likely/certain relationship should be highlighted in the SVR and presentation.

2. Signal validation

The signal validation activity is defined in Article 19(1) of the Commission Implementing Regulation (EU) No 520/212, and corresponds to "*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 of the signal"*.

The concept of signal validation requires the evaluation of all the information available in the cases to determine whether a case series, less frequently one single case which has raised attention, can be considered a validated signal.

Once this step has been completed, the signal can either be

i. Validated and submitted to the PRAC Rapporteur for confirmation,

ii. Refuted and closed,

iii. Monitored.

The following elements should be taken into consideration (as presented in the order of prioritisation for each element) to determine whether a signal can be considered valid and subsequently sent to the PRAC Rapporteur for confirmation:

2.1. Strength of the signal

i. There is a plausible temporal association in the majority of the cases with a compatible chronology in the occurrence of the adverse reaction (including first signs or symptoms) and the administration of the suspected medicinal product.

ii. Some clinically relevant cases of positive dechallenge or even rechallenge (if applicable) with compatible time intervals have been reported.

iii. A sufficient number of the cases (without information on dechallenge or rechallenge outcome) do not present confounders or risk factors such as concurrent conditions/comorbidities, co-medications, patients' medical histories or demographics. The number of supportive cases should be considered together with
    - the cumulative patients' exposure for the suspected medicinal product (based on the data from the most recent PSUR), and
    - the disproportionality[9] of reporting for the adverse reaction (based on the value of the Reporting Odds Ratio, 95% CI lower bound (ROR-)).

[9] See guidance on disproportionality methods in 'Screening for adverse reactions in EudraVigilance' (EMA/849944/2016)

iv. The signal is detected from noteworthy findings reported in solicited or spontaneous cases or published in the scientific and medical literature.

v. A dose relationship is observed in several of the reported cases.

vi. Some consistency is observed in the reported cases regarding the pattern of symptoms and across available sources of evidence.

vii. There is a causal pharmacological, biological or pharmacokinetic link between the adverse reaction and the administration of the suspected medicinal product.

viii. The reported signs, symptoms, diagnoses and the performed tests are compatible with the medical definitions and practices.

2.2. Clinical relevance of the signal

i. The suspected adverse reaction is life-threatening, or it requires patient hospitalisation with clinical interventions (e.g. dialysis, organ transplant, blood transfusion), or there is a high proportion of reported fatalities or disabilities, which cannot be linked to the expected development of the treated disease or to the patient's comorbidities.

ii. The suspected adverse reaction occurs in vulnerable population subgroups (e.g. pregnant women, children, or elderly) or in patients with pre-existing risk factors (e.g. liver, cardiac or kidney diseases).

iii. The suspected adverse reaction develops in a context of drug interaction, occupational exposure, quality issue, counterfeit medicine, or it occurs in particular patterns of use (e.g. medication errors, off-label use, overdose, abuse, misuse).

iv. The suspected adverse reaction could impact on public health or on the public perception of the safety of the suspected medicinal product (e.g. new risk of demyelination in a vaccine).

In some situations, the clinical significance of the adverse reaction may affect the risk-benefit profile of the suspected medicinal product and as a consequence urgent actions may be required to minimise the risk. In other instances, the suspected adverse reaction may be preventable or measures could be put in place to manage the risk. The impact on the treated disease of the actions envisaged to mitigate the new risk and the availability of alternative treatments should be taken into consideration when assessing the clinical relevance of a signal.

2.3. Novelty of the signal

i. Some clinical or non-clinical similar findings were observed during the development of the suspected medicinal product. This step requires reviewing the assessment reports of the marketing authorisation application evaluation to verify whether the issue was already identified in other areas of the development.

ii. The adverse reaction has also been described in relevant scientific and medical literature in relation to the suspected medicinal product, active substance, or medicinal products of the same pharmacological class.

iii. The adverse reaction is already listed in third countries' product information for the same active substance.

iv. The adverse reaction can be linked to a safety concern already characterised in the EU product information, RMP, PSUR or other regulatory procedures for the suspected medicinal product. In

line with the Guidance for signal detection of terms related to listed terms/known risks[10], a signal could still be validated, for example to envisage further risk minimisation measures, should new cases (or literature) provide additional evidence that

- demonstrates a new seriousness criteria (e.g. fatal cases),
- confirms a potential risk in the RMP,
- further characterises a safety concern already listed in the product information, or
- overturns a recommendation on a safety concern previously approved in a PSUR.

3. Signal validation report (SVR)

For each signal evaluation, a succinct report should be submitted to the H-SD mailbox.

