28 July 2017
EMA/873138/2011 Rev 2*

Guideline on good pharmacovigilance practices (GVP)

Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)

Date for coming into effect of first version	2 July 2012
Date for coming into effect of Revision 1	16 September 2014
Draft Revision 2* finalised by the Agency in collaboration with Member States	15 July 2016
Draft Revision 2 agreed by the European Risk Management Facilitation Group (ERMS FG)	26 July 2016
Draft Revision 2 adopted by Executive Director	4 August 2016
Release for public consultation	8 August 2016
End of consultation (deadline for comments)	14 October 2016
Revised draft Revision 2 finalised by the Agency in collaboration with Member States	6 July 2017
Revised draft Revision 2 agreed by the EU Network Pharmacovigilance Oversight Group (EU-POG)	25 July 2017
Revised draft Revision 2 adopted by Executive Director as final	28 July 2017
Date for coming into effect of Revision 2*	22 November 2017

* Note: Revision 2 contains the following:

- Updated guidance on ICSRs submission, follow-up, duplicate detection and data quality management, taking into account the implementation of the new EudraVigilance system, and of the simplified submission of ICSRs in the EU in line with the provisions provided in Article 24 of Regulation (EC) No 726/2004 and Article 107 and 107a of Directive 2001/83/EC;
- Updated guidance on the validation of ICSRs based on patients and reporters identifiability;
- Updated guidance on the management of ICSRs described in the medical literature;
- Updated guidance on the collection of information on patient's age;
- Updated guidance on the management of suspected adverse reactions reported through medical enquiry and product information services;
- New guidance on the electronic submission modalities of ICSRs under the new ICH-E2B(R3) format;
- New guidance on the management of individual reports of off-label use, based on the Reflection Paper on Collecting and Reporting Information on Off-label Use in Pharmacovigilance (EMA/293194/2016), published for public consultation in 2016;
- New guidance on the management of reports from post-authorisation efficacy studies;
- Transfer of the guidance on emerging safety issue to GVP Module IX;
- Editorial amendments to align the format with other GVP Modules.

See websites for contact details

European Medicines Agency www.ema.europa.eu
Heads of Medicines Agencies www.hma.eu

The European Medicines Agency is an agency of the European Union

© European Medicines Agency and Heads of Medicines Agencies, 2017.
Reproduction is authorised provided the source is acknowledged.

TABLE OF CONTENTS

VI.A. Introduction 6
VI.A.1. Terminology 6
VI.A.1.1. Adverse reaction, causality 6
VI.A.1.2. Overdose, off-label use, misuse, abuse, occupational exposure, medication error, falsified medicinal product 7
VI.A.1.3. Active substance, excipient, medicinal product 7
VI.A.1.4. Primary source, healthcare professional, consumer 8
VI.A.1.5. Medical confirmation 8
VI.A.1.6. Seriousness 9
VI.A.1.7. Individual case safety report (ICSR) 9
VI.A.1.8 nullFlavors 9
VI.B. Structures and processes 11
VI.B.1. Collection of individual safety reports 11
VI.B.1.1. Unsolicited reports 11
VI.B.1.1.1. Spontaneous reports 11
VI.B.1.1.2. Literature reports 12
VI.B.1.1.3. Reports from non-medical sources 13
VI.B.1.1.4. Information on suspected adverse reactions from the internet or digital media 13
VI.B.1.2. Solicited reports 13
VI.B.2. Validation of reports 14
VI.B.3. Follow-up of reports 16
VI.B.4. Data management 17
VI.B.5. Quality management 18
VI.B.6. Special situations 18
VI.B.6.1. Use of a medicinal product during pregnancy or breastfeeding 18
VI.B.6.2. Use of a medicinal product in a paediatric or elderly population 20
VI.B.6.3. Reports of overdose, abuse, misuse, medication error or occupational exposure 20
VI.B.6.4. Lack of therapeutic efficacy 20
VI.B.7. Submission of individual case safety reports (ICSRs) 21
VI.B.7.1. Submission time frames of ICSRs 22
VI.B.7.2. Report nullification 22
VI.B.7.3. Report amendment 22
VI.B.8. Modalities for submission of individual case safety reports (ICSRs) 22
VI.C. Operation of the EU network 24
VI.C.1. Management of individual safety reports for clinical trials, post-authorisation studies, compassionate use and named patient use in the EU 25
VI.C.1.1. Management of individual safety reports for clinical trials 26
VI.C.1.2. Management of individual safety reports for non-interventional post-authorisation studies, compassionate use and named patient use 27
VI.C.1.2.1. Non-interventional post-authorisation studies 28
VI.C.1.2.1.1. Non-interventional post-authorisation studies with a design based on primary data collection 29
VI.C.1.2.1.2. Non-interventional post-authorisation studies with a design based on secondary use of data 30
VI.C.1.2.2. Compassionate use and named patient use 30

VI.C.2. Collection of individual safety reports 31
VI.C.2.1. Responsibilities of Member States 31
VI.C.2.2. Responsibilities of the marketing authorisation holder in the EU 33
VI.C.2.2.1. Spontaneous reports 34
VI.C.2.2.2. Solicited reports 34
VI.C.2.2.3. Case reports published in the medical literature 35
VI.C.2.2.3.1 Monitoring of the medical literature by the European Medicines Agency 35
VI.C.2.2.3.2 Exclusion criteria for the submission of ICSRs published in the medical literature 35
VI.C.2.2.4. Suspected adverse reactions related to quality defect or falsified medicinal products 36
VI.C.2.2.5. Suspected transmission via a medicinal product of an infectious agent 36
VI.C.2.2.6. Emerging safety issues 37
VI.C.2.2.7. Period between the submission of the marketing authorisation application and the granting of the marketing authorisation 38
VI.C.2.2.8. Period after suspension, revocation or withdrawal of marketing authorisation 38
VI.C.2.2.9. Period during a public health emergency 38
VI.C.2.2.10. Reports from class action lawsuits 38
VI.C.2.2.11. Reports from patient support programmes and market research programmes 39
VI.C.2.2.12. Reporting of off-label use 39
VI.C.3. Submission time frames of ICSRs in EU 40
VI.C.4. Submission modalities of ICSRs in EU 41
VI.C.5. Collaboration with the World Health Organization and the European Monitoring Centre for Drugs and Drug Addiction 42
VI.C.6. Electronic exchange of safety information in the EU 43
VI.C.6.1. Applicable guidelines, definitions, international formats, standards and terminologies 43
VI.C.6.2. Electronic submission of individual case safety reports 44
VI.C.6.2.1. EudraVigilance Database Modules 44
VI.C.6.2.1.1. Adverse reaction data collected in the EudraVigilance Post-Authorisation Module 44
VI.C.6.2.1.2. Adverse reaction data collected in the EudraVigilance Clinical Trial Module 45
VI.C.6.2.2. Preparation of individual case safety reports 46
VI.C.6.2.2.1. General principles 46
VI.C.6.2.2.2. Information on suspect, interacting and concomitant medicinal products 47
VI.C.6.2.2.3. Suspected adverse reactions 53
VI.C.6.2.2.4. Case narrative, comments and causality assessment 55
VI.C.6.2.2.5. Test results 57
VI.C.6.2.2.6. Supplementary records/information 58
VI.C.6.2.2.7. Follow-up information 58
VI.C.6.2.2.8. Amendment of cases 60
VI.C.6.2.2.9. Nullification of cases 62
VI.C.6.2.2.10. Data protection laws 63
VI.C.6.2.2.11. Handling of languages 64
VI.C.6.2.3. Special situations 65
VI.C.6.2.3.1. Use of a medicinal product during pregnancy or breastfeeding 65
VI.C.6.2.3.2. Suspected adverse reaction reports published in the medical literature 67

VI.C.6.2.3.3. Suspected adverse reactions related to overdose, abuse, off-label use, misuse, medication error or occupational exposure 68
VI.C.6.2.3.4. Lack of therapeutic efficacy 70
VI.C.6.2.3.5. Suspected adverse reactions related to quality defect or falsified medicinal products 71
VI.C.6.2.3.6. Suspected transmission via a medicinal product of an infectious agent 74
VI.C.6.2.3.7. Reports of suspected adverse reactions originating from organised data collection systems and other systems 75
VI.C.6.2.3.8. Receipt of missing minimum information 77
VI.C.6.2.4. Data quality of individual case safety reports transmitted electronically and duplicate management 78
VI.C.6.2.5. Electronic re-transmission of ICSRs between multiple senders and receivers 80
VI.C.6.2.6. Electronic submission of ICSRs through the headquarter of a marketing authorisation holder 81
VI.C.6.3. Electronic submission of information on medicinal products 81

VI. Appendix 1 Process for follow-up of ICSRs 82

VI.App.1.1. Follow-up of ICSRs by competent authorities in Member States and marketing authorisation holders 82
VI.App.1.2. Follow-up of ICSRs by competent authorities in Member States with involvement of marketing authorisation holders 88

VI. Appendix 2 Detailed guidance on the monitoring of the medical literature 93

VI.App.2.1. When to start and stop searching in the medical literature 93
VI.App.2.2. Where to look 93
VI.App.2.3. Database Searches 94
VI.App.2.3.1. Precision and recall 94
VI.App.2.3.2. Search construction 94
VI.App.2.3.3. Selection of product terms 94
VI.App.2.3.4. Selection of search terms 95
VI.App.2.3.5. Limits to a search 95
VI.App.2.4. Record keeping 96
VI.App.2.5. Outputs 96
VI.App.2.6. Review and selection of articles 96
VI.App.2.7. Day zero 97
VI.App.2.8. Duplicates 97
VI.App.2.9. Contracting out literature search services 97
VI.App.2.10. Electronic submission of copies of articles on suspected adverse reactions published in the medical literature 97
VI.App.2.11. Examples for the submission as ICSRs of suspected adverse reactions described in the medical literature and referring to more than one patient 99

VI. Appendix 3 Modalities for the submission of ICSRs in EU 102

VI.App.3.1. Modalities applicable to competent authorities in Member States and to marketing authorisation holders 102
VI.App.3.2. Requirements applicable to marketing authorisation holders 107
VI.App.3.3. Requirements applicable to competent authorities in Member States 107
VI.App.3.4. Rerouting to competent authorities in Member States of ICSRs submitted to EudraVigilance by marketing authorisation holders 108

VI. Appendix 4 Submission of ICSRs to the World Health Organization (WHO) 114

VI. Appendix 5 Nullification of cases 119

VI. Appendix 6 Data quality monitoring of ICSRs transmitted electronically 123

VI. Appendix 7 Duplicate detection and management of ICSRs 127

VI.App.7.1. Duplicate detection in EudraVigilance – Collaboration between the Agency, competent authorities in Member States and marketing authorisation holders - Duplicate ICSRs submitted to EudraVigilance by the same sender and identified by the Agency 127

VI.App.7.2. Duplicate detection in EudraVigilance – Collaboration between the Agency, competent authorities in Member States and marketing authorisation holders– Duplicate ICSRs submitted to EudraVigilance by different senders and identified by the Agency..... 130

VI.App.7.3. Duplicate detection in EudraVigilance – Collaboration between the Agency, competent authorities in Member States and marketing authorisation holders – Duplicate ICSRs submitted to EudraVigilance by the same sender and identified by the sender organisation prior to the detection by the Agency 135

VI.App.7.4. Duplicate detection in EudraVigilance – Collaboration between the Agency, competent authorities in Member States and marketing authorisation holders - Duplicate ICSRs submitted to EudraVigilance by different senders and identified by an organisation prior to the detection by the Agency..... 138

VI.App.7.5. Duplicate detection in EudraVigilance – Collaboration between the Agency, competent authorities in Member States and marketing authorisation holders – Duplicate ICSRs identified as part of signal management as outlined in GVP Module IX..... 142

VI.A. Introduction

This Module of GVP addresses the legal requirements detailed in Directive 2001/83/EC [DIR] and 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 submission of individual reports of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in the European Union (EU).

Section VI.B. of this Module highlights the general principles, based on the pharmacovigilance guidelines E2A, E2B and E2D of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (see GVP Annex IV), in relation to the collection, recording and submission of individual reports of suspected adverse reactions associated with medicinal products for human use. The definitions and guidance provided in Section VI.A. and the EU specific requirements presented in Section VI.C. should be followed.

All applicable legal requirements 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".

The guidance provided in this Module does not address the collection, management and submission of individual reports of events or patterns of use, which do not result in suspected adverse reactions (e.g. asymptomatic overdose, abuse, misuse or medication error) and which are not required to be submitted as individual case safety reports (ICSRs). 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. With regard to this, the guidance provided in GVP Module VII applies.

VI.A.1. 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 ICH-E2A and ICH-E2D (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.1.1. Adverse reaction, causality

Adverse reaction: A response to a medicinal product which is noxious and unintended [DIR Art 1 (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.

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[1]. 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 or consumers

[1] An adverse event is defined in ICH-E2D (see GVP Annex IV) as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

are considered suspected adverse reactions, since they convey the suspicions of the primary sources[2], unless the reporters specifically state that they believe the events to be unrelated or that a causal relationship can be excluded.

VI.A.1.2. Overdose, off-label use, misuse, abuse, occupational exposure, medication error, falsified medicinal product

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.

Off-label use: This relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation.

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

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)].

Occupational exposure: This refers to the exposure to a medicinal product (see definition in VI.A.1.3.), 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[3].

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
- 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.1.3. Active substance, excipient, medicinal product

Active substance: 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: Any constituent of a medicinal product other than the active substance and the packaging material [DIR Art 1(3b)]; E.g. colouring matter, preservatives, adjuvant, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances [DIR Annex I].

[2] See VI.A.1.4. for definition of primary source.
[3] From: Good practice guide on recording, coding, reporting and assessment of medication errors (EMA/762563/2014); EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ Medication errors.

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)].

VI.A.1.4. Primary source, healthcare professional, consumer

In accordance with ICH-E2B, the primary source of the information is the person who reports the facts about an ICSR. Several primary sources, such as healthcare professionals and/or consumers, may provide information on the same case. In this situation, all the primary sources' details, including the qualifications, should be provided in the ICSR and the "Primary source(s)" section should be repeated as necessary in line with ICH-E2B (see VI.B.2. for ICSRs validation based on the primary source identifiability).

In accordance 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.

The "Primary Source for Regulatory Purposes" is defined in ICH-E2B(R3)[4] and is not applicable for the electronic submission of ICSRs under the ICH-E2B(R2) format. This data element refers to the person who first reported the facts. In case of multiple primary sources from different countries, this data element identifies the country for the ICH-E2B data element "worldwide unique case identification number".

Where the patient experienced a suspected adverse reaction in another country than the one of the primary source, this information should be captured in the ICH-E2B data element "Identification of the Country Where the Reaction / Event Occurred", e.g. a male patient from Ireland is reporting experiencing an anaphylactic reaction with drug X while travelling in Spain, in this instance the primary source country is Ireland and the occurrence country is Spain. Guidance about the automatic rerouting of the ICSR to the competent authority of the EU Member State where the reaction occurred is provided in VI.C.4..

VI.A.1.5. Medical confirmation

A consumer may provide medical documentations (e.g. laboratory or other test data) that support the occurrence of a suspected adverse reaction and which indicate that an identifiable healthcare professional suspects a causal relationship between a medicinal product and the reported adverse reaction. Similarly, a report may be notified by a medically qualified patient, friend, relative or carer of the patient. In these situations, the reported information is considered medically confirmed.

In the same way, where one or more suspected adverse reactions initially reported by a consumer are subsequently confirmed by a healthcare professional, the ICSR should be considered medically

[4] ICH Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) E2B(R3) Data Elements and Message Specification; accessible at http://estri.ich.org/e2br3/index.htm.

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.1.6. 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. For example, life-threatening refers to a reaction in which the patient was at risk 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 serious. 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 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 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 Agency website[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 suspected adverse reaction in accordance with ICH-E2B(R3), depending on the ICH-E2B format used for the ICSR electronic submission.

VI.A.1.7. Individual case safety report (ICSR)

This refers to the format and content for the submission of an individual report of 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 (see VI.B.2. for ICSRs validation).

VI.A.1.8 nullFlavors

The nullFlavors are a collection of codes specifying why a valid value is not present in an ICSR. They are available with the ICH-E2B(R3) format and not with ICH-E2B(R2). They refer to instances, where for example a proper value is applicable, but not known (e.g. age of the patient is unknown: code UNK), or where the information is available to a sender of an ICSR but it is masked because it cannot be provided due to security, privacy or other reasons (e.g. date of birth of the patient cannot be shared due to local data protection laws: code MSK). ICH-E2B(R3) uses the nullFlavor code sets from the HL7 Messaging Standard primarily to classify the set of source data situations that may give rise to

[5] Examples are provided in section II.B of ICH-E2A (see GVP Annex IV).
[6] EMA website: Home/Human regulatory/Post-authorisation/Pharmacovigilance/EudraVigilance/System overview.

a missing value. For examples how a nullFlavors can be used to code values in the ICSR, refer to the ICH Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) E2B(R3) Data Elements and Message Specification[7]. Additional EU guidance on the use of the nullFlavor in some specific situations is also provided in the EU Individual Case Safety Report (ICSR) Implementation Guide[8].

[7] Accessible at: http://estri.ich.org/e2br3/index.htm.
[8] Ref. EMA/51938/2013; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Electronic reporting.

VI.B. Structures and processes

VI.B.1. Collection of individual safety reports

Competent authorities and marketing authorisation holders should take appropriate measures 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.6.2.2.10. for guidance on the processing of personal data in the EU).

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

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. It does not derive from a study or any organised data collection systems, as defined in VI.B.1.2.. With regard to this, the following situations should also be considered as spontaneous reports:

- stimulated reporting that occurs consequent to a direct healthcare professional communication (see GVP Module XV), publication in the press, questioning of healthcare professionals by company representatives, communication from patients' organisations to their members, or class action lawsuit;
- unsolicited consumer adverse reactions reports irrespective of any subsequent "medical confirmation;
- reports of suspected adverse reactions, which are not related to any organised data collection systems and (i) which are notified through medical enquiry/product information services or (ii) which are consequent of the distribution of information or educational materials;
- unsolicited reports of suspected adverse reactions collected from the internet or digital media (see VI.B.1.1.4. for guidance on ICSRs management from the internet or digital media);

- an individual case notified by different reporters, and at least one notification is done spontaneously;
- reports of suspected adverse reactions from non-interventional post-authorisation studies related to specified adverse events for which the protocol does not require their systematic collection (see VI.C.1.2.1.1. for EU guidance on this type of non-interventional post-authorisation studies, and VI.6.2.3.7 Subsection 2 for EU guidance on the electronic submission of these ICSRs);
- reports of suspected adverse reactions from compassionate use or named patient use conducted in countries where the systematic collection of adverse events in these programmes is not required (see VI.C.1.2.2. for EU guidance on compassionate use or named patient use, and VI.6.2.3.7 Subsection 2 for EU guidance on the electronic submission of these ICSRs).

The modalities for the submission of spontaneous reports of suspected adverse reactions and the applicable time frames are described in VI.B.7. and VI.B.8..

VI.B.1.1.2. Literature reports

The 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 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.

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 for literature review by the concerned marketing authorisation holder(s).

Valid ICSRs should be submitted in accordance with the time frames and modalities detailed in VI.B.7. and VI.B.8..

One case should be created for each single identifiable patient in line with the characteristics provided in VI.B.2.. Relevant medical information should be recorded and the first publication author (or the corresponding author, if designated) should be considered as the primary source of information. Details about the co-authors do not need to be documented among the primary sources of information.

EU requirements, concerning the active substances and the scientific and medical publications not monitored by the Agency and for which valid ICSRs shall be submitted to the EudraVigilance database by marketing authorisation holders, are provided in VI.C.2.2.3.1.. Exclusion criteria in relation to the submission in the EU of ICSRs published in the literature are also detailed in VI.C.2.2.3.2..

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

VI.B.1.1.3. Reports from non-medical sources

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 managed as a spontaneous report. Every attempt should be made to follow-up the case to obtain the minimum information that constitutes a valid ICSR. With regard to the submission of those ICSRs, the same modalities and time frames should be applied as for other spontaneous reports.

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

In line with ICH-E2D (see GVP Annex IV), marketing authorisation holders should regularly screen the internet or digital media[10] under their management or responsibility, for potential reports of suspected adverse reactions. With respect to this, a digital medium 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 submitted to the competent authorities within the appropriate regulatory submission time frames 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. for marketing authorisation holders' responsibilities in the EU on spontaneous reports).

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 submission as ICSR.

Unsolicited cases of suspected adverse reactions from the internet or digital media should be handled as spontaneous reports. The same submission time frames as for spontaneous reports should be applied (see VI.B.7.1. for ICSRs time frames submission).

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 based on the information available e.g. an email address under a valid format has been provided (see VI.B.2. for ICSRs 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 professionals, 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:

- reports of suspected adverse reactions from non-interventional post-authorisation studies related to specified adverse events for which the protocol does not require their systematic collection (see

[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.

VI.C.1.2.1.1. for EU guidance on this type of non-interventional post-authorisation studies, and VI.6.2.3.7 Subsection 2 for EU guidance on the electronic submission of these ICSRs),

- reports of suspected adverse reactions from compassionate use or named patient use conducted in countries where the systematic collection of adverse events in these programmes is not required (see VI.C.1.2.2. for EU guidance on compassionate use or named patient use, and VI.6.2.3.7 Subsection 2 for EU guidance on the electronic submission of these ICSRs).

With regard to the submission as ICSRs, solicited reports should be classified as study reports. They should have an appropriate causality assessment to consider whether they refer to suspected adverse reactions and therefore meet the minimum validation criteria (see VI.B.2. for ICSRs validation). Valid ICSRs should be submitted in line with the time frames and modalities detailed in VI.B.7. and VI.B.8..

General principles concerning the management of reports of 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 by marketing authorisation holders in the EU is provided in VI.C.2.2.2..

VI.B.2. Validation of reports

Only valid ICSRs qualify for submission. In accordance with ICH-E2D (see GVP Annex IV), all reports of suspected adverse reactions should be validated before submitting them to the competent authorities to make sure that the minimum criteria are included in the reports.

Four minimum criteria are required for ICSRs validation:

a. **one or more identifiable reporter** (see VI.A.1.4. for primary source definition), characterised by parameters such as qualification (e.g. physician, pharmacist, other healthcare professional, lawyer, consumer or other non-healthcare professional), name, initials, or address (e.g. reporter's organisation, department, street, city, state or province, postcode, country, email, phone number). Local data protection laws might apply.

In line with ICH-E2D, the term 'identifiable' indicates that the organisation notified about the case has sufficient evidence of the existence of the person who reports the facts based on the available information. In addition, in accordance with ICH E2B, an ICSR is not valid for submission unless information concerning the qualification and the country is available for at least one reporter. Thus, an ICSR is valid if the rules from ICH-E2D regarding the reporter's identifiability and from ICH-E2B regarding the reporter's qualification and country are fulfilled for at least one reporter.

If information on the reporter's qualification is missing, the notification should be considered by default as a consumer report. If information on the reporter's country is not available, the country where the notification was received or where the review took place should be used in the ICSR.

Whenever possible, contact details for the reporter should be recorded to facilitate follow-up activities. However, if the reporter does not wish to provide contact information, the ICSR should still be considered valid as long as the notified organisation is able to confirm the case directly with the reporter.

To enable duplicate detection activities, all parties providing case information or approached for case information should be recorded in the ICSR (not only the initial reporter).

When the information is based on second-hand or hearsay, the report should be considered non-valid until it can be verified directly with the patient, the patient's healthcare professional or a reporter who had direct contact with the patient.

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

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

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

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

c. **one or more suspected substance/medicinal product** (see VI.A.1.3. for definition). Interacting substances or medicinal products should also be considered suspected.

d. **one or more suspected adverse reaction** (see VI.A.1.1. for definition). 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 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 validation is incomplete (there is no suspected adverse reaction).

The report also does not qualify as a valid ICSR if it is reported that the patient experienced an unspecified adverse reaction and there is no information on the type of adverse reaction.

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 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 the valid ICSR should be submitted.

The lack of any of the four elements means that the case is considered incomplete and does not qualify for submission as ICSR. 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 be recorded within the pharmacovigilance system for use in on-going safety evaluation activities.

When the missing information has been obtained (including for example when the medicinal product causal relationship with the reported adverse event is no longer excluded), the ICSR becomes valid for submission and the EU guidance provided in VI.C.6.2.3.8. should be followed.

Further guidance is available in VI.C.6.2.2.10. for the electronic submission in the EU 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 valid report should still be submitted as ICSR. All the relevant information necessary for the detection of the duplicate case should be included in the ICSR. EU guidance on the electronic submission 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 notified by a consumer cannot be downgraded to a report of non-related adverse event if a contacted healthcare professional (nominated by the consumer for follow-up information) subsequently disagrees with the consumer's suspicion (see VI.A.1.1. for causality definition). In this situation, the opinions of both the consumer and the healthcare professional should be detailed in the narrative section of the ICSR. This information can also be submitted in a structured manner in ICH-E2B format, which provides the means to transmit the degree of suspected relatedness expressed by several primary sources for each reported drug event combination.

Similarly, a solicited report of suspected adverse reaction should not be downgraded to a report of non-related adverse event, when the notified recipient (competent authority or marketing authorisation holder) disagrees with the reasonable possibility of causal relationship expressed by the primary source on the supplied medicinal product. The opinions of both, the primary source and the recipient, should be recorded in the narrative section of the ICSR or in structured manner in line with ICH-E2B.

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

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 (see VI.B.6.1. for guidance on the management of pregnancy reports), 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 criteria for reports validation (see VI.B.2. for ICSRs validation). Any attempt to obtain follow-up information should be documented.

The provision in ICSRs of information on the patient's age is important in order to be able to identify safety issues occurring specifically in the paediatric or elderly population. Reasonable efforts should be made to follow-up on ICSRs where information on the patient's age or age group is initially not reported by the primary source (see VI.B.6.2. for guidance on paediatric or elderly population).

Similarly, for suspected adverse reactions related to biological medicinal products, the definite identification of the concerned products with regard to their manufacturing is of particular importance. Therefore, all appropriate measures should be taken to clearly identify the names of the products and their batch numbers. With respect to this, it is recommended to specify in the case narrative if information on the batch number has been requested, when it is missing in the initially submitted ICSR. The business process map and a process description in VI.App.1.1. take into account the mandatory follow-up in the EU of information for the identification of suspected biological medicinal products.

For cases related to vaccines, GVP Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases and GVP Product- or Population-Specific Considerations II: Biological medicinal products should also be followed as appropriate.

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.

When information is received directly from a consumer suggesting that an adverse reaction may have occurred, and if the information is incomplete, attempts should be made to follow-up with the consumer to obtain consent to contact a nominated healthcare professional to obtain further information. When the case is subsequently confirmed totally or partially by a healthcare professional, the medical confirmation should be captured in the ICSR in line with ICH-E2B (see VI.A.1.4. for healthcare professionals' definition, and VI.A.1.5. for ICSRs medical confirmation).

For some cases, it may not always be possible to perform follow-up activities taking into account that the reporter information may have been anonymised in accordance with local legal requirements or due to provisions that allow for anonymous reporting (see VI.C.6.2.2.10. for guidance on the processing of personal data in the EU), for example in case of medication error with harm and the reporter does not wish to disclose an identity. These cases should be considered valid for submission as ICSRs, providing that the notified organisation was able to confirm them directly with the primary sources and that the other minimum criteria for reports validation are satisfied (see VI.B.2. for ICSRs validation).

Further EU guidance on follow-up activities applicable to competent authorities in Member States and to marketing authorisation holders is provided respectively in VI.C.2.1. and VI.C.2.2. with business process maps and process descriptions included in VI.App.1.1. and VI.Ap.1.2.. Guidance on the electronic submission in the EU of follow-up reports is available in VI.C.6.2.2.7..

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 applicable data 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 regard 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 protection laws (see VI.C.6.2.2.10. for guidance on the processing of personal data in the EU).

To ensure pharmacovigilance data security and confidentiality, strict control measures should be in place to provide access to documents and to databases only to authorised personnel. This security measure should be extended to the complete data path. With regard to this, 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 set up 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.

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 submission. The reports should include the verbatim text as used by the primary source or an accurate translation of it (see VI.C.6.2.2.11. for EU guidance on languages management in ICSRs). The original verbatim text should be coded using the appropriate terminology as described in VI.B.8.. 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. for EU guidance on duplicate management).

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 submission and case archiving (see VI.C.6.2.4. and GVP Module I for EU guidance on data quality of ICSRs).

