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5 **Data Quality Framework (DQF) for EU medicines**
6 **regulation: application to collection, management and**
7 **submission of Adverse Drug Reaction reports**
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1. Executive Summary

This document presents the **Adverse Drug Reaction** (ADR) chapter of the [Data Quality Framework](#) (DQF) for medicines regulation published by the European Medicines Agency (EMA) [1] (hereafter referred to as **European Medicines Regulatory Network** (EMRN) DQF). It is an extension of the EMRN DQF that specifically addresses collection, management and submission of ADR¹ reports in both the human and veterinary domains.

The data quality concepts discussed in this chapter apply equally to medicinal products for human and for veterinary use. Nevertheless, the legal landscape in the veterinary field contains certain particularities related to terminology and roles and responsibilities in **pharmacovigilance** (PV) which differ from the legal provisions applicable to medicines for human use. Such differences have been flagged, where applicable, in this document.

This chapter builds upon existing guidelines and procedures, identifies gaps and provides actionable and focused recommendations for assessing and improving the **Data Quality** (DQ) of ADR reports pipeline in order to best-support regulatory decision making. This chapter is intended for all stakeholders involved in ADR collection, management and submission, as identified during the webinar “Multi-stakeholder workshop on Data Quality Framework for Adverse Drug Reaction reporting” [2], and therefore also provides a holistic overview of the overall ADR reporting ecosystem.

This chapter specifically provides:

- Background on collection, management and submission of ADR reports (guidelines & legislation, terminology, processes underpinning ADR reporting and an introduction to the ADR reports pipeline), Section 4;
- Insights into the current challenges of ADR reporting organised by the five DQ dimensions described in the EMRN DQF (reliability, extensiveness, coherence, timeliness, relevance), Section 5;
- Recommendations to improve DQ in ADR data for systems and processes underpinning data collection, management and submission, Section 6;
- Concluding remarks, Section 7.

Concepts in this chapter are founded on principles described in the EMRN DQF and require background knowledge of the EMRN DQF (e.g. determinants and dimensions). The chapter provides specific recommendations to improve DQ for human and veterinary ADR reporting.

It is important to note that this chapter is not a replacement for existing legislation or guidelines, and it does not supersede any guidance documents.

¹ For the purposes of this document and in relation to veterinary medicinal products, the term ‘adverse drug reaction’ (ADR) should be considered equivalent to the term ‘suspected adverse event’ defined in the Veterinary Medicines Regulation (EU) 2019/6

Acronym	Meaning
ADR	Adverse Drug Reaction
AE	Adverse Event
AER	Adverse Event report
ANSM	French National Agency for the Safety of Drugs and Health Products
AI	Artificial intelligence
CIOMS	Council for International Organizations of Medical Sciences
CRO	Contract Research Organisation
DQ	Data Quality
DQF	Data Quality Framework
EEA	European Economic Area
EMA	European Medicines Agency
ENCePP	The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMRN	European Medicines Regulatory Network
EPITT	European pharmacovigilance issues tracking tool
EV	EudraVigilance
EVCTM	EudraVigilance Clinical Trial Module
EVPM	EudraVigilance Post-Authorisation Module
EVV	EudraVigilance Veterinary
HCP	Healthcare Professional
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National Competent Authority
OTC	Over-the-counter
PM	Post-Marketing
PRAC	Pharmacovigilance Risk Assessment Committee
PSP	Patient Support Programme

Acronym	Meaning
PV	Pharmacovigilance
QA	Quality Assurance
QC	Quality Control
RA	Regulatory Authority
ROR	Reporting Odds Ratio
RSI	Reference Safety Information
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
UPD	Union Product Database: EMA database for veterinary medicinal products
VeDDRA	Veterinary Dictionary for Drug Regulatory Activities
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VICH GL	VICH Guideline
xEVMPD	Extended EudraVigilance Medicinal Product Dictionary: EMA database for human medicinal products

3. Scope and purpose of the ADR DQF

Many guidelines, methods and systems are already in place for the purpose of collection, management and submission of ADRs (see Appendix I). The purpose of this chapter is to build upon existing guidelines and procedures across all domains (human and veterinary, post-marketing and clinical trials), to identify gaps and provide actionable and focused recommendations for assessing and improving DQ of ADRs along the pipeline and for regulatory decision making. In order to do so, it extends and contextualises the principles of the EMRN DQF (see section 3.1.) to ADR reporting.

Moreover, this chapter provides an overview of all stakeholders involved (as identified during the workshop [2]), their interactions and their roles in ADR collection, management and submission and the overall pipeline as identified during interviews with stakeholders from each domain, in view of understanding DQ issues related to the larger ADR reporting ecosystem.

The chapter is aimed at addressing DQ aspects from the perspective of the use of ADR data in the regulatory process. It is applicable to all stakeholders that share ADR data with EudraVigilance (EV) or EudraVigilance Veterinary (EVV) (the databases and data processing networks for ADRs managed by EMA): national Competent Authorities (NCAs) in **European Economic Area** (EEA) Member States, marketing authorisation holders (MAH), sponsors of clinical trials, Ethics Committees and other regulatory bodies. This chapter focuses on both human and veterinary ADR reporting arising from all sources, independent of design or purpose, unsolicited and solicited reports including, but not limited to, interventional clinical trials, non-interventional studies, registries, patient-support programmes, medical literature and patient-reported ADRs.

This chapter is descriptive, not prescriptive. This chapter does not supersede or replace existing guidance, and it does not place additional requirements on stakeholders.

3.1. Contextualisation of the EMRN DQF framework to ADR reports

This section covers the main concepts of the EMRN DQF, contextualising them to ADR reports and introducing specific terminology. In particular, it introduces determinants, DQ dimensions and the data lifecycle.

3.1.1. DQ determinants

In order to take a systematic approach to dissect DQ issues, the EMRN DQF partitions them in foundational, intrinsic and question-specific determinants (See Figure 1).

Foundational determinants are defined as “everything that impacts DQ but is not related directly to the dataset and does not depend on any specific research question”. Foundational determinants are referred to as the characterisation of the **systems and processes** that have an impact on DQ. In most locations where ADRs are captured, managed, or processed, foundational determinants for ADRs are:

- Database systems;
- Software with an interface of entry form(s);
- SOPs and work instructions;
- Medical and product dictionaries available for coding.



Figure 1: Determinants of data quality in ADR reporting

Intrinsic determinants are defined as DQ aspects that can only be observed based on a given dataset without information about how the data was captured, or about its intended use. In this chapter, intrinsic determinants for ADR are for instance:

- The data model;
- Required and optional values;
- The way of reporting values (e.g. coding) as well as the structure of the data (e.g. structured narrative);
- Medical dictionaries (MedDRA & VeDDRA) and product dictionaries (**Extended EudraVigilance medicinal product dictionary (xEVMPD)** and the **Union Product Database (UPD)**) in use.

Question-specific determinants are defined as aspects of DQ that cannot be assessed independent of the research question. In realm of ADRs, questions are generally structured as inherently related to the safety of products, for example

- Specific queries (e.g. What is the overall risk-benefit profile of the drug? Is there an ADR possibly caused by the drug? Are the Risk Management Plans and/or Risk minimisation measures [3] working?);
- Specific analyses (e.g. Is there a subset of the patient population particularly affected?).

Therefore, question-specific determinants in ADR can be considered in terms of assessing the **suitability of a dataset for the different types of ADR question²**.

3.1.2. Data lifecycle for ADR reporting

The EMRN DQF introduces an abstract data lifecycle, whose phases for ADR reporting can be defined as follows:

² This fundamentally maps to a higher level of the question-specific maturity model in the EMRN DQF, as we are considering classes of related questions.

- **Definition of data requirements:** what data are sought and what their characteristics should be. For ADR reporting this is defined by international standards, such as ICH E2B(R3) [4] or VICH GL 35 [5] & GL 42 [6];
- **Data collection or generation:** gaining data that reflect the observed reality. This represents the data fields in the ADR entry forms, the ADRs reported by the primary source to MAHs/NCAs/Sponsors and ADRs or AEs identified by MAHs. The act of reporting an ADR to an MAH/NCA/Sponsor is referred to as ADR reporting;
- **Data management and processing:** including data transfers, normalisation, and cleaning. This is the ADR reporting and submission pathway with multiple reporting and submission options;
- **Data submission:** making data available to stakeholders. In the ADR reporting pipeline, this is when reports are submitted to the EV databases (EV & EVV). An organisation performing this submission is sometimes referred to in this document as a 'data submitter';
- **Data procurement and aggregation:** sourcing data from one or more stakeholders. For example, EMA shares partially redacted versions of all EEA ADR reports with WHO-UMC to record and analyse the data in VigiBase (see the EV Access Policy [7]);
- **Testing and acceptance:** assessing the suitability of the procured data for intended needs. Testing is performed before an organisation is permitted to send ICSRs to the live production database and acceptance is performed automatically by databases assessing whether the ICSRs pass their business rules each time an ICSR is submitted;
- **Delivery for consumption:** using data to support a specific activity, e.g. analysis. The ADR reports are forwarded from EV to NCAs and can be downloaded from EV by MAHs & NCAs for additional analysis, and archiving.

3.1.3. DQ dimensions

The EMRN DQF introduces five DQ dimensions:

- **Reliability:** Are data faithfully representing what they are meant to be?
- **Extensiveness:** Are data sufficient?
- **Coherence:** Are data analysable as a whole?
- **Timeliness:** Are data available at the right time?
- **Relevance:** Are data of the right kind?

4. Background on ADR collection, management and submission

4.1. ADR guidelines and legislation

For collection, management and submission of ADRs related to both human and veterinary medicines, many guidelines and rigorous procedures are in place to promote the highest possible quality. An overview of the guidelines for the characterisation of systems and processes underpinning data for ADR collection, management and submission is listed in Appendix I.

In order to provide a better understanding of the DQ issues related to the larger ADRecosystem, we summarise in this section the documents that are of particular relevance in supporting good DQ of ADR reports. As a starting point, it is important to refer to the relevant international ICH and VICH guidelines:

- ICH Harmonised Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A [8];
- ICH Implementation Guide for the Electronic Transmission of Individual Case Safety Reports (ICSRs) - E2B(R3) Data Elements and Message Specification [4];
- ICH Harmonised Tripartite Guideline: periodic benefit-risk evaluation report (PBRER) E2C(R2) [9];
- ICH Harmonised Guideline: Post-approval safety management: definitions and standards for management and reporting of individual case safety reports E2D(R1) [10];
- ICH Harmonised Tripartite guideline: Development Safety Update Report E2F [11];
- ICH Harmonised Guideline: A selective approach to safety data collection in specific late-stage pre-approval or post approval clinical trials E19 [12];
- ICH Harmonised Guideline: Guideline for good clinical practice E6(R3) [13];
- ICH M1 MedDRA - Medical Dictionary for Regulatory Activities;
- VICH GL24: Pharmacovigilance of Veterinary Medicinal Products: Management of adverse event reports (AERs) [6];
- VICH GL30: Pharmacovigilance of Veterinary Medicinal Products: Controlled list of terms [14];
- VICH GL35 (R1): Pharmacovigilance of Veterinary Medicinal Products: Electronic standards for transfer of data [5];
- VICH GL42 (R1): Pharmacovigilance of Veterinary Medicinal Products: Data elements for submission of adverse event reports (AERs) [15].

