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Information Management Division

Detailed guide regarding the EudraVigilance data management activities by the European Medicines Agency

Governance	Consultation steps	Date
Pharmacovigilance Business Team	Endorsement	05 December 2019
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Revision 1 – update of section 8 and addition of annex 4

Revision 1 Governance	Consultation steps	Date
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Executive Summary

This document provides an overview of the data management and quality assurance activities performed by the European Medicines Agency (hereafter "the Agency") on information of suspected adverse reactions and medicinal products reported to and held in EudraVigilance and the XEVMPD.

Introduction

In accordance with recital 5 of the Commission Implementing Regulation (EU) 520/2012 quality systems should form an integral part of the pharmacovigilance system. The minimum requirements for the quality system for the performance of pharmacovigilance activities should ensure that marketing authorisation holders (MAHs), national competent authorities (NCAs) and the European Medicines Agency (hereinafter 'the Agency') establish an adequate and effective quality system, which provides for an effective monitoring of compliance and the accurate and proper documentation of all measures

taken. This includes the collection, collation and reporting of suspected adverse reactions. MAHs, NCAs and the Agency should also have at their disposal sufficient competent, appropriately qualified and trained staff.

Adherence to a well-defined quality system should ensure that all pharmacovigilance activities are conducted in such a way that they are likely to produce the desired results or quality objectives for the fulfilment of pharmacovigilance tasks.

To this effect, the Guideline on good pharmacovigilance practices (GVP) Module I sets out the requirements for pharmacovigilance systems and their quality systems.

Furthermore, Article 24(3) of Regulation (EC) No 726/2004, states that "*the Agency shall, in collaboration either with the marketing authorisation holder or with the Member State that submitted an individual suspected adverse reaction report to the EudraVigilance database, be responsible for operating procedures that ensure the quality and integrity of the information collected in the EudraVigilance database*."

Consistent, complete, correct and well-structured information submitted in Individual Case Safety Reports (ICSRs) is one area of the operation of a quality system and is necessary to perform pharmacovigilance monitoring and evaluation activities including signal detection. These quality assurance activities can be summarised as follows:

a. Adherence to pharmacovigilance legislation and regulatory guidance;

b. Offering of hands-on training courses and the provision of e-learning modules;

c. Pre-production testing with organisations preparing for the electronic submission of ICSRs to EudraVigilance;

d. Application of business rules in EudraVigilance to assist an automatic validation against pre-defined parameters;

e. Duplicate detection and management to address duplicated information of duplicated cases submitted by same or different sender organisations;

f. Validation of data submitted to the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) in accordance with Article 57(2) of Regulation (EC) No 726/2004;

g. Automatic and manual reclassification of reported suspect or interacting medicinal product information against the XEVMPD to allow for reliable data retrieval and analysis;

h. EudraVigilance database-level checks to assess case validity and report retransmissions;

i. Periodic review of ICSRs submitted by organisations to EudraVigilance based on data sampling;

j. Compliance monitoring based on reporting timelines set out in the pharmaceutical legislation (pharmacovigilance and clinical trials)[1];

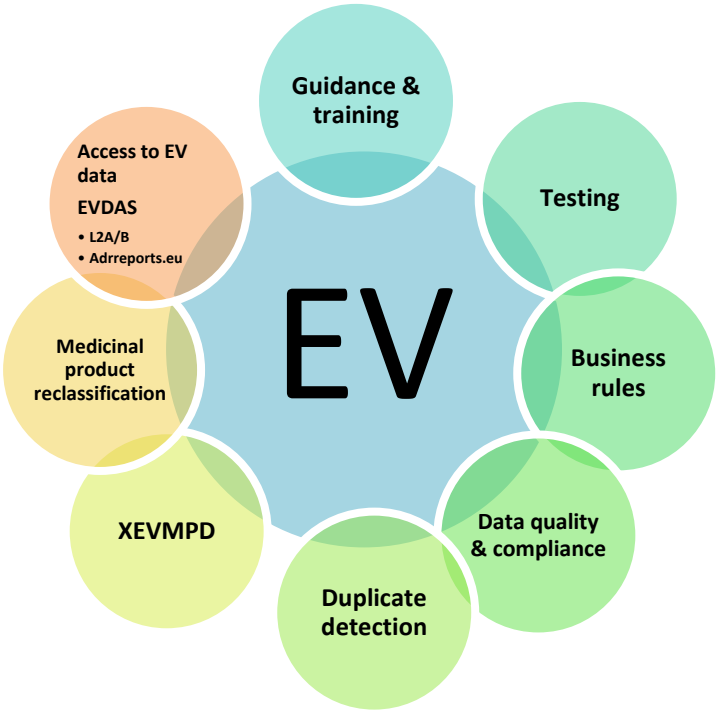
k. Quality audits;

l. Conduct of pharmacovigilance inspections by competent authorities in Member States.

These quality assurance activities are summarised in figure 1 with the points c-i further outlined in this document

[1] To be initiated by EMA based on initial pilot testing.

Figure 1. Elements of the systematic approach to improving EV data quality



The overlapping circles represent overlapping processes which significantly rely on each other

1. Pre-production testing

Organisations that have to submit ICSRs electronically to EudraVigilance in accordance with the pharmaceutical legislation, have to demonstrate that they have an ICH E2B(R2)[2] or E2B(R3)[3] compliant system. This system should comply with the defined business rules[4] and not inherently cause errors in the data. Eight test cases covering different reporting scenarios have to be processed to ensure that data elements and combinations thereof can be verified as being populated and processed correctly by a sender organisation. Details of the pre-production testing are available on the EudraVigilance: electronic reporting page of the EMA website.

Once a sender organisation (MAH, NCA, Sponsor of a clinical trial or a 3rd party service provider acting on their behalf) has demonstrated to the satisfaction of the Agency that their database is E2B(R2) or (R3) compliant, then the sender organisation can begin transmitting ICSRs to EudraVigilance.

2. EudraVigilance business rules

Demonstrating compliance with ICH E2B(R2) or (R3) standards during testing does not mean that all cases created using a particular database will be correct and thus every ICSR transmitted to EV is automatically assessed by the EudraVigilance parsers against the EudraVigilance business rules.

The business rules define a set of technical validations which are automatically performed by the EudraVigilance parsers on every ICSR received by EV. They cover population of mandatory fields, data type and field length (e.g. ICH E2B(R3) C.1.2 date of creation must be populated and must be in the format CCYYMMDDhhmmss[+/-ZZzz]) and also the logical follow-through of population with non-

[2] ICH E2B(R2) Guideline
[3] ICH E2B(R3) Guideline
[4] R2 business rules, R3 business rules

mandatory data (e.g. if an outcome of an adverse reaction is fatal, then the seriousness criterion "Results in Death" should be set to "Yes" and the Patient Death section should be populated with at least one cause of death reported).

