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

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TABLE OF CONTENTS

VI.A. Introduction 5
VI.A.1. Scope 5
VI.A.2. Definitions 5
VI.A.2.1. Adverse reaction 5
VI.A.2.1.1. Causality 5
VI.A.2.1.2. Overdose, misuse, abuse, medication error, occupational exposure 6
VI.A.2.2. Medicinal product 6
VI.A.2.3. Primary source 7
VI.A.2.4 Seriousness 7
VI.A.2.5. Individual Case Safety Report (ICSR) 8
VI.B. Structures and Processes 9
VI.B.1. Collection of reports 9
VI.B.1.1. Unsolicited reports 9
VI.B.1.1.1. Spontaneous reports 9
VI.B.1.1.2. Literature reports 9
VI.B.1.1.3. Reports from other sources 10
VI.B.1.1.4. Information on suspected adverse reactions from the internet or digital media. 10
VI.B.1.2. Solicited reports 11
VI.B.2. Validation of reports 11
VI.B.3. Follow-up of reports 12
VI.B.4. Data management 13
VI.B.5. Quality management 14
VI.B.6. Special situations 14
VI.B.6.1. Use of a medicinal product during pregnancy or breastfeeding 14
VI.B.6.2. Use of a medicinal product in a paediatric or elderly population 15
VI.B.6.3. Reports of overdose, abuse, misuse, medication error or occupational exposure . 16
VI.B.6.4. Lack of therapeutic efficacy 16
VI.B.7. Expedited reporting of ICSRs 17
VI.B.7.1. Expedited reporting time frames 17
VI.B.8. Reporting modalities 17
VI.C. Operation of the EU Network 19
VI.C.1. Interface with safety reporting rules for clinical trials in the EU 19
VI.C.2. Collection of reports 21
VI.C.2.1. Member States responsibilities 21
VI.C.2.2. Marketing authorisation holders responsibilities 22
VI.C.2.2.1. Spontaneous reports 22
VI.C.2.2.2. Solicited reports 23
VI.C.2.2.2.1. Reports from non-interventional studies 23
VI.C.2.2.2.2. Compassionate use, named patient use 24
VI.C.2.2.2.3. Patient support programme 24
VI.C.2.2.3. Reports published in the scientific and medical literature 24
VI.C.2.2.4. Suspected adverse reactions related to quality defect or falsified medicinal products 25

VI.C.2.2.5. Suspected transmission via a medicinal product of an infectious agent 26
VI.C.2.2.6. Emerging safety issues 26
VI.C.2.2.7. Period between the submission of the marketing authorisation application and the granting of the marketing authorisation 27
VI.C.2.2.8. Period after suspension, revocation or withdrawal of marketing authorisation 27
VI.C.2.2.9. Period during a public health emergency 28
VI.C.2.2.10. Reports from class action lawsuits 28
VI.C.3. Expedited reporting time frames 28
VI.C.4. Reporting modalities 28
VI.C.4.1. Interim arrangements 29
VI.C.4.2. Final arrangements 29
VI.C.5. Collaboration with the World Health Organization and the European Monitoring Centre for Drugs and Drug Addiction 30
VI.C.6. Electronic exchange of safety information in the EU 30
VI.C.6.1. Applicable guidelines, definitions, international formats, standards and terminologies 31
VI.C.6.2. Electronic Reporting of Individual Case Safety Reports 31
VI.C.6.2.1. EudraVigilance Database Modules 31
VI.C.6.2.1.1. Adverse reaction data collected in the EudraVigilance Post-Authorisation Module 31
VI.C.6.2.1.2. Adverse Reaction Data Collected in the EudraVigilance Clinical Trial Module 32
VI.C.6.2.2. Preparation of Individual Case Safety Reports 32
VI.C.6.2.2.1. General principles 32
VI.C.6.2.2.2. Information on suspect, interacting and concomitant medicinal products 33
VI.C.6.2.2.3. Suspected adverse reactions 34
VI.C.6.2.2.4. Case narrative and causality assessment 35
VI.C.6.2.2.5. Test results 36
VI.C.6.2.2.6. Supplementary information 36
VI.C.6.2.2.7. Follow-up information 36
VI.C.6.2.2.8. What to take into account for data privacy laws 37
VI.C.6.2.2.9. Handling of languages 38
VI.C.6.2.2.10. Nullification of cases 38
VI.C.6.2.3. Special situations 38
VI.C.6.2.3.1. Use of a medicinal product during pregnancy or breastfeeding 38
VI.C.6.2.3.2. Suspected adverse reaction reports published in the scientific and medical literature 39
VI.C.6.2.3.3. Suspected adverse reactions related to overdose, abuse, misuse, medication error or occupational exposure 39
VI.C.6.2.3.4. Lack of therapeutic efficacy 40
VI.C.6.2.3.5. Suspected adverse reactions related to quality defect or falsified medicinal products 40
VI.C.6.2.3.6. Suspected transmission via a medicinal product of an infectious agent 40
VI.C.6.2.3.7. Reports originating in non-interventional organised data collection schemes 41
VI.C.6.2.3.8. Receipt of missing minimum information 41
VI.C.6.2.4. Data quality of individual case safety reports transmitted electronically and duplicate management 41
VI.C.6.2.5. Electronic re-transmission of ICSRs between multiple senders and receivers 42

VI.C.6.2.6. Electronic reporting through company's headquarters 43
VI.C.6.3. Electronic submission of information on medicinal products 43
VI.Appendix 1. Identification of biological medicinal products 44
VI.Appendix 2. Detailed guidance on the monitoring of scientific and medical literature 47
VI.Appendix 3. Modalities for expedited reporting 56
VI.Appendix 3.1. Interim arrangements 56
VI.Appendix 3.1.1. Interim arrangements applicable to marketing authorisation holders 61
VI.Appendix 3.1.2. Interim arrangements applicable to competent authorities in Member States 61
VI.Appendix 3.2. Final arrangements 62
VI.Appendix 3.2.1. Final arrangements applicable to marketing authorisation holders 65
VI.Appendix 3.2.2. Final arrangements applicable to competent authorities in Member States 65
VI.Appendix 3.3. Transmission and rerouting of ICSRs to competent authorities in Member States 66
VI.Appendix 4. Transmission of ICSRs to World Health Organisation (WHO) Collaborating Centre 70
VI.Appendix 5. Nullification of cases 74
VI.Appendix 6. Data quality monitoring of ICSRs transmitted electronically 78
VI.Appendix 7. Duplicate detection and management of ICSRs 81

VI.A. Introduction

VI.A.1. Scope

This Module addresses the legal requirements detailed in Title IX of Directive 2001/83/EC and Chapter 3 of Regulation (EC) No 726/2004, which are applicable to competent authorities in Member States, marketing authorisation holders and the Agency as regards the collection, data management and reporting of suspected adverse reactions associated with medicinal products for human use authorised in the European Union (EU). Recommendations regarding the reporting of suspected adverse reactions occurring in special situations are also included in this Module.

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".

VI.A.2. Definitions

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 Chapter. Some general principles presented in the ICH-E2A and ICH-E2D guidelines[1] and in the Commission Implementing Regulation on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC should also be adhered to; they are included as well in this Chapter.

VI.A.2.1. Adverse reaction

An adverse reaction is a response to a medicinal product which is noxious and unintended [DIR Art 1]. This includes adverse reactions which arise from:

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

VI.A.2.1.1. Causality

In accordance with the ICH-E2A guideline, 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.

A reaction, in contrast to an 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 the ICH-E2D guideline, 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 submitted by healthcare professionals, patients or consumers are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the reporters specifically state they believe the events to be unrelated.

[1] http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

VI.A.2.1.2. Overdose, misuse, abuse, medication error, occupational exposure

a. Overdose

This refers to the administration of a quantity of a medicinal product given per administration or per day, which is above the maximal recommended dose according to the authorised product information. This shall also take into account cumulative effects due to overdose.

b. Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the prescribed or authorised dose, route of administration, and/or the indication(s) or within the legal status of its supply (e.g. without prescription for medicinal products subjects to medical prescription).

c. Abuse

As defined in Article 1 of Directive 2001/83/EC, this relates to the sporadic or persistent, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

d. Medication error

This refers to any unintentional error in the prescribing, dispensing or administration of a medicinal product while in the control of the healthcare professional, patient or consumer.

e. Occupational exposure

This corresponds to the exposure to a medicinal product for human use as a result of one's occupation.

VI.A.2.2. 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].

In accordance with Article 107 of Directive 2011/83/EC, the scope of this module is not only applicable to medicinal products authorised in the EU but also to any such medicinal products commercialised outside the EU by the same marketing authorisation holder (see VI.C.2.2). This is valid independently of the strengths, pharmaceutical forms, routes of administration, presentations, approved indications or trade names of the medicinal product. Since 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.

The guidance provided in this Module also applies mutatis mutandis to medicinal products supplied in the context of compassionate use (see VI.C.2.2.2.2) as defined in Article 83 of Regulation (EC) No 726/2004. 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.

VI.A.2.3. Primary source

The primary source of the information on a suspected adverse reaction(s) is the person who provides information about the case. Several primary sources, such as healthcare professionals and/or a patient or consumer, may provide information on the same case. In this situation, all the primary sources' details should be included in the case report, with the "Primary source(s)" section repeated as necessary in line with the ICH-E2B(R2) guideline[2].

In accordance with the ICH-E2D guideline,

- 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 or relative of a patient.

Medical documentations (e.g. laboratory or other test data) that support the occurrence of the suspected adverse reaction, or which indicate that an identifiable healthcare professional suspects a causal relationship between a medicinal product and the reported adverse reaction, are sufficient to consider the spontaneous report as confirmed by a healthcare professional.

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

VI.A.2.4 Seriousness

As described in the ICH-E2A guideline, 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, is a congenital anomaly/birth defect.

The characteristics/consequences should be considered at the time of the reaction to determine the seriousness of a case. For example, life-threatening refers to a reaction in which the patient was at risk 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 and scientific judgement should be exercised in deciding whether other situations should be considered as serious reactions. Some medical events may jeopardise the subject or may require an intervention to prevent one of the above characteristics/consequences. Such important medical events should be considered as serious[3]. 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). This IME list aims to facilitate the classification of suspected adverse reactions, the analysis of aggregated data and the assessment of the cases in the framework of the day-to-day pharmacovigilance activities. The IME list is intended for guidance purposes only and is available on the EudraVigilance web site[4]. It is regularly updated in line with the latest version of MedDRA.

[2] See VI.C.6 as regards the electronic reporting of ICSRs in the EU.
[3] Examples are provided in Section II.B of ICH E2A guideline.
[4] (http://eudravigilance.ema.europa.eu/human/textforIME.asp).

VI.A.2.5. Individual Case Safety Report (ICSR)

As described in [IM Annex I.1], this refers to the format and content for the reporting of one or several suspected adverse reactions in relation to a medicinal product that occur in a single patient at a specific point of time. A valid ICSR for expedited reporting shall include at least an identifiable reporter, an identifiable patient, at least one suspect adverse reaction and a suspect medicinal product.

VI.B. Structures and Processes

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

VI.B.1. Collection of reports

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

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

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

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

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

In accordance with the ICH-E2D guideline, 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, patient or consumer to a competent authority, marketing authorisation holder or other organisation (e.g. Regional Centre, Poison Control Centre) that describes one or more suspected adverse reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organised data collection schemes as defined in VI.B.1.2.

Stimulated reporting that occur consequent to a “Direct Healthcare Professional Communication”, publication in the press, questioning of healthcare professionals by company representatives, or class action lawsuits should be considered spontaneous reports.

Patient or consumer adverse reactions reports should be handled as spontaneous reports irrespective of any subsequent “medical confirmation”.

The expedited reporting time frames and reporting modalities for spontaneous reports are described in VI.B.7 and VI.B.8.

VI.B.1.1.2. Literature reports

The scientific and medical literature is a significant source of information for the monitoring of the safety profile and of the risk-benefit balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues. Marketing authorisation holders are

therefore expected to maintain awareness of possible publications through a systematic literature review of widely used reference databases (e.g. Medline, Excerpta Medica or Embase) no less frequently than once a week. The marketing authorisation holder should ensure that the literature review includes the use of reference databases that contain the largest reference of articles in relation to the medicinal product properties[5]. In addition, all company offices are encouraged to be aware of publications in their local journals and to bring them to the attention of the company safety department as appropriate.

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

If multiple medicinal products are mentioned in the publication, only those which are identified by the publication's author(s) as having at least a possible causal association with the suspected adverse reaction should be considered by the concerned marketing authorisation holder(s). This also applies to reports identified in the scientific and medical literature that originate in a country where a company holds a marketing authorisation but has never commercialised the medicinal product.

Valid ICSRs shall be reported according to the modalities detailed in VI.B.7 and VI.B.8. The regulatory reporting clock starts as soon as the marketing authorisation holder has knowledge that the case meets the minimum criteria for expedited reporting (see VI.B.2). One case should be created for each reported identifiable patient and relevant medical information should be provided. The publication reference(s) should be given as the report source.

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

VI.B.1.1.3. Reports from other sources

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

Marketing authorisation holders should regularly screen internet or digital media[6] under their management or responsibility, for potential reports of suspected adverse reactions. In this aspect, digital media is considered to be company sponsored if it is owned, paid for or controlled by the marketing authorisation holder[7]. The frequency of the screening should allow for potential valid ICSRs to be reported to the competent authorities within the appropriate expedited timeframe based on the date the information was posted.

It is also recommended that the marketing authorisation holder actively monitor special internet sites or digital media such as those of patients' support or special diseases groups in order to check if they

[5] See VI.Appendix 2. for the detailed guidance regarding the monitoring of the medical and scientific literature.
[6] 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.
[7] 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.

describe significant safety issues which may necessitate reporting in accordance with the recommendations described in VI.C.2.2.6. The frequency of the monitoring of those sites or digital media should depend on the risks associated to the medicinal product.

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

In relation to cases from the internet or digital media, the identifiability of the reporter refers to the existence of a real person, that is, it is possible to verify the contact details of the reporter (e.g., a valid email address has been provided). Contact details should only be used for pharmacovigilance purposes. If the country of the primary source is missing, the country where the information was received should be used as the primary source country, depending where the review takes place.

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

VI.B.1.2. Solicited reports

As defined in ICH-E2D guideline, solicited reports of suspected adverse reactions are those derived from organised data collection systems, which include clinical trials, non-interventional studies, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers, or information gathering on efficacy or patients compliance. Adverse reactions reports obtained from any of these data collection systems should not be considered spontaneous.

For the purpose of safety reporting, solicited reports should be classified as study reports, and should have an appropriate causality assessment, to consider whether they meet the criteria for expedited reporting.

General reporting rules for suspected adverse reactions occurring in organised data collection systems conducted in the EU under the scope of Directive 2001/83/EC, Regulation (EC) No 726/2004 or Directive 2001/20/EC, are presented in VI.C.1. EU reporting requirements applicable to marketing authorisation holders for reports of suspected adverse reactions originating from those organised data collection systems that do not fall under the scope of the clinical trials Directive 2001/20/EC are presented in VI.C.2.2.2.

VI.B.2. Validation of reports

Only valid ICSRs qualify for expedited reporting. All reports of suspected adverse reactions should therefore be validated before reporting them to the competent authorities to make sure that the minimum information is included in the reports. This is:

- An identifiable reporter (primary source), who may be identified by name or initials, address or qualification (e.g. physician, pharmacist, other health professional, lawyer, patient or consumer or other non healthcare professional)[8]. For the reporter to be considered identifiable, contact details need to be available in order to confirm or follow-up the case if necessary. All parties providing case information or approached for case information should be identifiable, not only the initial reporter. If a reporter does not wish to provide contact details, the ICSR should still be considered

[8] Local data privacy laws regarding patient's and reporter's identifiability might apply.

as valid providing the organisation who was informed of the case was able to confirm it directly with the reporter.

- An identifiable patient who may be characterised by initials, patient identification number, date of birth, age, age group or gender. The information should be as complete as possible[9].
- At least one suspected substance/medicinal product (see VI.A.2.2).
- At least one suspected adverse reaction (see VI.A.2.1). If the primary source has made an explicit statement that a causal relationship between the medicinal product and the adverse event has been excluded and the recipient (competent authority or marketing authorisation holder) agrees with this, the report does not qualify as a valid ICSR since the minimum information is incomplete[10]. The report does not also qualify as a valid ICSR if it is reported that the patient experienced an adverse reaction and there is no information provided on the type of adverse reaction experienced.

When collecting reports of suspected adverse reactions via the internet or digital media, the term "identifiable" refers to the possibility of verification of the existence of a reporter and a patient (see VI.B.1.1.4).

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

When one party (competent authority or a marketing authorisation holder) is made aware that the primary source may also have reported the suspected adverse reaction to another concerned party, the report should still be considered as a valid ICSR. All the relevant information necessary for the detection of the duplicate case should be included in the ICSR[11].

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

Similarly for non-interventional post-authorisation studies, where there is a disagreement between the investigator and the marketing authorisation holder on the assessment of the causal role of the suspected medicinal product, the case should not be downgraded. The opinions of both, the investigator and the marketing authorisation holder, should be provided in the ICSR (see VI.B.1.2).

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 relevant for

[9] See Footnote 8.
[10] There is no suspected adverse reaction.
[11] For further guidance on reporting of other duplicate ICSRs, refer to Section A.1.11 "Other case identifiers in previous transmission" of ICH-E2B(R2) guideline.

the scientific evaluation of the cases. This is in addition to any attempt to collect missing minimum information (see VI.B.2) where applicable.

