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3 Guideline on good pharmacovigilance practices (GVP)

4 Module VI – Management and reporting of adverse reactions to medicinal 5 products (Rev 2)

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8 - Update on ICSRs reporting, following-up, duplicate detection, data quality management, in line
9 with the provisions in Art. 24 of Reg. (EC) No 726/2004, Art 107 and 107a of Dir. 2001/83/EC;
10 - Update on the validation of ICSRs based on patients and reporters identifiability;
11 - Update on the management of ICSRs described in the scientific literature;
12 - Update on the collection of information on patient's age;
13 - Guidance on the management of suspected adverse reactions reported through medical enquiry
14 and product information services;
15 - Guidance on the management of reports from post-authorisation efficacy studies;
16 - Transfer of the guidance on Emerging Safety Issue to GVP Module IX;
17 - Editorial amendments to align the format with other GVP Modules.
18

Comments should be provided using this template. The completed comments form should be sent to gvp@ema.europa.eu

19 Note for public consultation:

20 The public consultation is restricted to the revised texts or deleted texts highlighted in "track changes"
21 mode. However, if revisions or deletions impact or contradict other existing texts, comments on such
22 non-highlighted texts will be processed and taken into account.

23 **See websites for contact details**

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VI.A. Introduction

VI.A.1. Scope

This Module of GVP addresses the legal requirements detailed in ~~Title~~TITLE IX of Directive 2001/83/EC [DIR] and ~~chapter~~Chapter 3 of TITLE II of Regulation (EC) No 726/2004 [REG], which are applicable to competent authorities in Member States, marketing authorisation holders and the Agency as regards the collection, data management and reporting of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in the European Union (EU). Recommendations regarding the reporting of ~~emerging safety issues or of~~ suspected adverse reactions occurring in special situations are also presented in this Module. The requirements provided in ~~chapters~~Chapters IV, V and IX of the Commission Implementing Regulation (EU) No 520/2012 [IR] shall be applied in this Module.

The guidance provided in this Module does not address the collection, management and reporting of events or patterns of use, which do not result in suspected adverse reactions (e.g. asymptomatic overdose, abuse, off-label use, misuse or medication error) or which ~~do~~are not ~~require~~required to be ~~reported~~submitted as individual case safety report ~~or as emerging safety issues~~. This information may however need to be collected and presented in periodic safety update reports for the interpretation of safety data or for the benefit risk evaluation of medicinal products. In this aspect, the guidance provided in GVP Module VII applies.

Section B of this Module highlights the general principles in relation to the collection, recording and reporting of reports of suspected adverse reactions associated with medicinal products for human use, which are applicable to competent authorities and marketing authorisation holders. The definitions and recommendations provided in VI.A. should be followed. EU requirements are presented in VI.C..

All applicable legal requirements detailed in this Module are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

VI.A.2. Definitions and terminology

The definitions provided in Article 1 of Directive 2001/83/EC shall be applied for the purpose of this Module; of particular relevance are those provided in this Section. Some general principles presented in the ICH-E2A and ICH-E2D guidelines (see GVP Annex IV) should also be adhered to; they are included as well in this Section (see GVP Annex I for all definitions applicable to GVP).

VI.A.2.1. Adverse reaction

An adverse reaction is a response to a medicinal product which is noxious and unintended [DIR Art 1~~].~~ ~~This includes adverse reactions which arise from:~~(11)]. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure [DIR Art 101(1)]. Use outside the marketing authorisation includes off-label use, overdose, misuse, abuse and medication errors.

- ~~the use of a medicinal product within the terms of the marketing authorisation;~~
- ~~the use outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors;~~
- ~~occupational exposure.~~

VI.A.2.1.1. Causality

In accordance with ICH-E2A (see GVP Annex IV), the definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event~~.~~ (see GVP Annex I). An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected. For regulatory reporting purposes, as detailed in ICH-E2D (see GVP Annex IV), if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse reaction. Therefore all spontaneous reports notified by healthcare professionals[1] or consumers[2] are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the reporters specifically state that they believe the events to be unrelated or that a causal relationship can be excluded.

VI.A.2.1.2. Overdose, off-label use, misuse, abuse, occupational exposure, medication error, falsified medicinal product

~~a.~~ Overdose

: This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.

~~b.~~ Off-label use

: This relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the ~~authorised product information~~terms of the marketing authorisation.

~~c.~~ Misuse

: This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the ~~authorised product information~~terms of the marketing authorisation.

~~d.~~ Abuse

: This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects [DIR Art 1~~).~~(16)].

~~e.~~ Occupational exposure

: This refers to the exposure to a medicinal product (as defined in [DIR Art 1~~),~~(2)]), as a result of one's professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release as finished product.

Medication error: This is an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the patient[2].

Falsified medicinal product: This relates to any medicinal product with a false representation of:

- its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients;
- its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or

[1] See VI.A.2.3. for definition of primary source
[2] See Good Practice Guide on Recording, Coding, Reporting and Assessment of Medication Errors, EMA/762563/2014

- its history, including the records and documents relating to the distribution channels used.

This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property rights [DIR Art 1(33)].

VI.A.2.2. Medicinal product, ~~A~~active substance, excipient

Medicinal product: A medicinal product is characterised by any substance or combination of substances,

- presented as having properties for treating or preventing disease in human beings; or
- which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis [DIR Art 1~~].~~(2)].

Active substance: An active substance corresponds to any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis [DIR Art 1(3a)].

Excipient: An excipient corresponds to any constituent of a medicinal product other than the active substance and the packaging material [DIR Art 1(3b)].

In accordance with Article 107 of Directive 2001/83/EC, the scope of this ~~module~~Module is not only applicable to medicinal products authorised in the EU but also to any such medicinal products commercialised outside the EU by the same marketing authorisation holder (see VI.C.2.2.). Given that a medicinal product is authorised with a defined composition, all the adverse reactions suspected to be related to any of the active substances being part of a medicinal product authorised in the EU should be managed in accordance with the requirements presented in this ~~module~~Module. This is valid independently of the strengths, pharmaceutical forms, routes of administration, presentations, authorised indications, or ~~trade~~ names of the medicinal product. For the definition of the name and strength of a medicinal product, refer to Article 1(20) and Article 1(22) of Directive 2001/83/EC.

The guidance provided in this Module also applies, ~~subject to amendments where appropriate~~, to medicinal products supplied in the context of compassionate use (see VI.C.1.2.2.) as defined in Article 83(2) of Regulation (EC) No 726/2004~~.~~, subject to and without prejudice to applicable national law of the EU Member States. As the case may be, this guidance may also apply to named patient use as defined under Article 5(1) of Directive 2001/83/EC.

For devices containing active substances, whether they are authorised in the EU as medicinal products or CE marked as medical devices determines which procedure should be followed for the safety reporting of suspected adverse reactions and/or incidents. In this aspect, medicinal products follow the requirements for pharmacovigilance provided in Directive 2001/83/EC and Regulation (EC) No 726/2004, whereas medical devices follow the requirements for medical device vigilance in accordance with Directive 90/385/EEC and Directive 93/42/EEC. As detailed in the Guidelines on a Medical Devices Vigilance System[3], a medical device incorporating a medicinal product or substance, where the action of the medicinal product or substance is ancillary to that of the device, follows the legal requirements of Directive 90/385/EEC and Directive 93/42/EEC.

[3] Ref.: MEDDEV 2.12-1 rev 8

VI.A.2.3. Primary source

~~The~~ In accordance with ICH-E2B, the primary source of the information ~~on a suspected adverse reaction(s)~~ is the person who reports the facts~~.~~ about an individual case safety report. Several primary sources, such as healthcare professionals and/or ~~a consumer~~consumers, may provide information on the same case. In this situation, all the primary sources' details, including the qualifications, should be provided in the case report~~, with~~ and the "Primary source(s)" section should be repeated as necessary ~~in line with ICH-E2B(R2)~~ (see ~~GVP Annex IV)~~[4]~~.~~ VI.B.2. for validation of reports).

In ~~accordance~~line with ~~the~~ ICH-E2D (see GVP Annex IV),

- a healthcare professional is defined as a medically-qualified person such as a physician, dentist, pharmacist, nurse , coroner or as otherwise specified by local regulations;
- a consumer is defined as a person who is not a healthcare professional such as a patient, lawyer, friend, relative of a patient or carer.

~~Medical documentations~~The "Primary Source for Regulatory Purposes" is defined in ICH-E2B(R3) and is not applicable for the electronic transmission under ICH-E2B(R2) format. This data element refers to the person who first reported the facts. In case of multiple sources, it identifies the source of the worldwide case unique identification number by defining the country where the case occurred.

A consumer may provide medical documentation (e.g. laboratory or other test data) ~~provided by a consumer~~ that ~~support~~supports the occurrence of ~~the~~a suspected adverse reaction, or which ~~indicate~~indicates that an identifiable healthcare professional suspects a ~~reasonable possibility of~~ causal relationship between a medicinal product and the reported adverse event~~, are sufficient to consider the spontaneous report as confirmed by a healthcare professional.~~

~~If a consumer initially reports more than one reaction and at least one receives medical confirmation, the whole report should be documented as a spontaneous report confirmed by a healthcare professional and be reported accordingly.~~. Similarly, ~~if~~ a report ~~is~~may be submitted by a medically qualified patient, friend, relative or carer of the patient~~ or carer~~. In these situations, the ~~case should also be~~reported information is considered ~~as a spontaneous report~~medically confirmed ~~by a healthcare professional~~.

In the same way, where one or more suspected adverse reactions initially reported by a consumer is subsequently confirmed by a healthcare professional or contains medical documentation that supports the occurrence of a suspected adverse reaction, the case should be considered medically confirmed. It should be updated at case level in line with ICH-E2B(R2), or at adverse reaction level in accordance with ICH-E2B(R3) for each subsequently medically confirmed suspected adverse reaction.

VI.A.2.4. Seriousness

As described in ICH-E2A (see GVP Annex IV), a serious adverse reaction corresponds to any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

The characteristics/consequences should be considered at the time of the reaction to determine the seriousness ~~of a case~~. For example, life-threatening refers to a reaction in which the patient was at risk

[4] ~~See VI.C.6 as regards the electronic reporting of ICSRs in the EU.~~

of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical judgement should be exercised in deciding whether other situations should be considered as serious reactions. Some medical events may jeopardise the patient or may require an intervention to prevent one of the above characteristics/consequences. Such important medical events should be considered ~~as~~ serious[5]. The EudraVigilance Expert Working Group has co-ordinated the development of an important medical event (IME) terms list based on the Medical Dictionary for Regulatory Activities (MedDRA) (see GVP Annex IV). This IME list aims to facilitate the classification of suspected adverse reactions, the analysis of aggregated data and the assessment of the individual case safety reports (ICSRs) in the framework of the day-to-day pharmacovigilance activities. The IME list is intended for guidance purposes only and is available on the EudraVigilance web site[6] to stakeholders who wish to use it for their pharmacovigilance activities. It is regularly updated in line with the latest version of MedDRA.

Where one or more serious suspected adverse reactions are reported in an ICSR, the information on the seriousness should be documented at case level in line with ICH-E2B(R2) or for each reported suspected adverse reaction in accordance with ICH-E2B(R3).

VI.A.2.5. Individual case safety report (ICSR)

This refers to the format and content for the reporting of one or several suspected adverse reactions in relation to a medicinal product that occur in a single patient at a specific point of time~~.~~ [IR Art 27]. A valid ICSR should include at least one identifiable reporter, one single identifiable patient, at least one suspect adverse reaction and at least one suspect medicinal product.

VI.A.2.6 Nullflavors

Nullflavors are a collection of codes specifying why a valid value is not present in an ICSR. This refers to instances, where for example a proper value is applicable, but not known (e.g. age of the patient), or the value is masked i.e. information is available to a sender of an ICSR but cannot be provided due to security, privacy or other reasons (e.g. date of birth of the patient). ICH ICSR uses Nullflavour code sets from the HL7 Messaging Standard primarily to classify the set of source data situations that may give rise to a missing value. For examples how a Nullflavors can be used to code values in the ICSR, refer to chapter 3.3.6. of the ICH Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) E2B(R3) Data Elements and Message Specification, Version 5.01, 12 April 2013[7]. Additional EU guidance on the use of the Nullflavor in some specific situations is also provided in chapter I.C.3.7. of the EU Individual Case Safety Report (ICSR) Implementation Guide[8].

VI.B. Structures and processes

~~Section B of this Module highlights the general principles in relation to the collection, recording and reporting of reports of suspected adverse reactions associated with medicinal products for human use, which are applicable to competent authorities and marketing authorisation holders. The definitions and recommendations provided in VI.A. should be followed. EU requirements are presented in VI.C..~~

[5] Examples are provided in section II.B of ICH-E2A (see GVP Annex IV).
[6] http://eudravigilance.ema.europa.eu/human/textforIME.asp.
[7] Accessible at http://estri.ich.org/e2br3/index.htm
[8] Ref. EMA/51938/2013, 4 December 2014.

VI.B.1. Collection of reports

Competent authorities and marketing authorisation holders should take appropriate measures ~~in order~~ to collect and collate all reports of suspected adverse reactions associated with medicinal products for human use originating from unsolicited or solicited sources.

For this purpose, a pharmacovigilance system should be developed to allow the acquisition of sufficient information for the scientific evaluation of those reports.

The system should be designed so that it helps to ensure that the collected reports are authentic, legible, accurate, consistent, verifiable and as complete as possible for their clinical assessment.

All notifications that contain pharmacovigilance data should be recorded and archived in compliance with the applicable data protection requirements (see VI.C.6.2.2.8. for EU requirements).

The system should also be structured in a way that allows for reports of suspected adverse reactions to be validated (see VI.B.2.) in a timely manner and exchanged between competent authorities and marketing authorisation holders within the legal reporting time frame (see VI.B.7.1.).

In accordance with the ICH-E2D (see GVP Annex IV), two types of safety reports are distinguished in the post-authorisation phase; reports originating from unsolicited sources and those reported as solicited.

VI.B.1.1. Unsolicited reports

VI.B.1.1.1. Spontaneous reports

A spontaneous report is an unsolicited communication by a healthcare professional, or consumer to a competent authority, marketing authorisation holder or other organisation (e.g. Regional Pharmacovigilance Centre, Poison Control Centre) that describes one or more suspected adverse reactions in a patient who was given one or more medicinal products ~~and that~~. It does not derive from a study or any organised data collection systems where adverse events reporting is actively sought, as defined in VI.B.1.2.. In this aspect, the following situations should also be considered as spontaneous reports:

- Stimulated reporting that occurs consequent to a direct healthcare professional communication (see ~~Module XV),~~GVP Module XV), publication in the press, questioning of healthcare professionals by company representatives, communication from patients' organisations to their members, or class action lawsuits ~~should be considered spontaneous reports.~~;
- Unsolicited consumer adverse reactions reports ~~should be handled as spontaneous reports~~ irrespective of any subsequent "medical confirmation~~".~~;
- Reports of suspected adverse reactions, which are not related to any organised data collection systems and which are notified through medical enquiry/product information services or which are consequent of the distribution of information materials;
- Cases notified by different reporters, referring to the same patient and same suspected adverse reaction, and at least one notification is done in an unsolicited manner;
- Reports of suspected adverse reactions originating from non-interventional post-authorisation studies and for which the protocol does not require a systematic collection (see VI.C.1.2.1. and VI.C.6.2.3.7., subsection 2);

Reports of suspected adverse reactions originating from compassionate use or named patient use conducted in a country where the active collection of adverse events occurring in these programmes is not required (see VI.C.1.2.2. and VI.C.6.2.3.7. subsection 2). The reporting modalities and applicable time frames for spontaneous reports are described in VI.B.7. and VI.B.8..

VI.B.1.1.2. Literature reports

The scientific and medical literature is a significant source of information for the monitoring of the safety profile and of the risk-benefit balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues. Marketing authorisation holders are therefore expected to maintain awareness of possible publications through a systematic literature review of widely used reference databases (e.g. Medline, Excerpta Medica or Embase) no less frequently than once a week. The marketing authorisation holder should ensure that the literature review includes the use of reference databases that contain the largest reference of articles in relation to the medicinal product properties[9]. In addition, marketing authorisation holders should have procedures in place to monitor scientific and medical publications in local journals in countries where medicinal products have a marketing authorisation, and to bring them to the attention of the company safety department as appropriate.

Reports of suspected adverse reactions from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, should be reviewed and assessed by marketing authorisation holders to identify and record ICSRs originating from spontaneous reports or non-interventional post-authorisation studies.

If multiple medicinal products are mentioned in the publication, only those which are identified by the publication's author(s) as having at least a possible causal relationship with the suspected adverse reaction should be considered by the concerned marketing authorisation holder(s).

Valid ICSRs should be ~~reported~~submitted according to the modalities detailed in VI.B.7. and VI.B.8..

One case should be created for each single patient identifiable based on characteristics provided in VI.B.2.~~.~~. Relevant medical information should be provided and the first publication author~~(s)~~ should be considered as the primary source~~(s).~~ as well as the primary source for regulatory purposes in line with ICH-E2B(R3) (see VI.A.2.3.). The co-authors should not be reflected as part of the primary source information.

EU specific requirements, as regards medicinal products and scientific and medical publications, ~~which are not monitored by the Agency and~~ for which valid ICSRs shall be ~~reported~~submitted by marketing authorisation holders, are provided in VI.C.2.2.3.

VI.B.1.1.3. Reports from other sources (e.g. general news or other media)

If a marketing authorisation holder becomes aware of a report of suspected adverse reactions originating from a non-medical source, for example the lay press or other media, it should be handled as a spontaneous report. Every attempt should be made to follow-up the case to obtain the minimum information that constitutes a valid ICSR. The same reporting time frames should be applied as for other spontaneous reports.

[9] See VI. ~~Appendix~~ App.2~~.~~ for ~~the~~ detailed guidance on the monitoring of medical and scientific literature.

VI.B.1.1.4. Information on suspected adverse reactions from the internet or digital media

~~Marketing~~In line with ICH-E2D, marketing authorisation holders should regularly screen internet or digital media[10] under their management or responsibility, for potential reports of suspected adverse reactions. In this aspect, digital media is considered to be company sponsored if it is owned, paid for and/or controlled by the marketing authorisation holder[11]. The frequency of the screening should allow for potential valid ICSRs to be ~~reported~~submitted to the competent authorities within the appropriate reporting timeframe based on the date the information was posted on the internet site/digital medium. Marketing authorisation holders may also consider utilising their websites to facilitate the collection of reports of suspected adverse reactions (see VI.C.2.2.1.).

If a marketing authorisation holder becomes aware of a report of suspected adverse reaction described in any non-company sponsored digital medium, the report should be assessed to determine whether it qualifies for reporting.

Unsolicited cases of suspected adverse reactions from the internet or digital media should be handled as spontaneous reports. The same reporting time frames as for spontaneous reports should be applied (see VI.B.7.).

In relation to cases from the internet or digital media, the identifiability of the reporter refers to the possibility of verification of the existence of a real person, ~~that is, it is possible to verify the contact details of the reporter (~~based on the information available e.g., an email address under a valid format has been provided (see VI.B.2. for case validation). If the country of the primary source is missing, the country where the information was received, or where the review took place, should be used as the primary source country.

VI.B.1.2. Solicited reports

As defined in ICH-E2D (see GVP Annex IV), solicited reports of suspected adverse reactions are those derived from organised data collection systems, which include clinical trials, non-interventional studies, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers, compassionate use or name patient use, or information gathering on efficacy or patient compliance. Reports of suspected adverse reactions obtained from any of these data collection systems should not be considered spontaneous. This is with the exception of:

- suspected adverse reactions in relation to those adverse events for which the protocol of non-interventional post-authorisation studies ~~provides differently and~~ does not require their systematic collection (see VI.C.1.2.1.),
- suspected adverse reactions originating from compassionate use or named patient use conducted in Member States where the active collection of adverse events occurring in these programmes is not required (see VI.C.1.2.2.).

For the purpose of safety reporting, solicited reports should be classified as study reports, and should have an appropriate causality assessment, to consider whether they refer to suspected adverse reactions and therefore meet the criteria for reporting. Valid cases of suspected adverse reactions should be sent according to the modalities detailed in VI.B.7. and VI.B.8..

[10] Although not exhaustive, the following list should be considered as digital media: web site, web page, blog, vlog, social network, internet forum, chat room, health portal.
[11] A donation (financial or otherwise) to an organisation/site by a marketing authorisation holder does not constitute ownership, provided that the marketing authorisation holder does not control the final content of the site.

General reporting rules for suspected adverse reactions occurring in organised data collection systems conducted in the EU under the scope of Directive 2001/83/EC, Regulation (EC) No 726/2004 or Directive 2001/20/EC, are presented in VI.C.1.. Guidance on the management of solicited reports in the EU by marketing authorisation holders is provided in VI.C.2.2.2..

VI.B.2. Validation of reports

Only valid ICSRs qualify for reporting. All reports of suspected adverse reactions should therefore be validated before reporting them to the competent authorities to make sure that the minimum criteria for reporting are included in the reports (see ICH-E2D (see GVP Annex IV)). These are:

- **one or more identifiable**[12] **reporter** (~~primary source),~~see VI.A.2.3.), characterised by a qualification (e.g. physician, pharmacist, other healthcare professional, lawyer, consumer or other non-healthcare professional) ~~name, initials or address~~[13]~~.~~**and** at least one of the following parameters[14]: name, address[15] or phone number. An ICSR should not be considered valid for reporting unless this information is available for at least one reporter. Whenever possible, contact details for the reporter should be recorded so that follow-up activities can be performed. However, if the reporter does not wish to provide contact details, the ICSR should still be considered ~~as~~ valid, providing the organisation who was informed of the case was able to confirm it directly with the reporter. All parties providing case information or approached for case information should be identifiable, (not only the initial reporter~~.~~);
- **one single identifiable**[12] **patient,** characterised by at least one of the following qualifying descriptors: initials, ~~patient~~ identification number, date of birth, age, age group or gender. The information should be as complete as ~~possible~~[16]~~.~~ possible[14]. An ICSR should not be considered valid for reporting unless information is available for at least one of the patient qualifying descriptors Furthermore, as specified in ICH-E2D, a report referring to a definite number of patients should not be regarded as valid until the patients can be characterised by one of the aforementioned qualifying descriptors. For example, "Two patients experienced nausea with drug X …" should not be considered valid without further information;
- **one or more suspected**[17] **substance / medicinal product** (see VI.A.2.2.).
- **one or more suspected adverse reaction** (see VI.A.2.1.).

Examples of case validity assessment based on the reporter and the patient identifiability are provided in VI.App.8.

If the primary source has made an explicit statement that a causal relationship between the medicinal product and the reported adverse event has been excluded and the ~~receiver (~~notified competent authority or marketing authorisation holder~~)~~ agrees with this assessment, the report does not qualify as a valid ICSR since the minimum information for reporting is incomplete[18]. The report also does not ~~also~~ qualify as a valid ICSR if it is reported that the patient experienced an unspecified adverse reaction and there is no information ~~provided~~ on the type of adverse reaction experienced. Similarly, 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, or (ii) the

[12] In line with ICH-E2D, the term 'identifiable' is considered in EU as referring to the possibility of verification of the existence of a reporter and of a patient based on the information available.
[13] ~~Local data privacy laws regarding patient's and reporter's identifiability might apply.~~
[14] Local data protection laws regarding reporter's and patient's identifiability might apply.
[15] Such as reporter's organisation, department, street, city, state/province, postcode, country, or email.
[16] ~~See Footnote 9.~~
[17] Interacting medications are also considered suspected.
[18] There is no suspected adverse reaction.

primary source has not indicated a possible causal relationship with the suspected medicinal product. 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 ~~reported~~the valid ICSR should be submitted to the competent authorities.

The lack of any of ~~these~~the four elements means that the case is considered incomplete and does not qualify for reporting. Competent authorities and marketing authorisation holders are expected to exercise due diligence in following up the case to collect the missing data elements~~.~~ and follow-up activities should be documented. Reports, for which the minimum information is incomplete, should nevertheless be recorded within the pharmacovigilance system for use in on-going safety evaluation activities. Recommendations on the electronic reporting of valid ICSRs, when missing information has been obtained, are provided in VI.C.6.2.3.8~~.~~

~~When collecting reports of suspected adverse reactions via the internet or digital media, the term "identifiable" refers to the possibility of verification of the existence of a reporter and a patient (see VI.B.1.1.4.).~~. Further guidance is available in VI.C.6.2.2.10. for the electronic reporting of ICSRs where primary source information cannot be transmitted for data protection considerations.

When one party (competent authority or a marketing authorisation holder) is made aware that the primary source may also have reported the suspected adverse reaction to another concerned party, the report should still be considered as a valid ICSR. All the relevant information necessary for the detection of the duplicate case should be included in the ICSR[19]. Guidance on the electronic transmission of information allowing the detection of duplicate ICSRs in line with ICH-E2B is provided in VI.C.6.2.2.6.

A valid case of suspected adverse reaction initially ~~submitted~~reported by a consumer cannot be downgraded to a report of non-related adverse event if the contacted healthcare professional (nominated by the consumer for follow-up information) subsequently disagrees with the consumer's suspicion (see VI.A.2.1.1.). In this situation, the opinions of both the consumer and the healthcare professional should be included in the ICSR. Guidance on the reporting of the medical confirmation of a case~~,~~ provided in ~~ICH-E2B(R2) Section A.1.14 ("Was the case medically confirmed, if not initially from a healthcare professional?") (see GVP Annex IV),~~VI.A.2.3. should be followed.

For solicited reports of suspected adverse reactions (see VI.B.1.2.), where the ~~receiver~~notified recipient (competent authority or marketing authorisation holder) disagrees with the reasonable possibility of causal relationship between the suspected medicinal product and the adverse reaction expressed by the primary source, the case should not be downgraded to a report of ~~non-~~not causally related adverse event. The opinions of both, the primary source and the receiver, should be recorded in the ICSR.

The same principle applies to the ICSR seriousness criterion, which should not be downgraded from serious to non-serious if the ~~receiver~~notified recipient disagrees with the seriousness reported by the primary source.

~~[19] For further guidance on reporting of other duplicate ICSRs, refer to section A.1.11 "Other case identifiers in previous transmission" of ICH-E2B(R2) (see GVP Annex IV).~~

VI.B.3. Follow-up of reports

When first received, the information in suspected adverse reactions reports may be incomplete. These reports should be followed-up as necessary to obtain supplementary detailed information significant for the scientific evaluation of the cases. This is particularly relevant for monitored events of special interest, prospective reports of pregnancy, cases notifying the death of a patient, or cases reporting new risks or changes in the known risks. This is in addition to any effort to collect missing minimum ~~information~~ criteria for reporting (see VI.B.2.).

The provision in ICSRs of patient's age information is important in order to be able to identify safety issues occurring specifically in the paediatric or elderly population. All possible efforts should be made to follow-up on an individual case to obtain age information of the patient, where it is initially not reported by the primary source (see VI.B.6.2.).

Any attempt to obtain follow-up information should be documented.

Follow-up methods should be tailored towards optimising the collection of missing information. This should be done in ways that encourage the primary source to submit new information relevant for the scientific evaluation of a particular safety concern. The use of targeted specific forms in the local language should avoid requesting the primary source to repeat information already provided in the initial report and/or to complete extensive questionnaires, which could discourage future spontaneous reporting. Therefore, consideration should be given to pre-populating some data fields in those follow-up report forms to make their completion by the primary source easy. Further requirements applicable to competent authorities in Member States and to marketing authorisation holders are provided respectively in VI.C.2.1. and VI.C.2.2. with business process maps and process descriptions included in VI.App.1. Guidance on the electronic reporting of follow-up reports is available in VI.C.6.2.2.7..

When information is received directly from a consumer suggesting that an adverse reaction may have occurred, if the information is incomplete, attempts should be made to ~~obtain~~ follow-up with the consumer to collect further information and to obtain consent to contact a nominated healthcare professional to obtain further ~~follow-up~~ information. When ~~such a~~the case~~, initially reported by a consumer, has been~~ is subsequently confirmed (totally or partially) by a healthcare professional, this information should be ~~clearly highlighted~~captured in the ICSR[20]~~.~~ in line with ICH-E2B (see VI.A.2.3.).

For suspected adverse reactions relating to biological medicinal products, the definite identification of the concerned product with regard to its manufacturing is of particular importance. Therefore, all appropriate measures should be taken to clearly identify the name of the product and the batch number. A business process map and a process description in relation to the mandatory follow-up of information for the identification of suspected biological medicinal products ~~is~~are presented in ~~VI.Appendix 1.~~VI.App.1.4.

For cases related to vaccines, GVP P.I. should also be followed as appropriate.

For individual cases related to medication errors that result in harm, it may not always be possible to perform follow-up activities taking into account that the primary source information may have been anonymised in accordance with local legal requirements or due to provisions that allow for anonymous reporting.

~~[20] For further guidance on reporting this information, refer to ICH-E2B(R2), section A.1.14 ("Was the case medically confirmed, if not initially from a healthcare professional?") (see GVP Annex IV).~~

VI.B.4. Data management

Electronic data and paper reports of suspected adverse reactions should be stored and treated in the same way as other medical records with appropriate respect for confidentiality regarding patients' and reporters' identifiability and in accordance with ~~local~~applicable data ~~privacy~~protection laws. Confidentiality of patients' records including personal identifiers, if provided, should always be maintained. Identifiable personal details of reporting healthcare professionals should be kept in confidence~~.~~ protected from unauthorised access. With regards to patient's and reporter's identifiability, case report information should be transmitted between stakeholders (marketing authorisation holders or competent authorities) in accordance with local data ~~privacy~~protection laws (see ~~VI.C.6.2.2.8.~~VI.C.6.2.2.10. for the processing of personal data in ICSRs ~~in the EU~~).

~~In order to~~To ensure pharmacovigilance data security and confidentiality, strict access controls should be applied to documents and to databases to authorised personnel only. This security extends to the complete data path. In this aspect, procedures should be implemented to ensure security and non-corruption of data during data transfer.

When transfer of pharmacovigilance data occurs within an organisation or between organisations having concluded contractual agreements, the mechanism should be such that there is confidence that all notifications are received; in that, a confirmation and/or reconciliation process should be undertaken.

~~Correct data entry, including the appropriate use of terminologies, should be verified by quality assurance auditing, either systematically or by regular random evaluation. Data entry staff should be instructed in the use of the terminologies, and their proficiency confirmed.~~

Data received from the primary source should be treated in an unbiased and unfiltered way and inferences as well as imputations should be avoided during data entry or electronic transmission. The reports should include the verbatim text as used by the primary source ~~or~~and an accurate translation of it~~.~~ where applicable (see VI.C.6.2.2.9 for EU requirements on languages handling). The original verbatim text should be coded using the appropriate terminology as described in VI.B.8. ~~In order to~~To ensure consistency in the coding practices, it is recommended to use, where applicable, the translation of the terminology in the local language to code the verbatim text.

Electronic data storage should allow traceability (audit trail) of all data entered or modified, including dates and sources of received data, as well as dates and destinations of transmitted data.

A procedure should be in place to account for identification and management of duplicate cases at data entry and during the generation of aggregated reports (see VI.C.6.2.4.).

VI.B.5. Quality management

Competent authorities and marketing authorisation holders should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, such as data collection, data transfer, data management, data coding, case validation, case evaluation, case follow-up, ICSR reporting and case archiving (see VI.C.6.2.4. and GVP Module I).

Correct data entry, including the appropriate use of terminologies, should be monitored by quality assurance auditing, either systematically or by regular random evaluation.

Conformity of stored data with initial and follow-up reports should be verified by quality control procedures, which permit for the validation against the original data or images thereof. In this aspect, the source data (e.g., letters, emails, records of telephone calls that include details of an event) or an image of the source data should be easily accessible.

Clear written standard operating procedures should guarantee that the roles and responsibilities and the required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of the system. This is equally applicable to activities that are contracted out to third parties, whose procedures should be reviewed to verify that they are adequate and compliant with applicable requirements.

Staff directly performing pharmacovigilance activities, should be appropriately trained in applicable pharmacovigilance legislation and guidelines in addition to specific training in report processing activities for which they are responsible and/or undertake. Data entry staff should be instructed in the use of the terminologies, and their proficiency confirmed. Other personnel who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be trained in adverse event collection and reporting in accordance with internal policies and procedures.

VI.B.6. Special situations

VI.B.6.1. Use of a medicinal product during pregnancy or breastfeeding

a. Pregnancy

Reports, where the embryo or foetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure), should be followed-up in order to collect information on the outcome of the pregnancy and development of the child after birth. The recommendations provided in the Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-Authorisation Data (see GVP Annex III) and in GVP P. III. should be considered as regard the monitoring, collection and reporting of information in these specific situations in order to facilitate the scientific evaluation. When an active substance (or one of its metabolites) has a long half-life, this should be taken into account when assessing the possibility of exposure of the embryo, if the medicinal product was taken before conception.

Not infrequently, pregnant women or healthcare professionals will contact either competent authorities or marketing authorisation holders to request information on the teratogenicity of a medicinal product and/or experience of use during pregnancy. Reasonable attempts should be made to obtain information on any possible medicinal product exposure to an embryo or foetus and to follow-up on the outcome of the pregnancy.

Reports of exposure to medicinal products during pregnancy should contain as many detailed elements as possible in order to assess the causal relationships between any reported adverse events and the exposure to the suspected medicinal product. In this context the use of standard structured questionnaires is recommended.

Individual cases with an abnormal outcome associated with a medicinal product following exposure during pregnancy are classified as serious reports and should be ~~reported~~submitted, in accordance with the requirements outlined in VI.B.7.[21] and with the electronic reporting recommendations provided in VI.C.6.2.3.1..

This especially refers to:

- reports of congenital anomalies or developmental delay, in the foetus or the child;
- reports of foetal death and spontaneous abortion; and
- reports of suspected adverse reactions in the neonate that are classified as serious.

[21] See VI.C.6.2.3.1 for electronic reporting recommendations in the EU.

Other 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 ~~reported~~submitted since there is no suspected adverse reaction. These reports should however be collected and discussed in the periodic safety update reports (see GVP Module VII).

However, in certain circumstances, reports of pregnancy exposure with no suspected reactions may necessitate to be ~~reported.~~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).

A signal of a possible teratogen effect (e.g. through a cluster of similar abnormal outcomes) should be notified immediately to the competent authorities in accordance with the recommendations presented in VI.C.2.2.6.

b. Breastfeeding

The guidance provided in GVP P. III. on the conduct of pharmacovigilance for medicines exposed via breastfeeding should be followed. Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk should be ~~reported~~submitted in accordance with the criteria outlined in VI.B.7.[22] ~~.~~ and in line with the recommendations on electronic reporting provided in VI.C.6.2.3.1..

VI.B.6.2. Use of a medicinal product in a paediatric or elderly population

The collection of safety information in the paediatric or elderly population is important. Reasonable attempts should therefore be made to obtain and submit the age or age group of the patient when a case is reported by a healthcare professional, or consumer in order to be able to identify potential safety signals specific to a particular population. General guidance in VI.B.3. on reports follow-up should be applied.

~~As regards the paediatric population, the guidance published by the Agency~~[23]Guidance provided in GVP P. IV. on the conduct of pharmacovigilance ~~in this~~for medicines used in paediatric population, and in GVP P. V. on the conduct of pharmacovigilance for medicines used in elderly population should be followed.

VI.B.6.3. Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure

~~For the purpose of this Module, medication error refers to any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional or consumer.~~

Definitions of overdose, abuse, off-label use, misuse, medication error or occupational exposure are detailed in VI.A.2.1.2..

Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure with no associated adverse reaction should not be ~~reported~~submitted as ICSRs. They should be considered in periodic safety update reports as applicable. When those reports constitute safety issues impacting on

[22] ~~See Footnote 16.~~
[23] ~~Guideline on conduct of pharmacovigilance for medicines used by the paediatric population.~~

the risk-benefit balance of the medicinal product, they should be notified to the competent authorities in accordance with the recommendations provided in VI.C.2.2.6.

Reports associated with suspected adverse reactions should be subject to reporting in accordance with the criteria outlined in VI.B.7. and with the electronic reporting requirements described in VI.C.6.2.3.3. They should be routinely followed-up to ensure that the information is as complete as possible with regards to the symptoms, ~~treatments~~suspected medicinal products name, outcomes, context of occurrence (e.g., error in prescription, administration, dispensing, dosage, unauthorised indication or population, etc.).

With regards to reports of medication errors, further guidance concerning their management and assessment, provided in the Good Practice Guide on Recording, Coding, Reporting and Assessment of Medication Errors[24], should be followed.

VI.B.6.4. Lack of therapeutic efficacy

Reports of lack of therapeutic efficacy should be recorded and followed-up if incomplete. They should not normally be ~~reported, but~~submitted as ICSRs if there is no associated suspected adverse reaction, but they should be discussed in periodic safety update reports as applicable~~.~~ (see GVP Module VII). However, in certain circumstances, these reports of lack of therapeutic efficacy may require to be ~~reported~~submitted within a 15-day time frame (see VI.C.6.2.3.4. as regards electronic reporting in the EU). 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.

The requirement to submit these reports of lack of efficacy does not apply when the notification occurred in the frame of a non-interventional efficacy study. This is because they refer to the main end point of the study. For those efficacy studies, the requirements provided in VI.C.1.2.1. for non-interventional post-authorisation studies should be followed.

Clinical judgement should be used when considering if other cases of lack of therapeutic efficacy qualify for reporting. For example, a report of lack of therapeutic efficacy with an antibiotic used in a life-threatening situation where the use of the medicinal product was not in fact appropriate for the infective agent should not be ~~reported~~submitted. However, a report of lack of therapeutic efficacy for a life-threatening infection, ~~where the lack of therapeutic efficacy~~which appears to be due to the development of a newly resistant strain of a bacterium previously regarded as susceptible, should be ~~reported~~submitted as ICSR within 15 days.

For vaccines, cases of lack of ~~therapeutic~~prophylactic efficacy should be ~~reported~~submitted as ICSRs, in particular with the view to highlight potential signals of reduced immunogenicity in a sub-group of vaccinees, waning immunity, or strain replacement. With regard to the latter, it is considered that spontaneously reported cases of lack of ~~therapeutic~~prophylactic efficacy by a healthcare professional may constitute a signal of strain replacement. Such a signal may need prompt action and further investigation through post-authorisation safety studies as appropriate. General guidance regarding the monitoring of vaccines failure, provided in the Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance[25], may be followed.

[24] Ref.: EMA/762563/2014

[25] Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012. Accessible at: http://www.cioms.ch/

VI.B.7. Reporting of individual case safety reports (ICSRs)

Only valid ICSRs (see VI.B.2.) should be ~~reported~~submitted. The clock for the reporting of a valid ICSR starts as soon as the information containing the minimum reporting criteria has been brought to the attention of the national or regional pharmacovigilance centre of a competent authority or of any personnel of the marketing authorisation holder, including medical representatives and contractors. This date should be considered as day zero. It is the first day when a receiver gains knowledge of a valid ICSR, irrespective of whether the information is received during a weekend or public holiday. Reporting timelines are based on calendar days.

Where the marketing authorisation holder has set up contractual arrangements with a person or an organisation, explicit procedures and detailed agreements should exist between the marketing authorisation holder and the person/organisation to ensure that the marketing authorisation holder can comply with the reporting obligations. These procedures should in particular specify the processes for exchange of safety information, including timelines and regulatory reporting responsibilities and should avoid duplicate reporting to the competent authorities.

For ICSRs described in the scientific and medical literature (see VI.B.1.1.2.), the clock starts (day zero) with awareness of a publication containing the minimum information for reporting. Where contractual arrangements are made with a person/organisation to perform literature searches and/or report valid ICSRs, detailed agreements should exist to ensure that the marketing authorisation holder can comply with the reporting obligations.

When additional significant information is received for a previously ~~reported~~submitted case, the ~~reporting time~~ clock ~~starts again~~ for the submission of a follow-up report starts again from the date of receipt of the relevant follow-up information. For the purpose of reporting, significant follow-up information corresponds to new medical or administrative information that could impact on the assessment or management of a case, or could change its seriousness criteria; non-significant information includes updated comments on the case assessment, or corrections of typographical errors in the previous case version. See also VI.C.6.2.2.7. as regards the distinction between significant and non-significant follow-up information.

VI.B.7.1. Reporting time frames

In general, the reporting of serious valid ICSRs is required as soon as possible, but in no case later than 15 calendar days after initial receipt of the information by the national or regional pharmacovigilance centre of a competent authority or by any personnel of the marketing authorisation holder, including medical representatives and contractors. This applies to initial and follow-up information. Where a case initially ~~reported~~sent as serious becomes non-serious, based on new follow-up information, this information should still be ~~reported~~submitted within 15 days; the reporting time frame for non-serious reports should then be applied for the subsequent follow-up reports.

Information as regards the reporting time frame of non-serious valid ICSRs in the EU is provided in VI.C.3..

ICH-E2B provides a mechanism to the sender to indicate whether the case fulfils the local expedited requirements. Further guidance on this aspect is provided in VI.C.3..

VI. B.7.2 Report nullification

The nullification of a report should be used to indicate that a previously transmitted ICSR is considered completely void (nullified), for example when the whole case was found to be erroneous. Guidance on ICSRs nullification in line with ICH-E2B is provided in VI.C.6.2.2.10..

VI.B.7.3. Amendment report

There may be instances, where a report may need to be amended for example when, after an internal review or according to an expert opinion some items have been corrected, such as adverse event/reaction terms, seriousness, seriousness criteria or causality assessment but without receipt of new information that would warrant submission of a follow-up report. The same would apply where documentation mentioned in ICSRs, translations or literature articles are requested by the Agency or other Member States and are further sent as attachments in line with ICH E2B(R3). Further guidance on the amendment of ICSRs in line with ICH-E2B is provided in VI.C.6.2.2.8..

VI.B.8. Reporting modalities

~~Taking into account~~Given the international dimension of adverse reactions reporting and the need to achieve harmonisation and high quality between all involved parties, ICSRs should be submitted electronically as structured data with the use of controlled vocabularies for the relevant data elements where applicable.

In this aspect, with regard to the content and format of electronic ICSRs, competent authorities and marketing authorisation holders should adhere to the following internationally agreed ICH[26] guidelines and standards (see GVP Annex IV) taking into count the transition from ICH-E2B(R2) to ICH-E2B(R3) formats:

- ICH M1 terminology - Medical Dictionary for Regulatory Activities (MedDRA) (see GVP Annex IV), which should be used at the lowest level term for the transmission of ICSRs;
- MedDRA Term Selection: Points to Consider Document - The latest version of the ICH-endorsed Guide for MedDRA Users (see GVP Annex IV);
- ~~ICH M2 EWG - Electronic Transmission of Individual Case Safety Reports Message Specification (see GVP Annex IV);~~
- ~~ICH E2B(R2) - Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (see GVP Annex IV);~~
- ~~ICH E2B Implementation Working Group - Questions & Answers (R5) (March 3, 2005) (see GVP Annex IV).~~
- The guidelines applicable based on ICSRs ICH-E2B format:

Reference	Guidelines
ICH-E2B(R2)	• ICH-M2 EWG - Electronic Transmission of Individual Case Safety Reports Message Specification (see GVP Annex IV); • ICH-E2B(R2) - Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety

[26] ~~http://www.ich.org/~~

Reference	Guidelines
	Reports (see GVP Annex IV); • ICH-E2B Implementation Working Group - Questions & Answers (R5) (see GVP Annex IV);
ICH-E2B(R3)	• ICH Implementation guide package including the ICH-E2B(R3) Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) - Data Elements and Message Specification (see GVP Annex IV); • ICH-E2B(R3) Implementation Working Group - Electronic Transmission of Individual Case Safety Reports (ICSRs) - Questions & Answers (see GVP Annex IV);

As technical standards evolve over time, the above referred documents may require ~~revision and~~ maintenance or revision. In this context, the latest version of these documents should always be taken into account.

~~Information regarding~~ EU specific reporting modalities ~~is~~for ICSRs and the applicable guidelines, definitions, formats, standards and terminologies are provided respectively in VI.C.4. and VI.C.6.1.