Moreover, relevant guidelines for human ADR reporting in the EEA are:

- Detailed guide regarding the EV data management activities by EMA [16] to help stakeholders understand the processes of their data management activities;
- Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (hereafter referred to as GVP module VI) for the collection, management and submission of ADR reports [17];
- Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management (hereafter referred to as GVP Module IX), which provides general guidance and requirements on scientific and quality aspects of signal management [18]. It also describes roles, responsibilities, and procedural

212 aspects in the setting of the EU signal management process overseen by the Pharmacovigilance
213 Risk Assessment Committee (PRAC);

214 • EMA Good practice guide on recording, coding, reporting and assessment of medication errors
215 [19];

216 • EU Individual Case Safety Report (ICSR) Implementation guide [20];

217 • EudraLex Volume 10, which contains multitude of guidelines and Q&As related to Regulation
218 536/2014 [21]

219 For clinical trials on human subjects, in addition to the aforementioned guidelines, sponsors and health
220 authorities may use a Risk proportionate approach in clinical trials [22]. This approach should be
221 adapted to the risk to the subject and/or trial integrity of the research carried out, as well as to the
222 risk related to the reliability of trial results.

223 Reporting requirements may vary based on safety surveillance stage of the licensed medicine based on
224 legislation as depicted in Table 1. The reporting timelines are relevant in the context of the DQ
225 dimension timeliness as discussed in Section 5.4. The Clinical Trials Coordination and Advisory Group
226 has produced guidance on the reporting of ADRs in clinical trials governed by Regulation (EU) No
227 536/2014 [23] in the form of a Question & Answer document [24] and Recommendations on the use of
228 Auxiliary Medicinal Products in Clinical Trials [25].

229 Relevant guidelines for veterinary AE reporting in the EEA are:

230 • Guideline on veterinary good pharmacovigilance practices (VGVP) Module: Collection and recording
231 of suspected adverse events for veterinary medicinal products [26];

232 • Veterinary Union Pharmacovigilance Database – Best Practice Guide [27];

233 • Guidance notes on the use of VeDDRA terminology for reporting suspected adverse events in
234 animals and humans [28].

235 • EU VICH adverse event report implementation guide [29]

236 • Guideline on veterinary good pharmacovigilance practices (VGVP) Module: Signal Management
237 [30].

238 For veterinary ADR reports, the reporting of suspected adverse events (AEs) is governed by Regulation
239 (EU) 2019/6 [31], particularly section 5 Pharmacovigilance, and Commission Implementing Regulation
240 2021/1281 of 2 August 2021 [32]. In addition, the requirements for the Quality management system
241 are outlined in Chapter 2, Article 4 of the EU Commission Implementing Regulation (EU) 2021/1281.
242 Veterinary ADR reports are used for signal management, compliance monitoring, and publication of
243 data. Guidance at VICH and EU level is also available for the management of AEs [26, 27, 33 & 34].

244 Table 1: Overview of (study) phase and submission requirements according to applicable legislation

(Study) phase	Submission timelines	Applicable legislation	Module for ICSRs/AERs
Phase 1-3 clinical trials (Human)	Fatal/life-threatening SUSARs ≤ 7 days Other SUSARs ≤ 15 days Unexpected events*: CTIS All SAEs: Annual Safety Report/ Development Safety Update Report	Regulation (EU) No 536/2014), Clinical trial regulation [23]	EVCTM
Phase 4 studies interventional (Human)	Fatal/life-threatening SUSARs ≤ 7 days All SUSARs ≤ 15 days Unexpected events*: CTIS All SAEs: Annual Safety Report/ Development Safety Update Report	Regulation (EU) No 536/2014), Clinical trial regulation [23]	EVCTM
Phase 4 studies non-interventional (Human)	Design based on primary data collection: Serious ADRs ≤ 15 days Design based on primary data collection: Non-serious EEA ADRs ≤ 90 days All ADRs: Periodic safety update reports, frequency dependent on European Union reference dates list	Directive 2001/83/EC [35] Regulation (EU) No 726/2004) [36] Commission Implementing Regulation (EU) No 520/2012 [37]	EVPM
Post-Marketing solicited reporting, e.g. PSP (Human)	Serious ADRs ≤ 15 days Non-serious EEA ADRs ≤ 90 days All ADRs: Periodic safety update reports, frequency dependent on European Union reference dates list	Directive 2001/83/EC [35] Regulation (EU) No 726/2004) [36] Commission Implementing Regulation (EU) No 520/2012 [37]	EVPM
Post-marketing unsolicited reporting (Human)	Serious ADRs ≤ 15 days Non-serious EEA ADRs ≤ 90 days All ADRs: Periodic safety update reports, frequency dependent on European Union reference dates list	Directive 2001/83/EC [35] Regulation (EU) No 726/2004) [36] Commission Implementing Regulation (EU) No 520/2012 [37]	EVPM
Post-authorisation reporting (Veterinary)	Suspected adverse events ≤ 30 days	Regulation (EU) 2019/6 [31]	EVVETPROD
Post-marketing surveillance studies (Veterinary)	Suspected adverse events <u>without delay and</u> within 30 days from the date of the closure of the final study report	Regulation (EU) 2019/6 [31]	EVVETPROD

* See 9. Note: Suspected adverse events recorded during clinical trials conducted with unauthorised veterinary medicinal products should not be submitted to EVVETPROD

4.2. Considerations for ADR terminology

The concepts that follow are described in a succinct non-exhaustive manner in order to support the understanding of DQ considerations presented in this chapter. The full definitions, guidance and requirements related to ADR reporting are presented, for human post-authorisation activities, in GVP Module VI [17], for Clinical Trials in Regulation 536/2014 [23] and, for veterinary medicinal products, in the VGVP Module: Collection and recording of suspected adverse events for veterinary medicinal products [26]. Figure 2 graphically depicts the ADR terminology in the Human domain. An **adverse event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment [8]. As a general rule for activities defined as Organised Data Collection Systems under ICH E2D(R1), all AEs should be collected in the stakeholder database(s)³.

If there is at least a reasonable possibility that the medicinal product is causally related to the AE, this is called an **adverse drug reaction (ADR)**⁴ (Figure 2) [17]. For cases reported spontaneously by a primary source, positive causality is implied and all spontaneous AEs should be treated as ADRs, unless causality is explicitly denied by the primary source (see GVP Module VI, section VI.A.1.1). In the human domain, only ADRs should be submitted to EV as an **Individual Case Safety Report (ICSR)**.

By contrast, in the veterinary domain there is no distinction between AEs and ADRs. EU veterinary legislation only refers to adverse events and not to adverse drug reactions. All suspected AEs should be submitted to EVV (Figure 3). An ICSR or AER is a document in specific ICH E2B or VICH E2B format for the recording and reporting of AEs/ADRs associated with the use of a medicinal product [17].

AEs/ADRs may occur following a single dose or prolonged administration of a medicine, they may result from the combination of two or more medicines or from combinations with food or drinks, and they can occur following use within or outside the terms of marketing authorisation (e.g. off-label use, medication error, misuse, etc.).

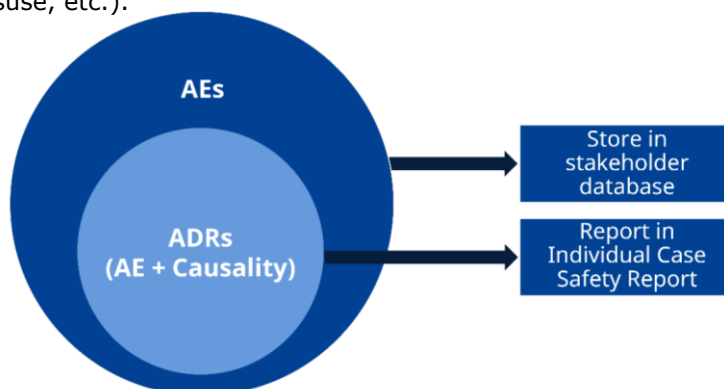


Figure 2: Graphical overview of Human AE/ADR terminology

³ All Human AEs should be collected and recorded except in the context of Non-interventional post-authorisation studies with a design based on primary data collection, if the protocol provides with a due justification for not collecting certain adverse events (see GVP Module VI [17], section VI.C.1.2.1.1.), and except in the context of interventional clinical trials where "The investigator shall record and document all adverse events, unless the protocol provides differently" (Regulation (EU) No 536/2014 [23], Art 41(2) and ICH E19 [12])

⁴ An adverse drug reaction can be defined in different ways. Directive 2001/83/EC [35], Article 1(11) defines an Adverse reaction as "A response to a medicinal product which is noxious and unintended". ICH E2D(R1) [10] adds "The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. A reaction, in contrast to an event, is characterised by the fact that a causal relationship between the medicinal product and the occurrence is suspected."

Throughout this document, the term Adverse Drug Reaction (or ADR) should be understood in this sense within the human domain* – always meaning that there is at least a suspicion of a causal relationship between drug and reaction.

*as described in footnote 1, the term ADR is also used to cover suspected AEs in the veterinary domain.