There are two sets of business rules applicable for the submission of ICSRs in ICH E2B(R2) format and ICSRs in ICH E2B(R3) format (see footnote 4).

The outcome of the ICSR validation against the business rules is reported in the acknowledgement transmitted to the sender organisation (ACK). It is the responsibility of the sender organisation to take corrective actions where necessary and retransmit any ICSRs which do not successfully pass the business rules within the original reporting timelines for that ICSR.

3. Duplicate detection and management

To ensure that the correct number of ADRs is available for pharmacovigilance purposes, particularly statistical signal detection, the Agency detects and merges different cases[5] which refer to the same ADR (the same reaction to the same suspect drug(s) occurring in the same patient at the same time). This process is performed in accordance with GVP Module VI Appendix 7 Duplicate detection and management of ICSRs and also GVP Module VI Addendum I - Duplicate management of suspected adverse reaction reports.

The process can be summarised as follows:

1. Duplicate detection algorithms assess all the cases in the database for potential duplication.
2. The potential duplicates are assessed.
3. If duplication is confirmed, a master case is made and transmitted to EV.

The master case is then the version of the case used for pharmacovigilance, whilst the underlying duplicates remain live in the database for MAHs/NCAs/Sponsors to transmit follow-up and for audit purposes.

Master cases are identifiable by both their message type (MASTER) and the sender identifier (EVHUMANWT). The Safety report identifier (SRID) will always start XX-EMA- (where XX is an ISO 3166-1 alpha-2 country code). Users will see the following differences in WWID/SRID formats of masters for the following reasons:

- If the master was based on two cases with the same Worldwide case identification number (WWID) and was created automatically by the EV automaster creation algorithm after 22 November 2017, then the WWID will be that of the cases it was based on;
- If the master case was created by the automaster creation algorithm before 22 November 2017, then both WWID & SRID will contain "autodup";
- If a master case was created manually based on cases with different WWIDs, then the master's WWID and SRID will both start XX-EMA- and neither will contain "autodup";
- Every time a master case is updated, the SRID updates to include the date the update was performed in the format XX-EMA-DD-YYYYMMDD-textstring-HHMMSS. Therefore, follow-up master

[5] A case is defined by the Worldwide Unique Case Identifier (WWID) and the message sender identifier (at HQ level). So, if two different affiliates of the same organisation send ICSRs with the same WWID, the second transmission is regarded as a follow-up to the first and there is only one case.

may contain a WWID in one format and the SRID in another format. This is done so that the sender of follow-up to an underlying duplicate can see if their follow-up has been included in the updated master.

Anyone accessing a master case can see which cases are the underlying duplicates by reviewing the "Other case identifiers" section of the master case (ICH E2B(R2) A.1.11, ICH E2B(R3) C.1.9.1), which will contain the WWID &, if different, SRID of the underlying duplicates.

If a stakeholder suspects that two or more cases found in EV are duplicates, then these can be reported to the Agency either via the Service Desk or by email to duplicates@ema.europa.eu.

4. Validation of data submitted to the XEVMPD

Article 57(1) & (1)(l) of Regulation (EC) No 726/2004 states "*The Agency shall provide the Member States and the institutions of the Community with the best possible scientific advice on any question relating to the evaluation of the quality, safety and efficacy of medicinal products for human or veterinary use which is referred to it in accordance with the provisions of Community legislation relating to medicinal products.*

To this end, the Agency, acting particularly through its committees, shall undertake the following tasks: …

(l) creating a database on medicinal products, to be accessible to the general public, and ensuring that it is updated, and managed independently of pharmaceutical companies; the database shall facilitate the search for information already authorised for package leaflets; it shall include a section on medicinal products authorised for the treatment of children; the information provided to the public shall be worded in an appropriate and comprehensible manner;"

Article 57(2) of Regulation (EC) No 726/2004 states "*The database provided for in paragraph 1(l) shall include the summaries of product characteristics, the patient or user package leaflet and the information shown on the labelling. The database shall be developed in stages, priority being given to medicinal products authorised under this Regulation and those authorised under Chapter 4 of Title III of Directive 2001/83/EC and of Directive 2001/82/EC respectively. The database shall subsequently be extended to include any medicinal product placed on the market within the Community. For the purposes of the database, the Agency shall set up and maintain a list of all medicinal products for human use authorised in the Union. To this effect the following measures shall be taken:*

(a) the Agency shall, by 2 July 2011 at the latest, make public a format for the electronic submission of information on medicinal products for human use;

(b) marketing authorisation holders shall, by 2 July 2012 at the latest, electronically submit to the Agency information on all medicinal products for human use authorised in the Union, using the format referred to in point (a);

(c) from the date set out in point (b), marketing authorisation holders shall inform the Agency of any new or varied marketing authorisations granted in the Union, using the format referred to in point (a)"

In accordance with Article 57(2)(b) & (c), MAHs report information on the medicinal products for which they hold marketing authorisations to the Extended EV Medicinal Product Dictionary (XEVMPD) in the form of Product Report Messages (PRMs) and update this information periodically whenever there are any new or varied MAs. In accordance with Article 57(1)(l), the information reported to the XEVMPD by the MAHs is validated and managed by the Agency independently of the MAHs.

The validation is performed by comparing the structured data entered into the XEVMPD against the mandatory attached Summary of Product Characteristics (SmPC), which is the source document for this purpose. The Agency makes any necessary changes to the product report and then submits a new validated version of the PRM to the XEVMPD. The original data submitted by the MAH remains in the database for audit purposes and for determining access to data from EVWEB for MAHs to the extent necessary for them to comply with their pharmacovigilance obligations in accordance with Article 24(2); whereas the validated version is used by the Agency for pharmacovigilance purposes and for providing information to NCAs, the Commission & the general public in accordance with Article 57(1). MAHs are encouraged to use the validated version as the basis for subsequent versions of that product information.

Each PRM receives an ACK when it has been transmitted, detailing whether or not the message was in accordance with the XEVMPD business rules. Validation then triggers a second ACK which is transmitted to the MAH, detailing the changes made by the Agency.

Every product submitted to the XEVMPD has at least one validated version and the Agency will always continue to validate 100% of products at least once. Follow-up versions containing variation information were initially all validated too; however as MAHs gain greater experience using the system and reporting to the XEVMPD, data quality is increasing and so follow-up versions are now validated using a risk-based approach, targeting the products of MAHs whose information required the greatest number of changes and whose follow-ups have continued to require correction.