VI.C. Operation of the EU network

Section C of this Module highlights the EU specific requirements, as defined in Directive 2001/83/EC and Regulation (EC) No 726/2004, in relation to the collection, management and reporting of reports of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in the EU, independently of their condition of use. They are applicable to competent authorities in Member States and/or to marketing authorisation holders. Section C should be read in conjunction with the definitions and general principles detailed in VI.A. and VI.B ~~of this Module~~. and with the requirements provided in chapters IV, V and IX of the Commission Implementing Regulation (EU) No 520/2012 [IR].

VI.C.1. Reporting rules for clinical trials and post-authorisation studies in the EU

The pharmacovigilance rules laid down in Directive 2001/83/EC and Regulation (EC) No 726/2004 do not apply to investigational medicinal products (IMPs) and non-investigational medicinal products[27] (NIMPs) used in clinical trials conducted in accordance with Directive 2001/20/EC[28] .

Post-authorisation safety or efficacy studies requested by competent authorities in Member States or the Agency in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004, or conducted voluntarily by marketing authorisation holders, can either be clinical trials or non-interventional post-authorisation studies as shown in Figure VI.1~~.~~. The safety reporting falls therefore either

- under the scope of Directive 2001/20/EC for any clinical trials; or
- under the provisions set out in Directive 2001/83/EC and Regulation (EC) No 726/2004 for any non-interventional post-authorisation studies.

Suspected adverse reactions should not be ~~reported~~submitted under both regimes, that ~~is~~are Directive 2001/20/EC as well as Regulation (EC) No 726/2004 and Directive 2001/83/EC, as this creates duplicate reports.

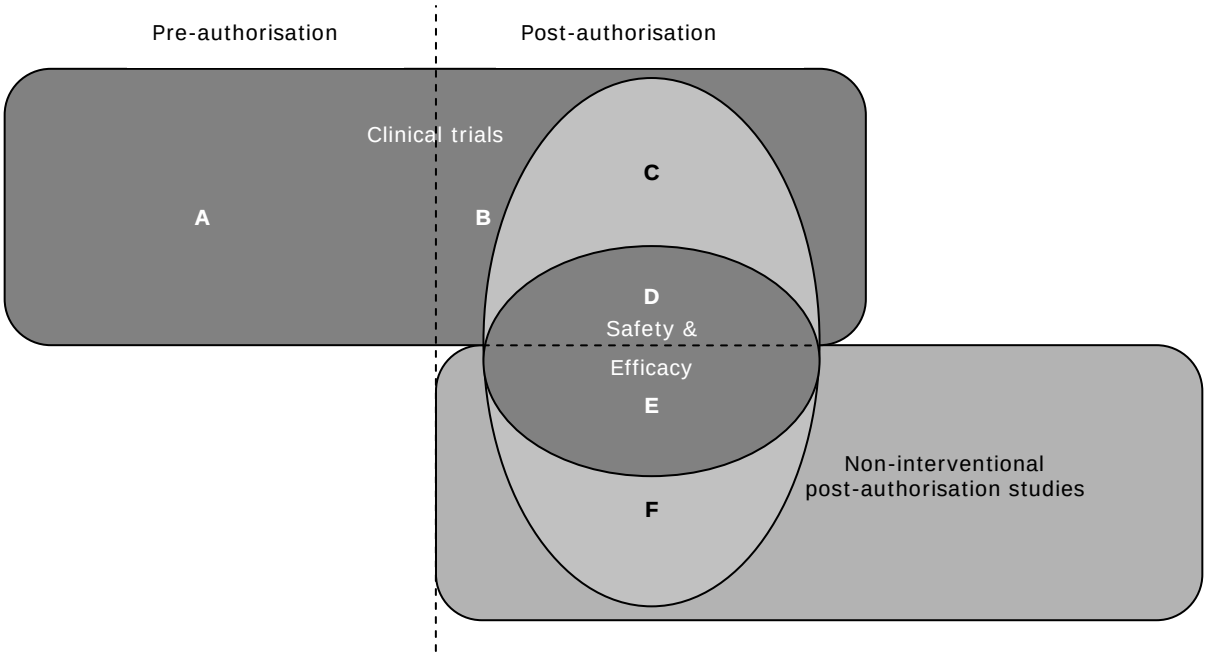
Further guidance on post-authorisation safety studies is provided in GVP Module VIII.

The different types of studies and clinical trials which can be conducted in the EU are illustrated in Figure VI.1~~.~~. The safety reporting for clinical trials corresponding to sections A, B, C and D of Figure VI.1. follows the requirements of Directive 2001/20/EC. The safety reporting for non-interventional post-authorisation studies corresponding to section E and F follows the requirements of Directive 2001/83/EC and Regulation (EC) No 726/2004. The reporting ~~rules~~rule of reports of suspected adverse reactions to the appropriate EudraVigilance database modules ~~are dependent~~ depends on the types of organised collection systems where ~~they~~the reactions occurred; recommendations provided in VI.C.6.2.1 should be followed.

[27] For guidance on these terms, see The Rules Governing Medicinal Products in the European Union, Volume 10, Guidance Applying to Clinical Trials, Guidance on Investigational Medicinal Products and Non-Investigational Medicinal Products (NIMPs) (Ares(2011)300458 - 18/03/2011), and the Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'), (2011/C 172/01) .

[28] See DIR Art 3(3) and Art 107(1) third subparagraph.

Figure VI.1. ~~Diagram illustrating different~~Different types of clinical trials and studies conducted in the EU



Section A: Clinical trials, which fall under the scope of Directive 2001/20/EC and which are conducted when no marketing authorisation exists in the EU.

Section B: Clinical trials, which fall under the scope of Directive 2001/20/EC and which are conducted in the post-authorisation period, e.g. for new indication.

Section C: Post-authorisation clinical trials conducted in accordance with the ~~summary~~terms of the marketing authorisation of the medicinal product~~ characteristics (SmPC) indication and condition of use~~, but which fall under the scope of Directive 2001/20/EC due to the nature of the intervention.

Section D: Post-authorisation safety or efficacy clinical trials requested in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004 or conducted voluntarily by marketing authorisation holders, but which fall under the scope of Directive 2001/20/EC due to the nature of the intervention.

Section E: Non-interventional post-authorisation safety or efficacy studies requested in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004 or conducted voluntarily by the marketing authorisation holders and which follow the same legal requirements.

Section F: Non-interventional post-authorisation studies conducted in accordance with ~~SmPC indication and condition of use~~the terms of the marketing authorisation of the medicinal product and which fall under the scope of Directive 2001/83/EC or Regulation (EC) No 726/2004.

VI.C.1.1. Reporting rules for clinical trials

A suspected adverse reaction to an investigational medicinal product occurring in a clinical trial which falls under the scope of Directive 2001/20/EC is only to be addressed by the sponsor based on the requirements detailed in that Directive. It is therefore excluded from the scope of this Module even if the clinical trial where the suspected adverse reaction occurred is a post-authorisation safety or efficacy study, requested in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004, or conducted voluntarily.

If a clinical trial, conducted under the scope of Directive 2001/20/EC, yields safety concerns which impact on the risk-benefit balance of an authorised medicinal product, the competent authorities in the Member States where the medicinal product is authorised and the Agency should be notified immediately in accordance with the modalities detailed in VI.C.2.2.6~~.~~. This applies as well if a safety concern arises from a clinical trial conducted exclusively outside the EU.

The safety data from clinical trials to be presented in the relevant sections of the periodic safety update report of the authorised medicinal product are detailed in GVP Module VII.

Where an untoward and unintended response originating from a clinical trial conducted in accordance with Directive 2001/20/EC, is suspected to be related only to a ~~non-investigational~~ medicinal product ~~(or another medicinal product, which is not part of~~other than the ~~clinical trial protocol)~~IMP or NIMP and does not result from a possible interaction with the ~~investigational medicinal product~~IMP or NIMP , it does not follow the expedited reporting requirements of Directive 2001/20/EC~~, which apply only to the investigational medicinal product~~. The investigator or the sponsor is encouraged to report the case to the competent authority in the Member State where the reaction occurred or to the marketing authorisation holder of the suspected medicinal product, but not to both to avoid duplicate reporting[29]. Where made aware of such case, the competent authority or the marketing authorisation holder should apply the reporting requirements described in VI.C.3~~.~~., VI.C.4. and VI.C.6~~.~~.. As regards electronic reporting, the recommendations detailed in VI.C.6.2.3.7.~~.~~, subsection 3 should be followed.

VI.C.1.2. Reporting rules for non-interventional post-authorisation studies, compassionate use and named patient use

This Section applies to non-interventional post-authorisation studies, compassionate use and named patient use. For these organised data collection schemes, a system should be put in place to record and document complete and comprehensive case information on solicited adverse events[~~30~~](see GVP Annex I) which need to be collected as specified in VI.C.1.2.1. and in VI.C.1.2.2.. ~~These~~In line with ICH-E2D (see GVP Annex IV), these adverse events should be systematically assessed to determine whether they are possibly related to the studied (or supplied) medicinal products ~~(see ICH-E2D (see GVP Annex IV)).~~. A method of causality assessment should be applied for assessing the causal role of the studied (or supplied) medicinal products in the solicited adverse events (for example, the WHO-UMC system for standardised case causality assessment). An adverse event should be classified as an adverse reaction, if there is at least a reasonable possibility of causal relationship. Only valid ICSRs (see VI.B.2.) of adverse reactions, which are suspected to be related to the studied (or supplied) medicinal product by the primary source or the receiver of the case, should be ~~reported~~submitted in accordance with the requirements provided in VI.C.3., VI.C.4. and VI.C.6.2.3.7.. Other reports of adverse events should be summarised as part of any interim safety analysis and in the final study report, where applicable. In situations where adverse reactions are suspected to be related to medicinal products other than the studied (or supplied) medicine, these reports should be managed, classified and ~~reported~~submitted as spontaneous ICSRs. They should be notified by the primary source to the competent authority in the Member State where the reactions occurred or to the marketing authorisation holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).

Where made aware, in the frame of these organised data collection schemes, of events which affect the known risk-benefit balance of the studied (or supplied) medicinal product and/or impact on public health, the marketing authorisation holder should notify the concerned competent authorities and the Agency in accordance with the modalities detailed in VI.C.2.2.6..

Further guidance on post-authorisation studies conducted by marketing authorisation holders is provided in VI.C.2.2.2..

The requirements provided in this Module do not apply to non-interventional post-authorisation studies conducted by organisations such as academia, medical research charities or research organisations in the public sector. These organisations should follow local requirements as regards the reporting of cases of suspected adverse reactions to the competent authority in the Member State where the

[29] See The Rules Governing Medicinal Products in the European Union, Volume 10, Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'). (2011/C 172/01).

[~~30~~] ~~See GVP Annex I for definition of adverse event.~~

reaction occurred. However, where a study conducted by one of these organisations is directly initiated, managed, financed, or where its design is controlled by a marketing authorisation holder (voluntarily or pursuant to obligations imposed in accordance with Articles 21a or 22a of Directive 2001/83/EC and Articles 10 or 10(a) of Regulation 726/2004), the requirements provided in this Module are applicable[31]. In this context, contractual agreements should be in place to clearly define the role and responsibilities for implementing these requirements (see GVP Module I).

VI.C.1.2.1. Non-interventional post-authorisation studies

Non-interventional post-authorisation studies[32] (see GVP Annex I) should be distinguished between those with primary data collection directly from healthcare professionals or consumers and study designs which are based on the secondary use of data. Depending on the study design, the requirements provided hereafter apply[33]. In case of doubt, the reporting requirements should be clarified with the concerned competent authorities in Member States. National legislation should be followed as applicable regarding the obligations towards local ethics committees.

a. *Non-interventional post-authorisation studies with primary data collection*

Information on all adverse events should be collected from healthcare professionals or consumers in the course of the study unless the protocol provides differently with a due justification for not collecting certain adverse events. For all collected adverse events, comprehensive and high quality information should be sought in a manner which allow for valid ICSRs to be ~~reported~~submitted within the appropriate timeframes (see VI.C.3.).

For all collected adverse events, cases of adverse reactions, which are suspected to be related to the studied medicinal product by the primary source or the receiver of the case, should be ~~reported~~submitted in accordance with the requirements provided in VI.C.3. and VI.C.4.. Valid ICSRs should be classified as solicited reports (see VI.C.2.2.2. and VI.C.6.2.3.7.). See summary in Table VI.1..

All fatal outcomes should be considered as adverse events which should be collected. In certain circumstances, suspected adverse reactions with fatal outcome may not be subject to ~~expedited~~ reporting as ICSRs, for example because they refer to study outcomes (efficacy end points), because the patients included in the study have a disease with high mortality, or because the fatal outcomes have no relation to the objective of the study. For these particular situations, the rational for not reporting as ICSRs certain adverse reactions with fatal outcomes should be clearly described in the protocol.

All collected adverse events should be summarised as part of any interim safety analysis and in the final study report.

[31] This does not concern donation of a medicinal product for research purpose if the marketing authorisation holder has no control on the study.

[32] ~~See GVP Annex I for definition of non-interventional study.~~

[33] For combined study designs ~~with~~based on primary ~~and secondary~~ data collection and secondary use of data , the same requirements as for studies with primary data collection should be followed.

Table VI.1. ~~Non-interventional post-authorisation studies with primary data collection:~~ Requirements concerning adverse events collection and suspected adverse reactions reporting~~.~~ for non-interventional post-authorisation studies with primary data collection

	Adverse events for which the protocol ~~does not provide differently~~requires their systematic collection and those with fatal outcomes
Collection requirements	• Collect comprehensive and high quality information. • Perform causality assessment.
Reporting requirements for suspected adverse reactions	• Cases of adverse reactions, which are suspected to be related to the studied medicinal product by the primary source or the receiver of the case, should be ~~reported~~submitted in the form of valid ICSRs in line with the appropriate timeframes (~~See VI.C.3)~~see VI.C.3.). • In certain circumstances, fatal outcome may not be subject to ~~expedited~~ reporting as ICSRs. A justification should always be provided in the protocol.
Reporting requirements for adverse events	• Summarise all collected adverse events as part of any interim safety analysis and in the final study report.

For adverse events for which the protocol ~~provides differently and~~ does not require their systematic collection, healthcare professionals and consumers should be informed in the protocol (or other study documents) of the possibility to report adverse reactions (for which they suspect a causal role of a medicine) to the marketing authorisation holder of the suspected medicinal product (studied or not) or to the concerned competent ~~authorities~~authority via the national spontaneous reporting system. ~~Valid~~The resulting valid ICSRs should be managed, classified and ~~reported~~submitted as spontaneous (see VI.C.6.2.3.7. subsection 2) by the ~~receiver of the reports.~~notified competent authority or marketing authorisation holder. When made aware of them, these reports should also be summarised by the marketing authorisation holder in the relevant study reports.

b. Non-interventional post-authorisation studies based on secondary use of data

The design of such studies is characterised by the secondary use of data previously collected from consumers or healthcare professionals for other purposes. Examples include medical chart reviews (including following-up on data with healthcare professionals), analysis of electronic healthcare records, systematic reviews, meta-analyses.

For these studies, the reporting of suspected adverse reactions in the form of ICSRs is not required. Reports of adverse events/reactions should be summarised as part of any interim safety analysis and in the final study report unless the protocol provides for different reporting.

VI.C.1.2.2. Compassionate use and named patient use

The guidance provided in this Module applies~~, subject to amendments where appropriate,~~ to medicinal products supplied in the context of compassionate use as defined in Article 83(2) of Regulation (EC) No 726/2004~~.~~, subject to and without prejudice to applicable national law in the EU Member States. As the case may be, this guidance may also apply to named patient use as defined under Article 5(1) of Directive 2001/83/EC. Local requirements should be followed as applicable.

Where an organisation[34] or a healthcare professional, supplying a medicinal product under compassionate use or named patient use, is notified or becomes aware of an adverse event, it should be managed as follows depending on the requirements in the concerned Member State:

- For compassionate use and named patient use conducted in Member States where the active collection of adverse events occurring in these programmes is required, reports of adverse reactions, which are suspected to be related to the supplied medicinal product by the primary source or the receiver of the case, should be ~~reported.~~submitted as ICSRs. They should be considered as solicited reports (see VI.C.2.2.2. and VI.C.6.2.3.7.~~).~~ subsection 1).
- For compassionate use and named patient use conducted in Member States where the active collection of adverse events occurring in these programmes is not required, any notified noxious or unintended response to the supplied medicinal product should be ~~reported.~~submitted as ICSR. It should be considered as a spontaneous report of suspected adverse reaction~~.~~ (see VI.C.6.2.3.7. subsection 2).

VI.C.2. Collection of reports

VI.C.2.1. Responsibilities of Member States

Each Member State shall have in place a system for the collection and recording of unsolicited and solicited reports of suspected adverse reactions that occur in its territory and which are brought to its attention by healthcare professionals, consumers, or marketing authorisation holders[35] [DIR Art 101(1) and 107a(1)]. In this context, competent authorities in Member States shall establish procedures for collecting and recording all reports of suspected adverse reactions that occur in their territory [IR Art 15 (2)]. The general principles detailed in VI.B~~.~~, together with the reporting modalities presented in VI.C.3., VI.C.4. and VI.C.6. ~~should be applied to those reports.~~ should be applied to those reports. Member States shall involve patients and healthcare professionals, as appropriate, in the follow-up of any reports they receive in order to comply with Article 102(c) and (e) [DIR Art 107a(1)]. Furthermore, for reports submitted by a marketing authorisation holder, Member States on whose territory the suspected adverse reaction occurred may involve the marketing authorisation holder in the follow-up of the reports [DIR Art 107a(2)]. In support of the operation of these follow-up procedures, business process maps and process descriptions are provided in VI.App.1.2 and VI.App.1.3. The criteria upon which competent authorities in Member States may involve a marketing authorisation holder in the follow-up of individual cases refer to the need to seek clarifications on inconsistent data in ICSRs, but also to the need to obtain further information in the context of the validation of a signal, the evaluation of a safety issue, the assessment of a periodic safety update report or the confirmation of a safety concern in a risk management plan. Further guidance on the follow-up of ICSRs is provided in VI.B.3..

Pharmacovigilance data and documents relating to individual authorised medicinal products shall be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has expired. However, the documents shall be retained for a longer period where Union law or national law so requires [IR Art 16(2)].

Each Member State shall take all appropriate measures to encourage healthcare professionals and consumers in their territory to report suspected adverse reactions to their competent authority. In addition, the competent authority in a Member State may impose specific obligations on healthcare

[34] E.g. sponsor, applicant, marketing authorisation holder, hospital or wholesaler.
[35] Marketing authorisation holders shall report ICSRs to the competent authorities in Member States in accordance with the transitional provisions set out in Article 2(4) and Article 2(5) of Directive 2010/84/EU and further detailed in VI.C.4.1.

professionals. To this end, competent authorities in Member States shall facilitate in their territory the reporting of suspected adverse reactions by means of alternative straightforward reporting systems, accessible to healthcare professionals and consumers, in addition to web-based formats [DIR Art 102]. Information on the different ways of reporting suspected adverse reactions related to medicinal products, shall be made publicly available including by means of national medicines web-based portals [DIR 106(e)]. To increase awareness of the reporting systems, organisations representing consumers and healthcare professionals may be involved as appropriate [DIR Art 102].

~~Standard~~In line with Article 25 of Regulation (EC) No 726/2004, standard web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and consumers ~~shall be~~have been developed by the ~~Agency~~Member States in collaboration with ~~Member States~~the Agency in order to collect across the EU harmonised information relevant for the evaluation of suspected adverse reactions, including errors associated with the use of medicinal products~~ [REG Art 25]. In this context, core data fields for reporting will be made available by the Agency to the competent authorities in Member States for use in their national reporting systems as applicable.~~.

The reports of suspected adverse reactions received from healthcare professionals and consumers should be acknowledged where appropriate and further information should be provided to the reporters as requested and when available.

~~For reports submitted by a marketing authorisation holder,~~ Member States ~~on whose territory the suspected adverse reaction occurred may involve the marketing authorisation holder in the follow-up of the reports [DIR Art 107a(2)].~~

~~Each Member State~~ shall ensure that the ~~competent authority~~reports of suspected adverse reactions arising from an error associated with the use of a medicinal product that are brought to their attention are made available to the EudraVigilance database and to any authorities, bodies, organisations and/or institutions, responsible for patient safety within that Member State. They shall also ensure that the authorities responsible for medicinal products within that Member State ~~is~~are informed of any suspected adverse ~~reaction,~~reactions brought to the attention of any other authority~~, body, institution or organisation responsible for patient safety within that Member State, and that valid ICSRs are made available to the EudraVigilance database. Therefore, where reports of suspected adverse reactions are sent directly to other authorities, bodies, organisations and/or institutions within a Member State, the competent authority in that Member State shall have data exchange agreements in place so that these reports are brought to its attention and are made available to EudraVigilance in a timely manner[DIR Art 107a(5)]. This applies as well to reports of suspected adverse reactions arising from an error associated with the use of a medicinal product. Those error reports of suspected adverse reactions for which a competent authority in a Member State is made aware of, including those received from the EudraVigilance database in accordance with Article 24(4) of Regulation (EC) No 726/2004, shall also be brought to the attention of other authorities, bodies, organisations and/or institutions responsible for patient safety within that Member State [DIR Art 107a(5)].~~ within that Member State [DIR Art 107a(5)]

To facilitate such reporting, it may be necessary to implement data exchange agreements or other arrangements, as appropriate.

Unless there are justifiable grounds resulting from pharmacovigilance activities, individual Member States shall not impose any additional obligations on marketing authorisation holders for the reporting of suspected adverse reactions [DIR Art 107a(6)].

VI.C.2.2. Responsibilities of the marketing authorisation holder in the EU

Each marketing authorisation holder shall have in place a system for the collection and recording of all reports of suspected adverse reactions which are brought to its attention, whether reported spontaneously by healthcare professionals or consumers or occurring in the context of a post-authorisation study [DIR Art 104(1), Art 107(1)]. Marketing authorisation holders shall establish procedures in order to obtain accurate and verifiable data for the scientific evaluation of suspected adverse reaction reports [Dir Art 107(4)]. They shall not refuse to consider reports of suspected adverse reactions received electronically or by any other appropriate means from patients and healthcare professionals [Art 107(2)]. ~~All those reports shall be accessible at a single point within the Union [Dir Art 107(1)].~~

All these reports of suspected adverse reactions shall be accessible at a single point within the Union [Dir Art 107(1)]. Marketing authorisation holders shall also collect follow-up information on these reports and submit the updates to the Eudravigilance database [Dir Art 107(4)]. In support of the operation of the follow-up procedures, a business process map and a process description are provided in VI.App.1.1. General guidance on the following-up of reports of suspected adverse reactions is provided in VI.B.3.. Marketing authorisation holders shall establish mechanisms enabling the traceability and follow-up of adverse reaction reports while complying with the data protection legislation [IR Art 12 (1)]. Pharmacovigilance data and documents relating to individual authorised medicinal products shall be retained as long as the product is authorised and for at least 10 years after the marketing authorisation has ceased to exist. However, the documents shall be retained for a longer period where Union law or national law so requires [IR Art 12 (2)].

With regard to the collection and recording of reports of suspected adverse reactions, marketing authorisation holders responsibilities apply to reports related to medicinal products (see VI.A.2.2.) for which ownership cannot be excluded on the basis of one the following criteria: medicinal product name, active substance name, pharmaceutical form, batch number or route of administration. Exclusion based on the primary source country or country of origin of the adverse reaction is possible if the marketing authorisation holder can demonstrate that the suspected medicinal product has never been supplied or placed on the market in that territory or that the product is not a travel medicine (e.g., anti-malarial medicinal product).

The marketing authorisation holder shall ensure that any information on adverse reactions, suspected to be related to at least one of the active substances of its medicinal products authorised in the EU, is brought to its attention by any company outside the EU belonging to the same mother company (or group of companies) [36]. The same applies to the marketing authorisation holder when having concluded a commercial agreement with a company outside the EU for one of its medicinal product authorised in the EU. Pursuant to Dir Art 107(1), those reports of suspected adverse reactions shall also be accessible at a single point within the EU. The clock for reporting (see VI.B.7.) starts when a valid ICSR is first received by one of these companies outside the EU.

In addition to the requirements presented in this Section, the general principles detailed in Section VI.B., together with the reporting modalities presented in VI.C.3., VI.C.4. and VI.C.6. should be applied by marketing authorisation holders to all reports of suspected adverse reactions.

[36] As outlined in the Commission Communication on the Community Marketing Authorization Procedures for Medicinal Products (98/C 229/03).

VI.C.2.2.1. Spontaneous reports

Marketing authorisation holders shall record all reports of suspected adverse reactions originating from within or outside the EU, which are brought to their attention spontaneously by healthcare professionals~~,~~ or consumers. This includes reports of suspected adverse reactions received electronically or by any other appropriate means [DIR Art 107(1), Art 107(2)]. In this context, marketing authorisation holders may consider utilising their websites to facilitate the collection of reports of suspected adverse reactions by providing adverse reactions forms for reporting, or appropriate contact details for direct communication (see VI.B.1.1.4.).

VI.C.2.2.2. Solicited reports

In accordance with Art 107(1) of Directive 2001/83/EC, marketing authorisation holders shall record all reports of suspected adverse reactions originating from within or outside the EU, which occur in post-authorisation studies, initiated, managed, or financed by them[37]. For non-interventional post-authorisation studies, this requirement applies to study designs based on primary data collection and the guidance provided in VI.C.1.2.1. should be followed. For all solicited reports (see VI.B.1.2.), marketing authorisation holders should have mechanisms in place to record and document complete and comprehensive case information and to evaluate that information, in order to allow meaningful assessment of individual cases and reporting of valid ICSRs (see VI.B.2.) related to the studied (or supplied) medicinal product. Marketing authorisation holders should therefore exercise due diligence in establishing such system, in following-up those reports (see VI.B.3.) and in seeking the view of the primary source as regard the causal role of the studied (or supplied) medicinal product on the notified adverse event. Where this opinion is missing, the marketing authorisation holder should exercise its own judgement based on the information available in order to decide whether the report is a valid ICSR, which should be ~~reported~~submitted to the competent authorities. This requirement does not apply to study designs based on secondary use of data since reporting of ICSRs is not required (see VI.C.1.2.1.). Safety data from solicited reports to be presented in the relevant sections of the periodic safety update report of the authorised medicinal product are detailed in GVP Module VII.

VI.C.2.2.3. Case reports published in the scientific literature

General principles in relation to the monitoring for individual cases of suspected adverse reactions described in the scientific and medical literature are provided in VI.B.1.1.2.. ~~As~~Detailed guidance on the monitoring of the scientific and medical literature is provided in VI.App.2. Electronic reporting recommendations for ICSRs published in the scientific and medical literature are provided in VI.C.6.2.3.2..

With regards the screening of the scientific and medical literature, the requirements provided in this Module are part of the reporting of individual cases of suspected adverse reactions as well as wider literature searches which need to be conducted for periodic safety update reports (see GVP Module VII).

VI.C.2.2.3.1 Monitoring of medical literature by the European Medicines Agency

The Agency shall monitor selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances. It shall publish a list of active substances being monitored and the medical literature subject to this monitoring. The Agency shall enter into the

[37] This does not concern donation of a medicinal product for research purpose if the marketing authorisation holder has no control on the study.

EudraVigilance database relevant information from the selected medical literature. The Agency shall, in consultation with the European Commission, Member States and interested parties, draw up a detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database [REG Art 27].

The medical literature and the active substances subject to the monitoring by the Agency are published at a dedicated webpage[38] of the Agency's website together with supporting documents. Further information is also provided in the Detailed Guide Regarding the Monitoring of Medical Literature and the Entry of Relevant Information into the EudraVigilance Database by the European Medicines Agency[39], which defines the different steps of the medical literature monitoring (MLM) business processes.

In accordance with Article 107(3) of Directive 2001/83/EC~~, in order~~ and to avoid the reporting of duplicate ICSRs, marketing authorisation holders shall only report those ICSRs described in the scientific and medical literature which is not reviewed by the Agency, for all medicinal products containing active substances which are not included in the list monitored by the Agency pursuant to Article 27 of Regulation (EC) No 726/2004. ~~Until such lists of scientific and medical literature and active substance names are published by the Agency, marketing authorisation holders should monitor all the active substances for which they hold a marketing authorisation in the EU by accessing a widely used systematic literature review and reference database, in line with the principles detailed in VI.B.1.1.2. and in VI. Appendix 2.~~

~~Articles can be excluded from the reporting of ICSRs by the marketing authorisation holder if another company's branded medicinal product is the suspected medicinal product. In the absence of a specified medicinal product source and/or invented name, ownership of the medicinal product should be assumed for articles about an active substance, unless alternative reasons for exclusion detailed hereafter apply:~~

VI.C.2.2.3.2 Exclusion criteria for the reporting of ICSRs published in the scientific literature

The following exclusion criteria for ICSR reporting by marketing authorisation holders apply for individual cases published in the scientific literature:

a. where ownership of the medicinal product by the marketing authorisation holder can be excluded on the basis of the criteria detailed in VI.C.2.2~~.~~ : medicinal product name, active substance name, pharmaceutical form, batch number or route of administration;

b. ~~for individual case safety reports identified in the scientific and medical literature that originate~~which originates in a country where a company holds a marketing authorisation but has never commercialised the medicinal product;

c. ~~for literature ICSRs~~ which ~~are~~is based on an analysis from a competent authority database within the EU. ~~The~~However, the reporting requirements remain for those ICSRs which are based on the analysis from a competent authority database outside the EU;

d. ~~for literature articles,~~ which ~~present~~presents aggregated data analyses or line listings from publicly available databases ~~or,~~ e.g. poison control centres,

e. which ~~summarise~~summarises results from post-authorisation studies ~~(see VI.C.1.2.). This type of literature article~~ or literature reviews,

[38] Monitoring of medical literature and entry of adverse reaction reports into EudraVigilance
[39] Ref.: (Doc Ref. EMA/161530/2014)

f. which describes suspected adverse reactions, which occur in a group of patients with a designated medicinal product ~~with the aim of~~and individual patients cannot be identified for creating valid case reports.

For points d to f, this type of literature aims at identifying or quantifying a safety hazard related to a medicinal product~~, and aggregated data on patients are often presented in tables or line listings.~~. The main objective ~~of those studies~~ is to detect/evaluate specific risks that could affect the overall risk-benefit balance of a medicinal product.

New and significant safety findings presented in these articles, for which reporting is not required, should however be discussed in the relevant sections of the concerned periodic safety update report (see GVP Module VII) and analysed as regards their overall impact on the medicinal product risk-benefit profile. In addition, any new safety information, which may impact on the risk-benefit profile of a medicinal product, should be notified immediately to the competent authorities in Member States where the medicinal product is authorised and to the Agency in accordance with the recommendations provided in VI.C.2.2.6..

~~A detailed guidance on the monitoring of the scientific and medical literature has been developed in accordance with Article 27(3) of Regulation (EC) No 726/2004; it is included in VI. Appendix 2.~~

~~The electronic reporting recommendations regarding suspected adverse reactions reports published in the scientific and medical literature are provided in VI.C.6.2.3.2..~~

VI.C.2.2.4. Suspected adverse reactions related to quality defect or falsified medicinal products

When a report of suspected adverse reactions is associated with a suspected or confirmed falsified medicinal product ~~or~~(see GVP Annex I) or with a quality defect of a medicinal product, a valid ICSR should be ~~reported~~submitted. The seriousness of the ICSR is linked to the seriousness of the reported suspected adverse reactions in accordance with the definitions provided in VI.A.2.4.. Electronic reporting recommendations provided in VI.C.6.2.3.5. should be followed.

In addition in order to protect public health, it may become necessary to implement urgent measures such as the recall of one or more defective batch(es) of a medicinal product from the market. Therefore, marketing authorisation holders should have a system in place to ensure that reports of suspected adverse reactions related to falsified medicinal products or to quality defects of a medicinal products are investigated in a timely fashion and that confirmed quality defects are notified separately to the manufacturer and to competent authorities in accordance with the provisions described in Article 13 of Directive 2003/94/EC.

VI.C.2.2.5. Suspected transmission via a medicinal product of an infectious agent

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product (including vaccines) should be considered as a serious adverse reaction and such cases should be ~~reported~~submitted within 15 days in accordance with the requirements outlined in VI.C.4.~~.~~[40]. If no other criterion is applicable, the seriousness of this ICSR should be considered as important medical event (see VI.A.2.4.). This also applies to vaccines. Electronic reporting recommendations provided in ~~VI.C.6.2.3.6.~~VI.C.6.2.3.6. should be followed.

In the case of medicinal products derived from human blood or human plasma, haemovigilance procedures may also apply in accordance with Directive 2002/98/EC. Therefore the marketing

[40] See VI.C.6.2.3.6. for electronic reporting recommendations.

authorisation holder should have a system in place to communicate suspected transmission via a medicinal product of an infectious agent to the manufacturer, the relevant blood establishment(s) and national competent authorities in Member States.

Any organism, virus or infectious particle (e.g. prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

A transmission of an infectious agent may be suspected from clinical signs or symptoms, or laboratory findings indicating an infection in a patient exposed to a medicinal product.

Emphasis should be on the detection of infections/infectious agents known to be potentially transmitted via a medicinal product, but the occurrence of unknown agents should also always be considered.

In the context of evaluating a suspected transmission of an infectious agent via a medicinal product, care should be taken to discriminate, whenever possible, between the cause (e.g. injection/ administration) and the source (e.g. contamination) of the infection and the clinical conditions of the patient at the time of the infection (immuno-suppressed /vaccinee).

Confirmation of contamination (including inadequate inactivation/attenuation of infectious agents as active substances) of the concerned medicinal product increases the evidence for transmission of an infectious agent and may therefore be suggestive of a quality defect for which the procedures detailed in VI.C.2.2.4. should be applied.

Medicinal products should comply with the recommendations provided in the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Products[41]. For advanced therapy medicinal products, Article 14(5) of Regulation (EC) No 1394/2007 and the Guideline on Safety and Efficacy Follow-up - Risk Management of Advanced Therapy Medicinal Products[42], should also be followed as appropriate.

VI.C.2.2.6. Emerging safety issues

Events may occur, which do not fall within the definition of reportable valid ICSRs, and thus are not subject to the reporting requirements, even though they may lead to changes in the known risk-benefit balance of a medicinal product and/or impact on public health. ~~Examples include:~~

- ~~major safety findings from a newly completed non-clinical study;~~
- ~~major safety concerns identified in the course of a non-interventional post-authorisation study or of a clinical trial;~~
- ~~signal of a possible teratogen effect or of significant hazard to public health;~~
- ~~safety issues published in the scientific and medical literature;~~
- ~~safety issues arising from the signal detection activity (see Module IX) or emerging from a new ICSR and which impact on the risk-benefit balance of the medicinal product and/or have implications for public health;~~
- ~~safety issues related to the use outside the terms of the marketing authorisation;~~
- ~~safety issues due to misinformation in the product information;~~

[41] Latest revision. (Ref.: EMA/410/01)
[42] Ref.: EMEA/149995/2008

- ~~marketing authorisation withdrawal, non-renewal, revocation or suspension outside the EU for safety related reasons;~~
- ~~urgent safety restrictions outside the EU;~~
- ~~safety issues in relation to the supply of raw material;~~
- ~~lack of supply of medicines.~~

These events/observations, which may affect the risk-benefit balance of a medicinal product, are not to be submitted as ICSRs. ~~They should be notified as emerging safety issues in writing to the competent authorities in Member States where the medicinal product is authorised and to the Agency via email (P-PV-emerging-safety-issue@ema.europa.eu); this should be done immediately when becoming aware of them. The document should indicate the points of concern and the actions proposed in relation to the marketing application/authorisation for the concerned medicinal product. Those safety issues should also be analysed in the relevant sections of the periodic safety update report of the authorised medicinal product~~They should be notified as emerging safety issues in accordance with the requirements provided in GVP Module IX.

VI.C.2.2.7. Period between the submission of the marketing authorisation application and the granting of the marketing authorisation

In the period between the submission of the marketing authorisation application and the granting of the marketing authorisation, information (quality, non-clinical, clinical) that could impact on the risk-benefit balance of the medicinal product under evaluation may become available to the applicant[43]. It is the responsibility of the applicant to ensure that this information is immediately submitted in accordance with the modalities described in VI.C.2.2.6. to the competent authorities in the Member States where the application is under assessment (including Reference Member State and all concerned Member States for products assessed under the mutual recognition or decentralised procedures) and to the Agency. For applications under the centralised procedure, the information should also be provided to the (Co-) Rapporteur.

In the situation where a medicinal product application is under evaluation in the EU while it has already been authorised in a third country, valid ICSRs from outside the EU, originating from unsolicited reports (see VI.B.1.1.) or solicited reports (see VI.B.1.2.), should be ~~reported~~submitted in accordance with the requirements provided in VI.C.3., VI.C.4. and VI.C.6.

VI.C.2.2.8. Period after suspension, revocation or withdrawal of marketing authorisation

The marketing authorisation holder shall continue to collect any reports of suspected adverse reactions related to the concerned medicinal product following the suspension of a marketing authorisation. The reporting requirements outlined in VI.C.4. remain.

Where a marketing authorisation is withdrawn or revoked, the former marketing authorisation holder is encouraged to continue to collect spontaneous reports of suspected adverse reactions originating within the EU to for example facilitate the review of delayed onset adverse reactions or of retrospectively notified cases.

[43] See also chapter 1, section 5.1.1 of Volume 2A (Notice to Applicants) of The Rules Governing Medicinal Products in the European Union~~.~~, accessible at http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm.

VI.C.2.2.9. Period during a public health emergency

A public health emergency is a public health threat duly recognised either by the World Health Organization (WHO) or the Community in the framework of Decision No. 2119/98/EC as amended of the European Parliament and of the Council. In the event of a public health emergency, regular reporting requirements may be amended. Such arrangements will be considered on a case-by-case basis and will be appropriately notified on the Agency website.

VI.C.2.2.10. Reports from class action lawsuits

Stimulated reports arising from class action lawsuits should be managed as spontaneous reports. Valid ICSRs should describe suspected adverse reactions related to the concerned medicinal product. They should be ~~reported~~submitted in accordance with the time frames and modalities described in VI.C.3., VI.C.4. and VI.C.6..

Where large batches of potential ICSRs are received, marketing authorisation holders may request, in exceptional circumstances, for an exemption in order to submit serious cases of suspected adverse reactions within 30 days from their date of receipt instead of 15 days. The 90 days reporting time frame for non-serious ICSRs remains unchanged. It will be possible to apply for this exemption only once the functionalities of the EudraVigilance database specified in Article 24(2) of Regulation (EC) No 726/2004 are established. The request should be made to the Agency's pharmacovigilance department.

VI.C.2.2.11. Reports from patient support programmes and market research programmes

A patient support programme is an organised system where a marketing authorisation holder receives and collects information relating to the use of its medicinal products. Examples are post-authorisation patient support and disease management programmes, surveys of patients and healthcare providers, information gathering on patient compliance, or compensation/re-imbursement schemes.

A market research programme refers to the systematic collection, recording and analysis by a marketing authorisation holder of data and findings about its medicinal products, relevant for marketing and business development.

Safety reports originating from those programmes should be considered as solicited reports. Marketing authorisation holders should have the same mechanisms in place as for all other solicited reports (see VI.C.2.2.2.) to manage that information and report valid cases of adverse reactions, which are suspected to be related to the concerned medicinal product.

Valid ICSRs should be ~~reported~~submitted as solicited in accordance with the electronic reporting requirements provided in VI.C.6.2.3.7..

VI.C.3. Reporting time frames

The general rules in relation to the reporting of initial and follow-up reports, including those for defining the clock start are detailed in VI.B.7..

According to Articles 107(3) and 107a(4) of Directive 2001/83/EC,

- serious valid ICSRs shall be ~~reported~~submitted by competent authorities in Member States or by marketing authorisation holders within 15 days from the date of receipt of the reports;
- non-serious valid ICSRs shall be ~~reported~~submitted by competent authorities in Member States or by marketing authorisation holders within 90 days from the date of receipt of the reports.

This should be done in accordance with the reporting modalities detailed in VI.C.4..

ICH-E2B provides a mechanism to the sender to indicate whether the case fulfils the local expedited requirements. In line with ICH-E2B the following applies for all serious and non-serious ICSRs reportable in the EU based on the modalities detailed in VI.C.4.:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Data element A.1.9 'Does this case fulfil the local criteria for an expedited report?' should be completed with the value 1 (YES).
ICH-E2B(R3)	• Data element C.1.7 'Does this Case fulfil the local criteria for an expedited report?' should be completed with the value TRUE.

VI.C.4. Reporting modalities of ICSRs in EU

In addition to the recommendations provided in VI.B.8., competent authorities in Member States and marketing authorisation holders shall use the formats, standards and terminologies for the electronic transmission of suspected adverse reactions as referred to in chapter IV of the Commission Implementing Regulation (EU) No 520/2012. ICSRs shall be used for reporting to the Eudravigilance database suspected adverse reactions to a medicinal product that occur in a single patient at a specific point in time [IR Art 27]. Competent authorities in Member States and marketing authorisation holders shall also ensure that all ~~reported~~submitted electronic ICSRs are well documented and as complete as possible in accordance with the requirements provided in ~~[IR Art 28].~~Art 28 of Commission Implementing Regulation (EU) No 520/2012.

The time frames for reporting serious and non-serious valid ICSRs are provided in VI.C.3.. The recommendations provided in VI.C.6. should be adhered to as regards the electronic exchange of pharmacovigilance information between competent authorities in Member States, marketing authorisation holders and the Agency.

~~ICSRs reported electronically to the EudraVigilance database will be made accessible to stakeholders such as competent authorities, healthcare professionals, consumers, as well as marketing authorisation holders and research organisations in accordance with Article 24(2) of Regulation (EC) No 726/2004 and the EudraVigilance Access Policy for Medicines for Human Use[44]. This policy defines the overall principles of the provision of access to EudraVigilance data in line with the current legal framework, while guaranteeing personal data protection. As detailed in the EudraVigilance access policy, a selection of ICSRs could be downloaded by marketing authorisation holders in ICH E2B format and in accordance with the ICH M2 message specifications, to facilitate their pharmacovigilance activities.~~

~~VI.C.4.1. Interim arrangements~~

In accordance with the provisions set out in Article ~~2(4), Article 2(5) and Article 2(6) of Directive 2010/84/EU, until the Agency can ensure the functionalities of the EudraVigilance database as specified in Article 24(2) of Regulation (EC) No 726/2004,~~ 107(3) and 107a(4) of Directive 2001/83/EC, the following reporting requirements shall apply~~ to valid unsolicited and solicited ICSRs reported by healthcare professionals and non-healthcare professionals. This is independently of the condition of use of the suspected medicinal product and of the expectedness of the adverse reaction.~~

~~*a. Serious ICSRs*~~

~~[44] http://www.ema.europa.eu~~

- ~~Marketing authorisation holders shall report all serious ICSRs that occur in the EU to the competent authority of the Member State on whose territory the suspected adverse reactions occurred.~~

- ~~Marketing authorisation holders shall report to the EudraVigilance database all serious ICSRs that occur outside the EU, including those received from competent authorities. If required by Member States, those reports shall also be submitted to the competent authorities in the Member States in which the medicinal product is authorised.~~

- ~~Competent authorities in Member States shall ensure that all serious ICSRs that occur in their territory and that are reported to them, including those received from marketing authorisation holders, are made available to the EudraVigilance database. Competent authorities in Member States should also make available, to the marketing authorisation holders of the suspected medicinal products, all serious ICSRs reported directly to them.~~

~~b. Non-Serious ICSRs~~

- ~~If required by Member States, marketing authorisation holders shall report all non-serious ICSRs that occur in the EU to the competent authority of the Member State on whose territory the suspected adverse reactions occurred.~~

~~Overviews of the reporting requirements of serious and non-serious reports during the interim period, applicable to marketing authorisation holders or competent authorities in Member States, are presented in VI.App3.1., together with a detailed business process map.~~

~~Member States reporting requirements for serious non-EU ICSRs and for non-serious EU ICSRs are also included in this Appendix.~~

~~VI.C.4.2. Final arrangements~~

~~Once the functionalities of the EudraVigilance database specified in Article 24(2) of Regulation (EC) No 726/2004 are established, the following requirements, detailed in Articles 107(3) and 107a(4) of Directive 2001/83/EC, shall apply within 6 months of the announcement by the Agency~~ to valid unsolicited and solicited ICSRs reported by healthcare professionals and non-healthcare professionals. This is ~~independently~~irrespective of the condition of use of the suspected medicinal product and of the expectedness of the adverse reaction.

a. Serious ICSRs

- Marketing authorisation holders shall submit all serious ICSRs that occur within or outside the EU, including those received from competent authorities outside the EU, to the EudraVigilance database only.