Follow-up methods should be tailored towards optimising the collection of missing information. Written confirmation of details given verbally should be obtained whenever possible. This routine pharmacovigilance activity should be conducted 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 should avoid the requirement to duplicate 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 less burdensome. Serious reports should be followed up appropriately to ensure comprehensive case information is obtained, including information on the outcome/resolution of the suspected adverse reaction. Similarly prospective reports of pregnancy should be monitored to obtain information on the outcome at the expected date of delivery.

When information is received directly from a patient or consumer suggesting that an adverse reaction may have occurred, if the information is incomplete, attempts should be made to obtain consent to contact a nominated healthcare professional to obtain further follow-up information. When such a case, initially reported by a consumer or patient, has been confirmed (totally or partially) by a healthcare professional, this information should be clearly highlighted in the ICSR[12].

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

VI.B.4. Data management

Electronic data and paper reports of suspected adverse reactions should be stored and treated in the same way as other medical records with appropriate respect for confidentiality regarding patients' and reporters' identifiability and in accordance with local data privacy 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.

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

When transfer of pharmacovigilance data occurs within an organisation or between organisations, 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.

Case report information should only be transmitted between stakeholders in an anonymous format (see VI.C.6.2.2.8 for the processing of personal data in ICSRs in the EU).

Electronic data storage should ensure on-line accessibility and electronic reporting of ICSRs in line with the requirements detailed in VI.B.8.

[12] For further guidance on reporting this information, refer to ICH-E2B(R2) guideline, Section A.1.14 ("Was the case medically confirmed, if not initially from a healthcare professional?").

The use of terminologies should be monitored and validated by quality assurance auditing, either systematically or by regular random evaluation. Data entry staff should be instructed in the use of the terminologies, and their proficiency verified. The reports received from the primary source should be treated in an unbiased and unfiltered way and inferences as well as imputations should be avoided during data entry or electronic transmission. The reports should include the verbatim text as used by the primary source or an accurate translation of it. The original verbatim text should be coded using the appropriate terminology as described in VI.B.8. In order 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.

Databases should be reviewed regularly to identify and manage duplicates ICSRs (see VI.C.6.2.4).

VI.B.5. Quality management

Regulatory organisations 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, coding and archiving, case validation, case evaluation, follow-up and ICSR reporting (see VI.C.6.2.4 and Module I). Conformity of stored data with initial and follow-up reports should be verified by quality control procedures, which permit for the validation against the original data or images thereof. In this aspect, the source data (e.g., letters, emails, records of telephone calls that include details of an event) or an image of the source data should be easily accessible.

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

Staff directly performing pharmacovigilance activities, and other personnel working in other departments who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) 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.

VI.B.6. Special situations

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

a. Pregnancy

Reports where the embryo or foetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure) should be followed-up in order to collect information on the outcome of the pregnancy and development of the child. The recommendations provided in the Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-Authorisation Data[13] should be considered as regard the monitoring, collection and reporting of information in these specific situations in order to facilitate the scientific evaluation. When an active substance (or one of its metabolites) has a long half-life, this

[13] (Ref.: EMEA/CHMP/313666/2005)

should be taken into account when assessing the possibility of foetal exposure, if the medicinal product was taken before conception.

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

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

Individual cases with an abnormal outcome associated with a medicinal product following exposure during pregnancy are classified as serious reports and should be reported in an expedited manner, in accordance with the requirements outlined in VI.B.7[14].

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 termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data or reports which have a normal outcome, should not be reported on an expedited manner since there is no suspected adverse reaction[15]. These reports should however be processed as for other ICSRs.

In certain circumstances, any reports of pregnancy exposure may necessitate expedited reporting. This may be a condition to 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 teratogenic effect (e.g. through a cluster of similar abnormal outcomes) should be notified immediately to the competent authorities in accordance with the recommendations presented in VI.C.2.2.6.

b. Breastfeeding

Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk should be reported in accordance with the criteria outlined in VI.B.7[16].

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. Every attempt 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, patient or consumer in order to be able to indentify potential safety signals specific to a particular population.

[14] See VI.C.6.2.3.1 for electronic reporting recommendations in the EU.
[15] See also Module VII for the presentation in the periodic safety update report of expedited reports and other reports on the outcome of exposure during pregnancy, including reports from prospective registries.
[16] See Footnote 14.

Where the use of a medicinal product is common in an unauthorised population, it is important for both the competent authorities and marketing authorisation holders to monitor for any consequential safety concerns and to take appropriate measures to address them. In this aspect, marketing authorisation holders and competent authorities should encourage the reporting of all suspected adverse reactions even if they occur in unauthorised populations. As regards the paediatric population, the specific guidance published by the Agency[17] on the conduct of pharmacovigilance in this population should be followed.

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

Reports of overdose, abuse, misuse, medication error or occupational exposure with no associated adverse reaction should not be reported in an expedited manner as ICSRs. They should be considered in the relevant periodic safety update report, and risk management plan where applicable. When those reports constitute safety issues impacting on the risk-benefit balance of the medicinal product, they should be notified to the competent authorities in accordance with the recommendations provided in VI.C.2.2.6.

Reports associated with suspected adverse reactions should be subject to expedited reporting[18]. They should be routinely followed-up to ensure that the information is as complete as possible with regards to symptoms, treatments and outcomes.

VI.B.6.4. Lack of therapeutic efficacy

Reports of lack of therapeutic efficacy should be recorded and followed-up if incomplete. They should not normally be reported in an expedited manner, but should be discussed in the relevant periodic safety update report and risk management plan. However, in certain circumstances, reports of lack of therapeutic efficacy should be expedited as ICSRs within a 15 days time frame[19]. Medicinal products used for the treatment of life-threatening diseases, vaccines and 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.

Judgement should be used when considering if other cases of lack of therapeutic efficacy qualify for expedited reporting. For example, an antibiotic used in a life-threatening situation where the medicinal product was not in fact appropriate for the infective agent should not be reported. However, a life-threatening infection where the lack of therapeutic efficacy appears to be due to the development of a newly resistant strain of a bacterium previously regarded as susceptible should be reported in an expedited manner.

For vaccines, cases of lack of therapeutic efficacy should be reported, in particular with the view to highlight potential signals of reduced immunogenicity in a sub-group of vaccinees, waning immunity, or strain replacement. With regard to the latter, it is considered that spontaneously reported cases of lack of therapeutic 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.

[17] Guideline on conduct of pharmacovigilance for medicines used by the paediatric population (EMEA/CHMP/PhVWP/235910/2005- rev.1).
[18] See VI.C.6.2.3.3 as regards electronic reporting in the EU.
[19] See VI.C.6.2.3.4 as regards electronic reporting in the EU.

VI.B.7. Expedited reporting of ICSRs

Only valid ICSRs (see VI.B.2) should be reported. The clock for expedited reporting of a valid ICSR starts as soon as the information containing the minimum reporting criteria has been brought to the attention of the national or regional pharmacovigilance centre of a competent authority or of any personnel of the marketing authorisation holder, including medical representatives and contractors. This date should be considered as day zero.

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

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

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

VI.B.7.1. Expedited reporting time frames

In general, expedited reporting of serious valid ICSRs is required as soon a 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. This applies to initial and follow-up information. Where an initially serious case is downgraded to non-serious, this information should still be reported within 15 days; the reporting time frame for non-serious reports should then be applied for the subsequent follow-up reports.

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

VI.B.8. Reporting modalities

Taking into account the international dimension of adverse reactions reporting and the need to achieve harmonisation and high quality between all involved parties, ICSRs should be submitted electronically as structured data with the use of controlled vocabularies for the relevant data elements where applicable. In this aspect, with regard to the content and format of electronic ICSRs, competent authorities and marketing authorisation holders should adhere to the following internationally agreed ICH[20] guidelines and standards:

- ICH M1 terminology - Medical Dictionary for Regulatory Activities (MedDRA);

[20] http://www.ich.org/

- MedDRA Term Selection: Points to Consider Documents - The latest version of the ICH-endorsed Guide for MedDRA Users;
- 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 Implementation Working Group - Questions & Answers (R5) (March 3, 2005);

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

Information regarding EU specific reporting modalities is provided in VI.C.4.

VI.C. Operation of the EU Network

Section C of this Module highlights the EU specific requirements, as defined in Directive 2001/83/EC and Regulation (EC) No 726/2004, in relation to the collection, management and reporting of suspected adverse reactions associated with medicinal products for human use authorised in the EU. They are applicable to competent authorities in Member States and/or to marketing authorisation holders. It should be read in conjunction with the definitions and general principles detailed in VI.A and VI.B of this Module.

VI.C.1. Interface with safety reporting rules for clinical trials in the EU

The pharmacovigilance rules laid down in Directive 2001/83/EC and Regulation (EC) No 726/2004 do not apply to investigational medicinal products and non-investigational medicinal products[21] used in clinical trials conducted in accordance with Directive 2001/20/EC[22].

Post-authorisation safety or efficacy studies requested by competent authorities in Member States in accordance with Directive 2001/83/EC or Regulation (EC) No 726/2004, or conducted voluntarily by marketing authorisation holders, can either be clinical trials or non-interventional studies as shown in Figure VI.1. Safety reporting falls 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 studies. Suspected adverse reactions should not be reported under both regimes, that is Directive 2001/20/EC as well as Regulation (EC) No 726/2004 and Directive 2001/83/EC. Further guidance on post-authorisation safety studies is provided in Module VIII.

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

EU reporting requirements for marketing authorisation holders applicable to reports of suspected adverse reactions originating from post-authorisation studies that do not fall under the scope of the clinical trials Directive 2001/20/EC are presented in VI.C.2.2.2.

If a clinical trial, conducted under the scope of Directive 2001/20/EC, yields safety concerns which impact of 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 Module VII.

The different types of studies and clinical trials which can be conducted in the EU are illustrated in Figure VI.1.

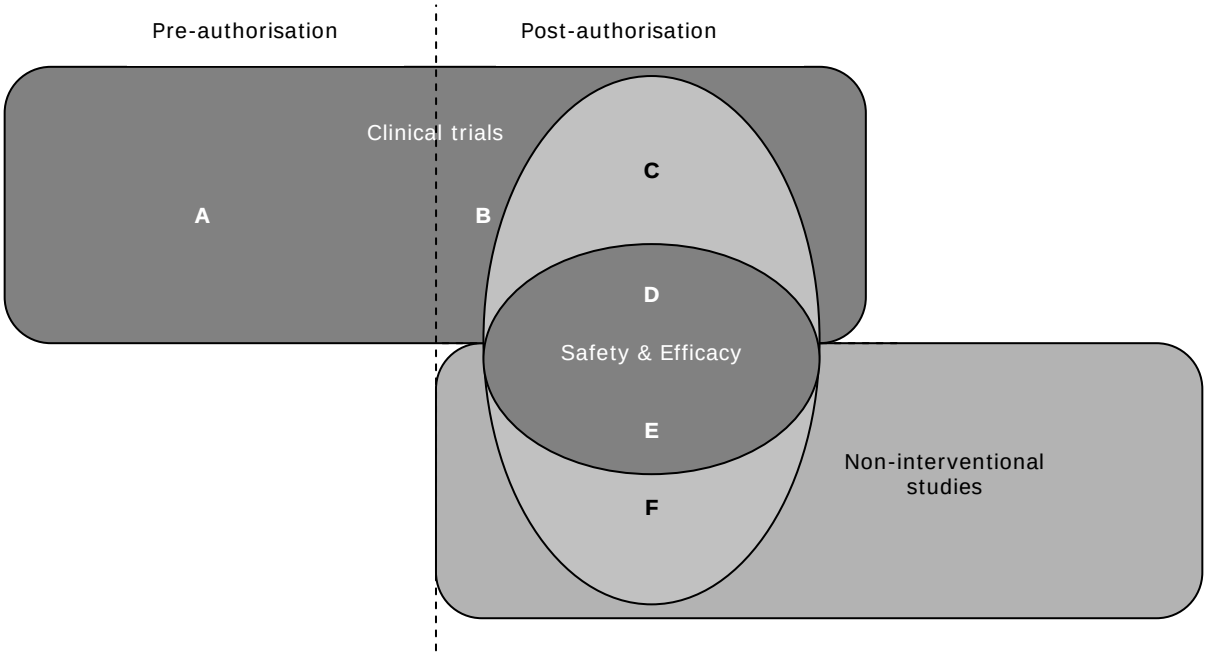
Based on the rules detailed in this chapter, the safety reporting for clinical trials corresponding to Section A, B, C and D of Figure VI.1. should follow the requirements of Directive 2001/20/EC. The

[21] For guidance on these terms, see The rules governing medicinal product in the European Union, Volume 10, Guidance applying to clinical Trials, Guidance on Investigational Medicinal Products and Non-Investigational Medicinal Products (NIMPs) (Ares(2011)300458 - 18/03/2011).
[22] See [DIR Art 3(3), Art 107(1) third subparagraph].

safety reporting for non-interventional studies corresponding to section E and F should follow the requirements of Directive 2001/83/EC and Regulation (EC) No 726/2004.

The reporting rules of solicited reports to the EudraVigilance database modules are dependent of the types of organised collection systems where they occurred; recommendations provided in VI.C.6.2.1 should be followed.

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



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

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

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

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

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

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

VI.C.2. Collection of reports

VI.C.2.1. Member States responsibilities

In accordance with Articles 101(1) and 107a(1) of Directive 2001/83/EC, each Member State shall have in place a system for the collection and recording of all reports of suspected adverse reactions that occur in its territory and which are brought to its attention by healthcare professionals, patients or consumers, or marketing authorisation holders[23]. In addition to the requirements presented in this chapter, the general principles detailed in VI.B, together with the reporting modalities presented in VI.C.3 and VI.C.4 should be applied to all reports of suspected adverse reactions.

Each Member State shall take all appropriate measures to encourage healthcare professionals and patients or 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, competent authorities in Member States shall facilitate in their territory the reporting of suspected adverse reactions by means of alternative straightforward reporting systems, accessible to healthcare professionals and patients or consumers, in addition to web-based formats [DIR Art 102].

Standard web-based structured forms for the reporting of suspected adverse reactions by healthcare professionals and patients or consumers shall be developed by the Agency in collaboration with Member States in order to collect across the EU harmonised information relevant for the evaluation of suspected adverse reactions, including errors associated with the use of medicinal products [REG Art 25]. The forms shall be made publicly available by means of national medicines web-portals together with information on the different ways of reporting suspected adverse reactions related to medicinal products [DIR 106(e)].

To increase awareness of the reporting systems, organisations representing patients or consumers and healthcare professionals may be involved as appropriate [DIR Art 102].

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

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

Each Member State shall ensure that the competent authority responsible for medicinal products within that Member State is informed of any suspected adverse reaction, brought to the attention of any other authority, body, institution or organisation responsible for patient safety within that Member State, and that valid ICSRs are made available to the EudraVigilance database [DIR Art 107a(5)]. Therefore, where reports of suspected adverse reactions are sent directly to other authorities, bodies, organisations and/or institutions within a Member State, the competent authority in that Member State shall have data exchange agreements in place so these reports are brought to its attention and are made available to Eudravigilance in a timely manner. In line with Article 107a(5) of Directive 2001/83/EC, this applies as well to reports of suspected adverse reactions arising from an error associated with the use of a medicinal product. Those error reports of suspected adverse reactions for which a competent authority in a Member State is made aware of, including those received from the

[23] Marketing authorisation holders shall report ICSRs to the competent authorities in Member States in accordance with the transitional provisions set out in Article 2(4) and Article 2(5) of Directive 2010/84/EC and further detailed in VI.C.4.1.

EudraVigilance database in accordance with Article 24(4) of Regulation (EC) No 726/2004, shall also be brought to the attention of other authorities, bodies, organisations and/or institutions responsible for patient safety within that Member State.

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

VI.C.2.2. Marketing authorisation holders responsibilities

Each marketing authorisation holder shall have in place a system for the collection and recording of all reports of suspected adverse reactions which are brought to its attention, whether reported spontaneously by healthcare professionals, patients or consumers or occurring in the context of a post-authorisation study [DIR Art 104(1), Art 107(1)]. In this context, marketing authorisation holders shall establish mechanisms enabling the traceability and follow-up of adverse reaction reports while complying with the data protection legislation [IM Art 15].

Regarding the collection of suspected adverse reactions, marketing authorisation holders responsibilities apply to reports related to medicinal products (see VI.A.2.2) for which ownership cannot be excluded on the basis of the active substance name, formulation, batch number, route of administration, primary source country or country of origin of the suspected adverse reactions. In addition to the requirements presented in this chapter, the general principles detailed in Section VI.B, together with the reporting modalities presented in VI.C.3 and VI.C.4 should be applied to all reports of suspected adverse reactions.

Marketing authorisation holders shall ensure that any information on adverse reactions suspected to be related to at least one of the active substances of medicinal products authorised in the EU is brought to their attention by any company outside the EU belonging to the same mother company (or group of companies), which holds the marketing authorisation in the EU for the concerned medicinal product, or any company not belonging to the same company or group of companies but having concluded commercial agreement with the company who holds the marketing authorisation in the EU for the concerned medicinal product[24]. The clock for expedited reporting (see VI.B.7) starts when a valid ICSR is first received by one of these companies belonging to the same marketing authorisation holder in the EU, or having concluded contractual arrangements with the marketing authorisation holder in the EU.