Correct data entry, including the appropriate use of terminologies (see VI.B.8. for ICSRs content and format), should be quality controlled, 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. With regard to this, the source data (e.g. letters, emails, records of telephone calls, which include details of an event) or an image of the source data should be easily accessible. The whole process should be monitored by quality assurance audits.

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 appropriate standards and terminologies (see VI.B.8. for ICSRs content and format), and their proficiency confirmed (see VI.C.6.2.4. for EU guidance on training of personnel for pharmacovigilance). Other personnel who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be trained in adverse events/reactions collection and submission to the pharmacovigilance department 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 and/or if the suspected medicinal product was taken by the father), should be followed-up in order to collect information on the outcome of the pregnancy and the development of the child after birth. The guidance provided in the Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-Authorisation Data and (see GVP Annex III)

and in GVP Product- or Population-Specific Considerations III. should be considered as regards the monitoring, collection and submission 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 through the mother and/or the father 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 on the 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 (see VI.B.3. for follow-up guidance).

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 reactions 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 submitted in accordance with the requirements outlined in VI.B.7. and in line with the guidance provided in VI.C.6.2.3.1. for the electronic submission of those ICSRs in the EU.

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.

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 submitted as ICSRs since there is no suspected adverse reaction (see VI.B.2. for ICSR validation). These reports should however be collected and discussed in the periodic safety update reports (see GVP Module VII and VI.C.6.2.3.1. Subsection c for the management of the individual reports in the EU).

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

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 guidance presented in GVP Module IX.

b. Breastfeeding

The guidance provided in GVP Product- or Population-Specific Considerations 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 submitted in accordance with the criteria outlined in VI.B.7. and in line with the guidance provided in VI.C.6.2.3.1. for the electronic submission of those ICSRs in the EU.

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.

Guidance provided in GVP Product- or Population-Specific Considerations IV. on the conduct of pharmacovigilance for medicines used in the paediatric population, and in GVP Product- or Population-Specific Considerations V. on the conduct of pharmacovigilance for medicines used in the geriatric population should be followed.

VI.B.6.3. Reports of overdose, abuse, misuse, medication error or occupational exposure

The definitions for overdose, abuse, misuse, medication error or occupational exposure provided in VI.A.1.2. should be applied.

Reports with no associated suspected adverse reaction should not be submitted as ICSRs. They should be recorded when becoming aware of them and considered in the periodic safety update reports as applicable (see GVP Module VII). When those reports constitute safety issues impacting on the risk-benefit balance of medicinal products authorised in the EU, they should be notified to the competent authorities in Member States and to the Agency in accordance with the guidance provided in VI.C.2.2.6..

Reports associated with suspected adverse reactions should be subject to submission in accordance with the modalities outlined in VI.B.7. and with the electronic submission requirements in the EU 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 regard to the symptoms, 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[12], should be followed.

Guidance is available in VI.C.2.2.12. with regard to the management in the EU of reported information on the off-label use of medicinal products.

VI.B.6.4. Lack of therapeutic efficacy

Reports of lack of therapeutic efficacy should be collected and recorded when notified and followed-up if incomplete. They should normally not be submitted as ICSRs if there is no associated suspected adverse reaction, but they should be discussed in periodic safety update reports as applicable (see GVP Module VII).

In certain circumstances, reports of lack of therapeutic efficacy with no suspected adverse reactions may require to be submitted within a 15-day time frame (see VI.C.6.2.3.4. for EU guidance on the management of these ICSRs). Medicinal products used in critical conditions or for the treatment of life-

[12] Ref.: EMA/762563/2014; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ Medication errors.

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 specific reports of lack of efficacy does not apply when the notification occurred in the frame of a non-interventional post-authorisation efficacy study. This is because they refer to the main end point of the study. EU guidance provided in VI.C.1.2.1. for non-interventional post-authorisation studies should be followed regarding the management of adverse events occurring in those efficacy studies.

Clinical judgement should be used when considering if cases of lack of therapeutic efficacy qualify for submission as ICSRs. 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 submitted. However, a report of lack of therapeutic efficacy for a life-threatening infection, which appears to be due to the development of a newly resistant strain of a bacterium previously regarded as susceptible, should be submitted as ICSR within 15 days.

For vaccines, cases of lack of prophylactic efficacy should be 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 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[13], may be followed.

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

Only valid ICSRs (see VI.B.2. for ICSRs validation) should be submitted. The clock for the submission of a valid ICSR starts as soon as the information containing the minimum 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 notified competent authority or marketing authorisation holder gets knowledge of a valid ICSR, irrespective of whether the information is received during a weekend or public holiday. The timelines for submission 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 submission of valid ICSRs within the appropriate time frames. These procedures should in particular specify the processes for the exchange of safety information, including the timelines and responsibilities for the regulatory submission of valid ICSRs. They should be organised in order to avoid the submission of duplicate ICSRs to the competent authorities.

For ICSRs described in the medical literature (see VI.B.1.1.2. for guidance on the management of medical literature reports), the clock starts (day zero) with awareness of a publication containing the minimum criteria (see VI.B.2. for ICSRs validation, and VI.App.2.7. for guidance on day zero estimation for medical literature reports). Where contractual arrangements are made with a person/organisation to perform literature searches and/or submit valid ICSRs, detailed agreements

[13] 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/.

should exist to ensure that the marketing authorisation holder can comply with its regulatory submission obligations.

When additional significant information is received for a previously submitted case, the clock 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 submission of ICSRs, 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. regarding the distinction between significant and non-significant follow-up information for the submission of ICSRs in the EU.

VI.B.7.1. Submission time frames of ICSRs

In general, the submission 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 sent as serious becomes non-serious based on new follow-up information, this information should still be submitted within 15 days; the submission time frame for non-serious reports should then be applied for the subsequent follow-up reports.

Information as regards the submission 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 EU 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. EU guidance on ICSRs nullification in line with ICH-E2B is provided in VI.C.6.2.2.9..

VI.B.7.3. Report amendment

There may be instances, where an ICSR which has already been submitted 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 documentations mentioned in an ICSR, translations or literature articles are requested by competent authorities and are further sent as attachments in line with ICH E2B(R3).These submissions are considered as amendment reports. Further EU guidance on the amendment of ICSRs in line with ICH-E2B is provided in VI.C.6.2.2.8..

VI.B.8. Modalities for submission of individual case safety reports (ICSRs)

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.

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

- the ICH M1 Terminology - Medical Dictionary for Regulatory Activities (MedDRA), which should be used at the lowest level term (LLT) level in the ICSRs. Stakeholders should follow the recommendations of the MedDRA Maintenance Support Service Organisation (MSSO) regarding the switch to a new MedDRA version[14];
- the latest version of the Guide for MedDRA Users MedDRA Term Selection: Points to Consider[15];
- the guidelines applicable for the ICH-E2B formats:

Reference	Guidelines
ICH-E2B(R2)	• ICH-M2 EWG - Electronic Transmission of Individual Case Safety Reports Message Specification; • ICH-E2B(R2) - Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports.
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; • ICH-E2B(R3) Implementation Working Group - Electronic Transmission of Individual Case Safety Reports (ICSRs) - Questions & Answers.

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

EU specific modalities for ICSRs submission and the applicable guidelines, definitions, formats, standards and terminologies are provided respectively in VI.C.4. and VI.C.6.1..

[14] The latest supported MedDRA versions in line with the official semi-annual releases are posted on the EudraVigilance webpage (EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ System overview).
[15] For off-label, misuse, abuse and medication error, the definitions provided in VI.A.1.2. should be followed.

VI.C. Operation of the EU network

Section VI.C of this Module highlights the EU specific requirements, as defined in Directive 2001/83/EC [DIR] and Regulation (EC) No 726/2004 [REG] in relation to the collection, management and submission of reports of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in the EU, irrespective of the products conditions of use within or outside the terms of the marketing authorisation in the EU. These requirements are applicable to competent authorities in Member States and/or to marketing authorisation holders in the EU.

The definitions and general principles detailed in Sections VI.A. and VI.B. should be applied in conjunction with the guidance provided in this Section. The requirements provided in Chapters IV, V and IX of the Commission Implementing Regulation (EU) No 520/2012 [IR] on the use of terminology, formats and standards, on the submission of reports of suspected adverse reactions, and on the processing of personal data shall also be followed.

In accordance with Article 107 of Directive 2001/83/EC, marketing authorisation holders have to submit in addition to information on adverse reactions that occur in the EU, information on serious suspected adverse reactions that occur in third countries. 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. This is valid irrespective of the strengths, pharmaceutical forms, routes of administration, presentations, authorised indications, or names of the medicinal product (see VI.C.2.2. for detailed requirements applicable to marketing authorisation holders). For the definition of the name and strength of a medicinal product, refer to Article 1(20) and 1(22) of Directive 2001/83/EC.

The guidance provided in this Module also applies to

- homeopathic and herbal medicinal products with the exception of homeopathic medicinal products authorised under the special simplified registration procedure detailed in Article 14 (1) of Directive 2001/83/EC [DIR Art 16 (3) and Art 16g], and 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 the applicable national laws of 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 (see VI.C.1.2.2. for ICSRs management in compassionate use and named patient use).

For devices containing active substances, the procedure to be followed for the submission of individual reports of suspected adverse reactions and/or incidents varies depending if these devices have been authorised in the EU as an integral part of medicinal products (products covered by the second paragraph of Article 1(3) of Directive 93/42/EEC) or CE marked as medical devices. With regard to this, devices authorised as an integral part of medicinal products follow the pharmacovigilance requirements provided in Directive 2001/83/EC and Regulation (EC) No 726/2004, whereas devices CE marked as medical devices follow the requirements for medical device vigilance given in Directive 90/385/EEC and Directive 93/42/EEC. As detailed in the Guidelines on a Medical Devices Vigilance System[16], a medical device incorporating a medicinal product or substance, where the action of the

[16] Ref.: MEDDEV 2.12-1 rev 8 (Ref. Ares(2016)856772 - 18/02/2016).

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.

VI.C.1. Management of individual safety reports for clinical trials, post-authorisation studies, compassionate use and named patient use in the EU

In line with Article 3(3) and 107(1) of Directive 2001/83/EC, the pharmacovigilance rules laid down in Directive 2001/83/EC and Regulation (EC) No 726/2004 do not apply to medicinal products intended for research and development trials conducted in accordance with Directive 2001/20/EC.

In the EU, post-authorisation safety or efficacy studies can be imposed by competent authorities in Member States or the Agency during the evaluation of the initial marketing authorisation application in accordance with Article 21a(b)(f) of Directive 2001/83/EC and Article 9(4)(cb)(cc) of Regulation (EC) No 726/2004, or they can be requested during the post-authorisation phase in line with Article 22a(1)(a)(b) of Directive 2001/83/EC and Article 10a(1)(a)(b) of Regulation (EC) No 726/2004. They can also be conducted voluntarily by the marketing authorisation holders.

As shown in Figure VI.1., post-authorisation studies can either be clinical trials or non-interventional post-authorisation studies and the management of individual safety reports 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.

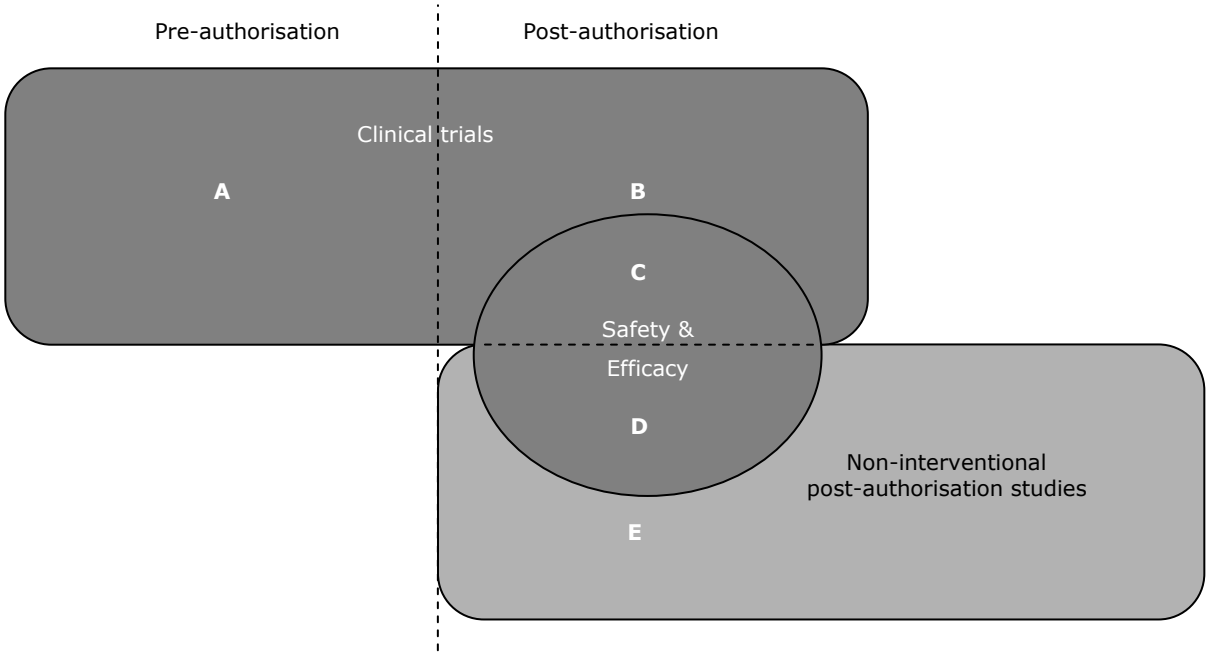
Reports of suspected adverse reactions should not be submitted under both legislations that are Directive 2001/20/EC as well as Regulation (EC) No 726/2004 and Directive 2001/83/EC since this creates duplicate reports.

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

Figure VI.1. illustrates the different types of clinical trials and post-authorisation studies which can be conducted in the EU. The management of individual safety reports for clinical trials designated by sections A, B, and C follows the requirements of Directive 2001/20/EC, whereas individual safety reports for non-interventional post-authorisation studies corresponding to section D and E follows the requirements of Directive 2001/83/EC and Regulation (EC) No 726/2004.

The rules for the submission of valid ICSRs to the appropriate EudraVigilance database modules depend on the types of organised collection systems where the suspected adverse reactions occurred and the guidance provided in VI.C.6.2.1. should be followed.

Figure VI.1. Different types of clinical trials and studies conducted in the EU



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

Section B: Post-authorisation clinical trials conducted by marketing authorisation holders or other organisations, and which fall under the scope of Directive 2001/20/EC due to the nature of the intervention, e.g. for the development of new indications or new formulations.

Section C: Post-authorisation safety or efficacy clinical trials imposed in accordance with Article 21a(b)(f) of Directive 2001/83/EC and Article 9(4)(cb)(cc) of Regulation (EC) No 726/2004, requested in accordance with Article 22a(1)(a)(b) of Directive 2001/83/EC and Article 10a(1)(a)(b) of Regulation (EC) No 726/2004, or conducted voluntarily by marketing authorisation holders or other organisations, and which fall under the scope of Directive 2001/20/EC due to the nature of the intervention.

Section D: Non-interventional post-authorisation safety or efficacy studies imposed in accordance with Article 21a(b)(f) of Directive 2001/83/EC and Article 9(4)(cb)(cc) of Regulation (EC) No 726/2004, requested in accordance with Article 22a(1)(a)(b) of Directive 2001/83/EC and Article 10a(1)(a)(b) of Regulation (EC) No 726/2004, or conducted voluntarily by marketing authorisation holders or other organisations. The assignment of the patient to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice. The prescription of the product in the usual manner in accordance with the terms of the marketing authorisation is clearly separated from the decision to include the patient in the study. The requirements set out in Article 107(3) and 107a(4) of Directive 2001/83/EC and Article 28(1) of Regulation (EC) No 726/2004 apply to studies initiated, managed, or financed by a marketing authorisation holder, or where the design is controlled by a marketing authorisation holder.

Section E: Non-interventional post-authorisation studies conducted voluntarily by marketing authorisation holders or other organisations. The assignment of the patient to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice. The prescription of the product in the usual manner in accordance with the terms of the marketing authorisation is clearly separated from the decision to include the patient in the study. The requirements set out in Article 107(3) and 107a(4) of Directive 2001/83/EC and Article 28(1) of Regulation (EC) No 726/2004 apply to studies initiated, managed, or financed by a marketing authorisation holder, or where the design is controlled by a marketing authorisation holder.

VI.C.1.1. Management of individual safety reports for clinical trials

A suspected adverse reaction to an investigational medicinal product (IMP) occurring in a clinical trial falls under the scope of Directive 2001/20/EC. It 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 clinical trial imposed in line with Article 21a of Directive 2001/83/EC and Article 9(4) of Regulation (EC) No 726/2004, requested in accordance with Article 22a of Directive 2001/83/EC and

Article 10a of Regulation (EC) No 726/2004, or if it is conducted voluntarily by a marketing authorisation holder.

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 from a clinical trial conducted in accordance with Directive 2001/20/EC is suspected to be related only to a medicinal product other than the IMP and does not result from a possible interaction with the IMP, it should be managed in line with the requirements provided in Art 107(3) and 107a(4) of Directive 2001/83/EC. The same applies when the adverse reaction is suspected to be related only to an authorised non-investigational medicinal product (NIMP)[17]. In this context, 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 ICSRs submission[18]. Where made aware of such case, the competent authority or the marketing authorisation holder should apply the time frames and modalities described in VI.C.3., VI.C.4. and VI.C.6.. The report should be managed, classified and submitted as spontaneous and the guidance detailed in VI.C.6.2.3.7. Subsection 3 should be followed with regard to the electronic submission of ICSRs.

VI.C.1.2. Management of individual safety reports for non-interventional post-authorisation studies, compassionate use and named patient use

This chapter 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 (see ICH-E2D and GVP Annex I for definition) which need to be collected as specified in VI.C.1.2.1. and in VI.C.1.2.2..

In line with ICH-E2D (see GVP Annex IV), these collected adverse events should be systematically assessed to determine whether they are possibly related to the studied (or supplied) medicinal products. A method of causality assessment should be applied for assessing the causal role of the studied (or supplied) medicinal products in the occurrence of the solicited adverse events (for example, the WHO-UMC System for Standardised Case Causality Assessment[19]). An adverse event should be classified as an adverse reaction, if there is at least a reasonable possibility of causal relationship with the product.

Reports of adverse reactions, suspected to be related to the studied (or supplied) medicinal product by the primary source or by the notified organisation, should be classified and submitted in accordance with the guidance provided in VI.C.1.2.1. VI.C.1.2.2. and VI.C.6.2.3.7.. Depending on the seriousness and country of origin of the suspected reaction, the submission time frames and modalities detailed in

[17] For guidance on investigational medicinal products (IMPs) and non-investigational medicinal products (NIMPs), see the Guidance on Investigational Medicinal Products and Non-Investigational Medicinal Products (NIMPs) (Ares(2011)300458 - 18/03/2011).
[18] See Chapter 7.11.3 of 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).
[19] https://www.who-umc.org/.

VI.C.3. and VI.C.4. should be applied. 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 an adverse reaction is suspected to be related to a medicinal product other than the studied (or supplied) medicine and does not result from a possible interaction with it, the report should be managed, classified and submitted as spontaneous ICSR. It should be notified by the primary source (healthcare professional or consumer) 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 ICSRs submission.

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 the local requirements as regards the submission of cases of suspected adverse reactions to the competent authority in the Member State where the reaction occurred. However, where a study conducted by one of these organisations is directly initiated, managed, or financed by a marketing authorisation holder, or where its design is controlled by a marketing authorisation holder (voluntarily or pursuant to obligations imposed in accordance with Article 21a and 22a of Directive 2001/83/EC, or Article 9(4) and 10a of Regulation (EC) No 726/2004), the requirements provided in this Module are applicable[20]. In this context, contractual agreements should be in place to clearly define the role and responsibilities of each party for implementing these requirements (see GVP Module I).

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

Non-interventional post-authorisation studies (see GVP Annex I) should be distinguished between

- studies with a design based on primary data collection directly from healthcare professionals or consumers (i.e. where the events of interest are collected as they occur specifically for the study), and
- studies with a design based on secondary use of data (i.e. where the events of interest have already occurred and have been collected for another purpose).

Depending on the study design, the requirements provided hereafter in VI.C.1.2.1.1. and VI.C.1.2.1.2. apply.

For combined studies with a design based on both primary data collection and secondary use of data, the submission of ICSRs is required exclusively for the data obtained through primary data collection and the guidance provided hereafter in VI.C.1.2.1.1. should be followed. For the events identified through secondary use of data, the guidance in VI.C.1.2.1.2. applies. All adverse events/reactions collected as part of this type of studies should be recorded and summarised in the interim safety analysis and in the final study report.

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

In case of doubt, the management of individual safety reports should be clarified with the concerned competent authority in the Member State.

National legislation should be followed as applicable regarding the obligations towards local ethics committees.

VI.C.1.2.1.1. Non-interventional post-authorisation studies with a design based on primary data collection

Information on all adverse events should be collected and recorded from healthcare professionals or consumers in the course of the study unless the protocol provides with a due justification for not collecting certain adverse events. Any reference to adverse events that are not collected should be made using the appropriate level of the MedDRA classification (see GVP Module VIII).

For all collected adverse events, comprehensive and high quality information should be sought in a manner which allow for valid ICSRs to be submitted within the appropriate time frames. Cases of adverse reactions, which are suspected to be related to the studied medicinal product by the primary source or the notified organisation, should be recorded in the pharmacovigilance database and submitted as ICSRs in accordance with the time frames and modalities provided in VI.C.3. and VI.C.4.. They should be classified as solicited reports (see summary in Table VI.1., and VI.6.2.3.7 Subsection 1 for guidance on the electronic submission of these ICSRs).

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 submission 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 rationale for not submitting as ICSRs certain adverse reactions with fatal outcome should be clearly described in the protocol together with a list using the appropriate level of the MedDRA classification (see GVP Module VIII).

All adverse events collected during the study should be summarised in the interim safety analysis and in the final study report.

For adverse events specified in the study protocol which are not systematically collected, 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 authority via the national spontaneous reporting system (see summary in Table VI.1.).The resulting valid ICSRs should be managed, classified and submitted as spontaneous by the notified competent authority or marketing authorisation holder (see VI.6.2.3.7 Subsection 2 for guidance on the electronic submission of these ICSRs). Where made aware of them, these reports should also be summarised in the relevant study reports by the marketing authorisation holder sponsoring the study.

Table VI.1. Management of adverse events for non-interventional post-authorisation studies with a design based on primary data collection

For collected adverse events, including all adverse events with fatal outcome	
Requirements for adverse events	• Collect and record comprehensive and high quality information. • Perform causality assessment. • Summarise all collected adverse events in the interim safety analysis and in the final study report.
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 notified organisation should be recorded in the pharmacovigilance database. • Valid ICSRs should be managed classified and submitted as solicited in line with the appropriate time frames. • In certain circumstances, suspected adverse reactions with fatal outcome may not be subject to submission as ICSRs. A justification should always be provided in the protocol.
For adverse events not collected, as specified in the study protocol	
Requirements for suspected adverse reactions	• Inform healthcare professionals and consumers of the possibility to report suspected adverse reactions to the marketing authorisation holder or to the concerned competent authority via the national spontaneous reporting system. • Valid ICSRs should be managed, classified and submitted as spontaneous in line with the appropriate time frames. • When made aware of them, these ICSRs should also be summarised in the relevant study reports by the marketing authorisation holder sponsoring the study.

VI.C.1.2.1.2. Non-interventional post-authorisation studies with a design based on secondary use of data

The design of such studies is characterised by 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 submission of suspected adverse reactions in the form of ICSRs is not required. All adverse events/reactions collected for the study should be recorded and summarised in the interim safety analysis and in the final study report unless the protocol provides for different reporting with a due justification (see GVP Module VIII).

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

The guidance provided in this Module applies 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 the applicable national laws in 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[21] 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 (or in countries outside the EU) where the active collection of adverse events occurring in these programmes is required, the reports of adverse reactions, suspected to be related to the supplied medicinal product by the primary source or the notified organisation, should be submitted as ICSRs in line with the time frames and modalities provided in VI.C.3. and VI.C.4.. They should be considered as solicited reports (see VI.6.2.3.7 Subsection 1 for guidance on the electronic submission of these ICSRs).
- for compassionate use and named patient use conducted in Member States (or in countries outside the EU) 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 submitted as ICSR in accordance with the time frames and modalities provided in VI.C.3. and VI.C.4.. It should be considered as a spontaneous report of suspected adverse reaction (see VI.6.2.3.7 Subsection 2 for guidance on the electronic submission of these ICSRs).

VI.C.2. Collection of individual safety 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[22] [DIR Art 101(1) and 107a(1)]. In this context, the competent authority in a Member State shall establish procedures for collecting and recording all reports of suspected adverse reactions that occur in its territory [IR Art 15 (2)]. The definitions and general principles detailed in VI.A.1. and Section VI.B., together with the time frames and modalities presented in VI.C.3., VI.C.4. and VI.C.6. should be applied with regard to their submission as ICSRs to the EudraVigilance database .

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 professionals. To this end, the competent authority in a Member State shall facilitate in its 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].

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 have been

[21] E.g. sponsor, applicant, marketing authorisation holder, hospital or wholesaler.
[22] The marketing authorisation holders shall submit ICSRs to EudraVigilance in accordance with the provisions set out in Article 107(3) of Directive 2001/83/EC and further detailed in VI.C.4..

developed by the Member States in collaboration with 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.

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.

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) of Directive 2001/83/EC [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)]. The criteria upon which a marketing authorisation holder may be involved include situations where:

- important additional information is necessary for case evaluation or reconciliation,
- clarifications is needed regarding inconsistent data within ICSRs,
- there is a 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.

In support of the operation of these follow-up procedures, business process maps and process descriptions are provided in VI.App.1.1. and VI.App.1.2.. Further guidance on the follow-up of ICSRs is provided in VI.B.3. and in VI.C.6.2.2.7..

Member States shall ensure that the reports of suspected adverse reactions arising from an error associated with the use of a medicinal product (see VI.A.1.2. for medication error definition) 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 are informed of any suspected adverse reactions brought to the attention of any other authority within that Member State. These reports shall be appropriately identified in the standard web-based structured forms referred to in Article 25 of Regulation (EC) No 726/2004, developed for the reporting of suspected adverse reactions by healthcare professionals and patients [DIR Art 107a(5)]. To facilitate such reporting, it may be necessary to implement data exchange agreements or other arrangements, as appropriate. Further guidance concerning the management and assessment of reports of medication errors is provided in the Good Practice Guide on Recording, Coding, Reporting and Assessment of Medication Errors[23].

Pharmacovigilance data and documents relating to individual authorised medicinal products shall be retained by the national competent authorities in Member States and the Agency 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)] (see VI.C.6.2.4. and GVP Module I for guidance on ICSRs data quality).

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)].

[23] Ref.: EMA/762563/2014; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ Medication errors.

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 in the EU or in third countries 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)].

The marketing authorisation holder shall not refuse to consider reports of suspected adverse reactions received electronically or by any other appropriate means from patients and healthcare professionals [DIR Art 107(2)].

The marketing authorisation holder 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 also collect follow-up information on these reports and submit the updates to the EudraVigilance database [Dir Art 107(4)]. The marketing authorisation holder shall establish mechanisms enabling the traceability and follow-up of adverse reaction reports while complying with the data protection legislation [IR Art 12 (1)]. In support of the operation of the follow-up procedures, business process maps and process descriptions are provided in VI.App.1.1. and VI.App.1.2.. Further guidance on the follow-up of ICSRs is provided in VI.B.3. and in VI.C.6.2.2.7..

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

Pharmacovigilance data and documents relating to individual authorised medicinal products shall be retained by the marketing authorisation holder 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)] (see VI.C.6.2.4. and GVP Module I for guidance on ICSRs data quality).

With regard to the collection and recording of reports of suspected adverse reactions, the marketing authorisation holder responsibilities apply to reports related to medicinal products 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 (see also the introduction to Section VI.C. for the type of medicinal products concerned by EU requirements). 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) [25]. 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 Article 107(1) of Directive 2001/83/EC, the marketing authorisation

[24] EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Access to data.
[25] As outlined in the Commission Communication on the Community Marketing Authorization Procedures for Medicinal Products (Ref.: 98/C 229/03).

holder shall record those reports of suspected adverse reactions and shall ensure that they are accessible at a single point within the EU. The source data or an image should be easily accessible in order to be made available to competent authorities in Member States upon request (see VI.B.5. for guidance on quality management). The clock for the submission (see VI.B.7. for day zero definition) starts when a valid ICSR is first received by one of these companies outside the EU.