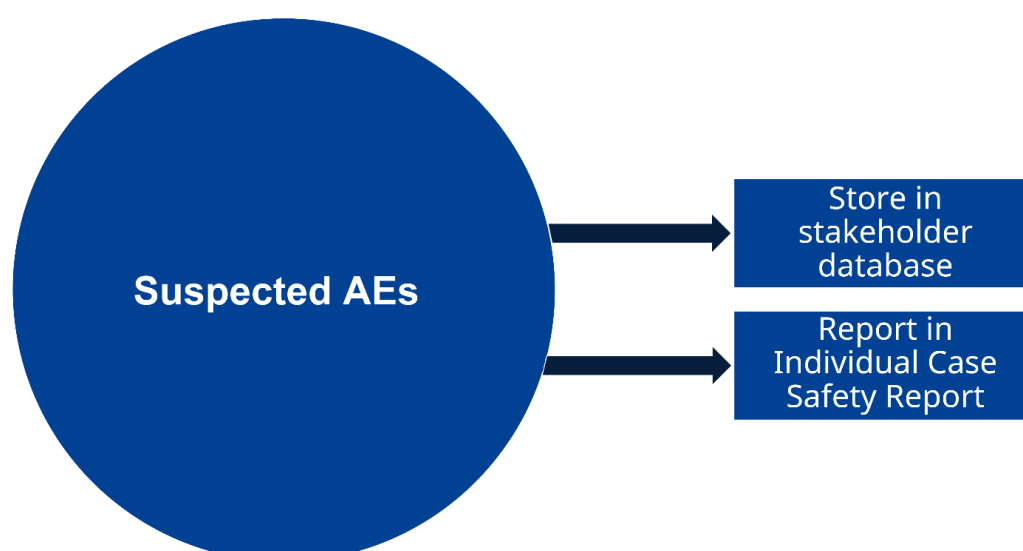


Figure 3: Graphical overview of Veterinary AE terminology

ADRs can be distinguished into two types of reports [10]: **solicited reports** and **unsolicited reports** (the latter is also known as spontaneous reports). The definitions of solicited and unsolicited reports are described for the human domain in E2D(R1) [10] and GVP Module VI [17] and for veterinary medicinal products, in the VGVP Module: Collection and recording of suspected adverse events for veterinary medicinal products [26]. As a summary:

- Solicited reports are derived from organised data collection systems such as clinical trials, registries, registry-based studies, post-approval patient support programmes, market research programmes, prospective cohort studies or surveys. The data derives from uniform collection methods and collected in a solicited manner;
- Unsolicited reports usually rely on the initiative of a patient (consumer), animal owner, healthcare professional (HCP), pharmacist, or lawyer to report an ADR to an NCA (possibly via a regional pharmacovigilance centre) or MAH.
- Reports originating from various sources such as medical literature reports or from non-medical sources, such as lay press or digital platforms (e.g. social media channels), can be part of either solicited or unsolicited reports, depending on the protocol for gathering the information (digital platforms) or how the information was gathered by the author (medical literature). Even if they are classed as unsolicited, reports from the medical literature, and other sources where the MAH has *identified* information rather than having *received* information, should initially be considered as adverse events, rather than adverse reactions unless the AEs/ADRs are clearly suspected by the article's author to be associated with one or more medicinal products. As described in ICH E2D(R1) [10], where the author's suspicion is not stated or not available, MAHs should consider the relationship between products and events in this context to determine if AEs/ADRs from literature should be reported. If an author explicitly states in an article that an event is not associated with a medicinal product, or the event occurred before the patient was exposed to the product, the MAHs should not report it as an ICSR.

Although the terminology of the types of reports has been defined in ICH E2D(R1) [10] and in GVP Module VI [17], the correct report type is not always used, leading to potential undersubmission (noncompliance) or oversubmission of ADRs to regulatory authorities.

4.3. Processes and systems underpinning ADR reporting

4.3.1. ADR data lifecycle

In this section we describe the systems and processes that underpin ADR reporting, framing them in the context of the data lifecycle introduced in the EMRN DQF (see also Section 3.1.). DQ of ADR data is derived from the interplay of multiple actors, and we introduce a holistic overview of the ADR reporting pipeline, including the main actors involved in the data lifecycle, along with the main components and stakeholders of this flow (Figure and 5).

Step 1: data requirements

This is incorporated by specific data fields in the ADR reporting forms. These forms have been released by many different organisations at different responsibility levels e.g. regional/national PV centres, MAHs and Sponsors. Variations in data entry forms can lead to DQ issues, including coherence, extensiveness and precision.

Step 2: data collection or data generation

ADR reports are generated by the primary source (the person who reports the facts about an ADR) such as patients or relatives, animal owners, HCPs, lawyers and, for clinical trials, investigators. The ADR reports can also be identified through another medium such as a digital platform or a literature and in this instance it is not directly generated by the primary source but by an MAH or a **regulatory authority (RA)** (see ICH E2D(R1) [10]). Lack of education or awareness on ADR reporting for HCPs or training at MAHs, CROs & Sponsors can affect extensiveness, specifically underreporting, incompleteness; and coherence issues such as semantic coherence (inconsistent wording). Primary sources can report to more than one organisation (e.g. to an MAH and to an NCA in parallel) or an article may be identified by multiple MAHs. This is referred to in this document as duplicate submission.

Step 3: data management and processing

Multiple reporting routes are possible, and it does not necessarily follow a linear path. A distinction is made between reporting routes:

- 1) **Post-Marketing (PM)** EEA reporting route - the ADR occurred in the EEA;
- 2) PM non-EEA reporting route – the ADR occurred outside the EEA but needs submitting within EEA;
- 3) CT (Human) reporting route

For the PM EEA reporting route, ADRs originating from the primary source may be reported directly to an MAH, an NCA or to a regional/national PV centre. Identified literature and digital platform cases (EEA or non-EEA) should be reported by MAHs or, for certain literature and substances in the human domain, by the EMA's Medical Literature Monitoring (MLM) service. Serious PM ADRs from non-EEA countries may be reported to the MAH, who may send the ADR reports to a third country regulatory authority (RA) who may make these reports available to other MAHs, depending on local regulations. Alternatively, non-EEA ADRs may be reported to a third country RA directly, from whom the MAHs may obtain the ADR reports, depending on local regulations. The serious non-EEA ADR reports will be submitted to EV by the MAH that obtains them, regardless of source or how many steps the report has been through before reaching the MAH. The number of steps in the reporting route can lead to duplication, data loss or data changes, due to corrections or compatibility issues with databases during data management, coding refinements and processing, resulting in a loss or change of information or differences in versioning. By contrast, the CT reporting path is far simpler. An ADR report is submitted by the investigator to the Sponsor & then, following assessments of causality and expectedness, a SUSAR will be reported by the Sponsor to EudraVigilance.

Step 4: data submission

In this phase reports are submitted to EV/EVV. Only registered organisations (MAHs/NCAs/Sponsors) are permitted to submit ICSRs to EV. Several DQ considerations apply to this step: is the ADR report submitted in a well-formed XML and does it comply with the EV/EVV business rules? Acknowledgement messages are returned to the submitting organisation to inform them whether their report was well-formed and conformed to the business rules. Has the reporting been performed in a timely fashion? If there has been duplicate submission, then this will lead to duplicate reports.

Step 5: data procurement and aggregation

In this step, the cases are loaded into EudraVigilance and processed to make available for data analysis. The EV and EVV systems do not change the data received, but they do link reported drug/substance to the xEVMPD and the UPD respectively, link ADR reports to cases and clusters and EMA performs duplicate detection and management, manually linking cases identified as duplicates. From EV and EVV the data can be used for regulatory activities or other purposes as secondary research.

Step 6: delivery for consumption

In this step in the human domain, post-marketing ADR reports can be downloaded from EV by MAHs. ADR reports are also rerouted to NCAs, or are downloaded by NCAs, to collect and analyse. Different stakeholders have different levels of access [7].

For EEA ADR reports, EMA copies the ICSRs and changes the sender (EV) and receiver (NCA) and reroutes them to the relevant NCA (or NCAs can download the ADR reports, as they prefer). Moreover, a version of the case is made available to MAHs without identifiable information (e.g. date of birth, initials), and without the narrative and most other free text fields (and a version with the free-text fields can be accessed by MAHs for signal investigation). Furthermore, EMA shares partially redacted versions of all human EEA ADR reports with World Health Organisation - Uppsala Monitoring Centre (WHO-UMC) to collect and analyse the data in VigiBase. Full details of the data available to each stakeholder are in the EV Access Policy [7].

There can be a DQ risk in this step, when the only identifier in the ADR report is the date of birth or patient initials: if this identifier is removed for MAHs, the case is no longer valid and may not be able to be processed in the MAH's database.

In this step, in the veterinary domain, the AE reports can be downloaded from EVV by MAHs and NCAs. Different stakeholders have different levels of access [38]. Additionally, NCAs with their own databases may request rerouting of AERs from EVV to their national systems.

4.3.2. ADR reporting pipeline

The journey of ADR reports from initiation (data collection) to delivery for consumption is long. The proverb 'no chain is stronger than its weakest link' is clearly valid. A problem at one level may not only be continued but exacerbated at a later stage.

Because ADR data is flowing from the reporter to the final receiver(s), the path that the data follow is described throughout this document as a "pipeline".

DQ checks occur at various steps of the data lifecycle and may include iterative feedback loops. Not all phases are present in all data workflows and the order may differ. The "testing" part of the step 'testing and acceptance', because it is performed intermittently, is not applicable in the ADR reporting pipeline.

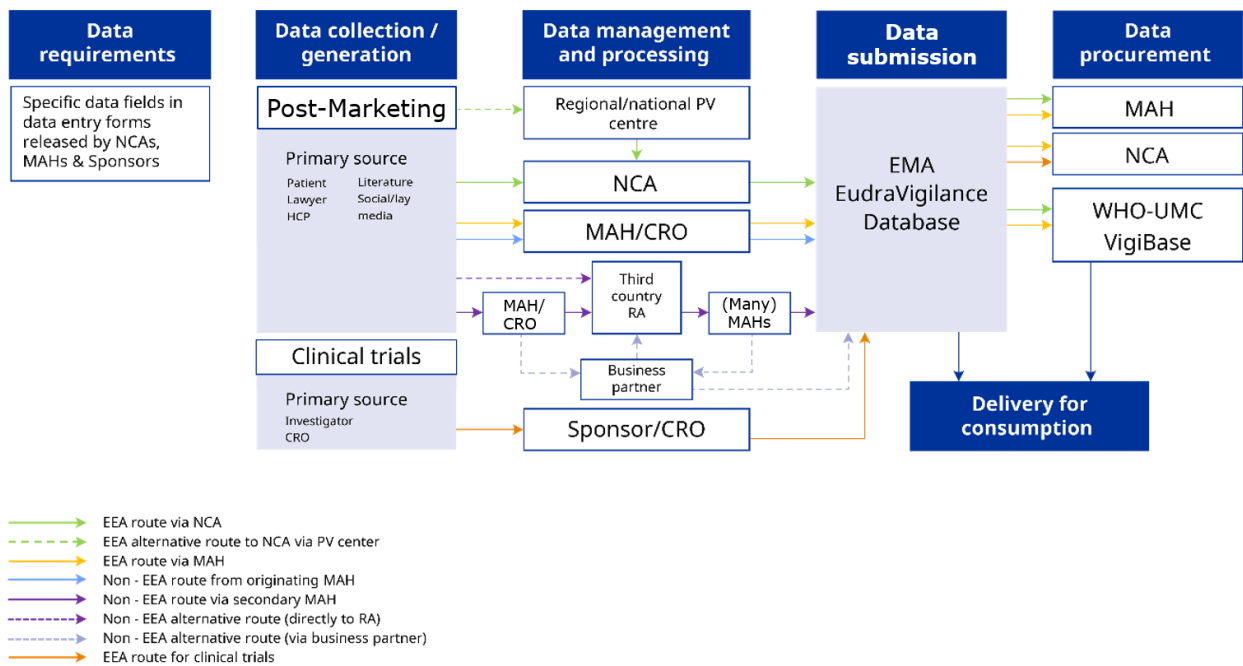


Figure 4: Overview of the human ADR reporting pipeline across stakeholders along the data lifecycle