VI.C.2.2.1. Spontaneous reports

Marketing authorisation holders shall record all reports of suspected adverse reactions originating from within or outside the EU, which are brought to their attention spontaneously by healthcare professionals, patients or consumers. This includes reports of suspected adverse reactions received electronically or by any other appropriate means [DIR Art 107(1), Art 107(2)].

In this context, marketing authorisation holders may consider utilising their websites to facilitate the collection of suspected adverse reactions by providing adverse reactions forms for reporting, or appropriate contact details for direct communication.

[24] As outlined in the Commission communication on the Community marketing authorization procedures for medicinal products (98/C 229/03).

VI.C.2.2.2. Solicited reports

Marketing authorisation holders shall record all reports of suspected adverse reactions originating from within or outside the EU, which occur in post-authorisation studies [DIR Art 107(1)]. In the context of this module, these solicited reports are those derived from organised data collection schemes initiated, managed, or financed by marketing authorisation holders and that do not fall under the scope of the clinical trials Directive 2001/20/EC. They include non-interventional post-authorisation studies, compassionate uses, named patient uses, other patient support and disease management programmes, registries, surveys of patients or healthcare providers, and information gathering on efficacy or patient compliance.

As for spontaneous reports, marketing authorisation holders should have mechanisms in place to collect full and comprehensive cases information at the time of initial reporting, in order to allow meaningful assessment of individual cases and expedited reporting of valid ICSRs to competent authorities as applicable. This does not apply to study designs based on secondary use of data.

The electronic reporting rules of solicited ICSRs originating from those organised data collection schemes are described in VI.C.6.2.3.7.

The safety data from non-interventional studies to be presented in the relevant sections of the periodic safety update report of the authorised medicinal product are detailed in Module VII.

VI.C.2.2.2.1. Reports from non-interventional studies

Non-interventional studies should be distinguished between those with primary data collection directly from patients and healthcare professionals, and study designs which are based on secondary use of data such as studies based on medical chart reviews or electronic health care records, systematic reviews or meta-analyses.

Only reports of adverse reactions where a possible causal relationship with the suspected medicinal product is considered by the primary source or the marketing authorisation holder should be reported; other reports of events should be included in the final study report.

- For non-interventional studies with primary data collection directly from patients and healthcare professionals, only reports of adverse reactions suspected to be related to the studied medicinal product by the primary source or the marketing authorisation holder should be reported. Other reports of adverse reactions, suspected to be related only to medicinal products which are not subject to the scope of the study, and where there is no interaction with the studied medicinal product(s), should be reported to the concerned competent authorities where applicable by the investigators.
- For non-interventional study designs which are based on secondary use of data, adverse reactions reporting is not required. All adverse events/reactions should be summarised in the final study report.
- In case of doubt, the marketing authorisation holder should clarify the reporting requirement with the concerned competent authorities in Member States.
- Marketing authorisation holders should also follow the national legislation where applicable as regards the reporting of cases of suspected adverse reactions to local ethics committees and investigators.

VI.C.2.2.2.2. Compassionate use, named patient use

Where an organisation[25] or a healthcare professional, supplying a medicinal product under compassionate use or named patient use (see VI.A.2.2 for definitions), is notified or becomes aware of a case of suspected adverse reaction(s), the case should be reported as follows:

- For compassionate and named patient uses where adverse events are actively sought, only reports of adverse reactions where a possible causal relationship with the suspected medicinal product is considered by the primary source or the marketing authorisation holder should be reported. They should be considered as solicited reports.
- For compassionate and named patient uses where the reporting of adverse events is not solicited, any noxious or unintended response to the medicinal product should be considered as a spontaneous report of a suspected adverse reaction and reported accordingly.

VI.C.2.2.2.3. Patient support programme

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

Adverse events may be actively sought during the conduct of these types of organised data collection schemes, in which case they should be considered as solicited reports. Only reports of adverse reactions where a possible causal relationship with the suspected medicinal product is considered by the primary source or the marketing authorisation holder should be reported.

- Example: a marketing authorisation holder contacts a patient or healthcare professional and asks if some adverse events were associated with the use of the medicinal product.

For organised data collection schemes where adverse event reporting is not solicited, any noxious or unintended response to a medicinal product which is notified to the marketing authorisation holder by a patient or healthcare professional should be considered as a spontaneous report of suspected adverse reaction and reported accordingly.

- Example: a marketing authorisation holder contacts a patient or healthcare professional for the purpose of refilling a prescription and is informed of a suspected adverse reaction.

VI.C.2.2.3. Reports published in the scientific and medical literature

General principles in relation to the monitoring of suspected adverse reactions described in the scientific and medical literature are provided in VI.B.1.1.2.

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

[25] E.g. sponsor, applicant, marketing authorisation holder, hospital or wholesaler.

systematic literature review and reference database, in line with the principles detailed in VI.B.1.1.2 and in VI.Appendix 2..

Marketing authorisation holders should also make themselves aware of publications in local journals in those Member States where the medicinal product is authorised and report valid ICSRs as appropriate.

The following exceptions should be applied for the expedited reporting of ICSRs identified in literature articles:

- Where ownership of the medicinal product by the marketing authorisation holder can be excluded on the basis of the active substance name, formulation, route of administration, primary source country or country of origin of the suspected adverse reaction, the ICSR should not be reported to the competent authorities in Member States, or to the EudraVigilance database.
- Literature ICSRs which are based on an analysis from a competent authority database within the EU do not need to be reported to the competent authority of the country where the database resides. The expedited reporting requirements remain for those ICSRs which are based on the analysis from a competent authority database outside the EU.
- Literature articles, which present summary data analyses from publicly available databases, or which only detail patients in tables or line listings, should not be reported as ICSRs. This type of literature articles describes adverse reactions, which occur in a group of patients with a designated medicinal product with the aim of identifying or quantifying a safety hazard related to a medicinal product. They are often linked to pharmacoepidemiological studies and the main objective is to detect/evaluate specific risks that could affect the overall risk-benefit balance of a medicinal product.
- The safety findings presented in these types of articles should however be discussed in the relevant sections of the concerned periodic safety update report (see Module VII) and analysed as regards their overall impact on the medicinal product risk-benefit profile. In addition, any new safety information, which may impact on the risk-benefit profile of a medicinal product, should be notified immediately to the competent authorities in Member States where the medicinal product is authorised and to the Agency in accordance with the recommendations provided in VI.C.2.2.6.

A detailed guidance on the monitoring of the scientific and medical literature has been developed by the Agency in accordance with Article 27(3) of Regulation (EC) No 726/2004; it is included in VI.Appendix 2.. The electronic reporting recommendations regarding suspected adverse reactions reports published in the scientific and medical literature are provided in VI.C.6.2.3.2.

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

When a report of suspected adverse reactions is associated with a suspected or confirmed falsified medicinal product or quality defect of a medicinal product, a valid ICSR should be reported. Electronic reporting recommendations provided in VI.C.6.2.3.5 should be followed.

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

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

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as a serious adverse reaction and such cases should be reported within 15 days in accordance with the requirements outlined in VI.C.4 [26]. If no other criterion is applicable, the seriousness of this ICSR should be considered as important medical event (see VI.A.2.4). This also applies to vaccines.

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 suspected transmission via a medicinal product of an infectious agent to the manufacturer, the relevant blood establishment(s) and the national competent authority.

Any organism, virus or infectious particle (e.g. prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

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

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

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

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

Medicinal products should comply with the recommendations provided in the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Products[27]. 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[28], should also be followed as appropriate.

VI.C.2.2.6. Emerging safety issues

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

- major safety findings from a newly completed non-clinical study;
- major safety concerns identified in the course of a non-interventional post-authorisation study or of a clinical trial;
- signals of a possible teratogenic effect or of significant hazard to public health;

[26] See VI.C.6.2.3.6 for electronic reporting recommendations.
[27] Latest revision. EMA/410/01.
[28] EMEA/149995/2008

- safety issues published in the scientific and medical literature;
- safety issues arising from the signal detection activity (see Module IX) or emerging from a new ICSR and which impact on the risk-benefit balance of the medicinal product;
- safety issues related to the use outside the terms of the marketing authorisation;
- safety issues due to misinformation in the product information;
- marketing authorisation withdrawal, non-renewal, revocation or suspension outside the EU for safety-related reasons;
- urgent safety restrictions outside the EU;
- safety issues in relation to the supply of raw material;
- lack of supply of medicines;

These events/observations, which may affect the risk-benefit balance of a medicinal product, are not to be submitted as ICSRs. They should be notified forthwith as Emerging Safety Issues in writing to the competent authorities in Member States where the medicinal product is authorised and to the Agency via email (address will be provided in the final Module); this should be done immediately when becoming aware of them. The document should indicate the points of concern and the actions proposed in relation to the marketing application/authorisation for the concerned medicinal product. Those safety issues should also be analysed in the relevant sections of the periodic safety report of the authorised medicinal product.

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 that could impact on the risk-benefit balance may become available to the applicant[29]. 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 spontaneous reports (see VI.C.2.1) or non-interventional solicited reports (see VI.C.2.2), should be reported in accordance with the requirements provided in VI.C.3 and VI.C.4.

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

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

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

[29] 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.2.2.9. 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 of the European Parliament and of the Council. In the event of a public health emergency, regular reporting requirements may be amended. Such arrangements will be considered on a case-by-case basis and will be appropriately notified on the Agency website.

VI.C.2.2.10. Reports from class action lawsuits

Reports arising from class action lawsuits should be managed as stimulated unsolicited reports. Only reports of adverse reactions where a possible causal relationship with the suspected medicinal product is considered by the primary source or the marketing authorisation holder should be reported in accordance with the time frames and modalities described in VI.C.3 and VI.C.4.

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

VI.C.3. Expedited reporting time frames

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

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

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

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

VI.C.4. Reporting modalities

In addition to the recommendations provided in VI.B.8, competent authorities in Member States and marketing authorisation holders shall use the formats and terminologies for the electronic transmission of suspected adverse reactions as referred to in [IM Chapter 5]. Competent authorities in Member States and marketing authorisation holders shall also ensure that all reported electronic ICSRs are well documented and as complete as possible in accordance with the requirements provided in [IM Annex I.3].

The recommendations provided in VI.C.6 should be adhered to as regards the electronic exchange of pharmacovigilance information between competent authorities in Member States, marketing authorisation holders and the Agency.

ICSRs reported electronically to the EudraVigilance database will be made accessible to stakeholders such as competent authorities, healthcare professionals, patients or consumers, as well as marketing authorisation holders and research organisations in accordance with Article 24(2) of Regulation (EC) No

726/2004 and the EudraVigilance access policy[30]. This policy defines the overall principles of the provision of access to EudraVigilance data in line with the current legal framework, while guaranteeing personal data protection.

VI.C.4.1. Interim arrangements

In accordance with the provisions set out in Article 2(4), Article 2(5) and Article 2(6) of Directive 2010/84/EC, until the Agency can ensure the functionalities of the EudraVigilance database as specified in Article 24(2) of Regulation (EC) No 726/2004, the following reporting requirements shall apply to healthcare professional and non-healthcare professional valid ICSRs:

a. Serious ICSRs

- Marketing authorisation holders shall report all serious ICSRs that occur in the EU to the competent authority of the Member State on whose territory the suspected adverse reactions occurred.
- Marketing authorisation holders shall report to the EudraVigilance database all serious ICSRs that occur outside the EU, including those received from competent authorities. If required, those reports shall also be reported to the competent authorities in the Member States in which the medicinal product is authorised.
- Competent authorities in Member States shall ensure that all serious ICSRs that occur in their territory and that are reported to them, including those received from marketing authorisation holders, are made available to the EudraVigilance database. Competent authorities in Member States should also make available, to the marketing authorisation holders of the suspected medicinal products, all serious ICSRs reported directly to them.

b. Non-Serious ICSRs

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

Overviews of the expedited reporting requirements during the interim period, applicable to marketing authorisation holders or competent authorities in Member States, are presented in VI.Appendix 3.1. together with a detailed business process map.

Member States requirements for serious non-EU ICSRs and for non-serious EU ICSRs will be included in VI.Appendix 3.1. in the final Module.

VI.C.4.2. Final arrangements

Once the functionalities of the EudraVigilance database specified in Article 24(2) of Regulation (EC) No 726/2004 are established, the following requirements, detailed in Articles 107(3) and 107a(4) of Directive 2001/83/EC, shall apply within 6 months of the announcement by the Agency to healthcare professional and non-healthcare professional valid ICSRs:

a. Serious ICSRs

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

[30] EudraVigilance Access Policy for Medicines for Human Use (EMA/759287/2009).

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

b. Non-Serious ICSRs

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

Overviews of the expedited reporting requirements applicable to marketing authorisation holders or competent authorities in Member States, once the final arrangements are implemented, are presented in VI.Appendix 3.2. together with a detailed business process map.

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

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 WHO Collaborating Centre all suspected adverse reaction reports occurring in the EU. This will take place on a weekly basis after their transmission to the EudraVigilance database by competent authorities in Member States or marketing authorisation holders. It will replace the requirements of Member States participating in the WHO Programme for International Drug Monitoring to directly report to WHO suspected adverse reactions reports occurring in their territory. This will be implemented once the functionalities of the EudraVigilance database specified in Article 24(2) of Regulation (EC) No 726/2004 are established.

A detailed business process map for the reporting of ICSRs, from the EudraVigilance database to the WHO Collaborating Centre, is presented in VI.Appendix 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

Part VI.C.6 highlights the requirements, as defined in Articles 24(1) and 24(3) 83 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 [IM Chapter 5, Annex I].

In addition the following guidelines should be applied:

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

The latest version of these documents should always be considered.

VI.C.6.2. Electronic Reporting of Individual Case Safety Reports

The reporting of valid ICSRs electronically, by competent authorities in Member States and marketing authorisation holders, is mandatory for all medicinal products authorised in the EU [DIR Art 107(3), Art 107a(4)]. Non-adherence to this requirement constitutes a non-compliance with EU legislation. Responsibilities in case of communication failure are detailed in Chapter IV of the Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in Pharmacovigilance during the Pre- and Post-authorisation Phase in the European Economic Area (EEA) (EMEA/115735/2004).

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

VI.C.6.2.1. EudraVigilance Database Modules

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

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

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

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

2001/20/EC (see VI.C.2.2.2). The ICSRs should be submitted with the value 'EVHUMAN' in the data element 'Message receiver identifier' (ICH M2 M.1.6).

Depending on their type, these ICSRs should be classified with one of the following options, in accordance with the EudraVigilance business rules[31]:

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

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 studied in clinical trials conducted under the scope of Directive 2001/20/EC (see VI.C.1), should be reported by the sponsor to the EudraVigilance Clinical Trial Module (EVCTM). The requirements provided in EudraLex Volume 10 of The Rules Governing Medicinal Products in the European Union should be applied. The ICSRs should be submitted with the value 'EVCTMPROD' in the data element 'Message receiver identifier' (ICH M2 M.1.6) and should be classified as followed, in accordance with the EudraVigilance business rules[32]:

- data element 'Type of report' (ICH-E2B(R2) A.1.4):
  - report from study; and
- data element 'Study type in which the reaction(s)/event(s) were observed' (ICH-E2B(R2) A.2.3.3):
  - clinical trials.

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 VI.C.6.1 and particularly:

- the requirements detailed in [IM Annex I.3];
- the latest version of the ICH-endorsed guide for MedDRA users - MedDRA Term Selection: Points to Consider Documents (reference to be included);

[31] Note for guidance - EudraVigilance Human - Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (EMA/H/20665/04/Final Rev. 2).
[32] See Footnote 31.

- the EudraVigilance business rules for the electronic transmission of ICSRs summarised in the Note for guidance - EudraVigilance Human - Processing of Safety Messages and Individual Case Safety Reports (ICSRs) (EMA/H/20665/04/Final Rev. 2).

It is recognised that it is often difficult to obtain all the details on a specific case. However, the complete information (medical and administrative data) for a valid ICSR that is available to the sender should be reported in a structured manner in the relevant ICH-E2B(R2) data elements (which should be repeated as necessary when multiple information is available) and in the narrative section (see VI.C.6.2.2.4). This applies to all types of ICSRs, such as reports with initial information on the case, follow-up information and cases highlighted for nullification[33].

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

Where the suspected adverse reactions reported in a single ICSR impact on the known risk-benefit balance of a medicinal product, this should be considered as an emerging safety issue (see VI.C.2.2.6), which should be immediately notified in writing to the competent authorities of the Member States where the medicinal product is authorised and to the Agency. This is in addition to the expedited reporting requirements detailed in VI.C.4. A summary of the points of concerns and the action proposed should be recorded in the ICSR in data element 'Sender's comments' (ICH-E2B(R2) B.5.4).

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

The suspect, interacting and/or concomitant active substances/invented names of the reported medicinal products should be provided in accordance with [IM Annex I.3(4)(g) to (i)], the ICH-E2B(R2) guideline (see Annex IV) and the EudraVigilance business rules.

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

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

- data element 'Proprietary medicinal product name' (ICH-E2B(R2) B.4.k.2.1) should be populated with the proprietary/branded medicinal product name as reported by the primary source;
- data element 'Active substance name(s)' (ICH-E2B(R2) B.4.k.2.2) should be completed with the active substance(s) that correspond(s) to the composition of the proprietary/branded medicinal product of the country where the reaction/event occurred.

However if the information is available on:

- the 'Identification of the country where the drug was obtained' (data element ICH E2B(R2) B.4.k.2.3),

[33] See also VI.C.6.2.2.10 on nullification of individual cases.