In addition to the requirements presented in this chapter, the definitions and general principles detailed in VI.A.1. and Section VI.B., together with the time frames and modalities presented in VI.C.3., VI.C.4. and VI.C.6. should be applied by the marketing authorisation holder to all reports of suspected adverse reactions.

VI.C.2.2.1. Spontaneous reports

The marketing authorisation holder shall record all reports of suspected adverse reactions originating from within or outside the EU, which are brought to its 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, the marketing authorisation holder may consider utilising its 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. for guidance on ICSRs management from the internet or digital media).

VI.C.2.2.2. Solicited reports

In accordance with Article 107(1) of Directive 2001/83/EC, the marketing authorisation holder 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 that organisation[26]. For non-interventional post-authorisation studies, this requirement applies to study designs based on primary data collection and the guidance provided in VI.C.1.2.1.1. should be followed.

For all solicited reports (see VI.B.1.2. for definition), the marketing authorisation holder should have mechanisms in place to record and document complete and comprehensive case information and to evaluate that information, in order to allow the meaningful assessment of individual cases and the submission of valid ICSRs (see VI.B.2. for ICSRs validation) related to the studied (or supplied) medicinal product. The marketing authorisation holder should therefore exercise due diligence in establishing such system, in following-up those reports (see VI.B.3. for follow-up guidance) and in seeking the view of the primary source as regards 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 to perform a causality assessment based on the information available in order to decide whether the report is a valid ICSR, which should be submitted in accordance with the time frames and modalities presented in VI.C.3., VI.C.4. and VI.C.6.. This requirement does not apply to study designs based on secondary use of data since the submission of ICSRs is not required (see VI.C.1.2.1.2. for guidance on this type of studies). 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.

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

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

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

With regard to the screening of the medical literature, the requirements provided in this Module are part of the marketing authorisation holder obligations in relation to (i) the submission of individual cases of suspected adverse reactions, and to (ii) the 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 the medical literature by the European Medicines Agency

In line with Article 27 of Regulation (EC) No 726/2004, the Agency monitors selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances. It publishes a list of active substances being monitored and the medical literature subject to this monitoring. The Agency enters into the EudraVigilance database relevant information from the selected medical literature. The Agency, in consultation with the European Commission, Member States and interested parties, draws up a detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database.

The medical literature and the active substances subject to the monitoring by the Agency are published on a dedicated webpage[27] 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[28], which defines the different steps of the medical literature monitoring (MLM) business processes.

ICSRs resulting from the MLM service performed by the Agency can be accessed from the EudraVigilance database by the marketing authorisation holder concerned. They are also made available for download in XML format. This refers to ICSRs of serious suspected adverse reactions occurring within and outside the EU, and to ICSRs of non-serious suspected adverse reactions from within the EU.

In accordance with Article 107(3) of Directive 2001/83/EC and to avoid the submission of duplicate ICSRs, the marketing authorisation holder shall only submit those ICSRs described in the 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.

VI.C.2.2.3.2 Exclusion criteria for the submission of ICSRs published in the medical literature

The following exclusion criteria for the submission of ICSRs to the EudraVigilance database by a marketing authorisation holder may be applied for cases published in the medical literature:

a. where ownership of the suspected medicinal product by the marketing authorisation holder can be excluded on the basis of the medicinal product name, active substance name, pharmaceutical form, batch number or route of administration;

[27] EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ Medical literature monitoring.
[28] Ref.: EMA/161530/2014; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ Medical literature monitoring.

b. which originates in a country where a company holds a marketing authorisation but has never commercialised the medicinal product;

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

d. which refers to data from publicly available databases (e.g. poison control centres) and where the cases are presented in aggregate tables or line listings. The submission requirement remains for valid cases described individually;

e. which presents the results from post-authorisation studies, meta-analyses, or literature reviews;

f. which describes suspected adverse reactions in a group of patients with a designated medicinal product and the patients cannot be identified individually for creating valid ICSRs (see VI.B.2. for ICSRs validation).

For points d to f, this type of literature aims at identifying or quantifying a safety hazard related to a medicinal product. The main objective 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 the submission of ICSRs 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 guidance provided in VI.C.2.2.6..

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[29] or with a quality defect of a medicinal product, a valid ICSR should be 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.1.6.. The guidance on the electronic submission of ICSRs 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, the marketing authorisation holder 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 the competent authorities in Member States 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

Any suspected transmission of an infectious agent via a medicinal product should be considered as a serious adverse reaction and such cases should be submitted within 15 days in accordance with the requirements outlined in VI.C.4. and the electronic submission guidance detailed in VI.C.6.2.3.6.. If no

[29] See GVP Annex I and EMA webpage on falsified medicines: Home/ Human regulatory/ Overview/ Public health threats/ Falsified medicines.

other criterion is applicable, the seriousness of this ICSR should be considered as important medical event (see VI.A.1.6. for seriousness definition). This also applies to vaccines.

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 authorisation holder should have a system in place to communicate any suspected transmission of an infectious agent via a medicinal product 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 /vaccinated).

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[30]. 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[31], should also be followed as appropriate.

VI.C.2.2.6. Emerging safety issues

Events/observations may occur in relation to an authorised medicinal product, which may have major impacts on the risk-benefit balance of the product and/or on patients or public health. They may require urgent attention of the competent authority and could warrant prompt regulatory action and communication to patients and healthcare professionals. These important new evidences should be considered as emerging safety issues (see GVP Annex I). They should be notified to the competent authorities and the Agency in accordance with the requirements provided in GVP Module IX. This is in addition to the ICSR submission requirements detailed in VI.C.3. and VI.C.4., when the emerging safety issue refers to a single case of suspected adverse reactions (see VI.C.6.2.2.1. for general guidance on ICSRs preparation).

[30] Ref.: EMA/410/01; EMA website: Home/ Human regulatory/ Research and development/ Advanced therapies/ Scientific guidelines.
[31] Ref.: EMEA/149995/2008; EMA website: Home/ Human regulatory/ Post-authorisation/ Advanced therapies/ Pharmacovigilance.

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[32]. 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. for definition) or solicited reports (see VI.B.1.2. for definition), should be submitted in accordance with the time frames and modalities 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 time frames and submission requirements outlined in VI.C.3., VI.C.4. and VI.C.6. remain for valid ICSRs.

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.

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 submission 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 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, the marketing authorisation holder 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 submission time frame for non-serious ICSRs remains unchanged. The request should be made to the Agency's pharmacovigilance department.

[32] See also chapter 1, section 5.1.1 of Volume 2A (Notice to Applicants) of The Rules Governing Medicinal Products in the European Union.

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 professionals, 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. The marketing authorisation holder should have the same mechanisms in place as for all other solicited reports (see VI.C.2.2.2. for marketing authorisation holders responsibilities on solicited reports) to manage that information and to submit, in line with the time frames and modalities outlined in VI.C.3. and VI.C.4., valid cases of adverse reactions which are suspected to be related to the concerned medicinal product.

Valid ICSRs should be submitted as solicited in accordance with the guidance provided in VI.6.2.3.7 Subsection 1.

VI.C.2.2.12. Reporting of off-label use

The off-label use of a medicinal product may occur for various reasons (see definition in VI.A.1.2. and GVP Annex I). Examples include the intentional use of a product in situations other than the ones described in the authorised product information, such as:

- a different indication in term of medical condition;
- a different group of patients;
- a different route or method of administration;
- a different posology.

With regard to the management of individual reports referring to the off-label use of a product, the responsibilities of the marketing authorisation holder can be summarised as follows, depending if the off-label use results in the patient's harm:

a. The off-label use of a medicinal product results in patient's harm with occurrence of a suspected adverse reaction

In line with Article 107(1), 107(3) and 107(4) of Directive 2001/83/EC, the marketing authorisation holder shall collect individual reports of suspected adverse reactions when becoming aware of them. The reports shall be routinely followed-up to ensure that the information is as complete as possible (see VI.C.2.2. for marketing authorisation holders' responsibilities on ICSRs). Valid ICSRs shall be submitted to the EudraVigilance database in accordance with the time frames, and modalities provided in VI.C.3., VI.C.4., and VI.C.6.2.3.3.

Where relevant and appropriate, the benefit-risk analysis evaluation presented in the periodic safety update report should take into account the clinical importance of a risk in relation to the off-label use of the concerned medicinal product (see GVP Module VII).

In line with the guidance provided in GVP Module V, where there is a scientific rationale that an adverse clinical outcome might be associated with the off-label use of the product, the adverse

reaction should be considered a potential risk, and if deemed important, should be included in the list of safety concerns of the risk management plan as an important potential risk. This is particularly relevant, when differences in safety concerns between the target and the off-label population are anticipated. Important potential risks included in the risk management plan would usually require further evaluation as part of the pharmacovigilance plan.

b. The off-label use of a medicinal product does not result in patient's harm and occurrence of a suspected adverse reaction

The potential obligations regarding the collection of data on the off-label use of a medicinal product are set out in Article 23(2) of Directive 2001/83/EC, which requires the marketing authorisation holder to report to competent authorities in Member States any other new information which might influence the evaluation of the benefits and risks of the medicinal product, including data on the use of the product where such use is outside the terms of the marketing authorisation.

Under this condition, the most appropriate way to deliver a planned and risk proportionate approach to enable the monitoring of the use of a specific medicinal product in routine clinical settings is through the risk management plan. Where the potential for off-label use has been identified for a product and such use could raise a safety concern (i.e. because there is a justified supposition that an important potential risk might be associated with the off-label use of the product) the risk management plan should discuss the need of pharmacovigilance activities in terms of:

- specific follow-up questionnaires for suspected adverse reactions derived from the off-label use;
- other required forms of routine pharmacovigilance activities for the targeted collection and follow-up of individual reports of off-label use not associated with suspected adverse reactions;
- additional structured investigations (such as drug utilisation studies, searches in databases).

If collected in the frame of the routine pharmacovigilance activities, individual reports of off-label use with no suspected adverse reaction should not be submitted to the EudraVigilance database since the minimum criteria for ICSRs validation are incomplete (see VI.B.2. for ICSRs validation).

As part of risk management planning, the monitoring of the off-label use should focus on collection and assessment of information which might influence the evaluation of the benefits and risks of the concerned medicinal product.

For products without a risk management plan, the marketing authorisation holder and the competent authority should consider whether the off-label use of the product constitutes a safety concern. If it does, then consideration should be given to requiring a risk management plan or a post-authorisation safety study.

Some Member States may already have put in place specific requirements at national level regarding the collection and submission by marketing authorisation holders of information on the off-label use of their products. The guidance presented in this chapter should not be interpreted as preventing the fulfilment of those local obligations.

VI.C.3. Submission time frames of ICSRs in EU

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

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

- serious valid ICSRs shall be submitted by the competent authority in a Member State or by the marketing authorisation holder within 15 days from the date of receipt of the reports;
- non-serious valid ICSRs shall be submitted by the competent authority in a Member State or by the marketing authorisation holder within 90 days from the date of receipt of the reports.

ICH-E2B provides a mechanism to the sender to indicate whether a valid ICSR fulfils the local regulatory requirements for submission to the EudraVigilance database within the 15 or 90-day time frame. In line with ICH-E2B the following applies for the serious and non-serious ICSRs which need to be submitted 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) when the ICSR needs to be submitted within the 15 or 90-day time frame. • The population of this data element is optional under ICH-E2B(R2).
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 when the ICSR needs to be submitted within the 15 or 90-day time frame. • The population of this data element is mandatory under ICH-E2B(R3).

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

In addition to the guidance provided in VI.B.8., the competent authority in a Member State and the marketing authorisation holder shall use the formats, standards and terminologies for the electronic submission of suspected adverse reactions as referred to in Chapter IV of the Commission Implementing Regulation (EU) No 520/2012. ICSRs shall be used for the submission to the EudraVigilance database of reports of suspected adverse reactions to a medicinal product that occur in a single patient at a specific point in time [IR Art 27]. The competent authority in a Member State and the marketing authorisation holder shall also ensure that all submitted ICSRs are well documented and as complete as possible in accordance with the requirements provided in Article 28 of the Commission Implementing Regulation (EU) No 520/2012.

The time frames for submitting serious and non-serious valid ICSRs are provided in VI.C.3.. The guidance 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.

In line with the provisions set out in Article 107(3) and 107a(4) of Directive 2001/83/EC, the following submission requirements shall apply to valid unsolicited and solicited ICSRs reported by healthcare professionals and non-healthcare professionals in relation to medicinal products for human use authorised in the EU in accordance with Directive 2001/83/EC and Regulation (EC) No 726/2004. This is relevant irrespective of the condition of use of the suspected medicinal product and of the expectedness of the adverse reaction.

a. Serious ICSRs

- The marketing authorisation holder 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.
- The competent authority in a Member State shall submit to the EudraVigilance database all serious ICSRs that occur in its territory and that are directly reported by healthcare professionals or consumers.

b. Non-Serious ICSRs

- The marketing authorisation holder shall submit all non-serious ICSRs that occur in the EU to the EudraVigilance database only.
- The competent authority in a Member State shall submit to the EudraVigilance database all non-serious ICSRs that occur in its territory and that are directly reported by healthcare professionals or consumers.

Overviews of the submission requirements for serious and non-serious ICSRs applicable to marketing authorisation holders and competent authorities in Member States, together with a business process map and a process description, are presented in VI.App.3.1., VI.App.3.2. and VI.App.3.3..

In line with the requirement detailed in Article 24(4) of Regulation (EC) No 726/2004, the ICSRs submitted to the EudraVigilance database by a marketing authorisation holder shall be automatically transmitted upon receipt, to the competent authority of the Member State where the reaction occurred. When the primary source country and the country of occurrence of the reaction differ, the competent authorities of the concerned member states in the EU will be automatically notified about these specific ICSRs. A business process map and a process description concerning the automatic retransmission of ICSRs are included in VI.App.3.4. .

In accordance with Article 24(2) of Regulation (EC) No 726/2004, the 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. Access is provided based on the latest version of the EudraVigilance Access Policy for Medicines for Human Use[33]. This policy defines the overall principles in relation to the provision of access to EudraVigilance data in line with the current legal framework, while guaranteeing personal data protection.

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)].

Further guidance on the access by stakeholders of the data submitted to the EudraVigilance database is available on the EudraVigilance webpage[34].

VI.C.5. Collaboration with the World Health Organization and the European Monitoring Centre for Drugs and Drug Addiction

In accordance with Article 28c(1) of Regulation (EC) No 726/2004, the Agency shall make available to the WHO (in practice the Uppsala Monitoring Centre (UMC) as the WHO Collaborating Centre for

[33] Ref.: EMA/759287/2009; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Access to data.
[34] EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Access to data.

International Drug Monitoring) all suspected adverse reaction reports occurring in the EU. In this regard, ICSRs from the EU submitted to the EudraVigilance database by competent authorities in Member States and marketing authorisation holders are transmitted to the WHO electronically in ICH-E2B(R3) format in line with the latest version of the EudraVigilance Access Policy for Medicines for Human Use[35]. Details are set out in a service level agreement between the Agency and the WHO, accessible on EMA website[36]. This replaces the requirements of EU Member States participating in the WHO Programme for International Drug Monitoring to directly report to WHO suspected adverse reactions reports occurring in their territory. A business process map and a process description for the submission of ICSRs, from the EudraVigilance database to the WHO Collaborating Centre for International Drug Monitoring, are presented in VI. 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

Chapter VI.C.6. highlights the requirements, as defined in Article 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.

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 and V of the Commission Implementing Regulation (EU) No 520/2012. In addition the following guidelines should be applied:

- the ICH Guidelines detailed in VI.B.8.;
- the guidelines applicable for the ICH-E2B(R2) and ICH-E2B(R3) formats:

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);
ICH-E2B(R3)	• EU Individual Case Safety Report (ICSR) Implementation Guide[37]; • EU ICSR Implementation Guide Business Rules Spreadsheet[38];

[35] Ref.: EMA/759287/2009; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Access to data.
[36] EMA website: Home/ Partners & Networks/ International organisations/ WHO.
[37] Ref.: EMA/51938/2013; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Electronic reporting.

- EU Backwards Forwards Conversion Element Mapping Spreadsheet[38];
- EU E2B(R3) code lists[38];
- EU reference instances[38];
- EU example instances[38].

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

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

The submission 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.

The responsibilities in case of communication failure (including adherence to compliance for submission of ICSRs) are detailed in the EU Individual Case Safety Report (ICSR) Implementation Guide[39].

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 submission requirements of ICSRs as defined in EU legislation. Information is available on the EudraVigilance webpage[40], together with some guidance on the access by stakeholders to the data submitted to the EudraVigilance database[41].

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:

- the EudraVigilance Post-Authorisation Module (EVPM), implemented based on the requirements defined in Regulation (EC) No 726/2004 and Directive 2001/83/EC; and
- the 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 2001/20/EC (see VI.C.1.2. for ICSRs management in non-interventional studies, compassionate and named patient use).

[38] EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/change management.
[39] Ref.: EMA/51938/2013; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Electronic reporting.
[40] EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance .
[41] EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Access to data.

In line with ICH-E2B the ICSRs should be submitted to EVPM 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 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': – 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, post-authorisation study.
ICH-E2B(R3)	• Data element C.1.3 'Type of report': – spontaneous report; – other; – 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, post-authorisation study.

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) studied in clinical trials which fall under the scope of Directive 2001/20/EC (see VI.C.1.1. for ICSRs management in clinical trials), should be 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[42] should be applied with

[42] EC website: European Commission/ DG Health and Food Safety/ Public health/ Vol 10: Clinical Trials.

regard to the collection, verification and presentation of adverse event/reaction reports arising from clinical trials.

The ICSRs should be submitted to EVCTM 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'.

These ICSRs should be classified as follows 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 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 MedDRA Term Selection: Points to Consider[43] (see GVP Annex IV);
- the EudraVigilance business rules or the EU Individual Case Safety Report (ICSR) Implementation Guide as referred to in VI.C.6.1., depending on the ICH-E2B format applied.

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 submitted in a structured manner in the relevant ICH-E2B data elements (which should be repeated as necessary when multiple information is available) and in the narrative section for serious

[43] For off-label, misuse, abuse and medication error, the definitions provided in VI.A.1.2. should be followed.

cases (see VI.C.6.2.2.4. for guidance on case narrative). This applies to all types of ICSRs, such as reports with initial information on the case, follow-up information and cases highlighted for amendment[44] or nullification[45].

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 submission 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. for guidance on ICSRs data quality).

Where the suspected adverse reactions reported in a single ICSR have a major impact on the risk-benefit balance of the medicinal product, this should be considered as an emerging safety issue and notified accordingly (see VI.C.2.2.6. and GVP Module IX for guidance on emerging safety issue). This is in addition to the ICSR submission requirements detailed in VI.C.3. and VI.C.4.. A summary of the points of concerns and the action proposed should be recorded in the ICSR in the data element 'Sender's comments' in line with ICH-E2B.

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

a. General guidance

Information on the active substances/invented names for the reported medicinal products (suspect, interacting, concomitant) should be provided in accordance with the requirements provided in Article 28 (3) (g) to (i) of the Commission Implementing Regulation (EU) No 520/2012. Depending on the ICH E2B format used, the guidance detailed in the Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)[46] and in the EU Individual Case Safety Report (ICSR) Implementation Guide[47] should also be followed.

The characterisation of the medicinal products as suspect, interacting or concomitant is based on the information provided by the primary source. Where the notified competent authority or marketing authorisation holder disagrees with the primary source characterisation, this should be indicated in the data element 'Sender's comments' in line with ICH-E2B while respecting the reporter description.

For medicinal products, which contain more than one active substance, the following applies in line with ICH-E2B:

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 should be repeated for each active substance contained in the medicinal product.

[44] See also VI.C.6.2.2.8. on amendment of individual cases.
[45] See also VI.C.6.2.2.9. on nullification of individual cases.
[46] Ref.: EMA/H/20665/04/Final Rev. 2; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Electronic reporting.
[47] Ref.: EMA/51938/2013; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Electronic reporting.

Reference	E2B(R2)/(R3) requirements
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 Individual Case Safety Report (ICSR) Implementation Guide[48].

b. Suspicion of a branded/proprietary medicinal product name without information on its active substance(s) or its pharmaceutical form and with different compositions depending on the country or on the pharmaceutical form

1. 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 different compositions depending on the country where the medicinal product is marketed, the ICSR should be populated as follows in line with ICH-E2B:

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. • 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.

[48] Ref.: EMA/51938/2013; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Electronic reporting.

However, the composition with regard the active substance(s) of the suspected or interacting proprietary medicinal product name should be provided accordingly if information is also available on the following ICH-E2B data elements for the reported product:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element B.4.k.2.3 'Identification of the country where the drug was obtained', • Data element B.4.k.4.1 'Authorization/application number', • Data element B.4.k.4.2 'Country of authorization/application', and/or • Data element B.4.k.3 'Batch/lot number'.
ICH-E2B(R3)	• Data element G.k.2.4 'Identification of the Country Where the Drug Was Obtained', • Data element G.k.3.1 'Authorization/application number', • Data element G.k.3.2 'Country of Authorisation/Application', and/or • Data element G.k.4.r.7 'Batch/lot number'.

2. 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:

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 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. • Data element G.k.2.3.r.1 'Substance/Specified Substance Name' should be completed with the 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, section G.k.2.3.r 'Substance/Specified Substance Identifier and Strength' should be repeated accordingly.

c. Suspicion of a therapeutic class of medicinal products

Where the medicinal product 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. The information should not be included in the structured data elements of the medicinal product name or the active substance name(s). The same applies if a suspected food interaction is reported (e.g. to grapefruit juice).

Where a case of adverse reactions is suspected to be related only to a therapeutic class, it is considered incomplete and does not qualify for submission as ICSR (see VI.B.2. for ICSRs validation). 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. for follow-up guidance).

d. Suspicion of drug interactions

For reports of drug interactions, which concern drug/drug (including biological products), drug/food, drug/device, and drug/alcohol interactions, the coding of the suspected interaction along with the resulting adverse reactions should be performed in the following ICH-E2B section in line with the appropriate recommendations provided in the latest version of the Guide for MedDRA Users - MedDRA Term Selection: Points to Consider (see GVP Annex IV).

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

In addition, the following applies for the suspected interacting medicinal products in line with ICH-E2B:

1. For drug/drug interactions

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

2. For drug/ food interactions or interactions with other non-drug compounds

   The information on the suspected interacting medicine should be included in ICH E2B section 'Drug information', however the information concerning the interacting food or other non-drug compounds should be provided in the case narrative.

e. Suspicion of one of the excipients

If the primary source suspects a possible causal role of one of the excipients (e.g. colouring matter, preservatives, adjuvant, stabilisers, thickeners, emulsifiers, flavouring and aromatic substances, see VI.A.1.3. for definition) of the suspected medicinal product, this information should be provided in line with ICH-E2B as follows:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• In the section B.4 'Drug information': as a separate entry specifying the suspected excipient, 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 excipient 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 specifying the suspected excipient, 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 excipient should be included in the section F.r 'Results of tests and procedures relevant to the investigation of the patient'.

f. Additional information on the medicinal product

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.

In line with ICH-E2B, the following applies to capture this information for the respective suspected medicinal products, along with the guidance provided

- in section VI.C.6.2.3.3. for the provision of information on the suspected adverse reactions associated to overdose, abuse, off-label use, misuse, medication error or occupational exposure, and
- in section VI C.6.2.3.5. for the provision of information on suspected adverse reactions associated to quality defect or falsified medicinal product

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• As a general principle, additional characteristics related to the medicines that cannot be structured in one of the data elements of section B.4 'Drug(s) information' and which are 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

Reference	E2B(R2)/(R3) requirements
	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. • Along with the resulting suspected adverse reactions, an appropriate MedDRA term should be provided in section B.2 'Reactions/events' where applicable in line with the latest version of the Guide for MedDRA Users, MedDRA Term Selection: Points to Consider[49]. • Data elements B.5.3 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' 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, with a reasoning included in the data element B.5.4 'Sender's comments'.
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 tested and found within specifications, Batch and lot tested and found not within specifications, Medication error, Misuse, Abuse, Occupational exposure, or 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. • Along with the resulting suspected adverse reactions, an appropriate MedDRA term should be provided in section E.i 'Reaction(s)/Event(s)' (where applicable in line with the latest version of the Guide for MedDRA Users, MedDRA Term Selection: Points to Consider[49]. • Section H.3.r 'Sender's Diagnosis' 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, with a reasoning included in the data element H.4 'Sender's comments'. 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.

[49] For off-label, misuse, abuse and medication error, the definitions provided in VI.A.1.2. should be followed.

Reference	E2B(R2)/(R3) requirements	
	Definitions for data element G.k.10.r 'Additional Information on Drug (coded)'. *Note: for overdose, off-label use, misuse, abuse, occupational exposure, medication error, the definitions in VI.A.1.2. should be applied.*	
	• Counterfeit[50]	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(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 product information 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.
	• Drug taken by father	This is to indicate that suspect drug was taken by the father for cases describing miscarriage, stillbirth or early spontaneous abortion. In this situation only a mother report is applicable and the data elements in Section D 'Patient Characteristics' apply to the mother (see VI.C.6.2.3.1. for guidance on the electronic submission of pregnancy ICSRs).

VI.C.6.2.2.3. Suspected adverse reactions

In line with Article 28(3)(j) of the Commission Implementing Regulation (EU) No 520/2012, all available information on the reported suspected adverse reactions shall be provided for each individual case. Examples of relevant information include: the start and end date or duration, seriousness, outcome at the time of last observation, time intervals between the suspect medicinal product administration and the start of the reactions, the original reporter's words or short phrases used to describe the reactions, the country of occurrence of the reactions.

The coding of diagnoses and provisional diagnoses with signs and symptoms should be performed with the supported versions[51] of the MedDRA dictionary used at the lowest level term (LLT) level and in line

[50] This value should not be 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 the European Commission Q&A: Directive on falsified medicines.

[51] Stakeholders should follow the recommendations of MedDRA MSSO regarding the switch to a new MedDRA version. The latest supported MedDRA versions in line with the official semi-annual releases are posted on the EudraVigilance webpage (EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance).

with the applicable recommendations provided in the latest version of the 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. If no diagnosis is provided, all reported signs and symptoms should be listed and MedDRA-coded. If these signs and symptoms are typically part of a diagnosis, the diagnosis can be MedDRA-coded in addition in the ICSR by the competent authority in the Member State or by the marketing authorisation holder as part of the sender's diagnosis and sender's comment.

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.

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 addition as part of the sender's diagnosis. In this situation, reasoning should be included as sender's comment (see VI.C.6.2.2.4. for guidance on the provision of comments in ICSRs).

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 completed in line with the EudraVigilance Business Rules[52], including the data element B.2.i.1 'Reaction/event in MedDRA terminology (Lowest Level Term)'. • Data element B.5.3 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' should be used where the sender would like to combine reported signs and symptoms into a succinct diagnosis. Reasoning should be included in the data element B.5.4 'Sender's comments'. • Data element 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 completed in line with the EU Individual Case Safety Report (ICSR) Implementation Guide[53], including the data element E.i.2.1b 'Reaction/Event (MedDRA code)'. • Section H.3.r 'Sender's Diagnosis' should be used where the sender would like to combine reported signs and symptoms into a succinct diagnosis. Reasoning should be included in the data element H.4 'Sender's 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

[52] Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs) (EMA/H/20665/04/Final Rev. 2); EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Electronic reporting.
[53] Ref.: EMA/51938/2013; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Electronic reporting.

Reference	E2B(R2)/(R3) requirements
	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)]. The recommendation provided in the EudraVigilance Business Rules[54] and the EU Individual Case Safety Report (ICSR) Implementation Guide[55] should be followed with regard to the provision in the ICSR of information on the patient's death. If the death is unrelated to the reported suspected adverse reaction(s) and is linked for example to disease progression, the seriousness criterion should not be considered as fatal.

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

a. Case narrative

In accordance with Article 28 (3)(m) of the Commission Implementing Regulation (EU) No 520/2012, a case narrative shall be provided, where possible[56], 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 detailed in ICH-E2D (see GVP Annex IV).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 events, diagnoses, 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 EU guidance on languages management in ICSRs). With regard to the identifiability of the patient, information should be provided in accordance with local data protection laws (see VI.C.6.2.2.10. for guidance on the processing of personal data in the EU). 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 data elements of the ICSR. 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 measures, outcome and additional relevant information'

[54] Note for guidance – EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs) (EMA/H/20665/04/Final Rev. 2); EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Electronic reporting.
[55] Ref.: EMA/51938/2013; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Electronic reporting.
[56] 'Where possible' is usually understood as meaning having received sufficient information from the primary source to prepare a concise clinical summary of the individual case.
[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
	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.

b. Comments

Where available, comments from the primary source should be provided on the diagnosis, the causality assessment, or on other relevant issues in the following ICH-E2B 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'.