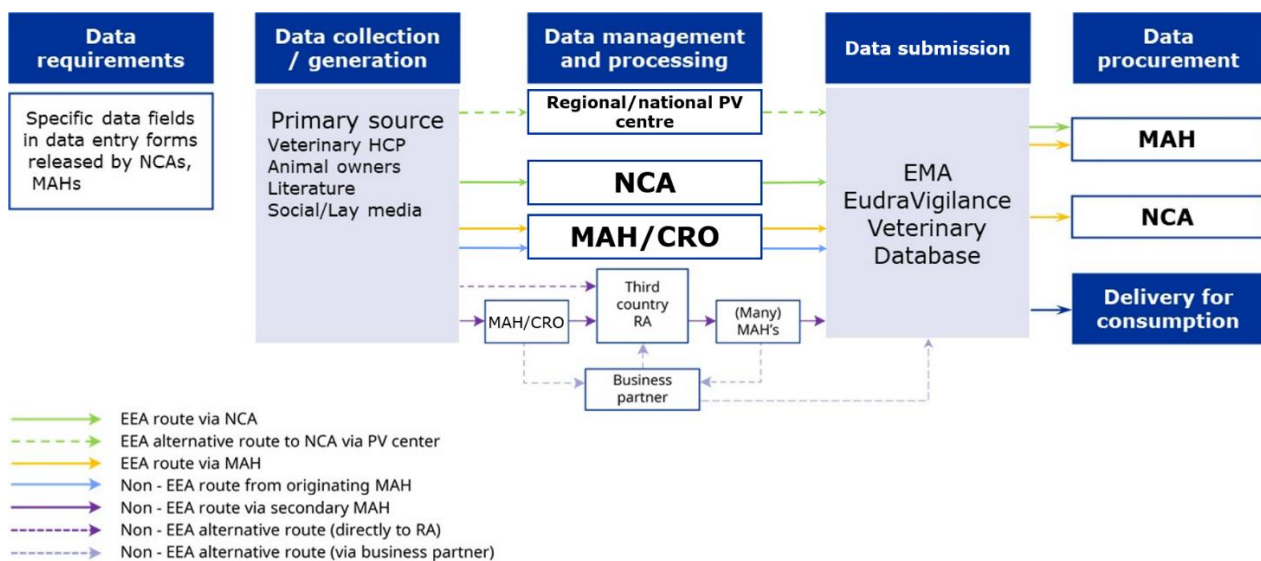


Figure 5: Overview of the veterinary AE reporting pipeline across stakeholders along the data lifecycle

4.3.3. EudraVigilance: the system underpinning human ADR reporting

EudraVigilance (EV) is the data-processing network and database for managing and analysing information on human ADRs from the EEA and the rest of the world, concerning medicinal products available in the EEA, since 2001, which operates on behalf of the EMRN. EMA is responsible for operating procedures to ensure the quality and integrity of the information collected in EV in collaboration with NCAs and MAHs. EV has processes in place to ensure good DQ. The data in EV comes from many sources - in 2025 ADR data was submitted by more than 2,000 different senders (MAHs, NCAs and Sponsors).

After marketing authorisation of a medicinal product, human ADR reports (both solicited and unsolicited) shall be reported to the EV post-authorisation Module (EVPM) [20] by MAHs and NCAs.

Reports of suspected unexpected serious adverse reactions (SUSARs) shall be reported to the clinical trial module (EVCTM) of EV by Sponsors of interventional Clinical Trials [20]. 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 should be submitted to EVPM [17] EV is operated by EMA and contains ADR reports originating from all around the world: within the EEA both serious and non-serious ADRs; outside EEA only serious ADRs. In EV, medicines are reported free-text and classified against the medicinal product dictionary (xEVMPD). ADRs, medical history, test names and all other medical terms are coded in accordance with the MedDRA® terminology (Medical Dictionary for Regulatory Activities) [39, 40].

4.3.4. EudraVigilance Veterinary: the system underpinning veterinary AE reporting

The safety and efficacy of animal medicines after they have been authorised and made available on the market include assessment of unsolicited AEs, and AE reporting. EVV is the system that supports the implementation of the Veterinary Medicinal Products Regulation[31, 41]. EVV uses VeDDRA for coding of suspected AEs and all other medical terms in animals and humans. In EVV, medicines or active substances may be reported by selecting an entry from the veterinary product dictionary (via the EVV web application) or using free-text, which are then classified against the UPD.

4.4. Current features of ADR data

When it comes to the intrinsic aspects of ADR data (Section 3.1.), the objectives of ADR reporting dictate that some minimum criteria elements are needed for a valid report:

- One identifiable patient (human or animal) or number of treated animals (veterinary);
- Adverse reaction(s);
- Suspected medicinal product(s);
- Identifiable reporter.

Other data elements critical for scientific evaluation present in a report may include:

- Patient information: age, sex, height, weight, species (veterinary only), past drug therapy, and medical history (including history of previous ADRs).
- Reaction section: description of the ADR with relevant clinical signs and symptoms, date of (or time to) onset of reaction, ADR outcomes, seriousness, actions taken and duration.
- Drug section: suspected, interacting and concomitant⁵ medicinal product information: treatment dates, product dosage, route of administration, indication, batch number (particularly for vaccines or biological products), dechallenge, rechallenge, time to onset, causality assessment (solicited reports), expectedness assessment (Human CT reports – the decision needs to be performed and documented).

These data are captured both in a structured and unstructured way (quite often some narrative text provides details on the structured information). The level of normalisation of structured data (e.g. by using standard vocabularies) can also vary.

Additional information on suspect and concomitant medicines adds more value to the ADR report by including medication name, pharmaceutical form, indication, dose, route of administration, dosing

⁵ In veterinary medicine there is no distinction made between suspect and concomitant medication

interval, duration and batch number. Past and current medical history is also very relevant information to assess whether the ADR can be possibly explained by other factors.

4.5. Considerations for use of ADRs in regulatory activities

The identification, documentation and reporting of ADRs is fundamental for both clinical trials and PV activities such as determining whether a product can receive a marketing authorisation, detecting early signals to ensure the benefit-risk balance of a drug remains favourable throughout its lifecycle and to support regulatory decision making. PV activities are particularly essential for detecting rare ADRs sometimes occurring in special populations or after prolonged exposure, and drug–drug or drug–disease interactions that may not have been observed in randomised clinical trials prior to authorisation. Special attention needs to be given to such reactions in order to prevent them as, without spontaneous reporting, potential safety signals may remain undetected for years, thereby exposing the public or the animal population to unanticipated risks. Therefore, effective and good quality ADR collection, management and submission is crucial for identifying potential drug-related risks, implementing risk minimisation measures, and improving patient safety.

Notably, for small populations, such as clinical trials, rare diseases and orphan drugs, the DQ of ADRs is even more important because each case is individually representing a greater fraction of the patient population and is statistically probably more impactful than a case concerning a widely used medicine.

4.5.1. Use of ADRs in human regulatory activities

On the ADRs collected via EV, EMA and NCAs perform analyses for several purposes for which “question specific” determinants can be defined.

SUSARs (transmitted to the EV Clinical Trials Module – EVCTM) are primarily collected in EV to permit Member States (Ethics Committees and NCAs) to assess whether a Clinical Trial should be permitted to continue, to supervise whether the sponsor is conducting adequate CT supervision including ensuring continuous positive benefit-risk of the CT and whether the protocol needs amending, and to inform on which ADRs are already known at the time of marketing authorisation application. Additionally, individual cases from Clinical Trials also contribute to aggregate safety assessments, including Development Safety Update Reports/Annual Safety Reports, benefit-risk evaluation and emerging safety issue assessments. Furthermore, Sponsors’ data safety monitoring boards will review individual cases from Clinical Trials within the Sponsor’s database to perform their safety assessments.

The primary purpose of collecting post-marketing ADRs in the EV Post-Authorisation Module (EVPM) is for safety activities, mainly focusing on signal detection and a deeper evaluation of ADRs. The EEA regulatory network process from ADR submission to EV to signal assessment in the human domain is described at a high level in GVP Module IX [18] and in detail in the guidance document Screening for adverse reactions in EudraVigilance [42]. A simplified version is depicted in *Figure 6*). A pre-processed cumulative output from EV is reviewed periodically by an EMA/NCA PV-assessor. In this output, some calculations have been performed to guide the PV-assessor: total number of cases per MedDRA PT, number of new cases, number of fatal cases, etc. Several criteria may be applied to assist with determining whether an ADR requires further investigation, such as type of reaction (serious/non-serious), reaction outcome (e.g. recovered, fatal, etc.), known pharmacological profile, patient population type (e.g. age group, sex), product type, indication, reporting frequency, and other aspects, such as inclusion of the reaction on the Important Medical Event Terms/Designated Medical Event lists [43, 44]. Additionally, MAHs and NCAs perform signal detection on their own databases.

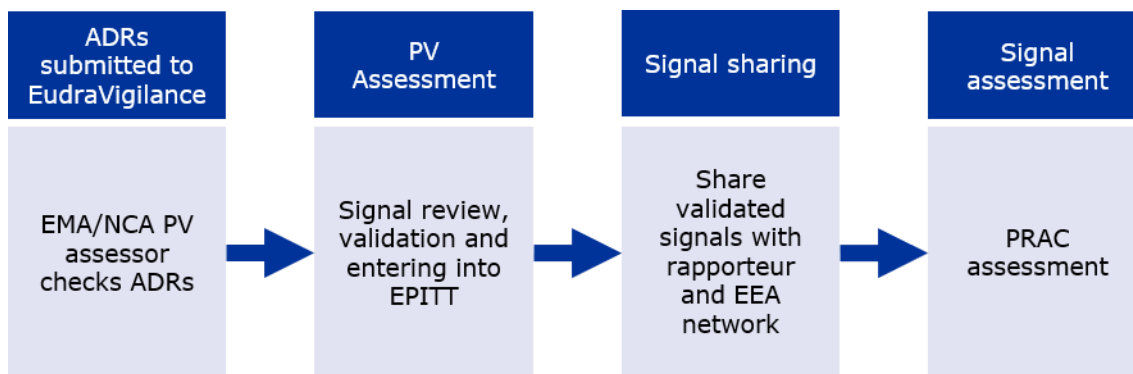


Figure 6: Overview of use of human ADRs for routine post-marketing signal management after submission to EudraVigilance.⁶ As described in section 4.3.1. and Figure 4, the ADRs submitted to EV may be rerouted to NCAs. Therefore, the first step may be performed in EV or an NCA database.