5. Reclassification against the XEVMPD of medicinal product information reported in ICSRs

One of the four mandatory criteria for a case to be valid is the presence of at least one suspect or interacting drug. These drugs, along with any concomitant drugs, have to be described using either the proprietary medicinal product name (ICH E2B(R2): B.4.k.2.1, ICH E2B(R3): G.k.2.2) or the active substance name (ICH E2B(R2): B.4.k.2.2, ICH E2B(R3): G.k.2.3.r.1). In the absence of a mandatory global medicinal product dictionary, these fields are free-text. In order to provide usable pharmacovigilance data and to make data available to MAHs and the public, this free-text data needs to be first normalised and reclassified against the data from the XEVMPD and then subsequently grouped by active substance.

The reclassification is initially performed automatically. The EMA's reclassification algorithm attempts to match the reported drug/substance data for every drug, substance, past drug & parent past drug reported in each ICSR against the product index[6]. This is performed overnight on all ICSRs received from 18.00 CET the previous day up to 18.00 CET that day. Over 99% of all reported drug/substance terms are successfully automatically reclassified.

If a product or substance name cannot be automatically reclassified, then it is sent for manual reclassification. The manual reclassification team work on the data from 2 days before to ensure that it will have first gone through the automatic reclassification algorithm. This means that any ICSR reported on a Monday with a term which fails automatic classification will be manually reclassified on the Wednesday. Each reclassification action triggers the flag to make cases available in the downloads

[6] The product index consists of all active substances, including translations, aliases and strengths, all medicinal product names and permutations thereof as reported to the XEVMPD and also all the links between misspelled terms and the substances/product names. The permutations of product names and substances for creation of the product index is described in Annex 2.

for MAHs. This is why the Agency recommends a 3-day delay in MAHs performing L2A downloads, to prevent a case being made available twice.

6. EudraVigilance database-level checks

6.1. Individual case validation

The Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products, Chapter VI.B.2 Validation of reports states "*Only valid ICSRs qualify for submission. In accordance with ICH-E2D (see GVP Annex IV), all reports of suspected adverse reactions should be validated before submitting them to the competent authorities to make sure that the minimum criteria are included in the reports.*

Four minimum criteria are required for ICSRs validation: …

b. one single identifiable patient characterised by at least one of the following qualifying descriptors: initials, medical record number (from general practitioner, specialist, hospital, or investigation), date of birth, age, age group, gestation period, or gender.

In line with ICH-E2D, the term 'identifiable' refers to the possibility of verification of the existence of a patient based on the available information.

The information should be as complete as possible in accordance with local data protection laws.

An ICSR should not be considered valid for submission unless information is available for at least one of the patient qualifying descriptors. Furthermore, as specified in ICH-E2D, in the absence of a qualifying descriptor, a notification referring to a definite number of patients should not be regarded valid until an individual patient can be characterised by one of the aforementioned qualifying descriptors for creating a valid ICSR. …

d. One or more suspected adverse reaction. … the report is not valid if only an outcome (or consequence) is notified "and (i) "*no further information about the clinical circumstances is provided to consider it as a suspected adverse reaction ... For instance a marketing authorisation holder is made aware that a patient was hospitalised or died, without any further information*. *In this particular situation, medical judgement should always be applied in deciding whether the notified information is an adverse reaction or an event. For example, a report of sudden death would usually need to be considered as a case of suspected adverse reaction and the valid ICSR should be submitted.*"

GVP Module VI, Chapter VI.B.6.1. Use of a medicinal product during pregnancy or breastfeeding states "*… cases, such as reports of induced termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data, or reports which have a normal outcome should not be submitted as ICSRs since there is no suspected adverse reaction. These reports should however be collected and discussed in the periodic safety update report.*

In certain circumstances, reports of pregnancy exposure with no suspected reactions may necessitate to be submitted as ICSRs. This may be a condition of the marketing authorisation or stipulated in the risk management plan; for example pregnancy exposure to medicinal products contraindicated in pregnancy or medicinal products with a special need for surveillance because of a high teratogenic potential (e.g. thalidomide, isotretinoin)."

GVP Module VI, Chapter VI.B.6.3. Reports of overdose, abuse, misuse, medication error or occupational exposure states "*Reports with no associated suspected adverse reaction should not be*

submitted as ICSRs. They should be recorded when becoming aware of them and considered in the periodic safety update reports as applicable."

GVP Module VI, Chapter VI.B.6.4. Lack of therapeutic efficacy states "*Reports of lack of therapeutic efficacy should be collected and recorded when notified and followed-up if incomplete. They should normally not be submitted as ICSRs if there is no associated suspected adverse reaction, but they should be discussed in periodic safety update reports as applicable. …*

In certain circumstances, reports of lack of therapeutic efficacy with no suspected adverse reactions may require to be submitted within a 15-day time frame. … Medicinal products used in critical conditions or for the treatment of life- threatening diseases, vaccines, contraceptives are examples of such cases. This applies unless the reporter has specifically stated that the outcome was due to disease progression and was not related to the medicinal product."

GVP Module VI, Chapter VI. C.6.2.2.10. Data protection laws states "*To detect, assess, understand and prevent adverse reactions and to identify, and take actions to reduce the risks of, and increase the benefits from medicinal products for the purpose of safeguarding public health, the processing of personal data concerning the patient or the primary source within the EudraVigilance database is possible while respecting EU legislation in relation to data protection (Directive 95/46/EC, and Regulation (EC) No 45/2001).*

Where in accordance with the applicable national legislation, the patient's direct identifiers cannot be transferred to the EudraVigilance database, pseudonymisation may be applied by the competent authority in the Member State and by the marketing authorisation holder, thereby replacing identifiable personal data such as name and address with pseudonyms or key codes…

Pseudonymisation or the use of the nullFlavor 'MSK' should be applied without impairing the information flow in the EudraVigilance database and the interpretation and evaluation of safety data relevant for the protection of public health; given the high-level nature of the information, data elements such as patient's age, age group and gender should in principle be kept un-redacted/visible."

Since the patient initials, reporter name and drug name fields are free-text and any current MedDRA LLT from the current or previous version is accepted, an individual case may truly lack one or more of the four criteria for a valid case report yet still pass the EudraVigilance business rules. For example, there are cases in EudraVigilance where the only patient identifiers are "UNKNOWN" in the patient initials field (ICH E2B(R2) B.1.1, ICH E2B(R3) D.1) and cases where the only reaction is "No adverse reaction". Therefore, there may be no (valid) adverse reaction, there may be no identifiable patient, there may be multiple patients or there may be no identifiable suspect or interacting drugs or the reporter may be unknown. Also, patient and/or reporter details may be excessively masked (e.g. even patient sex is removed) so that duplicate identification and signal analysis are harmed.

