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# EU VICH adverse event report implementation guide

Draft

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# 1. Introduction

This document aims to support stakeholders in the implementation of *Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC*[1] ('the Regulation'), by providing guidance on the technical specifications and the process of transmission of adverse event reports (AERs). It is targeted at all stakeholders responsible for submitting AERs electronically to the Union Pharmacovigilance Database.

The document is provided by the European Medicines Agency ('the Agency') to describe the rules that stakeholders must follow to ensure successful electronic communication between their own systems and EudraVigilance Veterinary (EVV), which is a constituent part of the Union Pharmacovigilance Database.

The focus of this implementation guide is therefore on technical specifications relating to the implementation of the legislative requirements and VICH standards. Detailed reporting requirements are out of scope; these are described in the *[draft] Commission Implementing Regulation [xxx] laying down rules for the application of Regulation (EU) 2019/6 of the European Parliament and of the Council as regards good pharmacovigilance practice and on the format, content and summary of the pharmacovigilance system master file for veterinary medicinal products* ('the Implementing Regulation') and in the *[draft] Guideline on good veterinary pharmacovigilance practices relating to recording, reporting and incidence calculation of suspected adverse events for veterinary medicinal products*.

## *1.1. Legal base*

The Regulation defines obligations for marketing authorisation holders (MAH) and national competent authorities (NCA) to report suspected adverse events following the administration of veterinary medicinal products, directly to the Union Pharmacovigilance Database, and that this reporting should be compliant with the relevant VICH guidelines.

Article 74 of the Regulation; as well as the Implementing Regulation, outline the requirements related to the establishment of a Union Pharmacovigilance Database as a data processing network and management system for the reporting and recording of suspected adverse events following marketing authorisation of veterinary medicinal products in the European Economic Area (EEA).

Article 73 of the Regulation lays down reporting obligations of competent authorities, the Agency and marketing authorisation holders and as regards the recording and reporting of suspected adverse events for veterinary medicinal products authorised in accordance with this Regulation.

Recital (58) of the Regulation further states that "it is necessary to take account of changes arising as a result of international harmonisation of definitions, terminology and technological developments in the field of pharmacovigilance."

Resulting from the above-mentioned legislative requirements, the existing EudraVigilance Veterinary system will be upgraded to provide the fundamental components of the Union Pharmacovigilance Database, in full compliance with the specifications of the relevant VICH[2] guidelines, specifically:

- VICH GL42 on Pharmacovigilance: data elements for submission of adverse event reports
- VICH GL35 on Pharmacovigilance: electronic standards for transfer of data
- VICH GL30 on Pharmacovigilance: controlled list of terms

[1] Regulation (EU) 2019/ of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC (europa.eu)
[2] International Cooperation on Harmonization of Technical Requirements (vichsec.org)

## 1.2. The VICH guidelines and step by step guide

The VICH Step by Step document[3] is a supplement to VICH GL35 on Pharmacovigilance: electronic standards for transfer of data and describes an approach for all partners striving towards the implementation of the VICH guidelines related to pharmacovigilance adverse event reporting. In practice, legislation and national or regional differences can lead to differing requirements in certain aspects of safety monitoring. Legislation may require information in one region that is inappropriate to share or transmit in another region. Differing priorities may require information in one region that is of no interest in another region or would not normally be collected.

The VICH standard itself contains a broad set of technical tools (elements and approaches) to capture information that may not be mandatory as part of the core, harmonised AER but may be used only by specific regions. This implementation guide clarifies the use of EU specific data elements that are not part of the mandatory VICH core AER. In addition, this guide provides the validation rules specific for the EU implementation.

This document sets out the specific requirements for the electronic exchange of AERs in the EU and is therefore an extension to the VICH guidelines and step by step document. This implementation guide should therefore not be used as a stand-alone document when implementing the VICH standard for submission of AERs but should be read in conjunction with the VICH Step by Step document and related guidelines and guidance materials published on the VICH and EMA websites.

## 1.3. Union Pharmacovigilance Database - EudraVigilance Veterinary

The Union Pharmacovigilance Database is established to operate services and processes to support pharmacovigilance in the EU. EudraVigilance Veterinary is the European Union data processing network and database management system for the exchange, processing and evaluation of AERs related to veterinary medicinal products authorised in the EEA and thus forms a fundamental component of the Union Pharmacovigilance Database.

## 1.4. Overview of AER message flow

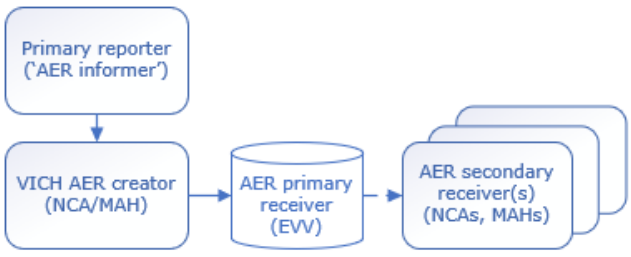


**Figure 1: VICH message flow**

The exchange of AER safety messages starts with the primary reporter of the adverse event. The primary reporter will provide information to a responsible organisation (NCA or MAH), who are usually subject to legal obligations to report the information to the Union Pharmacovigilance Database. In most situations the AER informer will not provide this information in the VICH format. The VICH AER creator is therefore responsible for creating an AER message in the correct format and submit the message to the Union Pharmacovigilance Database. The primary receiver (the database) may forward AERs to other parties; in which case the AERs might be updated with minor administrative changes but the information as captured from the original source is maintained.

[3] VICH step by step document (5 November 2014; version 1.0.2)

# 2. VICH adverse event reporting in the EU

## *2.1. Electronic data interchange*

The electronic data interchange (EDI) process is describing the electronic exchange of an AER message between a sender and a receiver. The acknowledgement message confirms the receipt and the outcome of the validation of an AER message and completes the EDI process. Technical tools such as a web-based interface have been made available to interested EDI partners to facilitate compliance with the electronic reporting requirements as defined in the legislative framework[4], removing the need to establish or adjust a national pharmacovigilance database.

This section describes the procedures concerning the EDI of AERs in the post-authorisation phase and the roles of all involved stakeholders in the EEA. It also describes the operational requirements and agreed standards for EDI and the secure exchange of adverse event and acknowledgement messages. In the EEA, the system used for exchange of AER messages is EudraVigilance Veterinary (EVV).

In addition, this section specifies the technical requirements and the process of transmission of electronic reports and messages through the EudraVigilance Veterinary gateway and describes the obligations that EDI partners must adhere to in this process to ensure successful electronic communication. The implications of electronic reporting regarding the legal reporting compliance as defined in EU legislation, the evaluation steps and the recovery procedures in the event of a communication failure are also described.

The definitions of the terms used in this document are provided in the Appendix under Electronic Data Interchange Definitions.

An overview of the process of EDI exchange is provided in the Appendix under Schema of AE report transactions using gateway and Schema of AE report transactions using EVWeb.

### 2.1.1. Registration process

Registration with EudraVigilance Veterinary is necessary to identify and manage organisation and user access to the system. This enables registered users to submit AERs on behalf of the organisation(s) they represent. The registration process ensures that adequate privacy and security measures are in place and that the principles of data integrity, accountability and availability are adhered to.

The registration[5] and management of EudraVigilance Veterinary organisations and individual users has been integrated with the EMA Account Management Portal and the Organisation Management Services (OMS).

Only registered organisations are permitted to exchange adverse event and acknowledgement messages by means of the Gateway. A list of registered organisations, which are part of the EudraVigilance Veterinary user community is maintained by the Agency and is accessible for all registered partners. The ID and description of the registered organisation is available in OMS.

### 2.1.2. Main functional components of EudraVigilance Veterinary

#### 2.1.2.1. EudraVigilance Database Management System (EVDBMS)

The EudraVigilance Database Management System (EVDBMS) consists of:

[4] More information is available here: EudraVigilance Veterinary
[5] Details and instructions for the registration process

- A fully integrated organisation and user management in the EudraVigilance community synchronised with the EudraVigilance Gateway profile management.
- A fully automated message processing mechanism, using XML-based messaging, supporting both asynchronous data interchange and interactive transactions.
- A large reference pharmacovigilance database, which is built by importing and consolidating data from multiple sources, including information on medicinal products and adverse drug reactions.
- An extensive query and tracking/tracing capability, both from a scientific and administrative business perspective.

#### 2.1.2.2. EudraVigilance ESTRI Gateway

The EudraVigilance gateway is an electronic regulatory submission environment, which follows the ICH M2 gateway recommendation on Electronic Standards for the Transmission of Regulatory Information (ESTRI).

The purpose of the EudraVigilance gateway is to operate a single, common, EEA-wide gateway for receiving regulatory submissions in a fully automated and secure way, including all aspects of privacy, authentication, integrity and non-repudiation of all transactions in pharmacovigilance.

The EudraVigilance gateway allows the pharmaceutical industry to report to a common reporting point within the EEA, from where the transactions are re-routed to the concerned regulatory authorities. It provides the NCAs with a secure reporting mechanism to the EMA. MAHs are responsible for implementing at least one of the supported ESTRI standards in order to ensure electronic communication with any EEA Regulatory Authority.

The EudraVigilance gateway supports two transmission modes:

- The EV WEB transmission mode
  The EudraVigilance Web transmission mode is an integrated component of the EudraVigilance gateway designed to support small and medium size enterprises (SMEs) or regional pharmacovigilance centres (RPCs) to generate, send and receive AERs in a secure way, to any registered organisation within the EVWEB system
- The Gateway transmission mode
  The Gateway transmission mode is available to an organization that has a pharmacovigilance database that is fully compliant with the applicable exchange standards, which permits the generation and receipt of AERs and the electronic transmission of them via a local gateway solution that meets the ICH M2 recommendations and has been successfully tested and connected with the EudraVigilance gateway.

### 2.1.3. Security

To facilitate the secure transmission of adverse event and acknowledgement messages over the internet, each party should implement and maintain security procedures and measures in order to ensure the protection of these messages against the risks of unauthorised access, disclosure, alteration, delay, destruction or loss, ensuring the verification of integrity, the non-repudiation of origin and receipt and ensuring the confidentiality of the individual message. This includes the installation and operation of applications that allow for the successful transmission and receipt of encrypted and digitally signed adverse event and acknowledgement messages via the EudraVigilance gateway or the use of service providers for this purpose. The software or service necessary to create, transmit, receive, translate, record and store adverse event and acknowledgement messages should be in full compliance with the specifications provided in this document.

The gateway uses a combination of public/private key encryption, which is also known as asymmetric encryption and symmetric key encryption. The gateway supports RC2, RC4, DES (Data Encryption Standard) and Triple DES encryption algorithms. Only X.509 certificates are accepted.

For the exchange of adverse event and acknowledgement messages the EDI partners are operating in a closed user group i.e. the parties are known to each other. Therefore, the parties agree to use the RSA cryptosystem for asymmetric encryption and the digital signatures provided by using certificates. Two types of RSA keys will be accepted:

- Keys issued by a certification authority, i.e. managed keys.
- Keys generated by the party individually, i.e. self-signed keys.