Statistical methods are applied to EV data, e.g. reporting odds ratio (ROR) among others, to support signal detection. Data supporting the detected signal are evaluated to verify the availability of sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, therefore justifying further analysis, taking into account the strength of the evidence, the clinical relevance and previous awareness of the association (see GVP module IX [18]). Signals which meet this threshold and are considered to require assessment by the PRAC are discussed at EU level (see Figure 6) [45]. The European pharmacovigilance issues tracking tool EPITT provides the functionalities for regulatory authorities of Member States and EMA to track signals at EU level.⁷ The list of signals assessed by PRAC is published on the EMA website [46]. Other question-specific activities include accommodating requests for information from stakeholders as MAHs, and EMA committees and targeted analyses. It is worth noting that signals can also be identified via Periodic Safety Update Reports, which can include ADR data that was not transmissible to EudraVigilance.

4.5.2. Use of AEs in veterinary regulatory activities

The primary purpose of collecting AEs in EVV is for safety activities, mainly focusing on signal management and a deeper evaluation of AEs. The process from AE submission to EVV to signal management in the veterinary domain is depicted in Figure 7. An MAH /NCA PV-assessor may access pre-defined queries in EVV DWH, such as the Signal detection query or Adverse events overview query. In these reports, some calculations have been performed to guide the PV-assessor: total number of cases per VeDDRA PT, number of new cases, overall number of fatal cases, etc. The PV-assessor investigates AEs based on several priorities such as type of reaction, reaction outcome (fatal), known pharmacological profile, patient population type (e.g. species, age group, sex), product type, indication, reporting frequency, and other aspects.

Specific statistical calculations and algorithm are performed in EVV, e.g. reporting odds ratio (ROR) to identify signals of disproportionate reporting. The MAH/NCAs PV-assessors periodically check AEs submitted to EVV and may use the Medical Important VeDDRA term (MI) lists, Appendix 1 to [47], as well as aggregated data analysis (ROR) and case narratives. The MAH/NCA PV-assessor submits the validated signals to the signal management module of the Union Pharmacovigilance database (IRIS). Signals are considered by the relevant NCAs and committees for further assessment and decision-

⁶ It is worth noting that signals can be triggered by sources other than ADRs, such as articles in the medical literature or study reports. In these instances, although the starting point would differ, the subsequent processes would be the same

⁷ This paragraph is largely describing the process of signal detection/management for Centrally authorised Products. For Nationally Authorised Products, Member State worksharing also needs to be taken into account.

making (see Figure 7). IRIS provides the functionalities for regulatory authorities of Member States and EMA to track signals at EU level, and the list of signals is also published on the IRIS public register.

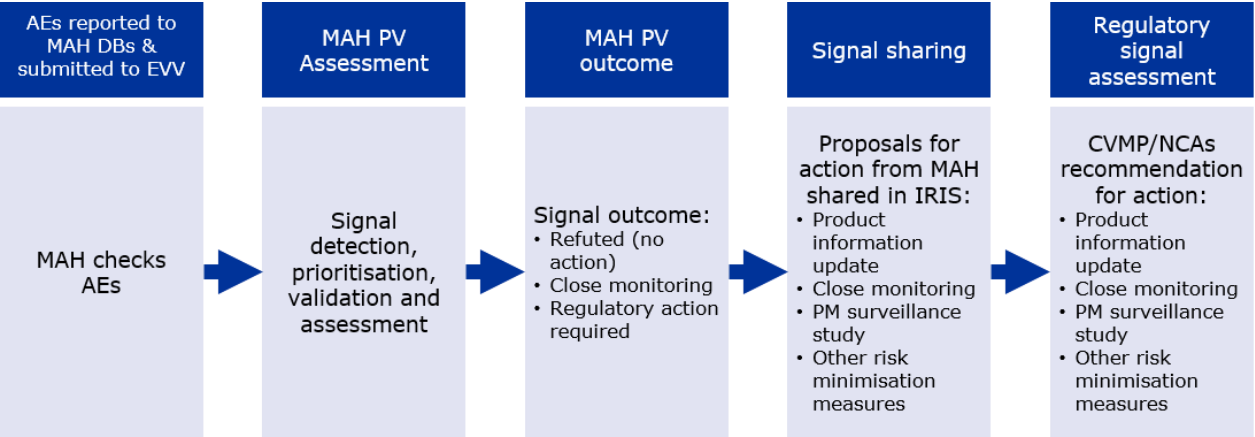


Figure 7: Overview of the signal management process for veterinary medicinal products

4.5.3. DQ considerations for ADRs in regulatory activities

In these steps of signal management by EMA, there are several DQ considerations. To start with, the pre-processed cumulative outputs are generated automatically from Eudravigilance by EMA. This process has been robustly validated by EMA and NCAs, and the code for generating the reports for EMA and NCAs includes the generation of outputs which require manual validation and control. Poor data quality in the ADR reports will negatively impact the outputs generated for regulatory activities, leading to weaker aggregate safety conclusions than could be generated from good quality ADR reports.

To ensure that the reliability is high and the risk of inadequate assessments is minimised, EMA has published work instructions for the design of an analysis in EV, which are followed when performing assessments [48]. Regular feedback sessions as described in Section 6.5. are recommended. Also, regular training of PV-assessors is recommended.

The aggregate safety assessments for Clinical Trials, including Development Safety Update Reports/Annual Safety Reports, benefit-risk evaluation and emerging safety issue assessments, are based on individual cases (both the SUSARs submitted to EV and other cases (unrelated, expected or non-serious), which do not require transmission to EV) and thus the completeness and quality of individual reports is also important for these aggregate safety activities.

5. Managing challenges in ADR reporting

Across the ADR reporting cycle, robust and thorough processes should be in place (regulatory frameworks, pharmacovigilance and quality system checks, training, record and compliance management, mechanisms for timely and effective communication regarding safety concerns, SOPs, work instructions and medical review sessions) for collection, management and submission of reports, sometimes even at automated level [16, 31]. This includes support for case entry, coding and, where practical, verification by the 4-eye principle (approval by at least 2 people). Nonetheless, some challenges with DQ emerge. In this section, we provide an overview of DQ issues organised by DQ dimensions (as summarised in Figure 8) with a brief discussion on how they originate from the systems and processes underpinning ADR reporting and, where relevant, how they manifest in data.

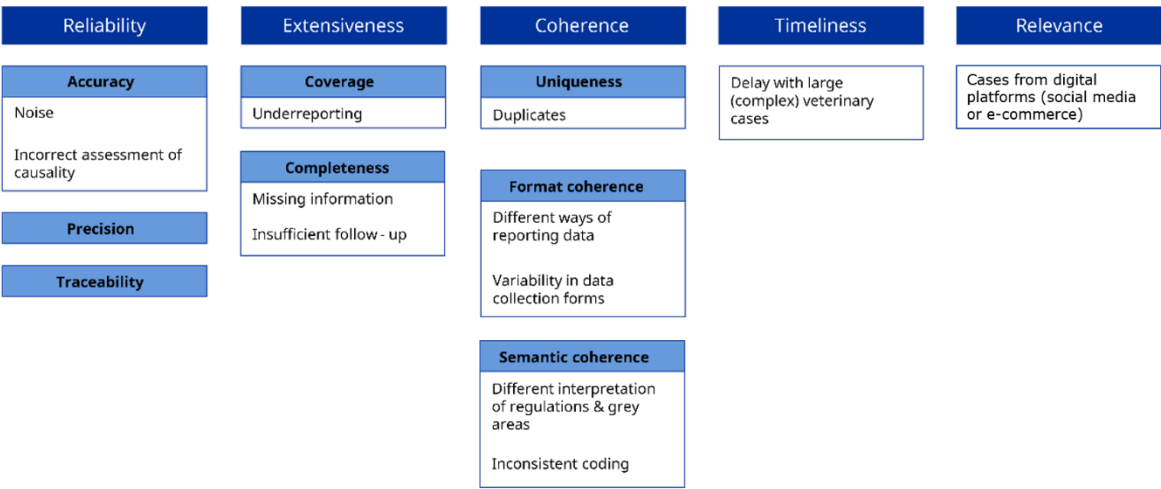


Figure 8: Challenges in ADR reporting organised by DQ dimensions

5.1. Reliability

As described in the EMRN DQF, the DQ dimension reliability covers how closely the data reflects what they are directly measuring. Are data faithfully representing what it's meant to be? Subdimensions of reliability are accuracy (the amount of discrepancy between data and reality) and precision (the degree of approximation by which data represents reality). Related to reliability is also the concept of traceability (are data presenting the knowledge of how data were reported, what source it originated from and what processing it went through before appearing in its current form) [1].

5.1.1. Noise (accuracy)⁸

In the human domain the collation of ADR reports available for analysis is affected by noise: ADRs and events are mixed in a way that makes it difficult to separate important signals from false signals.

Typical causes of noise are reporting and/or submitting incorrect data (e.g. in the human domain adverse events rather than adverse reactions), duplicate reporting, duplicate submission, overreporting by MAHs, and reporting of specific ADRs or of non-specific ADRs to particular drugs stimulated by media coverage, which can result in reporting bias.

Noise due to incorrect reporting manifests in ADR reports for which relatedness cannot be assessed with sufficient confidence, requiring a large number of cases to establish the reliability of a signal that

⁸ We note that noise arises from a collection of DQ issues not limited to reliability. For instance, over or under-representation of ADRs also contributes to noise, as well as duplicates and lack of coherence. In this chapter, we opted to consider noise under reliability, as per general practice and consideration of noise in signal detection.

in turn may have consequences for the timeliness of (downstream) regulatory actions. The inadequate assessment of causality is described in Section 5.1.2.

Moreover, noise is becoming an increasing issue as the volume of ADRs from particular sources has substantially increased in recent years. Since GVP Module VI [17] was released in 2012, **patient support programmes** (PSPs), market research programmes and digital platforms have specifically impacted the rising number of ADR reports [49]. The effects on DQ of post-marketing reporting in the context of PSPs and digital platforms is described in Section 5.6. Notably, particularly concerning PSPs and digital platforms, there may be a trade-off in quality versus quantity in ADR reporting.

To improve accuracy, good knowledge of submission rules by Sponsors, NCAs and MAHs is crucial to minimise noise (See section 6.1. – Education). Specifically, it is recommended to promote good adherence to reporting rules to EV and EVV.

5.1.2. Inadequate assessment of causality (accuracy)

One of the key issues related to false positives and noise in the human domain, is the inadequate assessment of causality in solicited reports that results in submission of reports that are in fact not ADRs as there is no causal link between the medicine administered and the AE observed.

In the context of clinical trials, SUSAR reporting is particularly challenging because the assessment of whether an unexpected event is suspected (i.e. considered related) can be difficult and create unstable DQ. As a result, some sponsors of clinical trials may report every SAE as a SUSAR, which leads to overreporting of (often) non-drug-related SAEs. On the other hand, other sponsors may not treat all SUSARs as SAEs and not submit them, which leads to underreporting. This can impact adequate and timely signal detection.