A number of data quality assurance queries have been developed to identify these cases which pass the business rules but are not valid according to the criteria detailed in GVP Module VI. These queries are run periodically in EudraVigilance to monitor the submission of invalid case reports. The queries are listed in Chapter 6.3 and further details on what these queries assess are provided in Annex 3.

The queries are run on all cases and the sender organisation contacted, via an email to both the QPPV/Responsible person and the functional email address, and asked to cease the inappropriate transmission, correct the errors, supply the unstructured or masked data, or nullify the invalid cases as applicable. Sender organisations are also required to amend their reporting practices to ensure that only correct data is transmitted to EudraVigilance. The results of the queries and the emails to sender

organisations are tracked by the Agency and this information is shared with NCAs upon request, including for pharmacovigilance inspections.

The Agency recognises that in some instances the cases may have been (re-)transmitted correctly in accordance with other instructions, such as a request from the PRAC or as a requirement of a risk management plan and thus sender organisations are invited to reply to the messages, informing the Agency if the data was actually correctly transmitted. These replies will be tracked and stored with the initial emails.

6.2. Retransmission of ICSRs to EudraVigilance

As a general principle, MAHs should not retransmit (to EV) ICSRs which they have downloaded from EV, unless they have since received additional information directly from the primary source.

Retransmitting ICSRs downloaded from EudraVigilance is the source of unnecessary duplicates, which have to be managed through the creation of master cases (see chapter 3). For a receiver/downloading organisation, this means that one erroneous retransmission turns 1 ICSR (the original) into 3 (the original, the retransmitted version and the master).

Therefore, the Agency has created queries to identify cases which MAHs have transmitted to EV which were already present in EV and which have the WWID of another organisation. The Agency then writes to the QPPV & functional email address of the apparently retransmitting organisation with a list of the retransmitted cases concerning one or more of the following 3 scenarios:

- retransmission of NCA cases;
- retransmission of Master cases;
- retransmission of other cases.

6.3. Invalid cases and other significant errors

Following consultation with NCAs, the Agency has developed data quality assurance queries to identify cases where the only reported adverse reaction is a MedDRA LLT linked to MedDRA PTs which is not by itself normally a valid adverse drug reaction which should be transmitted to EudraVigilance. Details of these queries are provided in Annex 3.

In addition, queries have been developed to identify the following situations:

- Unidentifiable drugs/non-drug terms used,
  - e.g. Drug name entered as "pink pill", active substance populated with "green lizard" or "antibiotics",

    If these unidentifiable/non-drug terms are the only drugs in the case, then it should be nullified, but if there are other drugs then it should be corrected;
- Patient details excessively obscured,
  - Only structured patient details provided are "PRIVACY" or similar,

    These cases should be corrected to provide the patient details in accordance with Article 28(3)(e) of Commission Implementing Regulation (EU) No 520/2012 in the structured fields of the patient section to allow for adequate duplicate detection and management and to aid investigation of signals;

- No identifiable patient,
  - Only patient details are "UNKNOWN" or similar,

    If an organisation does not have any patient identifiers, then per GVP VI.B.2 the case is invalid.

7. Periodic review of ICSRs submitted by organisations to EudraVigilance

In addition to the data quality assurance activities described above, periodic reviews of samples of ICSRs are performed by the EMA per sender organisation. The periodic review is based on the parameters for the content of an ICSR as set out in Article 28 of the Commission Implementing Regulation (EC) 520/2012.

To do this, the Agency selects a number of organisations each month (typically 10 – 20) and reviews 25 cases transmitted by each organisation within the last 3 months. The review includes spontaneous reports and reports from studies and focuses on scenarios such as ADRs described in the medical or scientific literature, parent–child reports and reports of ADRs with fatal outcome. Case narratives and other free-text information are checked against the data provided in the structured ICSR data elements. For ICSRs originating from the literature the articles and any other source documents if available, are also reviewed against the information reported. Compliance with the principles set out in the Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products[7], the latest MedDRA Term Selection Points to Consider document[8] and the R2/R3 guidelines are reviewed.

The Agency prepares a review report as a result of the review, providing details of identified errors where applicable. The errors are classified in accordance with Annex I – Classification of errors as part of the ICSR quality assurance. High impact & frequently identified errors are highlighted for special attention. In accordance with the process described in GVP Module VI Appendix 6 Data quality monitoring of ICSRs transmitted electronically, the report is sent to the EU QPPV/Responsible person of the sender organisation and the organisation is asked to reply within 15 days to confirm a corrective action plan will be put in place, provide additional training, amend coding practices and to make corrections and retransmit cases where necessary.

The Agency recognises that the sender organisation holds the original source documents and that therefore it is possible that coding, which may appear not to conform to regulatory guidance, may in fact be an accurate codification of the information provided. In such cases the sender organisation should explain why an identified error is in not an error which will be taken into account by the Agency in the review report as applicable.

8. Roles and responsibilities of different stakeholders

Article 24(3) of Regulation (EC) No. 726/2004 states "*The Agency shall, in collaboration either with the marketing authorisation holder or with the Member State that submitted an individual suspected adverse reaction report to the EudraVigilance database, be responsible for operating procedures that ensure the quality and integrity of the information collected in the EudraVigilance database.*"

[7] GVP Module VI (Rev 2) is available here
[8] MedDRA support documentation is available here

Article 107(5) of Directive 2001/83/EC states "*Marketing authorisation holders shall collaborate with the Agency and the Member States in the detection of duplicates of suspected adverse reaction reports.*"

Article 107a(3) of Directive 2001/83/EC states "*Member States shall collaborate with the Agency and the marketing authorisation holders in the detection of duplicates of suspected adverse reaction reports.*"

Article 28e of Regulation (EC) No. 726/2004 states "*The Agency and the Member States shall cooperate to continuously develop pharmacovigilance systems capable of achieving high standards of public health protection for all medicinal products, regardless of the routes of marketing authorisation, including the use of collaborative approaches, to maximise use of resources available within the Union.*"

Taking into account the legal obligations on the Agency, Member States & MAHs to collaborate to ensure the quality and integrity of the information collected in EudraVigilance, including in the detection of duplicates, and to collaborate to maximise the use of resources available within the Union, the Agency and Member States have agreed the following modes of cooperation to achieve these aims.

The Agency and Member States will share information with each other on the quality of ICSRs transmitted to EudraVigilance and retransmitted to Member States. Such information may come from spontaneous observations of errors found during signal detection, case processing or duplicate detection, the Agency's database-level checks of all sender organisations such as those described in section 6, the Agency's targeted analyses of data quality such as those described in section 7, pharmacovigilance inspections or any other source. This information will be shared routinely at periodic meetings and disseminated in writing to all NCAs.