- Competent authorities in Member States shall submit to the EudraVigilance database all serious ICSRs that occur in their territory and that are directly reported to them.

b. Non-Serious ICSRs

- Marketing authorisation holders shall submit all non-serious ICSRs that occur in the EU to the EudraVigilance database only.

- Competent authorities in Member States shall submit all non-serious ICSRs that occur in their territory to the EudraVigilance database.

Overviews of the reporting requirements of serious and non-serious reports~~,~~ applicable to marketing authorisation holders or competent authorities in Member States ~~once the final arrangements are~~

~~implemented, are~~ are presented in VI.~~App3~~App.3.2~~.~~, together with a ~~detailed~~ business process map and a process description.

In accordance with the requirement detailed in Article 24(4) of Regulation (EC) No 726/2004 ~~for the final arrangements~~, the ICSRs submitted to the EudraVigilance database by marketing authorisation holders shall be automatically transmitted upon receipt, to the competent authority of the Member State where the reaction occurred. ~~A detailed~~Relevant business process map ~~is~~ and process description are included in VI.~~App3~~App.3.3~~.~~.

In accordance with Article 24(2) of Regulation (EC) No 726/2004, data submitted to the EudraVigilance database are made accessible to stakeholders such as competent authorities, healthcare professionals, consumers, as well as marketing authorisation holders and research institutions. This is made based on the latest version of the EudraVigilance Access Policy for Medicines for Human Use[45]. This policy defines the overall principles of the provision of access to EudraVigilance data in line with the current legal framework, while guaranteeing personal data protection.~~VI.C.5.~~

Additionally, the EudraVigilance database shall also be accessible to marketing authorisation holders to the extent necessary for them to comply with their pharmacovigilance obligations [Reg. Art 24(2)].

VI.C.5. Collaboration with bodies outside the EU regulatory network

VI.C.5.1. Collaboration with the World Health Organization and the European Monitoring Centre for Drugs and Drug Addiction

The Agency shall make available to the WHO (in practice the Uppsala Monitoring Centre (UMC) as the WHO Collaborating Centre for International Drug Monitoring) all suspected adverse reaction reports occurring in the EU [REG Art 28c(1)]. This ~~will take~~takes place on a weekly basis after their transmission to the EudraVigilance database by competent authorities in Member States or marketing authorisation holders~~. It will replace~~ in line with the latest version of the EudraVigilance Access Policy for Medicines for Human Use[45]. It replaces the requirements of Member States participating in the WHO Programme for International Drug Monitoring to directly report to WHO suspected adverse reactions reports occurring in their territory. ~~This will be implemented once the functionalities of the EudraVigilance database specified in Article 24(2) of Regulation (EC) No 726/2004 are established.~~

A ~~detailed~~ business process map and a process description for the reporting of ICSRs, from the EudraVigilance database to the WHO Collaborating Centre for International Drug Monitoring, ~~is~~are presented in VI. ~~Appendix~~App 4.

The Agency and the European Monitoring Centre for Drugs and Drug Addiction shall also exchange information that they receive on the abuse of medicinal products including information related to illicit drugs [REG Art 28c(2)].

VI.C.6. Electronic exchange of safety information in the EU

VI.C.6. highlights the requirements, as defined in Articles 24(1) and 24(3) of Regulation (EC) No 726/2004, for the establishment and maintenance of the European database and data processing network (the EudraVigilance database) in order to collate and share pharmacovigilance information electronically between competent authorities in Member States, marketing authorisation holders and the Agency, in ways which ensure the quality and integrity of the data collected.

[45] Ref.: EMA/ 759287/2009

The information provided here is relevant for the electronic exchange of ICSRs in the EU between all stakeholders and for the electronic submission of information on medicinal products to the Agency.

VI.C.6.1. Applicable guidelines, definitions, international formats, standards and terminologies

For the classification, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medicinal product information, Member States, marketing authorisation holders and the Agency shall adhere to the legal requirements provided in chapter IV of the Commission Implementing Regulation (EU) No 520/2012.

In addition the following guidelines should be applied:

- ~~Note for guidance - EudraVigilance Human - Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (EMA/H/20665/04/Final Rev. 2) (EudraVigilance Business Rules);~~
- ~~Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Products (MPRS) in Pharmacovigilance during the pre- and post-authorisation phase in the European economic area (EEA) (EMEA/115735/2004);~~
- The ICH ~~guidelines~~Guidelines detailed in VI.B.8.;
- The ICH-M5 ~~guideline~~Guideline 'Routes of Administration Controlled Vocabulary' (CHMP/ICH/175860/2005), which provides standard terms for routes of administration~~;~~
- The guidelines applicable based on ICSRs ICH-E2B format:

Reference	Guidelines
ICH-E2B(R2)	• Note for guidance - EudraVigilance Human - Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (EMA/H/20665/04/Final Rev. 2) (also referred as EudraVigilance Business Rules); • Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Products (MPRS) in Pharmacovigilance during the pre- and post-authorisation phase in the European economic area (EEA) (EMEA/115735/2004).
ICH-E2B(R3)	• EU ICSR Implementation Guide (EMA/51938/2013); • EU ICSR Implementation Guide Business Rules Spreadsheet; • EU Backwards Forwards Conversion Element Mapping Spreadsheet; • EU E2B(R3) code lists; • EU reference instances; • EU example instances.

The latest version of these documents should always be ~~considered~~taken into account.

VI.C.6.2. Electronic reporting of individual case safety reports

The reporting of valid ICSRs electronically, by competent authorities in Member States and marketing authorisation holders, is mandatory for all medicinal products authorised in the EU [DIR Art 107(3), Art

107a(4)]. Non-adherence to this requirement constitutes a non-compliance with EU legislation.

~~Responsibilities~~

The responsibilities in case of communication failure (including adherence to compliance for reporting) are detailed in~~ chapter IV of the Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in Pharmacovigilance during the Pre- and Post-authorisation Phase in the European Economic Area (EEA) (EMEA/115735/2004).~~:

Reference	Guidelines
EudraVigilance database (current)	• Chapter IV of the Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in Pharmacovigilance during the Pre- and Post-authorisation Phase in the European Economic Area (EEA) (EMEA/115735/2004).
EudraVigilance database (new functionalities) Applicable six months following the announcement by the Agency that the new functionalities specified in Article 24(2) of Regulation (EC) No 726/2004 are established.	• Chapter I.C.2.1.6 of the EU ICSR Implementation Guide (EMA/51938/2013).

Technical tools (EVWEB) have been made available by the Agency to interested electronic data interchange partners, including small and medium-sized enterprises, to facilitate compliance with the electronic reporting requirements as defined in EU legislation. Information is available on EudraVigilance website[46].

VI.C.6.2.1. EudraVigilance Database Modules

Two modules are available in the EudraVigilance database to address the collection of reports of suspected adverse reactions related to medicinal products for human use, in accordance with EU legislation:

- EudraVigilance Post-Authorisation Module (EVPM), implemented based on the requirements defined in Regulation (EC) No 726/2004 and Directive 2001/83/EC; and
- EudraVigilance Clinical Trial Module (EVCTM), implemented based on the requirements defined in Directive 2001/20/EC.

VI.C.6.2.1.1. Adverse reaction data collected in the EudraVigilance Post-Authorisation Module

The adverse reaction reports collected in the EudraVigilance Post-Authorisation Module (EVPM) refer to unsolicited reports and solicited reports which do not fall under the scope of the Clinical Trials Directive

[46] http://eudravigilance.ema.europa.eu

2001/20/EC (see ~~VI.C.1.~~). ~~The ICSRs should be submitted with the value 'EVHUMAN' in the data element 'Message receiver identifier' (ICH M2 M.1.6).~~VI.C.1.1.).

In line with ICH-E2B the ICSRs should be submitted with the following value:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• 'EVHUMAN' in the data element M.1.6 'Message receiver identifier' (ICH M2).
ICH-E2B(R3))	• 'EVHUMAN' in the data elements N.1.4 'Batch Receiver Identifier' and 'N.2.r.3 Message Receiver Identifier'.

Depending on their type, these ICSRs should be classified ~~with~~based on one of the following options~~, in accordance with the EudraVigilance Business Rules~~[47]~~:~~

~~• Data element 'Type of report' (ICH-E2B(R2) A.1.4):~~

~~– spontaneous report;~~

~~– other;~~

~~– not available to sender (unknown); or~~

~~– report from study.~~

~~In addition, when the value in the data element ICH-E2B(R2) A.1.4 is 'Report from study', the data element 'Study type~~ in ~~which the reaction(s)/event(s) were observed' (ICH-E2B(R2) A.2.3.3) should be populated~~line with ICH-E2B:

~~– individual patient use, e.g. compassionate use or named-patient basis; or~~

~~– other studies, e.g. pharmacoepidemiology, pharmacoeconomics, intensive monitoring, PMS.~~

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element A.1.4 'Type of report' – spontaneous report; – other; – not available to sender (unknown); or – report from study. • When the value of the data element A.1.4 is 'Report from study', the data element A.2.3.3 'Study type in which the reaction(s)/event(s) were observed' should be populated with: – individual patient use, e.g. compassionate use or named-patient basis; or – other studies, e.g. pharmacoepidemiology, pharmacoeconomics, intensive monitoring, PMS.
ICH-E2B(R3)	• Data element C.1.3 'Type of report' – spontaneous report; – other;

~~[47] Note for guidance - EudraVigilance Human - Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (EMA/H/20665/04/Final Rev. 2).~~

Reference	E2B(R2)/(R3) requirements
	– not available to sender (unknown); or – report from study. • When the value of the data element C.1.3 is 'Report from study', the data element C.5.4 'Study type in which the reaction(s)/event(s) were observed' should be populated with: – individual patient use, e.g. compassionate use or named-patient basis; or – other studies, e.g. pharmacoepidemiology, pharmacoeconomics, intensive monitoring, PMS.

VI.C.6.2.1.2. Adverse reaction data collected in the EudraVigilance Clinical Trial Module

Only cases of suspected unexpected serious adverse reactions (SUSARs), related to investigational medicinal products (IMPs) or non-investigational medicinal products (NIMPs)[48] studied in clinical trials which fall under the scope of Directive 2001/20/EC (see ~~VI.C.1.),~~VI.C.1.1.), should be ~~reported~~submitted by the sponsor to the EudraVigilance Clinical Trial Module (EVCTM). The requirements provided in chapter II of EudraLex Volume 10 of The Rules Governing Medicinal Products in the European Union should be applied. ~~The ICSRs should be submitted with the value 'EVCTMPROD' in the data element 'Message receiver identifier' (ICH M2 M.1.6) and should be classified as followed, in accordance with the EudraVigilance Business Rules[49]:~~

~~• data element 'Type of report' (ICH E2B(R2) A.1.4):~~

~~– report from study; and~~

~~• data element 'Study type in which the reaction(s)/event(s) were observed' (ICH E2B(R2) A.2.3.3):~~

~~– clinical trials.~~

The ICSRs should be submitted with the following value in line with ICH-E2B:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• 'EVCTMPROD' in the data element M.1.6 'Message receiver identifier' (ICH M2).
ICH-E2B(R3)	• 'EVCTMPROD' in the data elements N.1.4 'Batch Receiver Identifier' and 'N.2.r.3 Message Receiver Identifier'.

Depending on their type, ICSRs submitted to EVCTM should be classified based on one of the following options in line with ICH-E2B:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element A.1.4 'Type of report' – report from study. • When the value of the data element A.1.4 is 'Report from study', the data

[48] For guidance on these terms, see The Rules Governing Medicinal Products in the European Union, Volume 10, Guidance Applying to Clinical Trials, Guidance on Investigational Medicinal Products and Non-Investigational Medicinal Products (NIMPs) (Ares(2011)300458 - 18/03/2011), and the Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3'), (2011/C 172/01) .

[49] ~~See Footnote 38.~~

Reference	E2B(R2)/(R3) requirements
	element A.2.3.3 'Study type in which the reaction(s)/event(s) were observed' should be populated with: – clinical trials
ICH-E2B(R3)	• Data element C.1.3 'Type of report' – report from study. • When the value of the data element C.1.3 is 'Report from study', the data element C.5.4 'Study type in which the reaction(s)/event(s) were observed' should be populated with: – clinical trials

VI.C.6.2.2. Preparation of individual case safety reports

VI.C.6.2.2.1. General principles

The content of each valid ICSR transmitted electronically between all stakeholders should comply with the legal requirements and guidelines detailed in the Commission Implementing Regulation (EU) No 520/2012 and in VI.C.6.1., particularly:

- the requirements provided in chapters IV and V of the Commission Implementing Regulation (EU) No 520/2012;
- the latest version of the ICH-Endorsed Guide for MedDRA Users - MedDRA Term Selection: Points to Consider Document (see GVP Annex IV);
- the EudraVigilance business rules ~~for the electronic transmission of ICSRs detailed in the Note for Guidance - EudraVigilance Human - Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (EMA/H/20665/04/Final Rev. 2).~~and EU ICSR Implementation Guide as referred to in VI.C.6.1..

It is recognised that it is often difficult to obtain all the details on a specific case. However, the complete information (medical and administrative data) for a valid ICSR that is available to the sender should be ~~reported~~submitted in a structured manner in the relevant ICH-E2B~~(R2)~~ data elements ~~(see GVP Annex IV)~~ (which should be repeated as necessary when multiple information is available) and in the narrative section for serious cases (see VI.C.6.2.2.4.). This applies to all types of ICSRs, such as reports with initial information on the case, follow-up information and cases highlighted for amendment[50] or nullification[51].

In the situation where it is evident that the sender has not transmitted the complete information available on the case, the receiver may request the sender to re-transmit the ICSR within 24 hours with the complete case information in electronic format in accordance with the requirements applicable for the electronic reporting of ICSRs. This should be seen in the light of the qualitative signal detection and evaluation activity, where it is important for the receiver to have all the available information on a case to perform the medical assessment (see VI.C.6.2.4.).

Where the suspected adverse reactions reported in a single ICSR impact on the known risk-benefit balance of a medicinal product, this should be considered as an emerging safety issue (see VI.C.2.2.6.), which should be immediately notified in writing to the competent authorities of the

[50] See also VI.C.6.2.2.8. on amendment of individual cases.
[51] See also VI.C.6.2.2.~~109~~. on nullification of individual cases.

Member States where the medicinal product is authorised and to the Agency. This is in addition to the reporting requirements detailed in VI.C.4.. A summary of the points of concerns and the action proposed should be recorded in the ICSR as follows in ~~data element 'Sender's comments' (~~line with ICH-E2B~~(R2) B.5.4).~~:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element B.5.4 'Sender's comments'.
ICH-E2B(R3)	• Data element H.4 'Sender's comments'.

VI.C.6.2.2.2. Information on suspect, interacting and concomitant medicinal products

The suspect, interacting and/or concomitant active substances/invented names of the reported medicinal products should be provided in accordance with ~~IR Art~~Article 28~~.~~(3) (g) to (i~~),~~) of the Commission Implementing Regulation (EU) No 520/2012, ICH-E2B~~(R2) (~~((see GVP Annex IV) and the EudraVigilance Business Rules~~.~~ and EU ICSR Implementation Guide (see VI.C.6.1.).

The characterisation of medicinal products as suspect, interacting or concomitant is based on the information provided by primary source.

For ~~combination~~ medicinal products, which contain more than one active substance, ~~each active substance needs to be reflected individually~~the following applies in ~~the data element 'Active substance name(s)' (~~line with ICH~~-~~E2B~~(R2) B.4.k.2.2), which needs to be repeated for each active substance contained in the combination medicinal product.~~:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• In addition to the information included in the data element B.4.k.2.1 'Proprietary medicinal product name', each active substance needs to be reflected individually in the data element B.4.k.2.2 'Active substance name(s)', which needs to be repeated for each active substance contained in the medicinal product.
ICH-E2B(R3)	• In addition to the information included in the mandatory data element G.k.2.2 'Medicinal Product Name as Reported by the Primary Source', each active substance needs to be reflected individually in the section G.k.2.3.r. 'Substance / Specified Substance Identifier and Strength', which should be repeated for each active substance contained in the medicinal product. This applies where there is no Medicinal Product Identifier (MPID), Pharmaceutical Product Identifier (PhPID) or where no Substance/Specified Substance TermID is available as referred to in the EU ICSR Implementation Guide (EMA/51938/2013).

When the primary source reports a suspect or interacting branded/proprietary medicinal product name without indicating the active substance(s) of the medicinal product and where the proprietary medicinal product can be one of two or more possible generics, which have a different composition depending on the country where the medicinal product is marketed, the ICSR should be populated as follows in line with ICH-E2B:

~~• data element 'Proprietary medicinal product name' (ICH-E2B(R2) B.4.k.2.1) should be populated with the proprietary/branded medicinal product name as reported by the primary source;~~

- ~~data element 'Active substance name(s)' (ICH-E2B(R2) B.4.k.2.2) should be completed with the active substance(s) that correspond(s) to the composition of the proprietary/branded medicinal product of the country where the reaction/event occurred.~~

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Data element B.4.k.2.1'Proprietary medicinal product name' should be populated with the proprietary/branded medicinal product name as reported by the primary source; • Data element B.4.k.2.2 'Active substance name(s)' should be completed with the active substance(s) that correspond(s) to the composition of the proprietary/branded medicinal product of the country where the reaction/event occurred. • Where there is more than one active substance contained in the medicinal product, data element B.4.k.2.2 'Active substance name(s)' should be repeated accordingly.
ICH-E2B(R3)	• Data element G.k.2.2 'Medicinal Product Name as Reported by the Primary Source' should be populated with the proprietary/branded medicinal product name as reported by the primary source; • The data element G.k.2.3.r.1 'Substance/Specified Substance Name' should be completed with the active substance(s) that correspond(s) to the composition of the proprietary/branded medicinal product of the country where the reaction/event occurred. • Where there is more than one active substance contained in the medicinal product, section G.k.2.3.r 'Substance/Specified Substance Identifier and Strength' should be repeated accordingly.

However ~~if the information is available on:~~

- ~~the 'Identification of the country where the drug was obtained' (data element ICH E2B(R2) B.4.k.2.3),~~
- ~~the 'Authorization/application number' (data element ICH E2B(R2) B.4.k.4.1),~~
- ~~the 'Country of authorization/application' (data element ICH E2B(R2) B.4.k.4.2), and/or~~
- ~~the 'Batch/lot number' (data element ICH E2B(R2) B.4.k.3),~~

, the composition with regard the active substance(s) of the proprietary medicinal product should be provided accordingly~~.~~, if information is available on the following ICH-E2B data elements:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• The data element B.4.k.2.3'Identification of the country where the drug was obtained', • The data element B.4.k.4.1'Authorization/application number', • The data element B.4.k.4.2 'Country of authorization/application', and/or • The data element B.4.k.3 'Batch/lot number' .

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R3)	• The data element G.k.2.4 'Identification of the Country Where the Drug Was Obtained' • The data element G.k.3.2 'Country of Authorisation/Application' and/or • The data element G.k.4.r.7 'Batch/lot number'

Where the primary source reports a suspect or interacting branded/proprietary medicinal product name without indicating the pharmaceutical form/presentation of the product and where the proprietary/branded medicinal product can be one of two or more possible pharmaceutical forms/presentations, which have different compositions in a country, the ICSR should be populated as follows in line with ICH-E2B:

~~• data element 'Proprietary medicinal product name' (ICH-E2B(R2) B.4.k.2.1) should be populated with the medicinal product name as reported by the primary source;~~

~~• data element 'Active substance name(s)' (ICH-E2B(R2) B.4.k.2.2) should be completed with those active substances which are in common to all pharmaceutical forms/presentations in the country of authorisation.~~

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element B.4.k.2.1'Proprietary medicinal product name' should be populated with the medicinal product name as reported by the primary source; • Data element B.4.k.2.2 'Active substance name(s)' should be completed with those active substances, which are in common to all pharmaceutical forms/presentations in the country of authorisation. • Where there is more than one active substance contained in the medicinal product, data element B.4.k.2.2 'Active substance name(s)' should be repeated accordingly.
ICH-E2B(R3)	• Data element G.k.2.2 'Medicinal Product Name as Reported by the Primary Source' should be populated with the proprietary/branded medicinal product name as reported by the primary source; • The data element G.k.2.3.r.1 'Substance/Specified Substance Name' should be completed with the active substance(s) that correspond(s) to the composition of the proprietary/branded medicinal product of the country where the reaction/event occurred. • Where there is more than one active substance contained in the medicinal product, section G.k.2.3.r 'Substance/Specified Substance Identifier and Strength' should be repeated accordingly.

a. Reporting of a therapeutic class of medicines

Where medicinal products cannot be described on the basis of the active substances or the invented names, for example when only the therapeutic class is reported by the primary source, or in case of other administered therapies that cannot be structured, this information should only be reflected in the case narrative ~~(data element ICH-E2B(R2) B.5.1).~~. The information should not be included in the structured data elements ~~'Proprietary~~related to the medicinal product ~~name' (ICH-E2B(R2)~~

~~B.4.k.2.1)~~name and ~~'Active~~/or the active substance name(s~~)' (ICH-E2B(R2) B.4.k.2.2) should not be populated.~~). The same applies if a suspected food interaction is reported (e.g. to grapefruit juice).

Where a case of adverse reactions is ~~reported~~suspected to be related only to a therapeutic class, it is considered incomplete and does not qualify for reporting (see VI.B.2.). Efforts should be made to follow-up the case in order to collect the missing information regarding the suspected medicinal product (see VI.B.3.).

~~a.~~b. Reporting of interactions

As regards the reporting of drug interactions, which concerns drug/drug (including biological products), drug/food, drug/device, and drug/alcohol interactions, the coding of the interaction should be performed in the following ICH-E2B section ~~'Reactions/Events' (ICH-E2B(R2) B.2)~~ in line with the latest version of the ICH-Endorsed Guide for MedDRA Users - MedDRA Term Selection: Points to Consider Document (see GVP Annex IV~~).~~) along with any adverse reactions resulting from the suspected interaction:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Section B.2 'Reactions/Events'
ICH-E2B(R3)	• Section E.i.1'Reaction/Events'

In addition, ~~for~~in instances of drug/drug interactions, ~~information on the active substances/proprietary medicinal product names~~the following applies in line with ICH-E2B:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Section B.4 'Drug information' should be completed with information on the active substances/proprietary medicinal products concerned • Data element B.4.k.1 'Characterisation of drug role' is to be completed as 'interacting'.
ICH-E2B(R3)	• Section G.k 'Drug(s) Information' should be completed with information on the active substances/proprietary medicinal products concerned • Data element G.k.1 'Characterisation of Drug Role' is to be completed as 'interacting' for all suspected interacting medicines.

If an interaction is suspected with food or other non-drug compounds, 'interacting' should be selected for the suspect medicine, however information concerning the interacting food should be provided in the ~~section 'Drug information' (ICH-E2B(R2) B.4), which should be characterised as interacting in the data element 'Characterisation of drug role' (ICH-E2B(R2) B.4.k.1).~~case narrative.

~~b.~~c. Reporting of excipients / adjuvants

If the primary source suspects a possible causal role of one of the ingredients (e.g., excipient or adjuvant) of the suspected medicinal product, this information should be ~~provided~~sent in ~~the section 'Drug information' (~~line with ICH-E2B~~(R2) B.4)~~ as ~~a separate entry in addition to the information given regarding the suspected medicinal product. This should also be specified in the case narrative (data element ICH-E2B(R2) B.5.1). If available, tests results (positive or negative) in relation to the causal role of the suspected ingredient should be included in the section 'Results of tests and procedures relevant to the investigation of the patient' (ICH-E2B(R2) B.3).~~follows:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• In the section B.4 'Drug information' - as a separate entry specifying the suspected excipient/adjuvant, in addition to the information given regarding the suspected medicinal product. This should also be specified in the case narrative. • If available, tests results (positive or negative) in relation to the causal role of the suspected ingredient should be included in the section B.3 'Results of tests and procedures relevant to the investigation of the patient'.
ICH-E2B(R3)	• In the section G.k 'Drug(s) Information' - as a separate entry in addition to the information given regarding the suspected medicinal product. This should also be specified in the case narrative. • If available, tests results (positive or negative) in relation to the causal role of the suspected ingredient should be included in the section F.r.3 'Test Result'.

d. Additional Information on Drug

Often, additional information on the medicine(s) is provided in individual cases, which is important for the purpose of data analysis and case review, for example in the context of counterfeit, overdose, drug taken by father, drug taken beyond expiry date, batch and lot tested and found within specifications, batch and lot tested and found not within specifications, medication error, misuse, abuse, occupational exposure and off label use.

The following applies in line with ICH-E2B to capture this information:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• As a general principle, additional characteristics related to the medicines and pertinent to the case should be provided in free text. Data element B.4.k.19 'Additional information on drug' should be used to specify any additional information (e.g., beyond expiration date, batch and lot tested and found to be within specifications). Additional information concerning the indication for the drug, which cannot be described in data element B.4.k.11 'Indication for use in the case' should also be provided as applicable in the data element B.4.k.19. • An appropriate MedDRA term should be provided in the data element B.2.i.1 'Reaction/event in MedDRA terminology (Lowest Level Term)' where applicable in line with the latest version of the ICH-Endorsed Guide for MedDRA Users, MedDRA Term Selection: Points to Consider. • Data elements 'B.5.3 Sender's diagnosis/syndrome and/or reclassification of reaction/event' and B.5.4 Sender's comments can also be used to combine reported signs and symptoms into a succinct diagnosis, or to provide the sender's assessment of the drug role.
ICH-E2B(R3)	• As a general principle, additional characteristics related to the medicines and pertinent to the case should be coded and further information provided in free text. • Data element G.k.10.r 'Additional Information on Drug (coded)' should be completed using one or more of the following values as applicable: Counterfeit, Overdose, Drug taken by father, Drug taken beyond expiry date, Batch and lot

Reference	E2B(R2)/(R3) requirements	
	tested and found within specifications, Batch and lot tested and found not within specifications, Medication error, Misuse, Abuse, Occupational exposure and Off label use. The value(s) should be used where the primary source has made a clear statement related to the additional characteristics of the drug. • An appropriate MedDRA term should be provided in the data element E.i.2.1b 'Reaction/Event (MedDRA code)' where applicable in line with the latest version of the ICH-Endorsed Guide for MedDRA Users, MedDRA Term Selection: Points to Consider. • Section H.3.r 'Sender's Diagnosis' and data element H.4 'Sender's Comments' can also be used to combine reported signs and symptoms into a succinct diagnosis, or to provide the sender's assessment of the drug role. If the primary source did not provide an explicit statement about the drug characterisation which would clearly transpose into a MedDRA term in the reaction section but there is an indication in the context of the clinical course description, the sender may also choose the most applicable value(s) of G.k.10.r 'Additional Information on Drug (coded)' at their discretion. The case should be followed up to obtain further information. • Data element G.k.11 'Additional Information on Drug (free text)' should be used to capture any additional drug information in free text format not described in G.k.10.r, e.g. expiry date for the lot number.	
	Values definition for data element G.k.10.r 'Additional Information on Drug (coded)'	
	• Counterfeit[52]	This is to indicate that the medicine was suspected or confirmed to be a falsified medicinal product in line with the definition provided in Article 1, paragraph 33 of Directive 2001/83/EC.
	• Drug taken beyond expiry date	This is to indicate that the medicine administered to or taken by the patient was beyond its expiry date as indicated in the SmPC or on the packaging of the medicine.
	• Batch and lot tested and found within specifications	This is to indicate that a batch or lot of a medicine was tested and found within the specifications of the marketing authorisation.
	• Batch and lot tested and found not within specifications	This is to indicate that a batch or lot of a medicine was tested and found outside the specifications of the marketing authorisation.

[52] This value should not been used to refer to medicines that do not comply with EU law on intellectual and industrial property rights, such as registered trademarks or patent rights, as defined for counterfeit medicines in Q&A: Directive on falsified medicines.

VI.C.6.2.2.3. Suspected adverse reactions

All available information as described in ~~[IR Art~~Article 28~~-~~(3) (j~~)]~~) of Commission Implementing Regulation (EU) No 520/2012 shall be provided for each individual case. The coding of diagnoses and provisional diagnoses with signs and symptoms ~~in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1)~~ should be performed in line with the latest version of the ICH-Endorsed Guide for MedDRA Users, MedDRA Term Selection: Points to Consider (see GVP Annex IV).

In practice, if a diagnosis is reported with characteristic signs and symptoms, the preferred option is to select a term for the diagnosis only and to MedDRA code it ~~in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'.~~. If no diagnosis is provided, all reported signs and symptoms should be listed and MedDRA~~-~~-coded ~~in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'.~~. If these signs and symptoms are typically part of a diagnosis, the diagnosis can be MedDRA~~-~~-coded in addition by competent authorities in Member States or marketing authorisation holders ~~in the ICH-E2B(R2) data element B.5.3 'Sender's~~as part of the sender's diagnosis/syndrome and/or reclassification of reaction/~~event'~~event in the ICSR.

If in the narrative other events have been reported, which are not typically signs or symptoms of the primary source's diagnosis or provisional diagnosis, and those events are suspected to be adverse reactions, they should also be listed and MedDRA ~~coded in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'~~-coded.

~~In case~~Where a competent authority in a Member State or a marketing authorisation holder disagrees with the diagnosis reported by the primary source, an alternative diagnosis can be provided in ~~the ICH-E2B(R2) data element B.5.3 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' in~~ addition to the reported diagnosis ~~provided in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'.~~. In this situation, ~~a~~ reasoning should be included ~~in the data element 'Sender's comments' (ICH-E2B(R2) B.5.4)~~as additional comment (see VI.C.6.2.2.4.).

In line with ICH-E2B the following applies:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Section B.2 'Reaction(s)/event(s)' should be used and the data element B.2.i.1 'Reaction/event in MedDRA terminology (Lowest Level Term)' completed. • Section B.5.3 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' should be used where the sender would like to combine signs and symptoms that were reported into a succinct diagnosis whereby the reasoning should be included in the data element B.5.4 'Sender's comments'. • Section B.5.3 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' should also be used, if there is disagreement with the diagnosis reported by the primary source and to provide an alternative diagnosis. Reasoning should be included in the in the data element B.5.4 'Sender's comments'.
ICH-E2B(R3)	• Section E.i 'Reaction(s)/Event(s)' should be used and the data element E.i.2.1b 'Reaction/Event (MedDRA code)' completed. • Section H.3.r 'Sender's Diagnosis' should be used where the sender would like to combine signs and symptoms that were reported into a succinct diagnosis whereby the reasoning should be included in the data element H.4 'Sender's

Reference	E2B(R2)/(R3) requirements
	Comments'. • Section H.3.r 'Sender's Diagnosis' should also be used, if there is disagreement with the diagnosis reported by the primary source and to provide an alternative diagnosis. Reasoning should be included in the in the data element H.4 'Sender's Comments'.

In the event of death of the patient, the date, cause of death including autopsy-determined causes shall be provided as available [IR 28 (3) (l)]. If the death is unrelated to the reported suspected adverse reaction(s) and is linked for example to disease progression, the seriousness criterion of the ICSR should not be considered as fatal; the recommendation provided in the ~~EudraVigilance Business Rules~~EudraVigilance Business Rules[53] and the EU ICSR Implementation Guide[54] should be followed.

VI.C.6.2.2.4. Case narrative, causality assessment and comments

In accordance with ~~[IR Art~~Article 28 (3) (m~~)],~~) of Commission Implementing Regulation (EU) No 520/2012, a case narrative ~~(data element ICH-E2B(R2) B.5.1)~~ shall be provided, where possible[55], for all cases with the exception of non-serious cases. The information shall be presented in a logical time sequence, in the chronology of the patient's experience including clinical course, therapeutic measures, outcome and follow-up information obtained. Any relevant autopsy or post-mortem findings shall also be summarised.

The narrative should be presented in line with the recommendations described in chapter 5.2 of ICH-E2D (see GVP Annex IV). In this aspect, it should serve as a comprehensive, stand-alone "medical report" containing all known relevant clinical and related information, including patient characteristics, therapy details, medical history, clinical course of the event(s), diagnosis, adverse reactions and their outcomes, relevant laboratory evidence (including normal ranges) and any other information that supports or refutes the suspected adverse reactions~~.~~ (see VI.C.6.2.2.11. for handling of languages). With regards to the identifiability of the patient, information should be provided in accordance with local data protection laws[56]. Case narratives should not include information that could lead to the identification of the patient, including references to healthcare professionals or treatment centres.

An example of a standard narrative template is available in the Report of the CIOMS Working Group V[57].

The information provided in the narrative should be consistent with the data appropriately reflected in all the other relevant ICH-E2B~~(R2)~~ data elements of the ICSR ~~(see GVP Annex IV).~~ In line with ICH-E2B the following applies:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Section B.5 'Narrative case summary and further information' should be used and the data element B.5.1 'Case narrative including clinical course, therapeutic

[53] Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs) (EMA/H/20665/04/Final Rev. 2)
[54] Ref.: (EMA/51938/2013)
[55] 'Where possible' should be interpreted as having received sufficient information from the primary source to prepare a concise clinical summary of the individual case.
[56] See VI.C.6.2.2.10. for the processing of personal data in ICSRs in the EU.
[57] Council for International Organizations of Medical Sciences (CIOMS). Current Challenges in Pharmacovigilance: Pragmatic Approaches (CIOMS V). Geneva: CIOMS; 2001. Accessible at: http://www.cioms.ch/.

Reference	E2B(R2)/(R3) requirements
	measures, outcome and additional relevant information' completed.
ICH-E2B(R3)	• Section H 'Narrative Case Summary and Further Information' should be used and the data element H.1 'Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information' completed.

During the interim arrangements (see VI.C.4.1.), the case narratives included in the ICSRs submitted to the competent authorities in Member States by marketing authorisation holders, should not be modified or deleted when the ICSRs are forwarded to the EudraVigilance database by the competent authorities.

Where available, comments from the primary source on the diagnosis, causality assessment or other relevant ~~issue,~~issues should be provided in the ~~data element 'Reporter's comments' (~~following ICH-E2B~~(R2) B.5.2).~~ data elements:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element B.5.2 'Reporter's comments'
ICH-E2B(R3)	• Data element H.2 'Reporter's Comments'

Competent authorities in Member States and marketing authorisation holders may provide an assessment of the case and describe a disagreement with, and/or alternatives to the diagnoses given by the primary source (see VI.C.6.2.2.3.). ~~This should be done in the data element 'Sender's comments' (ICH E2B(R2) B.5.4), where discrepancies~~Discrepancies or confusions in the information notified by the primary source may also be highlighted. Where applicable, a summary of the points of concerns and actions proposed should also be included in the ~~data element 'Sender's comments' (ICH-E2B(R2) B.5.4), if the ICSR~~ICSR where it leads to notification of an emerging safety issue (see VI.C.2.2.6.). ~~The degree of suspected relatedness of each medicinal product to the adverse reaction(s) may be indicated in the data element 'Relatedness of drug to reaction(s)/event(s)' (ICH E2B(R2) B.4.k.18), which should be repeated as necessary. This also allows presenting the degree of relatedness from different sources or with different methods of assessment.~~

In line with ICH-E2B this information should be provided in the following data elements:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element B.5.4 'Sender's comments'
ICH-E2B(R3)	• Data element H.4 'Sender's Comments'

The degree of suspected relatedness of each medicinal product to the adverse reaction(s) may be used to . present the degree of relatedness from different sources or with different methods of assessment. In line with ICH-E2B the following applies:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Section B.4.k.18 'Relatedness of drug to reaction(s)/event(s) should be completed and repeated as applicable.
ICH-E2B(R3)	• Section G.k.9.i 'Drug-reaction(s)/Event(s) Matrix' should be completed and repeated as applicable.

VI.C.6.2.2.5. Test results

Results of tests and procedures relevant to the investigation of the patient shall be provided [IR Art 28 (3) (k)].

~~As described in ICH E2B(R2) (see GVP Annex IV), the section B.3 'Results of tests and procedures relevant to the investigation of the patient' should capture the~~ This includes tests and procedures performed to diagnose or confirm the reaction/event, including those tests done to investigate (exclude) a non-drug cause, (e.g., serologic tests for infectious hepatitis in suspected drug-induced hepatitis). Both positive and negative results should be ~~reported.~~ included in the ICSR.

The coding of investigations should be performed in line with the latest version of the ICH-Endorsed Guide for MedDRA Users, MedDRA Term Selection: Points to Consider (see GVP Annex IV). If it is not possible to provide information on tests and test results in a structured manner, provisions have been made to allow for the transmission of the information as free text ~~in the data element ICH-E2B(R2) B.3.2. 'Results of tests and procedures relevant to the investigation'.~~.

In line with ICH-E2B the following applies:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Section B.3 'Results of tests and procedures relevant to the investigation of the patient' should be completed and repeated as applicable. • Data element B.3.1 'Structured information' should be used to structure the information on the test, the outcome and the date the test was performed. Where several tests or procedures were performed, the section should be completed accordingly. • Data element B.3.2 'Results of tests and procedures relevant to the investigation' should be used to provide information on tests and procedures, which cannot be captured in section B.3.1.
ICH-E2B(R3)	• Section F.r 'Results of Tests and Procedures Relevant to the Investigation of the Patient' should be used to structure the information on the test, the outcome and the date the test was performed. Where several tests or procedures were performed, the section should be completed accordingly. • Data element F.r.2.1 'Test Name (free text)' should be used for the description of a test when an appropriate MedDRA code is unavailable. • Data element F.r.3.4 'Result Unstructured Data (free text)' should be used when 'results' and 'units' cannot be split, often because a Unified Code for Units of Measure (UCUM) code is not available for the test unit. • Data element F.r.6 'Comments (free text)' should be used to capture any relevant comments made by the reporter about the test result.

VI.C.6.2.2.6. Supplementary records / information

Key information from supplementary records should be provided in the relevant section of the ICSR, and their availability should be mentioned ~~in the data element 'List of documents held by sender' (ICH-E2B(R2) A.1.8.2).~~.

In line with ICH-E2B the following applies:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element A.1.8 'Additional available documents held by sender' should be completed as applicable.
ICH-E2B(R3)	• Data element C.1.6.1 'Are Additional Documents Available' should be completed. • Section C.1.6.1.r 'Documents Held by Sender' should be completed, where the data element C.1.6.1.r.1 'Documents Held by Sender' should provide a description of the nature of documents (e.g. clinical records, hospital records, autopsy reports) and C.1.6.1.r.2 'Included Documents' should contain the actual document, if the sender chooses to send the document or is required to do so. The processing of personal data should be done in accordance with local data protection law (see VI.C.2.2.10.).

Other known case identifiers relevant for the detection of duplicates should be presented systematically ~~in the data element 'Other case identifiers in previous transmissions' (ICH-E2B(R2) A.1.11).~~.

In line with ICH-E2B the following applies:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element A.1.11 'Other case identifiers in previous transmissions' should be completed.
ICH-E2B(R3)	• Section C.1.9.1 'Other Case Identifiers in Previous Transmissions' should be completed as applicable.

VI.C.6.2.2.7. Follow-up information

In addition to the guidance in VI.B.3., the following guidance should be followed:

ICSRs are sent at different times to multiple receivers. Therefore the initial/follow-up status is dependent upon the receiver. For this reason an item to capture follow-up status is not included in ~~the~~ ICH-E2B~~(R2) data elements.~~. However, the ~~data element 'Date~~date of receipt of the most recent information for this ~~report' (ICH E2B(R2) A.1.7)~~ report taken together with the ~~data element 'Sender identifier' (ICH E2B(R2) A.3.1.2) and the data element 'Sender's~~sender's (case) report unique ~~identifier' (ICH-E2B(R2) A.1.0.1)~~identifier provide a mechanism for each receiver to identify whether the report being transmitted is an initial or a follow-up report. For this reason these items are considered critical for each transmission and a precise date should always be used (i.e. day, month, year). The ~~data element 'Date~~date of receipt of the most recent information for this ~~report' (ICH-E2B(R2) A.1.7)~~ report should therefore always be updated each time ~~a~~ follow-up information is received by a competent authority or a marketing authorisation holder, ~~independently~~irrespective whether the follow-up information received is significant enough to be ~~reported~~submitted. The ~~data element 'Date~~ date the report was first received from the ~~source' (ICH E2B(R2) A.1.6)~~source should remain unchanged to the date the competent authority or the marketing authorisation holder became aware of the initial report.

New information should be clearly identifiable in the case narrative ~~(data element ICH E2B(R2) B.5.1)~~ and should also be provided in a structured format ~~in the applicable ICH-E2B(R2) data elements.~~.

In line with ICH-E2B the following applies:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• The following data elements should always be completed: – Data element A.1.0.1 'Sender's (case) safety report unique identifier' – Data element A.1.6 'Date report was first received from source' – Data element A.1.7 'Date of receipt of the most recent information for this report' – Data element A.1.10 'Worldwide unique case identification number' – Data element A.3.1.2 'Sender identifier' – Data element B.5.1 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' (for serious reports of suspected adverse reactions)
ICH-E2B(R3)	• The following data elements should always be completed: – Data element C.1.1 'Sender's (case) Safety Report Unique Identifier' – Data element C.1.4 'Date Report Was First Received from Source' – Data element C.1.5 'Date of Most Recent Information for this Report' – Section C.1.8 'Worldwide Unique Case Identification' – Data element H.1 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' (for serious reports of suspected adverse reactions)

Competent authorities in Member States or marketing authorisation holders should report follow-up information if significant new medical information has been received. Significant new information relates to, for example, a new suspected adverse ~~reaction(s),~~reactions, a change in the causality assessment, and any new or updated information on ~~the~~a case that impacts on its medical interpretation. Therefore, the identification of significant new information requiring to be ~~reported~~submitted always necessitates medical judgement.

Situations where the seriousness criteria and/or the causality assessment are downgraded (e.g. follow-up information leads to a change of the seriousness criteria from serious to non-serious; causality assessment is changed from related to non-related) should also be considered as significant changes and thus ~~reported~~submitted as ICSR (see VI.B.7.1. for reporting time frames).

In addition, competent authorities in Member States or marketing authorisation holders should also ~~report follow-up information, where~~submit a new version of an ICSR, when new administrative information is available, that could impact on the case management~~; for~~. For example, if new case identifiers have become known to the sender, which may have been used in previous transmissions ~~(data element 'Other case identifiers in previous transmissions' (ICH-E2B(R2) A.1.11)).~~. This information may be specifically relevant to manage potential duplicates. ~~Another example refers to data element 'Additional available documents held by sender' (ICH-E2B(R2) A.1.8), whereby new documents that have become available to~~ In this context, the ~~sender may~~following data elements/sections should be ~~relevant for the medical assessment of the case.~~completed in line with ICH-E2B:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element A.1.11 'Other case identifiers in previous transmissions'

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R3)	• Section C.1.9.1 'Other Case Identifiers in Previous Transmissions'

Another example refers to additional documents held by sender, whereby new documents that have become available to the sender may be relevant for the medical assessment of the case. In this context, the following data elements/sections should be completed in line with ICH-E2B :

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Section A.1.8 'Additional available documents held by sender'
ICH-E2B(R3)	• Section C.1.6 'Additional Available Documents Held by Sender'

In contrast, a follow-up report which contains non-significant information does not require to be ~~reported~~submitted. This may refer, for example, to minor changes to some dates in the case with no implication for the evaluation or transmission of the case, or corrections of typographical errors in the previous case version. Medical judgement should be applied since a change to the birth date may constitute a significant modification (e.g. with implications on the age information of the patient). Similarly, a change of the status of a MedDRA code/term from current to non-current, due to a version change of MedDRA, can be considered as a non-significant change as long as this change has no impact on the medical content of a case. ~~However, an amendment of the MedDRA coding due to a change in the interpretation of a previously reported suspected adverse reaction may constitute a significant change and therefore should be reported.~~

~~In situations where the case is modified without impacting on its medical evaluation, while no new follow-up is received (e.g., for correcting a mistake or typographical error), the date of receipt of the most recent information reported in the data element 'Date of receipt of the most recent information for this report' (ICH E2B(R2) A.1.7) should not be changed. This data element should however be updated in any other situations, to the date when new follow-up information is received (independently whether it is significant or not) or to the date when changes are made which impact on the interpretation of the case.~~

Where follow-up information of a case initially ~~reported~~submitted by a marketing authorisation holder is received directly by a competent authority, the ~~'Worldwide~~worldwide unique case identification ~~number' (ICH E2B(R2) A.1.10)~~number of the initial report should be maintained, in adherence with ICH-E2B~~(R2)~~ (see GVP Annex IV). The same principle should be applied if a follow-up is received by a marketing authorisation holder of a case initially ~~reported~~submitted by a competent authority.