The following bullet points specify the algorithm and key lengths for symmetric and asymmetric keys acceptable to the EMA:

- Symmetric algorithm for document encryption
  Triple DES 168 bits
- Asymmetric algorithm for authentication
  RSA 1024 or 2048 bits

Dual keys are also supported.

Before encrypted and signed adverse event and acknowledgement messages can be exchanged, each party must obtain the other's public key. This will be done after each party has created its gateway profile. Each party generates a self-signed certificate or obtains one from a certification authority. Either way, the process must result in the creation of a public/private key pair for each party. The private half of this key always remains with the party, the public half is provided to the other party.

For each party to be connected to the gateway, profile information must be exchanged between the EDI partner and the Agency. The following items are required for the proper creation of the EDI partner's profile on the gateway:

- Organisation Name
- Complete Address (Street, City, State, Postcode, Country)
- Gateway Contact Name
- Gateway Contact E-Mail Address
- Gateway Contact Phone Number

The corresponding EMA-EudraVigilance information will then be supplied to the EDI partner.

There are 2 different scenarios for the exchange of this information.

- Gateway self-registration if using a product supporting such functions
- Manual exchange of the above information via e-mail with the addition of the EDI partner's public encryption certificate

A new certificate must be generated or obtained by each party when

- It becomes evident or it is suspected that a certificate has been compromised
- A certificate needs to be replaced because it expires
- The encryption key is changed at planned intervals

If the use of the above security procedures and measures result in the rejection of or in the detection of an error in an adverse event or acknowledgement message(s) transmission, the receiver should inform the sender thereof within two business days. The sender should initiate an alternative recovery procedure following the instructions of the Agency and resubmit the adverse event or acknowledgement message(s) until successful completion of this process as outlined in section 2.1.10.

### 2.1.4. Data protection

All adverse event and acknowledgement messages should be stored and treated confidentially in the same way as other medical documents. The EDI Message being an adverse event or acknowledgement message, sent or received, should, for the security of the transaction, be stored securely and without alteration.

The data transferred between EDI partners will constitute, if necessary, evidence of the adverse event or acknowledgement message, and should be stored in the format it has been originally sent or received, without any alteration of the message.

Data should be stored by the receiver in a dedicated pharmacovigilance information system in accordance with requirements detailed in the guideline on good veterinary pharmacovigilance practices on the recording, reporting and incidence calculation of suspected adverse events for veterinary medicinal products *[draft]*. It should be ensured that readability of historic EDI messages is maintained. Conformity of stored data with the initial AER, if not received electronically, should be ensured by a quality control procedure, which provides for validation against the original data.

Storage should ensure traceability (audit trail) of all data entered or modified, including dates and sources of received data, dates and destinations of transmitted data.

Each party should safeguard electronic data from tampering and unauthorised disclosure to ensure, at a minimum, the same level of protection as required for their paper equivalents.

This protection must be extended beyond the transactions to any files or databases that contain information conveyed via EudraVigilance Veterinary. Each party must ensure and provide the security to maintain the confidentiality of the information. When applicable, both parties must also maintain the confidentiality of passwords and other codes required for accessing this information.

Furthermore, any services performed by any intermediary in respect of such confidential information should likewise be subject to the same degree of confidentiality.

For NCAs and MAHs, the General Data Protection Regulation (GDPR), i.e. Regulation (EU) 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, applies accordingly. The Agency does not operate under the GDPR but is subject to the EU Data Protection Regulation (DPR), i.e. Regulation (EU) 2018/1725 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data.

### 2.1.5. Reporting

#### 2.1.5.1. EVWeb Mailbox

The EVWeb Mailbox provides an alternative solution to the use of a local gateway to support the electronic transmission of adverse event and acknowledgement messages. The EVWeb Mailbox allows registered EDI partners to exchange EDI messages with the EudraVigilance Veterinary database. The EVWeb Mailbox is only available to EDI partners which are not registered as gateway users in EudraVigilance Veterinary, i.e. organisations that do not have a local gateway established to support the EDI process in pharmacovigilance.

The message flow using the EVWeb Mailbox is outlined in the Appendix under Schema of AE report transactions using EVWeb.

In addition, EVWeb contains tracking functions that enable the EDI partner registered as EVWeb Mailbox user to view the date of the transmission of all EDI Messages that have been sent and received.

As a general principle, the responsibility for the use of EVWeb and the EVWeb Mailbox lies solely with the EDI partner that subscribes to these services.

### 2.1.5.2. EVWeb reporting (create and send AERs via EVWeb)

Interested registered parties can exchange adverse event and acknowledgement messages in a semi-automatic way using the EudraVigilance Veterinary web application (EVWeb), which allows the manual creation of adverse event and acknowledgement messages and their administration by a user via a web interface.

EVWeb can be used by any MAH or NCA in the EEA but is specifically targeted at SMEs which do not maintain a fully VICH compliant pharmacovigilance database and/or ESTRI gateway. It provides the necessary tool to allow EDI partners secure electronic reporting to the EMA.

EVWeb users must register and access to EVWeb is personal and non-transferable for each user of each organisation. It is achieved through personal login, and password access keys can be obtained following registration with EudraVigilance.

EVWeb allows registered EDI Partners to:

- Generate fully VICH compliant adverse event and acknowledgement messages and to electronically transmit these messages in secure way via the messaging gateway to the EudraVigilance Veterinary database.
- Access EVWeb for query purposes in line with the EudraVigilance access policy for medicines for veterinary use[6].

An adverse event message can be considered successfully transmitted by the sender when, after pressing the 'Send' button, the pop-up window in EVWeb displays the notice 'Message sent'. The sender can confirm the successful transmission of messages submitted via EVWeb by checking the presence of the sent adverse event message in the EVWeb Mailbox Outbox section. The sender should check the EVWeb Mailbox Inbox on a regular basis to obtain the acknowledgement message that confirms successful receipt and processing by the receiver of the adverse event message.

### 2.1.5.3. EVPOST (import and send AERs via EVPOST)

As part of EVWeb DEG/VICH files created by the EDI partner's pharmacovigilance system can, in the future, be transmitted without maintaining a local gateway connection, by allowing upload of files using the EVPOST function. *This functionality will only be made available later in 2022.*

### 2.1.5.4. Gateway reporting (create and send via gateway)

The gateway is typically most suitable for EDI partners with a large number of reports and an existing local pharmacovigilance database, providing a fully automated way to exchange adverse event and acknowledgement messages between the locally established pharmacovigilance database of and EDI partner in the EEA and the Agency.

[6] EudraVigilance access policy for medicines for veterinary use | European Medicines Agency (europa.eu)

## 2.1.6. System and testing requirements for gateway organisations

### 2.1.6.1. Gateway configuration and communication

This section describes the computer software and communication standards used by the gateway. Senders will be required to adopt hardware, software and data communication configurations to meet these standards, which are based on the recommendations of VICH.

The sender's EDI system must comply with the following standards for the EudraVigilance Veterinary gateway certification:

- direct connection via HTTP (AS2)
- Support for digitally signed MDNs
- X.509 digital certificate support
- EDIINT/AS2 compliance certification or interoperability
- Direct transmittal of XML documents

The EMA does not mandate any specific product for the EDI communication. If the sender's product adheres to the above standards and is fully interoperable with the gateway at the Agency, then the sender will receive certification from the Agency to use it.

Communications between the gateways of the sender and receiver will take place over the internet. The parties must comply with the full set of the VICH endorsed security standards.

EDI partners are responsible for the preparation of adverse event or acknowledgement messages in full compliance with the requirements detailed in this document

EDI partners, at their own expense, maintain the necessary equipment, software, services and testing to effectively and reliably create, transmit and manage valid adverse event and acknowledgement messages.

### 2.1.6.2. Testing procedure

To ensure the successful operation of EDI, each new EDI partner who wishes to transmit adverse event messages electronically via the gateway will undergo a staged test procedure, which includes the following phases:

1. **Communication test** to ensure successful gateway to gateway communication. The successful completion of the communication testing between the EudraVigilance Veterinary and the EDI Partner will be certified by the Agency so that the EDI partner can move into the subsequent stages of testing.

   The process of establishing the connection requires several steps.

   - Document transport choice
   - Exchange of profile information
   - Exchange of public keys for encryption
   - Testing the connection

   When a successful connection has been established adverse event and acknowledgement messages can be successfully transferred between the two parties. A list of registered parties will be maintained and made available by the Agency. Adverse event and acknowledgement message exchange can only take place between registered parties.

2. **Development and validation testing** of EDI partners with the EudraVigilance Veterinary test environment at the discretion of the EDI partner. Once the EDI partner has completed this test

phase, they will notify the Agency to move into the XML test phase. Step 2 of the testing is mandatory for the testing of all EDI partners wishing to exchange data with the Agency.

3. **XML test phase** with the submission of sample reports to the EudraVigilance Veterinary test environment, compliant with the requested specifications: syntax, field lengths, minimum information and data coding against VICH and other standard terminologies. The successful completion of the testing between EudraVigilance Veterinary and the EDI partner will be certified by the Agency so that the EDI partner can move into production.
4. **Production phase**. The EDI partners acknowledge the validity of adverse event or acknowledgement messages.

Any technical changes must be communicated immediately in writing between the EDI partners. Major technical changes may require the re-initiation of one or more test phases as described above. Organisations should not submit adverse event messages to the production EudraVigilance Veterinary system until they have completed the testing and have been approved for step 4 as described above. Organisations do not need to repeat the step 1 communication test if the gateway connection has previously been tested for AER submissions.

Organisations using EVPOST function as described in section 2.1.5.3. need to perform the XML test phase but do not need to perform the communication test.

Organisations using the EVWeb application as described in section 2.1.5.2. do not need to perform any system testing described in this section.

### 2.1.6.3. XML test phase

The Agency will provide a test script to be followed by the EDI partner and a set of sample files.

The EDI partner is expected to upload these sample files into the pharmacovigilance system they are testing and follow the test script to produce additional test files. Once uploaded, these test files should be transmitted to the EudraVigilance Veterinary external testing system for review by the Agency. Unexpected differences between the sample set of VICH files and the information received by the EudraVigilance Veterinary external testing system will be communicated to the EDI partner as issues that need to be addressed before allowing the EDI partner to transition into the production phase. The set of test files sent by the EDI partner should cover a range of different reporting scenarios in order to ensure the correct implementation of the data fields in accordance with VICH and the additional EU specific requirements detailed in this document.

The sample files and scripts will include the following scenarios:

- Initial and follow-up
- Human / animal reports
- Purebreed / Crossbred
- Off label use

Additional documents will be made available showing which fields in the VICH standard will be covered by each of these scenarios and provide further guidance on the testing process.