MAHs can share findings they may have on the ICSRs they download from EudraVigilance at the regular meetings with between industry associations, the Agency and Member States such as the EudraVigilance Expert Working Group.

As stated in GVP Module VI, chapter VI.C.2.2 "For the ICSRs made accessible to a marketing authorisation holder from the EudraVigilance database in accordance with Article 24(2) of Regulation (EC) No 726/2004 and in line with the EudraVigilance Access Policy for Medicines for Human Use[9], the routine request for follow-up by the marketing authorisation holder is not foreseen. If the follow-up of an ICSR is necessary for a specific situation, a justification should be provided with the request, which should be addressed directly to the sender organisation of the ICSR."

If an MAH finds a clear discrepancy in a case, such as where a brand name of a drug and the batch number have both been provided but the batch number does not exist for that brand name; or where an MAH has downloaded two or more cases transmitted to EudraVigilance by the same NCA and the MAH suspects they may be duplicates, then they should contact the sender of the ICSR(s) in question directly using the appropriate method as described in Annex 4. Should the question necessitate the transmission of confidential information, then EudraLink should be used.

MAHs should not contact NCAs where they and the NCA have both transmitted cases which the MAH suspects to be duplicates. In that case MAHs should, as described in Annex 4, contact the EV duplicate detection service desk.

MAHs and NCAs should ensure that their staff are adequately trained as part of their overall quality system and are striving for continuous improvement, and that they inform the Agency when duplicates

[9] EMA Access to EV data webpage: https://www.ema.europa.eu/en/human-regulatory/research-development/pharmacovigilance/eudravigilance/access-eudravigilance-data

are detected and take appropriate actions in accordance with GVP Module VI Addendum I - Duplicate management of suspected adverse reaction reports when informed of suspected duplicates being transmitted by them.

On occasion, either following data quality or duplicate detection activities, the Agency or an NCA may request that a sender organisation nullifies a particular case. In that instance the organisation which made the request will verify that the nullification has been correctly performed as requested.

Annex 1 – Classification of errors as part of the ICSR quality assurance

Individual Case Safety Reports (ICSRs) transmitted to EudraVigilance can be sufficiently well-structured as to pass the business rules[10],[11] and may be valid cases; but may still contain mistakes which cannot be identified as part of the business rule validation process nor via the database-level checks outlined in chapter 6 and Annex 3. Most of the most serious errors (e.g. missing drugs, missing reactions) can only be spotted by reviewing the narrative and, if available, the literature article on which the case is based.

As outlined in Chapter 7 and described in detail in GVP Module VI, Appendix 6, the Agency performs periodic data quality reviews on a sample of ICSRs for each sender organisation. As a result of this quality review, a review report is prepared listing identified issues which are classified as follows taking into account their impact on the conduct of pharmacovigilance, with particular focus on detection and investigation of signals of disproportionate reporting:

- High impact;
- Medium impact;
- Low impact.

High impact errors are those which affect signal detection (i.e. they would affect ROR calculations or other statistical signal detection methods). Any high-impact errors identified in the summary report should be corrected as soon as possible and normally within 15 days of receipt of the report. For each high impact error identified in the summary report, senders should, where possible, review their pharmacovigilance database to see if this is a repeated problem & then correct & (re)transmit any affected cases[12].

Medium impact errors are those which affect the most common signal analyses when an assessor is drilling down into the data or may show up on the eRMR. Any medium-impact errors identified in the summary report should be corrected in the ICSRs as soon as possible and normally within 15 days.

Low impact errors are mainly administrative or typographical errors. These should be corrected with the next ICSRs transmission, if there is one.

If an error could be deemed to fall under two categories (e.g. a 'reaction' which should be medical history) then it will be counted as the most serious error (in this example it would be an unnecessary reaction & thus High impact)).

In all cases senders should review and amend their processes and internal guidance as necessary to prevent a repeat of such errors.

Table 2, below, summarises the expected actions that each sender should take in response to each class of error identified and Chapter 7, above, describes the overall process of communication and rectification.

[10] E2B(R2) business rules: Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)
[11] E2B(R3) business rules: EU Individual Case Safety Report (ICSR) Implementation Guide
[12] If the sender organisation is transmitting in E2B(R3), then any cases previously transmitted to EV should be corrected & can be transmitted as Amendment reports

Table 1. Error classification and expected actions

Classification	Expected actions
High impact	Correct the identified errors as soon as possible and retransmit an updated ICSR as soon as possible, within 15 days of receipt of the quality review report. For each high impact error identified, review the pharmacovigilance database/ SUSAR reporting system to see if this is a repeated problem & then correct & retransmit any such cases.
Medium impact	Correct the identified errors as soon as possible and retransmit an updated ICSR as soon as possible, within 15 days of receipt of the report
Low impact	Correct the ICSR in the next transmission, if there is one
All errors	Review case processing processes and internal guidance to prevent a repeat of such errors

Table 3, below, details most frequently encountered errors acknowledging that the examples provided may not be exhaustive. Throughout the table, reference is made to ICH E2B(R2) or ICH E2B(R3) sections and fields. These are referred to as "R2" or "R3" sections or fields as applicable.

Table 2. Classification of errors found in ICSRs

Classification	Error
High impact– affects signal detection	H1. Drugs not structured in the Drug section (R2: B.4, R3: G). Typically, these are referenced in the case narrative or other free-text field or may be entered as past drug therapy, despite being concomitant or suspect/interacting.
	H2. Drugs or active substances incorrectly characterised (R2: B.4.k.1, R3: G.k.1) as concomitant when they should be suspect or interacting or vice versa
	H3. Drug sections provided when they should not have been, e.g.: • A suspect drug where the start of administration is after the start of the last suspect adverse reaction (and there is no aggravation of the condition); • A drug class such as "antibiotics" entered in the drug name field (R2: B.4.k.2.1, R3: G.k.2.2) or active substance field (R2: B.4.k.2.2, R3: G.k.2.3.r.1) • A non-drug term such as "radiotherapy" entered in the drug name field or active substance field
	H4. Drugs incorrectly named to such an extent as to render them unidentifiable • Includes some form of code structured in drug name field or active substance field or blinded medication – If a code was provided in the drug name field and the substance name is mentioned in narrative but not structured, then that would also fall under this scenario
	H5. Reactions (R2: B.2, R3: E) not entered (excluding signs and symptoms of a diagnosis)
	H6. Significantly incorrect reaction MedDRA coding (R2: B.2.i.1, R3: E.i.2.1) (there is a better MedDRA LLT available that goes to different PT)
	H7. Events entered as suspect reactions when they should not have been, for example: • A 'reaction' which pre-dates the first suspect drug & should be medical history;