VI.C.6.2.2.8. Amendment Report

Serious and non-serious cases may need to be amended when, after an internal review or according to an expert opinion some items have been corrected, without receipt of new information that would warrant for the submission of a follow-up report. For example, an amendment of the MedDRA coding due to a change in the interpretation of a previously submitted ICSR may constitute a significant change and therefore should be sent as amendment report.

Additionally, for reports for which case translations shall be provided by marketing authorisation holders when request by the Agency or other Member States (see VI.C.6.2.2.11.), the translations should be submitted in the form of amendment reports. The same would apply where documentations or articles mentioned in the ICSRs are requested by the Agency or other Member States and are further sent as attachments in ICH E2B(R3) C.4.r.2.

However when new information (significant or non-significant) is received, it should be considered as follow-up report and the guidance provided in VI.C.6.2.2.7. should be followed.

In line with ICH-E2B the following applies:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	The principle of amending a report as such is not supported. In situations, where the amendment of a report is necessary, the same principles as for a follow-up report can be applied, even where there is no receipt of new information. It should be noted that this can lead to situations, where these reports may appear as "late reports" i.e. do not meet the established reporting timelines. In situations where the case is modified without impacting on its medical evaluation, while no new follow-up is received (e.g., for correcting a mistake or typographical error), the date of receipt of the most recent information included in the data element A.1.7 'Date of receipt of the most recent information for this report' should not be changed.
ICH-E2B(R3)	• The data element C.1.11.1 'Report Nullification/Amendment' should be set to 'Amendment'. • The data element C.1.11.2 'Reason for Nullification/Amendment' should be completed to indicate the reason why a previously transmitted ICSR is amended. • The same 'Sender's (case) Safety Report Unique Identifier' (data element C.1.1) previously submitted should be used (see exceptions in ICH ICSR Implementation Guide for C.1.1). • The same 'Worldwide Unique Identifier' (data element C.1.8) previously submitted should be used. • The data element C.1.5 'Date of Most Recent Information for This Report' should remain unchanged. For example MedDRA coding needs to be changed following internal quality review; in this example the date should remain unchanged

VI.C.6.2.2.9. Nullification of cases

In line with ICH-E2B (see GVP Annex IV), the nullification of individual cases should be used to indicate that a previously transmitted report should be considered completely void (nullified), for example when the whole case was found to be erroneous or in case of duplicate reports.

The following principles should be followed:

- The nullification reason should be clear and concise to explain why this case is no longer considered to be a valid report. For example a nullification reason stating, 'the report no longer meets the reporting criteria' or 'report sent previously in error' are not detailed enough explanations;
- An individual case can only be nullified by the sending organisation;
- Once an individual case has been nullified, the case cannot be reactivated;
- Individual versions (i.e. follow-up reports) of a case cannot be nullified, only the entire individual case to which they refer;

- A nullified case is one that should no longer be considered for scientific evaluation. The process of the nullification of a case is by means of a notification by the sender to the receiver that this is no longer a valid case. However, the case should be retained in the sender's and receiver's pharmacovigilance database for auditing purposes.

In line with ICH-E2B the following should be applied:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• The data element A.1.13 'Report nullification' should be set to "Yes". • The data element A.1.13.1 'Reason for nullification' should be completed to indicate the reason why a previously transmitted ICSR is considered completely void. • The same 'Worldwide unique case identification number' (data element A.1.10) previously submitted should be used. • The data element A.1.7 'Date of receipt of the most recent information for this report' should either reflect the date when information was received that warrants the nullification of the report or otherwise should remain unchanged.
ICH-E2B(R3)	• The data element C.1.11.1 'Report Nullification/Amendment' should be set to 'Nullification'. • The data element C.1.11.2 'Reason for Nullification/Amendment' should be completed to indicate the reason why a previously transmitted ICSR is considered completely void. • The same 'Sender's (case) Safety Report Unique Identifier' (data element C.1.1) previously submitted should be used (see exceptions in ICH ICSR Implementation Guide for C.1.1). • The same 'Worldwide Unique Identifier' (data element C.1.8) previously submitted should be used. • The data element C.1.5 "Date of Most Recent Information for This Report" should either reflect the date when information was received that warrants the nullification of the report or otherwise should remain unchanged.

Examples of scenarios for which ICSRs should be nullified are provided in VI.App.5.

If it becomes necessary to resubmit the case that has been previously nullified the following should be considered:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• A new 'Sender's (case) safety report unique identifier' (data element A.1.0.1) and a new 'Worldwide unique case identification number' (data element A.1.10) should be assigned.
ICH-E2B(R3)	• A new 'Sender's (Case) Safety Report Unique Identifier' (data element C.1.1) and a new 'Worldwide Unique Case Identification' (Section C.1.8) should be assigned.

VI.C.6.2.2.10. What to take into account for data ~~privacy~~protection laws

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, Regulation (EC) No 45/2001).

Where in accordance with applicable national legislation, information related to personal data cannot be transferred to the EudraVigilance database, pseudonymisation may be applied by competent authorities in Member States and by marketing authorisation holders, thereby replacing identifiable personal data such as name and address with pseudonyms or key codes, for example in accordance with the ISO Technical Specification DD ISO/TS 25237:2008, Health informatics – Pseudonymization [IR Recital 17]. The application of pseudonymisation will facilitate the ability of the EudraVigilance system to adequately support case processing and detect duplicates. ~~This~~Alternatively where pseudonymisation is not feasible, the following may be applied in line with ICH-E2B:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• In certain data elements which can identify an individual such as in the reporter's name, initials, address, or in the patient's name, initials, medical record number, where the information cannot be transmitted for data protection reasons, the data element should be populated with the value 'PRIVACY'.
ICH-E2B(R3)	• The nullflavor 'MSK' (see VI.A.2.6.) should be used if personal information is available but cannot be provided by the sender due to local privacy legislation. It informs the receiver that the information does exist without providing personal details such as birth date or name.

Pseudonymisation or the use of the nullflavor 'MSK' should however be ~~done~~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.

VI.C.6.2.2.~~9~~11. Handling of languages

~~The ICH-E2B(R2) (see GVP Annex IV) concept for the~~The electronic reporting of ICSRs is based on the fact that structured and coded information is used for data outputs of pharmacovigilance systems (e.g. listings) and for signal detection. However, for scientific case assessment and signal evaluation~~, the medical summary provided in the data element 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' (ICH-E2B(R2) B.5.1)~~ a medical summary is normally required (see VI.6.2.2.4.).

Where suspected adverse reactions are reported by the primary source in narrative and textual descriptions in an official language of the Union other than English, the original verbatim text and the summary thereof in English shall be provided by the marketing authorisation holder[58]. Member States may report case narratives in their official language(s). For those reports, case translations shall be provided when requested by the Agency or other Member States for the evaluation of potential signals.

[58] In practice, the original verbatim text reported by the primary source in an official language of the Union other than English should be included in the ICSR, if it is requested by the Member State where the reaction occurred or by the Agency.

For suspected adverse reactions originating outside the EU, English shall be used in the ICSR [IR 28 (4)].

Additional documents held by the sender, which may be only available in a local language, should only be translated if requested by the receiver.

In line with ICH-E2B the following applies:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Data element B.5.1 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' should be used to capture the original verbatim text and the English summary thereof.
ICH-E2B(R3)	• Section H.5.r 'Case Summary and Reporter's Comments in Native Language (repeat as necessary)' should be used to provide information on the clinical course of the case, therapeutic measures, outcome and other relevant information, as well as the reporter's comments on the case in a language different from that used in sections H.1, H.2, and H.4.

~~***VI.C.6.2.2.10. Nullification of cases***~~

~~In line with ICH E2B(R2) (see GVP Annex IV), the nullification of individual cases should be used to indicate that a previously transmitted report should be considered completely void (nullified), for example when the whole case was found to be erroneous or in case of duplicate reports. It is essential to use the same case report numbers previously submitted in the data element 'Sender's (case) safety report unique identifier' (ICH E2B(R2) A.1.0.1) and in the data element 'Worldwide unique case identification number' (ICH E2B(R2) A.1.10).~~

~~A nullified case is one that should no longer be considered for scientific evaluation. The process of the nullification of a case is by means of a notification by the sender to the receiver that this is no longer a valid case. However, the case should be retained in the sender's pharmacovigilance database for auditing purposes.~~

~~The principles to be considered when nullifying a case are detailed in VI. Appendix 5.~~

VI.C.6.2.3. Special situations

VI.C.6.2.3.1. Use of a medicinal product during pregnancy or breastfeeding

General recommendations are provided in VI.B.6.1..

With regard to the electronic reporting of parent-child/foetus cases, the following should be adhered to:

a. ~~In the situation where~~If a foetus or nursing infant is exposed to one or several medicinal products through the parent and experiences one or more suspected adverse reactions (other than early spontaneous abortion/foetal demise~~), information on both the parent and the child/foetus should be provided in the same report. These cases are referred to as parent-child/foetus reports. The information provided in the section 'Patients characteristics' (ICH E2B(R2) B.1) applies only to the child/foetus. The characteristics concerning the parent (mother or father), who was the source of exposure to the suspect medicinal product should be provided in the data element 'For a parent-child/fetus report, information concerning the parent' (ICH E2B(R2) B.1.10). If both parents are the source of the suspect drug(s) then the case should reflect the mother's information in the data~~

~~element 'For a parent-child/fetus report, information concerning the parent' (ICH E2B(R2) B.1.10). The data element 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' (ICH E2B(R2) B.5.1) should describe the entire case, including the father's information.~~):

Information on both the parent and the child/foetus should be provided in the same report. This case is referred to as a parent-child/foetus report. The information provided for the patient's characteristics applies only to the child/foetus. The characteristics concerning the mother or father, who was the source of exposure to the suspect medicinal product, should be captured as part of the information concerning the parent. If both parents are the source of the suspect drug(s), the structured parent information in the case should reflect the mother's characteristics; information regarding the father should be provided in the narrative together with all other relevant information.

In line with ICH-E2B the following applies:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Section B.1 'Patient characteristics' should be completed for the child/fetus. • Section B.1.10 'For a parent-child/fetus report, information concerning the parent' should be completed for the mother or the father as applicable. • Data element B.5.1 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' should be used to provide the medical summary for the entire case and where both parents are the source of the suspected drug(s), the father's characteristics should be also reflected here.
ICH-E2B(R3)	• Section D 'Patient Characteristics' should be completed for the child/fetus. • Section D.10 'For a Parent-child / Foetus Report, Information Concerning the Parent' should be completed for the mother or the father as applicable. • Section H.5.r 'Case Summary and Reporter's Comments in Native Language (repeat as necessary)' should be used to provide the medical summary for the entire case and where both parents are the source of the suspected drug(s), the father's characteristics should be also reflected here.

b. If both the parent and the child/foetus experience suspected adverse reactions~~, two~~:

Two separate reports, i.e. one for the parent (mother or father) and one for the child/foetus, should be created ~~but they~~. Both reports should be linked ~~by using the data element 'Identification number of the report which is linked to this report' (~~in ICH-E2B~~(R2) A.1.12) in each report.~~ as followed:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Section A.1.12 'Identification number of the report which is linked to this report' should be used to identify cases that warrant being evaluated together e.g. a mother-child pair where both had reactions.
ICH-E2B(R3)	• Section C.1.10.r 'Identification Number of the Report Linked to this Report (repeat as necessary)' should be completed for all linked reports. For example, if a sender wishes to reference (link) an ICSR A to ICSR B, then

Reference	E2B(R2) / (R3) requirements
	the sender populates C.1.10.r in both reports.

c. If there has been no reaction affecting the child~~, the~~:

The parent-child/foetus report does not apply; i.e. ~~the section 'Patients characteristics' (ICH-E2B(R2) B.1) applies~~the parent's characteristics only apply to the parent (mother or father) who experienced the suspected adverse reaction.

~~For those cases describing~~In line with ICH-E2B the following applies:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Section B.1 'Patient characteristics' should be completed for the mother or father as applicable.
ICH-E2B(R3)	• Section D 'Patient Characteristics' should be completed for the mother or father as applicable.

d. If there has been a miscarriage or early spontaneous abortion~~, only~~:

Only a parent report is applicable~~, i.e.~~ with the ~~section 'Patients characteristics' (ICH-E2B(R2) B.1) apply~~patient's characteristics to be provided for the mother. However, if the suspect medicinal product was taken by the father, ~~the data element 'Additional~~this information ~~on drug' (ICH-E2B(R2) B.4.k.19) should specify that the medication was taken by the father~~should also be recorded.

In line with ICH-E2B the following applies:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Section B.1 'Patient characteristics' should be completed for the characteristics of the mother. • The data element B.4.k.19 'Additional information on drug' should be completed if suspect drug(s) were taken by the father.
ICH-E2B(R3)	• Section D 'Patient Characteristics' should be completed for the characteristics of the mother. • Data element G.k.10.r 'Additional Information on Drug (coded)' should be completed if suspect drug(s) were taken by the father. The value to be selected is 'Drug taken by father'.

VI.C.6.2.3.2. Suspected adverse reaction reports published in the scientific literature

EU requirements in relation to the monitoring of suspected drug reactions reported in the scientific and medical literature are provided in ~~VI.C.2.2.3.~~ VI.C.2.2.3.1.. With regard to the electronic reporting of ICSRs published in the scientific and medical literature, the following ~~applies~~recommendation should be followed:

The literature references shall be ~~included in the data element 'Literature reference(s)' (ICH-E2B(R2) A.2.2)~~provided in the Vancouver Convention (known as "Vancouver style"), developed by the International Committee of Medical Journal Editors [IR Art 28 (3) (b~~)]. The standard format as well as~~

~~those for special situations can be found in the following reference: International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med. 1997; 336: 309-16, which is in the Vancouver style)]~~[59].

In line with ICH-E2B the following applies:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• The data element A.2.2 'Literature reference(s)' should be populated with the literature reference. The Digital Object Identifier (DOI) for the article should be included where available, e.g.: "International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309-15. **doi:10.1056/NEJM199701233360422"**
ICH-E2B(R3)	• Section C.4.r 'Literature Reference(s)' should be populated with the literature reference reflected in the data element C.4.r.1 'Literature Reference(s)'. The Digital Object Identifier (DOI) for the article should be included where available e.g.:" International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309-15. **doi:10.1056/NEJM199701233360422"**

A comprehensive English summary of the article shall be provided ~~in~~as part of the ~~data element 'Case~~ narrative including clinical course, therapeutic measures, outcome and additional relevant ~~information' (ICH-E2B(R2) B.5.1)~~information [IR Art 28 (3) (b)].

In line with ICH-E2B the following applies:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element B.5.1 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' should be used to provide the comprehensive English summary.
ICH-E2B(R3)	• Section H.1 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' should be used to provide the comprehensive English summary.

Upon request of the Agency, for specific safety review, a full translation in English and a copy of the relevant literature article shall be provided by the marketing authorisation holder that transmitted the initial report, taking into account copyright restrictions [IR 28 (3)]. ~~The recommendations detailed in VI.App2.10, regarding the mailing of the literature article, should be adhered to.~~

In line with ICH-E2B the following applies:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• The recommendations detailed in VI.App2.10, regarding the mailing of the literature article, should be adhered to.

[59] ~~The Vancouver recommendations are also available on the International Committee of Medical Journal Editors website http://www.icmje.org.~~ See International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med. 1997; 336: 309-16.

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R3)	• The electronic version of the document (i.e. the journal article and a copy of the translation where applicable) should be attached to the ICSR in C.4.r.2. • If the article and/or translation are not provided at the time of ICSR reporting, attachments can be transmitted separately from the ICSR transmission. When the sender transmits an attachment later, the original ICSR along with all the same medical information captured in E2B(R3) data elements is retransmitted as an 'amendment' (see VI.C.2.2.8.). If new additional information is provided, then the ICSR with attachment is transmitted as a follow-up.

Recommendations presented in VI.App2.10~~.~~., for the reporting of several individual cases when they are published in the same literature article, should be followed.

VI.C.6.2.3.3. Suspected adverse reactions related to overdose, abuse, off-label use, misuse, medication error or occupational exposure

General principles are provided in VI.B.6.3..

If a case of overdose, abuse, off-label use, misuse, medication error or occupational exposure is reported with clinical consequences, the MedDRA Lowest Level Term code, corresponding to the term closest to the description of the reported overdose, abuse, off-label use, misuse, medication error or occupational exposure should be added to the observed suspected adverse reaction(s) in ~~the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1), in~~ line with recommendations included in the latest version of the ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider' (see GVP Annex IV).

In line with ICH-E2B the following applies:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element B.4.k.19 'Additional information on drug' can be used to specify any additional information (e.g., overdose, abuse, off-label use, misuse, medication error or occupational exposure). Additional information concerning the indication for the drug should be provided as applicable. • Likewise, the appropriate MedDRA term should be provided in the data element B.2.i.1 'Reaction/event in MedDRA terminology (Lowest Level Term)' or in the data element 'B.5.3 Sender's diagnosis/syndrome and/or reclassification of reaction/event' (in line with ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider').
ICH-E2B(R3)	• Data element G.k.10.r 'Additional Information on Drug (coded)' should be completed using one or more of the following values as applicable:, Overdose, Medication error, Misuse, Abuse, Occupational exposure and Off label use. The value(s) should be used where the primary source has made a clear statement related to the additional characteristics of the drug. • Likewise, an appropriate MedDRA term should be provided in the data element E.i.2.1b 'Reaction/Event (MedDRA code)'. Alternatively, section H.3.r 'Sender's Diagnosis' should be completed (in line with ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider').

Reference	E2B(R2)/(R3) requirements	
	• If the primary source did not provide an explicit statement about the drug characterisation which would clearly transpose into a MedDRA term in the reaction section but there is an indication in the context of the clinical course description, the sender may choose the most applicable value(s) of G.k.10.r at their discretion. The case should be followed up to obtain further information. • Data element G.k.11 'Additional Information on Drug (free text)' should be used to capture any additional drug information in free text format not described in G.k.10.r. • The data element G.k.1 'Characterisation of Drug Role' should be populated with the value 'Drug not administered' for medication errors if the patient did not receive the actual prescribed drug but another one, based on the information provided by the primary source or, if this information is missing, by the sender. This applies where the patient did not receive the actual prescribed drug. There is no equivalent in ICH-E2B(R2). Sections G 'Drug(s) Information' should be completed with the information about the prescribed drug (including the fact that it was not administered), as well as the information on the dispensed drug as the 'suspect' drug.	
	Values definition for data element 'G.k.10.r Additional Information on Drug (coded)'	
	• Overdose	This is to indicate that the medicine may have been subject to an overdose as defined in chapter VI.A.2.1.2.a.
	• Misuse	This is to indicate that the medicine may have been associated with misuse as defined in chapter VI.A.2.1.2.a.
	• Abuse	This is to indicate that the medicine may have been associated with abuse as defined in chapter VI.A.2.1.2.a.
	• Occupational exposure	This is to indicate that the medicine may have been associated with occupational exposure as defined in chapter VI.A.2.1.2.a.
	• Off label use	This is to indicate that the medicine may have been associated with off label use as defined in chapter VI.A.2.1.2.a.
	• Medication error	This is to indicate that the medicine may have been associated with a medication error as defined in chapter VI.A.2.1.2.a.

VI.C.6.2.3.4. Lack of therapeutic efficacy

General principles are provided in VI.B.6.4..

If the primary source suspects a lack of therapeutic efficacy, the MedDRA Lowest Level Term code, corresponding ~~to the term closest~~most closely to the description of the reported lack of therapeutic efficacy, should be provided in ~~the data element 'Reaction/event in MedDRA terminology (Lowest Level~~

~~Term)' (ICH-E2B(R2) B.2.i.1), in line~~accordance with recommendations ~~included~~ in the latest version of the ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider' (see GVP Annex IV).

In line with ICH-E2B the following applies:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• The appropriate MedDRA term should be provided in the data element B.2.i.1 'Reaction/event in MedDRA terminology (Lowest Level Term)'.
ICH-E2B(R3)	• The appropriate MedDRA term should be provided in the data element E.i.2.1b 'Reaction/Event (MedDRA code)'.

Unless aggravation of the medical condition occurs, the indication for which the suspected medicinal product was administered should not be included in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term~~).~~)' or 'Reaction/Event (MedDRA code)'.

The same reporting modalities as for serious ICSRs (see VI.C.4.) should be applied for those cases related to classes of medicinal products where, as described in VI.B.6.4., reports of lack of therapeutic efficacy should be ~~reported~~submitted within a 15-day time frame. If no seriousness criterion is available, it is acceptable to submit the ICSR within 15 days as non-serious.

VI.C.6.2.3.5. Suspected adverse reactions related to quality defect or falsified medicinal products

EU requirements are provided in VI.C.2.2.4~~..~~. In order to be able to clearly identify cases related to quality defect or falsified medicinal products (see GVP Annex I) when they are exchanged between stakeholders, the following recommendations should be applied:

a. ~~***a.***~~ ***Quality defect***

Where a report of suspected adverse reactions is associated with a suspected or confirmed quality defect of a medicinal product, the MedDRA Lowest Level Term code of the term corresponding most closely to the product quality issue, should be added to the observed suspected adverse reaction(s) in ~~the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1).~~ accordance with the recommendations in the latest version of the ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider.

~~***b.***~~In line with ICH-E2B the following applies:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• As a general principle, additional characteristics related to the medicines and pertinent to the case should be coded and further information related to the quality defect provided in free text. Data element B.4.k.19 'Additional information on drug' should be used to specify any additional information (e.g., beyond expiration date, batch and lot tested and found to be within specifications); additional information concerning the indication for the drug should be provided as applicable. • The appropriate MedDRA term should be provided in the data element B.2.i.1 'Reaction/event in MedDRA terminology (Lowest Level Term)'.
ICH-E2B(R3)	• Data element G.k.10.r 'Additional Information on Drug (coded)' should be

Reference	E2B(R2)/(R3) requirements	
	completed using one or more of the following values as applicable: Batch and lot tested and found within specifications; Batch and lot tested and found not within specifications. These values should be used where the primary source has made a clear statement related to the additional characteristics of the drug. • Likewise, an appropriate MedDRA term should be provided in the data element E.i.2.1b 'Reaction/Event (MedDRA code)'. Alternatively, section H.3.r 'Sender's Diagnosis' should be completed. • Data element G.k.11 'Additional Information on Drug (free text)' should be used to capture any additional drug information in free text format not described in G.k.10.r.	
	• Values definition for data element 'G.k.10.r Additional Information on Drug (coded)'	
	• Drug taken beyond expiry date	This is to indicate that the medicine administered to or taken by the patient was beyond its expiry date as indicated in the SmPC or on the packaging of the medicine.
	• Batch and lot tested and found within specifications	This is to indicate that a batch or lot of a medicine was tested and found within the specifications of the marketing authorisation.
	• Batch and lot tested and found not within specifications	This is to indicate that a batch or lot of a medicine was tested and was found outside the specifications of the marketing authorisation.

b. Falsified medicinal products

Where a report of suspected adverse reactions is associated with a suspected or confirmed falsified[60] ingredient, active substance or medicinal product, the MedDRA Lowest Level Term code of the term corresponding most closely to the reported information should be added to the observed suspected adverse reaction(s) in accordance with the ~~data element 'Reaction/event~~recommendations in ~~MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1).~~the latest version of the ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider. Information on the suspected medicinal product, active substance(s) or excipient(s) should be ~~provided in the data elements 'Proprietary medicinal product name' (ICH-E2B(R2) B.4.k.2.1) and/or 'Active substance name(s)' (ICH-E2B(R2) B.4.k.2.2) as reported by the primary source.~~also provided.

In line with ICH-E2B the following applies:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• As a general principle, additional characteristics related to the medicines and pertinent to the case should be coded and further information related to the falsified medicinal product provided in free text. Data element B.4.k.19 'Additional information on drug' should be used to specify any additional information (e.g., falsified medicine); additional information concerning the

[60] As presented in EU legislation (Directive 2011/62/EU).

Reference	E2B(R2)/(R3) requirements	
	indication for the drug should be provided as applicable. • An appropriate MedDRA term should be provided in the data element B.2.i.1 'Reaction/event in MedDRA terminology (Lowest Level Term)' or the data element 'B.5.3 Sender's diagnosis/syndrome and/or reclassification of reaction/event'. • Data element B.4.k.2.1 'Proprietary medicinal product name' and/or B.4.k.2.2 'Active substance name(s)' as reported by the primary source should be populated accordingly.	
ICH-E2B(R3)	• As a general principle, additional characteristics related to the medicines and pertinent to the case should be coded and further information provided in the case narrative. • An appropriate MedDRA term should be provided in the data element E.i.2.1b 'Reaction/Event (MedDRA code)'. Alternatively, section H.3.r 'Sender's Diagnosis' should be completed. • Section G.k 'Drug(s) Information' should be completed; information should be captured in the data element G.k.2.2 'Medicinal Product Name as Reported by the Primary source' and/or G.k.2.3.r.1 'Substance/Specified Substance name'. • Data element G.k.10.r 'Additional Information on Drug (coded)' should be completed using the following value 'Counterfeit'. The value should be used where the medicine is suspected or confirmed to be a falsified medicinal product. • If new information is received to confirm the product is not a counterfeit, the data element G.k.10.r should be changed appropriately in a follow up. If the product is confirmed as a counterfeit, the appropriate MedDRA code should be used in data element in H.3.r 'Sender's Diagnosis' and information should be provided in the case narrative. • Data element G.k.11 'Additional Information on Drug (free text)' should be used to capture any additional drug information in free text format not described in G.k.10.r e.g. medicine purchased over the internet.	
	Values definition for data element G.k.10.r 'Additional Information on Drug (coded)'	
	• Counterfeit[61]	This is to indicate that the medicine was suspected or confirmed to be a falsified medicinal product in line with the definition provided in Article 1, paragraph 33 of Directive 2001/83/EC.

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[61] This value should not been used to refer to medicines that do not comply with EU law on intellectual and industrial property rights, such as registered trademarks or patent rights, as defined for counterfeit medicines in Q&A: Directive on falsified medicines.

VI.C.6.2.3.6. Suspected transmission via a medicinal product of an infectious agent

EU requirements are provided in VI.C.2.2.5..

The coding of a suspected transmission of an infectious agent via a medicinal product ~~in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1)~~ should be performed in line with the latest version of the ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider' ~~(see GVP Annex IV).~~.

In addition, if the infectious agent is specified, the MedDRA Lowest Level Term code corresponding to the infectious agent should also be included ~~in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1).~~.

In line with ICH-E2B the following applies:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• The appropriate MedDRA term should be provided in the data element B.2.i.1 'Reaction/event in MedDRA terminology (Lowest Level Term)'.
ICH-E2B(R3)	• The appropriate MedDRA term should be provided in the data element E.i.2.1b 'Reaction/Event (MedDRA code)'.

VI.C.6.2.3.7. Reports of suspected adverse reactions originating from organised data collection systems and other systems

General safety reporting requirements in the EU for post-authorisation studies are provided in VI.C.1. and VI.C.2.2.2.. Individual case safety reports originating from those studies shall contain information on study type, study name and the sponsor's study number or study registration number [IR Art 28 (3)(c)]. ~~This should be provided in ICH E2B(R2) section A.2.3 'Study identification'.~~

In line with ICH-E2B the following applies:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Section A.2.3 'Study identification' should be completed accordingly.
ICH-E2B(R3)	• Section C.5 'Study Identification' should be completed accordingly.

Safety reporting requirements regarding patient support programmes or market research programmes are provided in VI.C.2.2.11..

All ICSRs which are reportable to the EudraVigilance database and which originate from organised data collection systems and other systems which do not fall under the scope of the clinical trials Directive 2001/20/EC , should be submitted to EVPM (see VI.C.6.2.1.). The same applies to cases of adverse reactions originating from clinical trials if they are suspected to be related to a medicinal product other than the IMP or NIMP and does not result from a possible interaction with the IMP or NIMP.

The following reporting rules should be applied based on (i) the type of data collection system and (ii) whether the suspected medicinal product is part of the scope of the data collection system.

1. For cases of suspected adverse reactions (i) in relation to those adverse events for which the protocol of non-interventional post-authorisation studies ~~does not provide differently and~~ requires their systematic collection (see VI.C.1.2.1.), (ii) originating from compassionate use or named patient use conducted in Member States where the active collection of adverse events occurring in

these programmes is required (see VI.C.1.2.2.), or (iii) originating from patient support programmes, or market research programmes (see VI.C.2.2.11.):

a~~).~~. Where the adverse reaction is suspected to be related at least to the studied (or supplied) medicinal product:

- the report should be considered as solicited;
- ~~the ICH E2B(R2) data element A.1.4 'Type of report' should be populated with the value 'Report from study';~~
- ~~the ICH E2B(R2) data element A.2.3.3 'Study type in which the reaction(s)/event(s) were observed' should be populated with the value 'Other studies' or 'Individual patient use'.~~
- in line with ICH-E2B the following applies:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Data element A.1.4 'Type of report' should be populated with the value 'Report from study'. • Data element A.2.3.3 'Study type in which the reaction(s)/event(s) were observed' should be populated with the value 'Other studies' or 'Individual patient use'.
ICH-E2B(R3)	• Data element C.1.3 'Type of Report' should be populated with the value 'Report from study'. • Data element C.5.4 'Study Type Where Reaction(s)/Event(s) Were Observed' should be populated with the value 'Other studies' or 'Individual patient use'.

b~~).~~. Where the adverse reaction is only suspected to be related to a medicinal product which is not subject to the scope of the organised data collection system and there is no interaction with the studied (or supplied) medicinal product:

- the report should be considered as spontaneous report; as such it conveys the suspicion of the primary source;
- ~~The ICH E2B(R2) data element A.1.4 'Type of report' should be populated with the value 'Spontaneous'.~~
- in line with ICH-E2B the following applies:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Data element A.1.4 'Type of report' should be populated with the value 'Spontaneous'.
ICH-E2B(R3)	• Data element C.1.3 'Type of Report' should be populated with the value 'Spontaneous'.

2. For suspected adverse reactions (i) in relation to those adverse events for which the protocol of non-interventional post-authorisation studies ~~provides differently and~~ does not require their systematic collection (see VI.C.1.2.1.) or (ii) originating from compassionate use or named patient use conducted in Member States where the active collection of adverse events occurring in these programmes is not required (see VI.C.1.2.2.):

- the report should be considered as spontaneous report; as such it conveys the suspicion of the primary source;

- ~~the ICH E2B(R2) data element A.1.4 'Type of report' should be populated with the value 'Spontaneous'.~~

- In line with ICH-E2B the following applies:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Data element A.1.4 'Type of report' should be populated with the value 'Spontaneous'.
ICH-E2B(R3)	• Data element C.1.3 'Type of Report' should be populated with the value 'Spontaneous'.

3. For clinical ~~trial~~trials conducted in accordance with Directive 2001/20/EC ~~and~~ where the adverse reaction is only suspected to be related to a ~~non-investigational~~ medicinal product ~~(~~other than the IMP or ~~another medicinal product which is~~NIMP and does not ~~subject to the scope of the clinical trial) and there is no~~result from a possible interaction with the ~~investigational medicinal product:~~IMP or NIMP (see VI.C.1.1.):

- the report should be considered as spontaneous report; as such it conveys the suspicion of the primary source;

- ~~the ICH E2B(R2) data element A.1.4 'Type of report' should be populated with the value 'Spontaneous'.~~

~~All ICSRs which are reportable to the EudraVigilance database and which originate from post-authorisation studies which do not fall under the scope of the clinical trials Directive 2001/20/EC, should be submitted to EVPM (see VI.C.6.2.1.). The same applies to cases of adverse reactions originating in clinical trials if they are not suspected to be related to the investigational medicinal product.~~

- in line with ICH-E2B the following applies:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• Data element A.1.4 'Type of report' should be populated with the value 'Spontaneous'.
ICH-E2B(R3)	• Data element C.1.3 'Type of Report' should be populated with the value 'Spontaneous'.

VI.C.6.2.3.8. Receipt of missing minimum information

When missing minimum information (see VI.B.2.) has been obtained about a non-valid ICSR, the following rules should be applied:

- the ~~data element 'Date~~date where the report was first received from ~~source' (ICH E2B(R2) A.1.6)~~source should ~~contain~~reflect the date of receipt of the initial non-valid ICSR;

- the ~~data element 'Date~~date of receipt of the most recent information ~~for this report' (ICH E2B(R2) A.1.7)~~ should ~~contain~~reflect the date when all the four elements of the minimum information required for reporting have become available;

- clarification should be provided in the case narrative ~~(data element ICH-E2B(R2) B.5.1)~~ that some of the four elements were missing in the initial report~~.~~;
- as for any ~~reported~~submitted cases, compliance monitoring is performed against the ~~data element 'Date~~date of receipt of the most recent information for this ~~report' (~~report.

In line with ICH-E2B~~(R2) A.1.7).~~ the following applies:

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	• The data element A.1.6 'Date report was first received from source' should capture the date of receipt of the initial non-valid ICSR; • The data element A.1.7 'Date of receipt of the most recent information for this report' should capture the date when all the four elements of the minimum information required for reporting have become available; • Clarification should be provided in the data element B.5.1 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' that some of the four elements were missing in the initial report.
ICH-E2B(R3)	• The data element C.1.4 'Date Report Was First Received from Source' should capture the date of receipt of the initial non-valid ICSR; • The data element C.1.5 'Date of Most Recent Information for This Report' should capture the date when all the four elements of the minimum information required for reporting have become available; • Clarification should be provided in the data element H.1 'Case Narrative Including Clinical Course, Therapeutic Measures, Outcome and Additional Relevant Information' that some of the four elements were missing in the initial report.

VI.C.6.2.4. Data quality of individual case safety reports transmitted electronically and duplicate management

The EudraVigilance database should contain all cases of suspected adverse reactions that are reportable according to Directive 2001/83/EC and Regulation (EC) No 726/2004 to support pharmacovigilance activities. This applies to all medicinal products authorised in the EU independent of their authorisation procedure.

The EudraVigilance database should also be based on the highest internationally recognised data quality standards.

To achieve these objectives, all competent authorities in Member States and marketing authorisation holders should adhere to:

- the electronic reporting requirements as defined in EU legislation;
- the concepts of data structuring, coding and reporting in line with the EU legislation, guidelines, standards and principles referred to in VI.C.6.2.2.1..

This is a pre-requisite to maintain a properly functioning EudraVigilance database intended to fully support the protection of public health.

In addition, the Agency in collaboration with stakeholders that submit ICSRs to EudraVigilance, are responsible to contribute to the quality and integrity of the data. This is also reflected in legislation as follows:

- The Agency shall, in collaboration with the stakeholder that submitted an ICSR to the EudraVigilance database, be responsible for operating procedures that ensure the highest quality and full integrity of the information collected in the EudraVigilance database [REG Art 24(3)]. This includes as well the monitoring of use of the terminologies referred to in chapter IV of the Commission Implementing Regulation (EU) No 520/2012 [IR Art 25(3)].

Specific quality system procedures and processes shall be in place in order to ensure~~:~~

- the submission of accurate and verifiable data on serious and non-serious suspected adverse reactions to the Eudravigilance database within the 15 or 90-day time frame [IR Art 11 (1) (c)];
- Specific quality system procedures and processes shall be in place in order to ensure the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions [IR Art 11 (1) (d)].
- Marketing authorisation holders shall collaborate with the Agency and the Member States in the detection of duplicates of suspected adverse reaction reports [DIR Art 107(5)].
- Member States shall collaborate with the Agency and the marketing authorisation holders in the detection of duplicates of suspected adverse reaction reports [DIR Art 107a (3)].

In this regard, marketing authorisation holders and competent authorities in Member States should have in place an audit system, which ensures the highest quality of the ICSRs transmitted electronically to the EudraVigilance database within the correct time frames, and which enables the detection and management of duplicate ICSRs in their system. Those transmitted ICSRs should be complete, entire and undiminished in their structure, format and content.

~~High level~~For the purpose of a systematic approach towards quality in accordance with the quality cycle as outlined in GVP Module I, managerial staff (i.e. staff with management responsibilities) in any organisation should be responsible for ensuring that adequate resources are available and that appropriate training is provided to their personnel for pharmacovigilance. Competent authorities in Member States and marketing authorisation holders should regularly update their training plans based on an assessment of the training needs of their personnel for pharmacovigilance, which should be subject to monitoring. Records for documenting and developing the competences of personnel should be maintained and updated accordingly. To support the training of personnel for pharmacovigilance, the Agency has made available a detailed training plan and catalogue based on a modular training approach focusing on adverse reactions reporting, signals management and EudraVigilance[62].

In support of the operation of the procedures that ensure the highest quality and full integrity of the information collected in EudraVigilance as well as the monitoring of use of the terminologies for the reporting of suspected adverse reactions, business process maps and process descriptions in relation to the quality review of ICSRs ~~and the~~ are provided in VI.App.6.

A review of the ICSRs quality, integrity and compliance with the reporting time frames will be performed by the Agency at regular intervals for all organisations reporting to EudraVigilance in line with the Agency's SOPs. Parameters upon which the review of organisations may be initiated, refer for example to the volume of reports being submitted to EudraVigilance, major changes to pharmacovigilance databases, quality issues identified as part of the signal management, requests

[62] Accessible on EudraVigilance training webpage.

from pharmacovigilance inspectors and the time interval since the last review. For the purpose of the monitoring of the 15 or 90 days reporting time frames, the Agency provides competent authorities in Member States and marketing authorisation holders with monthly compliance reports.

The outcome of the quality reviews will be provided to the organisations on the basis of a report, which include the need for corrective measures where applicable and the time frames for these measures to be applied. The time frames and the method for corrective measures will depend on the quality issues identified (e.g. corrections of the MedDRA coding of ICSRs to be performed by means of amendment reports).

With regard to the monitoring by the Agency of selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances (see VI.C.2.2.3.1.) and the entering of adverse reaction reports in EudraVigilance in accordance with Article 27 of Regulation (EC) 726/2004, two-yearly audits are planned to ensure the quality and integrity of the reports. SOPs and WINs for the routine quality review process are published at the Agency's dedicated medical literature monitoring webpage.[63]

In support of the operation of procedures that ensure detection and management of duplicate ICSRs ~~are provided in VI. Appendix 6 and VI. Appendix 7. Further guidance~~, business process maps and process descriptions are provided in VI.App.7 taking into account various scenarios acknowledging that duplicates may be detected at various stages of the processing of ICSRs by numerous stakeholders and in EudraVigilance. The collaboration between the Agency, competent authorities in Member States and marketing authorisation holders is required to ensure that potential duplicates of reports of suspected adverse reactions are reviewed, confirmed and processed as necessary. Guidance on the detection of duplicate ICSRs is ~~available~~provided in the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs) (EMA/13432/2009).

~~A review of the ICSRs quality, integrity and compliance with the reporting time frames will be performed by the Agency at regular intervals for all organisations reporting to the EudraVigilance database. Feedback from these reviews will be provided to those organisations.~~

VI.C.6.2.5. Electronic re-transmission of ICSRs between multiple senders and receivers

The electronic re-transmission of cases refers to the electronic exchange of ICSRs between multiple senders and receivers, for example where in case of contractual agreement, a third country ICSR is first ~~reported~~submitted by a marketing authorisation holder outside the EU to another marketing authorisation holder in the EU and from there to the Agency. This applies as well for the interim arrangements period, where based on the reporting requirements detailed in VI.C.4.1., ICSRs originating in the EU are submitted by marketing authorisation holders to the competent authorities in the Member State where the reaction occurred and then re-transmitted to the EudraVigilance database.

During this re-transmission process, information on the case should not in principle be omitted or changed if no new information on the case is available to the re-transmitting sender. Exceptions apply to the following ICH-E2B data elements or sections:

~~Exceptions apply to the following data elements or sections:~~

- ~~'Sender's (case) safety report unique identifier' (ICH-E2B(R2) A.1.0.1);~~
- ~~'Date of this transmission' (ICH-E2B(R2) A.1.3);~~

[63] Monitoring of medical literature and entry of adverse reaction reports into EudraVigilance

- ~~'Date report was first received from source' (ICH-E2B(R2) A.1.6), for initial reports;~~
- ~~'Date of receipt of the most recent information for this report' (ICH-E2B(R2) A.1.7);~~
- ~~'Information on sender and receiver of case safety report' (ICH-E2B(R2) A.3);~~
- ~~'Relatedness of drug to reaction(s)/event(s)' (ICH-E2B(R2) B.4.k.18);~~
- ~~'Sender's diagnosis/syndrome and/or reclassification of reaction/event' (ICH-E2B(R2) B.5.3);~~
- ~~'Sender's comments' (ICH-E2B(R2) B.5.4).~~

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element A.1.0.1 'Sender's (case) safety report unique identifier'; • Data element A.1.3 'Date of this transmission'; • Data element A.1.6 'Date report was first received from source', for initial reports; • Data element A.1.7 'Date of receipt of the most recent information for this report'; • Data element A.3 'Information on sender and receiver of case safety report'; • Data element B.4.k.18 'Relatedness of drug to reaction(s)/event(s)'; • Data element B.5.3 'Sender's diagnosis/syndrome and/or reclassification of reaction/event'; • Data element B.5.4 'Sender's comments'.
ICH-E2B(R3) guideline	• Data element C.1.1 'Sender's (case) Safety Report Unique Identifier'; • Data element C.1.4 'Date Report Was First Received from Source, for initial reports'; • Data element C.1.5 'Date of Most Recent Information for This Report'; • Data element G.k.9.i.2 'Assessment of Relatedness of Drug to Reaction(s)/Event(s)'; • Data element H.3.r 'Sender's Diagnosis (MedDRA code)'; • Data element H.4 'Sender's Comments'.

In the interest of improving data quality, in case of errors or inconsistencies in the report, the re-transmitters should go back to the originator of the report to correct the case accordingly. However, if this cannot be done within normal reporting time frame, the re-transmitter can correct information that has been incorrectly structured.

In addition, any electronic data interchange partner should adhere to the ICH-E2B~~(R2)~~ rules regarding the provision of follow-up information, ~~whereby the 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) should be maintained~~ in accordance with the ~~ICH-E2B(R2) guideline (see GVP Annex IV).~~principles set out in VI.C.6.2.2.7.. Non-adherence to these administrative requirements endangers the electronic case management and leads to the potential for unnecessary duplication of reports in the receiver's database.

VI.C.6.2.6. Electronic reporting through company's headquarters

If a pharmaceutical company decides to centralise the electronic reporting of ICSRs (e.g. by reporting through the company's global or EU headquarter), the following should be taken into account:

- the central reporting arrangement should be clearly specified in the marketing authorisation holder's pharmacovigilance system master file and in the internal standard operating procedures;
- the company's headquarter designated for reporting the ICSRs should be registered with EudraVigilance~~;~~.

~~the~~The same principles may be applied for reporting ICSRs from the competent authorities in Member States to the marketing authorisation holders during the interim arrangements period, that is the competent authorities in Member States report electronically to the company's headquarter instead of to the local affiliates.