## 2.1.7. Service Level Agreements (SLAs)

The services that the Agency is providing in relation to EudraVigilance Veterinary will be supported and made available during normal business hours from 9am to 5pm CET Monday through Friday, excluding public holidays observed by the Agency. The systems will normally be available 24 hours per day and 7 days per week. However, no guarantees of availability or support are provided outside of business

hours. Planned non-availability of these services during and outside of business hours will be communicated to all registered users of the system.

### 2.1.8. System failure procedures

Organisations should ensure that adequate business continuity processes and back-up systems are put in place to deal with system failures in line with the recommendations given in the relevant guideline on pharmacovigilance processes and business continuity. The intention should be to ensure that any system failures should be resolved within a short period of time to ensure that reporting compliance is maintained.

System failures can occur on the sender's side or the receiver's side, details of what organisations should do in these situations are described in the section below.

#### 2.1.8.1. Failure of adverse event message generation

In case of any mechanical, programme, electronic or communication failure, which prevents an EDI partner from generating an adverse event message to send to another EDI partner, the issue should be investigated quickly. If the issue with the system can be resolved without affecting compliance with pharmacovigilance obligations, the organisation should work on addressing the issue, and no other actions would be required at this stage.

If the issue cannot be resolved within a timeframe allowing continued compliance with pharmacovigilance obligations, the sending organisation should contact the receiving organisations to inform them of the issue. They should also include the expected timeframe for when the issue is expected to be addressed. When the issue has been fixed, the outstanding cases should be transmitted as quickly as possible.

This scenario also applies when an adverse event message concerning (a) valid case(s) which meet(s) the minimum reporting requirements and can be physically generated and transmitted but where the adverse event message is acknowledged with a transmission acknowledgement code indicating that the adverse event message has been rejected in part or in total (transmission acknowledgement code "AE" or "AR").

### 2.1.9. XML conformance

There are two levels of conformance in the XML specifications: a well-formed and a valid message.

1. A **well-formed** message is an XML document that conforms to the structural rules of XML:

    - The first line should be the XML document declaration (see 3.1. for details)
    - The document should contain at least one element (or tag)
    - Every starting tag should have a closing tag
    - <tag/> is also permitted for tags that do not contain data
    - Tags cannot overlap.

    In order to improve the readability of the XML file, a carriage return should be inserted after each closing tag e.g. <start tag>Value</end tag> [CR][LF]. CR: carriage return, LF: line feed.

    In addition, as XML is case sensitive, all the fields and attributes names must be in correct case in order to comply with the XML schema.

2. A **valid** XML file is one which has a schema reference, and which conforms to that schema. The schema is a document that defines the valid elements (tags), attributes and the order that they

may appear in an XML document. It also defines some of the valid content of the XML elements and attributes. A valid XML file should also be well-formed.

Regarding all aspects of XML, the W3C standards[7] should be followed.

Further details on the schema reference and encoding for the XML files are provided in section 3.1.

### 2.1.10. Processing and acknowledgement of receipt of adverse event messages

The EudraVigilance Veterinary system performs a basic validation of any incoming adverse event message against the specified XML schema. The sender is responsible for including the correct adverse event message XML header as specified in 3.1. In case the sender has not included the correct schema reference in the XML header as indicated in 3.1. the return of an acknowledgement message cannot be guaranteed.

In case of the detection of a parsing error by EudraVigilance Veterinary, the following scenarios may occur:

- If during the parsing process of the adverse event message, EudraVigilance Veterinary can detect a valid sender identifier, an acknowledgement message will be created and sent to the sender, listing the detected error. The transmission acknowledgement code reported in the data element ACK.A.4 will be 'AR' i.e. no data extracted.
- If during the parsing process of the adverse event message, EudraVigilance Veterinary cannot detect a valid sender identifier, an acknowledgement message cannot be created, as the sender cannot be identified. In this case no acknowledgement message will be returned. Senders of AERs should monitor receipt of acknowledgement messages and, if none is received after 2 business days, contact the Service Desk using the EMA service desk portal.
- If the parsing process of the adverse event message is successful and EudraVigilance Veterinary cannot detect a valid receiver identifier, an acknowledgement message will be created and sent to the sender, listing the detected error. The transmission acknowledgement code reported in the data element ACK.A.4 will be 'AR' i.e. no data extracted.

If the adverse event message is valid according the adverse event message XML schema validation, EudraVigilance Veterinary will perform the upload of the adverse event message with the Inbound Load process.

The process flow is described in Figure 2: Inbound Load process. Please read the flowchart in association with this section.

[7] http://www.w3.org/

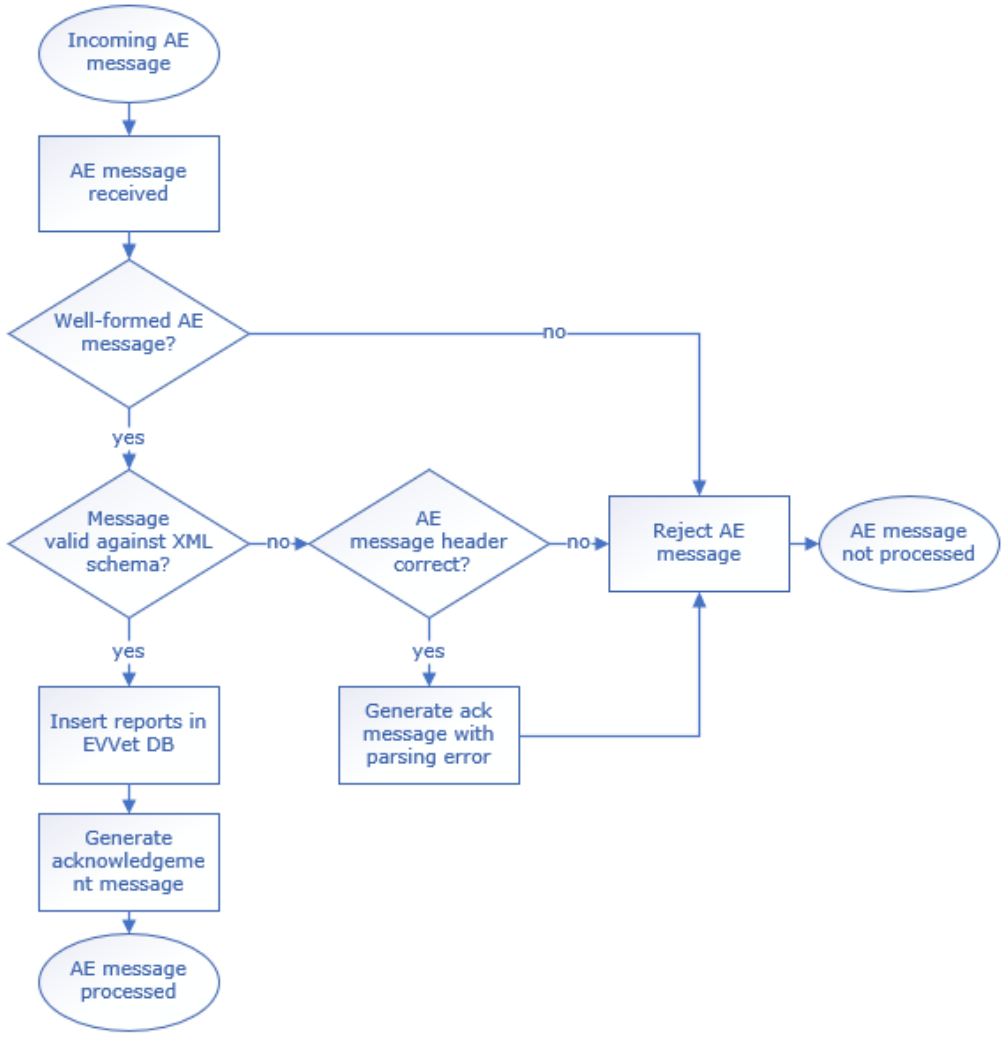


**Figure 2: Inbound Load process**

For routine electronic reporting an adverse event message including one or several AERs is sent by the report sender in internationally agreed electronic format through an electronic gateway to the report receiver (usually EudraVigilance Veterinary), which for the purpose of this guide is an EDI partner as defined in the Appendix. The electronic gateway of the report sender encrypts the message and dispatches it through the internet. The report receiver's gateway automatically returns a message disposition notification (MDN) upon receipt of the message, decrypts the message and forwards it to the report receiver's locally established pharmacovigilance system. This MDN will be subsequently referred to as the AER-MDN.

In the report receiver's locally established pharmacovigilance system the arriving adverse event message is processed following the acknowledgement of receipt procedure and a corresponding acknowledgement message (AERACK) is returned by the report receiver to the report sender. The AERACK will be transmitted from the report receiver's gateway to the report sender's gateway, which thereupon automatically returns an MDN upon receipt of the acknowledgement message. This MDN will be subsequently referred to as the AERACK-MDN.

An adverse event message is successfully recognised and validated when:

a. The Batch Sender Identifier ID (B.8.1.2) and the Batch Receiver Identifier (B.8.1.3) can be correctly identified in the adverse event message. The Sender ID and the Receiver ID must be

registered EDI partners of the gateway. In addition, the Batch Sender ID (B.8.1.2) provided must match the EDI gateway ID that was used to send the file

b. The adverse event message is a well-formed and valid XML file

c. The adverse event message is in accordance with the VICH XML schema

d. The adverse event message and the adverse event reports are in full compliance with the business rules adopted at EU level, see 4.

The EudraVigilance Veterinary system will reject adverse event messages automatically if they are not in accordance with point a), b) and c). As a result, it is the sole responsibility of the sender to ensure that the above criteria are fully met so that the adverse event message can be recognised successfully by the EudraVigilance Veterinary system.

An adverse event message is successfully transmitted, when the report sender receives an AER-MDN. The date of the AER-MDN will serve as the official receipt date of the transmission of the adverse event message by the gateway and documents the fulfilment of the reporting timelines as defined in EU legislation.

The successful transmission, though fulfilling the requirements of receipt of an AER-MDN, does not indicate acceptance of the adverse event message by the receiver's locally established pharmacovigilance system in the acknowledgement of receipt procedure.

In this procedure the receiver verifies the semantics, syntax, format and content both on the message and the report level. The acknowledgement message, as defined by VICH, is generated as further detailed in section 5. and indicates acceptance or rejection of the message. A rejection in the acknowledgement of receipt procedure resulting in an acknowledgement code "AR" or "AE" does not constitute regulatory compliance.

The sender of a message that has been rejected by the EudraVigilance Veterinary system in part or in total has the obligation to resubmit corrected versions immediately within the reporting timelines as defined in EU legislation, so that the message can be accepted in the locally established pharmacovigilance system of the receiver. In validated and tested systems and after passing a production pilot testing, this should rarely occur.

The detailed steps in the acknowledgement of receipt procedure are as follows:

Following successful receipt of the adverse event message, the report receiver is responsible for loading the AER(s) into the locally established pharmacovigilance system. The report receiver is responsible for generating an acknowledgement message, providing the validation status of each AER, which is the subject of the adverse event message of the transmission.