The competent authority in a Member State and the marketing authorisation holder 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. for guidance on the processing of suspected adverse reactions in ICSRs). 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 the actions proposed should also be included in the ICSR when it leads to the notification of an emerging safety issue (see VI.C.2.2.6. for guidance on emerging safety issue). 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'.

c. Causality assessment

The degree of suspected relatedness of each medicinal product to each reported adverse reaction can be presented in a structured manner in the ICSR. It can be expressed for multiple sources (reporters, competent authorities, marketing authorisation holders) while using multiple methods of causality assessment. In line with ICH-E2B this information should be provided in the following sections:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Section B.4.k.18 'Relatedness of drug to reaction(s)/event(s)'. The data elements of this section should be repeated as applicable to provide the assessment of relatedness of each drug-reaction pair expressed by multiple sources and with multiple methods of assessment.
ICH-E2B(R3)	• Section G.k.9.i 'Drug-reaction(s)/Event(s) Matrix'. The data elements of this section should be repeated as applicable to provide the assessment of relatedness of each drug-reaction pair expressed by multiple sources and with multiple methods of assessment.

VI.C.6.2.2.5. Test results

In accordance with the requirements provided in Article 28(3)(k) of the Commission Implementing Regulation (EU) No 520/2012, information on the results of tests and procedures relevant to the investigation of the patient shall be provided in the ICSR. 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 included in the ICSR.

The coding of investigations should be performed in line with the latest version of the 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 presentation of the information in free text.

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 the data elements repeated as applicable. • Data element B.3.1 'Structured information' should be used to structure the information on the test, the result and unit, the date the test was performed, and the normal low and high range. Where several tests or procedures were performed, the data element should be repeated as necessary. • 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 data element 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 date the test was performed (data element F.r.1 'Test date'), the test (section F.r.2 'Test name'), the outcome (section F.r.3 'Test result') and the normal low (data element F.r.4 'Normal low value') and normal high (data element F.r.5 'Normal high value'). • 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 for use in data element F.r.2.2b 'Test Name (MedDRA code)'. • Data element F.r.3.4 'Result Unstructured Data (free text)' should be used when the data elements F.r.3.1 'Test results (code)', F.r.3.2 'Test results (value / qualifier) and F.r.3.3 'Test result (unit)' cannot be used (often because a Unified Code for Units of Measure (UCUM) code is not available for the test unit). • Data elements F.r.4 'Normal low value' and F.r.5 'Normal high value' should be used to capture the lowest and highest values in the normal range for the test. The same units as used in F.r.3.3 are implied. • Data element F.r.6 'Comments (free text)' should be used to capture any relevant comments made by the reporter about the test result. • A separate block (r) should be used for each test/procedure.

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 E2B section 'Additional Available Documents Held by Sender'. Provision has been made in ICH-E2B(R3) format for the electronic submission of documents as attachments to the ICSR message itself. This option is not available in ICH-E2B(R2) and requested documents should be sent separately as specified in the request.

In line with ICH-E2B the following applies:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Section 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 as applicable, 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 attached 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.6.2.2.10. for guidance on the processing of personal data in the EU).

Other known case identifiers relevant for the detection of duplicates should be presented systematically in ICSRs in the following section in line with ICH-E2B:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Section A.1.11 'Other case identifiers in previous transmissions'.
ICH-E2B(R3)	• Section C.1.9.1 'Other case identifiers in previous transmissions'.

VI.C.6.2.2.7. Follow-up information

In addition to the general principles provided in VI.B.3., the following guidance should be followed concerning the management of follow-up information on ICSRs.

ICSRs are sent at different times to multiple receivers. Therefore the initial/follow-up status for a report is dependent upon the receiver. For this reason an item to capture follow-up status is not included in ICH-E2B. However, the date of receipt of the most recent information taken together with the worldwide unique case identification number and the sender's identifier provide a mechanism for each receiver to identify whether the report being transmitted is an initial or a follow-up report. These items are therefore considered critical for each submission and a precise date should always be used (i.e. day, month, year).

In this context, the date of receipt of the most recent information should always be updated each time follow-up information is received by a competent authority or a marketing authorisation holder, irrespective whether the follow-up information is significant enough to be submitted. The worldwide unique case identification number of the initial ICSR should be maintained and the date the report was first received from a reporter should remain unchanged to the date the competent authority or the marketing authorisation holder became aware of the initial report.

When an organisation (competent authority or marketing authorisation holder) is receiving follow-up information on a case initially received and submitted to the EudraVigilance database by a different organisation, the worldwide unique case identification number of the initial report submitted by the first organisation should be preserved in the subsequent submissions of the ICSR. In line with ICH E2B, the sender's (case) safety report unique identifier and the sender's identifier should be updated with the new organisation's own unique identifiers.

New follow-up information should always be clearly identifiable in the case narrative (required for serious reports of suspected adverse reactions) and should also be captured in structured format as applicable.

In line with ICH-E2B the following data elements/sections should always be completed for follow-up ICSRs submission:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element A.1.0.1 'Sender's (case) safety report unique identifier'. • Data element A.1.6 'Date report was first received from source' (which should remain unchanged). • 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' (which should remain unchanged). • 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)	• Data element C.1.1 'Sender's (case) Safety Report Unique Identifier'. • Data element C.1.4 'Date Report Was First Received from Source' (which should remain unchanged). • Data element C.1.5 'Date of Most Recent Information for this Report'. • Section C.1.8 'Worldwide Unique Case Identification' (which should remain unchanged). • Data element C.3.2 'Sender's organisation'. • Data element H.1 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' (for serious reports of suspected adverse reactions).

a. Significant information

Competent authorities in Member States or marketing authorisation holders should submit follow-up ICSRs if significant new medical information has been received. Significant new information relates to, for example, a new suspected adverse reaction, a change in the causality assessment, and any new or updated information on a case that impacts on its medical interpretation. Medical judgement should therefore be applied for the identification of significant new information requiring to be submitted as follow-up ICSR.

Situations where the seriousness criteria and/or the causality assessment are downgraded (e.g. the follow-up information leads to a change of the seriousness criteria from serious to non-

serious, or the causality assessment is changed from related to non-related) should also be considered as significant changes and thus submitted as ICSR (see VI.C.3. for ICSRs submission time frames).

In addition, the competent authority in a Member State or the marketing authorisation holder should also submit a new version of an ICSR, when new administrative information is available, that could impact on the case management. For example, if new case identifiers have become known to the sender, which may have been used in previous submissions. This information may be specifically relevant to manage potential duplicates. In this context, the following sections should be completed in line with ICH-E2B:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Section A.1.11 'Other case identifiers in previous transmissions'.
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 regard, the following 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'.

b. Non-significant information

In contrast, a follow-up report which contains non-significant information does not require to be submitted as ICSR. This may refer, for example, to minor changes to some dates with no implication for the evaluation or submission of the case, or to some 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.

VI.C.6.2.2.8. Amendment of cases

General guidance is provided in VI.B.7.3.. Serious and non-serious cases which have already been submitted to EudraVigilance 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.

Where the amendment significantly impacts on the medical evaluation of the case, an ICSR should be resubmitted and information on the amendment should be explained in the case narrative. 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 resubmitted as amendment report (see VI.C.6.2.2.7. Subsection a and b for examples of significant and non-significant information).

Additionally, for reports for which cases translations should be provided by a marketing authorisation holder when requested by the Agency or another Member State (see VI.C.6.2.2.11. for EU guidance on

languages management in ICSRs), the translations should be submitted in the form of amendment reports. The same applies where documentations or articles mentioned in the ICSRs are requested by the Agency or another Member State and are further sent as attachments in data element ICH E2B(R3) C.4.r.2 'Included documents' (the attachment of document is not available under the ICH E2B(R2) format).

New received information (significant or non-significant) should be considered as follow-up report and not as amendment report and in this context, the guidance provided in VI.C.6.2.2.7. should be followed.

In line with ICH-E2B the following applies for the submission of amendment ICSRs:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	The possibility of flagging an ICSR as amendment report is not supported under the ICH-E2B(R2) format. Where the amendment of an ICSR is necessary, the same principles as for a follow-up report should be applied as follows: • Data element A.1.0.1 'Sender's (case) Safety Report Unique Identifier' should remain unchanged. • Data element A.1.6 'Date report was first received from source' should remain unchanged. • Data element A.1.7 'Date of receipt of the most recent information for this report' should remain unchanged. • Data element A.1.10 'Worldwide Unique Case Identification Number' should remain unchanged. • Data element A.3.1.2 'Sender identifier' should remain unchanged. • Information on the amendment should be identifiable in the case narrative (data element B.5.1). It should be noted that amendment ICSRs submitted in the ICH-E2B(R2) format will appear as "late reports" in the compliance monitoring performed by the Agency (see VI.C.6.2.4. for guidance on ICSRs data quality) if they are submitted beyond the 15 or 90 days submission time frames since the date of receipt of the most recent information should remain unchanged.
ICH-E2B(R3)	• Data element C.1.1 'Sender's (case) Safety Report Unique Identifier' should remain unchanged. • Data element C.1.4 'Date Report Was First Received from Source' should remain unchanged. • Data element C.1.5 'Date of Most Recent Information for This Report' should remain unchanged. • Section C.1.8 'Worldwide Unique Identifier' should remain unchanged. • Data element C.1.11.1 'Report Nullification/Amendment' should be set to 'Amendment'. • Data element C.1.11.2 'Reason for Nullification/Amendment' should be completed to indicate the reason why a previously transmitted ICSR is amended.

Reference	E2B(R2)/(R3) requirements
	• Data element C.3.2 'Sender's organisation' should remain unchanged. • Information on the amendment should be identifiable in the case narrative (data element H.1). ICSRs set as amendment reports in the ICH-E2B(R3) format are not considered in the compliance monitoring performed by the Agency. They will be however monitored as part of the regular review of the ICSRs quality and integrity conducted by the Agency (see VI.C.6.2.4. for guidance on ICSRs data quality). This is to ensure that they have not been misclassified by the sending organisation as amendment reports instead of follow-up reports which should be taken into account in the compliance monitoring.

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 criteria for submission' or 'report sent previously in error' are not detailed enough explanations;
- An individual case can only be nullified by the original 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 applies for nullified ICSRs submission:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element A.1.0.1 'Sender's (case) Safety Report Unique Identifier' should remain unchanged. • Data element A.1.6 'Date report was first received from source' should remain unchanged. • 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. • Data element A.1.10 'Worldwide unique case identification number' should remain unchanged.

Reference	E2B(R2)/(R3) requirements
	• Data element A.1.13 'Report nullification' should be set to "Yes". • 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. • Data element A.3.1.2 'Sender identifier' should remain unchanged.
ICH-E2B(R3)	• Data element C.1.1 'Sender's (case) Safety Report Unique Identifier' (should remain unchanged. • Data element C.1.4 'Date Report Was First Received from Source' should remain unchanged. • 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. • Data element C.1.8 'Worldwide Unique Identifier' should remain unchanged. • Data element C.1.11.1 'Report Nullification/Amendment' should be set to 'Nullification'. • 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. • Data element C.3.2 'Sender's organisation' 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 in line with ICH-E2B:

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. Data 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, and Regulation (EC) No 45/2001).

Where in accordance with the applicable national legislation, the patient's direct identifiers cannot be transferred to the EudraVigilance database, pseudonymisation may be applied by the competent authority in the Member State and by the marketing authorisation holder, thereby replacing identifiable personal data such as name and address with pseudonyms or key codes, 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. 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', in line with the EudraVigilance business rules 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).
ICH-E2B(R3)	• The nullFlavor 'MSK' (see VI.A.1.8. for definition of nullFlavor) should be used if personal information is available but cannot be provided by the sender due to local protection legislation. It informs the receiver that the information does exist without providing personal details such as birth date or name. See EU Individual Case Safety Report (ICSR) Implementation Guide (EMA/51938/2013) for ICH-E2B(R3) sections/data elements where the use of the nullFlavor 'MSK' is not permitted.

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

VI.C.6.2.2.11. Handling of languages

The electronic submission 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 a medical summary is normally required (see VI.6.2.2.4. for guidance on case narrative).

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 [IR 28 (4)]. 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. The ICSR should be completed and submitted in English if not otherwise requested.

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. 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.

When requested by a Member State or the Agency, the following applies in line with ICH-E2B for the provision of the original verbatim text in an official language of the Union other than English for the suspected adverse reaction and the additional description of the case:

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 for the suspected adverse reactions, - the reporter's description and comments for the case in the original language (if provided), - the English summary of the case.
ICH-E2B(R3)	• Data element E.i.1.1a 'Reaction / Event as reported by the primary source in Native Language' should be completed with the original verbatim text for the suspected adverse reactions. • Data element E.i.1.1b 'Reaction / event as reported by the primary source language' should provide information on the language used in E.i.1.1a. • Data element E.i.1.2 'Reaction / event as reported by the primary source for translation' should provide the translation in English of the original reporter's words used to describe the suspected adverse reactions. • Data element H.1 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' should be used to provide the English summary of the case. • Section H.5.r 'Case Summary and Reporter's Comments in Native Language (repeat as necessary)' should be used to capture the reporter's description and comments for the case in the original verbatim text (if provided).

VI.C.6.2.3. Special situations

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

General principles provided in VI.B.6.1. should be followed.

With regard to the electronic submission of parent-child/foetus cases, the following should be adhered to for the creation of ICSRs depending on the situation. This is in addition to the recommendations included in the latest version of the Guide for MedDRA Users, MedDRA Term Selection: Points to Consider for the provision of the appropriate reaction/event terms in line with ICH-E2B.

a. The child/foetus experiences suspected adverse reactions other than early spontaneous abortion/foetal demise:

When the child or foetus, exposed to one or several medicinal products through the parent, 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. 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/foetus. • Section B.1.10 'For a parent-child/foetus 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/foetus. • Section D.10 'For a Parent-child/Foetus Report, Information Concerning the Parent' should be completed for the mother or the father as applicable. • Data element H.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.

b. Both the parent and child/foetus experience suspected adverse reactions:

When the parent and the exposed child/ foetus experience suspected adverse reactions other than early spontaneous abortion/foetal demise, two separate reports, i.e. one for the parent (mother or father) and one for the child/foetus, should be created. Both reports should be linked to identify cases that warrant being evaluated together by using the following data element in line with ICH-E2B:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element A.1.12 'Identification number of the report which is linked to this report'.
ICH-E2B(R3)	• Data element C.1.10.r 'Identification Number of the Report Linked to this Report (repeat as necessary)'.

c. No reaction is affecting the child/foetus:

When no reaction is reported for the exposed child/foetus, the parent-child/foetus report does not apply. Only a parent report should be created to describe the child exposure to the medicinal product. The patient characteristics refer only to the parent (mother or father) who may as well experience adverse reactions with the suspected medicinal product. Reports with no reaction should not be submitted as ICSRs (see VI.B.6.1. for general guidance on the management of these reports).

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. Miscarriage or early spontaneous abortion is reported:

When miscarriage or early spontaneous abortion is reported, only a parent report is applicable with the patient's characteristics to be provided for the mother. However, if the suspect medicinal product was taken by the father, this information 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 the suspect drug was taken by the father. The value to be selected is 'Drug taken by father'. Guidance on the use of data element G.k.10.r is provided in VI.C.6.2.2.2. Subsection f.

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

EU requirements in relation to the monitoring of suspected adverse reactions reported in the medical literature are provided in VI.C.2.2.3.1.. With regard to the electronic submission of ICSRs published in the medical literature, the following should be followed:

The literature references shall be provided in the Vancouver Convention (known as "Vancouver style"), developed by the International Committee of Medical Journal Editors [IR Art 28 (3) (b)][58].

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"**

[58] 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)	• Data element C.4.r.1 '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"**

In accordance with Article 28(3) (b) of the Commission Implementing Regulation (EU) No 520/2012, a comprehensive English summary of the article shall be provided in the following ICH-E2B data element/section:

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'.
ICH-E2B(R3)	• Data element H.1 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information'.

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)].

In line with ICH-E2B the following applies:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• The guidance detailed in VI.App2.10, regarding the mailing of the literature article, should be adhered to.
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 data element C.4.r.2 'Included Documents'. • If the article and/or translation are not provided at the time of the ICSR submission, attachments can be transmitted separately. In this situation, the original ICSR along with all the same medical information captured in the E2B(R3) data elements should be retransmitted as an 'amendment' report (see VI.C.6.2.2.8. for guidance on amendment reports). However if new additional information is provided, then the ICSR with the attachment should be submitted as a follow-up report.

Guidance presented in VI.App2.10., for the submission of several individual cases when they are presented 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 detailed in VI.B.6.3. should be followed. Further guidance on the management of individual reports of off-label use is provided in VI.C.2.2.12..

Along with the resulting suspected adverse reactions, an appropriate MedDRA LLT term corresponding most closely to the description of the reported overdose, abuse, off-label use, misuse, medication error or occupational exposure should be specified in the ICH-E2B section 'Reactions/Events'. This should be

done in accordance with the applicable recommendations given in the latest version of the Guide for MedDRA Users, MedDRA Term Selection: Points to Consider, while respecting the definitions provided in VI.A.1.2..

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 provided in free text. • Data element B.4.k.2.1 'Proprietary medicinal product name' and/or B.4.k.2.2 'Active substance name(s)' should be completed in accordance with the information reported by the primary source (see VI.C.6.2.2.2. for guidance on suspect, interacting and concomitant medicinal products). • Data element B.4.k.19 'Additional information on drug' can be used to specify any additional information pertinent to the case (e.g. overdose, medication error, misuse, abuse, occupational exposure, off-label use). This data element can also be used to provide additional information concerning the indication for the drug not covered in data element B.4.k.11 'Indication for use in the case'. • An appropriate MedDRA terms should be provided for the drug characterisation in the data element B.2.i.1 'Reaction/event in MedDRA terminology (Lowest Level Term)' along with the resulting suspected adverse reaction. If applicable, the data element B.5.3 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' should be completed with a reasoning provided in the data element B.5.4 'Sender's comments'. • If the primary source did not provide an explicit statement about the overdose, medication error, misuse, abuse, occupational exposure or off-label use, which would clearly transpose into a MedDRA term in the data element B.2.i.1 'Reaction/event in MedDRA terminology (Lowest Level Term)', but there is an suggestion in the context of the clinical course description, the sender may provide that information in the data element B.5.3 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' with a reasoning provided in the data element B.5.4 'Sender's comments'. The case should be followed up to obtain further information.
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. • In addition to the mandatory data element G.k.2.2 'Medicinal Product Name as Reported by the Primary Source', section G.k 'Drug(s) Information' should be completed in accordance with the information reported by the primary source (see VI.C.6.2.2.2. for guidance on suspect, interacting and concomitant medicinal products). • 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, off label use. The value(s) should be used where the primary source has made a clear statement

Reference	E2B(R2)/(R3) requirements	
	related to the additional characteristics of the drug. • An appropriate MedDRA terms should be provided for the drug characterisation in the data element E.i.2.1b 'Reaction/Event (MedDRA code)' along with the resulting suspected adverse reaction. If applicable, the section H.3.r 'Sender's Diagnosis' should be completed with a reasoning provided in the data element H.4 'Sender's comments'. • If the primary source did not provide an explicit statement about the overdose, medication error, misuse, abuse, occupational exposure or off label use, which would clearly transpose into a MedDRA term in the data element E.i.2.1b 'Reaction/Event (MedDRA code)', but there is an suggestion in the context of the clinical course description, the sender may choose the most applicable value(s) of G.k.10.r 'Additional Information on Drug (coded)'. 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 reports of medication error where the patient did not receive the actual prescribed drug but a different one, based on the information provided. 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.	
	Definitions 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 VI.A.1.2..
	• Medication error	This is to indicate that the medicine may have been associated with a medication error as defined in VI.A.1.2..
	• Misuse	This is to indicate that the medicine may have been associated with misuse as defined in VI.A.1.2..
	• Abuse	This is to indicate that the medicine may have been associated with abuse as defined in VI.A.1.2..
	• Occupational exposure	This is to indicate that the medicine may have been associated with occupational exposure as defined in VI.A.1.2..
	• Off label use	This is to indicate that the medicine may have been associated with off label use as defined in VI.A.1.2..

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 LLT term, corresponding most closely to the description of the reported lack of therapeutic efficacy, should be specified in the ICSR in accordance with the recommendations given in the latest version of the 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 ICH-E2B section 'Reactions/Events'.

When the lack of therapeutic efficacy is reported with no suspected adverse reaction, the same submission modalities as for serious ICSRs (see VI.C.4. for ICSRs submission modalities in EU) should be applied for cases related to medicinal products detailed in VI.B.6.4., for which ISCRs submission is required (e.g. medicinal products used in critical conditions or for the treatment of life-threatening diseases, vaccines, contraceptives). The ISCRs should be submitted within a 15-day time frame even if no seriousness criterion is specified.

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 guidance should be applied:

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 LLT term corresponding most closely to the product quality issue, should be added to the observed suspected adverse reaction(s) in accordance with the applicable recommendations given in the latest version of the Guide for MedDRA Users, MedDRA Term Selection: Points to Consider.

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.2.1 'Proprietary medicinal product name' and/or B.4.k.2.2 'Active substance name(s)' should be populated in accordance with the information reported by the primary source (see VI.C.6.2.2.2. for guidance on suspect, interacting and concomitant medicinal products). • Data element B.4.k.19 'Additional information on drug' should be used to specify any additional information pertinent to the case (e.g. beyond expiration date, batch and lot tested and found to be within/not within

Reference	E2B(R2)/(R3) requirements	
	specifications). This data element can also be used to provide additional information concerning the indication for the drug not covered in data element B.4.k.11 'Indication for use in the case'. • An appropriate MedDRA term should be provided for the drug characterisation in the data element B.2.i.1 'Reaction/event in MedDRA terminology (Lowest Level Term)' along with the resulting suspected adverse reaction. If applicable, the data element B.5.3 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' should be completed with a reasoning provided in the data element B.5.4 'Sender's comments'.	
ICH-E2B(R3)	• 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. • In addition to the mandatory data element G.k.2.2 'Medicinal Product Name as Reported by the Primary Source', section G.k 'Drug(s) Information' should be completed in accordance with the information reported by the primary source (see VI.C.6.2.2.2. for guidance on suspect, interacting and concomitant medicinal products). • Data element G.k.10.r 'Additional Information on Drug (coded)' should be completed using one or more of the following values as applicable: drug taken beyond expiry date, 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. • An appropriate MedDRA term should be provided for the drug characterisation in the data element E.i.2.1b 'Reaction/Event (MedDRA code)' along with the resulting suspected adverse reaction. If applicable, the section H.3.r 'Sender's Diagnosis' should also be completed with a reasoning provided in the data element H.4 'Sender's comments'. • 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.	
	Definitions 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 product information 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	This is to indicate that a batch or lot of a

Reference	E2B(R2)/(R3) requirements	
	found not within specifications	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 excipient, active substance or medicinal product, the MedDRA LLT term corresponding most closely to the reported information should be added to the observed suspected adverse reaction(s) in accordance with the applicable recommendations given in the latest version of the Guide for MedDRA Users, MedDRA Term Selection: Points to Consider. Information on the suspected medicinal product, active substance(s) or excipient(s) should be also provided in line with the guidance in VI.C.6.2.2.2..

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.2.1 'Proprietary medicinal product name' and/or B.4.k.2.2 'Active substance name(s)' should be populated in accordance with the information reported by the primary source (see VI.C.6.2.2.2. for guidance on suspect, interacting and concomitant medicinal products). • Data element B.4.k.19 'Additional information on drug' should be used to specify any additional information pertinent to the case (e.g. falsified medicine, medicine purchased over the internet). This data element can also be used to provide additional information concerning the indication for the drug not covered in data element B.4.k.11 'Indication for use in the case'. • An appropriate MedDRA term should be provided for the drug characterisation in the data element B.2.i.1 'Reaction/event in MedDRA terminology (Lowest Level Term)' along with the resulting suspected adverse reaction. If applicable, the data element B.5.3 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' should be completed with a reasoning provided in the data element B.5.4 'Sender's comments'. • If new information is received to confirm the product is not a counterfeit, the data element B.4.k.19 should be changed appropriately in a follow-up. If the product is confirmed as a counterfeit, the appropriate MedDRA code should be used in the data element 'B.5.3 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' with a reasoning provided in the data element B.5.4 'Sender's comments' and information should be provided in the case narrative.
ICH-E2B(R3)	• 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. • In addition to the mandatory data element G.k.2.2 'Medicinal Product Name as Reported by the Primary Source', section G.k 'Drug(s) Information' should

Reference	E2B(R2)/(R3) requirements	
	be completed in accordance with the information reported by the primary source (see VI.C.6.2.2.2. for guidance on suspect, interacting and concomitant medicinal products). • Data element G.k.10.r 'Additional Information on Drug (coded)' should be completed using the following value 'Counterfeit'[59]. The value should be used where the medicine is suspected or confirmed to be a falsified medicinal product. • An appropriate MedDRA term should be provided for the drug characterisation in the data element E.i.2.1b 'Reaction/Event (MedDRA code)' along with the resulting suspected adverse reaction. If applicable, the section H.3.r 'Sender's Diagnosis' should be completed with a reasoning provided in the data element H.4 'Sender's comments'. • 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 the section H.3.r 'Sender's Diagnosis' with a reasoning provided in the data element H.4 'Sender's comments' 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).	
	Definitions for data element G.k.10.r 'Additional Information on Drug (coded)'	
	• Counterfeit[59]	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(33) of Directive 2001/83/EC.

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

General guidance on the management of this type of reports in the EU is provided in VI.C.2.2.5..

The coding of a suspected transmission of an infectious agent via a medicinal product should be performed in line with the latest version of the Guide for MedDRA Users, MedDRA Term Selection: Points to Consider.

In addition, if the infectious agent is specified in the report, the MedDRA LLT term corresponding most closely to the infectious agent should also be included in the ICSR.

In line with ICH-E2B the following applies:

Reference	E2B(R2)/(R3) requirements

[59] 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.

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 guidance about the management of individual safety reports in the EU for post-authorisation studies (interventional clinical trials and non-interventional studies) is provided in VI.C.1.. Individual 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 the following ICH E2B section :

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

Guidance concerning the management of individual safety reports for patient support programmes or market research programmes is provided in VI.C.2.2.11..

All ICSRs 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. for guidance on EudraVigilance database modules). 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 and do not result from a possible interaction with the IMP.

The following submission rules for ICSRs 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 suspected adverse reactions (i) in relation to those adverse events for which the protocol of non-interventional post-authorisation studies requires their systematic collection** (see VI.C.1.2.1.1.)**, (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 solicited;
      - 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

Reference	E2B(R2)/(R3) requirements
	'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 spontaneous; as such it conveys the suspicion of the primary source;
- 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 specified adverse events for which the protocol of non-interventional post-authorisation studies does not require their systematic collection** (see VI.C.1.2.1.1.)**, 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 spontaneous; as such it conveys the suspicion of the primary source;
- 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 trials conducted in accordance with Directive 2001/20/EC where the adverse reaction is only suspected to be related to a medicinal product other than the IMP and does not result from a possible interaction with the IMP** (see VI.C.1.1.):

- the report should be considered spontaneous; as such it conveys the suspicion of the primary source;
- 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. for ICSRs validation) has been obtained about a non-valid ICSR, the following rules should be applied:

- the date where the report was first received from the reporter should reflect the date of receipt of the initial non-valid ICSR;
- the date of receipt of the most recent information should reflect the date when the minimum criteria required for ICSR validation have become available;
- clarification should be provided in the case narrative that some of the four elements were missing in the initial report;
- as for any submitted cases, compliance monitoring is performed against the date of receipt of the most recent information for this report.

In line with ICH-E2B the following applies:

Reference	E2B(R2)/(R3) requirements
ICH-E2B(R2)	• Data element A.1.6 'Date report was first received from source' should capture the date of receipt of the initial non-valid ICSR. • Data element A.1.7 'Date of receipt of the most recent information for this report' should capture the date when the minimum criteria required for ICSR validation 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)	• Data element C.1.4 'Date Report Was First Received from Source' should capture the date of receipt of the initial non-valid ICSR. • Data element C.1.5 'Date of Most Recent Information for This Report' should capture the date when the minimum criteria required for ICSR validation 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, the competent authority in a Member State and the marketing authorisation holder should adhere to:

- the electronic submission requirements as defined in EU legislation;
- the concepts of data structuring, coding and submission in line with the EU legislation, guidelines, standards and principles referred to in VI.C.6.1..