An action, followed by a conclusion should always be presented at the beginning of the report. Each section of the report should be clearly identified to facilitate the secretarial tasks of updating the Signal Detection Tracking table. For audit/tracking purpose the reference IDs (or the line listing) of the cases reviewed should be included in the report.

If relevant for the signal, additional comments may also be provided in the report to support the proposed action or the signal evaluation.

For closed signals, an action and a conclusion with a brief concise justification may be sufficient as SVR, together with the reference ID (or attached line listings) of the cases reviewed and if relevant the additional filters applied to the default EVDAS query to retrieve the cases.

3.1. Action

This section should only highlight the outcome of the evaluation for the detected signal. It helps the triage of the signals and the identification of those requiring discussion or presentation at a signal validation meeting.

The action proposed is either signal to close, to monitor, to discuss or to validate and it is based on the following principles:

i. Close: The information analysed does not constitute a validated signal and no further immediate action is needed. A signal should not normally be closed based only on the lack of EU evidence[11].

ii. Monitor: The suspected adverse reaction might represent a valid signal, but the supportive information is currently limited. For examples, few cases are considered related to the suspected product, or the reported symptoms are already described in the product information and the degree of severity of the reaction in the reviewed cases does not currently justify an update of the risk minimisation activities. New cases reported to EudraVigilance will need to be evaluated on a regular basis until the signal is either closed or validated. A rationale for keeping a signal under monitoring or for closing a signal under monitoring should always be provided in the conclusion.

iii. Discuss: Some of the reported cases or literature may be supportive of a signal. However the SML wishes to discuss the current evidence (including the existing product information, pharmacovigilance activities in the RMP, or PSUR recommendations) at a signal validation meeting to seek an orientation on the signal. The discussion should only provide a general overview of the signal without a presentation of the single cases. As outcome of the discussion, the signal will be

[10] EMA/446932/2016, accessible in DREAM under https://docs.eudra.org/webtop/drl/objectId/090142b28403fc6a.

[11] With exception of known geographical imbalances in the reporting of certain reactions (cf. Pinheiro et al., Pharmacoepidemiology and Drug Safety; 2016; 25: 705–712).

closed, monitored, or presented in detail at a future signal validation meeting (see the next action 'Validate' for information on the presentation).

iv. Validate: Some of the reported cases or literature are supportive of a signal; they are characterised by plausible temporal associations, few confounders or risk factors, and/or some of the cases present a positive dechallenge and eventually a positive rechallenge. The SML considers that the rapporteur needs to be informed and the signal should be presented at a signal validation meeting for detailed discussion and validation. A succinct presentation should be attached to the signal validation report and may include:

- A case definition of the adverse reaction,
- Some background information on the medicinal product/ active substance (e.g. therapeutic indications, pharmacodynamic properties, patient exposure, difference in safety profiles when the active substance is used in multiple products and this is relevant for the signal);
- Relevant information concerning the suspected medicinal product in relation to the signal (e.g. from the product information, RMP, PSURs, marketing authorisation application evaluation, or from other products of the same class if applicable),
- The level of evidence supporting the signal (e.g. based on the data from EudraVigilance, study report, literature review, meta-analysis, or third country decisions by competent authorities),
- A proposal of further evaluation,
- A summary of the supportive cases. Cases with a probable or a very likely/certain relationship should be highlighted, if applicable.
- A summary table presenting in an aggregated manner the most relevant evidence for the signal regarding the cases in EudraVigilance, with for examples information on demographic , origin country, time to onset, information on confounders (co-administered products, concurrent conditions, medical history), action on the suspected medicinal product, outcome, causality assessment, additional significant comments.

3.2. Conclusion

The conclusion should be concise and should contain the essential explanatory information justifying the proposed action for the signal. It is important that the conclusion reflects the data and the SML's justification in a synthesised way, rather than providing a summary of each individual case reviewed with their causal association or time to onset.

The conclusion will be copied directly into the Signal Detection Tracking table. In order to facilitate this task, the conclusion should be easily identifiable from any additional comments provided in the signal validation report in support of the evaluation and proposed action.