VI.C.6.3. Electronic submission of information on medicinal products

To support the objectives of Directive 2001/83/EC and Regulation (EC) No 726/2004, the provisions provided in second sub-paragraph of Article 57(2) of Regulation (EC) No 726/2004, regarding the electronic submission and update of information on medicinal products for human use authorised or registered in the EU, shall be followed by marketing authorisation holders. In this aspect marketing authorisation holders shall apply the internationally agreed formats and terminologies described in chapter IV of the Commission Implementing Regulation (EU) No 520/2012. Recommendations related to the electronic submission of information on medicines are provided on the Agency's website[64].

[64] See EMA documents for electronic submission of information on medicines: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000336.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580410138&jsenabled=true

VI. Appendix 1 ~~Identification~~Follow-up process of ~~biological medicinal products~~ICSRs

VI.App.1.1 Follow-up of ICSRs by marketing authorisation holders

Figure VI.2. Business process map - Follow-up of ICSRs by marketing authorisation holders

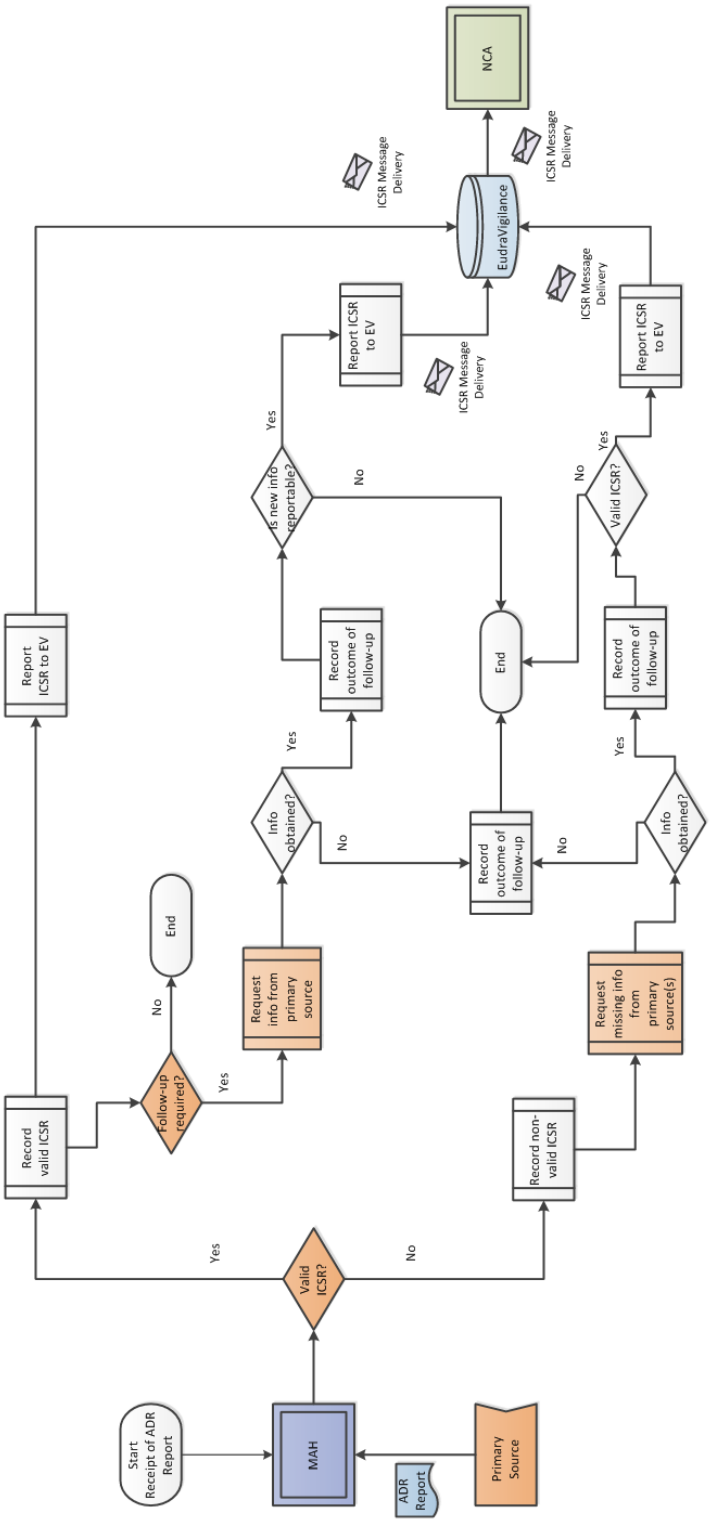

Table VI.2. Process description - Follow-up of ICSRs by marketing authorisation holders

No	Step	Description	Responsible Organisation
	Start	**Receipt of a report of a suspected adverse reaction related to a medicine (ADR report)**	
1	Receive report of suspected drug adverse reaction(s) from primary source	Day 0. Receipt of the information	MAH
2	Is the report valid?	Is the report received from the primary source a valid ICSR in accordance with VI.B.2.? If Yes, go to step 3. If No, go to step 10.	MAH
3	The report received is valid	The report received from the primary source is a valid ICSR in accordance with chapter VI.B.2	
3.1	Record the report	Record the valid ADR report received from the primary source in the pharmacovigilance database	MAH
3.2	Report ICSR to EudraVigilance (EV)	Report the valid ICSR to EudraVigilance in accordance with the principles set out in chapter VI.C.6.2 NOTE: the MAH can organise the reporting of the initial report and the follow-up report in accordance with the reporting timelines set out in the pharmacovigilance legislation i.e. if time permits and follow-up information can be obtained and processed within the initial reporting timeframes, the MAH is not required to report the initial and the follow-up report separately	MAH
3.3	Is follow-up required for the valid ICSR?	If Yes, go to step 4 If No, go to step 9	MAH
4	Follow-up required for valid ICSR		
4.1	Request information from primary source	Contact the primary source to obtain additional information pertinent to the valid case in accordance with the principles set out	MAH

No	Step	Description	Responsible Organisation
		in chapters VI.B.3 and VI.C.6.2.2.7 Note: MAHs should define in their SOPs how many attempts to obtain follow-up information are made	
4.2	Has new information on the case be obtained from the primary source?	If Yes, go to point 5. If No, go to point 8.	MAH
5	Additional information has been obtained		MAH
5.1	Record outcome of follow-up	Record the outcome of the follow-up and record information obtained in the pharmacovigilance database	MAH
5.2	Is new information significant and reportable?	Determine if information obtained is significant enough to be submitted in accordance with VI.C.6.2.2.7. If Yes, go to point 6. If No, go to point 7.	MAH
6	New information is significant and reportable		
6.1	Report ICSR to EudraVigilance	Report the ICSR with the follow-up information to EudraVigilance in accordance with VI.C.6.	MAH
7	New information is not significant and not reportable	The new information is not significant enough to be sent in accordance with VI.C.6.2.2.7.	
7.1	End		MAH
8	No information has been obtained	The follow-up with the primary source is unsuccessful and no additional information on the case can be obtained	
8.1	Record the outcome of follow-up	Record the fact that no further information has been obtained from the primary source in the pharmacovigilance database	MAH
8.2	End		
9	Follow-up is not required for valid ICSR	ICSR is valid. Follow-up is not performed	MAH
9.1	End		
10	The report received from the primary source is NOT a valid ICSR	The report received is not a valid report in accordance with VI.B.2.	

No	Step	Description	Responsible Organisation
10.1	Record non-valid ICSR	Record the non-valid ICSR in pharmacovigilance database	MAH
10.2	Request missing info from primary source	Request missing information for non-valid ICSR from the primary source through follow-up in line with VI.B.3. and VI.C.6.2.2.7.	MAH
10.3	Missing info has been obtained?	Has missing information been obtained for non-valid ICSR? If Yes, go to 11. If No, go to 14.	MAH
11	Missing information has been obtained for non-valid ICSR		MAH
11.1	Record the outcome of follow-up with primary source	Record the outcome of the follow-up of missing information in the pharmacovigilance database	MAH
11.2	Is the ICSR valid?	Is the report now valid taking into account the follow-up information obtained from the primary source? If Yes, go to 12. If No, go to 13.	MAH
12	ICSR is valid		
12.1	Report ICSR to EudraVgilance	Report the valid ICSR to EudraVigilance in line with the principles set out in VI.C.6.	MAH
13	ICSR is not valid		MAH
13.1	End		
14	Missing information has not been obtained for non-valid ICSR	No further information is obtained from the primary source in the pharmacovigilance database	
14.1	Record the outcome of the follow-up	Record the fact that no further information has been obtained from the primary source in the pharmacovigilance database	MAH
14.2	End		

VI.App.1.2 Follow-up of ICSRs by competent authorities in Member States involving consumers or healthcare professionals

Figure VI.3. Business process map - Follow-up of ICSRs by competent authorities in Member States involving consumers or healthcare professionals

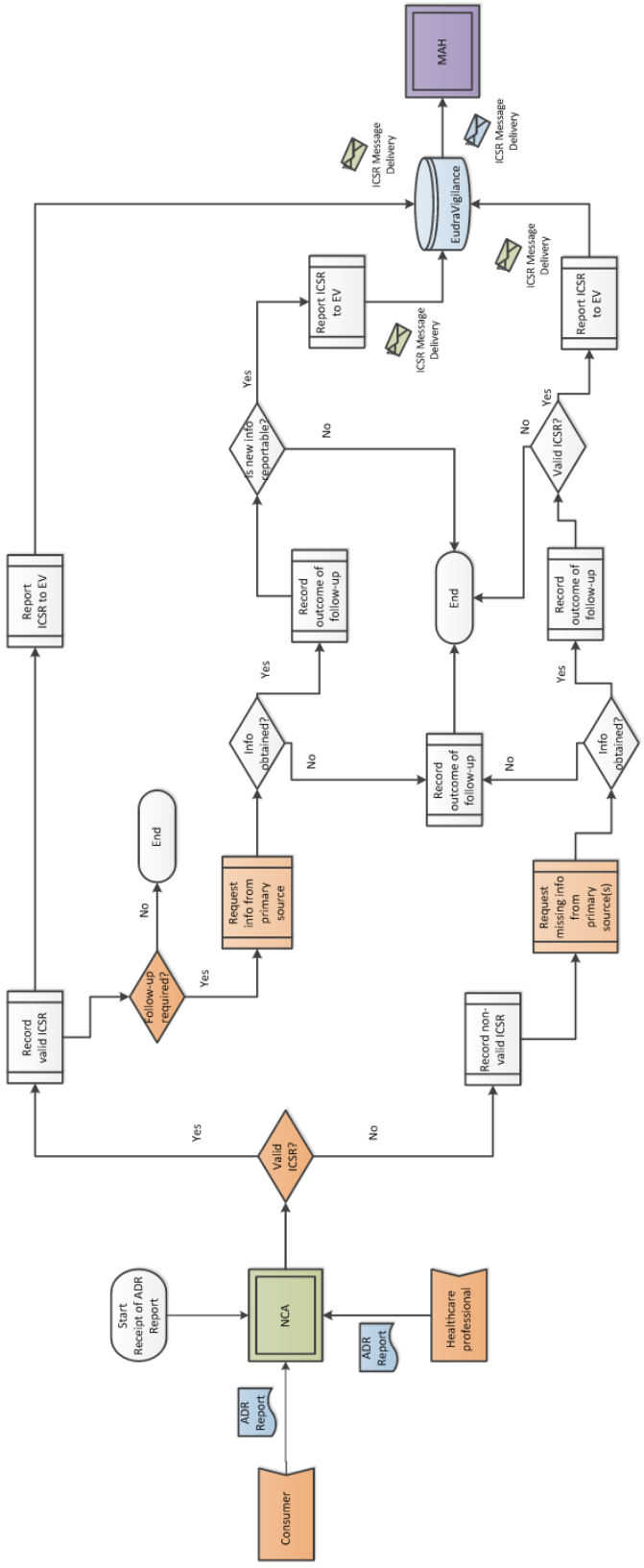

Table VI.3. Process description - Follow-up of ICSRs by competent authorities in Member States involving consumers or healthcare professionals

No	Step	Description	Responsible Organisation
	Start	**Receipt of a report of a suspected adverse reaction related to a medicine (ADR report)**	
1	Receive report of suspected drug adverse reaction(s) from primary source	Day 0. Receipt of the information	NCA
2	Is the report valid?	Is the report received from the primary source a valid ICSR in accordance with chapter VI.B.2? If Yes, go to step 3. If No, go to step 10.	NCA
3	The report received is valid	The report received from the primary source is a valid ICSR in accordance with chapter VI.B.2	
3.1	Record the report	Record the valid ADR report received from the primary source in the pharmacovigilance database	NCA
3.2	Report ICSR to EudraVigilance (EV)	Report the valid ICSR to EudraVigilance in accordance with the principles set out in VI.C.6.2. NOTE: the NCA can organise the reporting of the initial report and the follow-up report in accordance with the reporting timelines set out in the pharmacovigilance legislation i.e. if time permits and follow-up information can be obtained and processed within the initial reporting timeframes, the MAH is not required to report the initial and the follow-up report separately	NCA
3.3	Is follow-up required for the valid ICSR?	If Yes, go to step 4 If No, go to step 9	NCA
4	Follow-up required for valid ICSR		
4.1	Request information from primary source	Contact the primary source to obtain additional information pertinent to the valid	NCA

No	Step	Description	Responsible Organisation
		case in accordance with the principles set out in VI.B.3. and VI.C.6.2.2.7. Note: NCAs should define in their SOPs how many attempts to obtain follow-up information are made	
4.2	Has new information on the case be obtained from the primary source?	If Yes, go to point 5. If No, go to point 8.	NCA
5	Additional information has been obtained		NCA
5.1	Record outcome of follow-up	Record the outcome of the follow-up and record information obtained in the pharmacovigilance database	NCA
5.2	Is new information significant and reportable?	Determine if information obtained is significant enough to be reportable in accordance with VI.C.6.2.2.7. If Yes, go to point 6. If No, go to point 7.	NCA
6	New information is significant and reportable		NCA
6.1	Report ICSR to EudraVigilance	Report the ICSR with the follow-up information to EudraVigilance in accordance with VI.C.6.	NCA
7	New information is not significant and not reportable	The new information is not reportable in accordance with VI.B.3. and VI.C.6.2.2.7.	
7.1	End		NCA
8	No information has been obtained	The follow-up with the primary source is unsuccessful and no additional information on the case can be obtained	
8.1	Record the outcome of follow-up	Record the fact that no further information has been obtained from the primary source in the pharmacovigilance database	NCA
8.2	End		
9	Follow-up is not required for valid ICSR	ICSR is valid. Follow-up is not performed	NCA
9.1	End		
10	The report received from the primary source is NOT	The report received is not a valid report in	

No	Step	Description	Responsible Organisation
	a valid ICSR	accordance with VI.B.2.	
10.1	Record non-valid ICSR	Record the non-valid ICSR in pharmacovigilance database	NCA
10.2.	Request missing info from primary source	Request missing information for non-valid ICSR from the primary source through follow-up in line with VI.B.3. and VI.C.6.2.2.7.	NCA
10.3	Missing info has been obtained?	Has missing information been obtained for non-valid ICSR? If Yes, go to 11. If No, go to 14.	NCA
11	Missing information has been obtained for non-valid ICSR		NCA
11.1	Record the outcome of follow-up with primary source	Record the outcome of the follow-up of missing information in the pharmacovigilance database	NCA
11.2	Is the ICSR valid?	Is the report now valid taking into account the follow-up information obtained from the primary source? If Yes, go to 12. If No, go to 13.	NCA
12	ICSR is valid		NCA
12.1	Report ICSR to EudraVgilance	Report the valid ICSR to EudraVigilance in line with the principles set out in VI.C.6	NCA
13	ICSR is not valid		MAH
13.1	End		NCA
14	Missing information has not been obtained for non-valid ICSR	No further information is obtained from the primary source in the pharmacovigilance database	NCA
14.1	Record the outcome of the follow-up	Record the fact that no further information has been obtained from the primary source in the pharmacovigilance database	NCA
14.2	End		NCA

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VI.App.1.3 Follow-up of ICSRs by competent authorities in Member States with involvement of marketing authorisation holders

Figure VI.4. Business process map - Follow-up of ICSRs by competent authorities in Member States with involvement of marketing authorisation holders

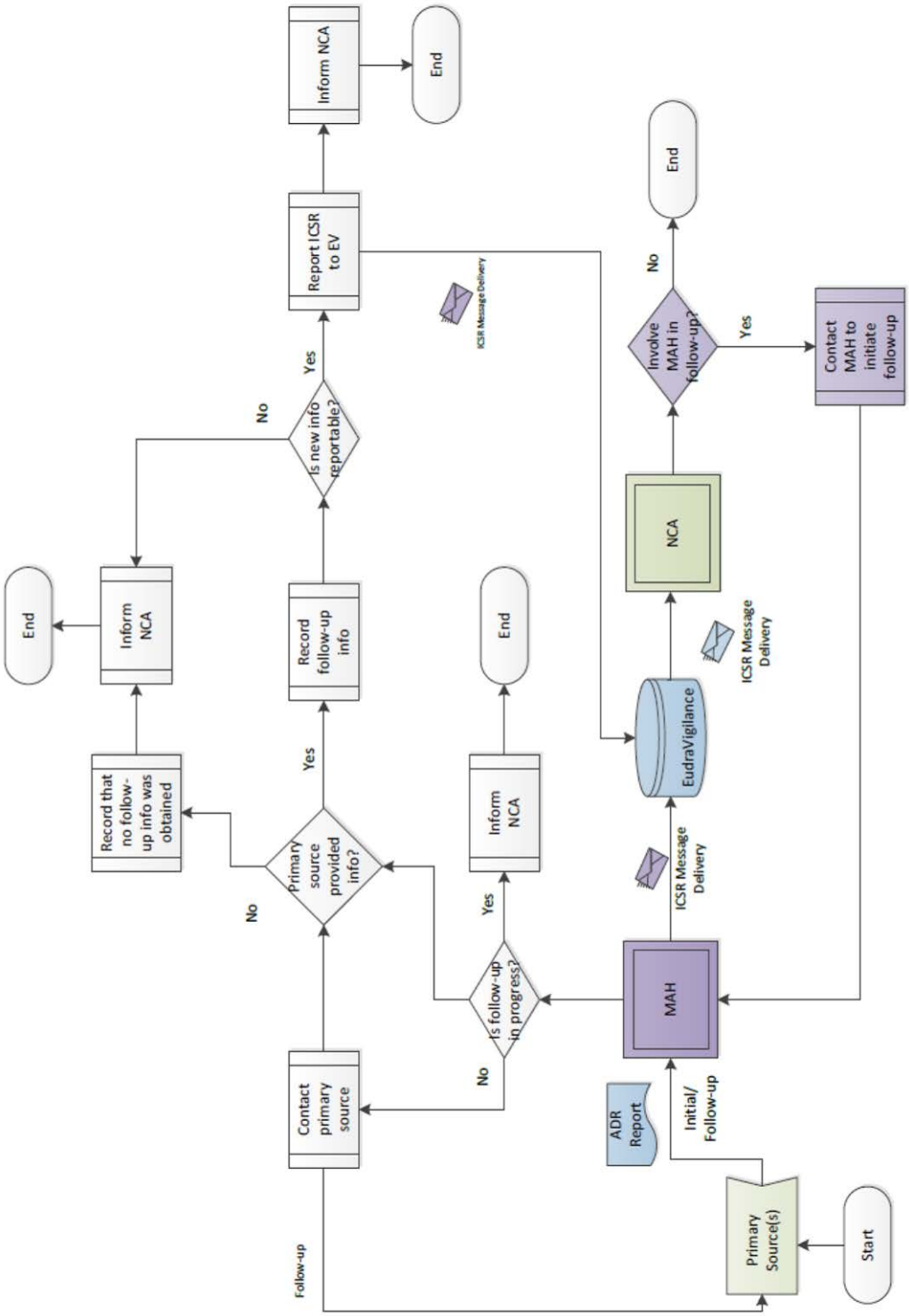

Table VI.4. Process description - Follow-up of ICSRs by competent authorities in Member States with involvement of marketing authorisation holders

No	Step	Description	Responsible Organisation
	Start	**Receipt of a report of a suspected adverse reaction related to a medicine (ISCR)**	
1	Receive report of suspected drug adverse reaction(s) from primary source	Day 0. Receipt of the information	MAH
2	Report ICSR to EudraVigilance	Report the valid ICSR to EudraVigilance in line with the principles set out in VI.C.6	MAH
3	Re-route ICSR to NCA	MAH ICSR is rerouted from EudraVigilance to the NCA of the country of the primary source for regulatory purposes	Agency
4	Is follow-up required with involvement of MAH?	If Yes, go to point 5. If No, go to point 12.	NCA
5	Follow-up is required		
5.1	Contact MAH to request follow-up information	Send email to QPPV or local contact person to request follow-up information Indicate reference to individual case(s) using World Wide Unique Case Identifier(s) for cases that require follow-up Indicate criterion/criteria for request to involve MAH in follow-up Indicate timeframe by when follow-up is to be provided	NCA
5.2	Is follow-up already in progress?	If Yes, progress to point 6. If No progress to point 7.	MAH
6	Follow-up is already in progress	Follow-up has already been initiated by the MAH	MAH
6.1	Inform NCA that follow-up is in progress	Inform NCA via e-mail that follow-up is already in progress using functional mailbox MAH.followup@ema.europa.eu Provide reference to individual case(s) using World Wide Unique Case Identifier Indicate timeline by when follow-up info	MAH

No	Step	Description	Responsible Organisation
		has been requested	
6.2	End		
7	Follow-up has not been initiated		MAH
7.1	Contact primary source	Contact primary source to obtain follow-up information as per request of NCA Note: When contacting the primary source(s), MAH is allowed to indicate that the follow-up is performed upon request of a NCA	MAH
7.2	Did primary source provide requested info?	If Yes, proceed to point 9 If No, proceed to point 8	
8	Primary source did not provide follow-up information		MAH
8.1	Record that no follow-up info was obtained	Record that primary source did not provide follow-up information	MAH
8.2	Inform NCA	Inform NCA via e-mail that it was not possible to obtain follow-up information from primary source using functional mailbox MAH.followup@ema.europa.eu Provide reference to individual cases using World Wide Unique Case Identifier	MAH
8.3	End		
9	Primary source did provide follow-up information		
9.1	Record follow-up information	Record follow-up information in pharmacovigilance database	MAH
9.2	Is new information significant and reportable?	Determine if follow-up information is significant enough to be reportable in accordance with principles set out in VI.C.6.2.2.7 If Yes, proceed to point 10. If No, proceed to point 11.	
10	Follow-up info is significant and reportable		

No	Step	Description	Responsible Organisation
10.1	Send follow-up ICSR to EudraVigilance	Send follow-up ICSR to EudraVigilance in accordance with principles set out in VI.C.6	MAH
10.2	Inform NCA that follow-up info was received	Inform NCA via e-mail that follow-up information from primary source was received using functional mailbox MAH.followup@ema.europa.eu Indicate reference to individual cases using World Wide Unique Case Identifier	MAH
10.3	End		
11	Follow-up information is not significant and not reportable		
11.1	Inform NCA	Inform NCA that no significant new information has been obtained in accordance with VI.C.6.2.2.7.	MAH
11.2	End		
12	MAH does NOT need to be involved in follow-up	There is no need to involve the MAH in the follow-up process	NCA
12.1	End		

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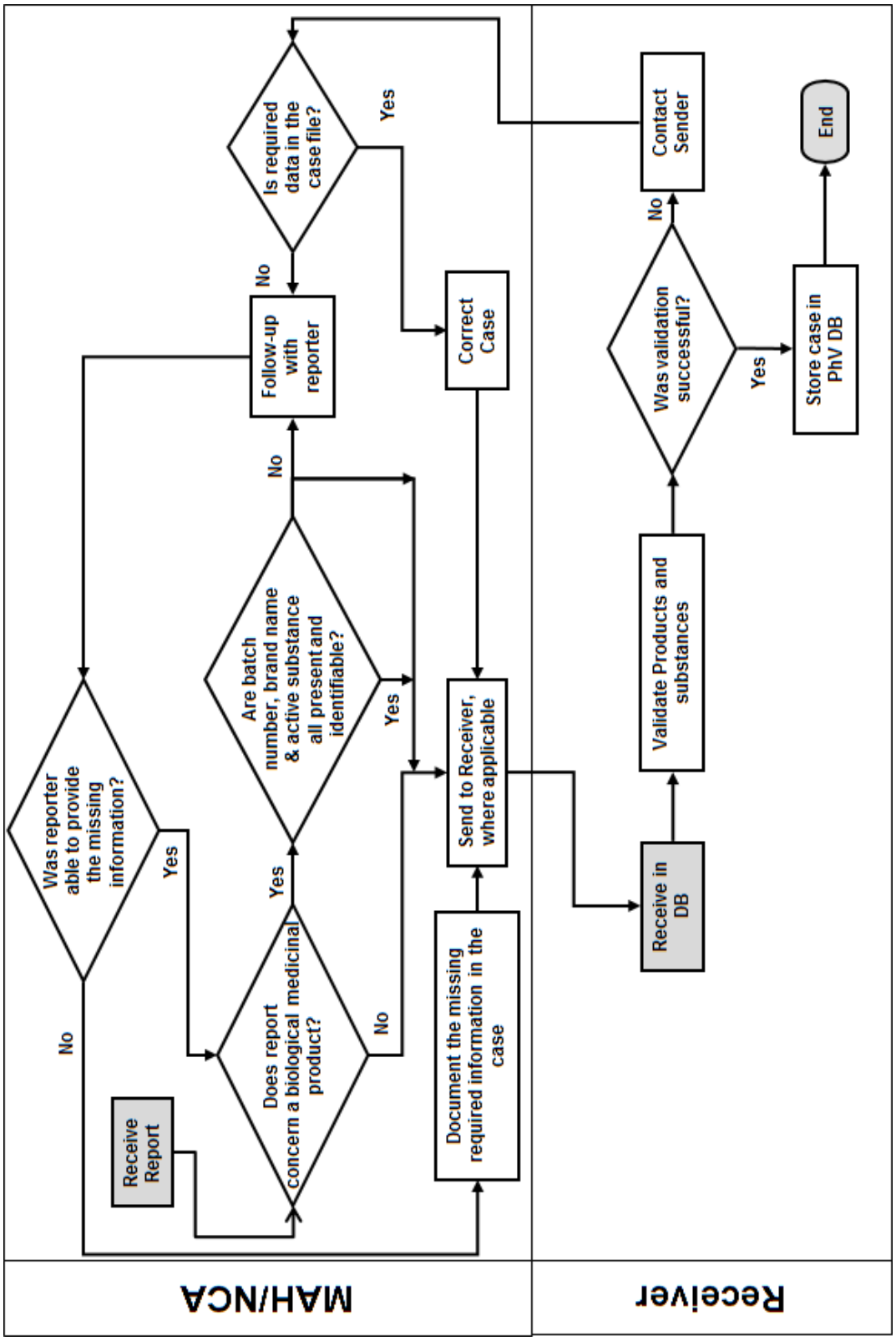
VI.App.1.4 Follow-up of ICSRs for identification of biological medicinal products

~~Figure VI.2.~~ **Figure VI.5.** Business process map - Identification of biological medicinal products[65]



[65] Mandatory when they are the subject of reports of suspected adverse reactions [DIR Art 102(e) and IR Art 28 (3)].

~~Table VI.2.~~ **Table VI.5.** Process description - Identification of biological medicinal products

No.	Step	Description	Responsible Organisation
1	**Start.** **Receive report.**	**Day 0. Receipt of the information for the case that indicates that one of the suspect drugs is of biological origin.**	**MAH / NCA**
2	Does report concern a biological medicinal product?	If Yes, go to step 3 If No, go to step 4	
3	Are batch number, brand name & active substance all present and identifiable?	If Yes, create the case and send it to the correct receiver (step ~~3~~4). If there is more than one batch number, structure the batch number that coincided with the adverse reaction ~~in the Drug section (ICH-E2B(R2) B.4) and enter the other batch numbers in the case narrative.~~: • **ICH-E2B(R2)** in the Drug section B.4, data element B.4.k.3 “Batch/lot number” and enter the other batch numbers in the case narrative. • **ICH-E2B(R3)** in the Drug section G.k, and repeat the data element G.k.4.r.7 “Batch/Lot Number” as necessary. If No, create the case and send it to the correct receiver (step ~~3~~4) and follow-up with the reporter (step 3.1).	MAH/NCA
3.1	Follow-up with reporter.	Follow-up with the reporter to attempt to identify the missing information.	MAH/NCA
3.2	Was reporter able to provide the missing information?	If Yes, return to step 1 – the information should be treated as follow-up and a new version created & transmitted. If No, document this (step 3.3).	MAH/NCA
3.3	Document the required missing information in the case.	Document in the case that the missing required information has been sought but the reporter was not able or willing to provide it.	MAH/NCA
4	Send to receiver, where applicable.	If the case requires transmission to a receiver, transmit the case electronically, in ICH-E2B~~(R2)~~ format within the relevant timelines (15 or 90 days), to the relevant receiver.	MAH/NCA
5	**Receive in PharmacoVigilance DataBase (PhV DB).**	Receive the case electronically and load it into the PharmacoVigilance DataBase.	**Receiver**
6	Validate products and	Validate the products and substances to	Receiver

No.	Step	Description	Responsible Organisation
	substances	ensure that the brand name, active substance & batch number are all present and identifiable. This validation should be complementary to the usual business rules validations.	
7	Was validation successful?	If Yes, store the case in the PharmacoVigilance DataBase (step 8). If No, contact the sender (Step 7.1).	Receiver
7.1	Contact sender.	Contact the sender regarding the missing or not identifiable information.	Receiver
7.2	**Is required data in the case file?**	Upon receipt of communication from the receiver, check in the case file to see if the missing or unidentifiable information is already on file. If it is on file, correct the case (step 7.3). If the information is not on file, contact the reporter to request the missing information (step 3.1).	**MAH / NCA**
7.3	Correct case.	Correct the case to include the missing information & send updated version to receiver (step 4).	MAH/NCA
8	**Store case in PharmacoVigilance DataBase (PhV DB).**	The case should now be stored in the pharmacovigilance database.	**Receiver**
9	**End.**	**The case is now available for signal detection and data quality analyses.**	

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VI. Appendix 2 Detailed guidance on the monitoring of scientific literature

VI.~~App2~~App.2.1~~.~~ When to start and stop searching in the scientific literature

EU specific requirements, as regards the monitoring of scientific and medical literature are provided in VI.C.2.2.3..

In addition to the reporting of serious and non-serious ICSRs or their presentation in periodic safety update reports, the marketing authorisation holder has an obligation to review the worldwide experience with medicinal product in the period between the submission of the marketing authorisation application and the granting of the marketing authorisation. The worldwide experience includes published scientific and medical literature. For the period between submission and granting of a marketing authorisation, literature searching should be conducted to identify published articles that provide information that could impact on the risk-benefit assessment of the product under evaluation. For the purpose of the preparation of periodic safety update reports (see GVP Module VII) and the notification of emerging safety issues (see VI.C.2.2.6.), the requirement for literature searching is not dependent on a product being marketed. Literature searches should be conducted for all products with a marketing authorisation, irrespective of commercial status. It would therefore be expected that literature searching would start on submission of a marketing authorisation application and continue while the authorisation is active.

VI.~~App2~~App.2.2 Where to look

Articles relevant to the safety of medicinal products are usually published in well-recognised scientific and medical journals~~,~~; however, new and important information may be first presented at international symposia or in local journals. Although the most well-known databases (e.g. Medline) cover the majority of scientific and medical journals, the most relevant publications may be collated elsewhere in very specialised medical fields, for certain types of product (e.g. herbal medicinal products) or where safety concerns are subject to non-clinical research. A marketing authorisation holder should establish the most relevant source of published literature for each product.

Medline, Embase and Excerpta Medica are often used for the purpose of identifying ICSRs. These databases have broad medical subject coverage. Other recognised appropriate systems may be used. The database providers can advise on the sources of records, the currency of the data, and the nature of database inclusions. It is best practice to have selected one or more databases appropriate to a specific product. For example, in risk-benefit assessment, safety issues arising during non-clinical safety studies may necessitate regular review of a database that has a less clinical focus and includes more laboratory-based publications.

Relevant published abstracts from meetings and draft manuscripts should be reviewed for reportable ICSRs and for inclusion in periodic safety update reports. Although it is not a requirement for marketing authorisation holders to attend all such meetings, if there are company personnel at such a meeting, or it is sponsored by a marketing authorisation holder, it is expected that articles of relevance would be available to the marketing authorisation holder's pharmacovigilance system. In addition, literature that is produced or sponsored by a marketing authorisation holder should be reviewed, so that any reportable ICSRs can be ~~reported~~submitted as required in advance of publication.

If ICSRs are brought to the attention of a marketing authorisation holder from this source, they should be processed in the same way as ICSRs found on searching a database or reviewing a journal.

Abstracts from major scientific meetings are indexed and available in some databases, but posters and communications are rarely available from this source.

~~VI.App2.3.~~Guidance in VI.C.2.2.3. should be followed for the searches of databases with broad medical coverage by the Agency in accordance with Article 27 of Regulation (EC) 726/2004 and the reporting obligations of marketing authorisation holders in accordance with Article 107 (3) of Directive 2001/83/EC.

VI.App.2.3 Database Searches

A search is more than a collection of terms used to interrogate a database. Decisions about the database selection, approach to records retrieval, term or text selection and the application of limits need to be relevant to the purpose of the search. For searches in pharmacovigilance, some of the considerations for database searching are described below.

VI.~~App2~~App.2.3.1~~.~~ Precision and recall

Medical and scientific databases are a collection of records relating to a set of publications. For any given record, each database has a structure that facilitates the organisation of records and searching by various means, from simple text to complex indexing terms with associated subheadings. Search terms (text or indexed) can be linked using Boolean operators and proximity codes to combine concepts, increasing or decreasing the specificity of a search. In addition, limits to the output can be set. When searching, the application of search terms means that the output is less than the entire database of the records held. The success of a search can be measured according to precision and recall (also called sensitivity). Recall is the proportion of records retrieved ("hits") when considering the total number of relevant records that are present in the database. Precision is the proportion of "hits" that are relevant when considering the number of records that were retrieved. In general, the higher recall searches would result in low precision.

VI.~~App2~~App.2.3.2~~.~~ Search construction

Databases vary in structure, lag time in indexing and indexing policy for new terms. While some database providers give information about the history of a particular indexing term or the application of synonyms, other databases are less sophisticated. In addition, author abstracts are not always consistent in the choice of words relating to pharmacovigilance concepts or medicinal products/active substances names.

When constructing a search for pharmacovigilance, the highest recall for a search would be to enter the medicinal product name and active substance name (in all their variants) only. In practice, additional indexing terms and text are added to increase precision and to reduce the search result to return records that are of relevance to pharmacovigilance. There is a balance to be achieved. It is~~,~~ therefore~~,~~ expected that complicated searches are accompanied by initial testing to check that relevant records are not omitted, however, there is no defined acceptable loss of recall when searching for pharmacovigilance purposes. Term selection should be relevant to the database used and the subject of the search.

VI.~~App2~~App.2.3.3~~.~~ Selection of product terms

Searches should be performed to find records for active substances and not for brand names only. This can also include excipients or adjuvants that may have a pharmacological effect. When choosing search terms for medicinal products, there are a number of considerations.

- Is the active substance an indexed term?
- What spellings might be used by authors (particularly if the active substance is not indexed)?
- What alternative names might apply (numbers or codes used for products newly developed, chemical names, brand names, active metabolites)?
- Is it medically relevant to search only for a particular salt or specific compound for an active substance?

During searches for ICSRs, it may be possible to construct a search that excludes records for pharmaceutical forms or routes of administration different to that of the subject product, however, restrictions should allow for the inclusion of articles where this is not specified. Search construction should also allow for the retrieval of overdose, medication error, abuse, misuse, off-label use or occupational exposure information, which could be poorly indexed. Searches should also not routinely exclude records of unbranded products or records for other company brands.

VI.~~App2~~App.2.3.4~~.~~ Selection of search terms

As described previously, there is no acceptable loss of recall when searching published literature for pharmacovigilance. The use of search terms (free text or use of indexing) to construct more precise searches may assist in managing the output. Deficiencies that have been found frequently during Competent Authority inspections include:

- the omission of outcome terms, for example "death" as an outcome may be the only indexed term in a case of sudden death;
- the omission of pregnancy terms to find adverse outcomes in pregnancy for ICSR reporting;
- the omission of terms to include special types of reports which needs to be addressed as well in periodic safety update reports, for example,
  - Reports of asymptomatic overdose, medication error, off-label use, misuse, abuse, occupational exposure;
  - Reports of uneventful pregnancy.

VI.~~App2~~App.2.3.5~~.~~ Limits to a search

Some databases apply indexing that allows the application of limits to a search, for example by subject age, sex, publication type. The limits applied to a search are not always shown in the "search strategy" or search string.

If limits are applied, they should be relevant to the purpose of the search. When searching a worldwide scientific and medical literature database, titles and abstracts are usually in English language. The use of limits that reduce the search result to only those published in the English language is generally not acceptable. Limits applied to patient types, or other aspects of an article, for example human, would need to be justified in the context of the purpose of a search.

Limits can be applied to produce results for date ranges, for example, weekly searches can be obtained by specifying the start and end date for the records to be retrieved. Care should be taken to ensure that the search is inclusive for an entire time period, for example, records that may have been added later in the day for the day of the search should be covered in the next search period. The search should also retrieve all records added in that period, and not just those initially entered or published

during the specified period (so that records that have been updated or retrospectively added are retrieved). This should be checked with the database provider if it is not clear.

Although one of the purposes of searching is to identify ICSRs for reporting, the use of publication type limits is not robust. ICSRs may be presented within review or study publications, and such records may not be indexed as "case-reports", resulting in their omission for preparation of periodic safety update reports from search results limited by publication type.

VI.~~App2~~App.2.4~~.~~ Record keeping

Records of literature searches should be maintained in accordance with the requirements described in [IR Art 12]. Marketing authorisation holders should demonstrate due diligence in searching published scientific and medical literature. It is always good practice to retain a record of the search construction, the database used and the date the search was run. In addition, it may be useful to retain results of the search for an appropriate period of time, particularly in the event of zero results. If decision making is documented on the results, it is particularly important to retain this information.

VI.~~App2~~App.2.5~~.~~ Outputs

Databases can show search results in different ways, for example, titles only or title and abstract with or without indexing terms. Some publications are of obvious relevance at first glance, whereas others may be more difficult to identify. Consistent with the requirement to provide the full citation for an article and to identify relevant publications, the title, citation and abstract (if available) should always be retrieved and reviewed.

VI.~~App2~~App.2.6~~.~~ Review and selection of articles

It is recognised that literature search results are a surrogate for the actual article. Therefore, it is expected that the person reviewing the results of a search is trained to identify the articles of relevance. This may be an information professional trained in pharmacovigilance or a pharmacovigilance professional with knowledge of the database used. Recorded confirmation that the search results have been reviewed will assist in demonstrating that there is a systematic approach to collecting information about suspected adverse reactions from literature sources. It is recommended that quality control checks are performed on a sample of literature reviews / selection of articles to check the primary reviewer is identifying the relevant articles.

A common issue in selecting relevant articles from the results of a search is that often this process is conducted for the purposes of identification of ICSRs only. Whereas the review should also be used as the basis for collating articles for the periodic safety update report production, therefore relevant studies with no ICSRs should also be identified, as well as those reports of events that do not qualify for reporting.

Outputs from searches may contain enough information to be a valid ICSR, in which case the article should be ordered. All articles for search results that are likely to be relevant to pharmacovigilance requirements should be obtained, as they may contain valid ICSRs or relevant safety information. The urgency with which this occurs should be proportionate to the content of the material reviewed and the resulting requirement for action as applicable for the marketing authorisation holder.

Articles can be excluded from reporting by the marketing authorisation holder if another company's branded medicinal product is the suspected medicinal product. In the absence of a specified medicinal product source and/or invented name, ownership of the medicinal product should be assumed for

articles about an active substance. Alternative reasons for the exclusion of a published article for the reporting of ICSRs are detailed in VI.C.2.2.3..

VI.~~App2~~App.2.7~~.~~ Day zero

As described in VI.B.7., day zero is the date on which an organisation becomes aware of a publication containing the minimum information for an ICSR to be reportable. Awareness of a publication includes any personnel of that organisation, or third parties with contractual arrangements with the organisation. It is sometimes possible to identify the date on which a record was available on a database, although with weekly literature searching, day zero for a reportable adverse reaction present in an abstract is taken to be the date on which the search was conducted. For articles that have been ordered as a result of literature search results, day zero is the date when the minimum information for an ICSR to be valid is available. Organisations should take appropriate measures to obtain articles promptly in order to confirm the validity of a case.

VI.~~App2~~App.2.8~~.~~ Duplicates

Consistent with the requirements for reporting ICSRs, literature cases should be checked to prevent ~~reporting~~the submission of duplicates~~, and previously reported cases should be identified as such when reported~~. It is, therefore, expected that ICSRs are checked in the organisation database to identify literature articles that have already been ~~reported~~submitted. Where applicable, this should include ICSRs resulting from the Agency's activities in accordance with Article 27 of Regulation (EC) 726/2004.

VI.~~App2~~App.2.9~~.~~ Contracting out literature search services

It is possible to use the services of another party to conduct searches of the published scientific and medical literature. In this event, the responsibility for the performance of the search and subsequent reporting still remains~~.~~ with the exception of the provisions set out in Article 27 of Regulation EC) 726/2004 and Article 107(3) of Directive 2001/83/EC. The transfer of a pharmacovigilance task or function should be detailed in a contract between the organisation and the service provider. The nature of third party arrangements for literature searching can range from access to a particular database interface only (access to a technology) to full literature searching, review and reporting (using the professional pharmacovigilance services of another organisation). It is recognised that more than one organisation may share services of a third party to conduct searches for generic active substances. In this instance, each organisation should satisfy itself that the search and service is appropriate to their needs and obligations.

Where an organisation is dependent on a particular service provider for literature searching, it is expected that an assessment of the service(s) is undertaken to determine whether it meets the needs and obligations of the organisation. In any case, the arrangement should be clearly documented.

The clock start for the reporting of ICSRs begins with awareness of the minimum information by either the organisation or the contractual partner (whichever is the earliest). This also applies where a third party provides a review or a collated report from the published scientific and medical literature, in order to ensure that published literature cases are ~~reported~~submitted as required within the correct time frames. That is, day zero is the date the search was run if the minimum criteria are available in the abstract and not the date the information was supplied to the organisation.

VI.~~App2~~App.2.10~~.~~ Electronic submission of copies of articles on suspected adverse reactions published in the scientific literature

~~Until standards for the electronic transmission of attachments (e.g. copies of literature articles) are developed in the framework of ICH, the sender should follow the rules outlined below for the submission of a copy of the literature article as detailed in VI.C.6.2.3.2.:~~

~~1. Mailing address and format of literature articles:~~

~~Literature articles reportable to the Agency should be provided in PDF format and sent via e-mail to the following e-mail address: EVLIT@ema.europa.eu.~~

~~In relation to copies of articles from the published scientific and medical literature, marketing authorisation holders are recommended to consider potential copyright issues specifically as regards the electronic transmission and handling of electronic copies in the frame of regulatory activities.~~

~~2. File name of literature articles sent in electronic format to the Agency:~~

~~The file name of a literature article sent in PDF format should match exactly the 'World-Wide Unique Case Identification Number' (ICH-E2B(R2) A.1.10.1 or A.1.10.2 as applicable) assigned to the individual case, which is described in the article and which is reported in the E2B(R2) ICSR format.~~

~~If there is a follow-up article to the individual case published in the literature, the file name with the World-Wide Unique Case Identification Number must be maintained but should include a sequence number separated with a dash.~~

~~Examples:~~

- ~~Initial ICSR published in the literature: FR-ORGABC-23232321 (data element 'World-Wide Unique Case Identification Number' (ICH-E2B(R2) A.1.10.1));~~

  ~~File name of the literature article: FR-ORGABC-23232321.pdf.~~

- ~~Follow-up information published in the literature in a separate article:~~

  - ~~ICSR: FR-ORGABC-23232321 (data element World-Wide Unique Case Identification Number remains unchanged (ICH-E2B(R2) A.1.10.1));~~

  - ~~File name: FR-ORGABC-23232321-1.pdf.~~

~~3. Reporting of cases reported in the scientific and medical literature referring to more than one patient:~~

~~When the literature article refers to the description of more than one patient, the copy of the literature article should be sent only once.~~

~~The file name of a literature article sent in PDF format should match exactly the 'World-Wide Unique Case Identification Number' (data element ICH-E2B(R2) A.1.10.1 or A.1.10.2 as applicable) assigned to the first reportable individual case described in the article.~~

~~In addition, all ICSRs which relate to the same literature article should be cross referenced in the data element 'Identification number of the report which is linked to this report' (ICH-E2B(R2) A.1.12). The data element should be repeated as necessary to cross refer all related cases (see Table VI.2.).~~

~~Examples for the reporting of ICSRs~~In accordance with Article 28(3) of the Commission Implementing Regulation (EU) 520/2012 and upon request of the Agency, the marketing authorisation holder that transmitted the initial report shall provide a copy of the relevant article taking into account copyright restrictions, and a full translation of that article into English.