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, are responsible to contribute to the quality and integrity of the data. This is reflected in the legislation as follows:

- The Agency shall, in collaboration with the marketing authorisation holder or with the competent authority in Member State 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, either systematically or by regular random evaluation [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)].;
- the quality, integrity and completeness of the ICSRs submitted, which should also be entire and undiminished in their structure, format and content [IR Art 11 (1) (d) and Art 15 (1) (a)];
- the detection of duplicates of suspected adverse reactions reports in collaboration with the Agency [DIR Art 107(5) and Art 107a (3)].

To confirm that the quality system enables for the detection and management of duplicate ICSRs and the submission to the EudraVigilance database of ICSRs of the highest quality within the correct time frames, the marketing authorisation holder and the competent authority in a Member State shall perform risk-based audits of the quality system at regular interval [IR Art 13(1) and Art 17(1)]. Corrective action, including a follow-up audit of deficiencies shall be taken where necessary. The dates and results of audits and follow-up audits shall be documented [IR Art 13 (2) and Art 17(2)].

For the purpose of a systematic approach towards quality in accordance with the quality cycle as outlined in GVP Module I, the marketing authorisation holder, the competent authority in Member States and the Agency shall have sufficient and appropriately qualified and trained personnel for the performance of pharmacovigilance activities [IR Art 10(1) and 14(1)]. All personnel involved in the performance of pharmacovigilance activities shall receive initial and continued training in relation to

their role and responsibilities. Stakeholders shall keep training plans and records for documenting, maintaining and developing the competences of personnel based on an assessment of the training needs and make them available for audit or inspection [IR Art 10 (3) and Art 14 (2)].

To assist 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 the management of individual safety reports, signals management and EudraVigilance. It is accessible on the EudraVigilance training webpage[60] to stakeholders who wish to use it for their pharmacovigilance activities.

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

A review of the ICSRs quality, integrity and compliance with the submission time frames is performed by the Agency at regular intervals for all organisations submitting ICSRs to the EudraVigilance database 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 the EudraVigilance database, major changes to pharmacovigilance databases, quality issues identified as part of the signal management, requests from pharmacovigilance inspectors, or the time interval since the last review. The outcome of the review of the ICSRs quality and integrity is provided to the organisations on the basis of a report, which includes 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 depend on the quality issues identified (e.g. corrections of the MedDRA coding of ICSRs to be performed by means of amendment reports).

For the purpose of the monitoring of the compliance with the 15 or 90 days submission time frames, the Agency also provides the competent authority in a Member State and the marketing authorisation holder with monthly compliance reports, which apply to both initial and follow-up ICSRs. Specific rules on the compliance monitoring for amendment reports are detailed in VI.C.6.2.2.8..

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. for EU guidance on medical literature monitoring), and the entering of these reports in the EudraVigilance database in accordance with Article 27 of Regulation (EC) No 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 on the Agency's dedicated medical literature monitoring webpage[61].

In support of the operation of procedures that ensure detection and management of duplicate ICSRs, 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 . The collaboration between the Agency, the competent authority in a Member State and the marketing authorisation holder 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 also provided in GVP Module VI Addendum I – Duplicate management of adverse reaction reports.

[60] EudraVigilance training and support; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ EudraVigilance training.
[61] Monitoring of medical literature and entry of adverse reaction reports into EudraVigilance; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ Medical literature monitoring.

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 submitted by a marketing authorisation holder outside the EU to another marketing authorisation holder in the EU and from there to the Agency.

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:

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'. • Section A.3 'Information on sender and receiver of case safety report'. • Section 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.1.2 'Date of creation'. • 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'. • Section C.3 'Information on Sender of Case Safety Report'. • Section G.k.9.i.2.r 'Assessment of Relatedness of Drug to Reaction(s)/Event(s)'. • Section 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 submission time frames, the re-transmitter can correct information that has been incorrectly structured.

In addition, any electronic data interchange partner should adhere to the ICH-E2B rules regarding the provision of follow-up information, in accordance with the 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 submission of ICSRs through the headquarter of a marketing authorisation holder

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

- the central submitting 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 submitting the ICSRs should be registered with EudraVigilance.

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 the marketing authorisation holder. With regard to this, the marketing authorisation holder shall apply the internationally agreed formats and terminologies described in Chapter IV of the Commission Implementing Regulation (EU) No 520/2012. Guidance related to the electronic submission of information on medicines is provided on the Agency's website[62].

[62] EMA website: Home/ Human regulatory/ Post-authorisation/ Data submission on medicines (Article 57)/ Reporting requirements for authorised medicines/ Guidance documents.

VI. Appendix 1 Process for follow-up of ICSRs

VI.App.1.1. Follow-up of ICSRs by competent authorities in Member States and marketing authorisation holders

Figure VI.2. Business process map - Follow-up of ICSRs by competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs). See steps description in Table VI.2.

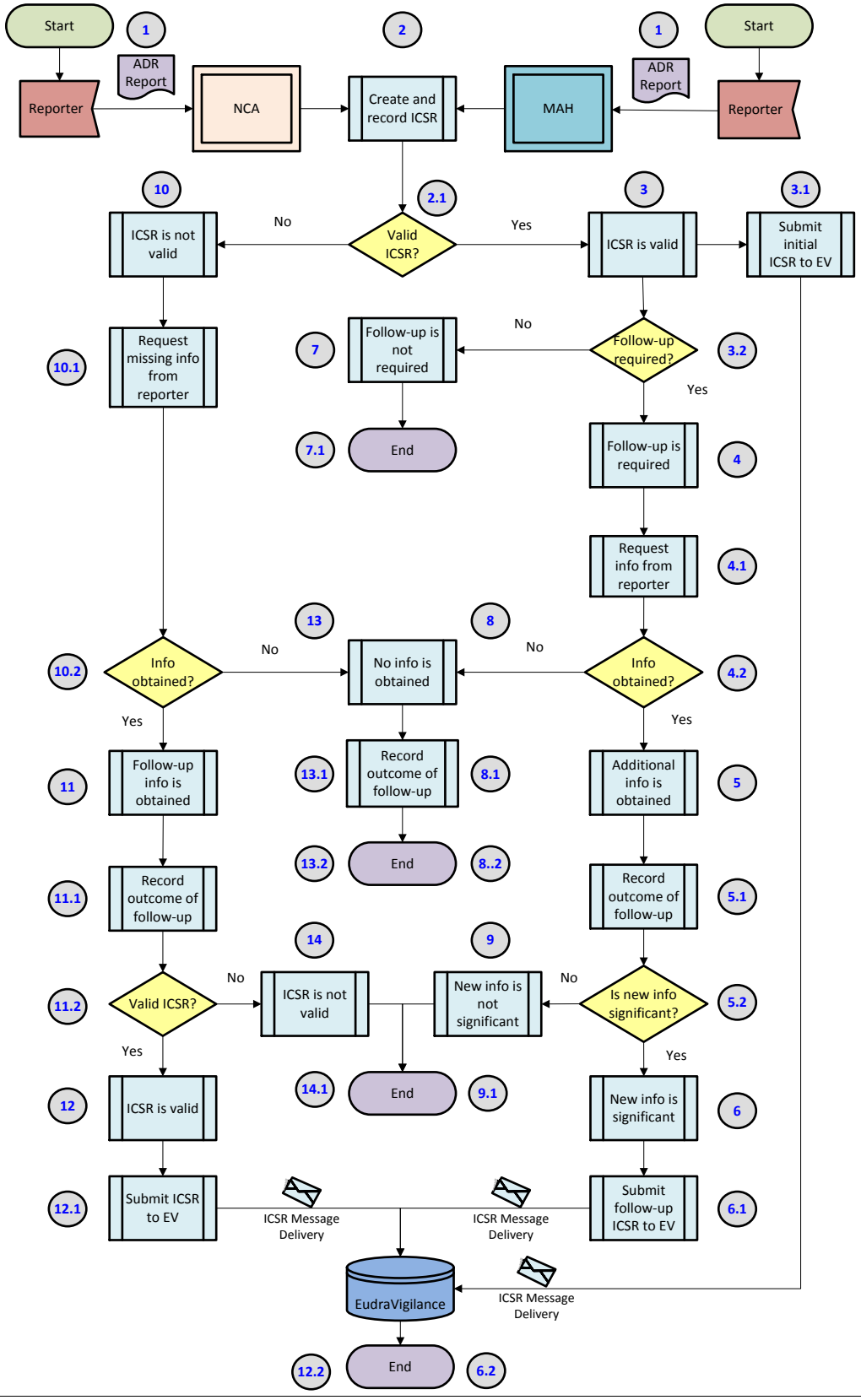


Table VI.2. Process description - Follow-up of ICSRs by competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs). See process map in Figure VI.2..

No	Step	Description	Responsible Organisation
1	**Start.**	**Receipt by the NCA or the MAH of a report of suspected adverse reaction related to a medicinal product (ADR report). Go to step 2.**	**NCA/MAH**
2	Create and record ICSR.	Create an individual case safety report (ICSR) and record it in the pharmacovigilance database. Go to step 2.1	NCA/MAH
2.1	Is ICSR valid?	Is the report received from the reporter a valid ICSR in accordance with VI.B.2.? If Yes, go to step 3. If No, go to step 10.	NCA/MAH
3	ICSR is valid.	The report received from the reporter is a valid ICSR. The clock start (D0) for the submission of the valid ICSR is the date of receipt of the report (see VI.B.7. for day zero definition). Go to step 3.1.	NCA/MAH
3.1	Submit initial ICSR to EV.	Submit the initial valid ICSR (EEA and non-EEA serious and EEA non-serious) to EudraVigilance (EV) within the relevant time frames (15 or 90 days, as applicable). Non-serious non-EEA ICSRs should not be submitted to EV. Go to step 6.2 for the end of the process for this ICSR. Go to step 3.2 for follow-up activity. NOTE: NCA/MAH can organise the submission of the initial and follow-up report in accordance with the appropriate time frames. If time permits and the follow-up information can be obtained and processed within the initial submission time frame, the NCA/MAH is not required to submit the initial and the follow-up report separately.	NCA/MAH
3.2	Is follow-up required?	Is follow-up with the reporter required for the valid ICSR? If Yes, go to step 4. If No, go to step 7.	NCA/MAH
4	Follow-up is required.	The ICSR is valid. Follow-up is necessary to obtain significant missing information for the evaluation of the ICSR. This includes information on the patient age or age group if missing, or the mandatory	NCA/MAH

No	Step	Description	Responsible Organisation
		information on the medicinal product batch number when it is missing and the reaction is suspected to be related to a biological medicinal product [DIR Art 102(e) and IR Art 28 (3)]. With respect to this, it is recommended to specify in the case narrative if information on the batch number has been requested, when it is missing in the initially submitted ICSR. Go to step 4.1.	
4.1	Request information from reporter.	Contact the reporter to obtain additional information pertinent to the valid case. (see follow-up guidance in VI.B.3. and VI.C.6.2.2.7.). Go to step 4.2. Note: Stakeholders should define in their SOPs how many attempts to contact the reporter should be made until the follow-up information is obtained (or the follow-up attempts can be ceased).	NCA/MAH
4.2	Is follow-up information obtained?	Has follow-up information been obtained from the reporter on the ICSR? If Yes, go to step 5. If No, go to step 8.	NCA/MAH
5	Additional information obtained.	Additional follow-up information has been obtained from the reporter. Go to step 5.1.	NCA/MAH
5.1	Record outcome of follow-up.	Record the follow-up information in the pharmacovigilance database. Go to step 5.2.	NCA/MAH
5.2	Is new information significant?	Determine if the new obtained information is significant enough (see VI.C.6.2.2.7. Subsection a for examples of significant and non-significant information) to be submitted to EV. If Yes, go to step 6. If No, go to step 9.	NCA/MAH
6	New information is significant.	The new follow-up information is significant enough to be submitted to EV. Go to step 6.1.	NCA/MAH
6.1	Submit follow-up ICSR to EV.	Submit the follow-up ICSR (EEA and non-EEA serious and EEA non-serious) with the new information to EV within the relevant time frames (15 or 90 days, as applicable). Non-serious non-EEA ICSRs should not be submitted to EV. Go to step 6.2.	NCA/MAH
6.2	End.	The ICSR is stored in EV for signal detection and data quality analyses following recoding and duplicate detection (see VI.App.6 for ICSRs data quality	NCA/MAH

No	Step	Description	Responsible Organisation
		monitoring in EV, and VI.App.7 for duplicate detection and management). It is also available for rerouting to the relevant NCA (See VI.App.3.4), and for access to MAHs to fulfil their pharmacovigilance activities. Go back to step 1 on the receipt of a new information for the ICSR.	
7	Follow-up is not required.	ICSR is valid. Follow-up may be performed as necessary to obtain administrative information not required for the scientific evaluation of the ICSR. Go to step 7.1.	NCA/MAH
7.1	End.	End of the process for this ICSR. Go back to step 1 on the receipt of a new information for the ICSR.	NCA/MAH
8	No information has been obtained.	The follow-up with the reporter is unsuccessful and no additional information on the ICSR can be obtained. Go to step 8.1.	NCA/MAH
8.1	Record the outcome of follow-up.	Record the fact that no further information has been obtained from the reporter. Go to step 8.2.	NCA/MAH
8.2	End.	End of the process for this ICSR. Go back to step 1 on the receipt of a new information for the ICSR. Note: when the suspected medicinal product is a biological product and the batch number information is not available in the initially submitted ICSR, a follow-up (or amendment) report should be submitted when no information is received on the missing batch number despite contact attempts with the reporter (see step 4). This should be specified in the narrative and with the nullFlavor ASKU where applicable under ICH-E2B(R3) format.	NCA/MAH
9	New information is not significant.	The new follow-up information is not significant enough to be submitted to EV. Go to step 9.1.	NCA/MAH
9.1	End.	End of the process for this ICSR. Go back to step 1 on the receipt of a new information for the ICSR.	NCA/MAH
10	ICSR is not valid.	The report received from the reporter is NOT a valid ICSR in accordance with VI.B.2.. Go to step 10.1.	NCA/MAH
10.1	Request missing info from reporter.	Request the missing information for the non-valid ICSR from the reporter (see guidance in VI.B.3. and VI.C.6.2.2.7.). Go to step 10.2.	NCA/MAH
10.2	Is follow-up information obtained?	Is follow-up information obtained from the reporter? If Yes, go to 11.	NCA/MAH

No	Step	Description	Responsible Organisation
		If No, go to 13.	
11	Follow-up information obtained.	Follow-up information has been obtained for the non-valid ICSR. Go to step 11.1.	NCA/MAH
11.1	Record the outcome of follow-up with reporter.	Record the new follow-up information in the pharmacovigilance database. Go to step 11.2.	NCA/MAH
11.2	Is the ICSR valid?	Is the ICSR with the new follow-up information valid in accordance with the guidance in VI.B.2. If Yes, go to 12. If No, go to 14.	NCA/MAH
12	ICSR is valid.	The ICSR is now valid taking into account the new information obtained from the reporter. The clock start (D0) for the submission of the valid ICSR is the date of receipt of the new information (see VI.B.7. for guidance on day zero). Go to step 12.1.	NCA/MAH
12.1	Submit ICSR to EV.	Submit the ICSR (EEA and non-EEA serious and EEA non-serious) with the new information to EV within the relevant time frames (15 or 90 days, as applicable). Non-serious non-EEA ICSRs should not be submitted to EV. Go to step 12.2.	NCA/MAH
12.2	End.	The ICSR is stored in EV for signal detection and data quality analyses following recoding and duplicate detection (see VI.App.6 for ICSRs data quality monitoring in EV, and VI.App.7 for duplicate detection and management). It is also available for rerouting to the relevant NCA (See VI.App.3.4), and for access to MAHs to fulfil their pharmacovigilance activities. Go back to step 1 on the receipt of a new information for the ICSR.	NCA/MAH
13	No information is obtained for non-valid ICSR.	No further information is obtained from the reporter for the non-valid ICSR. Go to step 13.1	NCA/MAH
13.1	Record outcome of the follow-up.	Record the fact that no further information has been obtained from the reporter for the non-valid ICSR. Go to step 13.2.	NCA/MAH
13.2	End.	End of the process for this non-valid ICSR. It should be considered as applicable in the safety evaluation activities. Go back to step 1 on the receipt of a new	NCA/MAH

No	Step	Description	Responsible Organisation
		information.	
14	ICSR is not valid.	The ICSR remains non-valid despite the new follow-up information received from the reporter. Go to step 14.1.	NCA/MAH
14.1	End.	End of the process for this non-valid ICSR. It should be considered as applicable in the safety evaluation activities. Go back to step 1 on the receipt of a new information.	NCA/MAH

VI.App.1.2. Follow-up of ICSRs by competent authorities in Member States with involvement of marketing authorisation holders

Figure VI.3. Business process map - Follow-up of ICSRs by competent authorities in Member States (NCAs) with involvement of marketing authorisation holders (MAHs). See steps description in Table VI.3..

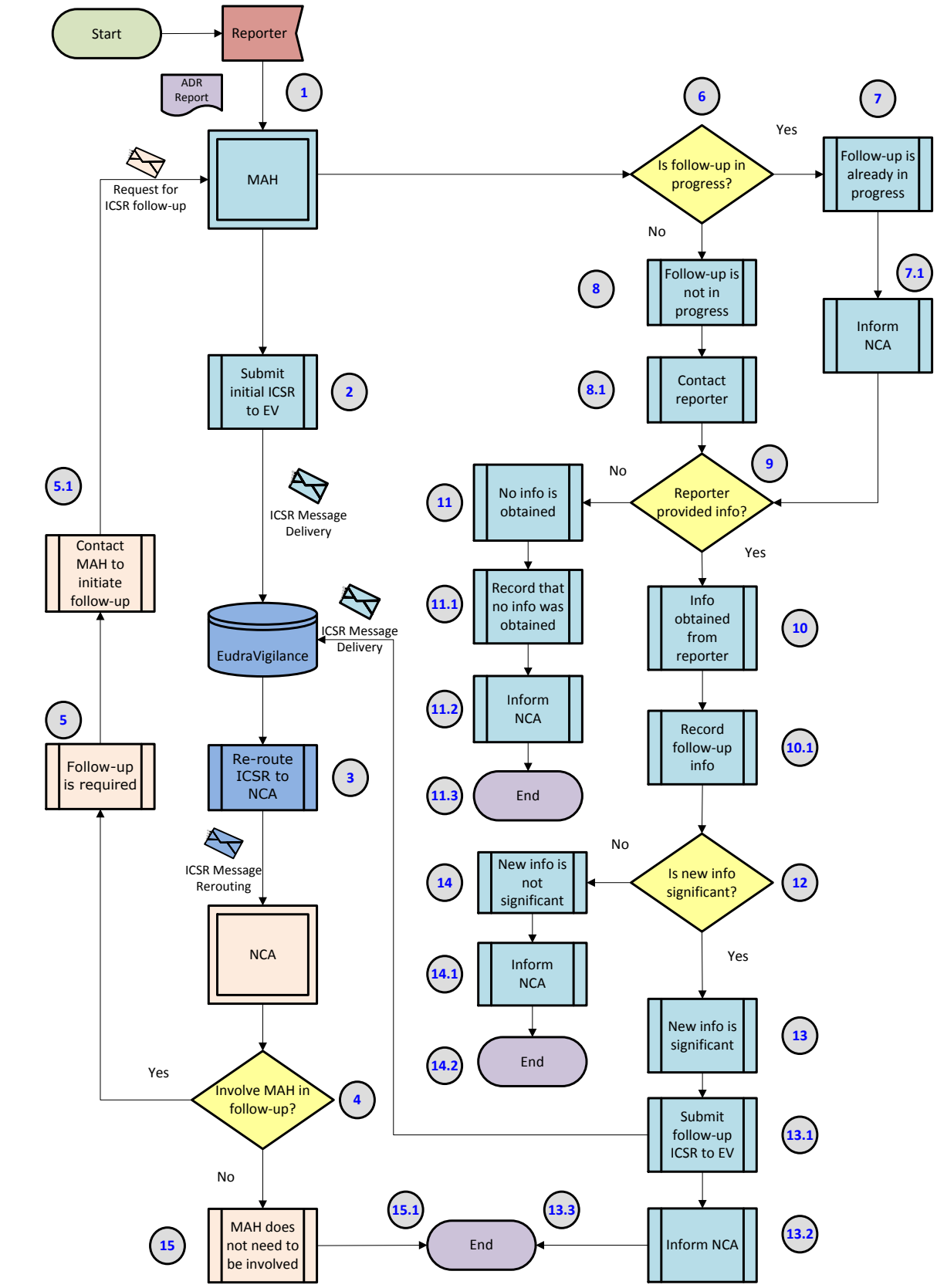


Table VI.3. Process description - Follow-up of ICSRs by competent authorities in Member States (NCAs) with involvement of marketing authorisation holders (MAHs). See process map in Figure VI.3..

No	Step	Description	Responsible Organisation
1	**Start.**	**Receipt by the MAH of a valid report of suspected adverse reaction related to a medicinal product (ADR report). The clock (D0) for the submission of the valid ICSR starts** (see VI.B.7. for day zero definition). Go to step 2.	MAH
2	Submit ICSR to EV.	Submit the valid ICSR (EEA and non-EEA serious and EEA non-serious) to EudraVigilance (EV) within the relevant time frames (15 or 90 days, as applicable). Non-serious non-EEA ICSRs should not be submitted to EV. Go to step 3.	MAH
3	Re-route ICSR to NCA.	Following technical validation and process, the EEA ICSR submitted by the MAH is rerouted from EV to the relevant NCA. Go to step 4.	EMA
4	Involve MAH in follow-up?	Is follow-up required for the ICSR with involvement of the MAH? If Yes, go to step 5. If No, go to step 15.	NCA
5	Follow-up is required.	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)] (see VI.C.2.1. for Member States responsibilities on ICSRs collection). The criteria for involving the MAH include: - Need for important additional information for the ICSR evaluation or reconciliation, - Need for clarifications regarding inconsistent data, - 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. Go to step 5.1.	NCA
5.1	Contact MAH to initiate follow-up.	Send an email to the MAH QPPV (or the local contact person where applicable) to request for the missing information. Identify the reference of the concerned ICSR(s) by using the World Wide Unique Case Identifier(s). Indicate the criteria for the request to involve the	NCA

No	Step	Description	Responsible Organisation
		MAH in the ICSR(s) follow-up. Indicate the timeframe by when follow-up information should be provided. Go to step 6.	
6	Is follow-up in progress?	Has follow-up of the reporter already been initiated by the MAH? If Yes, go to step 7. If No go to step 8.	MAH
7	Follow-up is already in progress.	Follow-up has already been initiated by the MAH to request additional information from the reporter. Go to step7.1.	MAH
7.1	Inform NCA.	Inform the NCA that follow-up is already in progress. Indicate if the follow-up information cannot be provided within the requested time frame and clarify the time by when the follow-up can be expected. Provide the reference to the individual case using the World Wide Unique Case Identifier in the communication. Go to step 9.	MAH
8	Follow-up is not in progress.	Follow-up has not yet been initiated by the MAH with the reporter. Go to step 8.1.	MAH
8.1	Contact reporter.	Contact the reporter as soon as possible to obtain follow-up information as per the NCA's request. Go to step 9. Note: MAH may indicate that the follow-up is performed upon request of a NCA.	MAH
9	Reporter provided information?	Was the requested information provided by the reporter? If Yes, proceed to step 10. If No, proceed to step 11.	MAH
10	Information obtained from reporter.	The requested information was obtained from the reporter. Go to step 10.1.	MAH
10.1	Record follow-up information.	Record the follow-up information in pharmacovigilance database. Go to step 12.	MAH
11	No information is obtained.	The reporter did not provide follow-up information. Go to step 11.1.	MAH

No	Step	Description	Responsible Organisation
11.1	Record that no follow-up information was obtained.	Record that the reporter did not provide follow-up information. Go to step 11.2.	MAH
11.2	Inform NCA.	Inform the NCA that it was not possible to obtain follow-up information from the reporter. Provide the reference to the individual case using the World Wide Unique Case Identifier in the communication. Go to step 11.3.	MAH
11.3	End.	End of this follow-up process.	NCA/MAH
12	Is new information significant?	Determine if the new obtained follow-up information is significant enough (see VI.C.6.2.2.7. Subsection a for examples of significant and non-significant information) to be submitted to EV. If Yes, proceed to step 13 If No, proceed to step 14.	MAH
13	New information is significant.	The new follow-up information is significant enough to be submitted to EV. Go to step 13.1.	MAH
13.1	Submit follow-up ICSR to EV.	Submit the follow-up ICSR to EV within the relevant time frames (15 or 90 days, as applicable). Following technical validation and process, the follow-up ICSR is rerouted from EV to the relevant NCA. Go to step 13.2.	MAH
13.2	Inform NCA.	Inform the NCA that significant follow-up information was received from the reporter and submitted to EV. Provide the reference to the individual case using the World Wide Unique Case Identifier in the communication. Go to step 13.3.	MAH
13.3	End.	End of this follow-up process. The follow-up ICSR is now stored in the NCA database. It is available for signal detection and data quality analyses.	NCA/MAH
14	New information is not significant.	The new follow-up information is not significant enough to be submitted to EV. Go to step 14.1.	MAH
14.1	Inform NCA.	Inform the NCA that the new follow-up information received from the reporter is not significant and does not require submission to EV. Provide the reference to the individual case using the World Wide Unique Case Identifier in the	MAH

No	Step	Description	Responsible Organisation
		communication. Go to step 14.2.	
14.2	End.	End of this follow-up process.	NCA/MAH
15	MAH does NOT need to be involved.	There is no need to involve the MAH in the ICSR follow-up.	NCA
15.1	End.	The ICSR is now stored in the NCA database. It is available for signal detection and data quality analyses.	NCA

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

VI.App.2.1. When to start and stop searching in the medical literature

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

In addition to the submission 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 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. and GVP Module IX for guidance on emerging safety issue), 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.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. The 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 valid 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 valid ICSRs can be 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.

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) No 726/2004 and the ICSRs submission 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.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.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.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.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 submission as ICSR ;
- 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, misuse, abuse, occupational exposure;
  - reports of uneventful pregnancy.

VI.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 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 valid ICSRs which qualify for submission, 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.App.2.4. Record keeping

Records of literature searches should be maintained in accordance with the requirements described in Article 12 of the Commission Implementing Regulation (EU) No 520/2012. Marketing authorisation holders should demonstrate due diligence in searching published 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.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.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 submission as ICSR (see VI.C.2.2.3.2. for the exclusion criteria in the submission of ICSRs published in the medical literature).

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 for the submission of valid 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. Alternative reasons for the exclusion of a published article for the submission of ICSRs are detailed in VI.C.2.2.3.2..

VI.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 qualify for submission. 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 the submission of an 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.App.2.8. Duplicates

Consistent with the general requirements for the submission of cases of suspected adverse reactions, literature cases should be checked to prevent the submission of duplicates ICSRs. It is, therefore, expected that ICSRs are checked in the organisation database to identify literature articles that have already been submitted. Where applicable, this should include ICSRs resulting from the Agency's Medical Literature Monitoring activities in accordance with Article 27 of Regulation (EC) No 726/2004.

VI.App.2.9. Contracting out literature search services

It is possible to use the services of another party to conduct searches of the published medical literature. In this event, the responsibility for the performance of the search and subsequent submission of ICSRs still remains with the exception of the provisions set out in Article 27 of Regulation (EC) No 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 ICSRs submission (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 submission 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 medical literature, in order to ensure that published literature cases are 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.App.2.10. Electronic submission of copies of articles on suspected adverse reactions published in the medical literature

In accordance with Article 28(3) of the Commission Implementing Regulation (EU) No 520/2012, 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.4. Electronic submission of copies of literature articles/translations in line with ICH-E2B

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 medical literature, marketing authorisation holders are recommended to consider potential copyright issues specifically as regards the electronic submission 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. Submission of cases described in the 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 submitted individual case described in the article. In addition, all ICSRs which relate to the same literature article should be cross 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.

Reference	E2B(R2)/(R3) requirements
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[63]. • 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 hereafter highlights 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 submission, attachments can be submitted separately. 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. for guidance on amendment reports). 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. • In addition, all ICSRs which relate to the same literature article should be cross referenced in data element C.1.10.r 'Identification Number of the Report Linked to this Report (repeat as necessary)'.

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

Table VI.5. Examples for the submission as ICSRs of suspected adverse reactions described in the 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 more than one identifiable patient. ICSRs should be created and submitted for each individual identifiable patient described in the literature article. Each ICSR should contain all the	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' 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 one, as in the example below. *Example for the submission of cases originally described in*

[63] Accessible at http://estri.ich.org/e2br3/index.htm.