- the 'Authorization/application number' (data element ICH-E2B(R2) B.4.k.4.1),
- the 'Country of authorization/application' (data element ICH-E2B(R2) B.4.k.4.2), and/or
- the 'Batch/lot number' (data element ICH-E2B(R2) B.4.k.3),

the composition with regard the active substance(s) of the proprietary medicinal product should be provided accordingly.

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

- the data element 'Proprietary medicinal product name' (ICH-E2B(R2) B.4.k.2.1) should be populated with the medicinal product name as reported by the primary source;
- the data element 'Active substance name(s)' (ICH-E2B(R2) B.4.k.2.2) should be completed with those active substances which are in common to all formulations/presentations in the country of authorisation.

Where medicinal products cannot be described on the basis of the active substances or the invented names, for example when only the therapeutic class is reported by the primary source, or in case of other administered therapies that cannot be structured, this information should only be reflected in the case narrative (data element ICH-E2B(R2) B.5.1). The data elements 'Proprietary medicinal product name' (ICH-E2B(R2) B.4.k.2.1) and 'Active substance name(s)' (ICH-E2B(R2) B.4.k.2.2) should not be populated. The same applies if a food interaction is reported (e.g. to grapefruit juice).

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

As regards the reporting of drug interactions, which concerns drug/drug (including biological products), drug/food, drug/device, and drug/alcohol interactions, the coding of the interaction should be performed in Section 'Reactions/Events' (ICH-E2B(R2) B.2) in line with the latest version of the ICH-Endorsed Guide for MedDRA Users - MedDRA Term Selection: Points to Consider Documents. In addition, for drug/drug interactions, information on the active substances/proprietary medicinal product names should be provided in the Section 'Drug information' (ICH-E2B(R2) B.4), which should be characterised as interacting in the data element 'Characterisation of drug role' (ICH-E2B(R2) B.4.k.1).

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

VI.C.6.2.2.3. Suspected adverse reactions

All available information as described in [IM Annex I.3(4)(j)] shall be provided for each individual case. The coding of diagnoses and provisional diagnoses with signs and symptoms in the data element

'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1) should be performed in line with the latest version of the ICH-Endorsed Guide for MedDRA Users, MedDRA Term Selection: Points to Consider.

In practice, events, which are typically signs or symptoms of a diagnosis or a provisional diagnosis reported by a primary source, should be listed and MedDRA coded in the section 'Reaction(s)/event(s)' (ICH-E2B(R2) B.2). It is however considered sufficient to select a term for only the diagnosis or provisional diagnosis and not for the signs and symptoms.

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

If no diagnosis is provided by the primary source, all reported signs and symptoms should be listed and MedDRA coded in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'. If these signs and symptoms are typically part of a diagnosis, the diagnosis can be MedDRA coded in addition in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'.

VI.C.6.2.2.4. Case narrative and causality assessment

In accordance with [IM Annex I.3(4)(m)], a case narrative (data element ICH-E2B(R2) B.5.1) shall be provided, where possible[34], for all cases in accordance with the recommendations described in Chapter 5.2 of the ICH-E2D guideline. 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. This should be consistent with the data appropriately reflected in all the other relevant ICH-E2B(R2) data elements of the ICSR. It shall be confirmed that no additional information is available.

The narrative should serve as a comprehensive, stand-alone "medical report" containing all known relevant clinical and related information, including patient characteristics, therapy details, medical history, clinical course of the event(s), diagnosis, adverse reactions and their outcomes, relevant laboratory evidence (including normal ranges) and any other information that supports or refutes the suspected adverse reactions. Any relevant autopsy or post-mortem findings shall be summarised and related documents should be provided according to national regulation and if allowed by local data privacy laws. An example of a standard narrative template is available in the Report of the CIOMS Working Group V[35].

Competent authorities in Member States and marketing authorisation holders may comment on the causal relationship between the suspected medicinal product(s) and the suspected adverse reaction(s) in addition to the primary source causality assessment, if provided. This information should be indicated in the data element 'Relatedness of drug to reaction(s)/event(s)' (ICH-E2B(R2) B.4.k.18), which should be repeated as necessary. During the interim arrangements period (see VI.C.4.1), the case narratives provided in ICSRs submitted to a competent authority by a marketing authorisation holder, should not be modified or deleted when the ICSRs are then reported to the EudraVigilance database by the competent authority.

[34] 'Where possible' should be interpreted as having received sufficient information from the primary source to prepare a concise clinical summary of the individual case.
[35] Council for International Organizations of Medical Sciences (CIOMS). Current Challenges in Pharmacovigilance: Pragmatic Approaches (CIOMS V). Geneva: CIOMS; 2001. http://www.cioms.ch/.

VI.C.6.2.2.5. Test results

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

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

VI.C.6.2.2.6. Supplementary information

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

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

VI.C.6.2.2.7. Follow-up information

ICSRs are sent at different times to multiple receivers. Therefore the initial/follow-up status is dependent upon the receiver. For this reason an item to capture follow-up status is not included in the ICH-E2B(R2) data elements. However, the data element ‘Date of receipt of the most recent information for this report’ (ICH-E2B(R2) A.1.7) taken together with the data element ‘Sender identifier’ (ICH E2B(R2) A.3.1.2) and the data element ‘Sender’s (case) report unique identifier’ (ICH-E2B(R2) A.1.0.1) provide a mechanism for each receiver to identify whether the report being transmitted is an initial or a follow-up report. For this reason these items are considered critical for each transmission and a precise date should always be used (i.e. day, month, year). The data element ‘Date of receipt of the most recent information for this report’ (ICH-E2B(R2) A.1.7) should therefore always be updated each time follow-up information is received by the sender.

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

The sender should report follow-up information in an expedited manner if significant new medical information has been received. Significant new information relates to for example new suspected adverse reaction(s), a change in the causality assessment and any new or updated information on the case that impacts on its medical interpretation. Therefore, the identification of significant new information requiring expedited reporting always necessitates medical judgement.

Situations where the seriousness criteria and/or the causality assessment relating to an individual case are downgraded (e.g. follow-up information leads to a change of the seriousness criteria from serious to non-serious; causality assessment is changed from related to non-related) should also be considered as significant changes and thus reported in an expedited manner.

In addition, the sender should also report follow-up information, where 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 transmissions (data element 'Other case identifiers in previous transmissions' (ICH-E2B(R2) A.1.11)). This information may be specifically relevant for the receiver to manage potential duplicates. Another example refers to data element 'Additional available documents held by sender' (ICH-E2B(R2) A.1.8), whereby new documents that have become available to the sender may be relevant for the medical assessment of the case.

In contrast, a follow-up report which contains non-significant information does not require expedited reporting. This may refer, for example, to minor changes to some dates with no implication for the evaluation or transmission of the case, or corrections of typos in the previous case version. Naturally, medical judgment should be applied since a change to the birth date may constitute a significant modification (e.g. with implications on the age information of the patient).

Similarly, a change of the status of a MedDRA code/term from current to non-current, due to a version change of MedDRA, can be considered as a non-significant change as long as this change has no impact on the medical content of a case. However, an amendment of the MedDRA coding due to a change in the interpretation of a previously reported suspected adverse reaction may constitute a significant change and therefore should be reported in an expedited manner.

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

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

VI.C.6.2.2.8. What to take into account for data privacy 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 within the EudraVigilance database is possible while respecting EU legislation in relation to data protection (Directive 95/46/EC, Regulation (EC) No 45/2001).

Where in accordance with applicable national legislation, information related to personal data cannot be transferred to the EudraVigilance system, pseudonymisation may be applied by competent authorities in Member States and by marketing authorisation holders[36], thereby replacing identifiable health 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. The application of pseudonymisation will facilitate the ability of the EudraVigilance system to adequately support case processing and detect duplicates. This should however be done without impairing the information flow in the EudraVigilance system 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.

[36] As set out in [IM Annex I.3.3].

VI.C.6.2.2.9. Handling of languages

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

Taking into account the international dimension of pharmacovigilance, an English summary shall be provided with the initial verbatim text for narrative and textual descriptions where they are reported in an official language in the EU other than English[37]. Member States may report case narratives in their official language or languages. For these reports, case translations should be provided within 24 hours 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.

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

VI.C.6.2.2.10. Nullification of cases

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

A nullified case is one that should no longer be considered for scientific evaluation. The process of the nullification of a case is by means of a notification by the sender to the receiver that this is no longer a valid case. However, the case should be maintained in the sender's pharmacovigilance database. The principles to be considered when nullifying a case are detailed in VI.Appendix 5..

VI.C.6.2.3. Special situations

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

General recommendations are provided in VI.B.6.1.

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

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

[37] As described in [IM Annex I.3.5].

additional relevant information' (ICH-E2B(R2) B.5.1) should describe the entire case, including the father's information.

- If both the parent and the child/foetus experience suspected adverse reactions, two separate reports, i.e. one for the parent (mother or father) and one for the child/foetus, should be created but they should be linked by using the data element 'Identification number of the report which is linked to this report' (ICH-E2B(R2) A.1.12) in each report.
- If there has been no reaction affecting the child, the parent-child/foetus report does not apply; i.e. the section 'Patients characteristics' (ICH-E2B(R2) B.1) applies only to the parent (mother or father) who experienced the suspected adverse reaction.
- For those cases describing miscarriage or early spontaneous abortion, only a parent report is applicable, i.e. the section 'Patients characteristics' (ICH-E2B(R2) B.1) apply to the mother. However, if the suspect medicinal product was taken by the father, the data element 'Additional information on drug' (ICH-E2B(R2) B.4.k.19) should specify that the medication was taken by the father. Also since it is a mother report, the data element 'Route of administration' (ICH-E2B(R2) B.4.k.8) should be indicated as 'Unknown'.

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

EU requirements in relation to the monitoring of suspected drug reactions reported in the scientific and medical literature are provided in VI.C.2.2.3.

With regard to the electronic reporting of ICSRs published in the scientific and medical literature, the requirements detailed in [IM Annex I.3(4)(b)] shall be applied:

- The literature references shall be included in the data element 'Literature reference(s)' (ICH-E2B(R2) A.2.2) in the Vancouver Convention (known as "Vancouver style"), developed by the International Committee of Medical Journal Editors. The standard format as well as those for special situations can be found in the following reference: International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med. 1997; 336: 309-15, which is in the Vancouver style[38].
- A comprehensive English summary of the article shall be provided in the data element 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' (ICH-E2B(R2) B.5.1).
- Upon request, for specific safety review, a full translation and a copy of the relevant literature article shall be provided by the marketing authorisation holders. The recommendations detailed in VI.App2.10. regarding the mailing of the literature article should be followed.
- Examples for the reporting of several cases, when they are published in the same literature article, are also presented in VI.App2.10.

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

General principles are provided in VI.B.6.3.

If a case of overdose, abuse, misuse, medication error or occupational exposure is reported with clinical consequences, the MedDRA Lower Level Term code, corresponding to the term closest to the

[38] The Vancouver recommendations are also available on the International Committee of Medical Journal Editors website http://www.icmje.org.

description of the reported overdose, abuse, misuse, medication error or occupational exposure should be added to the observed suspected adverse reaction(s) in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1.b), in line with recommendations included in the latest version of the ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider'.

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 Lower Level Term code, corresponding to the term closest to the description of the reported lack of therapeutic efficacy, should be provided in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1.b), in line with recommendations included in the latest version of the ICH-Endorsed Guide for MedDRA Users 'MedDRA Term Selection: Points to Consider'.

Unless aggravation of the medical condition occurs, the indication for which the suspected medicinal product was administered should not be included in the data element 'Reaction/event in MedDRA terminology' (ICH-E2B(R2) B.2.1).

It should be noted that it is acceptable to submit ICSRs as non-serious (if no seriousness criteria are available) for those reports related to classes of medicinal products where, as described in VI.B.6.4, reports of lack of therapeutic efficacy should be expedited within a 15 days time frame.

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 when they are exchanged between stakeholders, the following recommendations should be applied:

a. Quality defect

Where an adverse reaction(s) report is associated with a quality defect of a medicinal product, the MedDRA Lower Level Term code 10069327, corresponding to the term "Product quality issue", should be added to the observed suspected adverse reaction(s) in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1.b).

b. Falsified medicinal products

Where an adverse reaction(s) report is associated with a suspected or confirmed falsified medicinal product, the MedDRA Lower Level Term codes 10071287 corresponding to the term "Suspected counterfeit product", or 10063180 corresponding to the term "Pharmaceutical product counterfeit" should be added accordingly to the observed suspected adverse reaction(s) in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1.b)[39]. Information on the suspected medicinal product, active substance(s) or excipient(s) should be provided in the data elements 'Proprietary medicinal product name' (ICH-E2B(R2) B.4.k.2.1) and/or 'Active substance name(s)' (ICH-E2B(R2) B.4.k.2.2) as reported by the primary source.

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

EU requirements are provided in VI.C.2.2.5.

[39] Counterfeit medicines are known as falsified medicinal products in EU legislation (Directive 2011/62/EU).

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

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

VI.C.6.2.3.7. Reports originating in non-interventional organised data collection schemes

General reporting requirements in the EU for organised data collection schemes which do not fall under the scope of the clinical trials Directive 2001/20/EC are provided in VI.C.2.2.2.

For reports of suspected adverse reactions originating from data collection schemes where adverse events/reactions may be actively sought, the following reporting rules should be applied:

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

Where adverse events/reactions reporting is not actively sought, any reports received by the marketing authorisation holder should be considered as spontaneous reports of suspected adverse reaction:

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

All ICSRs reportable to the EudraVigilance database, originating from non-interventional organised data collection schemes 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).

VI.C.6.2.3.8. Receipt of missing minimum information

When missing minimum information has been obtained about a non-valid ICSR, the following rules should be applied:

- the data element 'Date report was first received from source' (ICH-E2B(R2) A.1.6) should contain the date of receipt of the initial non-valid ICSR;
- the data element 'Date of receipt of the most recent information for this report' (ICH-E2B(R2) A.1.7) should contain the date when all the four elements of the minimum information required for reporting have become available;
- clarification should be provided in the case narrative (data element ICH-E2B(R2) B.5.1) that some of the four elements were missing in the initial report.

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

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

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

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

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

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

The Agency shall in collaboration with the stakeholder that submitted an ICSR to the EudraVigilance database, be responsible for operating procedures that ensure the highest quality and full integrity of the information collected in the EudraVigilance database [REG Art 24(3)]. In this regard, marketing authorisation holders and competent authorities in Member States should have in place an audit system, which enables the detection and management of duplicate ICSRs and, which ensures the highest quality of the ICSRs transmitted electronically to the EudraVigilance database. Those ICSRs should be complete, entire and undiminished in their structure, format and content.

High level business process maps and process descriptions in relation to the quality review of ICSRs and the detection and management of duplicate ICSRs are provided in VI.Appendix 6. and VI.Appendix 7.. Further guidance on the detection of duplicate ICSRs is available in the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs) (EMA/13432/2009).

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

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

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

During this re-transmission process, information on the case should not be omitted or changed if no new information on the case is available to the re-transmitting sender.

Exceptions apply to the following data elements or sections:

- ‘Sender’s (case) safety report unique identifier’ (ICH-E2B(R2) A.1.0.1);
- ‘Date of this transmission’ (ICH-E2B(R2) A.1.3);
- ‘Date report was first received from source’ (ICH-E2B(R2) A.1.6), for initial reports;
- ‘Date of receipt of the most recent information for this report’ (ICH-E2B(R2) A.1.7);
- ‘Information on sender and receiver of case safety report’ (ICH-E2B(R2) A.3);

- 'Relatedness of drug to reaction(s)/event(s)' (ICH-E2B(R2) B.4.k.18);
- 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' (ICH-E2B(R2) B.5.3);
- 'Sender's comments' (ICH-E2B(R2) B.5.4).

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

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

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

- the central reporting arrangement should be clearly specified in the marketing authorisation holder's pharmacovigilance system master file and in the internal standard operating procedures;
- the company's headquarter designated for reporting the ICSRs should be registered with EudraVigilance;
- the same principles may be applied for reporting from the competent authorities in the Member States to the marketing authorisation holders during the interim arrangements period, that is competent authorities in the Member States report electronically to the company's headquarter instead of to the local affiliate.