The acknowledgement message can reflect three different types of transmission acknowledgements at the batch message level:

**ACK code AA:** *Application Acknowledgement Accept* (message successfully processed, no further action)

**ACK code AE**: *Application Acknowledgement Error* (error detected, error response has additional detail, some AER message(s) need further action)

**ACK code AR:** *Application Acknowledgement Reject* (parsing error, no data extracted, re-send the entire transaction)

The acknowledgement message can reflect two different types of transmission acknowledgements at AER message level:

**ACK code CA:** *Commit Accept* (the AER message successfully loaded)

**ACK code CR:** *Commit Reject* (the AER message contains fatal error that prevents the AER from being loaded)

Details of warnings or errors are found in the acknowledgement details.

An AER must be acknowledged by the report receiver with the AER acknowledgement code "CA" when it is in full compliance with the VICH guidance documents. Thereupon it will be loaded into the report receiver's locally established pharmacovigilance system.

In case the validation status of one or more AER(s) within one adverse event message is assigned the AER acknowledgement code "CR", resulting in the transmission acknowledgement ACK code "AE" i.e. AER error, the report sender must retransmit, upon receipt of the acknowledgement message, immediately a corrected version of the affected AER(s) electronically (ie. not all AERs loaded into the report receiver's locally established pharmacovigilance database must be retransmitted).

If, following the receipt of the acknowledgement message, the transmission acknowledgement code is "AR" in accordance with the VICH standard, VICH AER implementation guide and EU validation rules, the entire corrected adverse event message needs to be immediately retransmitted electronically. adverse event messages with the transmission acknowledgement code "AR" are not regarded as valid for reporting compliance purposes.

The acknowledgement message is sent by the report receiver of an adverse event message to the report sender of the adverse event message. At the gateway level, an AERACK-MDN will be returned to the sender of the acknowledgement message.

The date of the AERACK-MDN will serve as the official receipt date of the transmission of the acknowledgement message by the gateway.

From a conceptual point of view, the following principles apply:

- The report receiver of an adverse event message, that requires an acknowledgement, should not act upon the content of the adverse event message until such an AERACK is sent by the report receiver and successfully received by the report sender. If an adverse event message is entirely rejected (transmission acknowledgement code "AR") by the report receiver, the report receiver of the adverse event message should not act upon the content of the adverse event message until a corrected version is received and successfully acknowledged with an acknowledgement code "AA".
- If an adverse event message contains AER errors leading to a transmission acknowledgement code "AE", the report receiver of the adverse event message should not act upon the AERs with the AER acknowledgement code "CR" of this adverse event message until a corrected version of the AER(s) is received and successfully acknowledged with an AER acknowledgement code "CA".

However, if (a) rejected AER(s) within an adverse event message contain(s) important safety information, which raise(s) public health concerns, the report receiver in liaison with the report sender may act upon this AER(s).

The same requirements outlined above for the successful recognition of an adverse event message apply to the acknowledgement message. It is the sole responsibility of the sender of the

acknowledgement message to ensure that these criteria are met and that the acknowledgement message can be recognised and routed successfully by the gateway.

In summary, two different levels of acknowledgement are available.

One acknowledgement for the transmission of messages via the gateway of the EDI partners is the message disposition notification (MDN), which is automatically sent upon the receipt of an EDI Message being either an adverse event or acknowledgement message at the level of the receiver's gateway without any content verification. This MDN is the proof to the sender that an adverse event message was received successfully by the receiver and serves as evidence for any reporting timeline compliance measures as defined in EU legislation, if the adverse event message was successfully validated and recognised in accordance with the VICH and requirements detailed in this document i.e. transmission acknowledgement code "AA" and AER acknowledgement code "CA".

The second acknowledgement is the acknowledgement message, which summarises the outcome of the adverse event message and AER validation by the report receiver.

If for technical reasons the report receiver does not return an MDN (being either an AER-MDN or an AERACK-MDN), the process described in section 2.1.8. should be followed.

## *2.2. Rerouting of AERs from EudraVigilance Veterinary to National Competent Authorities*

EudraVigilance Veterinary will automatically forward copies of the valid AERs received to National Competent Authorities that have requested to receive them.

AERs that have parsing errors and AERs that contain errors resulting in the acknowledgement code "CR" (Commit Reject) will not be forwarded to NCAs. Original cases received from an NCA will be excluded from being retransmitted back to the sending NCA.

The EudraVigilance Veterinary system will retransmit messages as received, section 2.2. describes the rules and processes for retransmission of AER messages. NCAs should return acknowledgements for rerouted AERs within 48 hours of the initial receipt. If no acknowledgement is received within 48 hours, EudraVigilance Veterinary will automatically resubmit the re-routed AERs. For resubmitted AERs NCAs should return acknowledgements within 24 hours. EudraVigilance Veterinary will make a maximum of three attempts to resubmit AERs when no acknowledgement has been returned by an NCA. After the maximum number of attempts has been reached, the NCA concerned will be contacted by the EMA in order to understand if the NCA is experiencing technical issues. It should be noted that this retry functionality will only be available later in 2022.

Concerning the rerouting of DEG messages, information is provided in the Appendix under Rerouting of DEG messages.

### 2.2.1. Rerouting rules for VICH AERs

NCAs will provide and maintain a list of ISO 3166 country codes for which they wish to receive copies of AERs that have been entered in to EudraVigilance.

The only defined VICH fields that will be changed when retransmitting AERs will be the Batch wrapper fields as shown below, non-VICH/EU data fields will not be retransmitted.

| VICH field code | VICH field description |
|---|---|
| B.8.1.1 | Batch Number |

| VICH field code | VICH field description |
|---|---|
| B.8.1.2 | Batch Sender Identifier |
| B.8.1.3 | Batch Receiver Identifier |
| B.8.1.4 | Date of Batch Transmission |

Cases submitted by NCAs to EudraVigilance Veterinary will not be retransmitted back to the sending NCA, this check will be based on the sending organisation's *Batch Sender Identifier* (B.8.1.2).

1. A MAH or NCA sends AER(s) in an adverse event message to EudraVigilance Veterinary;
2. EudraVigilance Veterinary returns an acknowledgement message (ACK) to confirm the receipt of the adverse event message to the sender.
3. EudraVigilance Veterinary forwards the AER(s) in an adverse event message to the NCAs that have requested to receive them.
4. The NCA sends an acknowledgement message (ACK) to EudraVigilance Veterinary to confirm the receipt of the adverse event message.

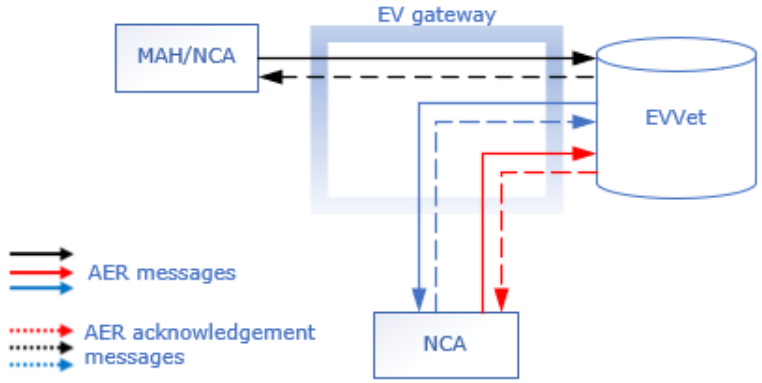


**Figure 3: Message exchange**

# 3. VICH messages and adverse event reports

## *3.1. Message header*

The XML message header contains two important references, the first is the text encoding used within the XML file and the second refers to the location of the schema file that should be used to parse the XML file to ensure that it is correctly structured.

XML files can be submitted with the text encoding formats as provided and as XML snippet shown below. The VICH Step by Step document recommends the use of UTF-8 as the preferred encoding format.

| Text encoding | XML file header |
|---|---|
| UTF-8 | <?xml version="1.0" encoding="UTF-8"?> |
| UTF-16 | <?xml version="1.0" encoding="UTF-16"?> |

The schema location for VICH AERs is the following:
http://eudravigilance.ema.europa.eu/xsd/vich/multicacheschemas/MCCI_IN200100UV01.xsd
The schema location for AER acknowledgements is the following:
http://eudravigilance.ema.europa.eu/XSD/multicacheschemas/MCCI_IN200101UV01.xsd

Below is an XML snippet of the header of a VICH AER message showing the text encoding used and the schema location.

**XML Snippet: VICH AER Header**

```
<?xml version="1.0" encoding="UTF-8"?>
<MCCI_IN200100UV01 ITSVersion="XML_1.0" xsi:schemaLocation="urn:hl7-org:v3
http://eudravigilance.ema.europa.eu/xsd/vich/multicacheschemas/MCCI_IN200100UV01.xsd
xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" xmlns="urn:hl7-org:v3">
```

### 3.1.1. Submission types

When submitting an AER message to EudraVigilance Veterinary, the values accepted in the data element "*Types of Message*" (VICH B.4.4.1) in a message batch are one of the following:

| No | Report | Description |
|---|---|---|
| 1 | Expedited Report | This is an initial report to be submitted by the MAH or NCA using the information gathered from a primary source (Primary Reporter). |
| 2 | Follow-Up Report | This is a report that could be submitted by MAH or NCA subsequent to an initial report, providing additional information or making corrections to the initial report. In all cases this report MUST reference the original Worldwide AER Identification number of the initial report. |
| 3 | Nullification Report | This type of report is submitted to nullify an initial report. In all cases this report MUST reference the original Worldwide AER Identification number of the initial report. |

### 3.1.2. EudraVigilance message receiver identifiers

The table below provides the receiver identifiers that should be used in sending AER messages for processing by the different EudraVigilance modules.

| EudraVigilance system | B.8.1.3 Batch Receiver Identifier | B.8.2.3 Message Receiver Identifier |
|---|---|---|
| EVVET external testing environment (XCOMP) | **EVVETT** | **EVVETT** |
| EVVET production environment | **EVVETPROD** | **EVVETPROD** |

## *3.2. Adverse event report*

A VICH AER message can contain one or more AERs. Although the VICH standard does not provide a maximum number of AERs that could be submitted in an AER message, organisations must limit their

systems to send no more than 100 AERs per message, as resolving issues in submissions gets more complex when more AERs are included in one file. In order for efficient processing of messages in VICH format, it is required that the XML file size should be under 20 MB. Files above this size might cause potential issues with either parsing the message before sending it or the parsing and loading performed by the receiver.

Consideration should also be made for the impact on the file size when adding attachments to the AERs being submitted. Therefore, organisations are encouraged to make sure that, if scanned images or documents are being attached, appropriate scanning resolutions are used for the document in order to minimise the file size. Text based PDFs rather than scanned image PDFs are preferred, as this will significantly reduce the file size.

The sender of the AER should make every effort to reduce the size of an attachment if it is critical that it should be submitted with the AER.