Ex.	Scenario	Action
	available information on the case. The cross reference with all the linked ICSRs from this literature article should only be provided in the first submitted ICSR, 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.	*the medical literature referring to a large number of patients:* For 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) 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)': 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/translation: follow steps as outlined in Table VI.4. 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)': 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.

Ex.	Scenario	Action
		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)': 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.

VI. Appendix 3 Modalities for the submission of ICSRs in EU

VI.App.3.1. Modalities applicable to competent authorities in Member States and to marketing authorisation holders

Figure VI.4. Business process map - ICSRs submission in EU by competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs). See steps description in Table VI.6..

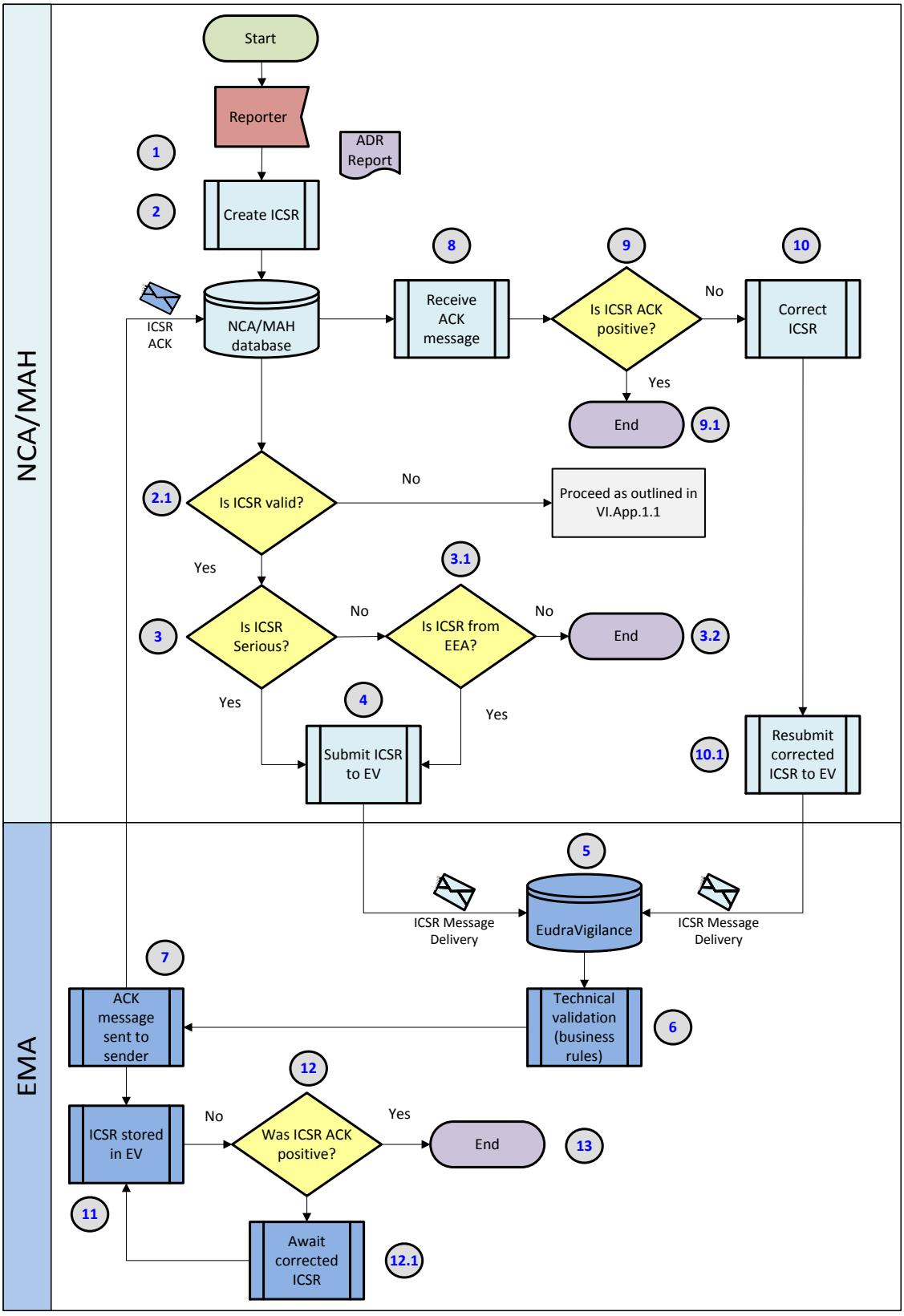


Table VI.6. Process description - ICSRs submission in EU by competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs). See process map in Figure VI.4..

No.	Step	Description	Responsible Organisation
1	**Start.**	**Receipt by the NCA or the MAH of a report of suspected adverse reaction related to a medicinal product (ADR report). Go to step 2.**	**NCA/MAH**
2	Create ICSR.	Create an individual case safety report (ICSR). Go to step 2.1.	NCA/MAH
2.1	Is ICSR valid?	Is the report a valid ICSR in accordance with VI.B.2.? If no, follow-up on the ICSR as described in VI.App.1.1. If yes, go to step 3.	NCA/MAH
3	Is ICSR serious?	Is the ICSR serious? If No go to step 3.1. If Yes, go to step 4.	NCA/MAH
3.1	Is ICSR from EEA?	Is the ICSR from EEA? If No go to step 3.2. If Yes, go to step 4.	NCA/MAH
3.2	End.	The ICSR is not serious and it is not from the EEA. It should not be sent to EV.	NCA/MAH
4	Submit ICSR to EV.	Submit the ICSR (EEA and non-EEA serious, and EEA non-serious) to EudraVigilance (EV) in ICH-E2B(R2/R3) format as an XML message within the relevant time frame (15 or 90 days, as applicable). Non-serious non-EEA ICSRs should not be submitted to EV. Go to step 5. See guidance in the EU Individual Case Safety Report (ICSR) Implementation Guide (EMA/51938/2013) in case of system failure in safety message generation, submission, receipt, processing and rerouting.	NCA/MAH
5	Message received in EV.	Receive the message in the EV. Go to step 6.	EMA
6	Technical Validation (EV Business Rules).	Every message received in EV is validated against the EudraVigilance Business Rules and an acknowledgement message (ACK) is created specifying whether the message & ICSR(s) therein are correct. The acknowledgement message is sent to the sender	EMA

No.	Step	Description	Responsible Organisation
		(Go to step 7). - E2B(R2) messages will receive an E2B(R2) acknowledgement. - E2B(R3) messages will receive an E2B(R3) acknowledgement. - A correct E2B(R2) ICSR will have an E2B(R2) ACK code 01 (ACK_B.1.8). - An E2B(R2) ICSR not correct will have an E2B(R2) ACK code 02 (ACK_B.1.8). - An E2B(R2) message will receive a transmission acknowledgement code 03 (ACK_A.1.6) if the message is not correctly formatted. - A correct E2B(R3) ICSR will have an E2B(R3) ACK code "CA" (ACK.B.r.6). - An E2B(R3) ICSR not correct will have an E2B(R3) ACK code "CR" (ACK.B.r.6). - An E2B(R3) message will receive a transmission acknowledgement code "AR" (ACK.A.4) if the message is not correctly formatted.	
7	ACK message sent.	The acknowledgement message created in step 6 is transmitted to the sender no later than 2 business days following the receipt of the ICSR. Go to step 11 for the EMA's next step. Go to step 8 for MAH/NCA's next step.	EMA
8	Receive ACK message.	Receive the ACK message. Associate it with the relevant ICSR and check that it was considered valid. Go to step 9.	NCA/MAH
9	Is ICSR ACK positive?	Is a positive acknowledgement code received for the ICSR? If yes, go to step 9.1. If no, then the regulatory timeline clock has not stopped and the ICSR should be corrected and re-transmitted to EV within the relevant regulatory timelines. Day 0 remains as the day that the first information was received. Go to step 10 to correct the ICSR. Neither an ICSR not correct (with an E2B(R2) ACK code 02 or E2B(R3) ACK code "CR"), nor a message not correct (with an E2B(R2) transmission acknowledgement code 03 or E2B(R3) transmission	NCA/MAH

No.	Step	Description	Responsible Organisation
		acknowledgement code "AR") constitute new information.	
9.1	End.	End the process for this ICSR. Normal follow-up activities should continue and if any follow-up report is received, return to step 1.	NCA/MAH
10	Correct ICSR.	Correct the ICSR to remove the errors identified in the ACK. Go to step 10.1.	NCA/MAH
10.1	Resubmit corrected ICSR.	Resubmit the corrected ICSR to EV. Go back to step 5 for the receipt of the corrected ICSR in EV.	NCA/MAH
11	Store ICSR in EV.	Once the ICSR has been technically validated (step 6) and the acknowledgement message is transmitted to the sender (step 7), the ICSR is stored in the EV. Go to step 12.	EMA
12	Was ICSR ACK positive?	Did the technical validation of the ICSR in step 6 create a positive ACK code? If no, perform no further processing on this version of the ICSR and go to step 12.1 If Yes, go to step 13.	EMA
12.1	Await corrected case.	The sender should correct every ICSR with an error ACK and retransmit it within the appropriate regulatory timelines. EMA periodically assesses all ICSRs with an error ACK for which a corrected version has not been transmitted and contact the sender to inform of these missing corrected ICSRs. If a sender fails to correct the ICSRs, this information is incorporated into data quality assessments and the appropriate committee is informed. The ICSR stored in EV (step 11) while waiting for corrected version. Go back to step 5 upon receipt of the corrected ICSR.	EMA
13	End.	The ICSR is now stored in EV. It is available for signal detection and data quality analyses following duplicate detection and recoding. If the ICSR occurred in the EU and was transmitted to EV by a MAH, it will be rerouted to the relevant NCA (see VI.App.3.4). See guidance in the EU Individual Case Safety Report	EMA

No.	Step	Description	Responsible Organisation
		(ICSR) Implementation Guide (EMA/51938/2013) in case of system failure in safety message generation, submission, receipt, processing and rerouting.	

VI.App.3.2. Requirements applicable to marketing authorisation holders

Table VI.7. ICSRs submission requirements applicable to marketing authorisation holders

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.App.3.3. Requirements applicable to competent authorities in Member States

Table VI.8. ICSRs submission requirements applicable to competent authorities in Member States

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.App.3.4. Rerouting to competent authorities in Member States of ICSRs submitted to EudraVigilance by marketing authorisation holders

Figure VI.5. Business process map - Rerouting to competent authorities in Member States (NCAs) of ICSRs submitted to EudraVigilance by marketing authorisation holders (MAHs). See steps description in Table VI.9..

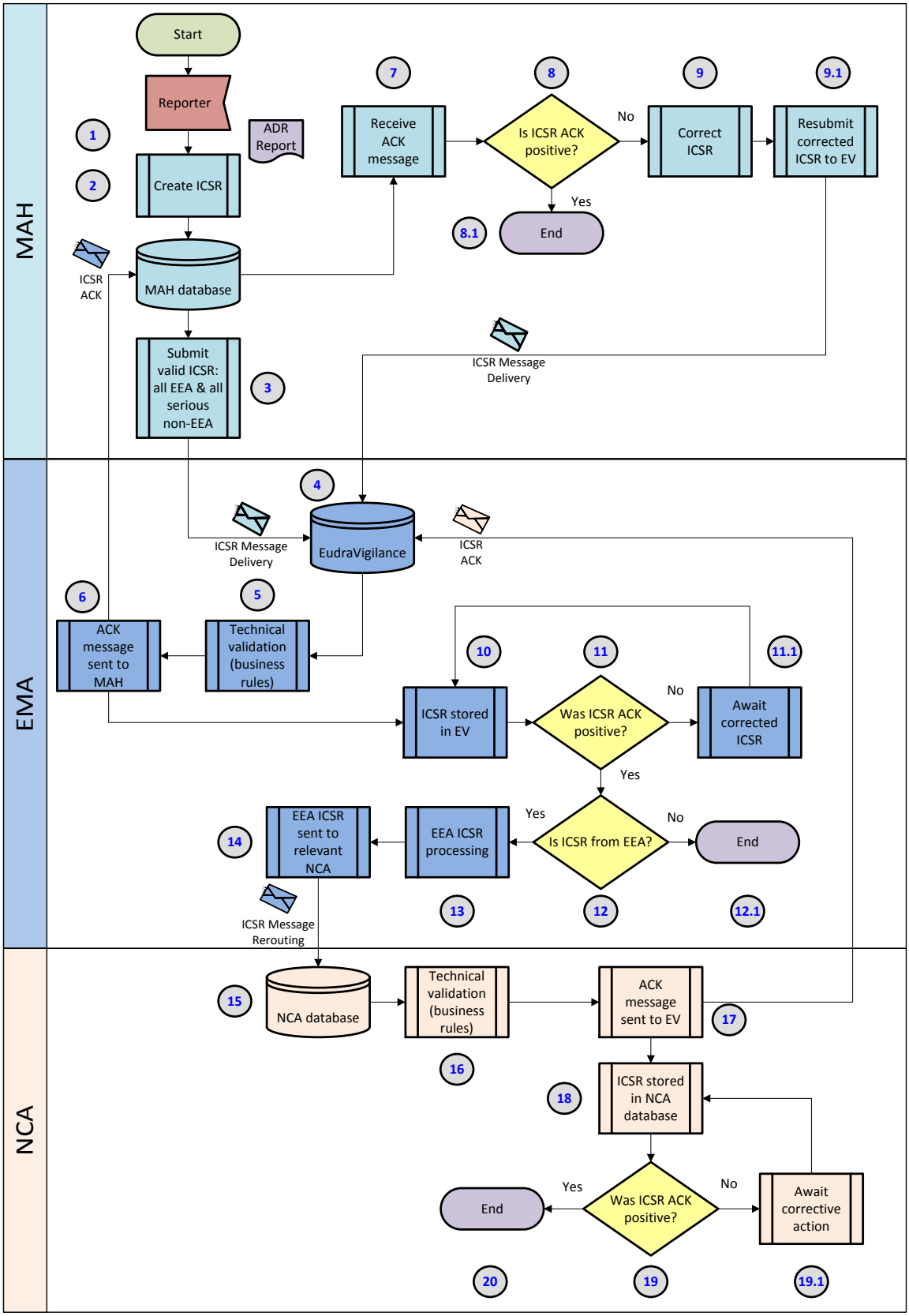


Table VI.9. Process description - Rerouting to competent authorities in Member States (NCAs) of ICSRs submitted to EudraVigilance by marketing authorisation holders (MAHs). See process map in Figure VI.5..

No.	Name	Description	Responsible organisation
1	**Start.**	**Receipt by the MAH of a report of suspected adverse reaction related to a medicinal product (ADR report). Go to step 2.**	**MAH**
2	Create ICSR.	Create an individual case safety report (ICSR). Go to step 3.	MAH
3	Submit valid ICSR to EV.	Submit the valid ICSR (EEA and non-EEA serious, and EEA non-serious) to EudraVigilance (EV) in ICH-E2B(R2/R3) format as an XML message within the relevant time frames (15 or 90 days, as applicable). Non-serious non-EEA ICSRs should not be submitted to EV. Go to step 4. Proceed as outlined in VI.App.1.1. if the ICSR is not valid. See guidance in the EU Individual Case Safety Report (ICSR) Implementation Guide (EMA/51938/2013) in case of system failure in safety message generation, submission, receipt, processing and rerouting.	MAH
4	Message received in EV.	Receive the message in the EV. Go to step 5.	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 the message and the ICSR(s) therein are valid. The acknowledgement message is sent to the MAH (Go to step 6). - E2B(R2) messages will receive an E2B(R2) acknowledgement. - E2B(R3) message will receive an E2B(R3) acknowledgement. - A correct E2B(R2) ICSR will have an E2B(R2) ACK code 01 (ACK_B.1.8). - An E2B(R2) ICSR not correct will have an E2B(R2) ACK code 02 (ACK_B.1.8). - An E2B(R2) message will receive a transmission acknowledgement code 03 (ACK_A.1.6) if the message is not correctly formatted. - A correct E2B(R3) ICSR will have an E2B(R3) ACK	EMA

No.	Name	Description	Responsible organisation
		code "CA" (ACK.B.r.6). - An E2B(R3) ICSR not correct will have an E2B(R3) ACK code "CR" (ACK.B.r.6). - An E2B(R3) message will receive a transmission acknowledgement code "AR" (ACK.A.4) if the message is not correctly formatted.	
6	ACK message sent.	The acknowledgement message created in step 5 is transmitted to the MAH no later than 2 business days following the receipt of the ICSR. Go to step 10 for EMA's next step. Go to step 7 for MAH's next step.	EMA
7	Receive ACK message.	Receive the ACK message. Associate it with the relevant ICSR and check to ensure that it was considered valid. Go to step 8.	MAH
8	Is ICSR ACK positive?	Is a positive acknowledgement code received for the ICSR? If Yes, go to step 8.1. If no, then the regulatory timeline clock has not stopped and the ICSR should be corrected and re-transmitted to EV within the relevant regulatory timelines. Day 0 remains as the day that the first information was received. Go to step 9 to correct the ICSR. Neither an ICSR not correct (E2B(R2) ACK code 02 or E2B(R3) ACK code "CR"), nor a message not correct (E2B(R2) transmission acknowledgement code 03 or E2B(R3) transmission acknowledgement code "AR") constitute new information.	MAH
8.1	End.	End the process of transmitting this version of the ICSR to EV. Normal follow-up activities should continue and if any follow-up is received, return to step 1.	MAH
9	Correct ICSR.	Correct the ICSR to remove the errors identified in the ACK. Go to step 9.1.	MAH
9.1	Resubmit corrected ICSR.	Resubmit the corrected ICSR to EV. Go back to step 4 for the receipt of the corrected ICSR in EV.	MAH
10	ICSR stored in EV.	Once the ICSR has been technically validated (step 5) and the acknowledgement message is transmitted	EMA

No.	Name	Description	Responsible organisation
		to the MAH (step 6), the ICSR is stored in EV. Go to step 11.	
11	Was ICSR ACK positive?	Did the technical validation of the ICSR in step 5 create a positive ACK code? If no, perform no further processing on this version of the ICSR and go to step 11.1 If Yes, go to step 12.	EMA
11.1	Await corrected ICSR.	The sender should correct every ICSR with an error ACK and retransmit it within the appropriate regulatory timelines. EMA periodically assesses all ICSRs with an error ACK for which a corrected version has not been transmitted and contact the sender to inform of these missing corrected ICSRs. If a sender fails to correct the ICSRs, this information is incorporated into data quality assessments and the appropriate committee is informed. ICSR stored in EV (step 10) while waiting for corrected version. Go back to step 4 upon receipt of the corrected ICSR.	EMA
12	Is ICSR from EEA?	Whenever a message has passed the technical validation (step 11), the ICSRs therein are immediately assessed to determine the primary source country for regulatory reporting purposes. Is the ICSR from EEA? If Yes, go to step 13. If No, go to step 12.1.	EMA
12.1	End.	The ICSR is now stored in EV. It is available for signal detection and data quality analyses following duplicate detection and recoding.	EMA
13	EEA ICSR processing for rerouting.	The ICSRs occurring in the EEA are extracted from the message for processing prior to retransmission to the relevant NCA. For the retransmission of E2B(R2) messages the 'Message sender identifier' (ICH E2B(R2) M.1.5) of the sending MAH is inserted in data element 'Sender organisation' (ICH-E2B(R2) A.3.1.2) prior to retransmission. This is to permit the receiving National Competent Authority (NCA) to	EMA

No.	Name	Description	Responsible organisation
		unambiguously identify the MAH responsible for transmitting the ICSR to EV. For the retransmission of E2B(R3) messages the data element N.2.r.2 'Message sender identifier' remains unchanged with the MAH identifier. Go to step 14. See guidance in the EU Individual Case Safety Report (ICSR) Implementation Guide (EMA/51938/2013) in case of system failure in safety message generation, submission, receipt, processing and rerouting.	
14	ICSR sent to relevant NCA.	The ICSR is transmitted to the relevant NCA with no other changes. Where a Member State has more than one NCA responsible for post-marketing reports, the ICSRs occurring in that Member State are sent to all relevant NCAs. Go to step 15.	EMA
15	Message received in NCA database.	Message with EEA ICSRs are received in the relevant NCA database. Go to step 16.	NCA
16	Technical Validation (EV Business Rules).	Every message should be validated against the EudraVigilance Business Rules (the same business rules as in step 5 and an Acknowledgement message (ACK) is created specifying whether the message and the ICSRs therein are valid. The acknowledgement message is sent to EV (step 17). - A correct E2B(R2) ICSR will have an E2B(R2) ACK code 01 (ACK_B.1.8). - An E2B(R2) ICSR not correct will have an E2B(R2) ACK code 02 (ACK_B.1.8). - An E2B(R2) message not correct will receive a transmission acknowledgement code 03 (ACK_A.1.6) if the message is not correctly formatted. - A correct E2B(R3) ICSR will have an E2B(R3) ACK code "CA" (ACK.B.r.6). - An E2B(R3) ICSR not correct will have an E2B(R3) ACK code "CR" (ACK.B.r.6). - An E2B(R3) message not correct will receive a transmission acknowledgement code "AR" (ACK.A.4) if the message is not correctly formatted.	NCA

No.	Name	Description	Responsible organisation
17	ACK message sent.	The acknowledgement message created in step 16 is transmitted to EV within 2 business days following the receipt of the ICSR. Go to step 18.	NCA
18	ICSR stored.	The ICSR is stored in the NCA database. Go to step 19.	NCA
19	Was ICSR ACK positive?	Did the technical validation of the ICSR in step 16 create a positive ACK code? If no go to step 19.1. If yes go to step 20.	NCA
19.1	Await corrective action.	The concerned NCA with negative acknowledgement is contacted by EMA to resolve the technical issues and the message is retransmitted if needed. The ICSR is stored in the NCA database (step 18 while waiting for a corrected version). Go back to step 15 upon receipt of the corrected ICSR.	NCA
20	End.	The ICSR is now stored in the NCA database. It is available for signal detection and data quality analyses.	NCA

VI. Appendix 4 Submission of ICSRs to the World Health Organization (WHO)

Figure VI.6. Business process map - Submission of ICSRs to the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring. See steps description in Table VI.10..

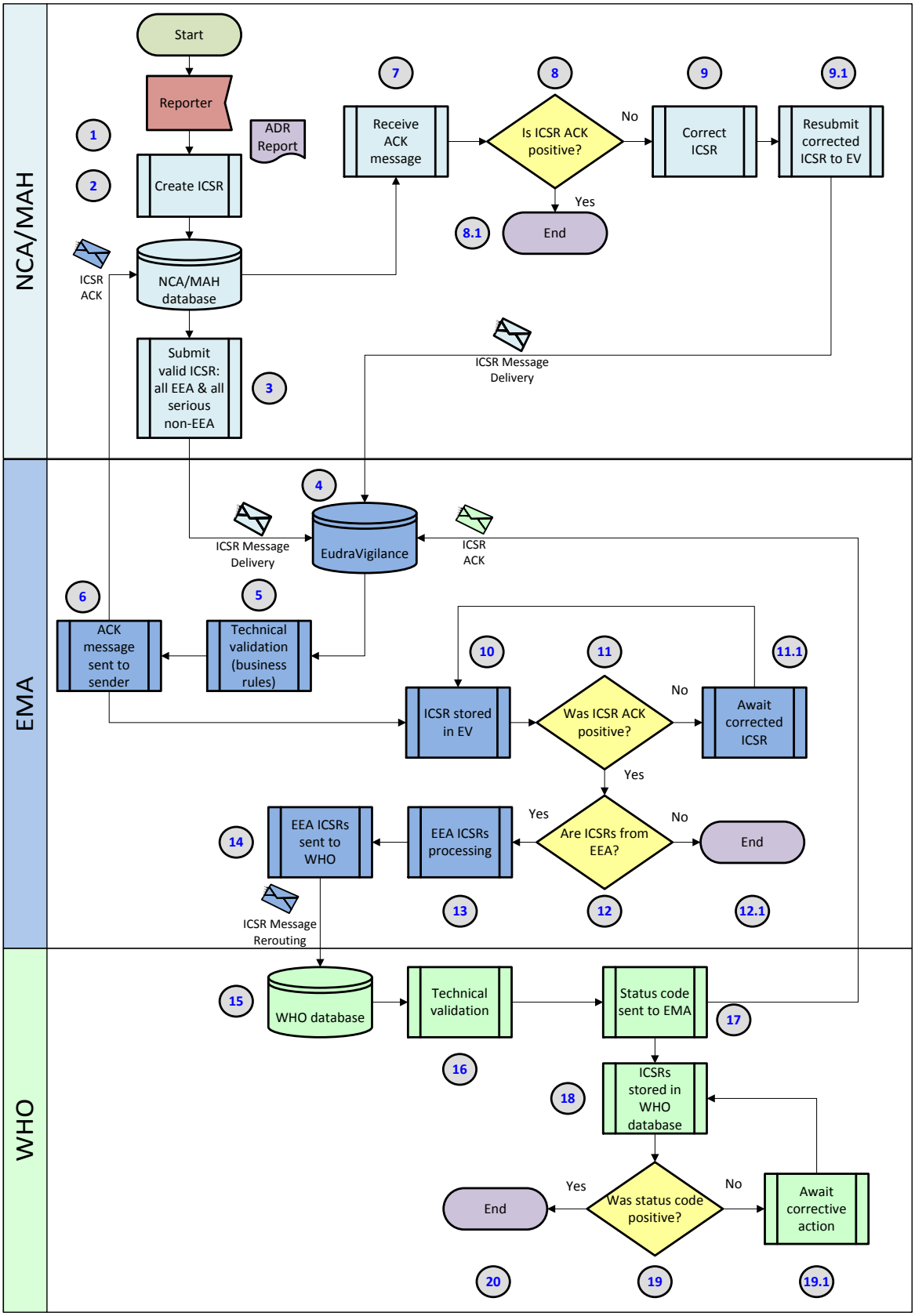


Table VI.10. Process description - Submission of ICSRs to the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring. See process map in Figure VI.6..

No.	Step	Description	Responsible organisation
1	**Start.**	**Receipt by the NCA or the MAH of a report of suspected adverse reaction related to a medicinal product (ADR report). Go to step 2.**	**NCA/MAH**
2	Create ICSR.	Create an individual case safety report (ICSR). Go to step 3.	NCA/MAH
3	Submit valid ICSR to EV.	Submit the valid ICSR (EEA and non-EEA serious, and EEA non-serious) to EudraVigilance (EV) in ICH-E2B(R2/R3) format as an XML message within the relevant time frames (15 or 90 days, as applicable). Non-serious non-EEA ICSRs should not be submitted to EV. Go to step 4. Proceed as outlined in VI.App.1.1. if the ICSR is not valid. See guidance in the EU Individual Case Safety Report (ICSR) Implementation Guide (EMA/51938/2013) in case of system failure in safety message generation, submission, receipt, processing and rerouting.	NCA/MAH
4	Message received in EV.	Receive the message in EV. Go to step 5.	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 the message and the ICSR(s) therein are valid. The acknowledgement message is sent to the sender (step 6). - E2B(R2) messages will receive an E2B(R2) acknowledgement. - E2B(R3) message will receive an E2B(R3) acknowledgement. - A correct E2B(R2) ICSR will have an E2B(R2) ACK code 01 (ACK_B.1.8). - An E2B(R2) ICSR not correct will have an E2B(R2) ACK code 02 (ACK_B.1.8). - An E2B(R2) message will receive a transmission acknowledgement code 03 (ACK_A.1.6) if the message is not correctly formatted. - A correct E2B(R3) ICSR will have an E2B(R3) ACK code "CA" (ACK.B.r.6).	EMA

No.	Step	Description	Responsible organisation
		- An E2B(R3) ICSR not correct will have an E2B(R3) ACK code "CR" (ACK.B.r.6). - An E2B(R3) message will receive a transmission acknowledgement code "AR" (ACK.A.4) if the message is not correctly formatted.	
6	ACK message sent.	The acknowledgement message created in step 5 is transmitted to the sender no later than 2 business days following the receipt of the ICSR. Go to step 10 for EMA's next step. Go to step 7 for NCA/MAH's next step.	EMA
7	Receive ACK message.	Receive the ACK message. Associate it with the relevant ICSR and check to ensure that the ICSR was considered valid.	NCA/MAH
8	Is ICSR ACK positive?	Is a positive acknowledgement code received for the ICSR? If Yes, go to step 8.1. If no, then the regulatory timeline clock has not stopped and the ICSR should be corrected and re-transmitted to EV within the relevant regulatory timelines. Day 0 remains as the day that the first information was received. Go to step 9 to correct the ICSR. Neither an ICSR not correct (E2B(R2) ACK code 02 or E2B(R3) ACK code "CR"), nor a message not correct (E2B(R2) transmission acknowledgement code 03 or E2B(R3) transmission acknowledgement code "AR") constitute new information.	NCA/MAH
8.1	End.	End the process of transmitting this version of the ICSR to EV. Normal follow-up activities should continue and if any follow-up is received, return to step 1.	NCA/MAH
9	Correct ICSR.	Correct the ICSR to remove the errors identified in the. Go to step 9.1.	NCA/MAH
9.1	Resubmit corrected ICSR.	Resubmit the corrected ICSR to EV. Go back to step 4 for the receipt of the corrected ICSR in EV.	NCA/MAH
10	ICSR stored in EV.	Once the ICSR has been technically validated (step 5) and the acknowledgement message is transmitted	EMA

No.	Step	Description	Responsible organisation
		to the MAH (step 6), the ICSR is stored in EV. Go to step 11.	
11	Was ICSR ACK positive?	Did the technical validation of the ICSR in step 5 create a positive ACK code? If no, perform no further processing on this version of the ICSR and go to step 11.1. If Yes, go to step 12.	EMA
11.1	Await corrected ICSR.	The sender should correct every ICSR with an error ACK and retransmit it within the appropriate regulatory timelines. EMA periodically assesses all ICSRs with an error ACK for which a corrected version has not been transmitted and contact the sender to inform of these missing corrected ICSRs. If a sender fails to correct the ICSRs, this information is incorporated into data quality assessments and the appropriate committee is informed. The ICSR is stored in EV (step 10) while waiting for a corrected version. Go back to step 4 upon receipt of the corrected ICSR.	EMA
12	Is ICSR from EEA?	Once a week, for every message that has passed the technical validation, the ICSRs therein are assessed to determine the country where the reaction occurred for regulatory reporting purposes. Is the ICSR from EEA? If Yes, go to step 13. If No, go to step 12.1.	EMA
12.1	End.	The ICSR is now stored in EV. It is available for signal detection and data quality analyses following duplicate detection and recoding.	EMA
13	EEA ICSR processing.	Prior to sending the ICSRs to the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, the ICSRs occurring in the EEA are extracted in line with the EudraVigilance Access Policy for Medicines for Human Use[64]. Go to step 14.	EMA
14	ICSRs sent to WHO.	The ICSRs are sent through the VigiBase API. Go to step 15.	EMA

[64] Ref.: EMA/759287/2009; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Access to data.