Classification	Error
	• A 'reaction' entered when all causality assessments state that it is not related, including that from the original reporter – This includes solicited reports with no causality provided by the reporter, and the MAH assessment is that the event is not related • The indication for the suspect drug when there has been no aggravation of the condition.
	H8. Invalid cases transmitted. Includes, but is not limited to: • No known patient; • Multiple patients in a single case (e.g. from literature); • A reaction under the MedDRA PT "No adverse event"; • The only reaction is under the MedDRA PT "Adverse reaction"; • Outcome (e.g. hospitalisation) reported as reaction; • Treatment reported as a reaction; • Narrative states that the case is not valid and should be nullified, but it has not been
	H9. Retransmission of cases downloaded from EV without significant new information obtained from primary source
	H10. Errors in Worldwide unique case safety ID (R2: A.1.10, R3: C.1.8.1) which cause duplicates
	H11. Incorrect country identification (R2: Occurrence country (A.1.2) /Primary source country (A.1.1), R3: Reporter country for the reporter for regulatory reporting purposes iteration (C.2.r.5))
	H12. Incorrect module (EVPM/EVCTM) This also includes situations where a comparator in a study (i.e. an IMP) is marked as suspect in a case transmitted to EVPM
	H13. Incorrect report type (R2: A.1.4, R3: C.1.3) either "Report from studies" when it should be "Spontaneous"/"Other"/"Not available to sender" or vice versa
	H14. Case seriousness (R2: A.1.5.1) missing or wrong (note: R2 only)
	H15. Incorrect or missing seriousness type if Fatal or Congenital Anomaly (R2: A.1.5.2, R3: E.i.3.2.a & e). For example, it is clear from the narrative that the patient died of the reaction, but the seriousness flag "Fatal" has not been set to "Yes"; or if the patient's mother took a drug while pregnant, the patient was born with polydactyly & the this was reported as the reaction, but the seriousness flag "Congenital anomaly" was not set to yes.
	H16. Incorrect receipt date (R2: A.1.7b, R3 C.1.5): which makes a late ICSR appear to have been transmitted within the appropriate expedited reporting timelines
	H17. Missing, incoherent or contradictory narrative (R2: B.5.1, R3: H.1)
	H18. Completely hidden sections (excessive PRIVACY flag usage which hides all fields in the section, including, for example, patient age and sex)
	H19. SUSAR where the sender is not the sponsor (e.g. literature SUSAR)
	H20. Blinded drugs entered in the drug name (R2: B.4.k.2.1, R3: G.k.2.2)
	M1. Incorrect or unstructured test data (R2: B3, R3: F) (excluding filler - see L7)

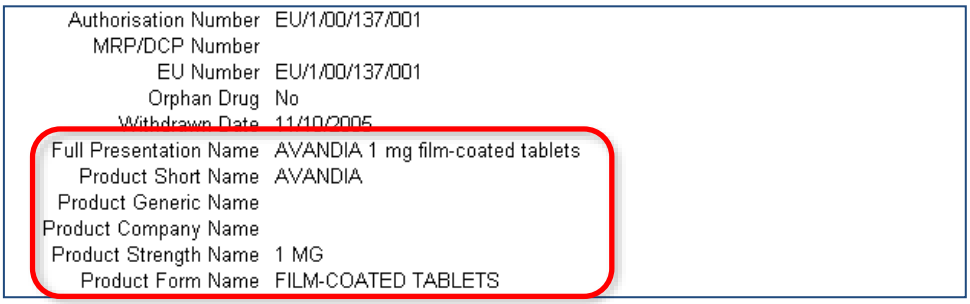
Classification	Error
Medium impact – affects signal analysis	M2. Any errors in the concomitant medication fields other than missing drug sections, which are High impact
	M3. Imperfect drug name coding (e.g. "Optiray" when it should be "Optiray 320", both of which have the same active substance
	M4. Missing iterations of a drug that has been entered at least once (e.g. Aspirin was given at 50 & 75 mg/day, but only the 75 mg/day is structured)
	M5. Excessive iterations of a drug that was correctly entered at least once but other iterations were not correct
	M6. Incorrect or missing drug strength (R3: G.k.2.3.r.3)/dosage (R2: B.4.k.5.1-5, R3: G.k.4.r.1-3)
	M7. Incorrect or missing Drug/reaction dates/intervals (Drug: R2: B.4.k.12-15, R3: G.k.4.r.4-6, Reaction: R2: B.2.i.4-7, R3: E.i.4-6)
	M8. Incorrect or missing action taken with drugs (R2: B.4.k.16, R3: G.k.8)
	M9. Incorrect or missing route of administration (R2: B.4.k.7, R3: G.4.k.r.10)
	M10. Patient demographic details (R2: B1, R3: D1-6) in narrative but unstructured
	M11. Errors in the medical history, past drug therapy, parent medical history or parent past drug therapy sections, unless the data should have been entered as reactions or in the drug section, in which case they would be high impact
	M12. Suboptimal MedDRA coding (better LLT available, but they go to the same PT)
	M13. Reaction outcome (excluding fatal – if a fatal outcome missed then High impact) (R2: B.2.i.8, R3: E.i.7)
	M14. Any errors in the Patient death section (R2: B.1.9, R3: D.9)
	M15. Incorrect or missing seriousness type (not including Fatal or congenital anomaly) if overall seriousness is correct (e.g. "Hospitalisation" selected when "Disabling" would have been correct)
	M16. Incorrect report type (Spontaneous vs other/not available to sender)
	M17. Drugs characterised as suspect when they should be interacting & vice versa
	M18. Case narrative containing conflicting and mutually contradictory information (e.g. referring to a patient as both male & female; patient reported in narrative as recovered and not recovered, drugs reported in the narrative as discontinued and ongoing), when the correct information is not clear from the structured fields
	M19. Literature reference mentioned in case narrative, but not entered in literature reference field (R2: A.2.2, R3: C.4.r.1)
	M20. Linked reports (R2: A.1.12, R3: C.1.10.r) or duplicates (R2: A.1.11, R3: C.1.9.1)) not structured or entered in the wrong section (e.g. in linked reports