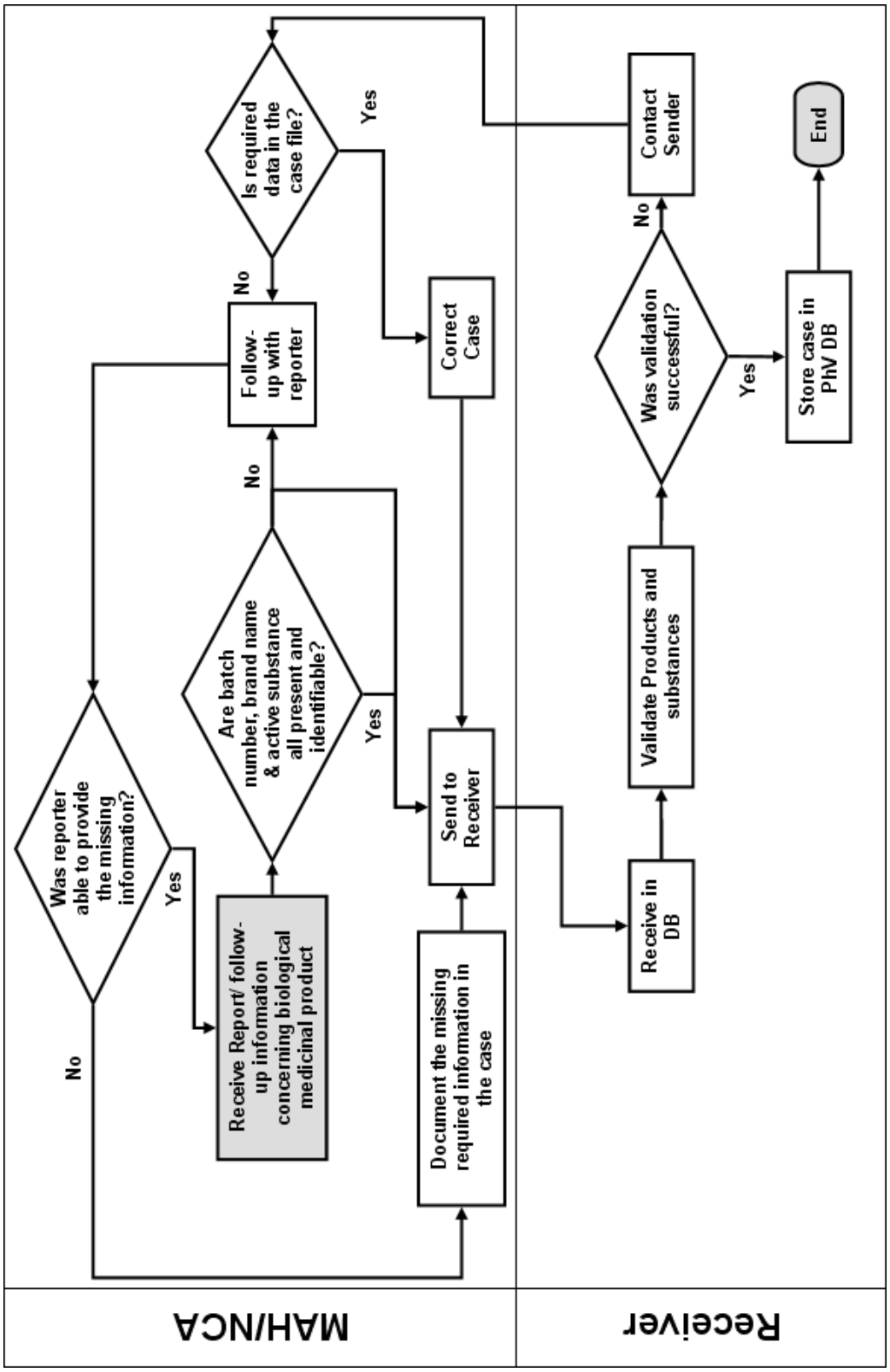
VI.C.6.3. Electronic submission of information on medicinal products

To support the objectives of Directive 2001/83/EC and Regulation (EC) No 726/2004, the provisions provided in second sub-paragraph of Article 57(2) of Regulation (EC) No 726/2004, regarding the electronic submission and update of information on medicinal products for human use authorised or registered in the EU, shall be followed by marketing authorisation holders. In this aspect marketing authorisation holders shall apply the internationally agreed formats and terminologies described in [IM Chapter 5]. Information related to the electronic submission of information on medicines is provided on the Agency's website[40].

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

VI.Appendix 1. Identification of biological medicinal products[41]

Figure VI.2. Business process map - Identification of biological medicinal products



[41] When they are the subject of reports of suspected adverse reactions [DIR Art 102(e)].

1578 **Table VI.1.** Process description - Identification of biological medicinal products

No.	Step	Description	Responsible Organisation
1	**Start.** **Receive report/follow-up information concerning biological medicinal product.**	**Day 0. Receipt of the information for the case that indicates that one of the suspect drugs is of biological origin.**	**MAH/NCA**
2	Are batch number, brand name & active substance all present and identifiable?	If Yes, create the case and send it to the correct receiver (step 3). If there is more than one batch number, structure the batch number that coincided with the adverse reaction in the Drug section (ICH-E2B(R2) B.4) and enter the other batch numbers in the case narrative. If No, create the case and send it to the correct receiver (step 3) and follow-up with the reporter (step 2.1).	MAH/NCA
2.1	Follow-up with reporter.	Follow-up with the reporter to attempt to identify the missing information.	MAH/NCA
2.2	Was reporter able to provide the missing information?	If Yes, return to step 1 – the information should be treated as follow-up and a new version created & transmitted. If No, document this (step 2.3).	MAH/NCA
2.3	Document the required missing information in the case.	Document in the case that the missing required information has been sought but the reporter was not able or willing to provide it.	MAH/NCA
3	Send to receiver.	Transmit the case electronically, in E2B(R2) format within the relevant timelines (15 or 90 days), to the relevant receiver.	MAH/NCA
4	**Receive in DataBase (DB).**	Receive the case electronically and load it into the pharmacovigilance database.	**Receiver**
5	Validate products and substances	Validate the products and substances to ensure that the brand name, active substance & batch number are all present and identifiable. This validation should be complementary to the usual business rules validations.	Receiver
6	Was validation successful?	If Yes, store the case in the pharmacovigilance database (step 7). If No, contact the sender (Step 6.1).	Receiver
6.1	Contact sender.	Contact the sender regarding the missing or not identifiable information.	Receiver
6.2	**Is required data in the case file?**	Upon receipt of communication from the receiver, check in the case file to see if the missing or unidentifiable information is already on file.	**MAH/NCA**

No.	Step	Description	Responsible Organisation
		If it is on file, correct the case (step 6.3). If the information is not on file, contact the reporter to request the missing information (step 2.1).	
6.3	Correct case.	Correct the case to include the missing information & send updated version to receiver (step 3).	MAH/NCA
7	**Store case in PharmacoVigilance DataBase (PhV DB).**	The case should now be stored in the pharmacovigilance database.	**Receiver**
8	**End.**	**The case is now available for signal detection and data quality analyses.**	

1579

1580

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

VI.App2.1. When to start and stop searching in the scientific and medical literature

In addition to routine expedited and periodic reporting requirements, the marketing authorisation holder has an obligation to report 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 would include published scientific and medical literature. For the period between submission and granting of a marketing authorisation, literature searching should be conducted to identify published articles that provide information that could impact on the risk-benefit assessment of the product under evaluation.

It should be noted that the requirement for literature searching is not dependent on a product being marketed. Literature searches should be conducted for all products with a marketing authorisation, irrespective of commercial status. It would therefore be expected that literature searching would start on submission of a marketing authorisation application and continue while the authorisation is active.

VI.App2.2. Where to look

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

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

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

If ICSRs are brought to the attention of a marketing authorisation holder from this source, they should be processed in the same way as ICSRs found on searching a database or reviewing a journal. Abstracts from major scientific meetings are indexed and available in some databases, but posters and communications are rarely available from this source.

VI.App2.3. Database Searches

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

VI.App2.3.1. Precision and recall

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

VI.App2.3.2. Search construction

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

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

VI.App2.3.3. Selection of product terms

Searches should be performed to find records for active substances and not for brand names only. This can include excipients and 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 formulations 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 or occupational exposure information, which could be poorly indexed. Searches should also not routinely exclude records of unbranded products or records for other company brands.

VI.App2.3.4. 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 unexplained death;
- the omission of terms to include special types of report (for example asymptomatic overdose);
- the omission of pregnancy terms:
  - to find uneventful pregnancy reports for periodic safety update reports and risk-benefit purposes;
  - to find adverse outcomes in pregnancy for ICSR reporting.

VI.App2.3.5. Limits to a search

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

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

Limits can be applied to produce results for date ranges, for example, weekly searches can be obtained by specifying the start and end date for the records to be retrieved. Care should be taken to ensure that the search is inclusive for an entire time period, for example, records that may have been added later in the day for the day of the search should be covered in the next search period. The search should also retrieve all records added in that period, and not just those initially entered or published during the specified period (so that records that have been updated or retrospectively added are retrieved). This should be checked with the database provider if it is not clear.

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

VI.App2.4. Record keeping

Records of literature searches should be maintained in accordance with the requirements described in [IM Art 15]. Marketing authorisation holders should demonstrate due diligence in searching published scientific and medical literature. It is always good practice to retain a record of the search construction, the database used and the date the search was run. In addition, it may be useful to retain results of the search for an appropriate period of time, particularly in the event of zero results. If decision making is documented on the results, it is particularly important to retain this information.

VI.App2.5. Outputs

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

VI.App2.6. 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 qualified 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.

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 ICSRs that do not qualify for expedited reporting.

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

Articles can be excluded from reporting by the marketing authorisation holder if another company's branded medicinal product is the suspected medicinal product. In the absence of a specified medicinal product source and/or invented name, ownership of the medicinal product should be assumed for articles about an active substance. Alternative reasons for exclusion of a published article are a specified formulation or a route of administration that is not consistent with the marketing authorisation holder's medicinal product presentation. The caveat is that articles may describe the preparation of an extemporaneous product (for example making solutions from solid dose forms), and could, therefore, be reportable.

VI.App2.7. 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 a reportable adverse reaction. Awareness of a publication includes any personnel of that organisation, or third parties with contractual arrangements with the

organisation. It is sometimes possible to identify the date on which a record was available on a database, although with weekly literature searching, day zero for a reportable adverse reaction present in an abstract is taken to be the date on which the search was conducted. For articles that have been ordered as a result of literature search results, day zero is the date when the minimum information for an ICSR to be valid is available. Organisations should take appropriate measures to obtain articles promptly in order to confirm the validity of a case.

VI.App2.8. Duplicates

Consistent with the requirements for reporting ICSRs, literature cases should be checked to prevent reporting of duplicates, and previously reported cases should be identified as such when reported. It is, therefore, expected that ICSRs are checked to identify literature articles that have already been reported.

VI.App2.9. Contracting out Literature Search Services

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

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

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

VI.App2.10. Electronic submission of suspected adverse reactions reports published in the scientific and medical literature

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

1. Mailing address and format of literature articles:

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

   Literature articles reportable to the competent authorities in Member States should be provided in PDF format and sent according to the local requirements.

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

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

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

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

Examples:

- Initial ICSR published in the literature: FR-ORGABC-23232321 (data element 'World-Wide Unique Case Identification Number' (ICH-E2B(R2) A.1.10.1));
  - File name of the literature article: FR-ORGABC-23232321.pdf.
- Follow-up information published in the literature in a separate article:
  - ICSR: FR-ORGABC-23232321 (data element World-Wide Unique Case Identification Number remains unchanged (ICH-E2B(R2) A.1.10.1));
  - File name: FR-ORGABC-23232321-1.pdf.

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

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

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

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

Table VI.2. Examples for the reporting of cases originally reported in the scientific and medical literature and referring to more than one patient

Ex.	Scenario	Action
1	A literature article describes suspected adverse reactions that have been experienced by up to 3 patients. 3 ICSRs should be created and reported for each individual identifiable patient. Each ICSR should contain all the available information on the case.	For Case 1 described in the literature article: • ICH-E2B(R2) A.1.10.1 'World-Wide Unique Case Identification Number': UK-ORGABC-0001 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0002 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0003 • ICH-E2B(R2) A.2.2 'Literature reference(s): Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals: N Engl J Med. 1997;336:309-15. • File name for the copy of literature article to be sent via e-mail to EVLIT@ema.europa.eu: UK-ORGABC-0001.pdf For Case 2 described in the literature article: • ICH-E2B(R2) A.1.10.1 'World-Wide Unique Case Identification Number': UK-ORGABC-0002 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0001 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0003 • ICH-E2B(R2) A.2.2 'Literature reference(s): Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals: N Engl J Med. 1997;336:309-15. • No copy of the literature article required since the copy was already submitted for case 1. For Case 3 described in the literature article: • ICH-E2B(R2) A.1.10.1 'World-Wide Unique Case Identification Number': UK-ORGABC-0003 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0001 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0002

Ex.	Scenario	Action
		• ICH-E2B(R2) A.2.2 'Literature reference(s): Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals: N Engl J Med. 1997;336:309-15. • No copy of the literature article required since the copy was already submitted for case 1.
2	A literature article describes suspected adverse reactions that have been experienced by more than 3 patients. An ICSR should be created and reported for each individual identifiable patient. Each ICSR should contain all the available information on the case.	For the ICSRs which relate to the same literature article, the cross reference in the data element 'Identification number of the report which is linked to this report' ICH (E2B(R2) field A.1.12) should be conducted as follows: • The first case should be linked to all other cases related to the same article; • All the other cases should be only linked to the first one, as in the example below. *Example for the reporting of cases originally reported in the scientific and medical literature referring to a large number of patients:* For Case 1 described in the literature article: • ICH E2B(R2) A.1.10.1 'Worldwide Unique Case Identification Number': UK-ORGABC-0001 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0002 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0003 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0004 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-000N • ICH-E2B(R2) A.2.2 'Literature reference(s)': N Engl J Med. 1997;336:309-15. • File name for the copy of literature article to be sent via e-mail to EVLIT@ema.europa.eu: UK-ORGABC-0001.pdf. For Case 2 described in the literature article: • ICH E2B(R2) A.1.10.1 'Worldwide Unique Case Identification Number': UK-ORGABC-0002 • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0001 • ICH-E2B(R2) A.2.2 'Literature reference(s)':

Ex.	Scenario	Action
		N Engl J Med. 1997;336:309-15. • No copy of the literature article required since the copy was already submitted for case 1. For Case N described in the literature article: • ICH-E2B(R2) A.1.10.1 'Worldwide Unique Case Identification Number': UK-ORGABC-000N • ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0001 • ICH-E2B(R2) A.2.2 'Literature reference(s)': N Engl J Med. 1997;336:309-15. • No copy of the literature article required since the copy was already submitted for case 1.

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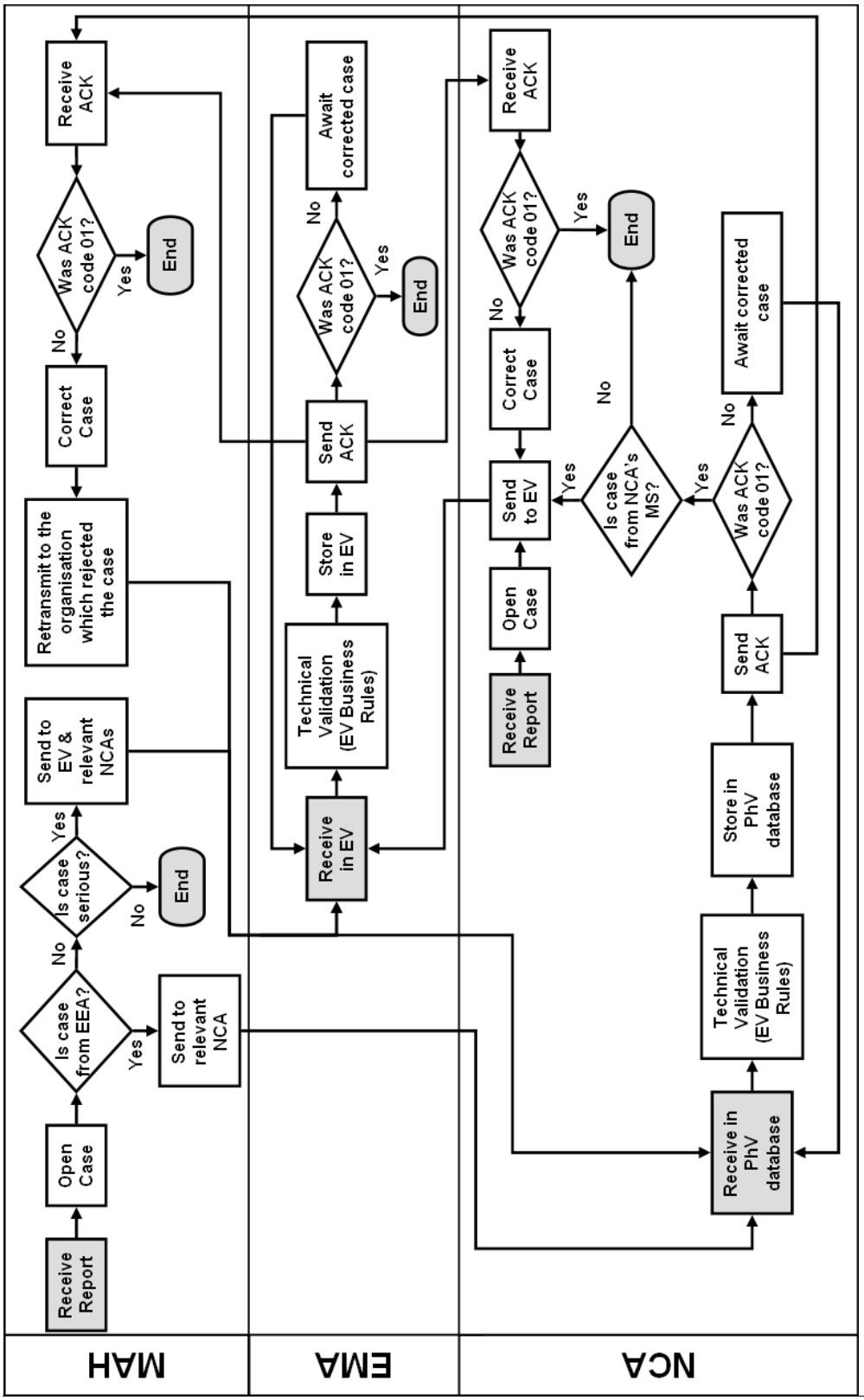
VI.Appendix 3. Modalities for expedited reporting

VI.Appendix 3.1. Interim arrangements

Figure VI.3. Business process map - Suspected adverse reaction reporting in EU – Interim arrangements