## *3.3. Attachments*

In order to provide supplemental information, the sender of an AER can attach documents to the AER message itself. Attachments are provided as in-line data transmitted using the encapsulated data type.

| **Document Type** | **Description** |
|---|---|
| Analysis | Examination and interpretation: the process of identifying an issue to be understood and addressed, modelling the issue, investigating the model results, interpreting the results, and possibly making a recommendation. The concept also refers to the examination. |
| Article | Nonfictional prose forming an independent part of a publication. |
| Certificate | A document earned by a person indicating that the person has specific knowledge, skills, or abilities in the view of a certifying body. Similarly, a document indicating that a product or process is suitable or in working order for a specific purpose. |
| Computer Tomography | Pictures of structures inside the body. In CT scanning, an X-ray machine linked to a computer is used to produce detailed pictures of organs inside the body. |
| Cytology report | The light microscopic study of normal and abnormal cells in fine needle aspirates (FNAs), body cavity fluids, and smears. |
| Echocardiogram | An image of the heart produced by ultrasonography. |
| Histopathology report | The description of cells and tissues made by a pathologist based on microscopic evidence, sometimes used to make a diagnosis of a disease. |
| Investigation report | The act or process of a systematic and thorough examination, research, study; the process of inquiring into or following up, intended to develop facts. |
| Labelling Materials | All written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce. |

| Document Type | Description |
|---|---|
| Laboratory Report | The outcome of a laboratory test. |
| Letter | A written message addressed to a person or organization. |
| Magnetic Resonance Imaging | Imaging that uses radiofrequency waves and a strong magnetic field to provide amazingly clear and detailed pictures of internal organs and tissues. The technique is valuable for the diagnosis of many pathologic conditions, including cancer, heart and vascular disease, stroke, and joint and musculoskeletal disorders inside the body. MRI scans use a large magnet connected to a computer to create pictures of areas inside the body. |
| Medical Records | A chronological written account of a patient's examination and treatment that includes the patient's medical history and complaints, the physician's physical findings, the results of diagnostic tests and procedures, and medications and therapeutic procedures |
| Multiple document types | Supplemental document is made up of multiple documents. |
| Necropsy (Autopsy) report | A post mortem examination of the body that includes an examination of the internal organs and structures after dissection to determine the cause of death and the nature of pathological changes. |
| Other | The actual value is not an element in the value domain of a variable (e.g. concept not provided by required code system). |
| Photograph | A visual representation of an object, scene, person or abstraction. |
| Product Label | Any display of a written, printed, or graphic matter upon the immediate container of any substance or device to identify something and to indicate the nature, ownership, contents and other characteristic particulars of the object. |
| Promotional Material | Promotional Material Document |
| QA Report | The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial related activities have been fulfilled. |
| Radiographs | An image produced on a radiosensitive surface by X-ray radiation that has penetrated and passed through a structure. |
| Record | Anything (e.g. a document) providing permanent evidence of or information about past events. |
| Sonogram | Computer picture of areas inside the body created when sound waves bounce off organs and other tissues. |
| Specification | A detailed description of criteria for a piece of work. |

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708 The case narrative should not be provided as file attachments but inserted in the appropriate field.

709 The table below lists the file formats that are supported in the EU along with the media type that
710 should be provided in the relevant AER field.

| File type extension | File type | Media Type (values) |
|---|---|---|
| PDF | Portable Document Format | application/pdf |
| JPEG/JPG | Joint Photographic Experts Group | image/jpg |
| TXT | Text file | text/plain |
| RTF | Rich text file | text/rtf |
| TIFF/TIF | Tagged Image File Format | image/tiff |
| HTML | HyperText Markup Language | text/html |
| Doc | Word document | application/msword |
| Docx | Office Open XML (ISO/IEC 29500) wordprocessing | application/vnd.openxmlformats-officedocument.wordprocessingml.document |
| XLS | Excel document | application/vnd.ms-excel |
| XLSX | Office Open XML (ISO/IEC 29500) spreadsheet | application/vnd.openxmlformats-officedocument.spreadsheetml.sheet |
| DICOM | Digital Imaging and Communications in Medicine | application/dicom |

If additional documents are subsequently received by the sender which contain medically relevant information, a follow-up case containing the additional information should be created and submitted.

In order to submit an attachment, the following fields need to be completed in the AER message:

1. **B.7.1 Attached document file name:** This is a free text name that identifies the document that is being attached to the AER. This file document name will be added to the file name stored in the EV Web database in the following format: <<AER_batchSenderIdentifier_batchTransmissionDate_MessageNumber_DocumentName_xxxxxx.file_type_ext>>
2. **B.7.1.1: Attached Document Type:** This is a selection from a drop down list of document types that describes the information in the attached document. The document file type will also be appended to the file name stored in the EV database stated in B.7.1 above.

In addition to the above, please refer to Annex 1: Field level specification for more clarification.

## *3.4. Additional ISO/HL7 VICH data fields for EU regional implementation*

This section of the implementation guide highlights information on specific data fields of the VICH GL35 and GL42 guidelines, where special consideration for EU regulations and requirements should be considered in providing information for AE reporting.

**Batch sender personal information**: Due to EU GDPR and personal data protection regulations, all personal data in the message batch wrapper which are specified as optional in the field listed below should not be provided.

1. B.8.1.2.3 Batch Sender - Title
2. B.8.1.2.4 Batch Sender - Last name
3. B.8.1.2.5 Batch Sender - First name
4. B.8.1.2.6 Batch Sender - Telephone
5. B.8.1.2.7 Batch Sender - Fax
6. B.8.1.2.8 Batch Sender - E-mail

**Message sender personal information:** Due to EU GDPR and personal data protection regulations, all personal data in the message wrapper which are specified as optional in the field listed below should not be provided.

1. B.8.2.2.3 Message Sender - Title
2. B.8.2.2.4 Message Sender - Last name
3. B.8.2.2.5 Message Sender - First name
4. B.8.2.2.6 Message Sender - Telephone
5. B.8.2.2.7 Message Sender - Fax

However, a general e-mail address could be provided for each message in the batch in field "B.8.2.2.8 Message Sender - E-mail" for the purpose of contact for clarification, if and when required.

**Primary Reporter information:** Due to EU GDPR and personal data protection regulations, all personal data in the AER message listed below should be withheld. For the purpose of duplicate management, some of the fields as detailed below should provide limited information that will enable easy identification of duplicate reports.

Where provided in an AER, all personal information will be stored in the EV database for the following reason:

- The MAH and NCA may not have this information stored anywhere else except the EudraVigilance Veterinary Database
- This information may be required for follow up reporting and the reporter will need to be able to access it.

1. A.3.1.2 Primary Reporter Last name – Include First letter of first and last name + first 2 digits of the post code
2. A.3.1.3 Primary Reporter First name
3. A.3.1.4 Primary Reporter Telephone
4. A.3.1.5 Primary Reporter Fax
5. A.3.1.6 Primary Reporter E-mail
6. A.3.1.7 Primary Reporter Business Name
7. A.3.1.8 Primary Reporter Street address

8. A.3.1.9 Primary Reporter City
9. A.3.1.10 Primary Reporter State/county code
10. A.3.1.11 Primary Reporter Postal/zip code – However, the following fields are mandatory and should be provided.
11. A.3.1.1 Primary Reporter Category
12. A.3.1.12 Country code

NOTE: The section A.3.2 – Other Reporter is not mandatory. But where provided, this should follow the same guideline as for the Primary Reporter.

**Unique Adverse Event Report Identification:** This field (A.4.1) contains information that uniquely identifies an AER. MAH should consider the following in the creation of the Unique Adverse Event Report Identification:

MAH should use an existing MAH ID or should generate a new one based on an 8 characters ash from the Routing ID following the CRC32 example: https://crccalc.com/

Formation of Unique Adverse Event Report Identification should be as follows:

<Country>-<MAHORGID>-<Routing ID><remaining text>

Which maps to the structure defined by the VICH as:

<OccurCountry>-<OrganisationCode>-<TextString>

- Occur Country = 3 character ISO 3166 alpha 3 country code

- Organisation Code = 8 character MAH organisation code

- Text String = Maximum of 47 character (Routing ID + remaining text)

**Seriousness:** In the EU, it has been considered that seriousness, as a metric for adverse event reporting, should be deprecated. However, the field B.3.6: "Serious AER Reported" (Y/N)? should be provided for compliance with VICH, although it will not be considered for AER data analysis in the EU.

**Previous Exposure to VMP:** In VICH GL35 and GL42, this field B.3.9 Previous Exposure to the VMP (Y/N)? is linked to the report. However, this field should be linked to the VMP and hence in all AER messages each added VMP should have "Previous Exposure to VMP" associated.

**Previous AE to VMP**: In VICH GL35 and GL42, this field B.3.10 Previous AE to VMP (Y/N?) is linked to the report. However, this field should be linked to the VMP and hence in all AER messages each added VMP should have "Previous AE to VMP" associated.

**De-challenge and Re-challenge:** In VICH GL35 and GL42, the following fields B.4.1 - Did AE Abate After Stopping the VMP? and B.4.2 - Did AE Reappear "After Re-introduction of the VMP?" are linked to the report. However, these fields should be linked to the VMP and hence in all AER messages each added VMP should have "Did AE Abate after Stopping the VMP?" and "Did AE Reappear After Re-introduction of the VMP?" associated.

### 3.4.1. Integration with Union Product Database (UPD)

The Union Product Database (UPD) is the data source for all Veterinary Medicinal Products (VMP) and active substances for centrally and nationally authorised products.

For enhanced data quality and to reduce the amount of effort required for recoding, AE reporters should endeavour to link their AERs to products and active substances contained in the UPD. However, in circumstances where the VMP cannot be specifically identified from the UPD, AERs should still be submitted.

When an AER is linked to a VMP from the UPD, product related information should also be linked to further enhance the quality of product data submitted. These include:

- Product Code – VICH B2.1.1
- Registration Identifier (Product Registration Number) – VICH B2.1.2
- Anatomical Therapeutic Chemical Vet Code (ATC VET Code) – VICH B.2.1.3
- Company or Marketing Authorisation Holder (MAH) – VICH B.2.1.4
- Active Ingredient(s) – B.2.2.1. Also note that when the product is not known, the AER could be reported with just this information.

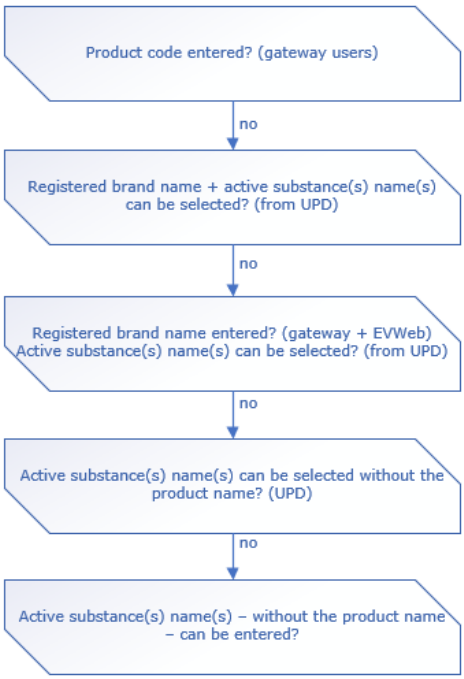
### 3.4.1.1. Veterinary Medicinal Product Code (VMP)

**Product Code (VICH B.2.1.1):** The veterinary medicinal product (VMP) code uniquely identifies the medicinal product. For EV Web users, this is associated with the product name selected from the UPD. For gateway users, transmission of this code will help in uniquely identifying the product associated with the AER.