Inadequate assessment of causality in clinical trials may be caused by insufficient training of Investigators. It requires thorough training to analyse the causality of an ADR, because the assessment of causality is partly based on time-to-onset, the pharmacological mechanism of action, the patient's medical history and concomitant medications, and potential adverse reactions. This touches upon foundational determinants, as study protocols, work instructions and SOPs may not be clear enough. For the primary source (consumers, HCPs, Investigators), inadequate causality assessment can also relate to intrinsic determinants, such as a lack of structure in the ADR data entry form. The data entry forms for ADRs do not always make reporters think systematically about the report, which might lead to over-complete case narratives with unstructured information, without a clear causality assessment.

To improve the adequacy of the causality assessments and consequently improve accuracy, better training and education of investigators is recommended (see Section 6.1. - Training). Better understanding of the pharmacological profile is of importance (see Section 6.2. - Integration of clinical pharmacology in ADR processes). Moreover, it is recommended that ADR reporting forms are improved, particularly regarding causality. For clinical trials reporting forms, investigators should be encouraged to document the reasoning supporting the causality assessment, including key elements such as temporal relationship, alternative explanations, dechallenge/rechallenge information and relevant medical history (see 6.3. – Improvement of standard implementation).

5.1.3. Precision

The challenge of precision is the lack of specificity in the description of an ADR. This can arise when multiple patients or events are conflated, which can happen for a variety of reasons.

In human ADR reports, a lack of precision can emerge when an MAH incorrectly makes a single case referring to multiple patients described in a literature article or, by contrast when an MAH operating a PSP makes a single case for a patient that covers many years of their life, conflating many events and reactions which should be separate cases into one. Additionally, a lack of precision can emerge from the selection of an overly broad MedDRA or VeDDRA term, rather than the most-specific term(s) for the reported reaction(s).

In the human domain, a lack of precision can emerge due to a lack of format coherence (see 5.3.2.) because PV databases may still be based on the ICH E2B(R2) format rather than the ICH E2B(R3) format. A key difference between these formats is that in R2 seriousness is captured at case level, whereas in R3 seriousness is captured at reaction level. This means that if an ADR report describes a patient who experienced a headache and a fatal myocardial infarction, in R3 only the myocardial infarction would be classed as fatal; whereas for the same report stored in R2 format both reactions would be classed as fatal.

In veterinary AE reports for instance, for animals treated as a group, one report can refer to approximately 1,000 animals, often identified by age/weight range (or in the case of fish, by tonnage). AE reports include and conflate different events with no specificity to the individual animal. This is different for pets, where AEs are usually reported on an individual basis.

A potential challenge related to precision based on an intrinsic determinant of DQ in veterinary AE reporting, compared to human ADR reporting, is the lack of granularity in VeDDRA compared to MedDRA.

5.1.4. Traceability

Data lineage (or traceability) describes the history of data, detailing its origins, the sources it came from and the transformations it underwent before reaching its current state [1]. The pipeline for ADR reporting can be extensive with many stakeholders involved in the same case.

Traceability issues manifest in missing links between ADRs, when these derive from each other (e.g. mother & baby reports) or from the same primary source (e.g. same reporter or same literature article).

Retention of the integrity of the report, which should remain as faithful as possible to the source data (e.g. the original report, follow-up requests and replies), is considered a challenge in ADR reporting. The primary source narrative may change along the ADR reporting pipeline, and the original narrative is not always available. This is specifically important for health authorities, who receive the data from MAHs and then distribute it to other MAHs. If different stakeholders have adapted versions of the same ADR report this leads to reliability issues (limited traceability, data entry errors, transcription errors, translation errors), and coherence issues (duplicates).

Ensuring traceability and maintaining data ownership⁹ as the ADR travels through the pipeline could improve reliability and could reduce duplication. To improve traceability, it is recommended that the entire process of data management (SOPs, manuals, trainings) is documented, true, verifiable, and versioned. Moreover, it is recommended that the concept of "data immutability" is applied to ADR data (See Section 6.6. - Maintain immutability of data at the point of transmission). Lastly, to improve traceability, good feedback across the ADR pipeline would improve DQ (See Section 6.5. - Implementation of feedback mechanisms to allow for data corrections).

⁹ In this context, data ownership refers to the right and responsibility of senders of ADR data to correct/update that data through the submission of follow-up versions of the originally submitted reports

5.2. Extensiveness

As described in the EMRN DQF, extensiveness is defined as the dimension capturing the amount of data available. Extensiveness answers the question, “how much data do we have”? When considering the “fit for purpose” definition of quality, extensiveness covers how sufficient the data are for the intended purposes – clinically meaningful safety information needs to be as complete as possible, but other information is less relevant, and more data of this type is not always better. Subdimensions of extensiveness are coverage, and completeness [1].

5.2.1. Underreporting (coverage)

Underreporting in ADRs is the lack of reported ADRs that could have been reported. Underreporting is a significant challenge in PV. It has been estimated that only 5-10% of spontaneous ADRs & AEs (both human & veterinary) are reported, indicating that the majority of the cases is unknown [50, 51].

The level of reporting is likely dependent on seriousness and may be relatively lower for non-serious events, well-established side-effects and for ADRs specific for certain medicines. This problem may lead to a reporting bias. Furthermore, variations between ADR reports are often influenced by HCP attitudes and beliefs, knowledge and skills, clinical expertise, and practice settings, as well as familiarity with local protocols and reporting requirements and possibilities from regulatory bodies [52]. This can lead to issues of extensiveness (underreporting), completeness, and coherence.

To improve coverage, continuing education and communication programmes for the primary source are recommended (see Section 6.1. – Training).

5.2.2. Missing information (completeness)

Completeness issues in ADR reports are missing information that ideally would have been provided (or, in the case of information that was provided by the reporter to the sender organisation, should have been provided) because this information is both necessary and useful to assess an ADR.

Unsolicited reports can have a low level of completeness, with data either not reported at the start or after follow-up, or lost in the journey (unintentionally, e.g. through data entry errors; or intentionally to protect privacy, e.g. when implementing the General Data Protection Regulation (either correctly or incorrectly) in the human domain).

In 2025, a total of 2,002,916 valid ADR reports were submitted to EV of which 1,181,416 (59%) included both time-to-onset data and reaction outcome. The lack of information in the other 41% of cases especially complicates signal validation by affecting reliability. The value of ADR reports in signal detection is inherently related to the completeness of clinically relevant information [53, 54]. An incomplete or low-quality report undermines the strength of the association between a medicine and the reaction. Furthermore, a low level of completeness can create problems with uniqueness (risk of apparent duplicates).

The challenge with missing information is related to foundational determinants. In the current processes, it is possible to report AEs and ADRs to stakeholders without even sufficient information to make the report valid and to submit AE and ADR reports with only the minimum criteria required to validate the case (see Section 4.4.). Furthermore, for patients or animal owners with limited medical or veterinary knowledge, it may be challenging to provide precise medical/veterinary information and to know what ancillary medical/veterinary information (e.g. test results) would be useful. Moreover, HCPs and vets may lack an understanding of the work of PV and the information that assessors need. Also, time constraints can hinder complete reporting of potential ADRs. In addition, MAHs often need to seek permission to obtain follow-up and this is often denied or retracted after the first follow-up.

To improve completeness, it is recommended to include assessments of completeness in the DQ processes focussing on key-data elements (6.4. – Early implementation of data validation processes) [53, 55]. It is recommended that, where appropriate and in addition to established pharmacovigilance quality systems, sender organisations develop general metrics and also metrics that are specific for certain products or reactions of particular interest, because key data elements may differ for each product or ADR. For example, a key element of the reaction could be to include relevant test data, e.g. an ADR of a drug-induced liver injury should ideally include liver function tests.

Moreover, to improve completeness it is recommended that automated checks are integrated in the database and electronic reporting tools to reduce missing information upon data entry (see Section 6.4. - Early implementation of data validation processes). Additionally, a clear explanation and/or automated notifiers will guide the reporter (patients and HCPs) to provide the critical data elements resulting in higher DQ.

One significant problem affecting completeness is the difficulty in follow-up on an initial ADR report to receive more detail, particularly for unsolicited ADR reports. Initial ADR reports may be incomplete for a variety of reasons, including legitimate ones such as speedy reporting for severe cases. Although follow-up information is very important for DQ of the ADRs and its use in signal detection, especially because it often provides more information on the diagnosis, nevertheless, MAHs report that the majority of follow-up attempts for unsolicited reports are unsuccessful [56]. By contrast, in clinical trials the sponsors usually have direct access to investigators and structured mechanisms for obtaining additional information. As a result, follow-up success rates and completeness are generally higher than reports from other sources.

Furthermore, there is heterogeneity in the way follow-up is reported, leading to coherence issues. If follow-up is provided, the extensiveness of the report ranges from one-word answers to the specific questions, to the full case notes of the patients. Moreover, some NCAs and MAHs submit a separate small follow-up summary, while others submit a fully integrated follow-up in the original narrative. When the full case notes are provided, the NCA or MAH needs to decide what is relevant, which can lead to incomplete or excessive information. Next to missing information (completeness issues), the heterogeneity in reports can lead to issues with coherence.

Prior to 2025, a potential cause for this challenge was a lack of guidance on how to acquire and report follow-up information. This has been somewhat alleviated in the human domain by the publication of the Guideline on specific adverse reaction follow-up questionnaires [57]. A cause for the variability in the ways of reporting follow-up may be a lack of structure in the data entry forms to incorporate follow-up.

To improve completeness of follow-up information, it is recommended that customisable template forms are developed to standardise information collected at the primary source (see Section 6.3. - Improvement of standard implementation).

5.3. Coherence

As described in the generic EMRN DQF, coherence is the dimension that expresses how different parts of an overall dataset are consistent in their representation and meaning. Coherence answers the questions: is the format of values the same across the dataset? Is the precision of values the same? When considering the “fit for purpose” definition of quality, coherence relates to the analysability of data. Subdimensions of coherence are uniqueness, format coherence, and semantic coherence [1].

5.3.1. Duplicates (uniqueness)

Duplicate ADR reports are the problem of multiple same records being present in a database without using coherent identifiers and hence making it hard to detect them. This in turn creates accuracy issues in that it distorts the relation between data, and what is observed, in terms of sampling biases. Duplicate reports pose several problems for PV by creating false or misleading signals and therefore impact the safety monitoring and potential regulatory actions. The most obvious challenge is related to signal detection when the observed ADR counts are higher than the expected ADR counts. Duplicates arise from various causes as depicted in Figure 9.

Some duplicates arise by manual errors such as incompleteness of reports, data entry errors or multiple reporters. There may be multiple reports in EV or EVV about the same ADR in the same patient, reported by different senders through different routes, whereby the ADR information may be handled differently by the processor of the case, which makes it difficult to identify the reported cases as duplicates. It could also happen that a single patient or HCP reports the ADR in multiple places. Another possibility is that follow-up information may be mistakenly unlinked to the original report, thus creating a new report [58].