1824 **Table VI.3.** Process description - Suspected adverse reaction reporting in EU - Interim arrangements

No.	Step	Description	Responsible Organisation
1	**Start.** **Receive report.**	**Marketing Authorisation Holder (MAH) receives information on a suspected adverse reaction from a patient, healthcare professional or other valid reporter.** **If the case has been received from a National Competent Authority (NCA), do not retransmit it to another NCA nor to EudraVigilance (EV).**	**MAH**
2	Open case.	Open and create an individual case safety report.	MAH
3	Is case from EU?	Did the adverse reactions occur in the EU? If No, go to step 3.1. If Yes, got so step 5.	MAH
3.1	Is case serious?	If No, go to step 3.2. If Yes, got so step 4.	MAH
3.2	**End.**	**The case is now stored in the MAHs pharmacovigilance database. Normal follow-up activities should continue and if any follow-up is received, return to step 1.**	**MAH**
4	Send to EV & relevant NCAs.	Transmit the serious case electronically, in E2B(R2) format as an xml message within the 15 days timeline to EV and to the relevant NCAs, where required. The case goes to step 4.1 & step 6.	MAH
4.1	**Receive in EV.**	Receive the message in EV database from MAH or NCA.	**EMA**
4.2	Technical Validation (EV Business Rules).	Every message that is received in EV is validated against the EudraVigilance Business Rules and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. A valid message will have an ACK code 01. A non-valid message will have an ACK code 02 (if a case contained therein is non-valid) or 03 (if the message itself is not correctly formatted).	EMA
4.3	Store in EV.	Once the case has been validated, it is stored in EV.	EMA
4.4	Send ACK.	The acknowledgement message created in step 4.2 is transmitted to the case sender, no later than 2 business days following receipt of the case.	EMA

No.	Step	Description	Responsible Organisation
		Go to step 15 for MAHs receiving the ACK. Go to step 19 for NCAs receiving the ACK. Go to step 4.5 for the EMA's next step.	
4.5	Was ACK code 01?	If No, go to step 4.6. If Yes, go to step 4.7.	EMA
4.6	Await corrected case.	The sender should correct every case with an error ACK and retransmit within the regulatory reporting timelines. Periodically the EMA should assess all cases with an error ACK for which a corrected case has not been transmitted and contact the Qualified Person responsible for PharmacoVigilance (QPPV) to inform of these missing corrected cases. If a sender fails to correct cases, then this information should be incorporated into data quality assessments and the appropriate committees should be informed. Go back to step 4.1 upon receipt of the corrected case.	EMA
4.7	**End.**	**The case is now stored in EV &, following duplicate detection & recoding will be available for signal detection and data quality analyses.**	**EMA**
5	**Send to relevant NCA.**	Transmit the case (serious, and if required non-serious) electronically, in E2B(R2) format as an xml message within the relevant timelines (15 or 90 days, as applicable), to the relevant NCA for the Member State where the reaction occurred. If country of occurrence has not been specified, then country of primary source should normally be taken to be the occurrence country.	**MAH**
6	**Receive in PharmacoVigilance (PhV) database.**	Receive the message from MAH in the NCA's PhV database.	**NCA**
7	Technical Validation (EV Business Rules).	Every message that is received in the NCA's PhV database should be validated against the EudraVigilance Business Rules and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. A valid message will have an ACK code 01. A non-valid message will have an ACK	NCA

No.	Step	Description	Responsible Organisation
		code 02 (if a case contained therein is non-valid) or 03 (if the message itself is not correctly formatted).	
8	Store in EV.	Once the case has been validated, it is stored in the NCA's PhV database.	NCA
9	Send ACK.	The acknowledgement message created in step 7 is transmitted to the case sender no later than 2 business days following receipt of the case. Go to step 15 for MAHs receiving the ACK. Go to step 10 for the NCA's next step.	NCA
10	Was ACK code 01?	If No, go to step 10.1. If Yes, go to step 11.	NCA
10.1	Await corrected case.	The MAH should correct every case with an error ACK and retransmit it within the regulatory reporting timelines. Periodically the NCA should assess all cases with an error ACK for which a corrected case has not been transmitted and contact the QPPV to inform them of these missing corrected cases. If a sender fails to correct cases, then this information should be incorporated into any data quality assessments performed and the appropriate action can be taken. Go back to step 6 upon receipt of the corrected case.	NCA
11	Was case from NCA's MS?	Did the case occur in the territory of the receiving NCA? If No, go to step 11.1. If Yes, go to step 12.	NCA
11.1	**End.**	**The case is now stored in the NCA's pharmacovigilance database &, following duplicate detection & recoding will be available for signal detection and data quality analyses.**	**NCA**
12	Send to EV.	Transmit the serious case electronically, in E2B(R2) format as an xml message within the 15 days timeline to EV. Go to step 4.1 for reception of the case in EV.	NCA
13	**Start.** **Receive report.**	**NCA receives information on a suspected adverse reaction from a patient, healthcare professional or other valid reporter concerning a suspected adverse reaction occurring**	**NCA**

No.	Step	Description	Responsible Organisation
		in the territory of the receiving competent authority.	
14	Open case.	Open and create an individual case safety report. Go to step 12.	NCA
15	**Receive ACK.**	Receive the ACK message, associate it with the relevant case(s) and check to ensure that the case was considered valid.	**MAH**
16	Was ACK code 01?	If yes, go to step 16.1. If no, then the regulatory timeline clock has not stopped and the case should be corrected and re-transmitted to EV within the relevant regulatory reporting timelines. Day 0 remains as the day that the first information was received. A 02 or 03 ACK does not constitute new information. Go to step 17 (Correct case).	MAH
16.1	**End.**	**End the process of transmitting this version of the case to EV or NCA. Normal follow-up activities should continue and if any follow-up is received, return to step 1.**	**MAH**
17	Correct case.	Correct the case to remove the errors identified in the ACK.	MAH
18	Retransmit to the organisation which rejected the case.	Retransmit the corrected case to the organisation which rejected the case with ACK code 02 or 03. Got to step 4.1 &/or step 6 as appropriate.	MAH
19	**Receive ACK.**	Receive the ACK message, associate it with the relevant case(s) and check to ensure that the case was considered valid.	**NCA**
20	Was ACK code 01?	If yes, go to step 22. If no, then the regulatory timeline clock has not stopped and the case should be corrected and re-transmitted to EV within the relevant regulatory reporting timelines. Day 0 remains as the day that the first information was received. A 02 or 03 ACK does not constitute new information. Go to step 21 (Correct case).	NCA
21	Correct case.	Correct the case to remove the errors identified in the ACK and retransmit the case to EV (go back to step 12).	NCA
22	**End.**	**End the process of transmitting this**	**NCA**

No.	Step	Description	Responsible Organisation
		version of the case to EV. Normal follow-up activities should continue and if any follow-up is received, return to step 6 or 13.	

VI.Appendix 3.1.1. Interim arrangements applicable to marketing authorisation holders

Table VI.4. Expedited reporting requirements applicable to marketing authorisation holders - Interim arrangements

Marketing authorisation procedure	Origin	Adverse reaction type	Destination	Time frame
• Centralised • Mutual recognition, decentralised or subject to referral • Purely national	EU	All serious	• Member State where suspected adverse reaction occurred	15 days
		All non-serious	• Member State where suspected adverse reaction occurred, if required	90 days
	Non-EU	All serious	• EudraVigilance database • Member States where medicinal product is authorised, if required	15 days

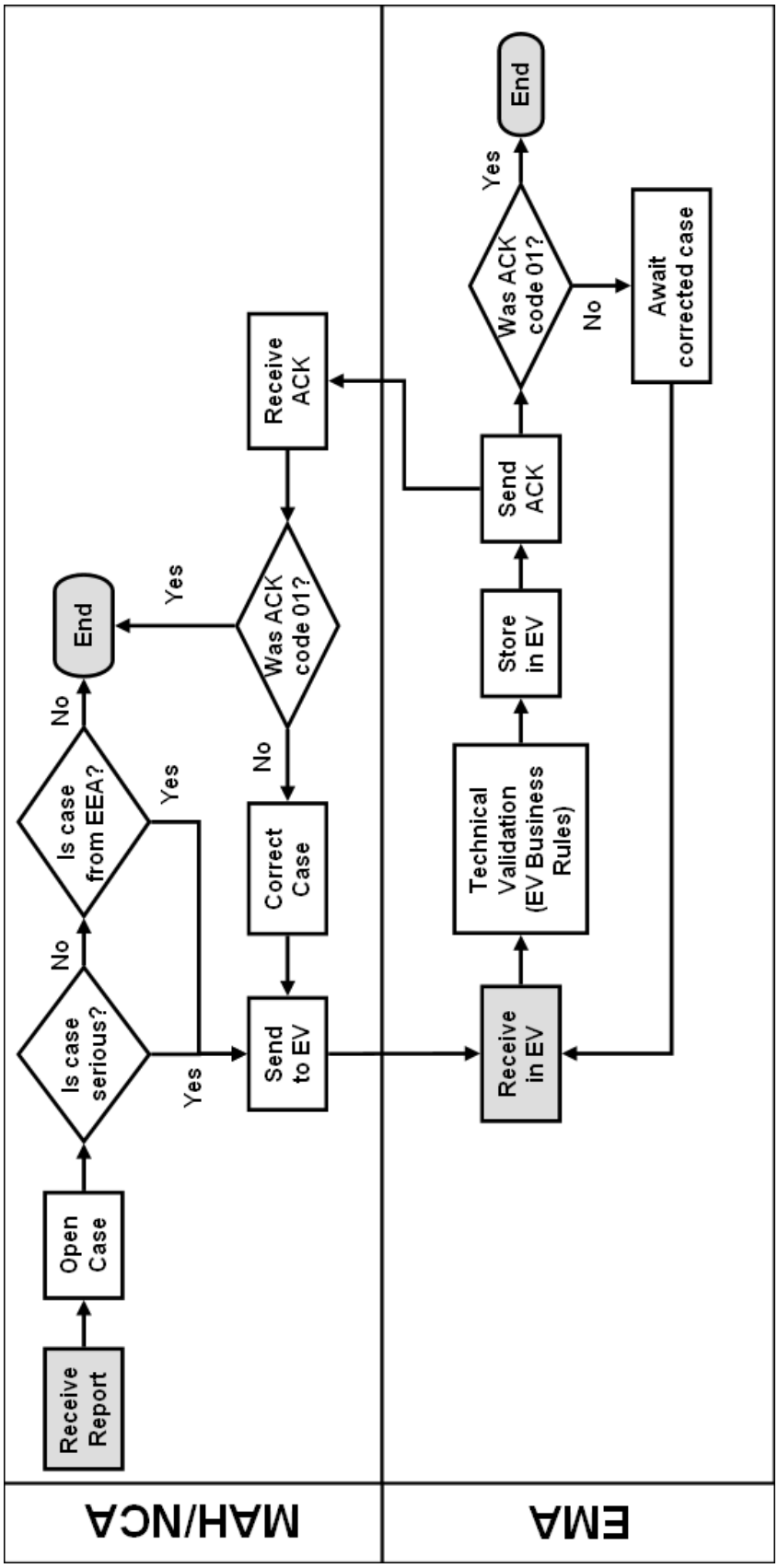
VI.Appendix 3.1.2. Interim arrangements applicable to competent authorities in Member States

Table VI.5. Expedited reporting requirements applicable to competent authorities in Member States - Interim arrangements

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

VI.Appendix 3.2. Final arrangements

Figure VI.4. Business process map - Suspected adverse reaction reporting in EU - Final arrangements



1839 **Table VI.6.** Process description - Suspected adverse reaction reporting in EU - Final arrangements

No.	Step	Description	Responsible Organisation
1	**Start.** **Receive report.**	**National Competent Authority (NCA) or Marketing Authorisation Holder (MAH) receives information on a suspected adverse reaction from a patient, healthcare professional or other valid reporter.** **If the case has been received from a NCA, do not retransmit it to another NCA nor to EudraVigilance (EV).**	**MAH / NCA**
2	Open case.	Open and create an individual case safety report.	MAH/NCA
3	Is case serious?	If No go to step 3.1. If Yes, go to step 4.	
3.1	Is case from EEA?	If No go to step 11.1. If Yes, go to step 4.	
4	Send to EV.	Transmit the case (all serious and EU non-serious) electronically, in E2B(R2) format as an xml message within the relevant timelines (15 or 90 days, as applicable), to EV.	MAH/NCA
5	**Receive in EV.**	Receive the message in the EV.	**EMA**
6	Technical Validation (EV Business Rules).	Every message that is received in EV is validated against the EudraVigilance Business Rules and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. A valid message will have an ACK code 01. A non-valid message will have an ACK code 02 (if a case contained therein is non-valid) or 03 (if the message itself is not correctly formatted).	EMA
7	Store in EV.	Once the case has been validated, it is stored in the EV.	EMA
8	Send ACK.	The acknowledgement message created in step 6 is transmitted to the case sender no later than 2 business days following receipt of the case. Go to step 9 for the EMA's next step. Go to step 10 for MAH/NCA's next step.	EMA
9	Was ACK code 01?	If No go to step 9.1. If Yes, go to step 9.2.	EMA
9.1	Await corrected case.	The sender should correct every case with an error ACK and retransmit it within the regulatory reporting timelines. Periodically	EMA

No.	Step	Description	Responsible Organisation
		the EMA should assess all cases with an error ACK for which a corrected case has not been transmitted and contact the Qualified Person responsible for PharmacoVigilance (QPPV) to inform these missing corrected cases. If a sender fails to correct cases, this information should be incorporated into data quality assessments and the appropriate committees should be informed. Go back to step 5 upon receipt of the corrected case.	
9.2	**End.**	**The case is now stored in EV &, following duplicate detection & recoding will be available for signal detection and data quality analyses. If the case occurred in the EU and was transmitted to EV by a MAH, it will be rerouted to the relevant NCA (see VI.Appendix 3.3.)**	**EMA**
10	**Receive ACK.**	Receive the ACK message, associate it with the relevant case(s) and check to ensure that the case was considered valid.	**MAH / NCA**
11	Was ACK code 01?	If yes, go to step 11.1. If no, then the regulatory timeline clock has not stopped and the case should be corrected and re-transmitted to EV within the relevant regulatory reporting timelines. Day 0 remains as the day that the first information was received. A 02 or 03 ACK does not constitute new information. Go to step 12 (Correct case)	MAH/NCA
11.1	**End.**	**End the process for this version of the case. Normal follow-up activities should continue and if any follow-up is received, return to step 1.**	**MAH / NCA**
12	Correct case.	Correct the case to remove the errors identified in the ACK and retransmit the case to EV (go back to step 4).	MAH/NCA

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VI.Appendix 3.2.1. Final arrangements applicable to marketing authorisation holders

Table VI.7. Expedited reporting requirements applicable to marketing authorisation holders - Final arrangements

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

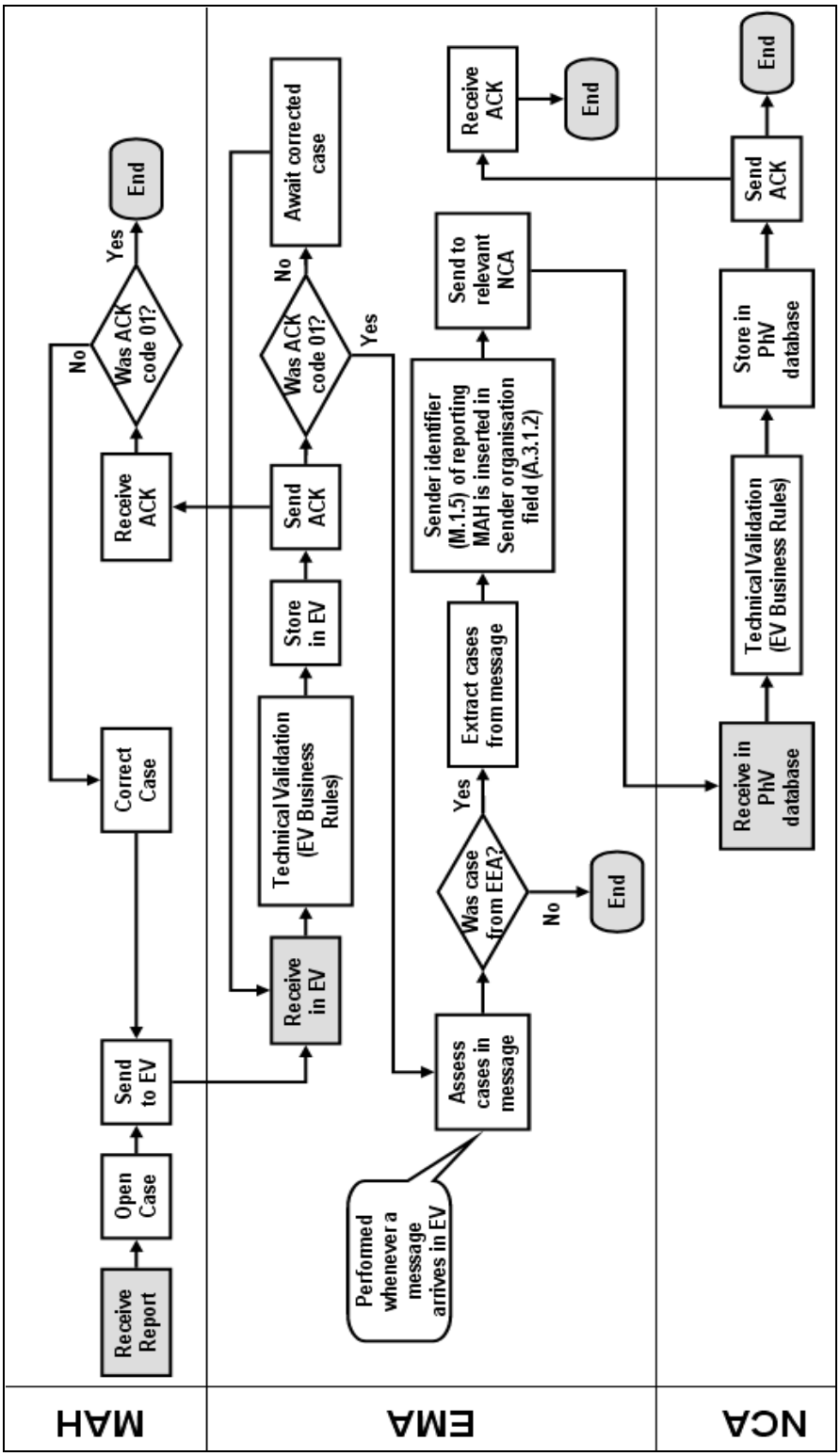
VI.Appendix 3.2.2. Final arrangements applicable to competent authorities in Member States