The following information should be included in the conclusion as applicable:

i. Total number of cases without duplicates. For re-opened signals the cumulative number of cases and the number of new cases reviewed for the period should be mentioned.

ii. Number of cases lacking information and number of other cases unrelated or strongly confounded with clear alternative explanations.

iii. Any relevant information supportive of the signal and of the proposed action, including as applicable:

- Number of supportive cases with relevant information on (median) time to onset, number of cases with positive dechallenge and with positive rechallenge if applicable,

- Information on any potential confounders or risk factors in supportive cases (e.g. concurrent conditions and co-administered active substances),
- Suggestive pathophysiological mechanisms (if available),
- Relevant pharmacovigilance activities in RMP, product information, or recommendations in previous PSURs.
- Relevant evidences from study reports, literature reviews, meta-analyses, EudraVigilance analyses;

The following information should normally not be provided in the conclusion unless it is considered relevant for the understanding of the proposed action:

i. Reference ID of cases;

ii. Demographic information with age and gender(unless relevant for the signal);

iii. Geographic distribution of the cases (unless relevant for the signal). A signal should not normally be closed based only on the lack of EU evidence[12];

iv. Corrective treatments (unless relevant for the signal);

v. Detail of symptoms (unless relevant for the signal);

vi. Wording from product information (unless relevant for the signal);

vii. Description of non-suggestive cases;

viii. The routinely inclusion of standard sentences, for examples stating that the assessed information derives from patient support programmes, is reported by non-healthcare professionals, or does not provide sufficient evidence to support a signal.

3.3. Additional comments

This section is optional and may be included in the report to provide detailed information relevant for the understanding of the signal evaluation, or to facilitate the reopening of the signal. The provision of additional comments may be more applicable for signals proposed to discuss or validate. Examples of information to be provided in this section may include:

i. Summaries of the relevant cases;

ii. Additional information from the product information, marketing authorisation application evaluation, or other regulatory procedures (e.g. PSUR, RMP);

iii. Additional evidences from study reports, literature reviews, meta-analyses, EudraVigilance analyses;

iv. Third country information on decisions taken by competent authorities or on product information of medicinal products containing the same active substance;

v. Information on the MedDRA terms queried in EVDAS for the identification of the reviewed cases (if multiple terms and different grouping levels have been applied in the signal evaluation);

vi. Information on additional filters applied to the default EVDAS query for the identification of the reviewed cases (e.g. specific age group, gender, route of administration, indication, seriousness, type of report, gateway date, etc.).

[12] With exception of known geographical imbalances in the reporting of certain reactions (cf. Pinheiro et al., Pharmacoepidemiology and Drug Safety; 2016; 25: 705–712).

4. Sending the report to the H-SD mailbox

The Signal Validation Report (SVR) should be sent to the H-SD mailbox by the SML.

The subject field of the email should be populated as presented hereafter; this is important in order to easily retrieve in the H-SD mailbox signals previously evaluated which are reopened, and also when it is necessary to highlight a specific medicinal product concerned by the signal (e.g. in situations where the suspected active substance is contained in multiple medicinal products with distinct safety profiles):

- If the signal concerns the suspected active substance without distinction on some specific medicinal products:

  SVR - ACTIVE SUBSTANCE NAME(S) - MedDRA term(s) used to open the signal (MedDRA hierarchy level if not PT) [or if applicable, non-MedDRA overarching term used to open the signal] – date of the signal validation meeting,

  Example: SVR - CICLOSPORIN - Hepatic viral infections (HLT) – 11 Oct 2018;

- If the signal concerns some specific products for the suspected active substance:

  SVR - PRODUCT NAME(S) (active substance name(s)) - MedDRA term(s) used to open the signal (MedDRA hierarchy level if not PT) [or if applicable, non-MedDRA overarching term used to open the signal] – date of validation meeting,

  Example: SVR - IKERVIS (ciclosporin) - Angioedema and Urticaria (HLGT) – 11 Oct 2018.

If the evaluation is a follow-up of a previously validated/monitored/closed signal, the email previously sent to the H-SD mailbox should be updated with the new information and resubmitted with the subject field amended as applicable. This is in order to create a single message containing cumulative information.

5. List of acronyms

CAP	Centrally authorised medicinal product
CI	Confidence interval
EMA	European Medicines Agency
eRMR	Electronic reaction monitoring report
EU	European Union
EVDAS	EudraVigilance data analysis system
GVP	Good pharmacovigilance practices
HLGT	High level group term
HLT	High level term
H-SD	Human signal detection
ICH	International conference for harmonisation
ICSR	Individual case safety report
ID	Identification

IM	Intensive monitoring
MAH	Marketing authorisation holder
MedDRA	Medical dictionary for regulatory activities
MLM	Medical literature monitoring
NAP	Nationally authorised medicinal product
NCA	National competent authority
PRAC	Pharmacovigilance risk assessment committee
PSUR	Periodic safety update report
PT	Preferred term
RM	Routine monitoring
RMP	Risk management plan
ROR	Reporting odds ratio
SML	Signal management lead
SMQ	Standardised MedDRA query
SOC	System organ class
SVR	Signal validation report
WHO-UMC	World Health Organisation - Uppsala Monitoring Centre