### 3.4.1.2. Decision flow diagram for entering Medicinal Product Information

The decision tree provided below should be used for entering veterinary medicinal product information. The product name as reported by the primary source is a mandatory field, the sender of AERs should attempt to use VMPs from UPD where available and if appropriate, provide structured name parts.

If the sender can answer 'yes' to a question listed in the diagram below, this is the information that should be provided in the AER message in addition to the product name as provided by the primary source. If the answer is 'no' then the sender should progress to the next question as shown below.



## 3.5. VeDDRA Version control

A new release version of VeDDRA should become the reporting version on the first Monday of the second month after it is released. To synchronize this event over the VICH regions, the MSSO recommends midnight GMT, Sunday to Monday, for the switchover, as an example.

The stated change over date and time need to be adhered to consistently by all stakeholders to avoid any disruptions with regards to the electronic exchange of VICHs. VeDDRA subscribers who are able to quickly update and validate their systems with each release of VeDDRA should recognise that if they submit AERs using the updated VeDDRA version prior to the receiving party, which has not switched to the updated version, the transmitted VICHs will be rejected. Please see section 4.1. for additional information on VeDDRA versioning.

# 4. Business rules for AER message processing

The business rules for VICH data fields validation and XML message validity, including the error and warning messages that should be displayed if there is a failure, can be found in Annex 2: Business Rules.

Further clarification and guidance on how to construct each data field in an VICH XML message, including snippets for each field, can also be found in Annex 1: Field level specification.

## 4.1. Business rules notes

The table below provides additional information on some of the business rules that give specific context to some elements of VICH XML message.

| # | Note | Description |
|---|---|---|
| **1.** | **VeDDRA Version** | The supported VeDDRA versions are related to the EV environment (EV compliance testing environment or production environment) that is the recipient of the AE report transmission.<br><br>It also relates to the current VeDDRA version officially published on the EMA corporate website. The EV compliance testing environment supports VeDDRA version 4.0 and higher. The EV production environment supports the previous and the current VeDDRA versions. It should also be noted that a new version of VeDDRA is released on 01/10 (first of October) each year. The last two approved versions can be used. This will be the version for the current year version and the version for the previous year considering that the calendar is 01/10 to 30/09.<br><br>The validation process of the AERs accepts only current lower level term (LLT) numeric codes of the supported VeDDRA versions. All stakeholders should follow the recommendations in guidance regarding the switch to a new VeDDRA version. The use of non-valid or non-current numeric VeDDRA LLT codes generates an error message in the validation process. |
| **2.** | **Dates & Time** | No date/time value should exceed the current CET time plus 12 hours. Failure of the validation of the date format generates an error.<br><br>All dates should be inferior or equal to the EudraVigilance Gateway date plus 12 hours. Failure of this validation generates an error. |

| # | Note | Description |
|---|---|---|
| | | A minimum date of the year 1900 applies to all date/time fields.<br>Provision of time zone offsets are expressed in the following formats:<br>"CCYYMMDDhhmmss[+/-ZZzz]" or "CCYYMMDDhhmmss[+/-ZZ]"<br>The ZZ (uppercase) is for the Hour offset and zz (lowercase) are for minute offsets. The lowercase minute offsets do not need to be provided if the offset is in units of an hour, therefore the following examples will be treated as the same however the leading zero should be included:<br>-6<br>-06<br>-0600 |
| **3.** | **Batch Receiver Identifier and Message Receiver Identifier** | When submitting an AE report to EudraVigilance, the value accepted in the data element *Batch Receiver Identifier* (VICH B.8.1.3) and Message Receiver Identifier (VICH B.8.2.3.1) should be one of the following, depending on to which module the message is addressed:<br>• 'EVVETT' (Test environment – XCOMP)<br>• 'EVVETPROD' (Production environment – EVPM) |
| **4.** | **Report nullification** | Details on the nullification process and specific rules are provided in section 6.1.1. |
| **5** | **AER within the same batch** | The Unique Adverse Event Report Identification Number cannot be repeated for separate AERs within the same batch. |

# 5. AER acknowledgement messages

The acknowledgement message is an integral part of the exchange of VICH AER messages. The message model for an acknowledgement message is shown below. The sections below the model explain how acknowledgment messages are generated by the EudraVigilance system, and in particular how error messages are generated when AERs do not fulfil the business rule requirements.

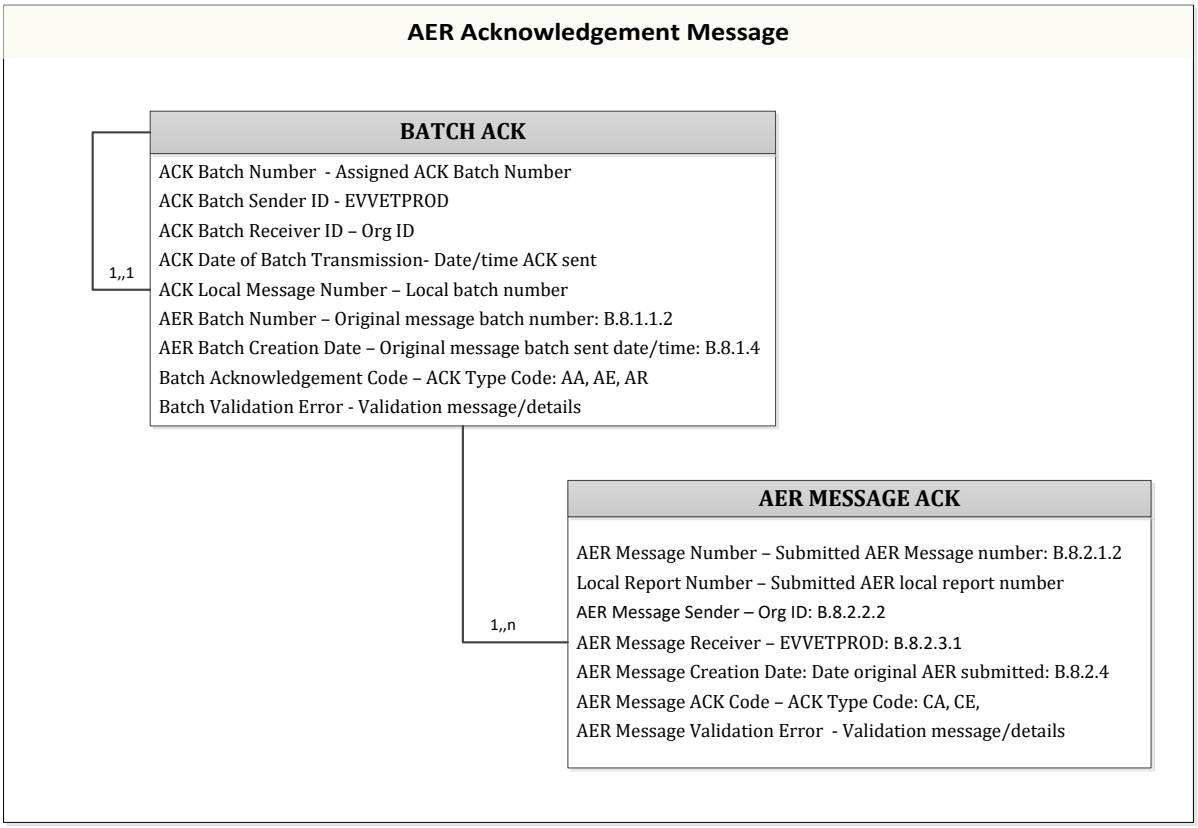



**Figure 4: ACK message model**

## *5.1. Acknowledgement batch level elements*

The data element *Transmission Acknowledgement Code* (AER ACK.A.4) is a field that informs the sender of the AER message to either re-send the complete transmission, review the acknowledgments of individual AERs within the message or that no further action is required.

The possible Transmission Acknowledgement Code values are:

**AA** – Application Acknowledgement Accept (message successfully processed, no further action)

**AE** – Application Acknowledgement Error (error detected, error response has additional detail, some AER message(s) need further action)

**AR** – Application Acknowledgement Reject (parsing error, no data extracted, re-send the entire transaction)

## *5.2. Parsing error*

The *Batch Validation Error* data element (AER ACK.A.5) is a text field (250 characters) and it is included in the Acknowledgement Message only if the data *Transmission Acknowledgement Code* (AER ACK.A.4) has the value "AR": i.e. XML parsing error, no data extracted. This field describes the error generated by the EudraVigilance XML parser or from the cardinality checks described below.

### 5.2.1. AER message cardinality checks – pre-validation before loading

In accordance with VICH specifications (logical model) certain sections should appear only once, e.g. B.3 Adverse Event Data section. The ISO VICH schema is flexible and does not prevent some sections from being repeated. Therefore, the EV message processing system performs cardinality checks to

ensure that non-repeatable sections are not repeated within a message. If such inconsistences are detected the AER message is rejected with an "AR" acknowledgement.

Please refer to Annex 1: Field level specification for more detailed explanations.

## *5.3. Acknowledgement message level elements*

The data element *Acknowledgement Code* for an AER Message (AER ACK.B.r.6) is a field that informs the sender of the status of each AER within a batch and if the AER needs to be corrected and resent.

The possible Acknowledgement Codes values for an AER are:

**CA** – Commit Accept (the AER message successfully loaded; no further action required)

**CR** – Commit Reject (the AER message contains a fatal error that prevents the AER from being loaded, the AER needs to be corrected and resent)

## *5.4. Acknowledgement message*

The data element *Error / Warning Message or Comment* (AER ACK.B.r.7) appears in the section ACK.B *AER message acknowledgement*, which is provided for each AER included in the batch. This field is 250AN in the VICH Step by Step document, however, to allow for additional information to be provided by senders of AERs on the issues identified in transmissions, the field is extended to 2000AN in the EU.

- If the value for the data element *Acknowledgement Code for an AER Message* (AER ACK.B.r.6) is "CR" (Commit Reject) there are one or more errors in the AER and not all the data have been loaded successfully. In the data element *Error / Warning Message or Comment* (AER ACK.B.r.7) the errors and warnings encountered during the validation processes of the AER are described. After this, the system adds the classification outcome for the analysed AERs.
- If the value for the data element value for the data element *Acknowledgement Code for a AER Message* (AER ACK.B.r.6) is "CA" (Commit Accept) the corresponding AER is loaded successfully and in the data element *Error / Warning Message or Comment* (AER ACK.B.r.7) the classification result is presented. In case the validation processes of the AER have detected warnings, their textual description is included in the data element *Error / Warning Message or Comment* (AER ACK.B.r.7).