Table VI.8. Expedited reporting requirements applicable to competent authorities in Member States - Final arrangements

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

VI.Appendix 3.3. Transmission and rerouting of ICSRs to competent authorities in Member States [42]

Figure VI.5. Business process map - Transmission and rerouting of icsrs to competent authorities in Member States



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

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1859 **Table VI.9.** Process description - Transmission and rerouting of ICSRs to competent authorities in
1860 Member States [43]

No.	Name	Description	Responsible Organisation
1	**Start.** **Receive report.**	**Marketing Authorisation Holder (MAH) receives information on a suspected adverse reaction from a patient, healthcare professional or other valid reporter.**	**MAH**
2	Open case.	Open and create an individual case safety report.	MAH
3	Send to EudraVigilance (EV).	Transmit the case electronically, in E2B(R2) format as an xml message within the relevant timelines (15 or 90 days, as applicable), to EV.	MAH
4	**Receive in EV.**	Receive the message in the EV.	**EMA**
5	Technical Validation (EV Business Rules).	Every message that is received in EV is validated against the EudraVigilance Business Rules and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. A valid message will have an ACK code 01. A non-valid message will have an ACK code 02 (if a case contained therein is non-valid) or 03 (if the message itself is not correctly formatted).	EMA
6	Store in EV.	Once the case has been validated, it is stored in EV.	EMA
7	Send ACK.	The acknowledgement message created in step 5 is transmitted to the case sender no later than 2 business days following receipt of the case.	EMA
7.1	**Receive ACK.**	Receive the ACK message, associate it with the relevant case(s) and check to ensure that the case was considered valid.	**MAH**
7.2	Was ACK code 01?	If Yes, go to step 7.2.1. If no, then the regulatory timeline clock has not stopped and the case should be corrected and re-transmitted to EV within the relevant regulatory reporting timelines. Day 0 remains as the day that the first information was received. A 02 or 03 ACK does not constitute new	MAH

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

No.	Name	Description	Responsible Organisation
		information. Go to step 7.2.2 (Correct case).	
7.2.1	**End.**	**End the process of transmitting this version of the case to EV. Normal follow-up activities should continue and if any follow-up is received, return to step 1.**	**MAH**
7.2.2	Correct case.	Correct the case to remove the errors identified in the ACK and retransmit the case to EV (go back to step 3).	MAH
8	**Was ACK code 01?**	If yes, go to step 9. If no, perform no further processing on this version of the case and go to step 8.1	**EMA**
8.1	Await corrected case.	The sender should correct every case with an error ACK and retransmit it within the regulatory reporting timelines. Periodically the EMA should assess all cases with an error ACK for which a corrected case has not been transmitted and contact the Qualified Person responsible for PharmacoVigilance (QPPV) to inform of these missing corrected cases. If a sender fails to correct cases, his information should be incorporated into data quality assessments and the appropriate committees should be informed.	EMA
9	Assess cases in message.	Whenever a message has passed the technical validation, the cases therein should be immediately assessed to determine the country where the reaction occurred for regulatory reporting purposes.	EMA
10	Was case from EU?	For every case, assess whether the country of occurrence is in the EU. If Yes, go to step 11. If No, go to step 10.1	EMA
10.1	**End.**	**The case is now stored in EV &, following duplicate detection & recoding will be available for signal detection and data quality analyses.**	**EMA**
11	Extract cases from message.	The cases occurring in the EU will be extracted from the message for processing prior to retransmission.	EMA
12	Technical Validation.	Message sender identifier (ICH M2 M.1.5) of reporting MAH is inserted in Sender organisation field (ICH-E2B(R2) A.3.1.2)	EMA

No.	Name	Description	Responsible Organisation
		prior to retransmission. This is to permit the receiving National Competent Authority (NCA) to unambiguously identify the MAH responsible for transmitting the case to EV.	
13	Send to relevant NCA	The case is transmitted to the relevant NCA of the Member State where the reaction occurred with no other changes. Where a Member State has more than one NCA responsible for post-marketing reports, the cases occurring in that Member State are sent to all relevant NCAs.	EMA
14	**Receive in PharmacoVigilance (PhV) database.**	The relevant NCA receives the message in its pharmacovigilance database	**NCA**
15	Technical Validation (EV Business Rules).	Every message should be validated against the EudraVigilance Business Rules (the same business rules as in Step 5 and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. A valid message will have an ACK code 01. A non-valid message will have an ACK code 02 (if a case contained therein is non-valid) or 03 (if the message itself is not correctly formatted).	NCA
16	Store in PhV database.	Once the case has been validated, it is stored in the pharmacovigilance database.	NCA
17	Send ACK.	The acknowledgement message created in step 15 is transmitted to EV no later than 2 business days following receipt of the case.	NCA
17.1	**End**	**The case is now stored in the NCA's pharmacovigilance database &, following duplicate detection & recoding will be available for signal detection and data quality analyses.**	**NCA**
18	Receive ACK	The acknowledgement message sent in step 17 is received & stored in EV.	EMA
19	**End**	**The case has now been successfully retransmitted to the relevant NCA.**	**EMA**

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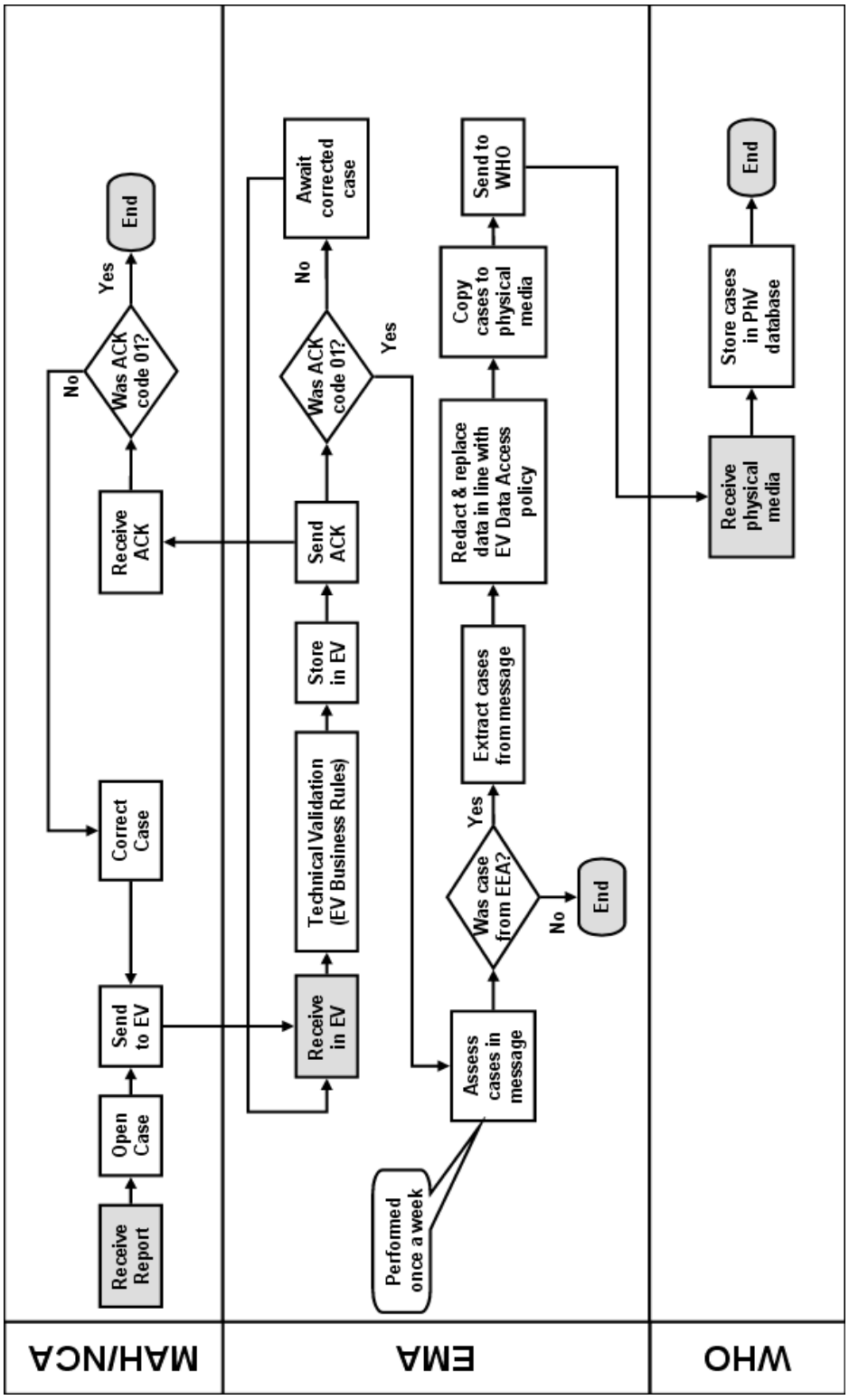
VI.Appendix 4. Transmission of ICSRs to World Health Organisation (WHO) Collaborating Centre[44]

Figure VI.6. Business process map - Transmission of ICSRs to World Health Organisation (WHO) Collaborating Centre



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

1868 **Table VI.10.** Process description - Transmission of ICSRs to World Health Organisation (WHO)
1869 Collaborating Centre [45]

No.	Step	Description	Responsible Organisation
1	**Start.** **Receive report.**	**National Competent Authority (NCA) or Marketing Authorisation Holder (MAH) receives information on a suspected adverse reaction from a patient, healthcare professional or other valid reporter.**	**MAH / NCA**
2	Open case.	Open and create an individual case safety report.	MAH/NCA
3	Send to EV.	Transmit the case electronically, in E2B(R2) format as an xml message within the relevant timelines (15 or 90 days, as applicable), to EudraVigilance (EV).	MAH/NCA
4	**Receive in EV.**	**Receive the message in EV.**	**EMA**
5	Technical Validation (EV Business Rules).	Every message that is received in EV is validated against the EudraVigilance Business Rules and an Acknowledgement message (ACK) is created specifying whether or not the message & the case(s) therein are valid. A valid message will have an ACK code 01. A non-valid message will have an ACK code 02 (if a case contained therein is non-valid) or 03 (if the message itself is not correctly formatted).	EMA
6	Store in EV.	Once the case has been validated, it is stored in EV.	EMA
7	Send ACK.	The acknowledgement message created in step 5 is transmitted to the case sender no later than 2 business days following receipt of the case.	EMA
7.1	**Receive ACK.**	Receive the ACK message, associate it with the relevant case(s) and check to ensure that the case was considered valid.	**MAH / NCA**
7.2	Was ACK code 01?	If Yes, go to step 7.2.1. If no, then the regulatory timeline clock has not stopped and the case should be corrected and re-transmitted to EV within the relevant regulatory reporting timelines. Day 0 remains as the day that the first information was received. A 02 or 03 ACK does not constitute new information. Go to step 7.2.2 (Correct	MAH/NCA

[45] Once the functionalities of the EudraVigilance database specified in Article 24 of Regulation (EC) No 726/2004 are established.

No.	Step	Description	Responsible Organisation
		case).	
7.2.1	**End**	**End the process of transmitting this version of the case to EV. Normal follow-up activities should continue and if any follow-up is received, return to step 1.**	**MAH / NCA**
7.2.2	Correct case	Correct the case to remove the errors identified in the ACK and retransmit the case to EV (go back to step 3).	MAH/NCA
8	**Was ACK code 01?**	If yes, go to step 9 If no, perform no further processing on this version of the case and go to step 8.1	**EMA**
8.1	Await corrected case.	The sender should correct every case with an error ACK and retransmit within the regulatory reporting timelines. Periodically the EMA should assess all cases with an error ACK for which a corrected case has not been transmitted and contact the Qualified Person responsible for PharmacoVigilance (QPPV) to inform of these missing corrected cases. If a sender fails to correct cases, this information should be incorporated into data quality assessments and the appropriate committees should be informed.	EMA
9	Assess cases in message.	Once a week, for every message that has passed the technical validation, the cases therein should be assessed to determine the country where the reaction occurred for regulatory reporting purposes.	EMA
10	Was case from EU?	For every case, assess whether the country of occurrence is in the EU. If Yes, go to step 11. If No, go to step 10.1.	EMA
10.1	**End.**	**The case is now stored in EV &, following duplicate detection & recoding will be available for signal detection and data quality analyses.**	**EMA**
11	Extract cases from message	The cases occurring in the EU is extracted from the message for processing prior to retransmission.	EMA
12	Redact & replace data in line with EV Data Access policy.	Prior to sending the cases to the World Health Organisation (WHO) Collaborating Centre, the extracted copies of the cases have some data elements redacted and replaced in line with the EV Data Access	EMA

No.	Step	Description	Responsible Organisation
		Policy in order to ensure personal data protection.	
13	Copy cases to physical media.	The cases are copied to physical media.	EMA
14	Send to WHO.	The physical media is sent to WHO Collaborating Centre.	EMA
15	**Receive physical media**	**WHO Collaborating Centre receives the physical media.**	**WHO**
16	Store cases in pharmacoVigilance (PhV) database.	Once the cases have been validated, they are stored in the pharmacovigilance database.	WHO
17	**End.**	**Cases are stored in the WHO Collaborating Centre's pharmacovigilance database &, following duplicate detection & recoding will be available for signal detection and data quality analyses.**	**WHO**

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VI.Appendix 5. Nullification of cases

General principles regarding the nullification of cases are provided in VI.C.6.2.2.10. The following recommendations should also be applied:

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

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

Ex.	Scenario	Action
1	An individual case has been identified as a duplicate of another individual case previously submitted.	One of the individual cases should be nullified. The remaining valid case should be updated with any additional relevant information from the nullified case.
2	A wrong 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) 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) should be nullified. A new case should be created with a correct 'Worldwide unique case identification number'.
3	On receipt of further information it is confirmed that that the adverse reaction 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. Minimum reporting criteria for an ICSR as outlined in VI.B.2 are no longer met.	The case should be nullified.
5	On receipt of further information it is confirmed that the reported adverse reaction(s) did not occur to the patient. Minimum reporting criteria for an ICSR	The case should be nullified.

Ex.	Scenario	Action
	as outlined in VI.B.2are no longer met.	
6	On receipt of further information it is confirmed that there was no valid patient for the individual case. Minimum reporting criteria for an ICSR as outlined in VI.B.2 are no longer met.	If it is not possible to obtain confirmation of the patient's existence, then the case should be nullified.

- Individual cases that have been nullified should not be used for scientific evaluation, however, they should remain in the database for auditing purposes.
- In addition, in case of duplicate reports where one report needs to be nullified, the update of the remaining case should be performed in the form of a follow-up report[46]. Information on the identification of the nullified case(s) should be provided in the data element 'Source(s) of the case identifier (e.g. name of the company, name of regulatory agency)' (ICH-E2B(R2) A.1.11.1) and in the data element 'Case identifier(s)' (ICH-E2B(R2) A.1.11.2).

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

Ex.	Scenario	Action
7	A wrong 'Worldwide unique case identification number' (ICH E2B(R2) A.1.10) was accidentally used. This wrong ICH-E2B(R2) A.1.10 'Worldwide unique case identification number' referred to an existing case.	The report with the wrong 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) should not be nullified. A follow-up 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 suspect drug. However, the patient received other suspect drugs and the minimum reporting criteria for an ICSR are still met.	The case should not be nullified.
9	On receipt of further information it is confirmed that the individual case was not medically confirmed.	The case should not be nullified. A follow-up report should be submitted within the appropriate time frame with the primary source information updated: The data element 'Qualification' (ICH-E2B(R2) A.2.1.4) should be populated with the value 'Consumer or other non health professional' or

[46] As presented in the guideline on detection and management of duplicate individual cases and individual case safety reports (ICSRs), EMA/13432/2009.