Table VI.6. In line with ICH-E2B the following applies as regards the electronic submission of a copy of an article including a full translation where applicable: Electronic transmission of copies of literature articles/translations on suspected adverse reactions

Reference	E2B(R2) / (R3) requirements
ICH-E2B(R2)	1. Mailing address and format of literature articles: Literature articles reportable to the Agency should be provided in PDF format and sent via e-mail to the following e-mail address: EVLIT@ema.europa.eu. In relation to copies of articles from the published scientific and medical literature, marketing authorisation holders are recommended to consider potential copyright issues specifically as regards the electronic transmission and handling of electronic copies in the frame of regulatory activities. 2. File name of literature articles sent in electronic format to the Agency: The file name of a literature article sent in PDF format should match exactly the data element A.1.10.1 or A.1.10.2 'World-Wide Unique Case Identification Number' assigned to the individual case, which is described in the article and which is provided in the E2B(R2) ICSR format. If there is a follow-up article to the individual case published in the literature, the file name with the World-Wide Unique Case Identification Number must be maintained but should include a sequence number separated with a dash. Examples: • Initial ICSR published in the literature: FR-ORGABC-23232321 data element A.1.10.1 'World-Wide Unique Case Identification Number'; – File name of the literature article: FR-ORGABC-23232321.pdf. • Follow-up information published in the literature in a separate article: – ICSR: FR-ORGABC-23232321 data element A.1.10.1''World-Wide Unique Case Identification Number' remains unchanged; – File name: FR-ORGABC-23232321-1.pdf. 3. Reporting of cases described in the scientific and medical literature referring to more than one patient: When the literature article refers to the description of more than one patient, the copy of the literature article should be sent only once. The file name of a literature article sent in PDF format should match exactly data element A.1.10.1 or A.1.10.2 as applicable 'World-Wide Unique Case Identification Number' assigned to the first reportable individual case described in the article. In addition, all ICSRs which relate to the same literature article should be cross

Reference	E2B(R2)/(R3) requirements
	referenced in data element A.1.12 'Identification number of the report which is linked to this report'. The data element should be repeated as necessary to cross refer all related cases.
ICH-E2B(R3)	• Information on how to attach documents to an ICSR is provided in section 3.5 'Document Attachments' of the ICH-E2B(R3) Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) - Data Elements and Message Specification. • When a literature article is sent as an attachment, the literature citation in Vancouver style is captured in data element C.4.r.1 'Literature Reference(s)'. The Digital Object Identifier (DOI) for the article should be included where available. The example reference below highlighted how this should be done: "International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med 1997; 336:309-15. doi:10.1056/NEJM199701233360422." • The electronic version of the document (i.e. the journal article and a copy of the translation where applicable) should be attached to the ICSR in data element C.4.r.2. 'Included Documents'. • If the article and/or translation are not provided at the time of ICSR reporting, attachments can be transmitted separately from the ICSR transmission. When the sender transmits an attachment later, the original ICSR along with all the same medical information captured in E2B(R3) data elements is retransmitted as an 'amendment' (see VI.C.6.2.2.8.). If new information has been received and the data elements in E2B(R3) have been updated, then the ICSR with attachment is transmitted as a follow-up.

VI.App.2.11 Examples for the reporting of suspected adverse reactions described in the scientific and medical literature and referring to more than one patient

~~Table VI.3.~~ **Table VI.7.** Examples for the reporting of suspected adverse reactions described in the scientific and medical literature and referring to more than one patient

Ex.	Scenario	Action
~~1~~	~~A literature article describes suspected adverse reactions that have been experienced by up to 3 single patients.~~ ~~3 ICSRs should be created and reported for each individual identifiable patient described in the literature article.~~ ~~Each ICSR should contain all the available information on the~~	~~For Case 1 described in the literature article:~~ ~~• ICH-E2B(R2) A.1.10.1 'World-Wide Unique Case Identification Number':~~ ~~UK-ORGABC-0001~~ ~~• ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report':~~ ~~UK-ORGABC-0002~~ ~~• ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report':~~ ~~UK-ORGABC-0003~~ ~~• ICH-E2B(R2) A.2.2 'Literature reference(s):~~

Ex.	Scenario	Action
	~~case.~~	~~Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals: N Engl J Med. 1997;336:309-15.~~ • ~~File name for the copy of literature article to be sent via e-mail to EVLIT@ema.europa.eu: UK-ORGABC-0001.pdf~~ ~~For Case 2 described in the literature article:~~ • ~~ICH E2B(R2) A.1.10.1 'World Wide Unique Case Identification Number': UK-ORGABC-0002~~ • ~~ICH E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0001~~ • ~~ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0003~~ • ~~ICH-E2B(R2) A.2.2 'Literature reference(s): Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals: N Engl J Med. 1997;336:309-15.~~ • ~~No copy of the literature article required since the copy was already submitted for case 1.~~ ~~For Case 3 described in the literature article:~~ • ~~ICH E2B(R2) A.1.10.1 'World Wide Unique Case Identification Number': UK-ORGABC-0003~~ • ~~ICH E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0001~~ • ~~ICH E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0002~~ • ~~ICH E2B(R2) A.2.2 'Literature reference(s): Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals: N Engl J Med. 1997;336:309-15.~~ • ~~No copy of the literature article required since the copy was already submitted for case 1.~~
~~2~~1	A literature article describes suspected adverse reactions that have been experienced by more than ~~3 single patients.~~one identifiable patient. ICSRs should be created ~~and reported~~submitted for each	For the ICSRs which relate to the same literature article, the cross reference in the data element ICH (E2B(R2) A.1.12/ ICH-E2B(R3) C.1.10.r 'Identification number of the report which is linked to this report' ~~ICH (E2B(R2) field A.1.12)~~ should be conducted as follows: • The first case should be linked to all other cases related to the same article~~;~~ (1-n); • All the other cases (n) should be only linked to the first

Ex.	Scenario	Action
	individual identifiable patient described in the literature article. Each ICSR should contain all the available information on the case. The cross reference with all the linked ICSRs from this literature article should only be provided in the first case, in the data element ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report'. There is no need to repeat all the cross references in the other ICSRs.	one, as in the example below. *Example for the reporting of cases originally ~~reported~~described in the scientific and medical literature referring to a large number of patients:* For ~~Case~~case 1 described in the literature article: • data element ICH~~-~~-E2B(R2) A.1.10.1/ ICH-E2B(R3) C.1.8.1 'Worldwide Unique Case Identification Number': UK-ORGABC-0001 • data element ICH-E2B(R2) A.1.12/ ICH-E2B(R3) C.1.10.r 'Identification number of the report which is linked to this report': UK-ORGABC-0002 • data element ICH-E2B(R2) A.1.12/ ICH-E2B(R3) C.1.10.r 'Identification number of the report which is linked to this report': UK-ORGABC-0003 • data element ICH-E2B(R2) A.1.12/ ICH-E2B(R3) t C.1.10.r 'Identification number of the report which is linked to this report': UK-ORGABC-0004 • data element ICH-E2B(R2) A.1.12/ICH-E2B(R3) C.1.10.r 'Identification number of the report which is linked to this report': UK-ORGABC-000N • data element ICH-E2B(R2) A.2.2/ ICH-E2B(R3) C.4.r. 'Literature reference(s)': ~~N Engl J Med. 1997;336:309-15.~~ ~~File name for the copy~~Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals including DOI if available: e.g. "N Engl J Med 1997; 336:309-15. doi:10.1056/NEJM199701233360422" • Copy of literature article ~~to be sent via e-mail to EVLIT@ema.europa.eu:~~/translation: follow steps as outlined in Table VI.6. ~~UK-ORGABC-0001.pdf.~~ For Case 2 described in the literature article: • data element ICH~~-~~-E2B(R2) A.1.10.1/ ICH-E2B(R3) C.1.8.1 'Worldwide Unique Case Identification Number': UK-ORGABC-0002 • data element ICH-E2B(R2) A.1.12/ ICH-E2B(R3) C.1.10.r 'Identification number of the report which is linked to this report': UK-ORGABC-0001 • data element ICH-E2B(R2) A.2.2/ ICH-E2B(R3) C.4.r. 'Literature reference(s)':

Ex.	Scenario	Action
		~~N Engl J Med. 1997;336:309-15.~~ Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals including DOI if available: e.g. „N Engl J Med 1997; 336:309-15. doi:10.1056/NEJM199701233360422“ • No copy of the literature article required since the copy was already submitted for case 1. For Case N described in the literature article: • data element ICH-E2B(R2) A.1.10.1/ ICH-E2B(R3) C.1.8.1 ‘Worldwide Unique Case Identification Number’: UK-ORGABC-000N • data element ICH-E2B(R2) A.1.12/ ICH-E2B(R3) C.1.10.r ‘Identification number of the report which is linked to this report’: UK-ORGABC-0001 • data element ICH-E2B(R2) A.2.2/ ICH-E2B(R3) C.4.r. ‘Literature reference(s)’: ~~N Engl J Med. 1997;336:309-15.~~ Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals including DOI if available: e.g. „N Engl J Med 1997; 336:309-15. doi:10.1056/NEJM199701233360422“ • No copy of the literature article required since the copy was already submitted for case 1.

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VI. Appendix 3 ~~Modalities for reporting~~Reporting modalities of ICSRs in EU

~~VI.App3.1. Interim arrangements~~

~~Business process map – Suspected adverse reaction reporting in EU – Interim arrangements~~

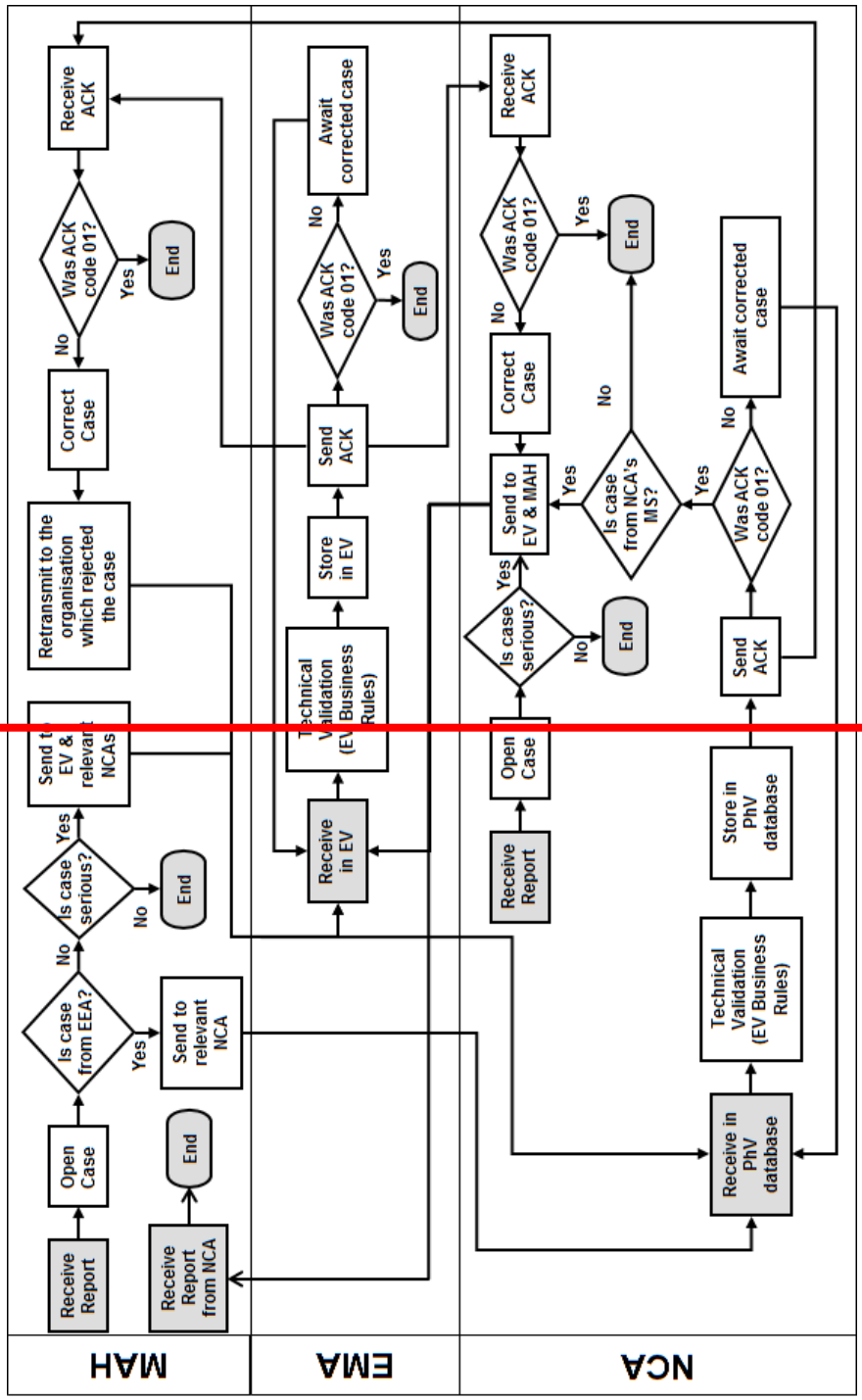

Table VI.4. Table VI.8. Process description - Suspected adverse reaction reporting in EU - Interim arrangements

No.	Step	Description	Responsible Organisation
1	**Start.** **Receive report.**	**Marketing Authorisation Holder (MAH) receives information on a suspected adverse reaction from a patient, healthcare professional or other valid reporter. If the case has been received from an EU NCA, do not retransmit it to EudraVigilance (EV).**	**MAH**
2	Open case.	Open and create an individual case safety report.	MAH
3	Is case from EEA?	Did the adverse reactions occur in the EU? If No, go to step 3.1. If Yes, got so step 5.	MAH
3.1	Is case serious?	If No, go to step 3.2. If Yes, got to step 4.	MAH
3.2	**End.**	**The case is now stored in the MAHs pharmacovigilance database. Normal follow-up activities should continue and if any follow-up is received, return to step 1.**	**MAH**
4	Send to EV & relevant NCAs.	Transmit the serious case electronically, in ICH E2B(R2) format as an xml message within the 15-day time frame to EV and to the relevant NCAs, where required. The case goes to step 4.1 & step 6.	MAH
4.1	**Receive in EV.**	Receive the message in EV database from MAH or NCA.	**EMA**
4.2	Technical Validation (EV Business Rules).	Every message that is received in EV is validated against the EudraVigilance Business Rules and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. A valid message will have an ACK code 01. A non-valid message will have an ACK code 02 (if a case contained therein is non-valid) or 03 (if the message itself is not correctly formatted).	EMA
4.3	Store in EV.	Once the case has been validated, it is stored in EV.	EMA
4.4	Send ACK.	The acknowledgement message created in step 4.2 is transmitted to the case sender, no later than 2 business days following receipt of the case. Go to step 16 for MAHs receiving the ACK.	EMA

No.	Step	Description	Responsible Organisation
		Go to step 20 for NCAs receiving the ACK. Go to step 4.5 for the EMA's next step.	
4.5	Was ACK code 01?	If No, go to step 4.6. If Yes, go to step 4.7.	EMA
4.6	Await corrected case.	The sender should correct every case with an error ACK and retransmit within the regulatory reporting timelines. Periodically the EMA should assess all cases with an error ACK for which a corrected case has not been transmitted and contact the Qualified Person responsible for PharmacoVigilance (QPPV) to inform of these missing corrected cases. If a sender fails to correct cases, then this information should be incorporated into data quality assessments and the appropriate committees should be informed. Go back to step 4.1 upon receipt of the corrected case.	EMA
4.7	**End.**	**The case is now stored in EV &, following duplicate detection & recoding will be available for signal detection and data quality analyses.**	**EMA**
5	**Send to relevant NCA.**	Transmit the case (serious, and if required non-serious) electronically, in ICH E2B(R2) format as an xml message within the relevant time frames (15 or 90 days, as applicable), to the relevant NCA for the Member State where the reaction occurred. If country of occurrence has not been specified, then country of primary source should normally be taken to be the occurrence country.	**MAH**
6	**Receive in PharmacoVigilance DataBase (PhV DB).**	Receive the message from MAH in the NCA's PhV DB.	**NCA**
7	Technical Validation (EV Business Rules).	Every message that is received in the NCA's PhV DB should be validated against the EudraVigilance Business Rules and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. A valid message will have an ACK code 01. A non-valid message will have an ACK code 02 (if a case contained therein is	NCA

No.	Step	Description	Responsible Organisation
		non-valid) or 03 (if the message itself is not correctly formatted).	
8	Store in EV.	Once the case has been validated, it is stored in the NCA's PhV DB.	NCA
9	Send ACK.	The acknowledgement message created in step 7 is transmitted to the case sender no later than 2 business days following receipt of the case. Go to step 16 for MAHs receiving the ACK. Go to step 10 for the NCA's next step.	NCA
10	Was ACK code 01?	If No, go to step 10.1. If Yes, go to step 11.	NCA
10.1	Await corrected case.	The MAH should correct every case with an error ACK and retransmit it within the regulatory reporting timelines. Periodically the NCA should assess all cases with an error ACK for which a corrected case has not been transmitted and contact the QPPV to inform them of these missing corrected cases. If a sender fails to correct cases, then this information should be incorporated into any data quality assessments performed and the appropriate action can be taken. Go back to step 6 upon receipt of the corrected case.	NCA
11	Was case from NCA's MS?	Did the case occur in the territory of the receiving NCA? If No, go to step 11.1. If Yes, go to step 12.	NCA
11.1	**End.**	**The case is now stored in the NCA's PharmacoVigilance DataBase &, following duplicate detection & recoding will be available for signal detection and data quality analyses.**	**NCA**
12	Send to EV & MAH.	Transmit the serious case electronically, in ICH E2B(R2) format as an xml message within the 15-day time frame to EV and to the relevant MAH(s). Go to step 4.1 for reception of the case in EV Go to step 24 for reception of the case by the relevant MAH(s)	NCA
13	**Start.** **Receive report.**	**NCA receives information on a suspected adverse reaction from a patient, healthcare professional or**	**NCA**

No.	Step	Description	Responsible Organisation
		other valid reporter concerning a suspected adverse reaction occurring in the territory of the receiving competent authority.	
14	Open case.	Open and create an individual case safety report.	NCA
15	Is case serious?	If No, go to step 15.1 If Yes, go to step 12	NCA
15.1	**End**	**The case is now stored in the NCA's PharmacoVigilance DataBase &, following duplicate detection & recoding will be available for signal detection and data quality analyses.**	NCA
16	**Receive ACK.**	Receive the ACK message, associate it with the relevant case(s) and check to ensure that the case was considered valid.	**MAH**
17	Was ACK code 01?	If yes, go to step 17.1. If no, then the regulatory timeline clock has not stopped and the case should be corrected and re-transmitted to EV within the relevant regulatory reporting timelines. Day 0 remains as the day that the first information was received. A 02 or 03 ACK does not constitute new information. Go to step 18 (Correct case).	MAH
17.1	**End.**	**End the process of transmitting this version of the case to EV or NCA. Normal follow-up activities should continue and if any follow-up is received, return to step 1.**	**MAH**
18	Correct case.	Correct the case to remove the errors identified in the ACK.	MAH
19	Retransmit to the organisation which rejected the case.	Retransmit the corrected case to the organisation which rejected the case with ACK code 02 or 03. Got to step 4.1 &/or step 6 as appropriate.	MAH
20	**Receive ACK.**	Receive the ACK message, associate it with the relevant case(s) and check to ensure that the case was considered valid.	**NCA**
21	Was ACK code 01?	If yes, go to step 23. If no, then the regulatory timeline clock has not stopped and the case should be corrected and re-transmitted to EV within	NCA

No.	Step	Description	Responsible Organisation
		the relevant regulatory reporting timelines. Day 0 remains as the day that the first information was received. A 02 or 03 ACK does not constitute new information. Go to step 22 (Correct case).	
22	Correct case.	Correct the case to remove the errors identified in the ACK and retransmit the case to EV and to the relevant MAH(s) (go back to step 12).	NCA
23	**End.**	**End the process of transmitting this version of the case to EV and to the relevant MAH(s). Normal follow-up activities should continue and if any follow-up is received, return to step 6 or 13.**	**NCA**
24	**Receive report from NCA**	**MAH receives information on a suspected adverse reaction from an NCA.** **This case should not be retransmitted to EV and to the NCA which transmitted it to the MAH**	**MAH**
25	**End**	**The case is now stored in the MAH's PharmacoVigilance DataBase &, following duplicate detection & recoding will be available for signal detection and data quality analyses.**	**MAH**

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~~VI.App3.1.1. Interim arrangements applicable to marketing authorisation holders~~

~~Reporting requirements of individual case safety reports applicable to marketing authorisation holders during the interim period are detailed in the latest version of Doc. EMA/321386/2012 available on EMA website.~~

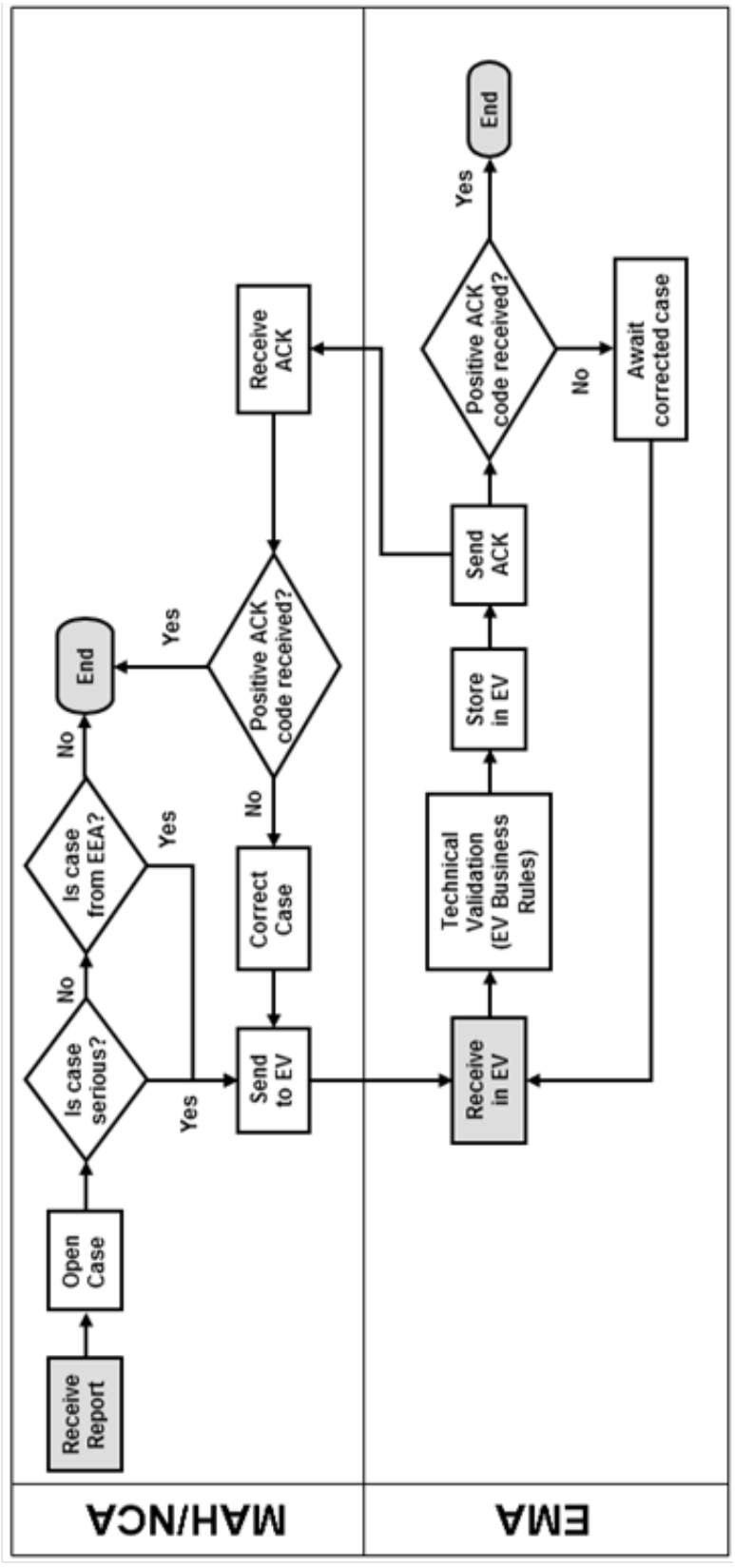
~~VI.App3.1.2. Interim arrangements applicable to competent authorities in Member States~~

~~**Table VI.5.** Reporting requirements applicable to competent authorities in Member States – Interim arrangements~~

~~Marketing authorisation procedure~~	~~Origin~~	~~Adverse reaction type~~	~~Destination~~	~~Time frame~~
~~• Centralised~~ ~~• Mutual recognition, decentralised or subject to referral~~ ~~• Purely national~~	~~EU~~	~~All serious~~	~~• EudraVigilance database~~ ~~• Marketing authorisation holder of the suspected medicinal product~~	~~15 days~~

~~VI.App3.2. Final arrangements~~

~~Figure VI.3.~~ Figure VI.6. Business process map - ~~Suspected adverse reaction~~ ICSRs reporting in EU ~~- Final arrangements~~



~~Table VI.6.~~ Table VI.9. Process description - ~~Suspected adverse reaction~~ ICSRs reporting in EU ~~- Final arra-gements~~

No.	Step	Description	Responsible Organisation
1	**Start.** **Receive report.**	**National Competent Authority (NCA) or Marketing Authorisation Holder (MAH) receives information on a suspected adverse reaction from a patient, healthcare professional or other valid reporter.** **If the case has been received from an EU NCA, do not retransmit it to EudraVigilance (EV).**	**MAH / NCA**
2	Open case.	Open and create an individual case safety report.	MAH/NCA
3	Is case serious?	If No go to step 3.1. If Yes, go to step 4.	
3.1	Is case from EEA?	If No go to step 11.1. If Yes, go to step 4.	
4	Send to EV.	Transmit the case (all serious and EU non-serious) electronically, in ICH~~-~~ E2B(R2/R3) format as an ~~xml~~XML message within the relevant time frame (15 or 90 days, as applicable), to EV.	MAH/NCA
5	**Receive in EV.**	Receive the message in the EV.	**EMA**
6	Technical Validation (EV Business Rules).	Every message that is received in EV is validated against the EudraVigilance Business Rules and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. E2B(R2) messages will receive an E2B(R2) acknowledgement and an E2B(R3) message will receive an E2B(R3) acknowledgement. A valid ~~message~~E2B(R2) ICSR will have an E2B(R2) ACK code 01~~-~~ (ACK_B.1.8). A non-valid E2B(R2) ICSR will have an E2B(R2) ACK code 02(ACK_B.1.8). A non-valid message will ~~have an ACK~~receive an 03 transmision acknowledgement code ~~02~~(ACK_A.1.6) (if ~~a case contained therein~~the message itself is not correctly formatted). A valid E2B(R3) ICSR will have an E2B(R3) ACK code “CA” (ACK.B.r.6). A non-valid~~) or 03~~ E2B(R3) ICSR will have an E2B(R3) ACK code “CR” (ACK.B.r.6). A	EMA

No.	Step	Description	Responsible Organisation
		non-valid message will receive an "AR" transmision acknowledgement code (ACK.A.4) (if the message itself is not correctly formatted).	
7	Store in EV.	Once the case has been validated, it is stored in the EV.	EMA
8	Send ACK.	The acknowledgement message created in step 6 is transmitted to the case sender no later than 2 business days following receipt of the case. Go to step 9 for the EMA's next step. Go to step 10 for MAH/NCA's next step.	EMA
9	Was a positive ACK code ~~01~~received?	If No go to step 9.1. If Yes, go to step 9.2.	EMA
9.1	Await corrected case.	The sender should correct every case with an error ACK and retransmit it within the regulatory reporting timelines. Periodically the EMA should assess all cases with an error ACK for which a corrected case has not been transmitted and contact the ~~Qualified Person responsible for PharmacoVigilance (QPPV) to inform these missing corrected cases.~~sender. If a sender fails to correct cases, this information should be incorporated into data quality assessments and the appropriate committees should be informed. Go back to step 5 upon receipt of the corrected case.	EMA
9.2	**End.**	**The case is now stored in EV &, following duplicate detection & recoding will be available for signal detection and data quality analyses. If the case occurred in the EU and was transmitted to EV by a MAH, it will be rerouted to the relevant NCA (see VI.~~Appendix~~App.3.3)**	**EMA**
10	**Receive ACK.**	Receive the ACK message, associate it with the relevant case(s) and check to ensure that the case was considered valid.	**MAH / NCA**
11	Was a positive ACK code ~~01~~received?	If yes, go to step 11.1. If no, then the regulatory timeline clock has not stopped and the case should be corrected and re-transmitted to EV within	MAH/NCA

No.	Step	Description	Responsible Organisation
		the relevant regulatory reporting timelines. Day 0 remains as the day that the first information was received. ~~A~~ Neither a non-valid ICSR (E2B(R2) ACK code 02 or E2B(R3) ACK code “CR”) nor a non-valid message (E2B(R2) 03 ~~ACK does not constitute~~or E2B(R3) “AR” transmision acknowledgement code) constitutes new information. Go to step 12 (Correct case)	
11.1	**End.**	**End the process for this version of the case. Normal follow-up activities should continue and if any follow-up is received, return to step 1.**	**MAH / NCA**
12	Correct case.	Correct the case to remove the errors identified in the ACK and retransmit the case to EV (go back to step 4).	MAH/NCA

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VI.~~App3.2~~App.3.1. ~~Final arrangements~~Requirements applicable to marketing authorisation holders

~~**Table VI.7.** **Table VI.10.** Reporting requirements applicable to marketing authorisation holders – Final arrangements~~

Marketing authorisation procedure	Origin	Adverse reaction type	Destination	Time frame
• Centralised • Mutual recognition, decentralised or subject to referral • Purely national	EU	All serious	• EudraVigilance database	15 days
		All non-serious	• EudraVigilance database	90 days
	Non-EU	All serious	• EudraVigilance database	15 days

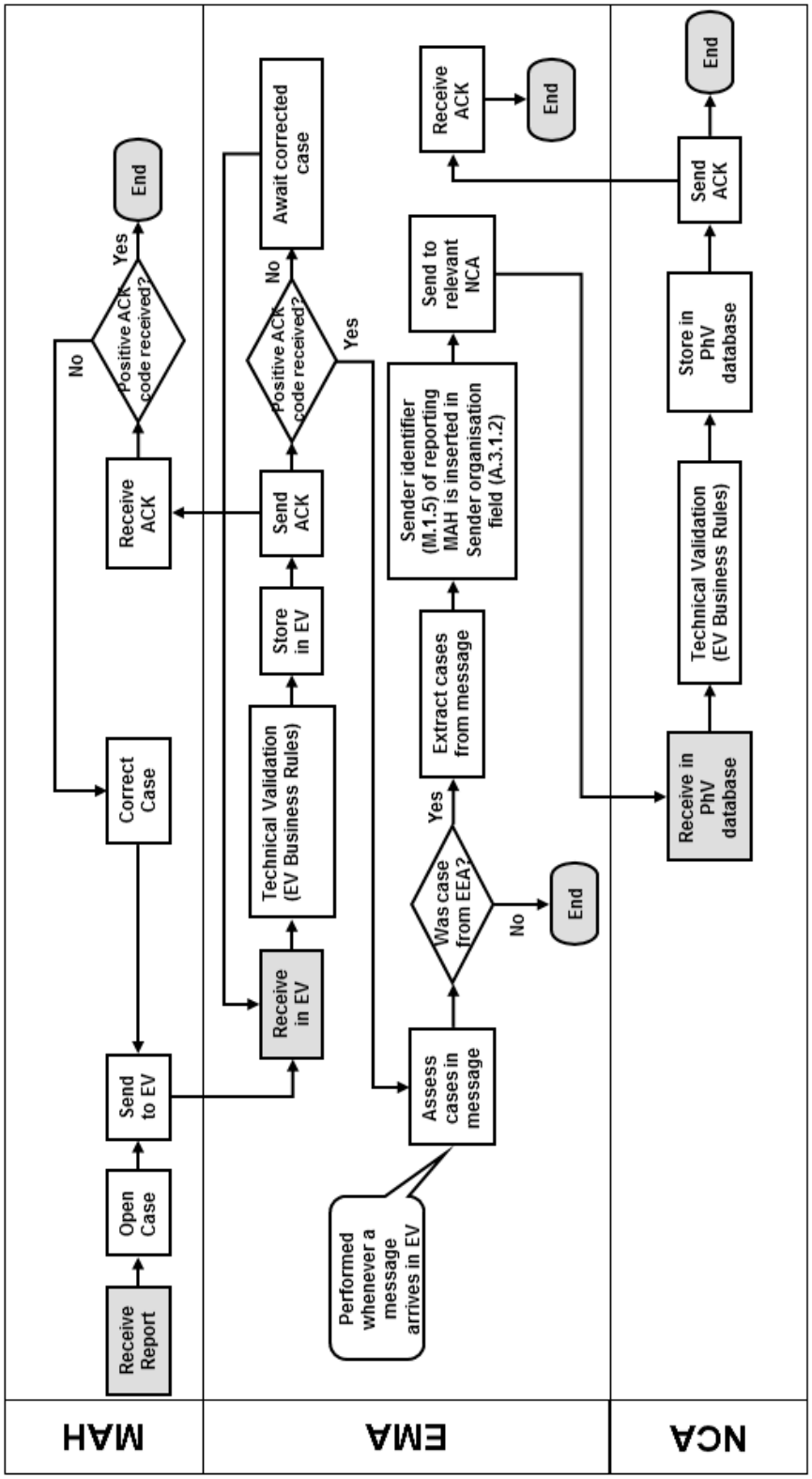
VI.~~App3.2.2. Final arrangements~~App.3.2. Requirements applicable to competent authorities in Member States

~~**Table VI.8.** **Table VI.11.** Reporting requirements applicable to competent authorities in Member States – Final arrangements~~

Marketing authorisation procedure	Origin	Adverse reaction type	Destination	Time frame
• Centralised • Mutual recognition, decentralised or subject to referral • Purely national	EU	All serious	• EudraVigilance database	15 days
		All non-serious	• EudraVigilance database	90 days

VI.~~App3~~App.3.3 Transmission and rerouting of ICSRs to competent authorities in Member States [66]

~~Figure VI.4.~~ **Figure VI.7.** Business process map - Transmission and rerouting of ICSRs to competent authorities in Member States



[66] Once the functionalities of the EudraVigilance database specified in [REG Art 24(2)] are established.

~~**Table VI.9.** **Table VI.12.** Process description - Transmission and rerouting of ICSRs to competent authorities in Member States [67]

No.	Name	Description	Responsible Organisation
1	**Start.** **Receive report.**	**Marketing Authorisation Holder (MAH) receives information on a suspected adverse reaction from a patient, healthcare professional or other valid reporter.**	**MAH**
2	Open case.	Open and create an individual case safety report.	MAH
3	Send to EudraVigilance (EV).	Transmit the case electronically, in ICH~~--~~ E2B(R2/R3) format as an ~~xml~~XML message within the relevant time frames (15 or 90 days, as applicable), to EV.	MAH
4	**Receive in EV.**	Receive the message in the EV.	**EMA**
5	Technical Validation (EV Business Rules).	Every message that is received in EV is validated against the EudraVigilance Business Rules and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. E2B(R2) messages will receive an E2B(R2) acknowledgement and an E2B(R3) message will receive an E2B(R3) acknowledgement. A valid ~~message~~E2B(R2) ICSR will have an E2B(R2) ACK code 01~~.~~ (ACK_B.1.8). A non-valid ~~message~~E2B(R2) ICSR will have an E2B(R2) ACK code 02~~ (if a case contained therein is~~(ACK_B.1.8). A non-valid~~) or 03~~ message will receive an 03 transmision acknowledgement code (ACK_A.1.6) (if the message itself is not correctly formatted). A valid E2B(R3) ICSR will have an E2B(R3) ACK code "CA**"** (ACK.B.r.6). A non-valid E2B(R3) ICSR will have an E2B(R3) ACK code "CR" (ACK.B.r.6). A non-valid message will receive an "AR" transmision acknowledgement code (ACK.A.4) (if the message itself is not correctly formatted).	EMA
6	Store in EV.	Once the case has been validated, it is stored in EV.	EMA

[67] Once the functionalities of the EudraVigilance database specified in [REG Art 24(2)] are established.

No.	Name	Description	Responsible Organisation
7	Send ACK.	The acknowledgement message created in step 5 is transmitted to the case sender no later than 2 business days following receipt of the case.	EMA
7.1	**Receive ACK.**	Receive the ACK message, associate it with the relevant case(s) and check to ensure that the case was considered valid.	**MAH**
7.2	Was a positive ACK code ~~01~~received?	If Yes, go to step 7.2.1. If no, then the regulatory timeline clock has not stopped and the case should be corrected and re-transmitted to EV within the relevant regulatory reporting timelines. Day 0 remains as the day that the first information was received. ~~A~~ Neither a non-valid ICSR (E2B(R2) ACK code 02 or E2B(R3) ACK code "CR") nor a non-valid message (E2B(R2) 03 ~~ACK does not constitute~~or E2B(R3) "AR" transmision acknowledgement code) constitutes new information. Go to step 7.2.2 (Correct case).	MAH
7.2.1	**End.**	**End the process of transmitting this version of the case to EV. Normal follow-up activities should continue and if any follow-up is received, return to step 1.**	**MAH**
7.2.2	Correct case.	Correct the case to remove the errors identified in the ACK and retransmit the case to EV (go back to step 3).	MAH
8	**Was a positive ACK code ~~01~~received?**	If yes, go to step 9. If no, perform no further processing on this version of the case and go to step 8.1	**EMA**
8.1	Await corrected case.	The sender should correct every case with an error ACK and retransmit it within the regulatory reporting timelines. Periodically the EMA should assess all cases with an error ACK for which a corrected case has not been transmitted and contact the ~~Qualified Person responsible for PharmacoVigilance (QPPV)~~sender to inform of these missing corrected cases. If a sender fails to correct cases, his information should be incorporated into data quality assessments and the appropriate committees should be	EMA

No.	Name	Description	Responsible Organisation
		informed.	
9	Assess cases in message.	Whenever a message has passed the technical validation, the cases therein should be immediately assessed to determine the country where the reaction occurred for regulatory reporting purposes.	EMA
10	Was case from EU?	For every case, assess whether the country of occurrence is in the EU. If Yes, go to step 11. If No, go to step 10.1	EMA
10.1	**End.**	**The case is now stored in EV &, following duplicate detection & recoding will be available for signal detection and data quality analyses.**	**EMA**
11	Extract cases from message.	The cases occurring in the EU will be extracted from the message for processing prior to retransmission.	EMA
12	Technical Validation.	For the retransmission of E2B(R2) messages the 'Message sender ~~identifier~~identifier' (ICH ~~M2~~E2B(R2) M.1.5) of reporting MAH is inserted in data element 'Sender ~~organisation field~~organisation' (ICH-E2B(R2) A.3.1.2) prior to retransmission. This is to permit the receiving National Competent Authority (NCA) to unambiguously identify the MAH responsible for transmitting the case to EV. For the retransmission of E2B(R3) messages the data element N.2.r.2 'Message sender identifier' will remain unchanged	EMA
13	Send to relevant NCA	The case is transmitted to the relevant NCA of the Member State where the reaction occurred with no other changes. Where a Member State has more than one NCA responsible for post-marketing reports, the cases occurring in that Member State are sent to all relevant NCAs.	EMA
14	**Receive in PharmacoVigilance DataBase (PhV DB).**	The relevant NCA receives the message in its PhV DB	**NCA**
15	Technical Validation (EV Business Rules).	Every message should be validated against the EudraVigilance Business Rules (the same business rules as in Step 5 and	NCA

No.	Name	Description	Responsible Organisation
		an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. A valid ~~message~~ICSR will have an E2B(R2) ACK code 01~~.~~ or E2B(R3) ACK code "CA". A non-valid ~~message~~ICSR will have an E2B(R2) ACK code 02 ~~(if a case contained therein is~~or E2B(R3) ACK code "CR". A non-valid~~) or 03~~ message will receive an E2B(R2) 03 or E2B(R3) "AR" transmision acknowledgement code (if the message itself is not correctly formatted).	
16	Store in PharmacoVigilance DataBase (PhV DB).	Once the case has been validated, it is stored in the PhV DB.	NCA
17	Send ACK.	The acknowledgement message created in step 15 is transmitted to EV no later than 2 business days following receipt of the case.	NCA
17.1	**End**	**The case is now stored in the NCA's PharmacoVigilance DataBase &, following duplicate detection & recoding will be available for signal detection and data quality analyses.**	**NCA**
18	Receive ACK	The acknowledgement message sent in step 17 is received & stored in EV.	EMA
19	**End**	**The case has now been successfully retransmitted to the relevant NCA.**	**EMA**

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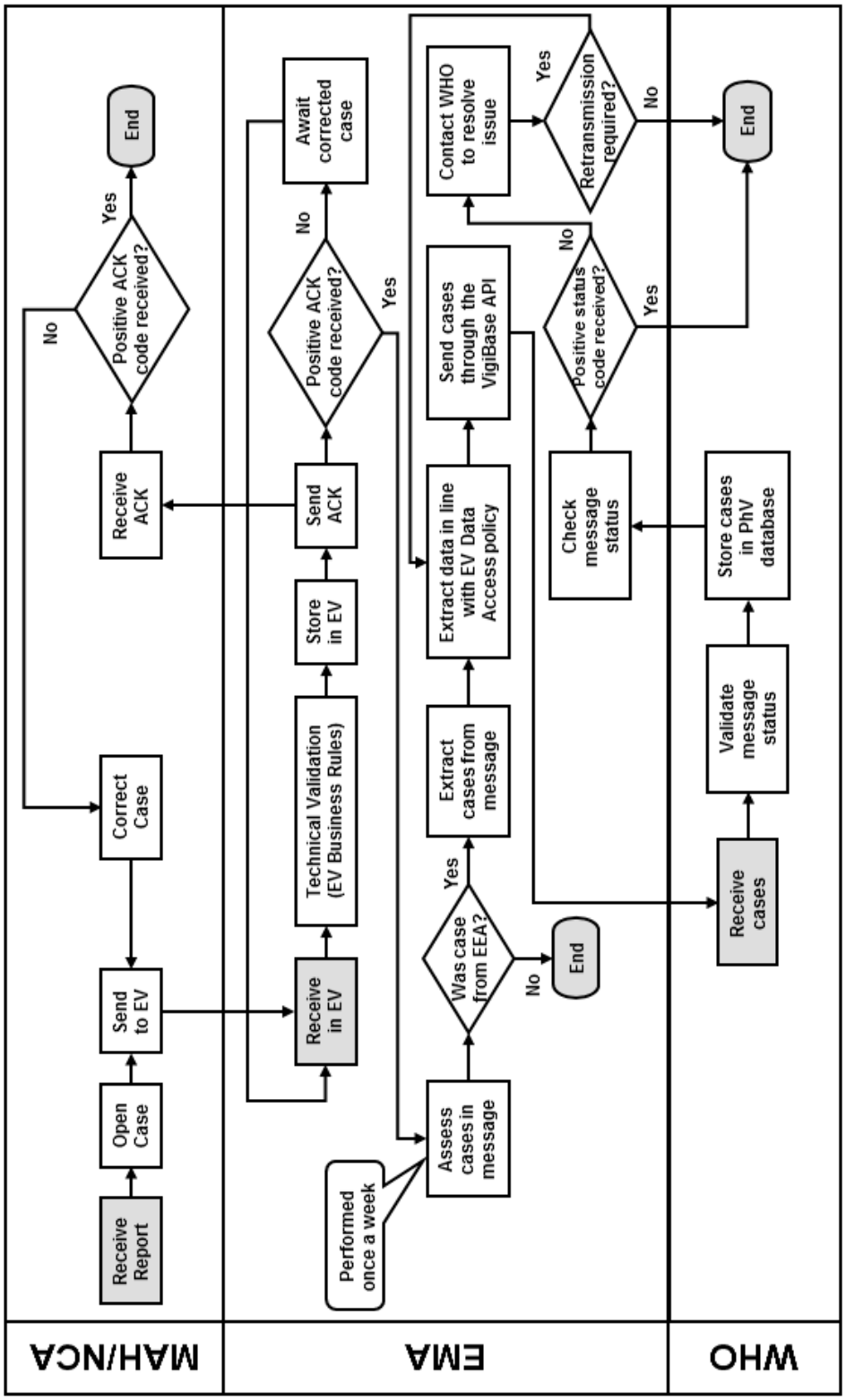
VI. Appendix 4 Transmission of ICSRs to the World Health Organization (WHO)[68]

~~Figure VI.5.~~ **Figure VI.8.** Business process map - Transmission of ICSRs to the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring



[68] Once the functionalities of the EudraVigilance database specified in [REG Art 24(2)] are established.