The business rules are also published as two Excel files on the EudraVigilance section of the Agency website. One of the Excels provides an overview of the business rules and the second one provides a list of all the business rules and the parameters that they use. The business rule number is also provided in the detailed rules list and this number will be referenced in the acknowledgement message if the rule is triggered.

### 5.4.1. Acknowledgement message for valid report

The XML snippet below shows an example of an acknowledgement message comment for a valid report without errors.

```
<acknowledgementDetail>
      <text>safety report loaded; Validated against 1.1 business rules;
Comments: Parsing process: Parsing process:  Correct Report; Classification: new: EU-EC -
123202 = Case Report - old: EU-EC -123174 = Replaced Report </text>
  </acknowledgementDetail>
```

907 The table below shows the structure of the *acknowledgement message* (VICH ACK.B.r.7) as produced
908 by the EudraVigilance system. It also includes an example of the text that would be produced for a
909 valid submission as shown in the XML snippet above.

| Section | Error message comment section | Example |
|---|---|---|
| 1 | **Loading & Validation Information:**<br>1. AER loaded<br>2. AER not loaded<br>Validated against <current business rules> | *AER loaded; Validated against 1.1 business rules;* |
| 2 | **Error and Warning List (May not be present)** | *Comments:* |
| 3 | **Error/Warning Element(s)** | |
| 4 | **Parsing Information:**<br>Correct Report<br>Report with Warnings<br>Report with Errors | Parsing process: Correct Report; |
| **5** | **Classification information:**<br>See section **Error! Reference source not found.** AER Classification for details | Classification: |
| 6 | **Current Report Classification:**<br>Displays the Unique Adverse Event Report Identification Number and the classification outcome | new: EU-EC -123202 = Case Report - |
| 7 | **Old Report Classification:**<br>Displays the Unique Adverse Event Report Identification Number which was previously stored in the system, and the reclassification status of the previously stored report. | old: EU-EC -123174 = Replaced Report |

910

## 911 5.4.2. Acknowledgement message for non-valid report

912 The XML snippet below shows an example of an acknowledgement message for a non-valid report.

```
<acknowledgementDetail>
      <text>safety report not loaded; Validated against 1.1 business rules;
Comments:1- [101] :In section Drug(s) on field Medicinal Product Identifier (MPID) VICH
G.k.2.1.1b) Value: '837336' Reported error BUSINESSRULES – LOOKUP CheckMPID '837336'
must be a valid MPID code; Parsing process:
Report with Errors </text>
    </acknowledgementDetail>
```

913

914 The table below shows how the system structures section 3 of 8 above (Error/Warning Element(s)). It
915 also includes a breakdown of the example text shown in the XML snippet above.

| Section | Error/Warning Element(s) | Example |
|---|---|---|
| a | A sequence number for each rule triggered is followed by the business rule number in square brackets that has been triggered | 1- [R101] |
| b | The section in which there is the wrong element | In section DRUG(s) |
| c | The element name to which the warning/error is referring to | on field Registered Name or Brand Name (VMPID) (VICH B.2.1) |
| d | The element value to which the warning/error is referring to | Value: 837336 |
| e | Describes if the comment reported is referring to an error or a warning | Reported error |
| f | The class of error/warning that it is reported | BUSINESSRULES – LOOKUP |
| g | A more detailed textual description of the warning/error | CheckMPID 837336 must be a valid MPID code; |

### 5.4.3. Field level errors

Please reference Annex 2: Business rules for additional explanations.

### 5.4.4. Field pair error description

The Table below provides details on the field pair error descriptions that can be found in section "g" of the error/warning element(s) that can be seen the table above.

| Field Level error | Error description | Comment format |
|---|---|---|
| Element Null Error | When the element must be null, as the value of another corresponding element requires this. | *Since the element <e.g. Regulatory Authority - VICH A.1 has a value the element < e.g. Marketing Authorisation Holder - VICH A.2.> cannot contain a value.* |
| Element Value required | The element value must be specified, as the value of another element requires it. This error is signalled when a VedDRA term has been specified but the corresponding VedDRA version field has been left empty. | Since the element < B.1.8.2 – Minimum Weight> has a value, the element < B.1.8.2.1 - Minimum Weight Unit> must contain a value. |

### 5.4.5. Section level error description

The table below provides details on the section level errors descriptions, that can be found in section "g" of the error/warning element(s), that can be seen above. These errors occur where multiple

instances of the same section are used within the same report or where errors do not pertain to a single field.

| Field Level error | Error description | Comment format |
|---|---|---|
| At Least One Error | If one element between n-elements must be present, but no element is specified. | At least one field must be populated in this section e.g." B.3.2 – AER Term and Code" cannot be empty. |
| At Most One Error | If at most one element can be present, but there is more than one element specified. | *This element can only contain one value: e.g. A.3.1.1 - Primary Reporter Country* |
| At Least One Section Field Value Error | The element value must be present with a specific value given in at least one of the repeated sections.<br><br>This error is generated when one section must have information provided for at least one data element. | The value for one product in B.2.1 - Registered or Brand Name must be provided in the repeated section B.2 – VMP Data and Usage. |

# 6. AER classification

**<<AER classification is currently in discussion and this section will be updated once this has been concluded>>**

## *6.1. Classification algorithm*

### 6.1.1. Nullification reports

### 6.1.2. Master cases

### 6.1.3. Case clustering

## *6.2. Recoding of veterinary medicinal product information*

# Annexes

## *Annex 1: Field level specification*

## *Annex 2: Business rules*

# Appendix

## *Electronic Data Interchange Definitions*

The definitions that are described in this chapter are the general definitions used in this document for Electronic Data Interchange.

Selected terminology as defined in the frame of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Veterinary Use has been included with particular emphasis on the type of format (XML), information (reports) and messages (safety and acknowledgement messages) used in the EDI process in the area of pharmacovigilance in the post-authorisation phase. As there are different types of acknowledgement of receipt of an EDI message, it is clearly indicated which level of acknowledgement is referred to, in order to avoid confusion.

For the purpose of this Note for Guidance, the following terms are defined as:

**EDI:**
Electronic Data Interchange is the electronic transfer, from computer to computer, of commercial and administrative data using an agreed standard to structure an EDI message. EDI is based on the use of structured and coded messages, the main characteristic of which is their ability to be processed by computers and transmitted automatically and without ambiguity. This makes EDI specific in comparison with other data exchange such as electronic mail.

**EDI Message:**

An EDI Message consists of a set of segments, structured using an agreed standard, prepared in a computer readable format and capable of being automatically and unambiguously processed.

**Gateway:**

A Gateway is defined as a data exchange service, which consists of all core standards and functionality required for supporting the standards of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Veterinary Use (VICH) (e.g. Simple Mail Transfer Protocol/Secure Multipurpose Internet Mail Extension -SMTP/SMIME- protocol).

**Message Disposition Notification (MDN):**

The MDN is a notification on the receipt of an EDI Message returned by the Receiver's Gateway to the Sender's Gateway. The MDN concludes a Message Transaction performed between two parties in a Gateway to Gateway communication.

**EDI Partner:**
An organisation exchanging EDI Messages in the area of pharmacovigilance in the pre- and post-authorisation phase with another organisation. For the purpose of this Note for Guidance EDI partners in the pre- and post-authorisation phase in pharmacovigilance are as follows:

- Competent Authorities in the EEA
- Marketing Authorisation Holders in the EEA

**Sender:**
The Sender is the person or entity creating an EDI Message for transmission.

**Receiver:**

The Receiver is the intended recipient of the EDI Message.

**Report Sender:**

The Report Sender is the person or entity creating an AE message as EDI Message in order to submit an Adverse Event Report, which for the purpose of this Note for Guidance is an EDI Partner. In the Report Transaction the Report Sender will always remain the same, whereas with the exchange of messages the "Sender" and "Receiver" roles will change (see graph in Annex I).

**Report Receiver:**

The Receiver is the intended recipient of the transmission of a Safety Message, which for the purpose of this Note for Guidance is an EDI Partner

**Sender Identifier (Sender ID):**

The Sender Identifier is the identification (ID) or combined EDI qualifier and ID of the Sender.

**Receiver Identifier (Receiver ID):**

The Receiver Identifier is the identification or combined EDI qualifier and ID of the recipient.

**Message Transaction:**

A Message Transaction is a set of actions encompassing the electronic transmission of an EDI Message (Adverse Event or Acknowledgement Message,) between a Sender and a Receiver including the return of the Message Disposition Notification for that message.

**Adverse Event Message:**

An AE message is an EDI Message including the information provided for one/more Adverse Event Reports contained in one Safety File exchanged between one Sender and one Receiver in one Message Transaction.

**Safety File:**

The Safety File is the electronic file transmitted in one Message Transaction between one Sender and one Receiver containing one Adverse Event Message.

**Individual Case:**

An Individual Case is the information provided by a primary source to describe suspected adverse event(s)/suspected unexpected adverse events related to the administration of one or more medicinal products

**Adverse Event Report (AER):**

An Adverse Event Report is a report providing the most complete information related to an Individual Case at a certain point of time.

**Acknowledgement of Receipt:**

The Acknowledgement of Receipt is the procedure by which on receipt of the Adverse Event Message the syntax and semantics are checked.

**Acknowledgement Message (AER ACK):**

The Acknowledgement Message is an EDI Message with the information on the result of the Acknowledgement of Receipt procedure to acknowledge the receipt of one or several AE Report(s) contained in the same message.

**Report Transaction:**

A Report Transaction is the complete set of actions in the electronic reporting of Adverse Event Messages to comply with regulatory requirements which routinely include the following:

- Creation of an AE Message;
- Transmission of the AE Message to the Report Receiver;
- On receipt of the AE Report by the Receiver's Gateway return of an MDN;
- This MDN will be referred to as AER-MDN;
- The AER-MDN is received and stored by the Report Sender to document the success of the AE Report transmission;
- The AE Report is subjected to the Acknowledgement of Receipt procedure by the Report Receiver;
- The Acknowledgement Message is created;
- The Acknowledgement Message is returned to the Report Sender (technically the Report Receiver is a Message Sender for this part of the transaction);
- On receipt of the Acknowledgement Message by the Report Sender's Gateway return of an MDN;
- This MDN is referred to as AERACK-MDN;
- The AERACK-MDN is received and stored by the Report Receiver to document the successful transmission of the Acknowledgement Message;
- The Acknowledgement Message is evaluated to document the success of the Report Transaction.

**Competent Authorities:**

An authority within the EEA including the EMA and the European Commission responsible for the granting of marketing authorisations for medicinal products and the supervision of marketing of such products in accordance with the relevant laws and regulations established under EU law.

**Marketing Authorisation Holders:**

All Marketing Authorisation Holders (MAHs) holding a valid marketing authorisation for a medicinal product in the EEA including any part thereof, independent of the authorisation procedure of this medicinal product.