Ex.	Scenario	Action
		'Lawyer' as applicable; the data element 'Was the case medically confirmed, if not initially from a health professional?' (ICH-E2B(R2) A.1.14) should be populate with the value 'No'.
10	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.
11	Change of the individual case from serious to non-serious (downgrading).	The case should not be nullified. A follow-up report should be submitted with the data element 'Seriousness' (ICH-E2B(R2) A.1.5.1) populated with the value 'No' without selection of a value for the data element 'Seriousness criteria' (ICH-E2B(R2) A.1.5.2). The data element 'Does this case fulfil the local criteria for an expedited report?' (ICH-E2B(R2) field A.1.9) should remain populated with the value 'Yes'.
12	The primary source country has changed, which has an impact on the ICH-E2B(R2) convention regarding the creation of the 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10).	The case should not be nullified. The 'Sender's (case) safety report unique identifier' (ICH-E2B(R2) A.1.0.1) can be updated on the basis of the new primary source country code. However, the 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) should remain unchanged. If, for some technical reason, the sender's local system is not fully ICH-E2B(R2) compliant and cannot follow this policy, then the sender should nullify the original case. A new case should be created with a new 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) reflecting the changed primary source country code. The 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) of the case that was nullified should be reflected in the data elements 'Other case identifiers in previous transmissions' (ICH-E2B(R2) A.1.11).
13	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) used). The original organisation should also submit a follow-up report to

Ex.	Scenario	Action
		provide this new information. The other concerned marketing authorisation holder should create a new case and specify the reference case number and the name of the initial sending marketing authorisation holder in the data elements 'Source(s) of the case identifier (e.g. name of the company name of regulatory agency)' (ICH-E2B(R2) A.1.11.1) and 'Case identifier(s)' (ICH-E2B(R2) A.1.11.2).
14	The suspected medicinal product taken does not belong to the marketing authorisation holder (same active substance, the invented name is unknown and the report originates from a country, where the marketing authorisation holder has no marketing authorisation for the medicinal product in question).	The case should not be nullified. The marketing authorisation holder should submit a follow-up report with this information within the appropriate time frame.
15	The case is mistakenly reported by the marketing authorisation holder A although the marketing authorisation holder B as co-marketer is responsible for reporting the case.	The case should not be nullified. An explanation should be sent by the marketing authorisation holder A to the co-marketer marketing authorisation holder B that the case has already been reported. 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).

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

Figure VI.7. Business process map - Data quality monitoring of ICSRs transmitted electronically

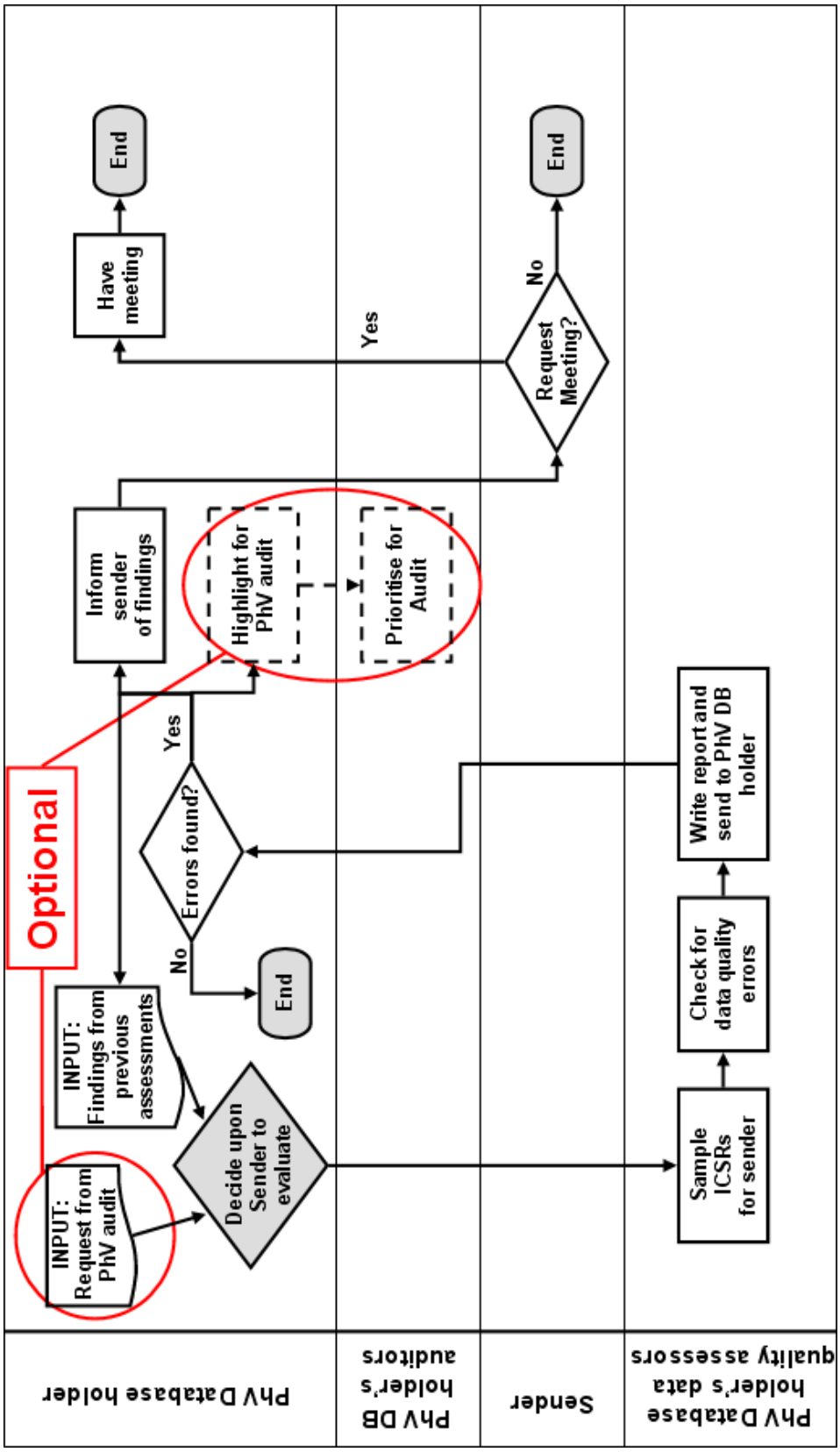

Table VI.13. Process description - Data quality monitoring of ICSRs transmitted electronically

The business map and process description describe a system where there is a separation between a PharmacoVigilance DataBase (PhV DB) holder, the PhV DB holder's data Quality Assessors (QA) and the PhV DB holder's auditors; however this is not mandatory and these functions may be performed by the same people or groups.

No.	Step	Description	Responsible Organisation
1	**Start.** **Decide upon Sender to evaluate.**	**Select one of the organisations that has transmitted ICSRs to your database.** **Inputs into this decision can include, but need not be limited to findings from previous assessments and requests from pharmacovigilance audits.**	**PhV DB holder**
2	**Sample ICSRs from Sender.**	Take a sample of ICSRs that were transmitted by the selected sender	**QA**
3	Check for data quality errors.	Check the cases for data quality errors. The cases should be assessed against appropriate published standards and similar documents, for example the MedDRA Term Selection Points to Consider document.	QA
4	Write report and send to PhV DB holder.	The findings from the data quality assessment should be collated into a single report. These can include related checks, such as 15-day reporting compliance, whether error reports are corrected and similar statistical information.	QA
5	**Errors found?**	Were any errors found during the analysis of the cases? If No, go to step 5.1. If Yes go to steps 5.2, 5.3 & 6.	**PhV DB holder**
5.1	**End.**	**If there were no errors found, then no further action needs to be taken. The process can end until the next time the sender is assessed.** **The pharmacovigilance database (PhV DB) holder may choose to share this information with the assessed sender and their auditors who may wish to factor this in to determinations of which sender to assess.**	**PhV DB holder**
5.2	Highlight for PhV audit.	If the PhV DB holder's organisation has an audit department, any significant findings	PhV DB holder

No.	Step	Description	Responsible Organisation
		should always be shared with them.	
5.2.1	**Prioritise for Audit.**	The audit or inspections department should use the information provided to them to feed into decisions about prioritising organisations for audit or inspection.	**PhV DB holder's auditors**
5.3	**INPUT: Findings from previous assessments.**	Any errors found (or even lack thereof) should be incorporated into decisions about which senders to evaluate & should also inform the performance of the assessments (e.g. targeting particular types of case) and the report (documenting whether previously identified issues have been addressed).	**PhV DB holder**
6	Inform sender of findings.	Inform the sender of the findings, including requested remedial actions (e.g. retransmitting certain cases) and time frames for those actions	PhV DB holder
7	**Request meeting?**	The sender should have the option to choose to request a meeting to discuss the findings and appropriate remedial action and time frames. If no meeting is requested, go to step 7.1. If a meeting is requested go to step 8.	**Sender**
7.1	Address the findings & retransmit any required cases.	Address all findings, take necessary steps to prevent recurrence of such findings & retransmit any required cases.	Sender
7.2	**End.**	**Once all findings have been addressed, the necessary steps taken to prevent recurrence of such findings and any required cases have been retransmitted, the process can end until the next time the sender is assessed.**	**Sender**
8	**Have meeting.**	Upon request from one party, a meeting should be held to discuss the findings of quality assessments and appropriate remedial and preventive actions to ensure that the cases in the database are correct and shall be so in the future.	**PhV DB holder & Sender**
9	**End.**	**Unless further action has been specified (e.g. future meetings or assessments), the process can end until the next time the sender is assessed.**	**PhV DB holder**

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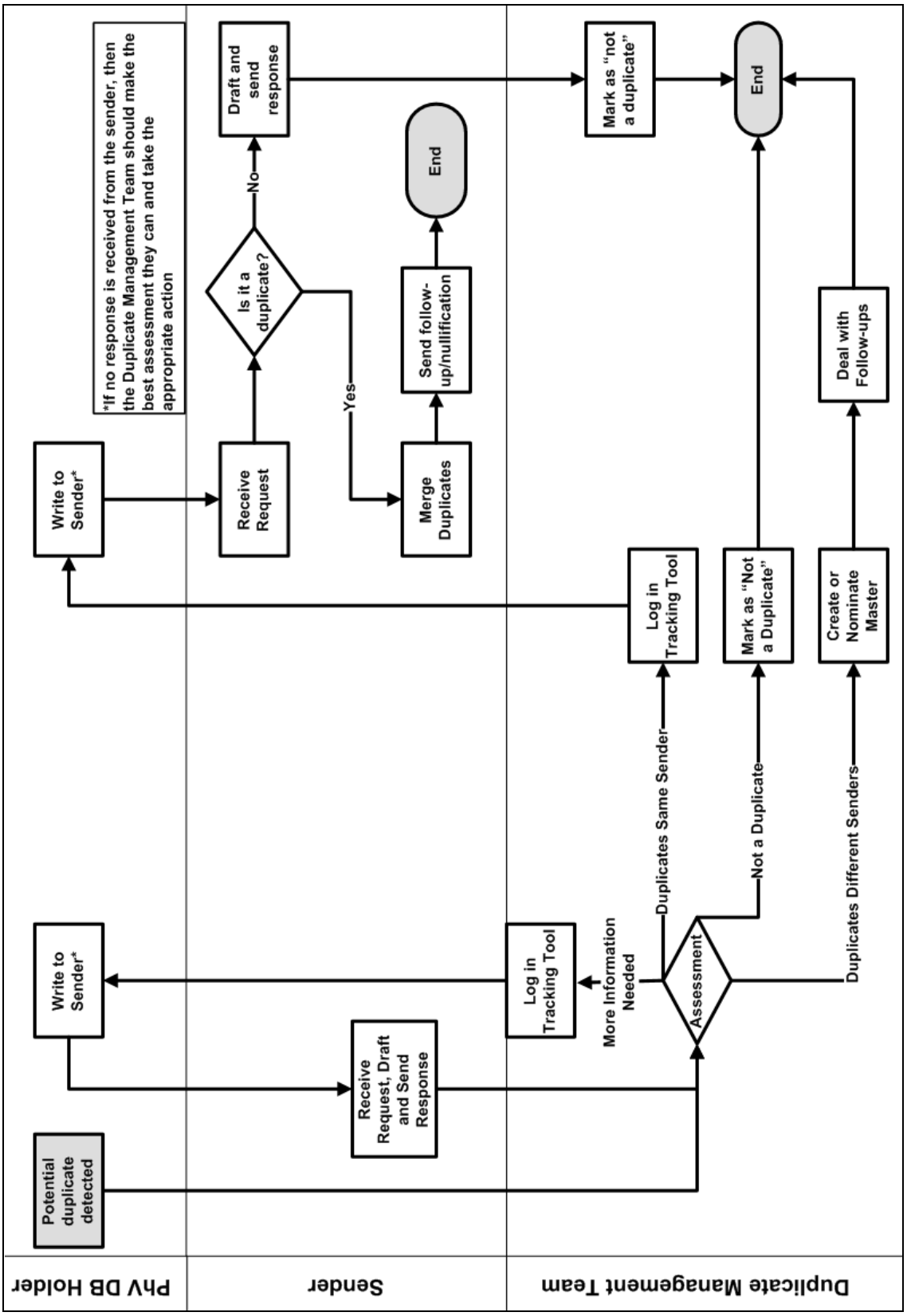
VI.Appendix 7. Duplicate detection and management of ICSRs

Figure VI.8. Business process map - Duplicate detection and management of ICSRs



1914 **Table VI.14.** Process description - Duplicate detection and management of ICSRs

No.	Step	Description	Responsible organisation
1	**Start.** **Potential duplicate detected.**	**Potential duplicates have been detected by the PharmacoVigilance Database (PhV DB) holder organisation or the PhV DB holder organisation is notified of potential duplicates by a receiver of the cases.**	**PhV DB holder**
2	**Assessment.**	**All potential duplicates need assessment by the Duplicate Management Team (DMT) to confirm or deny their duplicate status.** Following assessment there are 4 possible outcomes: • Not a Duplicate (go to step 2.1), • More Information Needed (go to step 2.2), • Duplicates From Different Sender (go to step 2.3), • Duplicates From Same Sender (go to step 2.4). The outcome of all assessments should be recorded to avoid continually reassessing the same cases when further versions arrive. These recorded outcomes can also be used to refine the duplicate detection methods during future development.	**DMT**
2.1	Not a Duplicate: Mark as not a duplicate.	If the cases are assessed as not being duplicates of one another, then mark both cases as such. Go to step 3 (End).	DMT
2.2	More information needed: Log in tracking tool.	There should be some form of tool for tracking when more information is needed, when correspondence has been sent, whether an answer was received and, if so, when.	DMT
2.2.1	**Write to Sender.**	More information is required in order to be able to make a definite assessment. The sender (who transmitted the case(s) in question to the PhVDB holder's organisation) should be contacted to request specific information necessary to confirm or deny duplication. Personal data protection must remain paramount, so unsecured communications should not include sufficient data to identify an individual.	**PhV DB holder**

No.	Step	Description	Responsible organisation
2.2.2	**Receive request, draft and send response.**	Once a request for more information has been received, the Sender of the case should respond promptly, either as a follow-up version of the case or by responding to the requester. The DMT should then reassess the case based on the new information (Go back to step 2).	**Sender**
2.3	**Duplicates Different Senders: Create or nominate master.**	Once cases have been determined to be duplicates of one another and have been transmitted to the PhV DB holder by different senders or reporters, then they should be merged under a master case, following the process described in chapter 2.3 “Management of duplicate cases” of the Guideline on Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs), EMA/13432/2009.	**DMT**
2.3.1	Deal with follow-ups.	If any follow-ups arrive for any of the cases, this information may require a reassessment of the master case. Reassess and, if necessary, amend the master case as with any received follow-up information. Go to step 3 (End).	DMT
2.4	**Duplicates Same Sender: Log in tracking tool.**	Once cases have been determined to be duplicates of one another, and have been transmitted to the PhV DB holder by the same sender, then this decision and the correspondence referred to in step 2.4.1 should be logged in the tracking tool referred to in step 2.2.	**DMT**
2.4.1	**Write to Sender.**	The sender organisation, as the source of the duplicates, should be contacted in accordance with chapter 2.3.3 of the Guideline on Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs), EMA/13432/2009. The sender should be asked to confirm or deny duplication and take appropriate steps in accordance with chapter 2.3.1 of the aforementioned Guideline.	**PhV DB holder**
2.4.2	**Receive request.**	Receive and log the communication containing information on suspected	**Sender**

No.	Step	Description	Responsible organisation
		duplicates in the Sender's PhV DB.	
2.4.3	Is it a duplicate?	Assess the potential duplicates. Are the cases duplicates of one another? If Yes, go to step 2.4.3.1. If No, go to step 2.4.3.2.	Sender
2.4.3.1	Merge duplicates.	Merge the duplicates, taking into account Flowchart 1 of Chapter 2.3.1.3 of the Guideline on Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs), EMA/13432/2009.	Sender
2.4.3.1.1	Send follow-up/nullification.	For the cases that are merged under the master, send a nullification message to the PhV DB holder. For the case that is master, send the updated case to the PhV DB holder as follow-up information. The merging & transmission should be completed promptly and in any case within 15 days of the date of receipt of the information from the PhV DB holder that the cases were considered to be possible duplicates. This date should be treated as the date of receipt of most recent information for regulatory reporting purposes.	Sender
2.4.3.1.2	**End.**	**The duplicates have now been removed from both the Sender's system and that of the PhV DB holder and only the master should be available for signal detection and data quality analyses.** **Unless follow-up information is received, then no further steps need be taken.**	**Sender**
2.4.3.2	Draft and send a response.	Reply to the PhV DB holder who sent the communication informing that the cases are not duplicates.	Sender
2.4.3.2.1	**Mark as "Not a duplicate".**	Upon receipt of confirmation from the Sender organisation that the cases are not duplicates, mark the cases as "Not a duplicate" & go to step 3 (End).	**DMT**
3	**End.**	**No further action is required for this couple.**	**DMT**

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