Classification	Error
	when it should be in duplicates or vice versa) or narrative refers to some kind of code number and it is not possible to work out what it refers to
	M.21 Concomitant therapies flag (R3: D.7.3) field set to "True", but no information regarding concomitant therapy is provided in the narrative
	M22. Information which should be in the case narrative, but is not, is in the Reporter's comments (R2: B.5.2, R3: H.2) or Sender's comments (R2: B.5.4 R3: H4) field
Low impact – administrative	L1. Administrative case dates incorrectly entered, excluding errors that would make cases seem to have been on-time when they were late (which is High impact)
	L2. Primary source data entry errors (e.g. incorrect reporter name, city or state, etc)
	L3. Incorrect or unstructured non-demographic patient identifiers (initials, record numbers, etc.)
	L4. Drug-reaction relatedness (unless it affects case validity (e.g. for ICSRs submitted to EVCTM), in which case it is high impact)
	L5. An error in the narrative which contradicts the correctly structured information where it is clear that the structured information is correct (e.g. patient has prostate cancer, is structured as Male in the patient section, but narrative refers to "She")
	L6. Brand name (for a marketed product) correctly structured and active substance mentioned in narrative but not structured
	L7. Filler entered in an unimportant field when it should be left blank, e.g. "N/A" in test units when the test is INR
	L8. Unimportant, content-free information in narrative but not structured (e.g. Narrative reports that it was unknown if an autopsy was performed however 'unknown' is not structured in Autopsy field)
	L9. Typographical error in the literature reference (R2: A.2.2, R3: C.4.r.1)
	L10. First sender of this case (R3: C.1.8.2) is incorrectly set to Regulator/Other

Annex 2 - permutations of product names and active substance data for creation of the product index

Considering that the drug and substance name fields are free text and that these are reported to EV by over 5,000 different organisations, each with their own way of describing drug/substance information, in order to maximise the chances of automatic reclassification being successful the Agency has developed a 'product index' based on the information submitted to the XEVMPD. This requires the product and substance name data to be correctly split into each different field of the Product Report Message (PRM) so that it can be recombined as in the following examples.

Figure 2. Product Report Message for Avandia – Product name fields



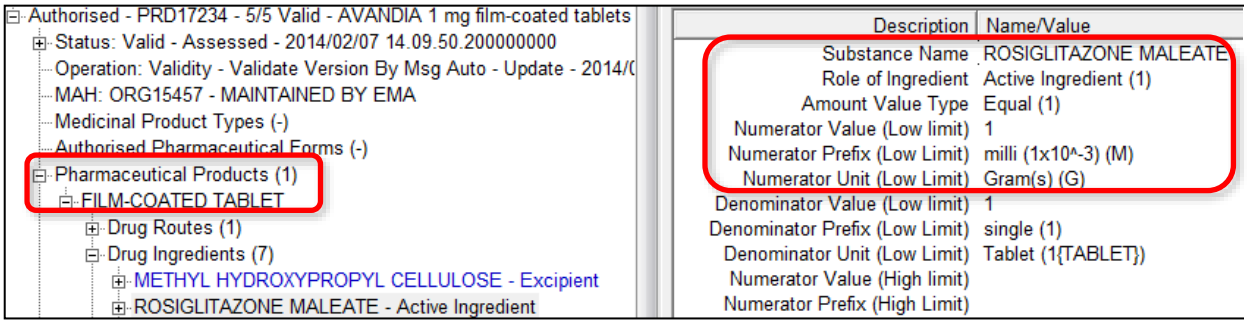
Note how the Full Presentation Name is split into 3 constituent parts: Product Short Name, Product Strength Name and Product Form Name

Figure 3. Product index showing automatic reclassification possibilities from the product name

	PRODUCTINDEXCODE	PRODUCTNAMEVARIATION
1	58736	AVANDIA
2	58743	AVANDIA 1 MG
3	58744	AVANDIA 1 mg film-coated tablets
4	81769	AVANDIA FILM-COATED TABLETS

If the full presentation name had included the MAH and/or the active substance, then there would have been further automatic reclassification possibilities

Figure 4. Product Report Message for Avandia – substance information



Note how five different fields are combined to create reclassification possibilities that match typical ways that drugs are described in ICSRs

Figure 5. Product index showing automatic reclassification possibilities from the substance information

5	3507	ROSIGLITAZONE MALEATE
6	58690	ROSIGLITAZONE MALEATE - FILM-COATED TABLET
7	58707	ROSIGLITAZONE MALEATE 1 mg
8	58708	ROSIGLITAZONE MALEATE 1 mg - FILM-COATED TABLET

These possibilities are recreated for all translations and aliases of the active substance reported to the XEVMPD

Annex 3 – Detailed description of the database-level queries for identifying invalid cases

For a case to pass the business rules and be accepted into EV it must contain at least one reaction section containing at least the current or previous MedDRA version in the field ICH E2B(R2) B.2.i.1a/ICH E2B(R3) E.i.2.1a and an 8-digit code number corresponding to a current MedDRA LLT in the field ICH E2B(R2) B.2.i.1b/ICH E2B(R3) E.i.2.1b.

Aside from version number and currency, there is no other check in the EV business rules on which adverse reaction is reported. This means that any current MedDRA term could be reported as a

reaction. Due to the way that statistical signal detection is performed[13], the reporting of non-reaction terms as adverse reactions serves to mask the degree of disproportionality of true reactions and could lead to important safety information being missed or signals being detected later than they should be, thus putting patients at risk of harm.

The Agency and NCAs have noticed many MAHs reporting terms which should not be reported as adverse reactions as per the sections of GVP Module VI quoted in chapter 6. In many cases these are the only '*reactions*' in the case and thus either the case itself should not have been reported to EudraVigilance, or the case is missing important ADR information and should be corrected (both of these errors would be classified as High impact using the classification system described in Annex I). Therefore, in order to detect all such errors and to assure the quality of data in EudraVigilance, queries have been developed which search for ICSRs which meet the following criteria:

- ICSR was transmitted after the last time the query was run;
- This is the latest version of this case transmitted by that sender;
- The ICSR was successfully loaded into EV;
- The case has not been nullified;
- The case contains **only one** reaction section;
- The reported reaction in field ICH E2B(R2) B.2.i.1b/ICH E2B(R3) E.i.2.1b is a MedDRA LLT linked to one of the preferred terms listed in Table 4.