Other causes appear due to computational errors such as a lack of standardised management practises, multiple representation of the same data due to the merging of PV databases and challenges in data integration and harmonisation in PV databases.

There can also be automated causes of duplicates when organisations automatically share data with other organisations that already receive copies of it (e.g. MAH-MAH sharing as business partners¹⁰); this type of duplication is also known as ‘case replication’ and appears to be a greater problem in the human domain than veterinary. Replication includes reproducing or recreating ADR reports for various purposes, for example, research, regulatory compliance or data analysis. Replication proceeds by making multiple copies of reports for different stakeholders or systems without necessarily meaning that the content or details of the reports are identical. Replication could result in duplication, when multiple stakeholders report the same case to the same regulatory authority for compliance. This is an important DQ problem as it also undermines data integrity [58, 59].

To improve uniqueness and coherence, it is recommended that databases are routinely screened to detect and eliminate duplicate reports by collaboration of stakeholders across the ADR pipeline (see Section 6.7. - Routine duplicate detection and elimination by databases).

Furthermore, to reduce case replication across multiple partners, it is highly recommended that data interchange agreements are developed with a focus on eliminating the submission to EV of the same replicated case by multiple MAHs. These agreements should be regularly reviewed particularly when new partnerships are initiated.

¹⁰ A business partner is an organisation with a medicinal product licensed to another pharmaceutical company.

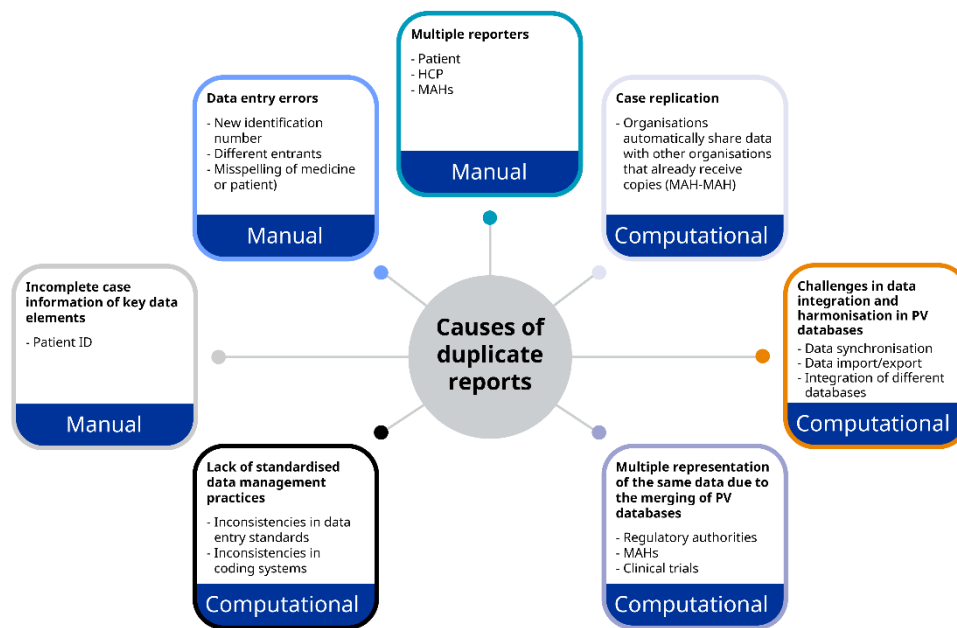


Figure 9: Causes of duplicate reports classified by manual or computational cause

5.3.2. Different ways of reporting data (format coherence)

Format coherence is impacted by the use of different ways to represent data from different sources in a collection of ADRs.

An important challenge in format coherence, is that data is collected using different collection methods, different data collection forms and, for non-EEA-regulators, even different systems.

In clinical trials, structured data collection processes are in place using case report forms. For post-marketing unsolicited reports, data can be gathered in multiple ways. Most ADR reports are reported electronically by the primary source, however, some are reported by phone (especially for PSPs) and a small proportion is reported by regular mail, e-mail or fax, and entered by the recipient in a form which often follows the Council for International Organizations of Medical Sciences (CIOMS) format. The CIOMS format does not collect the same data elements as defined in the ISO ICSR/ICH E2B(R3) electronic format. This can lead to differences in how CIOMS information is entered into ISO ICSR format compliant databases.

Moreover, stakeholders use their own data collection forms for the primary source, which introduces variability in the data collected. Some of the differences in forms between stakeholders will be for product/disease/population-specific reasons, but not all the differences are down to this and there is room for a degree of harmonisation.

Lastly, non-EEA-regulators use PV systems based on different standards, indicating variability between systems and used definitions across the globe. [60] In the human domain, even those organisations using ICH E2B format databases can have important differences, as some will use ICH E2B(R2)-format databases and others ICH E2B(R3). In the veterinary domain, many non-EEA regulators do not use the VICH GL35 format.

This all introduces practical challenges for NCAs and MAHs, in terms of inconsistent input and inconsistent coding (format coherence). See section 5.1.3. for an example of such a challenge.

To improve format coherence, it is recommended that template data collection forms are developed to standardise the collected information (see Section 6.3. - Improvement of standard implementation). It is also recommended that the data collection forms support population of the ISO ICSR/ICH E2B(R3)/VICH GL35 electronic formats. Additionally, to improve coherence, it is recommended that webforms for data collection have drop-downlists or suggested names for medicines to guide the primary source. Furthermore, it is recommended to upgrade any human PV databases based on the E2B(R2) format to be based on the E2B(R3) format.

5.3.3. Different interpretation of regulations & grey areas (semantic coherence)

Semantic coherence is the issue that the same values, in a collection of ADR reports from multiple sources, correspond to different real observations, due to different ways of interpreting such values across sources.

Differences in submission rules between EEA and non-EEA can make it challenging to have a consistent dataset within and across stakeholders. As an example from the human post-authorisation domain, an ADR report concerning “a patient” that is valid in one region, would be invalid in the EEA. Where reports are included in datasets in one region but excluded in another, this may lead to variations in the cases available for aggregate review, trend analysis and signal detection activities. Similarly, differing reporting requirements or validation criteria may influence the composition of datasets used for signal detection, potentially affecting case counts, reporting frequencies and the interpretation of observed reporting patterns. Such differences may also present challenges for duplicate detection activities, when reports are captured, validated, or coded differently across regions.

In addition, there may be differences in interpretation of guidelines on ADR collection, management and submission, which means that the same values of data correspond to different situations across submitters and/or geographies. Examples are:

- When should an ADR be considered as new report and when should it be handled as a rechallenge or follow-up?
- When should death reports with no reaction or information about the clinical circumstances be submitted?
- When should cases be considered as duplicates?
- Which events described in a literature case should be considered to be reactions?
- Literature cases can be erroneously reported as multi-patient cases by MAH, although the guidelines are clear that ADR reports should only contain individual patient information (individual case safety reports).

To improve semantic coherence, it is recommended to reach improved alignment between regulators at international levels within the boundaries of local legislation. It is recommended that industry associations outline where these differences exist between important regulatory spheres, and to actively engage with all relevant authorities to clarify the differences in interpretations to develop harmonised interpretations for these specific scenarios.

5.3.4. Inconsistent coding (semantic coherence)

The quality of data entry can be measured by the degree to which the recorded data is representative of the original information when retrieved and presented as data output. DQ is influenced by a certain

degree of judgement from free text to a standardised code. Inconsistent coding of events can lead to lack of coherence in the data.

This problem is most prominent for coding of the product name: the product can be identified with the brand name (at the country level), but also as the active substance(s), and then as only the active moiety as a salt or salts. There are myriad different dictionaries and implementations of rules regarding the names of medicines in MAHs' databases, and these are free-text fields in both EV and EVV. Input systems offer guidance, but they are different, not enforced and multiple routes are possible.

Moreover, for diagnosis codes, the same type of event for the same medical product can receive a different MedDRA or VeDDRA code, for example application site pain or ear pain for a topical product applied in the ear. This problem can be caused by different people responsible for coding; many plausible codes in the dictionary; or increasing insights (after thorough assessment something that starts with a headache, can become migraine). Moreover, lack of guidance for some specific fields can lead to subjective judgement and thereby inconsistent coding. This is important to bear in mind when reviewing ADR data for signal detection: there can be different expressions of a single pathophysiological mechanism, which may be missed when filtering on clinical diagnosis. For literature cases the same source documentation can be interpreted differently by stakeholders, which can lead to inconsistent coding.

To ensure that the same value means the same thing throughout a dataset, it is recommended that one standard coding terminology for product name/active substance is applied to all systems and stakeholder databases (see Section 6.3. - Improvement of standard implementation). Moreover, implementing thorough training for ADR processing and submitting organisations and establishing a standardised coding manual (implementation rules) is recommended to reduce coding inconsistencies and avoid misinterpretation of data (see Section 6.1. - Education).

5.4. Timeliness

Timeliness is defined as the availability of data at the right time for regulatory decision making. That, in turn, entails that data are collected and made available within an acceptable timeframe. Timeliness answers the question: are the data reflecting the intended reality at the point of time of its use? When considering the "fit for purpose" definition of quality, timeliness covers how closely the data reflect the intended reality, at the time in which it is used [1].

The problem of timeliness in ADRs is on four levels: the time it takes for a primary source to report an ADR, the time it takes for an ADR to be submitted to EV/EVV and the time it takes for a validated signal to be flagged as a signal of disproportionate reporting and, more notably, the time that it takes to get regulatory action from the validated signal.

This can be affected by the need to procure missing information, the time needed to consult other data sources, the time to assess weak causal assessment or the need to accumulate more cases to compensate for DQ issues.

Timely submission is crucial for rapid identification of potential safety issues. The timelines required for submission of ADRs to EV/EVV are laid down in the legislation, which outlines the requirements governing the regulatory process. Table 1 shows an overview of the legislation and submission requirements. In the human domain, EMA informs all organisations submitting ICSRs to EV about their compliance with the regulatory timelines every month to help them identify areas for improvement [61, 62].

5.5. Relevance

In terms of DQ assessment, relevance is defined as the extent to which a dataset presents the data elements useful to answer a given research question. The relevance DQ dimension answers the question: does the dataset present the values (or data elements) that are needed to address a specific question, using a specific method? When considering the “fit for purpose” definition of quality, the relevance DQ dimension describes how the data cover the aspects of reality that are intended to be measured [1].

In ADR collection, specifically in some solicited reporting scenarios, the data that is provided may not be describing adverse drug reactions.

Spontaneous reports by a patient or HCP are, by definition, relevant and classed as suspected. Solicited ADR reports originating from an organised data collection system require a causality assessment (see ICH E2D(R1) [10], sections 2.8 and 3.2) and should only be submitted to a regulatory authority if suspected to be causally related. Unsolicited reports originating from various sources such as literature, or non-medical sources (lay press or digital platforms), where the MAH has obtained the information, rather than it being reported to them, require a causality assessment for the events reported in the source documents unless the author of the documents is clear in attributing causality. As described in Section 5.6.2. , digital platform data in particular are generally difficult to analyse due to their unstructured nature and lack of credibility [63].