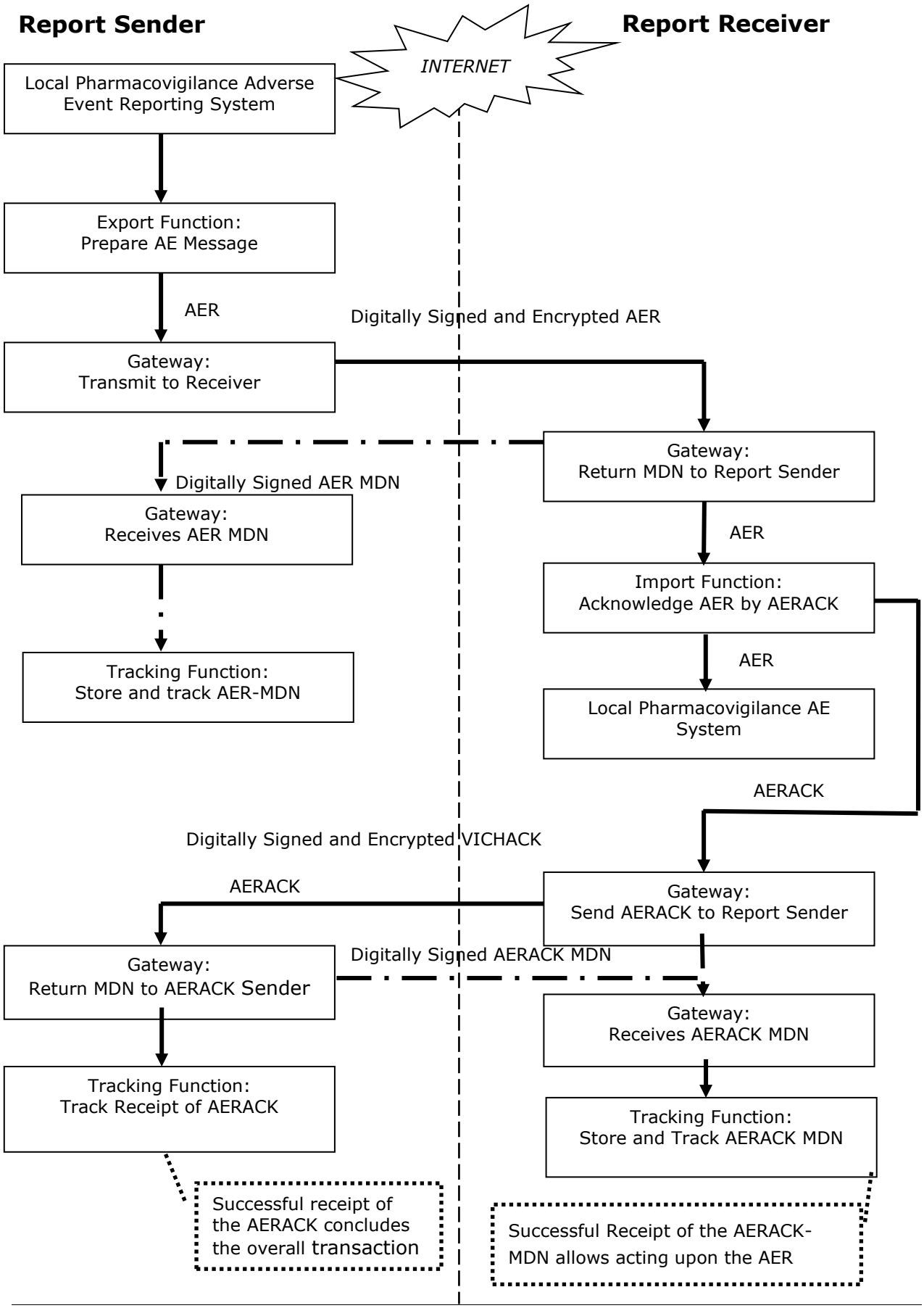
**XML:**

Extensible Mark-up Language (XML) is a subset of the International Standard (ISO 8879) called Standard Generalized Mark-up Language (SGML)

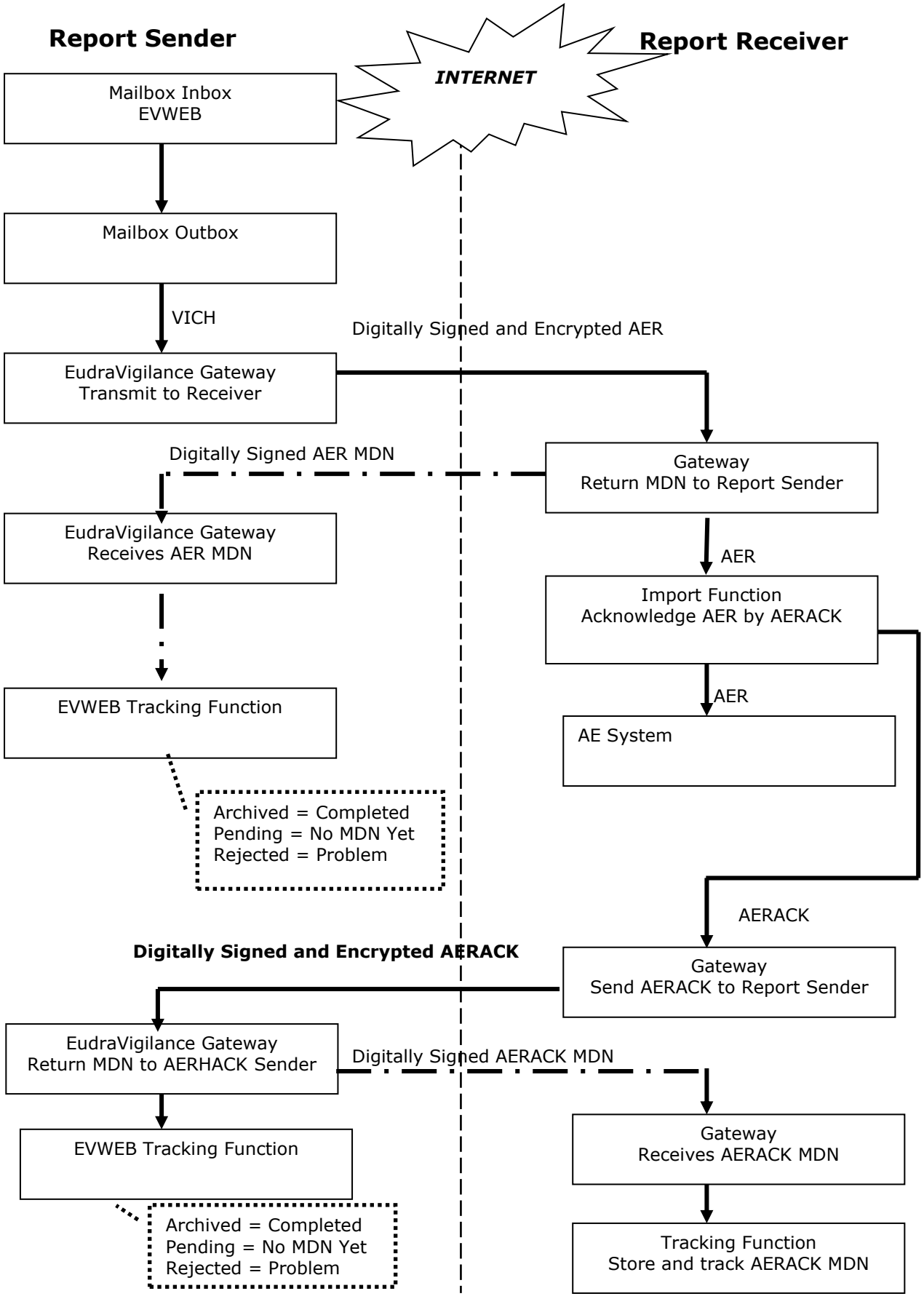
**The Gateway:**

The Gateway is the data-processing network as defined in the EU legislation and is providing a single point of contact between MAHs and Competent Authorities in the EEA. By doing so, the Gateway is considered a hub and all connections to the EDI Partners are known as spokes. Safety and Acknowledgement Messages are routed through the hub to the desired spoke.

***Schema of AE report transactions using gateway***



***Schema of AE report transactions using EVWeb***



### *Rerouting of DEG messages*

The AER format forwarded on to National Competent Authorities (NCAs) will be the same as the original format received.

## Rerouting timeframes for DEG Messages

The following technical aspects will apply to DEG messages received by the EMA that are required to be forwarded to concerned NCAs:

The EMA will automatically forward on, without delay, copies of the valid AERs received into EudraVigilance Veterinary to National Competent Authorities that have requested to receive them. AERs that have parsing errors and AERs that contain errors resulting in the DEG AER Acknowledgement Code CR.02" will not be forwarded to NCAs. Original cases received from an NCA will be excluded from being retransmitted back to the sending NCA.

Save for periods of planned downtime of the EudraVigilance system the following timeframes will apply to the forwarding of valid AERs:

- 95% of valid AERs will be re-routed to the relevant NCAs within 12 hours of receipt by the EV Gateway
- 99% of valid AERs received during EMA office hours will be re-routed to the relevant NCAs within 24 hours of receipt by the EV Gateway
- 99.9% of valid AERs will be re-routed to the relevant NCAs within 48 hours of receipt by the EV Gateway

NCAs should return acknowledgements for rerouted AERs within 48 hours of the initial receipt. If no acknowledgement is received within 48 hours, EudraVigilance Veterinary will automatically resubmit the re-routed AERs. For resubmitted AERs NCAs should return acknowledgements within 24 hours. EudraVigilance Veterinary will make a maximum of three attempts to resubmit AERs when no acknowledgement has been returned by an NCA. After the maximum number of attempts has been reached the NCA concerned will be contact by the EMA in order to understand if the NCA is experiencing technical issues. It should however be noted that this functionality will only be available late in 2022.

## Rerouting rules for DEG AERs

NCAs will provide and maintain a list of ISO 3166 country codes for which they wish to receive copies of AERs that have been submitted into EudraVigilance Veterinary.

The DEG field *Occur Country* (R.11) will be used to identify the National Competent Authority requesting that AER in accordance with the list of ISO 3166 country codes described above.

The fields that will be changed when retransmitting AERs are shown in the table below. The Message type (M.1.1) for the retransmission of AERs as received from the sending organisation will be "AER".

**Table 15 - Fields changed upon retransmission**

| DEG field code | AER field Description | Notes |
|---|---|---|
| M.1.4 | Message Number | |
| M.1.5 | Message Sender Identifier | Will be set to "EVVET" |

| DEG field code | AER field Description | Notes |
|---|---|---|
| M.1.6 | Message Receiver Identifier | Will be set to the receiving NCA gateway identifier |
| M.1.7b | Message date | |
| A.3.1.2 | Sender Identifier | Will be set to the Message sender Identifier (M.1.5) of the AER message as received by EudraVigilance |

Cases submitted by NCAs to EudraVigilance will not be retransmitted back to the sending NCA, this check will be based on the sending organisation's *Message Sender Identifier* (M.1.5).