No.	Step	Description	Responsible organisation
15	Message received by WHO.	The submitted message with the EEA ICSRs is received by WHO Collaborating Centre. A Message ID for each submitted file is created and sent back to EMA. Go to step 16.	WHO
16	Technical Validation.	Technical validation is performed on the submitted ICSRs. A status code is recorded for each message. Go to step 17.	WHO
17	Status code sent to EMA.	The message status code created in step 16 is transmitted to EMA with the corresponding Message ID. Go to step 18.	WHO
18	ICSRs stored in WHO database.	Once the ICSRs have been validated, they are stored in the WHO database. Go to step 19.	WHO
19	Was status code positive?	Did the technical validation in step 16 create a positive status code? If no, go to step 19.1. If yes, go to step 20.	WHO
19.1	Await corrective action.	WHO UMC is contacted by EMA to resolve the technical issues and the message is retransmitted if needed. ICSRs are stored in WHO database (step 18 while waiting for corrected version). Go back to step 15 upon receipt of the corrected ICSRs.	WHO
20	End.	ICSRs are now stored in the WHO Collaborating Centre's database and are available for signal detection.	WHO

VI. Appendix 5 Nullification of cases

General principles regarding the nullification of cases are outlined in VI.C.6.2.2.9.

Table VI.11. Examples of scenarios for which cases 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[65]. Information on the identification of the nullified case(s) should be provided in the follow-up ICSR (Section ICH-E2B(R2) A.1.11/ ICH-E2B(R3) C.1.9.1 'Other case identifiers in previous transmissions').
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.
3	On receipt of further information it is confirmed that that the adverse reaction(s) occurred before the suspect drug(s) was taken.	The case should be nullified.
4	On receipt of further information on an individual case, it is confirmed that the patient did not receive the suspect drug(s). Minimum criteria for ICSR submission 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 criteria for ICSR submission 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 patient for the individual case. The minimum criteria for an ICSR as outlined in VI.B.2 are no	If there is confirmation in a follow-up report that no patient was involved, the case should be nullified.

[65] See guidance provided in GVP Module VI Addendum I – Duplicate management of adverse reaction reports.

Ex.	Scenario	Action
	longer met.	

Table VI.12. Examples of scenarios for which cases 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 'Worldwide unique case identification number' referred to 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. 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 individual case, it is confirmed that the patient did not receive the marketing authorisation holder's medicinal product. However, the patient received another suspected product (active substance) previously not reported and the minimum criteria for ICSR submission are still met.	The case should not be nullified. A follow-up should be submitted within the appropriate time frame. The case narrative should clearly indicate that the patient did not receive the company's medicinal product. The new suspected medicinal product (active substance) should be specified in section 'Drug information' (ICH-E2B(R2) B.4/ ICH-E2B(R3) G.k) of the ICSR.
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: • **ICH-E2B(R2):** the data element A.1.5.1 'Seriousness' should be populated with the value

Ex.	Scenario	Action
		'No' without selection of a value for the data element A.1.5.2 'Seriousness criteria'. The data element A.1.9 'Does this case fulfil the local criteria for an expedited report?' 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 remain populated with the value 'Yes'.
11	The primary source country has changed, which has an impact on the 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. • **ICH-E2B(R2):** The data element A.1.0.1 'Sender's (case) safety report unique identifier' can be updated on the basis of the new primary source country code. However, the data element A.1.10 '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 A.1.10 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 section A.1.11 'Other case identifiers in previous transmissions'. • **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'.

Ex.	Scenario	Action
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' (ICH-E2B(R2) A.1.10/ 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 (ICH-E2B(R2) section A.1.11/ ICH-E2B(R3) section C.1.9.1'Other case identifiers in previous transmissions').
13	The suspected medicinal product received by the patient 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 submitted by the marketing authorisation holder A although the marketing authorisation holder B as co-marketer is responsible for the submission of the case.	The case should not be nullified. An explanation should be sent by the marketing authorisation holder A to the co-marketer B that the case has already been 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).

VI. Appendix 6 Data quality monitoring of ICSRs transmitted electronically

Figure VI.7. Business process map - Review of quality and integrity of ICSRs by the Agency in collaboration with competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs). See steps description in Table VI.13..

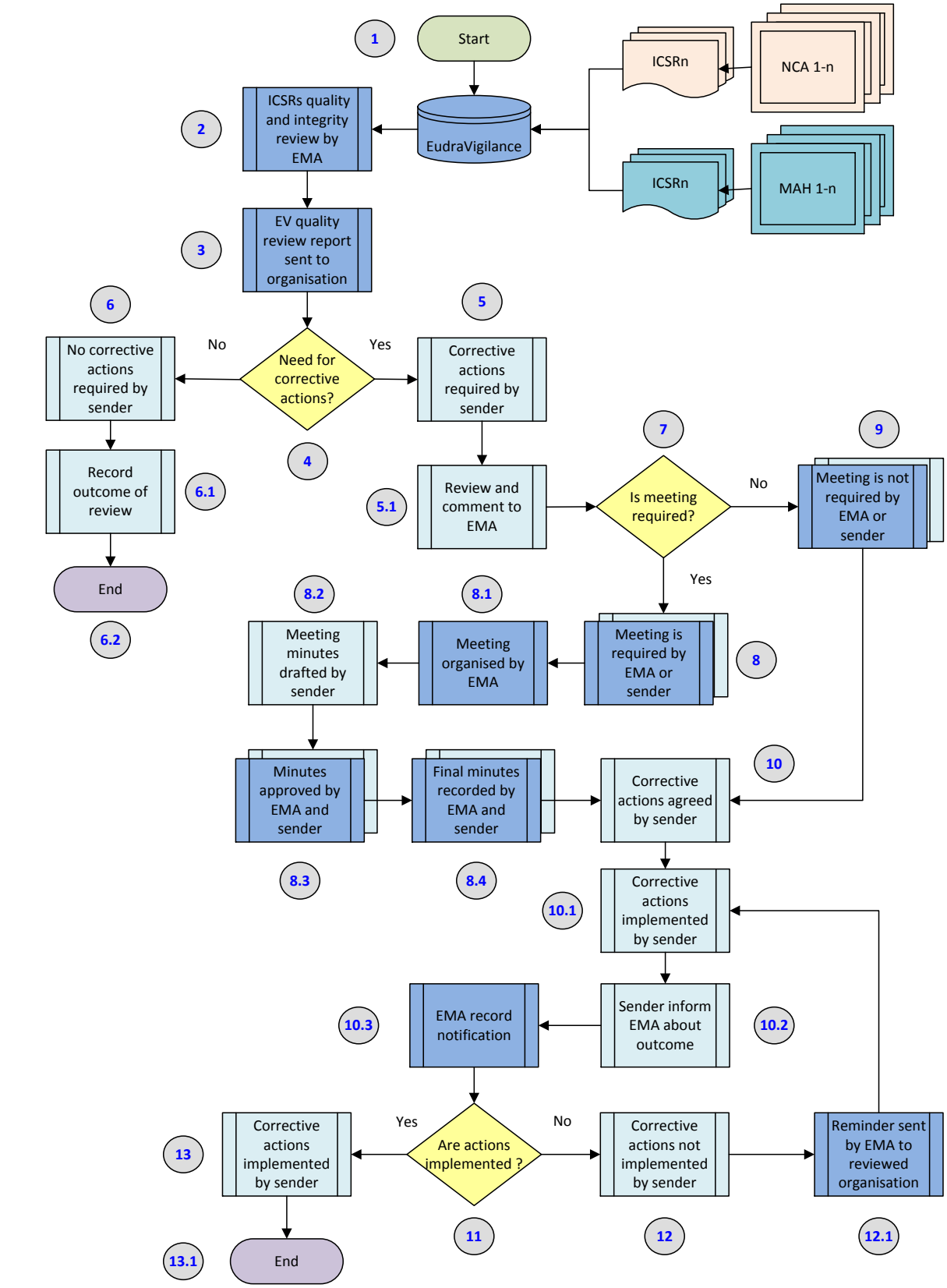


Table VI.13. Process description – Review of quality and integrity of ICSRs by the Agency in collaboration with competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs). See process map in Figure VI.7..

No.	Step	Description	Responsible organisation
1	**Start.**	**Receipt of ICSRs in EudraVigilance (EV) from sender organisations (NCAs and MAHs) with obligations for the submission of ICSRs related to medicinal products authorised in the EEA. Go to step 2.**	**EMA**
2	ICSRs quality and integrity review by EMA.	A review of the quality, integrity, use of terminologies, and compliance with submission time frames is performed in accordance with the applicable SOP and WINs on the ICSRs submitted to EV. Go to step 3.	EMA
3	EV quality review report sent to organisation.	A draft report summarising the outcome of the quality review is sent by e-mail to the concerned sending organisation (NCA head of Pharmacovigilance Department or MAH EU QPPV). Go to step 4.	EMA
4	Need for corrective actions?	Are corrective actions required by the organisation being reviewed (NCA/MAH)? If Yes, go to step 5. If No, go to step 6.	Organisation being reviewed (NCA/MAH)
5	Corrective actions required.	Corrective actions are required by organisation being reviewed. Go to step 5.1.	Organisation being reviewed (NCA/MAH)
5.1	Review and comment.	Review the draft quality report and provide comments to EMA within the requested time frame. Go to step 7.	Organisation being reviewed (NCA/MAH)
6	No corrective actions required by sender.	No corrective actions are required following the quality review of the ICSRs submitted by the concerned organisation. Go to step 6.1.	Organisation being reviewed (NCA/MAH)
6.1	Record outcome of review.	Record the outcome of the quality review report. Go to step 6.2.	Organisation being reviewed (NCA/MAH)
6.2	End.	End of the quality review procedure.	EMA/ Organisation being reviewed (NCA/MAH)
7	Is meeting required?	Is there a need to organise a meeting between the reviewed organisation and EMA?	EMA/ Organisation being reviewed

No.	Step	Description	Responsible organisation
		If Yes, go to step 8. If No, go to step 9.	(NCA/MAH)
8	Meeting is required by EMA or sender.	A review meeting is requested by the sender organisation or is proposed by EMA. Go to step 8.1.	EMA/ Organisation being reviewed (NCA/MAH)
8.1	Meeting organised by EMA.	A meeting is organised (via TC or face-to-face). Go to step 8.2.	EMA
8.2	Meeting minutes drafted by sender.	Agreed actions and outcome of discussions to be summarised in draft meeting minutes. Go to step 8.3.	Organisation being reviewed (NCA/MAH)
8.3	Minutes approved by EMA and sender.	Approve the meeting minutes as final. Go to step 8.4.	EMA/ Organisation being reviewed (NCA/MAH)
8.4	Final minutes recorded by EMA and sender.	Record the final meeting minutes. Go to step 10.	EMA/ Organisation being reviewed (NCA/MAH)
9	A meeting is not required by EMA or sender.	No review meeting is required (requested by the sender organisation or proposed by EMA). Go to step 10.	EMA/ Organisation being reviewed (NCA/MAH)
10	Corrective actions agreed by sender.	The corrective actions and time frames are agreed by the sending organisation being reviewed. The agreement is to be reflected on the basis of the final quality review report, which is to be recorded. Go to step 10.1.	Organisation being reviewed (NCA/MAH)
10.1	Corrective actions implemented by sender.	The sending organisation should implement the corrective actions in accordance with the agreed methods and time frames. Go to step 10.2.	Organisation being reviewed (NCA/MAH)
10.2	Inform EMA about outcome.	The sending organisation informs EMA when the corrective actions have been implemented in line with the final quality review report. Go to step 10.3.	Organisation being reviewed (NCA/MAH)
10.3	EMA record notification.	The notification of implementation of the corrective actions in line with the final quality review report is recorded by the Agency. Go to step 11.	EMA
11	Are corrective actions	Have the agreed corrective actions been implemented by the sending organisation? EMA monitors and checks if the agreed corrective actions	EMA

No.	Step	Description	Responsible organisation
	implemented?	have been implemented. If No, go to step 12. If Yes, go to step 13.	
12	Corrective actions not implemented by sender.	The agreed corrective actions have not been implemented by the sending organisation. Go to step 12.1	Organisation being reviewed (NCA/MAH)
12.1	Reminder sent by EMA to reviewed organisation.	Send reminder to the sending organisation being reviewed to implement corrective actions. Go back to step 10.1.	EMA
13	Corrective actions implemented.	The agreed corrective actions have been implemented by the sending organisation. Go to step 13.1	Organisation being reviewed (NCA/MAH)
13.1	End.	The ICSRs quality review procedure ends.	EMA/ Organisation being reviewed (NCA/MAH)

VI. Appendix 7 Duplicate detection and management of ICSRs

VI.App.7.1. Duplicate detection in EudraVigilance – Collaboration between the Agency, competent authorities in Member States and marketing authorisation holders - Duplicate ICSRs submitted to EudraVigilance by the same sender and identified by the Agency

Figure VI.8. Business process map - Duplicate Detection (DD) in EudraVigilance – Collaboration between the Agency, competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs) - Duplicate ICSRs submitted to EudraVigilance by the same sender and identified by the Agency. See steps description in Table VI.14..

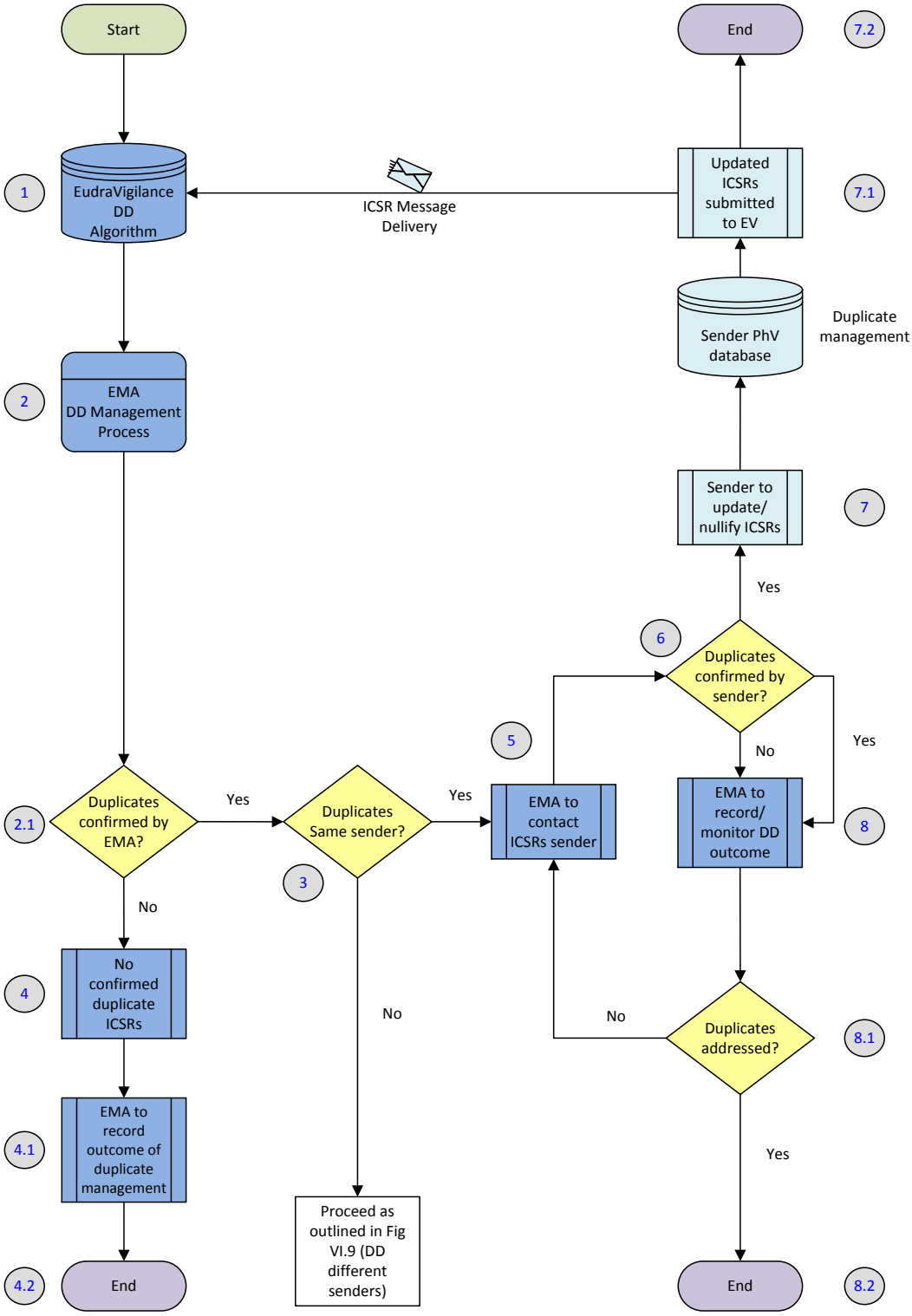


Table VI.14. Process description - Duplicate Detection (DD) in EudraVigilance – Collaboration between the Agency, competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs) - Duplicate ICSRs submitted to EudraVigilance by the same sender and identified by the Agency. See process map in Figure VI.8..

No.	Step	Description	Responsible organisation
	Start.	**Duplicate ICSRs submitted to EudraVigilance by the same sender and identified by the Agency.**	
1	EudraVigilance DD algorithm.	A duplicate detection algorithm is operated in EudraVigilance to detect potential duplicate ICSRs. Go to step 2.	EMA
2	EMA DD Management Process.	The potential duplicate ICSRs identified by the EudraVigilance duplicate detection algorithm are reviewed by EMA in accordance with the applicable SOP and WINs. Go to step 2.1.	EMA
2.1	Are duplicate ICSRs confirmed by EMA?	Are the duplicate ICSRs identified by the EudraVigilance duplicate detection algorithm confirmed by EMA? If Yes, proceed to step 3. If No, proceed to step 4.	EMA
3	Are the duplicate ICSRs from the same sender organisation?	Are the confirmed duplicate ICSRs from the same sender organisation? If Yes, proceed to step 5. If No, proceed according to the business process map related to duplicate detection of ICSRs from different senders outlined in Figure VI.9 and Table VI.15 for the management of duplicate ICSRs submitted to EudraVigilance by different senders and identified by the Agency.	EMA
4	No confirmed duplicate ICSRs.	As a result of the duplicate detection management process by EMA, it is confirmed that the individual cases are not duplicate ICSRs. Go to step 4.1.	EMA
4.1	EMA to record outcome of duplicate management.	The outcome of the duplicate detection management process is recorded in accordance with the applicable SOP and WINs. Go to step 4.2.	EMA
4.2	End.		EMA
5	EMA to contact ICSRs sender.	EMA contacts the sender organisation (MAH/NCA) to inform about the potential duplicate ICSRs identified in EudraVigilance. Go to step 6.	EMA
6	Are duplicates confirmed by	Does the sender organisation confirm EMA assessment of the duplicate ICSRs?	EMA/ Sender organisation

No.	Step	Description	Responsible organisation
	sender?	If Yes, proceed to step 7 for sender next step and to step 8 for EMA next step. If No, proceed to step 8 for EMA next step.	(MAH/NCA)
7	Sender to update/nullify cases.	The sender organisation updates/nullifies the duplicate ICSRs in their pharmacovigilance database in line with the guidance provided in GVP Module VI Addendum I – Duplicate management of adverse reaction reports. Go to step 7.1.	Sender organisation (MAH/NCA)
7.1	Updated ICSRs submitted to EV.	The sender organisation submits the updated ICSRs/nullification reports to EudraVigilance in accordance with the guidance provided in GVP Module VI Addendum I – Duplicate management of adverse reaction reports. Go to step 7.2.	Sender organisation (MAH/NCA)
7.2	End.		Sender organisation (MAH/NCA)
8	EMA to record/monitor duplicate management outcome.	If the ICSRs are not confirmed as duplicates by the sender, EMA records the outcome of the duplicate management. Go to step 8.1. If the sender confirms the duplicate ICSRs, EMA monitors that the sender has addressed them by submitting updated/nullified ICSRs to EV. Go to step 8.1.	EMA
8.1	Are the duplicate ICSRs addressed?	Have the duplicate ICSRs been addressed by the sender organisation? If Yes, process to step 8.2. If No, process back to step 5.	EMA
8.2	End.		

VI.App.7.2. Duplicate detection in EudraVigilance – Collaboration between the Agency, competent authorities in Member States and marketing authorisation holders– Duplicate ICSRs submitted to EudraVigilance by different senders and identified by the Agency

Figure VI.9. Business process map - Duplicate Detection (DD) in EudraVigilance – Collaboration between the Agency, competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs) – Duplicate ICSRs submitted to EudraVigilance by different senders and identified by the Agency. See steps description in Table VI.15..

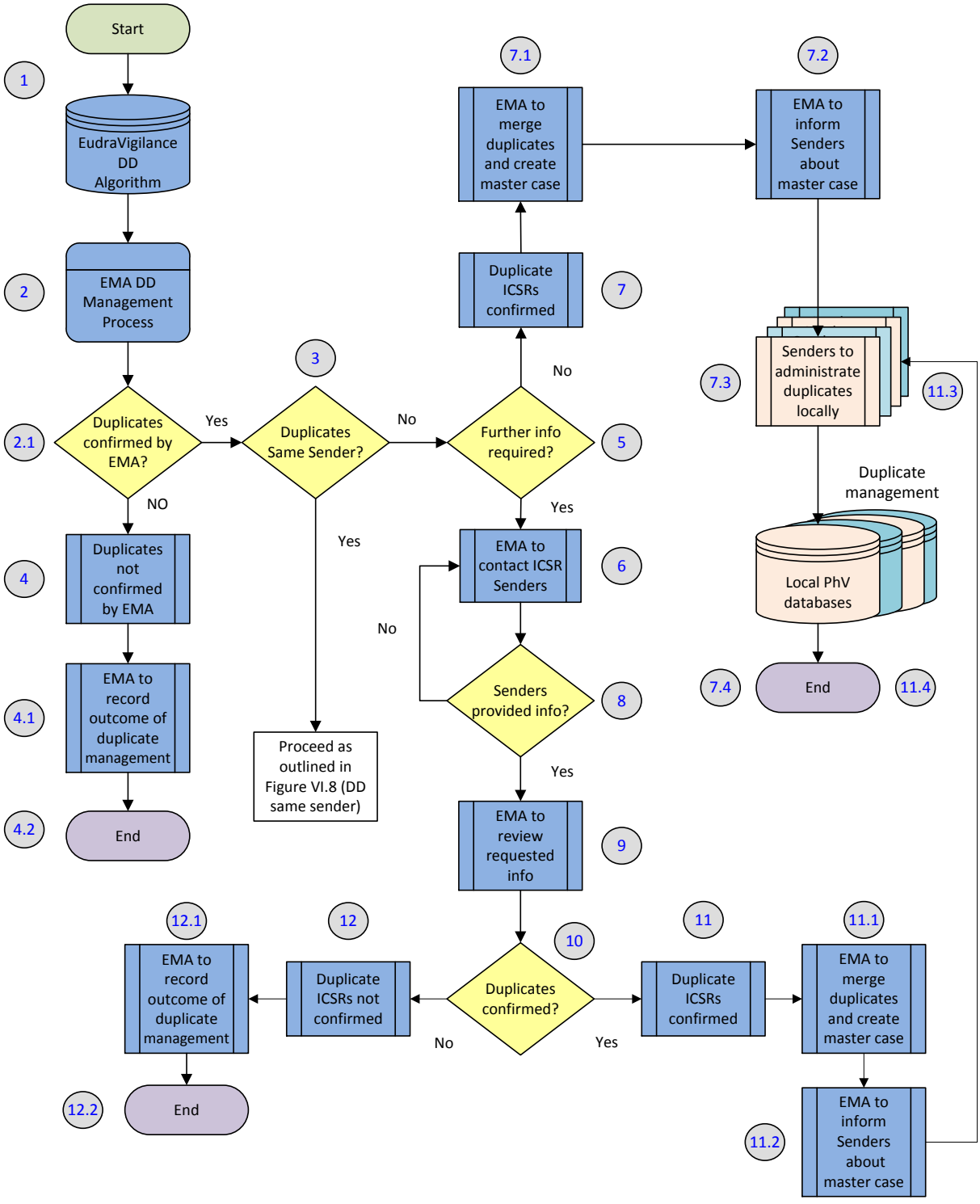


Table VI.15. Process description - Duplicate Detection (DD) in EudraVigilance – Collaboration between the Agency, competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs) - Duplicate ICSRs submitted to EudraVigilance by different senders and identified by the Agency. See process map in Figure VI.9..

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 to EV by two senders; the patient reported the same adverse reaction to a NCA and the MAH.*	
1	EudraVigilance DD Algorithm.	A duplicate detection algorithm is operated in EudraVigilance to detect potential duplicate ICSRs. Go to step 2.	EMA
2	EMA DD Management Process.	The potential duplicate ISCRs identified by the EudraVigilance duplicate detection algorithm are reviewed in accordance with the applicable SOP and WINs. Go to step 2.1.	EMA
2.1	Are duplicate ICSRs confirmed by EMA?	Are the potential duplicate ICSRs identified by the EudraVigilance duplicate detection algorithm confirmed? If Yes, proceed to step 3. If No, proceed to step 4.	EMA
3	Are the duplicate ICSRs from the same sender?	Are the duplicate ICSRs from the same sender organisation (NCA or MAH)? If Yes, proceed as outlined in Figure VI.8 and Table VI.14 for the management of duplicate ICSRs submitted to EudraVigilance by the same sender and identified by the Agency. If No, proceed to step 5.	EMA
4	Duplicates not confirmed by EMA.	The potential duplicate ICSRs have been reviewed and are not considered as duplicate of a single case. Go to step 4.1.	EMA
4.1	EMA to record outcome of duplicate management.	The outcome of the duplicate detection management process is recorded in accordance with the applicable SOP and WINs. Go to step 4.2.	EMA
4.2	End.		EMA
5	Is further information	Is further information necessary from the senders' organisations to confirm if the potential duplicate ICSRs identified by the duplicate detection algorithm	EMA

No	Step	Description	Responsible organisation
	required?	are duplicates? If Yes, proceed to step 6. If No, proceed to step 7.	
6	EMA to contact Senders' organisations (MAH/NCA).	Contact the senders' organisations to obtain additional information on the individual cases that have been identified as potential duplicate ICSRs. Go to step 8.	EMA
7	Duplicate ICSRs confirmed.	The ICSRs are confirmed as duplicate of a single case. Go to step 7.1.	EMA
7.1	EMA to merge duplicate ICSRs and create master case.	EMA merges the duplicate ICSRs in line with the guidance provided in GVP Module VI Addendum I – Duplicate management of adverse reaction reports. Go to step 7.2.	EMA
7.2	EMA to inform senders' organisations about master case.	EMA informs the senders' organisations (MAH/NCA) about the outcome of the duplicate management (creation of master case) to allow them to take action where necessary[66;67;68]. Go to step 7.3.	EMA
7.3	Senders' organisations to administrate duplicate ICSRs locally.	The senders' organisations of the individual cases identified as duplicate ICSRs manage the duplicate ICSRs locally in line with the guidance provided in GVP Module VI Addendum I – Duplicate management of adverse reaction reports. The reference numbers of the duplicate ICSRs and of EMA master case are captured in data element 'Other case identifiers in previous transmissions' (ICH-E2B(R2) A.11/ ICH-E2B(R3) section C.1.9.1.). Go to step 7.4.	Sender organisations (MAH/NCA)
7.4	End.		Sender organisations

[66] NOTE: MAHs will be able to download "master cases" from EudraVigilance in line with the EudraVigilance Access Policy for Medicines for Human Use (EMA/759287/2009). The message type (E2B(R2) data element M.1.1; E2B(R3) data element N.1.1) will have the code "master" to distinguish it from all other ICSR messages, which will have the message type "ichicsr" (see EU Individual Case Safety Report (ICSR) Implementation Guide; EMA/51938/2013).
MAHs will 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 Individual Case Safety Report (ICSR) Implementation Guide; EMA/51938/2013). 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 results in the update of one of its own individual cases with the information from the EudraVigilance master case, the MAH MUST NOT resubmit an updated version of this individual case to EudraVigilance if there is no receipt of new information that warrants the submission of a follow-up report.