~~**Table VI.10.**~~ **Table VI.13.** Process description - Transmission of ICSRs to the World Health Organisation (WHO) Collaborating Centre for International Drug Monitoring[69]

No.	Step	Description	Responsible Organisation
1	**Start.** **Receive report.**	**National Competent Authority (NCA) or Marketing Authorisation Holder (MAH) receives information on a suspected adverse reaction from a patient, healthcare professional or other valid reporter.**	**MAH / NCA**
2	Open case.	Open and create an individual case safety report.	MAH/NCA
3	Send to EV.	Transmit the case electronically, in ICH~~--~~E2B(R2/R3) format as an ~~xml~~XML message within the relevant time frames (15 or 90 days, as applicable), to EudraVigilance (EV).	MAH/NCA
4	**Receive in EV.**	**Receive the message in EV.**	**EMA**
5	Technical Validation (EV Business Rules).	Every message that is received in EV is validated against the EudraVigilance Business Rules and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. E2B(R2) messages will receive an E2B(R2) acknowledgement and an E2B(R3) message will receive an E2B(R3) acknowledgement. A valid ~~message~~E2B(R2) ICSR will have an E2B(R2) ACK code 01~~.~~ (ACK_B.1.8). A non-valid ~~message~~E2B(R2) ICSR will have an E2B(R2) ACK code 02~~ (if a case contained therein is~~(ACK_B.1.8). A non-valid~~) or 03~~ message will receive an 03 transmision acknowledgement code (ACK_A.1.6) (if the message itself is not correctly formatted). A valid E2B(R3) ICSR will have an E2B(R3) ACK code "CA" (ACK.B.r.6). A non-valid E2B(R3) ICSR will have an E2B(R3) ACK code "CR" (ACK.B.r.6). A non-valid message will receive an "AR" transmision acknowledgement code (ACK.A.4) (if the message itself is not correctly formatted).	EMA

[69] Once the functionalities of the EudraVigilance database specified in [REG Art 24(2)] are established.

No.	Step	Description	Responsible Organisation
6	Store in EV.	Once the case has been validated, it is stored in EV.	EMA
7	Send ACK.	The acknowledgement message created in step 5 is transmitted to the case sender no later than 2 business days following receipt of the case.	EMA
7.1	**Receive ACK.**	Receive the ACK message, associate it with the relevant case(s) and check to ensure that the case was considered valid.	**MAH / NCA**
7.2	Was a positive ACK code ~~01~~received?	If Yes, go to step 7.2.1. If no, then the regulatory timeline clock has not stopped and the case should be corrected and re-transmitted to EV within the relevant regulatory reporting timelines. Day 0 remains as the day that the first information was received. ~~A~~Neither a non-valid ICSR (E2B(R2) ACK code 02 or E2B(R3) ACK code "CR") nor a non-valid message (E2B(R2) 03 ~~ACK does not constitute~~or E2B(R3) "AR" transmision acknowledgement code) constitutes new information. Go to step 7.2.2 (Correct case).	MAH/NCA
7.2.1	**End**	**End the process of transmitting this version of the case to EV. Normal follow-up activities should continue and if any follow-up is received, return to step 1.**	**MAH / NCA**
7.2.2	Correct case	Correct the case to remove the errors identified in the ACK and retransmit the case to EV (go back to step 3).	MAH/NCA
8	**Was** a positive ACK code ~~**01?**~~received?**?**	If yes, go to step 9 If no, perform no further processing on this version of the case and go to step 8.1	**EMA**
8.1	Await corrected case.	The sender should correct every case with an error ACK and retransmit within the regulatory reporting timelines. Periodically the EMA should assess all cases with an error ACK for which a corrected case has not been transmitted and contact the Qualified Person responsible for PharmacoVigilance (QPPV) to inform of these missing corrected cases. If a sender fails to correct cases, this information should be incorporated into data quality assessments and the appropriate	EMA

No.	Step	Description	Responsible Organisation
		committees should be informed.	
9	Assess cases in message.	Once a week, for every message that has passed the technical validation, the cases therein should be assessed to determine the country where the reaction occurred for regulatory reporting purposes.	EMA
10	Was case from EU?	For every case, assess whether the country of occurrence is in the EU. If Yes, go to step 11. If No, go to step 10.1.	EMA
10.1	**End.**	**The case is now stored in EV &, following duplicate detection & recoding will be available for signal detection and data quality analyses.**	**EMA**
11	Extract cases from message	The cases occurring in the EU is extracted from the message for processing prior to retransmission.	EMA
12	~~Redact & replace~~Extract data in line with EV Data Access policy.	Prior to sending the cases to the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, the cases are extracted ~~copies of the cases have some data elements redacted and replaced~~ in line with the EV ~~Data~~ Access Policy ~~in order to ensure personal data protection~~.	EMA
13	~~Copy~~Send cases ~~to physical media~~through the VigiBase API .	The cases are ~~copied to physical media.~~sent through the VigiBase API which returns a messageID for each file submitted	EMA
~~14~~	~~Send to WHO.~~	~~The physical media is sent to WHO Collaborating Centre.~~	~~EMA~~
~~15~~14	**Receive ~~physical media~~Cases**	**WHO Collaborating Centre receives the ~~physical media~~cases.**	**WHO**
~~16~~15	Store cases in PharmacoVigilance DataBase (PhV DB).	Once the cases have been validated, they are stored in the PhV DB~~.~~ a status code is recorded for each message	WHO
16	**EMA Checks status of ICSR Messages**	**EMA uses the messageID to check the status code of each submitted message.**	**EMA**
17	Was a positive status code received?	If yes, go to step 19 If no, go to step 18	EMA
18	Contact WHO to resolve technical issue	WHO UMC is contacted to resolve technical issues. If a message needs to be retransmitted go to step 12, if this is not required go to step 19.	EMA
~~17~~19	**End.**	**Cases are stored in the WHO**	**WHO**

No.	Step	Description	Responsible Organisation
		Collaborating Centre's PharmacoVigilance DataBase &, following duplicate detection & recoding will be available for signal detection and data quality analyses.	

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VI. Appendix 5 Nullification of cases

General principles regarding the nullification of cases are ~~provided in VI.C.6.2.2.10. The following recommendations~~outlined in VI.C.6.2.2.9.

Examples of scenarios for which ICSRs should ~~also be applied:~~be nullified, are provided in Table VI.13..

- ~~The value in the data element 'Report nullification' (ICH E2B(R2) A.1.13) should be set to 'Yes' and the nullification reason should be provided in the data element 'Reason for nullification' (ICH-EB(R2) A.1.13.1). The nullification reason should be clear and concise to explain why this case is no longer considered to be a valid report. For example a nullification reason stating, 'the report no longer meets the reporting criteria' or 'report sent previously in error' are not detailed enough explanations.~~
- ~~An individual case can only be nullified by the sending organisation.~~
- ~~Once an individual case has been nullified, the case cannot be reactivated.~~
- ~~If it becomes necessary to resubmit the case that has been previously nullified, a new 'Sender's (case) safety report unique identifier' (ICH E2B(R2) A.1.0.1) and 'Worldwide unique case identification number' (ICH E2B(R2) A.1.10) should be assigned.~~
- ~~Individual versions (i.e. follow-up reports) of a case cannot be nullified, only the entire individual case to which they refer.~~

~~Table VI.11.~~ Table VI.14. Examples of scenarios for which ICSRs should be nullified

Ex.	Scenario	Action
1	An individual case has been identified as a duplicate of another individual case previously submitted~~.~~ by the same sender.	One of the individual cases should be nullified. The remaining valid case should be updated with any additional relevant information from the nullified case. • NOTE: In case of duplicate reports where one report needs to be nullified, the update of the remaining case should be performed in the form of a follow-up report[70]. Information on the identification of the nullified case(s) should be provided (ICH-E2B(R2) A.1.11/ICH-E2B(R3) C.1.11).
2	A wrong 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10/ICH-E2B(R3) C.1.8.1) was accidentally used and does not refer to an existing case.	The case with the wrong 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10/ ICH-E2B(R3) C.1.8.1) should be nullified. ~~A new case should be created with a correct 'Worldwide unique case identification number'.~~
3	On receipt of further information it is confirmed that that the adverse reaction(s) occurred before the suspect	The case should be nullified.

[70] See Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs), EMA/13432/2009.

Ex.	Scenario	Action
	drug(s) was taken.	
4	On receipt of further information on an individual case, it is confirmed that the patient did not receive the suspect drug~~-~~(s). Minimum reporting criteria for an ICSR as outlined in VI.B.2 are no longer met.	The case should be nullified.
5	On receipt of further information it is confirmed by the same reporter that the reported adverse reaction(s) did not occur to the patient. Minimum reporting criteria for an ICSR as outlined in VI.B.2are no longer met.	The case should be nullified.
6	On receipt of further information it is confirmed that there was no ~~valid~~identifiable patient for the individual case. Minimum reporting criteria for an ICSR as outlined in VI.B.2 are no longer met.	If it is not possible to ~~obtain confirmation of~~verify the patient's existence, then the case should be nullified.

~~• Individual cases that have been nullified~~Examples of scenarios for which ICSRs should ~~not~~NOT be ~~used for scientific evaluation, however, they should remain in the database for auditing purposes.~~

~~In addition, in case of duplicate reports where one report needs to be nullified, the update of the remaining case should be performed in the form of a follow-up report[71]. Information on the identification of the nullified case(s) should be~~nullified, are provided in ~~the data element 'Source(s) of the case identifier (e.g. name of the company, name of regulatory agency)' (ICH E2B(R2) A.1.11.1) and in the data element 'Case identifier(s)' (ICH E2B(R2) A.1.11.2).~~Table VI.14..

~~Table VI.12.~~ Table VI.15. Examples of scenarios for which ICSRs should NOT be nullified

Ex.	Scenario	Action
7	A wrong 'Worldwide unique case identification number' (ICH~~-~~-E2B(R2) A.1.10/ ICH-E2B(R3) C.1.8.1) was accidentally used. This wrong ~~ICH-E2B(R2) A.1.10~~ 'Worldwide unique case identification number' referred to ~~an~~a different existing case.	The report with the wrong 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10/ICH-E2B(R3) C.1.8.1) should not be nullified. ~~A follow-up~~An amendment report should be submitted to correct the information previously submitted. A new ICSR should be created and submitted with the correct 'Worldwide unique case identification number'.
8	On receipt of further information on an	The case should not be nullified. A follow-up should

~~[71] As presented in the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs), EMA/13432/2009.~~

Ex.	Scenario	Action
	individual case, it is confirmed that the patient did not receive the marketing authorisation holder's suspect drug. However, the patient received other suspect drugs and the minimum reporting criteria for an ICSR are still met.	be submitted within the appropriate time frame with the updated information on the case. Further, it is recommended that the initial sender informs the other marketing authorisation holder about this case (including the 'Worldwide Unique Case Identification Number' (ICH-E2B(R2) A.1.10 / ICH-E2B(R3) C.1.8.1). The other concerned marketing authorisation holder should create a new case and specify the reference case number and the name of the initial sending marketing authorisation holder (ICH-E2B(R2) section A.1.11 / ICH-E2B(R3) section C.1.11).
9	On receipt of further information the reporter has confirmed that the reported adverse reaction is no longer considered to be related to the suspect medicinal product(s).	The case should not be nullified. A follow-up report should be submitted within the appropriate time frame with the updated information on the case. • **ICH-E2B(R2):** Section B.4.k.18 'Relatedness of drug to reaction(s)/event(s) (repeat B.4.k.18.1 through B.4.k.18.4 as necessary)' should be populated as necessary. • **ICH-E2B(R3):** Section G.k.9.i 'Drug-reaction(s) / Event(s) Matrix (repeat as necessary)' should be populated as necessary.
10	Change of the individual case from serious to non-serious (downgrading).	The case should not be nullified. A follow-up report or an amendment report (depending on whether new information was received or not) should be submitted ~~with~~: **ICH-E2B(R2):** the data element A.1.5.1 'Seriousness' ~~(ICH-E2B(R2) A.1.5.1)~~should be populated with the value 'No' without selection of a value for the data element A.1.5.2 'Seriousness criteria' ~~(ICH-E2B(R2) A.1.5.2).~~ • . The data element A.1.9 'Does this case fulfil the local criteria for an expedited report?' ~~(ICH-E2B(R2) field A.1.9)~~should remain populated with the value 'Yes'. • **ICH-E2B(R3):** the data element E.i.3.2 'Seriousness Criteria at Event Level' should not be populated if the reaction is not serious. The data element C.1.7 'Does This Case Fulfil the Local Criteria for an Expedited Report?' should

Ex.	Scenario	Action
		remain populated with the value 'Yes'.
11	The primary source country has changed, which has an impact on the ~~ICH-E2B(R2)~~ convention regarding the creation of the 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10~~).~~/ICH-E2B(R3) C1.8.1).	The case should not be nullified. ~~The~~**ICH-E2B(R2):** The data element A.1.0.1 'Sender's (case) safety report unique identifier' ~~(ICH-E2B(R2) A.1.0.1)~~ can be updated on the basis of the new primary source country code. However, the data element A.1.10 'Worldwide unique case identification number' ~~(ICH-E2B(R2) A.1.10)~~ should remain unchanged. • If, for some technical reason~~,~~ the sender's local system ~~is not fully ICH-E2B(R2) compliant and~~ cannot ~~follow~~apply this policy, then the sender should nullify the original case. A new case should be created using the data element A.1.10 with a new 'Worldwide unique case identification number' ~~(ICH-E2B(R2) A.1.10)~~ reflecting the changed primary source country code. The 'Worldwide unique case identification number' ~~(ICH-E2B(R2) A.1.10)~~ of the case that was nullified should be reflected in the data elements A.1.11 'Other case identifiers in previous transmissions' ~~(ICH-E2B(R2) A.1.11).~~. • **ICH-E2B(R3):** The data element C.1.1 'Sender's (Case) Safety Report Unique Identifier' can be updated on the basis of the new primary source country code. However, the data element C.1.8.1 'Worldwide Unique Case Identification Number' should remain unchanged. If, for some technical reason the sender's local system cannot apply this policy, then the sender should nullify the original case. A new case should be created using the data element C.1.8.1 with a new 'Worldwide Unique Case Identification Number' reflecting the changed primary source country code. The 'Worldwide unique case identification number' of the case that was nullified should be reflected in the data elements C.1.9.1 'Other Case Identifiers in Previous Transmissions'.
12	The suspected medicinal product belongs to another marketing authorisation holder (e.g. a product with the same active substance but marketed under a different invented name).	The case should not be nullified. It is recommended that the initial sender informs the other marketing authorisation holder about this case (including the 'Worldwide ~~unique case identification number'~~Unique Case Identification Number' (ICH-

Ex.	Scenario	Action
		E2B(R2) A.1.10~~) used~~/ICH-E2B(R3) C.1.8.1). The original organisation should also submit a follow-up report to provide this new information. The other concerned marketing authorisation holder should create a new case and specify the reference case number and the name of the initial sending marketing authorisation holder ~~in the data elements 'Source(s) of the case identifier (e.g. name of the company name of regulatory agency)' (ICH-E2B(R2) A.1.11.1) and 'Case identifier(s)' (ICH-E2B(R2) A.1.11.2). This will allow grouping the cases in the EudraVigilance database.~~(ICH-E2B(R2) section A.1.11/ICH-E2B(R3) section C.1.11).
13	The suspected medicinal product taken does not belong to the marketing authorisation holder (same active substance, the invented name is unknown and the report originates from a country, where the marketing authorisation holder has no marketing authorisation for the medicinal product in question).	The case should not be nullified. The marketing authorisation holder should submit a follow-up report with this information within the appropriate time frame.
14	The case is mistakenly ~~reported~~submitted by the marketing authorisation holder A although the marketing authorisation holder B as co-marketer is responsible for reporting the case.	The case should not be nullified. An explanation should be sent by the marketing authorisation holder A to the co-marketer ~~marketing authorisation holder~~ B that the case has already been ~~reported~~submitted. The marketing authorisation holder B should provide any additional information on the case as a follow-up report with the same 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10~~).~~/ICH-E2B(R3) C.1.8.1).

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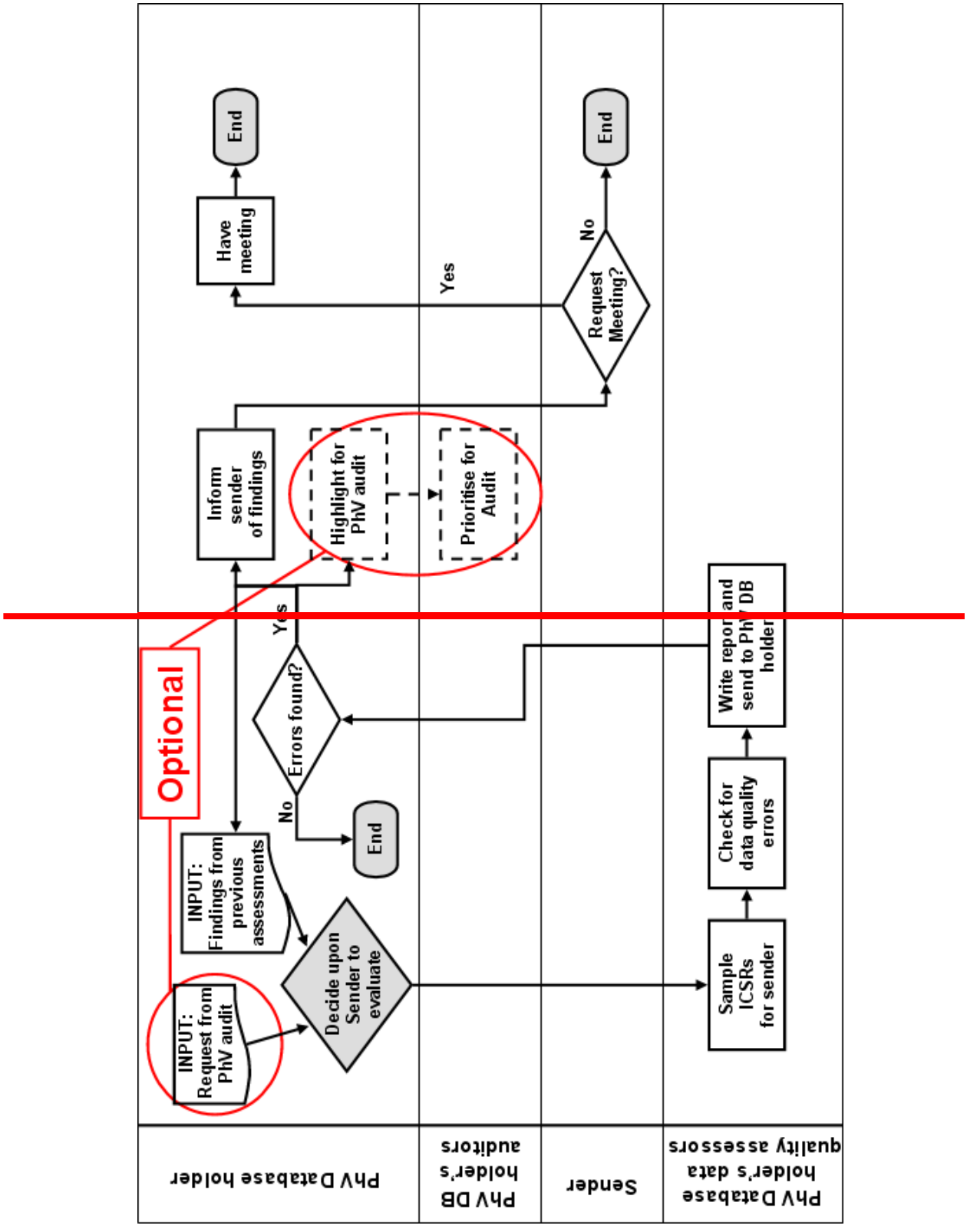
VI. Appendix 6 Data quality monitoring of ICSRs transmitted electronically

~~**Figure VI.6.** **Figure VI.9.** Business process map - ~~Data~~Review of quality ~~monitoring~~and integrity of ICSRs ~~transmitted electronically~~by the Agency in collaboration with NCAs and MAHs



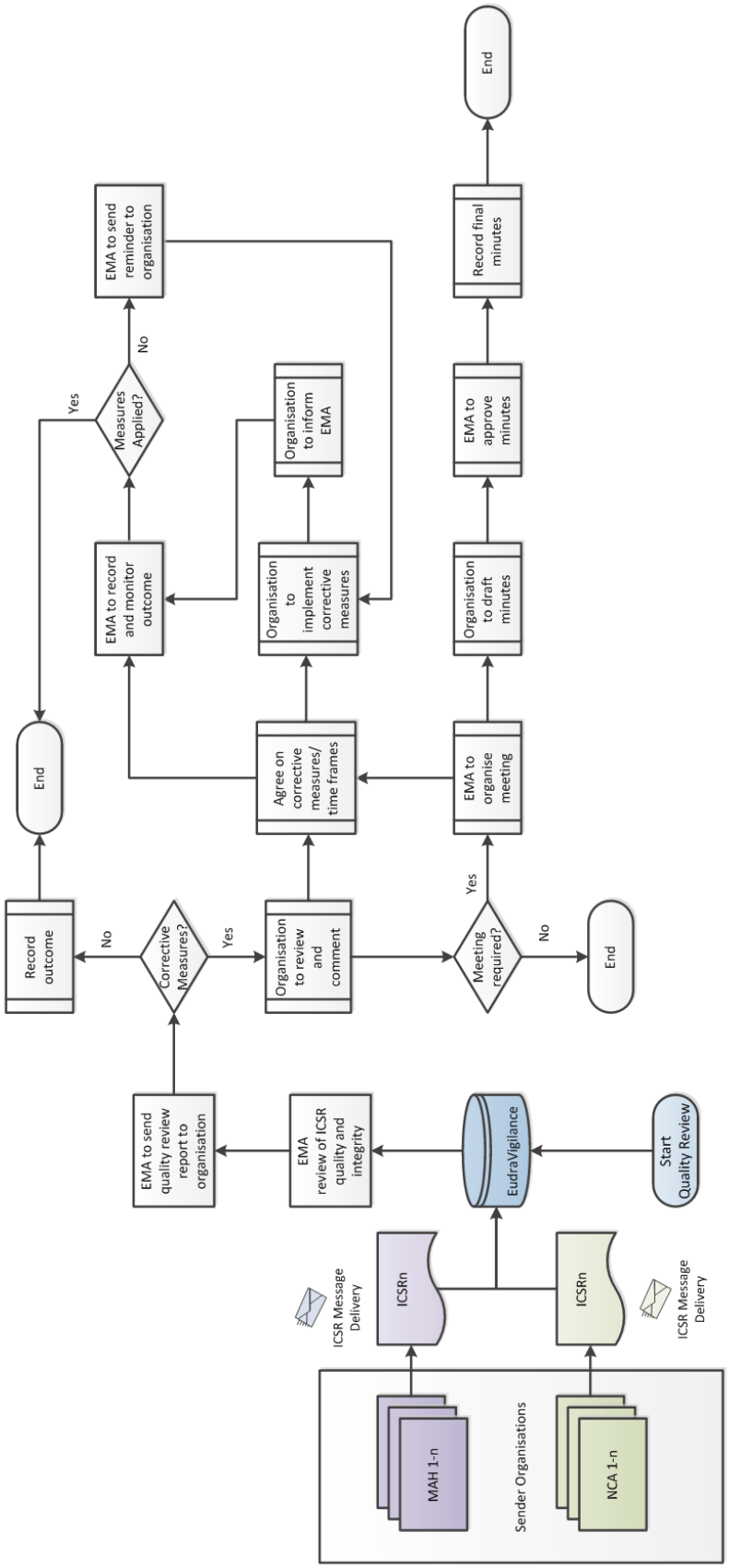

Sender Organisations
MAH 1-n
NCA 1-n
ICSRn
ICSRn
ICSR Message Delivery
ICSR Message Delivery
EudraVigilance
Start Quality Review
EMA review of ICSR quality and integrity
EMA to send quality review report to organisation
Corrective Measures?
No
Yes
Record outcome
End
Organisation to review and comment
Agree on corrective measures/ time frames
Organisation to implement corrective measures
EMA to record and monitor outcome
Measures Applied?
Yes
No
Organisation to inform EMA
EMA to send reminder to organisation
Meeting required?
Yes
No
End
EMA to organise meeting
Organisation to draft minutes
EMA to approve minutes
Record final minutes
End

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Table VI.13. Process description - Data quality monitoring of ICSRs transmitted electronically

Table VI.14. Table VI.16. The business map and process description describe a system where there is a separation between a PharmacoVigilance DataBase (PhV DB) holder, the PhV DB holder's data Quality Assessors (QA) and the PhV DB holder's auditors; however this is not mandatory and these functions may be performed by the same people or groups. Process description – Review of quality and integrity of ICSRs by the Agency in collaboration with NCAs and MAHs

No.	Step	Description	Responsible Organisation
1	**Start.** **Decide upon Sender to evaluate.**	**Select one of the organisations that has transmitted ICSRs to your database.** **Inputs into this decision can include, but need not be limited to findings from previous assessments and requests from pharmacovigilance audits.Review of quality and integrity of ICSRs by the Agency in collaboration with NCAs and MAHs in EEA Member States**	**PhV DB holder**EMA
21	**Sample ICSRs from Sender.**Receive reports of suspected drug adverse reaction(s) from NCAs and MAHs	Take a sample of ICSRs that were transmitted by the selected senderICSRs are received in electronic format in EudraVigilance from sender organisations with reporting obligations of suspected adverse reactions related to medicines authorised in the EEA	**QA**EMA
32	Check for dataReview of ICSR quality errors.and integrity	Check the cases for data quality errors. The cases should be assessed against appropriate published standards and similar documents, for example the MedDRA Term Selection Points to Consider document.A review of the quality, integrity and monitoring of compliance with reporting timeframes as well as the use of terminologies is performed in accordance with: • 3194 SOP - EudraVigilance individual case safety report data quality checking (in draft) • 3201 WIN - EudraVigilance how to check the quality of the data (in draft)	QAEMA
43	WriteA EV quality review report and sendis sent to PhV DB holder.organisation	The findings from the data quality assessment should be collated into a single report. These can include related	QAEMA

No.	Step	Description	Responsible Organisation
		checks, such as 15-day reporting compliance, whether error reports are corrected and similar statistical information.A draft report summarising the quality review outcome is sent to the organisation (EU QPPV for MAH/ Head of PhV Department of NCA) by e-mail	
53.1	**Errors found?**Are corrective actions required?	Were any errors found during the analysis of the cases? Are corrective actions required by the organisation being reviewed? If Yes, go to point 4. If No, go to step 5.1. If Yes go to steps 5.2, 5.3 & 6.point 10.	**PhV DB holder**
4.	Corrective actions are required by organisation being reviewed		
54.1	**End.**Review and comment	**If there were no errors found, then no further action needs to be taken. The process can end until the next time the sender is assessed. The PhV DB holder may choose to share this information with the assessed sender and their auditors who may wish to factor this in to determinations of which sender to assess.** Review draft quality review report and provide comments to EMA	**PhV DB holder**Organisation being reviewed (NCA/MAH)
5.2	Highlight for PhV audit.	If the PhV DB holder's organisation has an audit department, any significant findings should always be shared with them.	PhV DB holder
5.2.1	**Prioritise for Audit.**Is meeting required?	The audit or inspections department should use the information provided to them to feed into decisions about prioritising organisations for audit or inspection.If Yes, progress to 6. If No, progress to 7.	**PhV DB holder's auditors**Organisation being reviewed (NCA/MAH)
5.36	**INPUT: Findings from previous assessments.**A meeting is required	Any errors found (or even lack thereof) should be incorporated into decisions about which senders to evaluate &	**PhV DB holder**

No.	Step	Description	Responsible Organisation
		~~should also inform the performance of the assessments (e.g. targeting particular types of case) and the report (documenting whether previously identified issues have been addressed).~~A review meeting is requested by the Sender Organisation or is proposed by EMA	
6.1	A meeting is organised	A meeting is organised (via TC or face-to-face)	EMA
6.2	~~Inform sender~~Draft minutes of ~~findings.~~the meeting	~~Inform the sender of the findings, including requested remedial actions (e.g. retransmitting certain cases) and time frames for those actions~~Agreed actions and outcome of discussions to be summarised in draft meeting minutes	~~PhV DB holder~~Organisation being reviewed (NCA/MAH)
6.3	Approve meeting minutes	Approve meeting minutes as final	EMA
6.4	Record final minutes	Record final meeting minutes	EMA/Organisation being reviewed (NCA/MAH)
6.5	End		
7	~~**Request**~~A meeting~~?~~ is NOT required	~~The sender should have the option to choose to request a meeting to discuss the findings and appropriate remedial action and time frames.~~ ~~If no~~No review meeting is required (requested~~, go to step 7.1. If a meeting is requested go to step~~ by the Sender Organisation or proposed by EMA) Proceed with point 8.	~~**Sender**~~
~~7.1~~8	~~Address the findings & retransmit any required cases.~~Agree on corrective measures/timeframes	~~Address all findings, take necessary steps to prevent recurrence of such findings & retransmit any required cases.~~Reach agreement on corrective measures/timeframes; outcome of the agreement is to be reflected on the basis of the final quality review report, which is to be recorded	~~Sender~~Organisation being reviewed (NCA/MAH)
8.1	Implement corrective measures	Implement the corrective measures in accordance with the agreed methods	Organisation being reviewed (NCA/MAH)

No.	Step	Description	Responsible Organisation
		and timeframes	
7.8.2	**End.** Inform EMA about outcome	**Once all findings have been addressed, the necessary steps taken to prevent recurrence of such findings and any required cases have been retransmitted, the process can end until the next time the sender is assessed.** Inform EMA when corrective measures have been implemented in line with final quality review report	**Sender** Organisation being reviewed (NCA/MAH)
8.3	**Have meeting.** Record and monitor outcome	Upon request from one party, a meeting should be held to discuss the findings of quality assessments and appropriate remedial and preventive actions to ensure that the cases in the database are correct and shall be so in the future. Record the final quality review report and monitor the implementation the agreed corrective measures	**PhV DB holder & Sender** EMA
9.8.4	**End.** Have corrective measures been applied?	**Unless further action has** Check if corrective measures have been **specified (e.g. future meetings or assessments),** implemented by the organisation If Yes, the process **can** will end **until the next time the sender is assessed** If No, proceed to 9.	**PhV DB holder** EMA
9	Send reminder to organisation being reviewed	Send reminder to organisation being reviewed to implement corrective measures and proceed with point 8.4	EMA
10	Corrective Measures are NOT required	The quality review did not reveal any corrective measures	
10.1	Record outcome		EMA/Organisation being reviewed
10.2	End		

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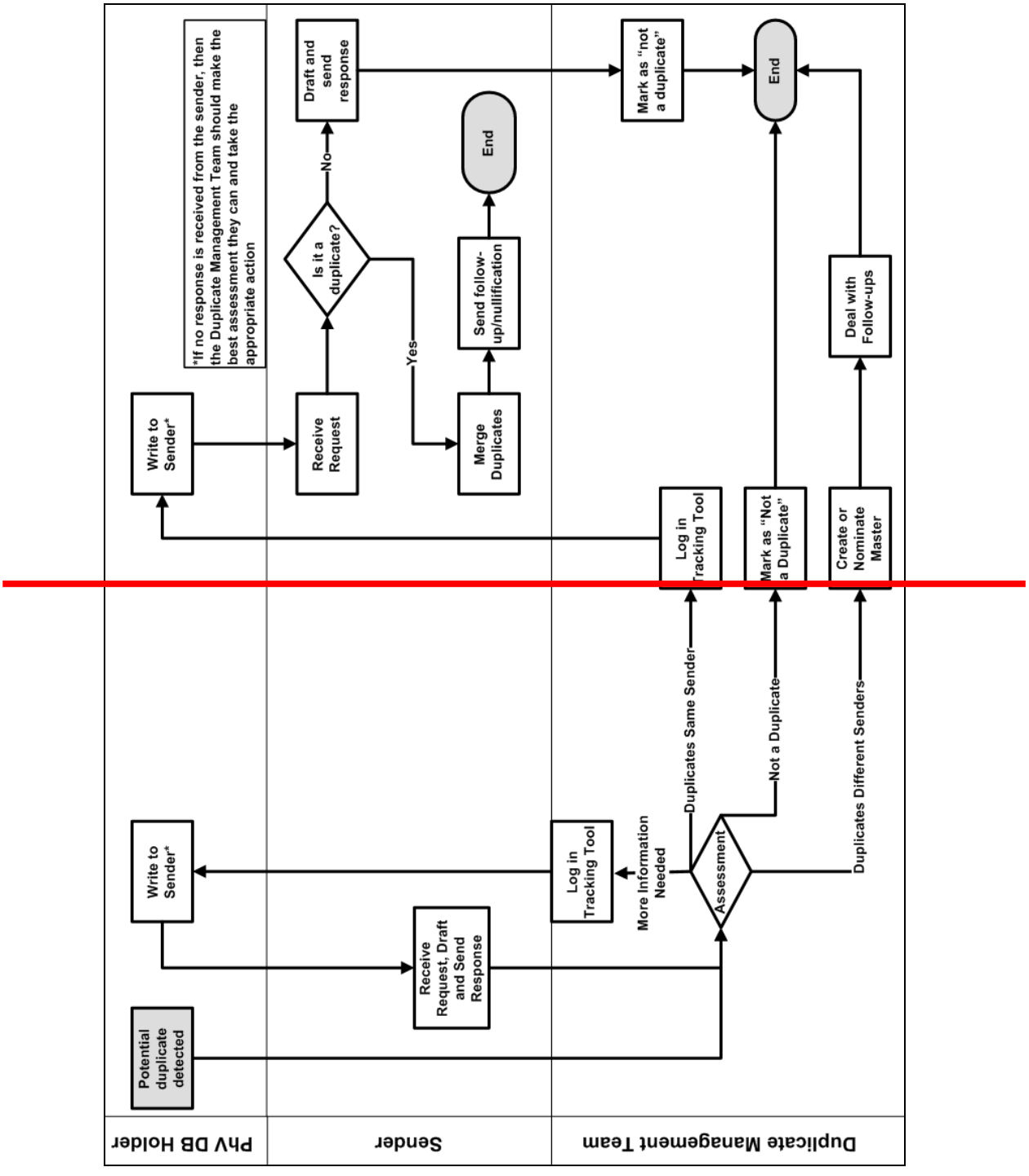
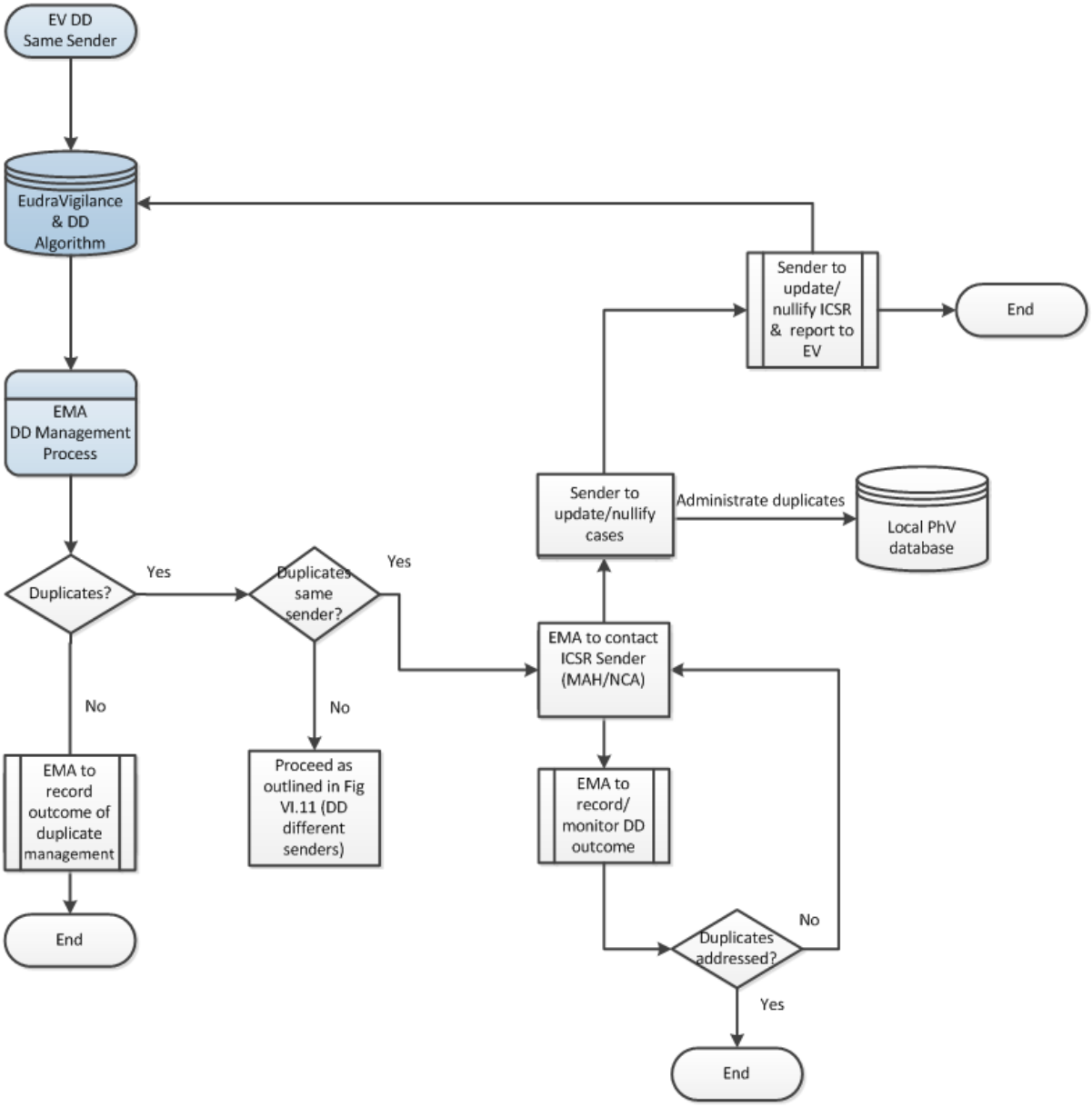
VI. Appendix 7 Duplicate detection and management of ICSRs

VI.App.7.1 Duplicate Detection in EudraVigilance – Collaboration between the Agency, Member States and MAHs where duplicates originate from the same sender

~~**Figure VI.7.** **Figure VI.10.** Business process map - Duplicate ~~detection and management of ICSRs~~Detection in EudraVigilance – Collaboration between the Agency, Member States and MAHs where duplicates originate from the same sender




EV DD
Same Sender
EudraVigilance
& DD
Algorithm
EMA
DD Management
Process
Duplicates?
Yes
No
Duplicates
same
sender?
Yes
No
EMA to
record
outcome of
duplicate
management
End
Proceed as
outlined in Fig
VI.11 (DD
different
senders)
EMA to contact
ICSR Sender
(MAH/NCA)
EMA to
record/
monitor DD
outcome
Duplicates
addressed?
No
Yes
End
Sender to
update/nullify
cases
Administrate duplicates
Local PhV
database
Sender to
update/
nullify ICSR
& report to
EV
End

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~~Table VI.15.~~ Table VI.17. Process description - Duplicate ~~detection and management of ICSRs~~Detection in EudraVigilance – Collaboration between the Agency, Member States and MAHs where duplicates originate from the same sender

~~No.~~	Step	Description	Responsible ~~organisation~~ Organisation
~~1~~	**Start.** ~~Potential duplicate detected.~~	~~Potential duplicates have been detected by the PharmacoVigilance DataBase (PhV DB) holder organisation or the PhV DB holder organisation is notified of potential duplicates by a receiver of the cases.~~**EudraVigilance (EV) Duplicate Detection with duplicates originating from the same Sender – Duplicates identified by the Agency**	~~PhV DB holder~~
1	Duplicate Detection (DD) in EudraVigilance	A duplicate detection algorithm is operated in EudraVigilance to detect potential duplicates	EMA
2	~~Assessment.~~EMA Duplicate Detection Management Process	~~All~~The potential duplicates ~~need assessment~~identified by the ~~organisation Duplicate Management Team (DMT) to confirm or deny their duplicate status.~~ ~~Following assessment there are 4 possible outcomes:~~ ~~• Not a Duplicate (go to step 2.1),~~ ~~• More Information Needed (go to step 2.2),~~ ~~• Duplicates From Different Sender (go to step 2.3),~~ ~~• Duplicates From Same Sender (go to step 2.4).~~ ~~The outcome of all assessments should be recorded to avoid continually reassessing the same cases when further versions arrive. These recorded outcomes can also be used to refine the~~EudraVigilance duplicate detection ~~methods during future development.~~algorithm are reviewed in accordance with the applicable SOP/WIN • 3323 SOP - Performing duplicate detection in EudraVigilance (in draft) • 3324 WIN - Evaluation and management of detected potential duplicates in EudraVigilance (in draft)	~~DMT~~EMA

No.	Step	Description	Responsible organisation Organisation
2.1	Not a Duplicate: Mark as not a duplicate.Are there duplicates?	IfAre the cases are assessed as not being duplicates of one another, then mark both cases as such.identified by the EudraVigilance duplicate detection algorithm confirmed? GoIf Yes, proceed to step 3 (End).. If No, proceed to 6.	DMTEMA
2.2	More information needed: Log in tracking tool.	There should be some form of tool for tracking when more information is needed, when correspondence has been sent, whether an answer was received and, if so, when.	DMT
2.2.13	**Write to Sender.**Are the confirmed duplicates from the same sender?	More information is required in order to be able to make a definite assessment. The sender (who transmitted the case(s) in question to the PhVDB holder's organisation) should be contacted to request specific information necessary to confirm or deny duplication. Personal data protection must remain paramount, so unsecured communications should not include sufficient data to identify an individual. Are the confirmed duplicates from the same sender organisation or a different sender organisation? If Yes, proceed to 4. If No, proceed according to the business process map related to duplicate detection of ICSRs from different senders outlined in Figure VI.11.	**PhV DB holder**EMA
2.2.24	**Receive request, draft and send response.**EMA to contact ICSR Sender (MAH/NCA)	Once a request for more information has been received, the Sender of the case should respond promptly, either as a follow-up version of the case or by responding to the requester. The DMT should then reassess the case based on the new information (Go back to step 2).Contact the ICSR sender organisation to inform about the ICSRs that have been identified and confirmed as duplicates in EudraVigilance in	**Sender**EMA