Table 3. Searches for identifying cases transmitted to EV with invalid reactions per GVP Module VI

Query short name	Only reaction section contains LLT linked to MedDRA PT
Adverse reaction	Adverse reaction Adverse drug reaction Adverse event Adverse event following immunisation Adverse food reaction Unevaluable event
Death (excluding sudden death)	Death
Drug exposure during pregnancy (excluding known teratogens)*	Exposure during pregnancy Foetal exposure during delivery Foetal exposure during pregnancy Foetal exposure timing unspecified Maternal exposure before pregnancy Maternal exposure during breast feeding Maternal exposure during delivery Maternal exposure during pregnancy Maternal exposure timing unspecified Paternal exposure before pregnancy Paternal exposure during pregnancy Paternal exposure timing unspecified
Drug ineffective**	Drug ineffective

[13] The Agency's signal detection and management processes are described in the guideline Screening for adverse reactions in EudraVigilance

Query short name	Only reaction section contains LLT linked to MedDRA PT
	Drug ineffective for unapproved indication Drug effect incomplete Therapeutic product ineffective Therapeutic product ineffective for unapproved indication
Drug interaction	Alcohol interaction Drug interaction Food interaction Herbal interaction
Hospitalisation	Hospitalisation
No adverse reactions	No adverse event Product administered to patient of inappropriate age Product use in unapproved indication Product use issue Inappropriate schedule of product administration Incorrect dose administered

*Once the query is run and the results returned, the cases with only these terms are assessed to see if there are any suspect drugs which are reported particularly frequently. If there are, then the SmPCs and the RMPs for these drugs will be reviewed to see if the product is a known teratogen or has an obligation under the RMP to proactively report such cases.
** Drug ineffective (unless the product is used as vaccine or contraceptive or in critical conditions, or for the treatment of life- threatening diseases): All cases with vaccines and contraceptives are excluded as are cases with the seriousness criteria of 'fatal' or 'life-threatening' and, once the results are returned, the indications are reviewed to ensure the drug is not being used in a critical condition.

Annex 4 – How to contact the sender of an ICSR

There are, broadly, 6 types of potential contact points regarding information in an ICSR you have downloaded from EudraVigilance. Which type you should use depends on the sender of the ICSR and the type of question you have:

- If an ICSR comes from the Medical Literature Monitoring (MLM) service, then you should contact them via the dedicated MLM Service desk;
- If an ICSR is a master, transmitted by EMA and you have questions about the creation of the master (either you disagree that the cases are duplicates or you think there was an error in the creation of the master), or if there are two or more ICSRs transmitted by different senders that you think are duplicates of one another, then you should contact the Agency via the dedicated duplicates service desk;
- If an ICSR that you have downloaded from EudraVigilance is invalid because certain mandatory information is missing from the version which you have downloaded, then you should raise a question via the general EMA Service Desk;
- If an ICSR raises a general pharmacovigilance-related question, then you should use the "Send a question to the European Medicines Agency" interface;
- If an ICSR you have downloaded was transmitted to EudraVigilance by an MAH, and you have a specific question regarding the data therein, then, taking into account the guidance provided in GVP Module VI, chapter VI.C.2.2, referenced in section 8, you should contact the MAH directly. The public data from the Article 57 database contains information on how to contact each MAH;
- If an ICSR you have downloaded from EudraVigilance was transmitted to EudraVigilance by an NCA, and you have a specific question regarding the data therein, then, taking into account the guidance provided in GVP Module VI, chapter VI.C.2.2, referenced in section 8, you should contact the NCA directly, using the method described in Table 4.

If you have other questions regarding EudraVigilance or the data contained therein and are not sure who to contact, then more information is available in the EudraVigilance support guide.

The sender of an ICSR can be identified from the file you have downloaded from EudraVigilance. In that file, the Batch sender identifier (ICH E2B(R3) N.1.3) will have the sender identifier of the ICSR. Additionally, the safety report identifier of a case should be populated by the sender of that ICSR. If a case is a master, then the message type will be "master" and the safety report ID will start XX-EMA-DD… Otherwise Table 4, below, shows how you can identify an ICSR coming from an NCA and how to contact that NCA. If an ICSR is not a master and does not come from an NCA, then it will have been transmitted by an MAH.

Table 4. Addresses for contacting NCAs regarding ICSRs

Member State	Sender Identifier	Typical first two sections of ICSR WWIDs	Contact address for ICSRs
Austria	BASGAGES	AT-BASGAGES-	nebenwirkung@basg.gv.at
Belgium	AFIGP	BE-FAMHP-	adr@fagg-afmps.be
Bulgaria	BDA	BG-BDA-	pharmacovig@bda.bg
Croatia	ALMP	HR-HALMED-	nuspojave@halmed.hr
Cyprus	CYPPVPR	CY-PPVPR-	phv@phs.moh.gov.cy

Member State	Sender Identifier	Typical first two sections of ICSR WWIDs	Contact address for ICSRs
Czech Republic	CZSUKL	CZ-CZSUKL-	el.icsr@sukl.cz
Denmark	DKMAEUDRA	DK-DKMA-	Send message via EudraLink only to ICSRquality@dkma.dk
Estonia	SAM	EE-SAM-	pharmacovig@ravimiamet.ee
Finland	FINAMW	FI-FIMEA-	fimea.ev@fimea.fi
France	AFSSAPS	FR-AFSSAPS-	anpv@ansm.sante.fr
Germany (BfArM)	BFARM	DE-ADRED- DE-AMK- DE-BFARM- DE-CADRBFARM- DE-DCGMA- DE-EMBRYOTOX-	uaw@bfarm.de
Germany (PEI)	PEI	DE-AMK- DE-DCGMA- DE-PEI-	pharmacovigilance1@pei.de
Greece	GREOF	GR-GREOF-	ev@eof.gr
Hungary	OGYIP	HU-OGYI-	adr.box@ogyei.gov.hu
Iceland	ADALIMCA01	IS-IMA-	Aukaverkun@lyfjastofnun.is
Ireland	IMB	IE-HPRA-	medsafety@hpra.ie
Italy	MINISAL02	IT-MINISAL02-	farmacovigilanza@aifa.gov.it
Latvia	LRZBP2005	LV-SAM-	info@zva.gov.lv
Liechtenstein	KARZNEI	LI-	
Lithuania	SMCAP	LT-SMCA-	NepageidaujamaR@vvkt.lt
Luxembourg	DPM	LU-ALMPS-	pharmacovigilance@ms.etat.lu
Malta	ADM	MT-ADM-	postlicensing.medicinesauthority@gov.mt
Netherlands	CBGMEB	NL-LRB-	Data quality: _Dienstpostbusmagmb@cbg-meb.nl Follow up and duplicates: info@lareb.nl
Norway	NOMAADVRE	NO-NOMAADVRE-	adr@noma.no
Poland	URPLWEBP	PL-URPL-	ndl@urpl.gov.pl
Portugal	INFARMED	PT-INFARMED-	farmacovigilancia@infarmed.pt
Romania	NMA	RO-NMA-	farmacovigilenta@anm.ro
Slovakia	SUKLSK	SK-SUKLSK-	neziaduce.ucinky@sukl.sk
Slovenia	ARSZMP	SI-JAZMP-	h-farmakovigilanca@jazmp.si
Spain	AGEMED	ES-AEMPS-	fvicsr@aemps.es
Sweden	SEMPA	SE-MPA-	Central.Biv@lakemedelsverket.se

MAHs Should NOT routinely contact NCAs for follow-up.
If the follow-up of an ICSR is necessary for a specific situation, a justification should be provided with the request.
Always use EudraLink when transmitting confidential information.