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

[68] 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 EU Individual Case Safety Report (ICSR) Implementation Guide; EMA/51938/2013). The "master cases" MUST NOT be retransmitted by the NCA to EudraVigilance if there is no receipt of new information that warrants the submission of a follow-up report.

No	Step	Description	Responsible organisation
			(MAH/NCA)
8	Have senders' organisations provided information?	Check if the sender's organisations have provided the requested information? If Yes, proceed to step 9. If No, proceed back to step 6.	EMA
9	EMA to review requested info.	Review the potential duplicate ICSRs together with the requested information provided by the senders' organisations. Go to step 10.	EMA
10	Are duplicate ICSRs confirmed?	Are the potential duplicate ICSRs confirmed following the receipt of the requested information from the sender's organisations? If Yes, proceed to step 11. If No, proceed to step 12.	EMA
11	Duplicate ICSRs confirmed.	The ICSRs are confirmed as duplicate of a single case. Go to step 11.1.	EMA
11.1	EMA to merge duplicate ICSRs and create master case.	EMA merges the duplicate ICSRs in EudraVigilance in line with the guidance provided in GVP Module VI Addendum I – Duplicate management of adverse reaction reports. Go to step 11.2.	EMA
11.2	EMA to inform senders' organisations about master case.	EMA informs the senders' organisations (MAH/NCA) about the outcome of the duplicate management (creation of master case) to allow them to take action where necessary[69;70;71]. Go to step 11.3.	EMA
11.3	Senders' organisations to administrate duplicate ICSRs	The senders' organisations of the individual cases identified as duplicate ICSRs manage the duplicate ICSRs locally in line with the guidance provided in GVP Module VI Addendum I – Duplicate management	Sender organisations (MAH/NCA)

[69] NOTE: MAHs will be able to download "master cases" from EudraVigilance in line with the EudraVigilance Access Policy for Medicines for Human Use (EMA/759287/2009). The message type (E2B(R2) data element M.1.1; E2B(R3) data element N.1.1) will have the code "master" to distinguish it from all other ICSR messages, which will have the message type "ichicsr" (see EU Individual Case Safety Report (ICSR) Implementation Guide; EMA/51938/2013).
MAHs will 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 Individual Case Safety Report (ICSR) Implementation Guide; EMA/51938/2013). 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 results in the update of one of its own individual cases with the information from the EudraVigilance master case, the MAH MUST NOT resubmit an updated version of this individual case to EudraVigilance if there is no receipt of new information that warrants the submission of a follow-up report.
[70] A table of master cases and associated duplicates will be made available to aid duplicate management by Sender organisations.
[71] 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 EU Individual Case Safety Report (ICSR) Implementation Guide; EMA/51938/2013). The "master cases" MUST NOT be retransmitted by the NCA to EudraVigilance if there is no receipt of new information that warrants the submission of a follow-up report.

No	Step	Description	Responsible organisation
	locally.	of adverse reaction reports. The reference numbers of the duplicate ICSRs and of EMA master case are captured in data element 'Other case identifiers in previous transmissions' (ICH-E2B(R2) A.11/ ICH-E2B(R3) section C.1.9.1.). Go to step 11.4.	
11.4	End.		Sender organisations (MAH/NCA)
12	Duplicate ICSRs not confirmed.	The potential duplicate ICSRs are not considered as duplicate of a single case based on the review of the information provided by the senders' organisations. Go to step 12.1.	EMA
12.1	EMA to record outcome of duplicate management.	The outcome of the duplicate management process is recorded in accordance with the applicable SOP and WINs. Go to step 12.2.	EMA
12.2	End.		EMA

VI.App.7.3. Duplicate detection in EudraVigilance – Collaboration between the Agency, competent authorities in Member States and marketing authorisation holders – Duplicate ICSRs submitted to EudraVigilance by the same sender and identified by the sender organisation prior to the detection by the Agency

Figure VI.10. Business process map – Duplicate Detection (DD) in EudraVigilance – Collaboration between the Agency, competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs) – Duplicate ICSRs submitted to EudraVigilance by the same sender and identified by the sender organisation prior to the detection by the Agency. See steps description in Table VI.16..

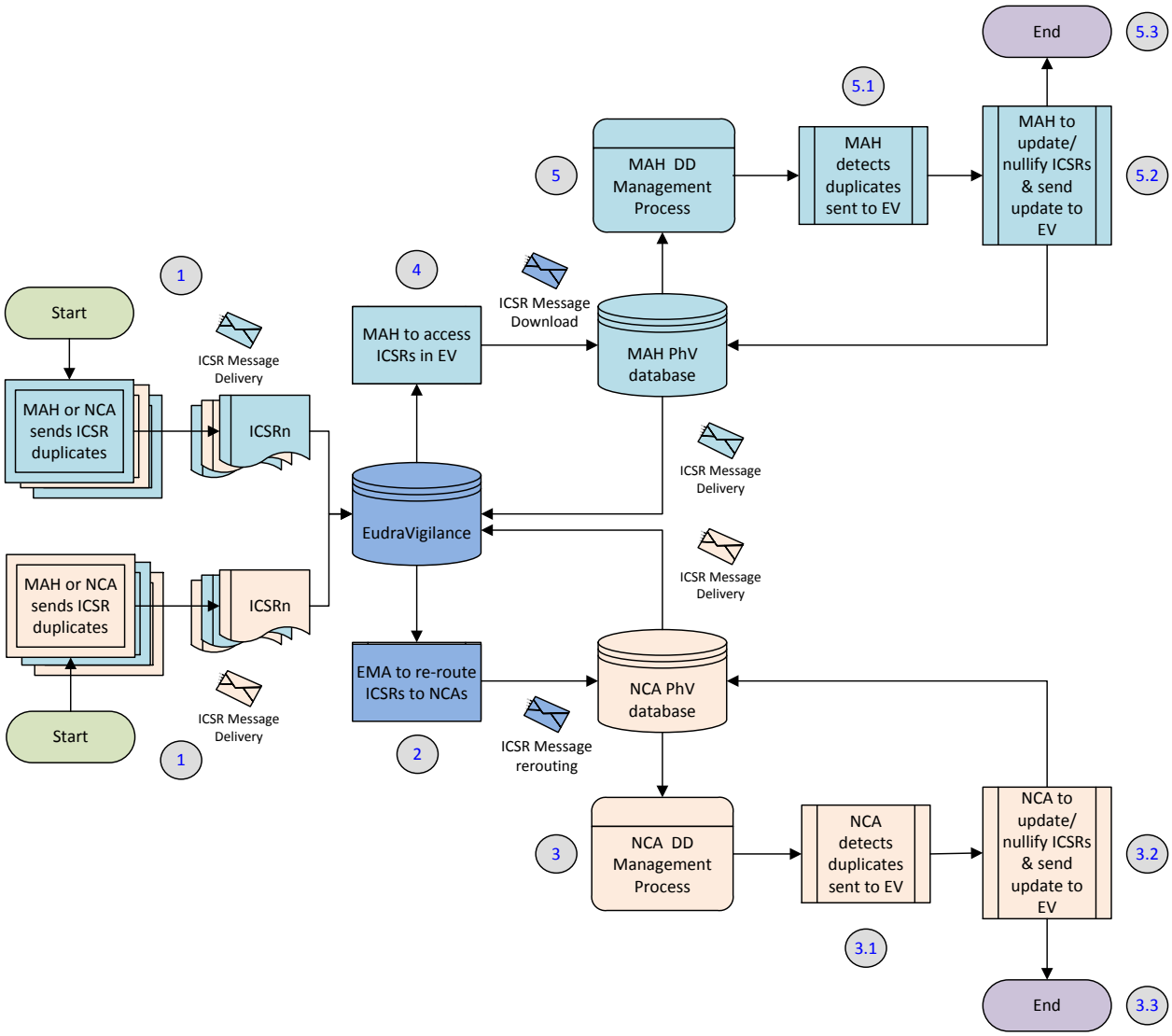


Table VI.16. Process description – Duplicate Detection (DD) in EudraVigilance – Collaboration between the Agency, Member States and MAHs - Duplicate ICSRs submitted to EudraVigilance by the same sender and identified by the sender organisation prior to the detection by the Agency. See process map in Figure VI.10..

No	Step	Description	Responsible organisation
	Start.	**Duplicate ICSRs submitted to EudraVigilance by the same sender (NCA or MAH) and identified by the sender organisation prior to the detection by the Agency.**	
1	Duplicate ICSRs submitted to EV.	Duplicate ICSRs are submitted to EudraVigilance (EV) by the same sender (MAH or NCA). Go to step 2 for duplicate ICSRs submitted by a NCA. Go to step 4 for duplicate ICSRs submitted by a MAH.	Sender organisation (MAH/NCA)
2	Re-routing of ICSRs to NCA.	EEA ICSRs are rerouted from EudraVigilance to the NCA in accordance with VI.C.4. and the rerouting principles described in the EU Individual Case Safety Report (ICSR) Implementation Guide (EMA/51938/2013). Go to step 3.	EMA/ EudraVigilance
3	NCA DD and management process.	A routine duplicate detection process is performed regularly by the NCA in its pharmacovigilance database. Go to step 3.1.	NCA
3.1	NCA detects duplicates sent to EV.	The NCA identifies duplicate ICSRs of its own cases after their submission to EudraVigilance as part of its routine duplicate management process. Go to step 3.2.	NCA
3.2	NCA to update/ nullify ICSRs and send update to EV.	The NCA reviews and updates/nullifies its own duplicate ICSRs and submits the updated ICSRs/ nullification ICSRs to EudraVigilance in line with the guidance provided in GVP Module VI Addendum I – Duplicate management of adverse reaction reports. Go to step 3.3.	NCA
3.3	End.		NCA
4	Access to ICSRs in EudraVigilance by MAHs.	ICSRs are made accessible to MAHs in line with the EudraVigilance Access Policy for Medicines for Human Use[72]. Go to step 5.	MAH
5	MAH DD and management Process.	A routine duplicate detection process is performed regularly by the MAH in its pharmacovigilance database. Go to step 5.1.	MAH

[72] Ref.: EMA/759287/2009; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Access to data.

No	Step	Description	Responsible organisation
5.1	MAH detects duplicates sent to EV.	The MAH identifies duplicate ICSRs of its own cases after their submission to EudraVigilance as part of its routine duplicate management process. Go to step 5.2.	MAH
5.2	MAH to update/ nullify ICSRs and send update to EV.	The MAH reviews and updates/nullifies its own duplicate ICSRs and submits the updated ICSRs/ nullification ICSRs to EudraVigilance in line with the guidance provided in GVP Module VI Addendum I – Duplicate management of adverse reaction reports. Go to step 5.3.	MAH
5.3	End.		MAH

VI.App.7.4. Duplicate detection in EudraVigilance – Collaboration between the Agency, competent authorities in Member States and marketing authorisation holders - Duplicate ICSRs submitted to EudraVigilance by different senders and identified by an organisation prior to the detection by the Agency

Figure VI.11. Business process map – Duplicate Detection (DD) in EudraVigilance – Collaboration between the Agency, competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs) - Duplicate ICSRs submitted to EudraVigilance by different senders and identified by an organisation prior to the detection by the Agency. See steps description in Table VI.17..

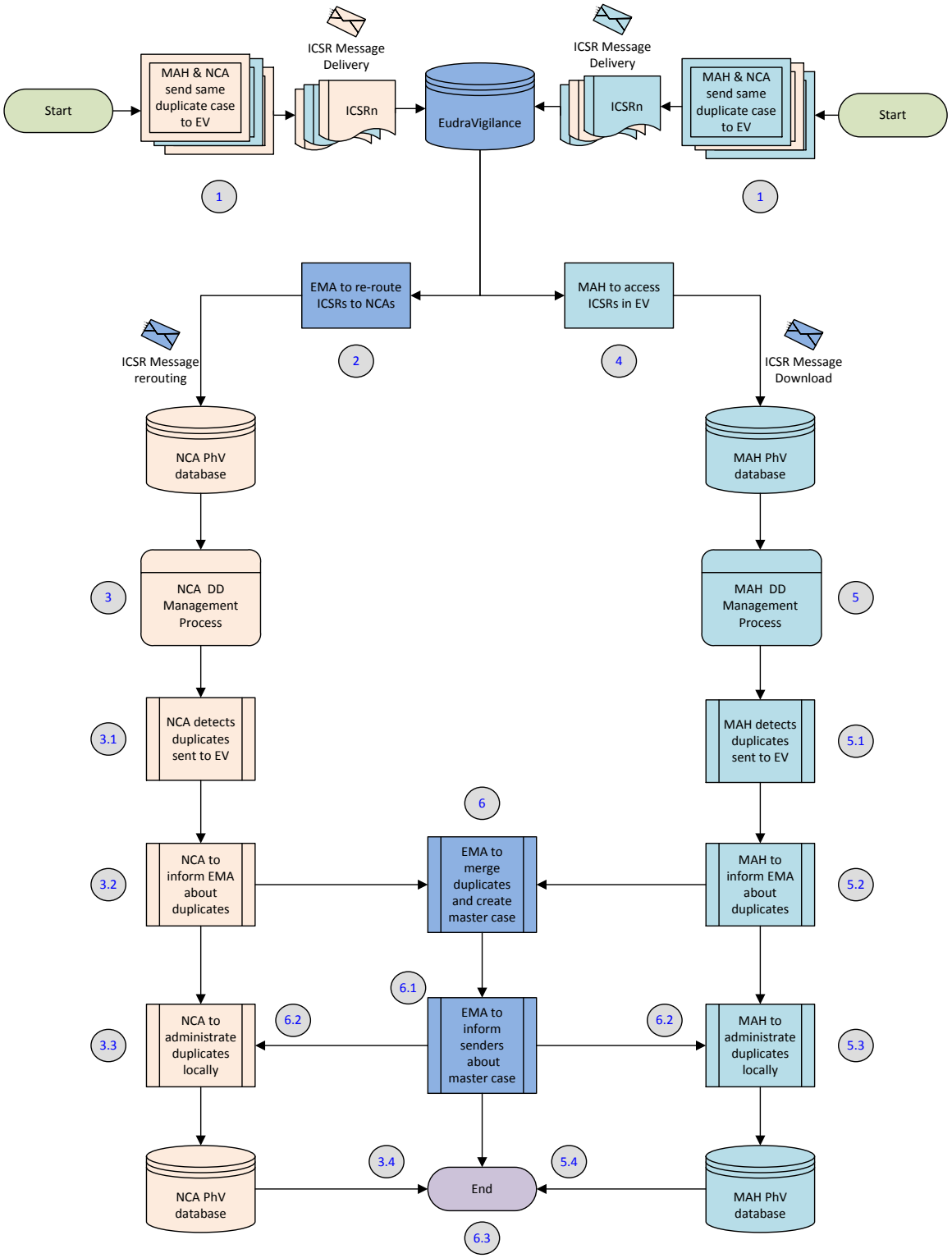


Table VI.17. Process description – Duplicate Detection (DD) in EudraVigilance – Collaboration between the Agency, competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs) - Duplicate ICSRs submitted to EudraVigilance by different senders and identified by an organisation prior to the detection by the Agency in EudraVigilance. See process map in Figure VI.11..

No	Step	Description	Responsible organisation
	Start.	**Duplicate ICSRs submitted to EudraVigilance by different senders and identified by an organisation prior to the detection by the Agency** *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 in EV did not identify the reports as potential duplicates.*	
1	MAH and NCA send same duplicate case to EV.	Duplicate ICSRs submitted to EudraVigilance by different senders (NCAs and MAHs). Go to step 2 for duplicate ICSRs submitted by a NCA. Go to step 4 for duplicate ICSRs submitted by a MAH.	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 Individual Case Safety Report (ICSR) Implementation Guide (EMA/51938/2013). Go to step 3.	EMA/ EudraVigilance
3	NCA duplicate detection and management Process.	A routine duplicate detection process is performed regularly by the NCA in its pharmacovigilance database. Go to step 3.1.	NCA
3.1	NCA detects duplicates sent to EV.	The NCA identifies the duplicate ICSRs after their submission to EudraVigilance by multiple senders as part of its routine duplicate management process. Go to step 3.2.	NCA
3.2	NCA to inform EMA about duplicates.	The NCA informs EMA by email (duplicates@ema.europa.eu) about the duplicate ICSRs. Go to step 3.3 for NCA next step. Go to step 6 for EMA next step.	NCA
3.3	NCA to administrate duplicates locally.	The NCA manages the duplicate ICSRs locally in line with the guidance provided in GVP Module VI Addendum I – Duplicate management of adverse	NCA

No	Step	Description	Responsible organisation
		reaction reports. The reference numbers of the duplicate ICSRs are captured in data element 'Other case identifiers in previous transmissions' (ICH-E2B(R2) A.11/ ICH-E2B(R3) section C.1.9.1.). Go to step 3.4	
3.4	End.		
4	Access to ICSRs in EudraVigilance by MAHs.	ICSRs are made accessible to MAHs in line with the EudraVigilance Access Policy for Medicines for Human Use[73]. Go to step 5.	MAH
5	MAH duplicate detection and management process.	A routine duplicate detection process is performed regularly by the MAH in its pharmacovigilance database. Go to step 5.1.	MAH
5.1	MAH detects duplicates sent to EV.	The MAH identifies the duplicate ICSRs after their submission by multiple senders to EudraVigilance as part of its duplicate management process. Go to step 5.2.	MAH
5.2	MAH to inform EMA about duplicates.	The MAH informs EMA by email (duplicates@ema.europa.eu) about the duplicate ICSRs. Go to step 5.3 for MAH next step. Go to step 6 for EMA next step.	MAH
5.3	MAH to administrate duplicates locally.	The MAH manages duplicate ICSRs locally in line with the guidance provided in GVP Module VI Addendum I – Duplicate management of adverse reaction reports. The reference numbers of the duplicate ICSRs are captured in data element 'Other case identifiers in previous transmissions' (ICH-E2B(R2) A.11/ ICH-E2B(R3) section C.1.9.1.). Go to step 5.4.	MAH
5.4	End.		
6	EMA to merge duplicate ICSRs and record outcome.	EMA merges duplicate ICSRs in EudraVigilance in line with the guidance provided in GVP Module VI Addendum I – Duplicate management of adverse reaction reports. Go to step 6.1.	EMA

[73] Ref.: EMA/759287/2009; EMA website: Home/ Human regulatory/ Post-authorisation/ Pharmacovigilance/ EudraVigilance/ Access to data.

No	Step	Description	Responsible organisation
6.1	EMA to inform senders about master case.	EMA informs the sender organisations (MAH/NCA) about the outcome of the duplicate management (creation of master case) to allow them to take action where necessary[74, 75, 76]. Go to step 6.2.	EMA
6.2	NCA/MAH to administrate duplicates locally.	Senders' organisations (NCA and MAH) of the ICSRs identified as duplicate administrate the information about the master case in their database (reference number of the master case created by EMA to be captured in ICH E2B(R2) A.1.11 / E2B(R3) C.1.9.1: 'Other case identifiers in previous transmissions'). The updated version of the ICSRs should not be resubmitted to EV. Go to step 6.3.	Sender organisations (MAH/NCA)
6.3	End.		

[74] NOTE: MAHs will be able to download "master cases" from EudraVigilance in line with the EudraVigilance Access Policy for Medicines for Human Use (EMA/759287/2009). The message type (E2B(R2) data element M.1.1; E2B(R3) data element N.1.1) will have the code "master" to distinguish it from all other ICSR messages, which will have the message type "ichicsr" (see EU Individual Case Safety Report (ICSR) Implementation Guide; EMA/51938/2013).
MAHs will 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 Individual Case Safety Report (ICSR) Implementation Guide; EMA/51938/2013). 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 results in the update of one of its own individual cases with the information from the EudraVigilance master case, the MAH MUST NOT resubmit an updated version of this individual case to EudraVigilance if there is no receipt of new information that warrants the submission of a follow-up report.
[75] A table of master cases and associated duplicates will be made available to aid duplicate management by Sender organisations.
[76] 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 EU Individual Case Safety Report (ICSR) Implementation Guide; EMA/51938/2013). The "master cases" MUST NOT be retransmitted by the NCA to EudraVigilance if there is no receipt of new information that warrants the submission of a follow-up report.

VI.App.7.5. Duplicate detection in EudraVigilance – Collaboration between the Agency, competent authorities in Member States and marketing authorisation holders – Duplicate ICSRs identified as part of signal management as outlined in GVP Module IX

Figure VI.12. Business process map - Duplicate Detection (DD) in EudraVigilance – Collaboration between the Agency, competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs) - Duplicate ICSRs identified as part of signal management process based on EudraVigilance data. See steps description in Table VI.18..

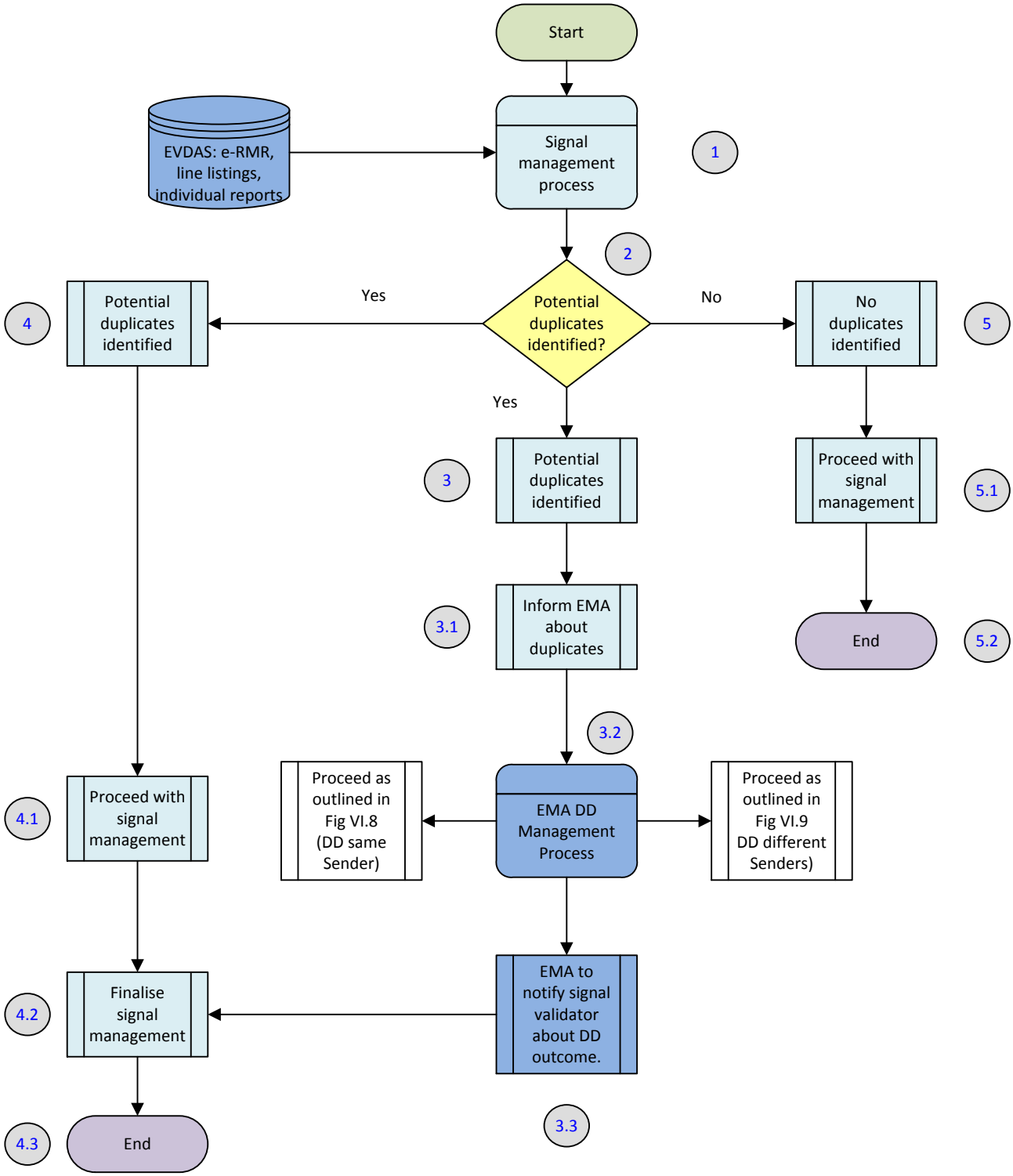


Table VI.18. Process description - Duplicate Detection (DD) in EudraVigilance – Collaboration between the Agency, competent authorities in Member States (NCAs) and marketing authorisation holders (MAHs) - Duplicate ICSRs identified as part of signal management process based on EudraVigilance data. See process map in Figure VI.12..

No	Step	Description	Responsible organisation
	Start.	**Duplicates identified as part of signal management as outlined in GVP Module IX.** *Example: as part of the signal management process based on EudraVigilance data, there may be instances where a signal validator of the Agency, a Member State or a MAH may identify potential duplicate ICSRs.*	
1	Signal Management process.	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). Go to step 2.	Signal validator (EMA/ NCA/ MAH)
2	Potential duplicates identified?	As part of the review of a 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 step 3 and step 4. If no potential duplicate are identified, proceed as outlined under step 5.	Signal validator (EMA/ NCA/ MAH)
3	Potential duplicates identified.	Potential duplicates have been identified as part of the review of a signal. Go to step 3.1	Signal validator (EMA/ NCA/ MAH)
3.1	Inform EMA about duplicates.	Inform EMA by email (duplicates@ema.europa.eu) about the potential identified duplicate ICSRs. Go to step 3.2	Signal validator (EMA/ NCA/ MAH)
3.2	EMA to 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.8 and Table VI.14. If duplicates are from different sender organisations, proceed as outlined in Figure VI.9 and Table VI.15. Go to step 3.3.	EMA
3.3	EMA to notify signal validator about DD outcome.	EMA informs the signal validator about the outcome of the duplicate management process. Go to step 4.2.	EMA
4	Potential duplicates	Potential duplicates have been identified as part of	Signal validator

No	Step	Description	Responsible organisation
	identified.	the signal management activities. Go to step 4.2	(EMA/ NCA/ MAH)
4.1	Proceed with signal management.	Proceed with the review of the signal in line with GVP Module IX guidance. Go to step 4.2.	Signal validator (EMA/NCA/ MAH)
4.2	Finalise signal management.	Finalise the management of the signal based on duplicate detection management feedback from EMA (step 3.3). Go to step 4.3.	Signal validator (EMA/ NCA/ MAH)
4.3	End.		
5	No duplicates identified.	No (potential) duplicates have been identified as part of the review of a signal. Go to step 5.1.	Signal validator (EMA/ NCA/ MAH)
5.1	Proceed with signal management.	Proceed with the review of the signal in line with GVP Module IX guidance. Go to step 5.2.	Signal validator (EMA/ NCA/ MAH)
5.2	End.		