No.	Step	Description	Responsible organisation Organisation
		accordance with the applicable WIN: • 3325 WIN Following-up potential duplicates ICSRs with the original senders (in draft)	
2.34.1	**Duplicates Different Senders: Create or nominate master.**EMA to record/monitor the outcome of the duplicate management	Once cases have been determined to be duplicates of one another and have been transmitted to the PhV DB holder by different senders or reporters, then they should be merged under a master case, following the process described in chapter 2.3 "Management of duplicate cases" of the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs), EMA/13432/2009.Record the outcome of the duplicate management and monitor that duplicates have been addressed by the sender organisation	DMTEMA
2.3.1	Deal with follow-ups.	If any follow-ups arrive for any of the cases, this information may require a reassessment of the master case. Reassess and, if necessary, amend the master case as with any received follow-up information. Go to step 3 (End).	DMT
4.2.4	**Duplicates Same Sender: Log in tracking tool.**Are the duplicates addressed?	Once cases have been determined to be duplicates of one another, and have been transmitted to the PhV DB holder by the same sender, then this decision and the correspondence referred to in step 2.4.1 should be logged in the tracking tool referred to in step 2.2.Have the duplicates been addressed by the Sender Organisation? If Yes, the process ends. If No, progress with point 4	**DMT**
2.4.15	**Write to** Sender. (MAH/NCA) to update/nullify cases	The sender organisation, asSender Organisation has to update/nullify the source of the duplicates, should be contacteduplicate cases in their pharmacovigilance database in accordance with chapter 2.3.3 of the Guideline on the	**PhV DB holder**Organisation (MAH/NCA)

No.	Step	Description	Responsible organisation Organisation
		Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs),) (EMA/13432/2009 The sender should be asked to confirm or deny duplication and take appropriate steps in accordance with chapter 2.3.1 of the aforementioned Guideline.).	
2.4.2	**Receive request.**	Receive and log the communication containing information on suspected duplicates in the Sender's PhV DB.	**Sender**
2.4.3	Is it a duplicate?	Assess the potential duplicates. Are the cases duplicates of one another? If Yes, go to step 2.4.3.1. If No, go to step 2.4.3.2.	Sender
2.4.35.1	Merge duplicates.Sender (MAH/NCA) to send updated ICSR/nullification report to EV	Merge the duplicates, taking into account Flowchart 1 of chapter 2.3.1.3 ofThe Sender Organisation has to send an updated ICSR/nullification report to EudraVigilance in accordance with the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs),) (EMA/13432/2009.).	SenderOrganisation (MAH/NCA)
5.2	End		
2.4.3.1.16	Send follow-up/nullification.There are no confirmed duplicates	For the cases that are merged under the master, sendAs a nullification message to the PhV DB holder. For the case that is master, send the updated case to the PhV DB holder as follow-up information. The merging & transmission should be completed promptly and in any case within 15 daysresult of the date of receipt of the information from the PhV DB holderduplicate detection management process it is confirmed that the individual cases were considered to be possibleare no duplicates. This date should be treated as the date of receipt of most recent information for regulatory reporting purposes.	SenderEMA
2.4.3.1.2	**End.**	**The duplicates have now been**	**Sender**

No.	Step	Description	Responsible organisation Organisation
		removed from both the Sender's system and that of the PhV DB holder and only the master should be available for signal detection and data quality analyses. Unless follow-up information is received, then no further steps need be taken.	
2.4.3.2	Draft and send a response.	Reply to the PhV DB holder who sent the communication informing that the cases are not duplicates.	Sender
2.4.3.26.1	Mark as "Not aEMA to record outcome of duplicate". management	Upon receiptThe outcome of confirmation from the Sender organisation thatduplicate detection management process is recorded in accordance with the cases are notapplicable SOP/WIN: • 3323 SOP - Performing duplicate detection in EudraVigilance (in draft) • 3324 WIN - Evaluation and management of detected potential duplicates, mark the cases as "Not a duplicate" & go to step 3 (End). in EudraVigilance (in draft)	DMTEMA
36.2	End.	No further action is required for this couple.	DMT

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VI.App.7.2 Duplicate Detection in EudraVigilance – Collaboration between the Agency, Member States and MAHs where duplicates originate from different Senders

Figure VI.11. Business process map - Duplicate Detection in EudraVigilance – Collaboration between the Agency, Member States and MAHs where duplicates originate from different senders

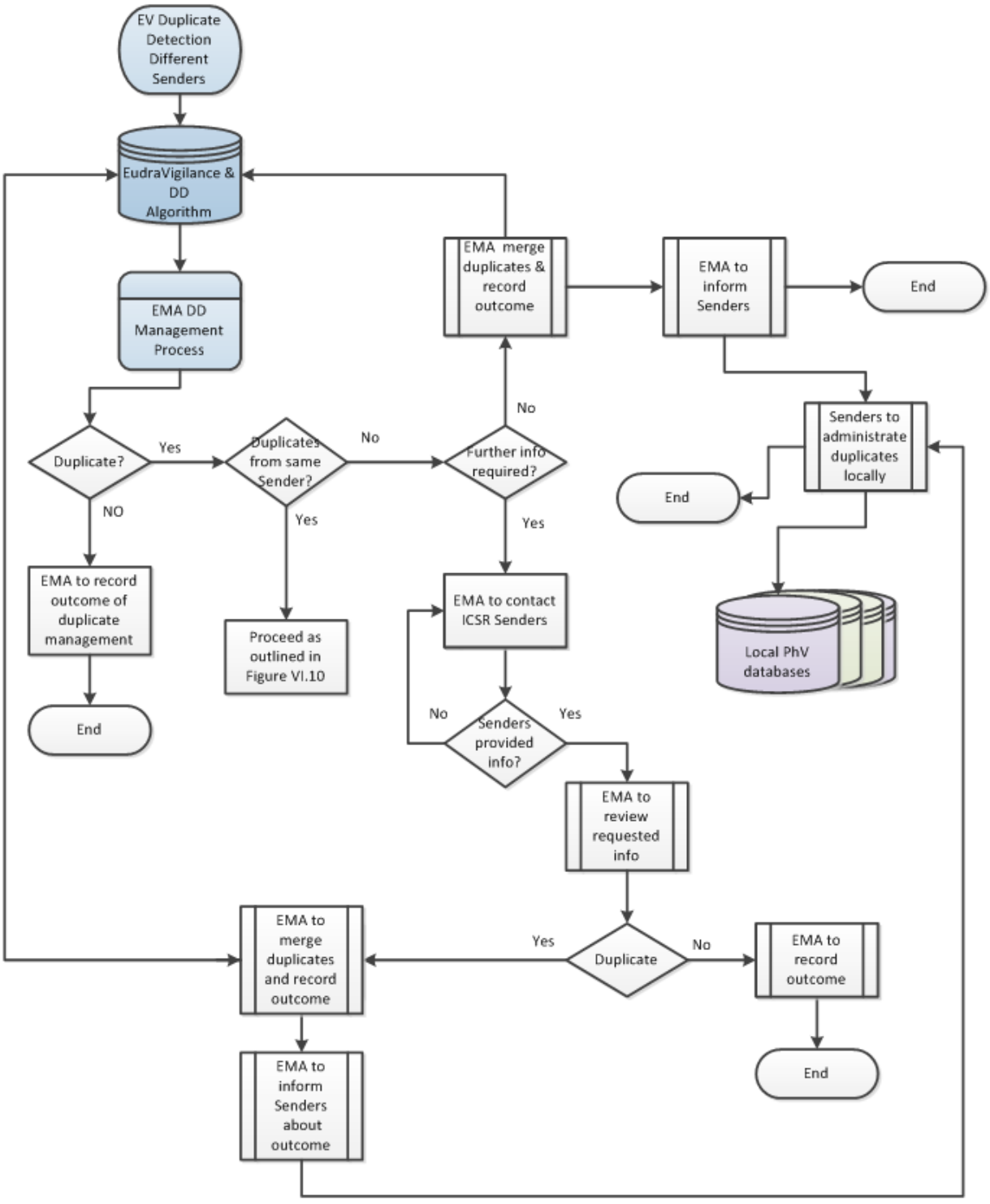

Table VI.18. Process description - Duplicate Detection in EudraVigilance – Collaboration between the Agency, Member States and MAHs where duplicates originate from different senders

No	Step	Description	Responsible Organisation
	Start	**EudraVigilance (EV) Duplicate Detection with duplicates originating from different Senders – Duplicates identified by the Agency** *Example: there is more than one suspect drug and the same case is submitted by two MAHs; the patient reported the same adverse reaction to a NCA and the MAH*	
1	Duplicate Detection (DD) in EudraVigilance	A duplicate detection algorithm is operated in EudraVigilance to detect potential duplicates	EMA
2	EMA Duplicate Detection Management Process	The potential duplicates identified by the EudraVigilance duplicate detection algorithm are reviewed in accordance with the applicable SOP/WIN • 3323 SOP - Performing duplicate detection in EudraVigilance (in draft) • 3324 WIN - Evaluation and management of detected potential duplicates in EudraVigilance (in draft)	EMA
2.1	Are there duplicates?	Are the duplicates identified by the EudraVigilance duplicate detection algorithm confirmed? If Yes, proceed to point 3. If No, proceed to point 9.	EMA
3	Are the duplicates from the same Sender?	Are the duplicates identified by the EudraVigilance duplicate detection algorithm confirmed? If Yes, proceed as outlined in Figure VI.10. If No, proceed to point 4.	
4	Is further information required?	Is there further information required to confirm if the duplicates identified by the duplicate detection algorithm are duplicates? If Yes, proceed to point 5. If No, proceed to point 8.	EMA
5	EMA to contact ICSR Senders (MAH/NCA)	Contact the ICSR senders to obtain additional information on the individual cases that have been identified as potential duplicates and indicate timeframe by when the information is to be provided • 3325 WIN Following-up potential duplicates ICSRs	EMA

No	Step	Description	Responsible Organisation
		with the original senders (in draft)	
6	Has Sender provided the information?	Check if the Senders have provided the requested information? If Yes, proceed to point 7. If No, proceed to 5.	EMA
7	EMA to review requested info	The duplicate cases are to be reviewed based on the requested info that has been provided by the Senders to confirm if they are duplicates. If Yes, proceed to point 8. If No, progress with point 9.	
8	The cases are confirmed duplicates		
8.1	EMA to merge duplicate reports and record outcome	Merge the potential duplicates in EudraVigilance in line with the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs) (EMA/13432/2009)	Sender Organisations (MAH/NCA)
8.2	EMA to inform Senders about outcome	Inform the Senders about the outcome of the duplicate management to allow Senders to take action where necessary[72],[73];[74]	EMA
8.3	Senders to administrate duplicates locally	Senders of the cases identified as duplicates in EudraVigilance should follow the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs) (EMA/13432/2009) Note: capture duplicate case reference numbers in data element 'Other case identifiers in previous	Sender Organisations (MAH/NCA)

[72] NOTE: MAHs will be able to download "master cases" from EudraVigilance in line with the EudraVigilance Access Policy. The message type (equivalent to E2B(R2) - M.1.1) will have the code "master" to distinguish it from all other ICSR messages, which will have the message type "ichicsr" (see EU ICSR Implementation Guide, chapter I.C.3.1.1).
MAHs will also be able to export from EudraVigilance the original ICSRs that have been merged under the "master case" and also any nullification to these ICSRs, where applicable (see EU ICSR Implementation Guide, chapter I.C.6.1.2). It is up to the MAH to decide if they wish to process "master cases" or not.
If the MAH does process the "master case" and it involves updating one of their own individual cases with information from the EudraVigilance master case, the MAH MUST NOT resubmit an updated version of this individual case to EudraVigilance.

[73] A table of master cases and associated duplicates will be made available to aid duplicate management by Sender organisations.

[74] NCAs can use the EudraVigilance Rerouting Rules Engine to update the rerouting rules to determine if they wish to receive EudraVigilance "master cases" or not. See also further guidance as outlined in EU ICSR Implementation Guide, chapter I.C.2.3 and I.C.6.1.2). The "master cases" must not be retransmitted by the NCA to EudraVigilance if there is no receipt of new information that warrants a follow-up report.

No	Step	Description	Responsible Organisation
		transmissions' (E2B(R2) A.11/E2B(R3) section C.1.9.1	
8.4	End		
9	The cases are NOT duplicates	The potential duplicates have been reviewed and are not duplicate cases	EMA
9.1	EMA to record outcome of duplicate management	The outcome of the Duplicate Detection Management process is recorded in accordance with the applicable SOP/WIN: • 3323 SOP - Performing duplicate detection in EudraVigilance (in draft) 3324 WIN - Evaluation and management of detected potential duplicates in EudraVigilance (in draft)	EMA
9.2	End		

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VI.App.7.3 Duplicates from same Sender Organisation – duplicates detected by the sender organisation prior to detection by the Agency in EudraVigilance

Figure VI.12. Business process map - Duplicates originating from a pharmacovigilance database of the same Sender Organisation (NCA/MAH), which were sent to EudraVigilance – Duplicates detected by the Sender Organisation prior detection by the Agency in EudraVigilance

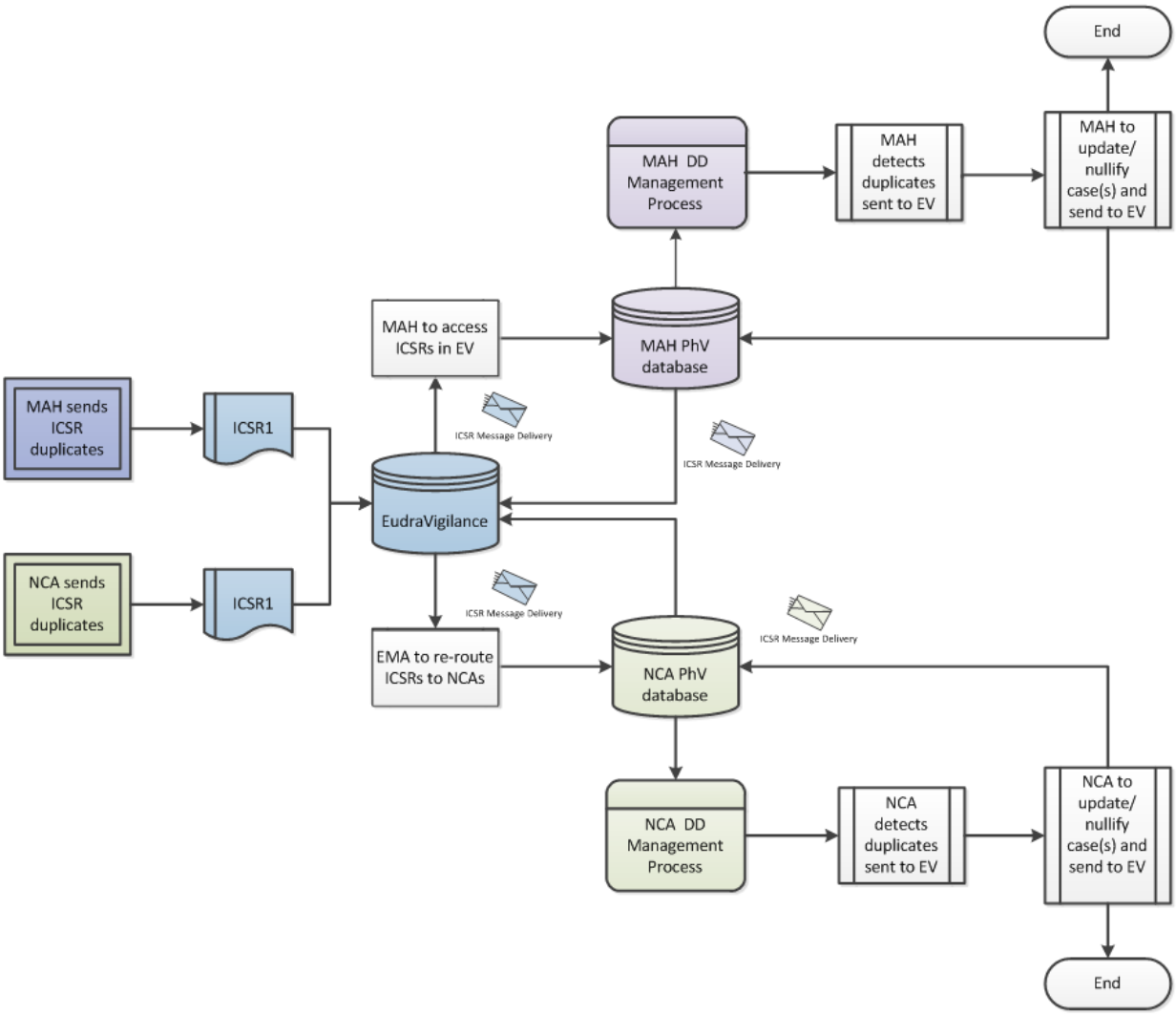

Table VI.19. Process description - Duplicates originating from a pharmacovigilance database of the same Sender Organisation (NCA/MAH) which were sent to EudraVigilance – Duplicates detected by the Sender Organisation prior detection by the Agency in EudraVigilance

No	Step	Description	Responsible Organisation
	Start	**Duplicates originating from a pharmacovigilance database of the same Sender Organisation (NCA/MAH) which were sent to EudraVigilance – Duplicates detected by the Sender Organisation**	
1	ICSR duplicates are sent to EudraVigilance	Duplicated ICSRs for the same individual case are sent to EudraVigilance by the same sender	Sender Organisation (NCA/MAH)
2	Re-routing of ICSRs to NCA	MAHs ICSRs are rerouted from EudraVigilance to the NCA in accordance with VI.C.4 and the rerouting principles described in the EU ICSR Implementation Guide (EMA/51938/2013)	EMA/EudraVigilance
3	Duplicate Management Process		NCA
3.1	Duplicates detected, which were sent to EudraVigilance	The NCA identifies the duplicates they sent to EudraVigilance as part of their duplicate management process	NCA
3.2	Review/update/ nullify cases and send to EV	Review and update/nullify duplicated individual cases and send updated ICSRs/nullification ICSRs to EudraVigilance in line with the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs) (EMA/13432/2009)	NCA
3.3	End		
4	Duplicate Management Process		MAH
4.1	Duplicates detected, which were sent to EudraVigilance	Duplicates sent to EudraVigilance are identified as part of their duplicate management process	MAH
4.2	Review/update/ nullify cases and send to EV	Review and update/nullify duplicated individual cases and send updated ICSR/nullification ICSR to EudraVigilance in line with the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs) (EMA/13432/2009)	MAH
4.3	End		

VI.App.7.4 Duplicates from different Sender Organisations - Duplicates detected by an Organisation prior detection by Agency in EudraVigilance

Figure VI.13. Business process map - Duplicates from different Sender Organisations - Duplicates detected by an Organisation prior detection by Agency in EudraVigilance

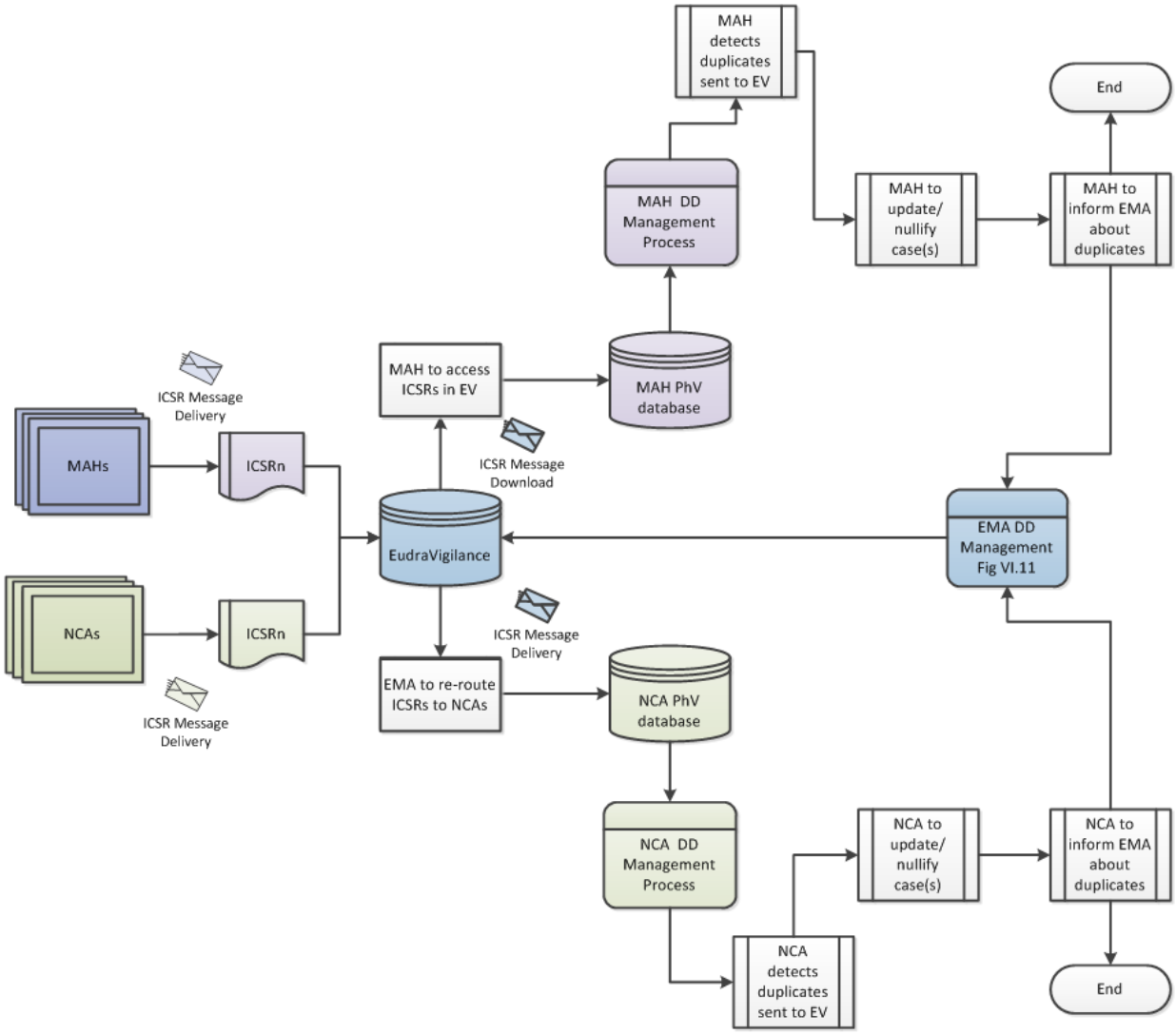

Table VI.20. Process description - Duplicates from different Sender Organisations - Duplicates detected by an Organisation prior detection by Agency in EudraVigilance

No	Step	Description	Responsible Organisation
	Start	**Duplicates from different Sender Organisations - Duplicates detected by an Organisation where duplicates were previously not identified in EudraVigilance** Example: case series described in the medical literature submitted by MAHs to EudraVigilance; these were previously reported by healthcare professionals to a NCA, which submitted the cases to EudraVigilance. Primary source identifiers or patient identifiers were masked and the duplicate detection algorithm did not identify the reports as potential duplicates	
1	ICSR duplicates are sent to EudraVigilance	Duplicated ICSRs for the same individual case are sent to EudraVigilance	Sender Organisation (NCA/MAH)
2	Re-routing of ICSRs to NCA	MAHs ICSRs are rerouted from EudraVigilance to the NCA in accordance with VI.C.4 and the rerouting principles described in the EU ICSR Implementation Guide (EMA/51938/2013)	EMA/EudraVigilance
3	Duplicate Management Process		NCA
3.1	Duplicates detected, which were sent to EudraVigilance	The NCA identifies the duplicates it sent to EudraVigilance as part of its duplicate management process	NCA
3.2	Review/update/ nullify cases and send to EV	Review and update/nullify individual cases and send updated ICSR/nullification ICSR to EudraVigilance in line with the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs) (EMA/13432/2009)	NCA
3.3	End		
4	Duplicate Management Process		MAH
4.1	Duplicates detected, which were sent to EudraVigilance	MAH identifies the duplicates it sent to EudraVigilance as part of its duplicate management process	MAH

No	Step	Description	Responsible Organisation
4.2	Review/update/ nullify cases and send to EV	Review and update/nullify duplicated individual cases and send updated ICSR/nullification ICSR to EudraVigilance in line with the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs) (EMA/13432/2009)	MAH
4.3	End		

VI.App.7.5 Duplicate Detection in EudraVigilance – Collaboration between the Agency, Member States and MAHs where duplicates are first detected in a database other than EudraVigilance

Figure VI.14. Business process map - Collaboration between the Agency, Member States and MAHs - Duplicates first detected in a database other than EudraVigilance

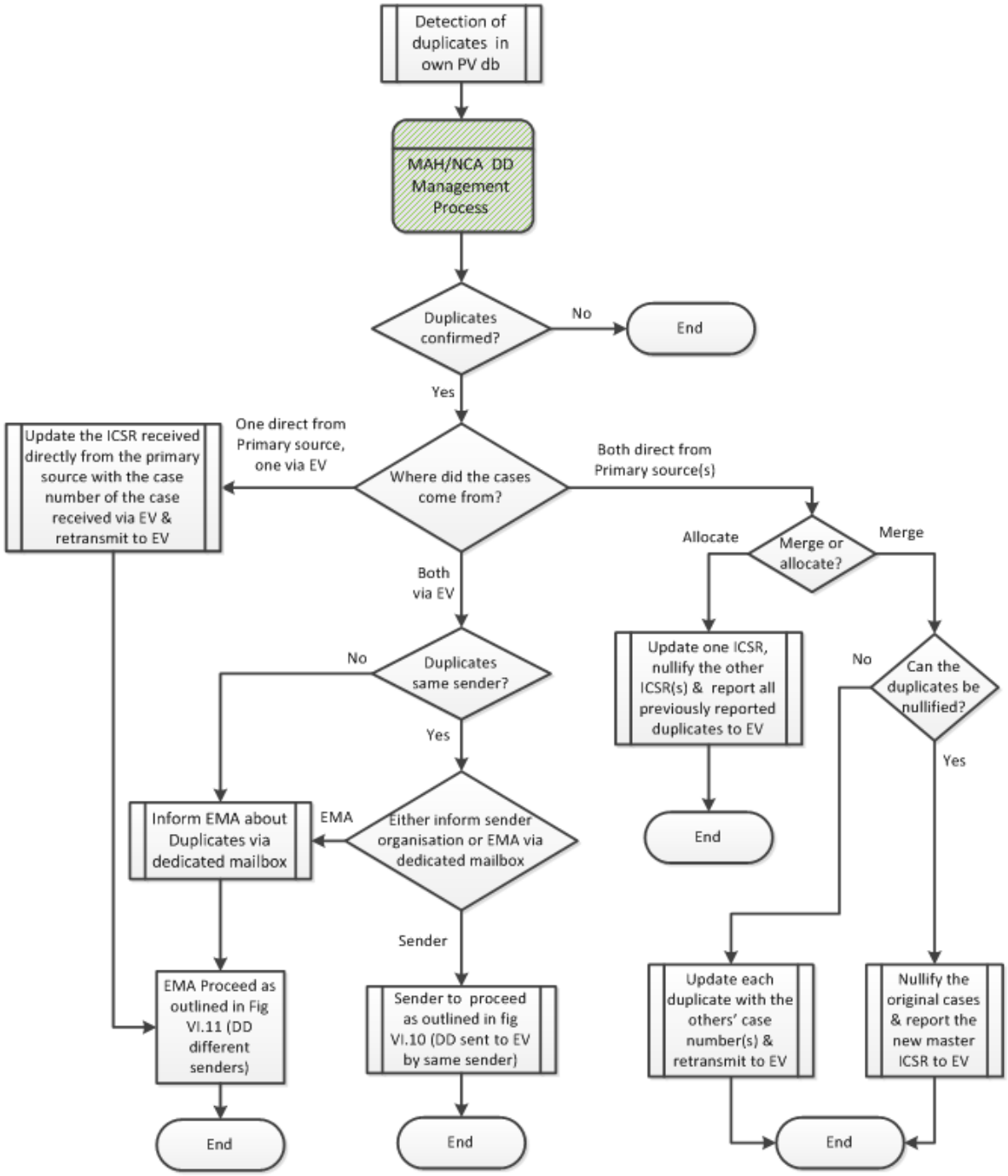

Table VI.21. Process description - Collaboration between the Agency, Member States and MAHs where duplicates are first detected in a database other than EudraVigilance

No	Step	Description	Responsible Organisation
	Start	**EudraVigilance (EV) Duplicate Detection with duplicates originating from the same Sender – Duplicates identified by the Agency**	
1	Duplicate Detection (DD) NOT in EudraVigilance	A duplicate detection process operating on a database other than EV detects potential duplicates. This is day zero for your process & for any updated versions that will be transmitted	MAH/NCA
2	MAH/NCA Duplicate Detection Management Process	The potential duplicates identified are reviewed in accordance with the applicable SOP/WIN	MAH/NCA
3	Are the duplicates confirmed?	Are the potential duplicates identified by the process confirmed? If Yes, proceed to 4. If No, proceed to 3.1.	MAH/NCA
3.1	End		
4	Where did the cases come from?	From where did your organisation receive the confirmed duplicate cases? If both cases came direct from a primary source or via non-EEA NCAs, proceed to 5 If both cases came via EV (either rerouted for an NCA or accessed from EV for an MAH), proceed to 6 If one case came direct from a primary source & one via EV, proceed to 7	MAH/NCA
5	Both cases came direct from primary source: MAH/NCA to administer the duplicates in accordance with internal policies	If the internal policy is to allocate one case as the master, proceed to step 5.1 If the internal policy is to merge duplicates under a master, proceed to 5.2	MAH/NCA
5.1	MAH/NCA allocates one case as the master	Update one ICSR with the case numbers & other relevant information from the other & send that to EV as follow-up. Nullify the other case &, if it was already transmitted to EV, send the nullification message to EV	MAH/NCA

No	Step	Description	Responsible Organisation
5.1.1	End		
5.2	MAH/NCA merges the duplicates under a master case	Can the underlying duplicates be nullified and a nullification message sent to EV? If No, proceed to 5.2.1 If Yes, proceed to 5.2.2	MAH/NCA
5.2.1	The underlying duplicates cannot be nullified	The Sender Organisation has to send updated ICSRs for the duplicate reports to EudraVigilance in accordance with the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs) (EMA/13432/2009). The updated duplicates should include the case numbers of the other duplicates and also of the master case in the report duplicates section. The master case created from the duplicates should NOT be sent to EV[75].	MAH/NCA
5.2.2	The underlying duplicates can be nullified	The Sender Organisation has to nullify the duplicate cases in their pharmacovigilance database in accordance with the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs) (EMA/13432/2009). The master case created from the duplicates should be sent to EV. This case should be sent as a standard ICSR & cannot be sent as message type MASTER.	MAH/NCA
5.3	End		
6	Both cases were received via EV	Were the duplicates transmitted to EV by the same sender organisation? If yes, proceed with step 6.1 If no, proceed with step 6.2	MAH/NCA
6.1	Either inform sender organisation or EMA via dedicated mailbox	If you wish to inform the EMA via the dedicated mailbox proceed with step 6.2 If you wish to inform the sender directly, proceed with step 6.3	MAH/NCA
6.2	Inform EMA about duplicates via	Email duplicates@ema.europa.eu to inform them that you have detected that cases you received from	MAH/NCA

[75] Where, in certain instances based on internal duplicate management process, the recommendation provided under section 5.2.1 cannot be applied by Member States, the management of duplicates will be handled by EMA. Requests should be sent to duplicates@ema.europa.eu with the relevant worldwide case safety IDs of the duplicate cases.

No	Step	Description	Responsible Organisation
	dedicated mailbox	Eudravigilance are duplicates of one another, including the worldwide case safety IDs of the duplicate cases	
6.2.1	EMA proceed as outlined in Figure VI.11.	EMA to administer duplicates in accordance with defined duplicate management process as outlined in Figure VI.11.	EMA
6.2.2	End		
6.3	Inform sender about duplicates	Contact the sender organisation to inform them about the duplicates that they have transmitted to EV. Proceed with step 6.4	MAH/NCA
6.4	Sender to proceed as outlined in Figure VI.10.	The sender has to assess the cases and, if confirmed, either merge the cases under a master or allocate as applicable, in accordance with the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs) (EMA/13432/2009).	Original sender organisation (MAH/NCA)
6.5	End		
7	One case came direct from a primary source & one via EV	The sender has to update the ICSR received directly from the primary source with the case number of the case received via EV & retransmit to EV. The duplicates in the sender's database should be managed in accordance with the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs) (EMA/13432/2009). Once the updated case has been received in EV from the sender, procced to step 6.2.1	MAH/NCA

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VI.App.7.6 Duplicates identified as part of signal management as outlined in GVP Module IX - Collaboration between the Agency, Member States and MAHs

Figure VI.15. Business process map - Duplicates identified as part of signal management as outlined in GVP Module IX

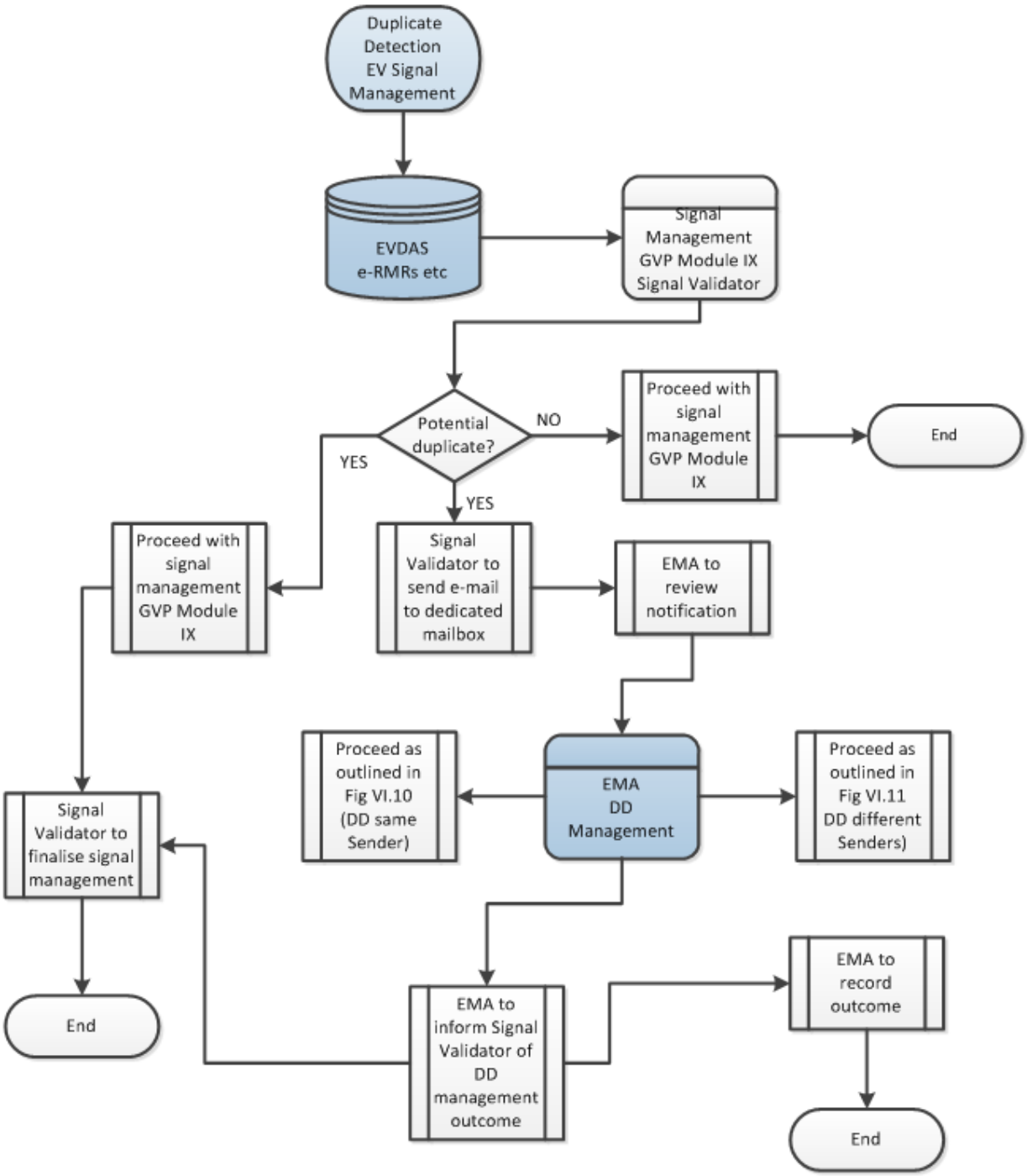

Table VI.22. Process description - Duplicates identified as part of signal management based on EudraVigilance data as outlined in GVP Module IX

No	Step	Description	Responsible Organisation
	Start	**Duplicates identified as part of signal management as outlined in GVP Module IX** As part of the signal management process based on EudraVigilance data as outlined in GVP Module IX, there may be instances where a signal validator of the Agency, a Member State or a MAH may identify potential duplicates.	
1	Signal Management in line with GVP Module IX	Signals are assessed in line with GVP Module IX based on electronic Reaction Monitoring Reports (eRMRs), case line listings and individual case report forms generated by EudraVigilance (EVDAS)	Signal validator (EMA/NCA/MAH)
2	Potential duplicates?	As part of the review of the signal there may be individual cases identified that could be potential duplicates from the signal validator's perspective: If potential duplicates are identified, proceed as outlined under point 3 and point 4. If no potential duplicate are identified, proceed as outlined under point 5.	
3	Potential duplicates have been identified		
3.1	Send e-mail to dedicated mailbox	Send detail request for the verification of the duplicates to duplicate-detection@ema.europa.eu with the Worldwide Unique Case Identifier for all individual cases, which are considered as potential duplicates	Signal validator (EMA/NCA/MAH)
3.2	Review notification	EMA to review notification of potential duplicates and initiate duplicate management process If duplicates are from the same Sender organisation, proceed as outlined in Figure VI.10. If duplicates are from different Sender organisations, proceed as outlined in Figure VI.11.	EMA
3.3	Notify signal validator about the outcome of the duplicate management	Inform the Signal Validator about the outcome of the duplicate management process	EMA
	Record the outcome of the duplicate	Record the outcome of the duplicate management	EMA

No	Step	Description	Responsible Organisation
3.4	management		
3.5	End		
4	Potential duplicates have been identified		
4.1	Proceed with signal management	Proceed with the review of the signal in line with GVP Module IX	Signal validator (EMA/NCA/MAH)
4.2	Finalise signal management	Finalise signal management based on duplicate detection management feedback from EMA	Signal validator (EMA/NCA/MAH)
4.3	End		
5	No (potential) duplicates have been identified		
5.1	Proceed with signal management	Proceed with the review of the signal in line with GVP Module IX	Signal validator (EMA/NCA/MAH)
5.2	End		

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VI. Appendix 8 Examples of assesment of case validity.

Table VI.23. Examples of assessment of the validity individual reports based on reporter and patient identifiability.

No.	Examples of case reports (source: Report of CIOMS Working Group V, 2001)	Validity assessment
1	*Dr. Isabella Queen reports that her patient, a 34 year old white male (initials A.V.) experienced hair loss after taking drug X. Dr. Queen's address and phone number are available.*	Valid case. Identifiable reporter and qualification. Patient's qualifying descriptors available (initials, age, gender).
2	*Dr. Isabella Queen reports her patient, a male, was reported to have experienced hair loss after taking drug X. Dr. Queen's phone number is available.*	Valid case. Identifiable reporter and qualification. Patient's qualifying descriptor available (gender).
3	*Dr. Feelgood reports that 2 patients were reported to have given birth, to a premature female infant in one case and a premature male infant in another, while on drug X. Dr.'s phone number and address are available.*	Valid case. Identifiable reporter and qualification. 2 patients with qualifying descriptors available (gender).
4	*Dr. Bones reports via e-mail that her patient (initials X.X.) developed a melanoma after taking drug Z. While the physician's e-mail address is available, attempts to reach her yielded no response. Address and phone number are not available.*	Valid case. Identifiable reporter and qualification. Patient's qualifying descriptor available (initials).
5	*A report from a Dr describes a patient (initials X.X.) who developed a melanoma after taking drug Z. No contact details are available regarding the reporter and the case cannot be followed-up.*	Non-valid case. Reporter qualification provided but no contact parameters available to allow verification of the case.
6	*Dr. Bones reports via e-mail that her patient developed a melanoma after taking drug X. Dr. Bone's address and phone number are not available, but she does respond by e-mail.*	Non-valid case. Identifiable reporter and qualification. No patient's qualifying descriptor available. Report should be followed-up.
7	*An employee of a drug company is at a barbecue at the house of paediatrician, Dr. Wiener, his neighbour. He hears from Dr. Wiener about his patient who developed hepatitis three weeks after one injection of the company's drug X. The employee sends a memo to the drug safety department with the*	Non-valid case. Identifiable reporter and qualification. No patient's qualifying descriptor available. Report should be followed-up.

No.	Examples of case reports (source: Report of CIOMS Working Group V, 2001)	Validity assessment
	clinical details he remembered on the patient and also includes Dr.Wiener's address and phone number.	
8	*Dr. Lindbergh on a commercial airplane flight from Paris to New York is seated next to an employee from a drug company. Dr. Lindbergh talks about his patient who experienced severe depression after taking the company's drug A (an oral contraceptive). The company employee, a marketing manager, reports the case to his drug safety department and provides the physician's business card.*	Valid case. Identifiable reporter and qualification. Patient's qualifying descriptors available (gender). Patient presumably female as suspected product is an oral contraceptive.
9	*The safety department of pharmaceutical company A sends to company B a report it received of a 23 year old female who developed Stevens Johnson Syndrome after taking drug A (a company A product) and drug B (a company B product). On follow-up with the reporting physician, Company A is told that their drug is not considered as a suspect causal agent. Company A sends the contact information on the identifiable physician to company B.*	Valid case. Identifiable reporter and qualification. Patient's qualifying descriptor available (age and gender).
10	*Professor Messer presents a paper at a medical convention (either orally or as a poster presentation) on a patient that developed thyroiditis after long-term therapy with Drug X. The paper is seen (or heard) by a company employee who reports it to the drug safety department.*	Non-valid case. Identifiable reporter and qualification. No patient's qualifying descriptor available. Report should be followed-up.
11	*The International Herald Tribune publishes an article describing a 5 year old patient who died after Drug Y ingestion. There is no physician mentioned and no author is listed for the article. The editor of the IHT (or, for example, a reader of the paper) forwards the article to the company.*	Valid case. Identifiable reporter and qualification (Editor to IHT, non-HCP). Patient's qualifying descriptor available (age).
12	*A company employee reads in a newspaper that several patients at Massachusetts General Hospital have given birth prematurely while taking drug X.*	Non-valid case. Identifiable reporter and qualification (Author of article or Journal editor, non-HCP). No patient's qualifying descriptor available. Report should be followed-up.

No.	Examples of case reports (source: Report of CIOMS Working Group V, 2001)	Validity assessment
13	*Pharmacist Gene Type reports that a neighbour told him that a female taking drug Z had dyspepsia at that neighbour's house last week. Only the pharmacist's address and phone number are available. Further information is not forthcoming despite rigorous follow-up.*	Non-valid case. No identifiable reporter and qualification (second hand information). Patient's qualifying descriptor available. Report should be followed-up.
14	*Dr. NoRed Cell reports that 6 patients developed aplastic anemia while on drug X. Dr.'s address and phone number are not available, but his/ her e-mail address is given.*	Non-valid case. Identifiable reporter and qualification. Report describing definite number of patients with no qualifying descriptor available for each patient. Report should be followed-up.
15	*Dr. Onko Gene communicates to a company that 50 patients developed ovarian cancer while on drug X. The Dr.'s address, phone number and e-mail address are available, but attempts to reach her by the usual means are unsuccessful.*	Non-valid case. Identifiable reporter and qualification. Report describing definite number of patients with no qualifying descriptor available for each patient. Report should be followed-up as possible.

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