ADRs collected from interventional clinical trials have specific challenges. All serious AEs should be reported by the investigator to the Sponsor (unless risk-adapted safety data collection is applicable – see ICH E19¹¹ [12] & the Guideline Risk proportionate approaches in clinical trials. [22]); whereas only unblinded Suspected Unexpected Serious Adverse Reactions should be submitted to EEA Member States (NCAs & Ethics Committees). This requires 3 separate assessments by different actors: Suspectedness (causality – assessed by investigator and also by the sponsor), Expectedness (assessed by the sponsor) and Seriousness (assessed by the investigator and the sponsor).

- **Suspected**

The requirement to assess causality and only submit suspected unexpected serious ADRs means that each adverse event identified during a clinical trial requires assessment of whether the investigator thinks that the event was caused by the (often blinded) investigational medicinal product that the patient received. In a blinded trial, it is vital to maintain the blinding of the investigator, so they must be required to assess the causality without knowing what the patient received. To prevent oversubmission while maintaining the blind, the reporting forms should ask the investigator to assess causality as though the patient had received the investigational medicinal product or the blinded placebo/comparator.

If the investigator decides that the event was not suspected, the Sponsor may perform their own assessment and may decide that it was suspected. If either party (investigator/sponsor) decides that the event was suspected, then it should be treated as suspected for the purposes of SUSAR submission;

- **Unexpected**

The assessment as to whether the reaction is expected, or unexpected, should be performed by the Sponsor with reference to the valid **Reference Safety Information (RSI)** at the time the reaction occurred. For this, it is important that the RSI is clearly labelled and version controlled, with a date range for the validity of each version. It is also important that the RSI has clear wording and is sufficiently granular, with precise descriptions of the expected

¹¹ This is not to say that risk-adapted safety data collection poses a challenge to ADR DQ – merely to acknowledge that there are situations when not all serious AEs should be reported by the investigator to the sponsor

reactions and symptoms, including the severity and seriousness of the reactions. The Sponsor, and any organisations operating on their behalf for the purposes of ADR recording/submission, should always have access to every version of the RSI and their staff need to be adequately trained to use the correct version.

Sponsor's staff should be sufficiently trained and experienced to understand that the same medical concept can be expressed in different ways, e.g. "increased LFTs" and "increased hepatic enzymes" should be understood to be equivalent terms. Additionally, staff need to be aware that the expectedness can be dependent on the seriousness or frequency of a reaction. For example, if the RSI lists 'transient increases in hepatic enzymes', but a patient experienced such a significant increase in the value of their LFTs that they are hospitalised for a week, then this should be considered unexpected. Equally, if an ADR is described as likely occurring rarely, yet the Sponsor identifies a large number of occurrences of this ADR, then this should be considered unexpected.

- **Serious**

There are 6 reasons why an event should be considered serious: Fatal, Life-threatening, Disabling/incapacitating, Hospitalisation, Congenital anomaly, Other medically important condition. These terms are defined in ICH E2A [8] and further in GVP Module VI [17], chapter VI.A.1.6.

Seriousness criteria should be assessed with respect to the specific event/reaction and not to the overall status/outcome of the patient. This can mean that even seemingly clear and binary seriousness criteria (did the patient die? Was the patient hospitalised?) are context-specific. A patient in a clinical trial for people with advanced lung cancer will have a very high chance of mortality. If that patient experiences a SUSAR of jaundice, for which they are hospitalised, and they subsequently die due to their lung cancer before they have recovered from the jaundice, then that does not mean that the jaundice was fatal.

Those seriousness criteria which the investigator has deemed apply to the reported event(s) should only be downgraded from serious to non-serious by the investigator (while maintaining the blind, as applicable).

The challenges relating to Suspectedness and Seriousness are not unique to interventional clinical trials and also apply to other domains: both apply to human post-marketing, and seriousness applies to the veterinary domain.

5.6. Special considerations for specific ADR data sources

5.6.1. Considerations on patient support programmes for ADR reporting

The volume of ADR reports originating from patient support programmes (PSPs) and submitted to EV is high, but the quality of the reports is highly variable. The quality of the reports ranges from low quality (comparable to e.g. digital platforms) and lacking any causality assessment, to being comparable to spontaneous reports from healthcare professionals [49]. Some reports from PSPs which should be regarded as solicited and requiring a causality assessment, are instead erroneously handled as spontaneous with implied causality, resulting in oversubmission and issues of accuracy (noise).

A possible cause for the variable DQ was the broad definition of patient support programmes leading to different designs of these programmes [49]. The requirements for data collection from patient support programmes differs across regulatory authorities. Although patient support programmes are not always designed to probe safety, information collected through these programmes should be considered solicited reporting [17].

To reduce noise in data resulting from patient support programmes, ICH E2D(R1) [10] has been published with sections focussing specifically on PSPs and other related forms of Organised Data Collection Systems (ODCS). Prompt implementation of E2D(R1) and further harmonisation of international guidelines, to facilitate alignment and to focus on collection of the relevant cases, would be an area of improvement. Furthermore, a risk-based approach (e.g. patient support programmes which will likely deliver valuable safety information) may be a solution; but this would require changes to existing guidance and possibly legislation in some regions.

Note: This section is not applicable to veterinary ADR reports.

5.6.2. Considerations on social media for ADR reporting

Social media has been identified as one of the data sources that could provide real-time, user-generated information about ADRs. It could play a complementary role as an early warning system for potentially new ADR signals.

The first issue with social media as a source for ADR reports is that it provides a vast amount of data, but these data are hard to analyse due to their unstructured nature and lack of credibility and could therefore possibly negatively impact signal detection systems [63, 64]. This leads to reliability issues (noise). Reactions/events described on social media might be unrelated, non-specific and written in nonsensical terms such as “My head feels sloppy” or “I’m off my feet”. Moreover, consumers, animal owners or malicious actors could easily write fake reports and may duplicate a report via several platforms. This process is very hard to verify in terms of who is the reporter.

A second issue where social media impacts ADR reporting, is stimulated reporting. When high media interest is involved, the median reporting rate might visibly increase [65, 66, 67]. An example is heavy menstrual bleeding after COVID-19 vaccination. At social media forums, women reported their experiences of a menstrual cycle disturbance and a potential link with recent COVID-19 vaccination. During the continuous safety review of COVID-19 vaccines, PRAC performed an analysis in EV of spontaneous reports of heavy menstrual bleeding reported by consumers. In some European Union countries with high reporting rates (e.g. the Netherlands, France), the consumer reporting appeared to be influenced by communications from media and/or health authorities, with high volume of reports shortly after publications. [65]

Patient/animal owner reporting directly to regulatory authorities and MAHs is of high value for regulatory safety reviews, albeit the reporting behaviours are not free of the influence of the media. Regardless, they provide a better understanding of the context of safety concerns of the public.

Regulatory organisations have produced guidelines on how unsolicited reports of ADRs collected from social media should be handled for PV purposes in the human domain, and MAHs hosting social media sites/pages or other digital platforms have additional responsibilities regarding the collection of ADR reports [10, 17]. For veterinary medicinal products, guidance on handling AE reports collected from the internet or from digital media is provided in the VGVP Module: Collection and recording of suspected adverse events for veterinary medicinal products [26].

Moreover, the research project WEB-RADR [68] has explored the value of social media (i.e., information exchanged through the internet, typically via online social networks) for identifying ADRs as well as for safety signal detection [69] and found limited value for formal, automated signal detection of new or unknown drug safety issues. This is due to the high volume of noise, lack of clinical context, and difficulty in verifying individual reports. Many patients and clinicians have discussed their positive and negative experiences of medications on social media, creating a source of publicly available information that has the potential to provide insights into medicinal product safety concerns. This research produced several recommendations that can be considered:

1020 • Social media platforms as Facebook and Twitter (currently known as X) are not recommended for
1021 broad statistical signal detection.

1022 • Social media channels may provide a useful adjunct to PV activities in specific niche areas such as
1023 exposure during pregnancy and abuse/misuse of medicines.

1024 Future enhancement of ADR recognition algorithms may broaden the scope and utility of social media
1025 over time.

1026 **5.6.3. E-commerce**

1027 E-commerce of medicines (the buying and selling of medicines over the internet), can lead to similar
1028 issues as digital platform reports: noise and excess reporting. Specific causes for noise in e-commerce
1029 for the MAH/NCA are that the medicine may not be authorised in the country where it is reported,
1030 making identification of the actual product particularly difficult. Furthermore, e-commerce can be a
1031 significant source of falsified or counterfeit medicines [70, 71], which can further complicate the
1032 analysis of signals.

1033 **5.6.4. Blinded clinical trials**

1034 Special consideration is needed for blinded clinical trials, where it is vital to maintain trial integrity
1035 while ensuring adequate safety reporting. In accordance with the Clinical Trials Regulation [23], Annex
1036 III Safety Reporting, SUSARs shall be accessible only to persons who need to be involved in the safety
1037 reporting to the Agency, to Data Safety Monitoring Boards ('DSMB'), or to persons performing ongoing
1038 safety evaluations during the clinical trial. By contrast, the blind shall be maintained for other persons
1039 responsible for the ongoing conduct of the clinical trial (such as the management, monitors,
1040 investigators) and those persons responsible for data analysis and interpretation of results at the
1041 conclusion of the clinical trial.

1042 It is standard practice of many sponsors to return a copy of the SUSAR to the investigator. This copy of
1043 the SUSAR must be blinded, so as not to risk unblinding the investigator or their personnel. Not only
1044 must the structured drug and substance information be blinded, but the case narrative and all free-text
1045 fields must also be blinded.

1046

6. Recommendations to improve DQ in ADR reporting

6.1. Education

Education is crucial for improving the DQ of ADR reports. All stakeholders in the ADR pipeline should ideally be educated about basic concepts such as what is the most important and relevant information to provide.

6.1.1. Training of primary source

The ADR reporting process requires technical skills and knowledge by HCPs, including knowledge of ADR signs and symptoms, risk factors, recognition of underlying comorbidities and concurrent conditions mimicking an ADR. Other skills are familiarity with pharmacological profiles of medications and drug interactions and the ability to construct a relevant medication timeline [39].

Ideally, HCPs would receive training on ADR recognition, reporting procedures, and the significance of reporting. This should preferably start at student level but more importantly should be continued at hospitals, veterinary surgeries and all care centres. This would improve coverage and completeness and the overall quality of ADR reports.

The ability of HCPs to understand and provide sufficient details in the reported verbatim can have a significant impact on ADR reporting. At database level, the narrative is coded to medical terms with the same medical vocabulary as they need to be mapped to the back-end system of the (local) regulator. However, HCPs from different countries may use different medical terminology in ADR reporting [59, 32, 72]. For instance, a skin rash on a leg, specifies the part of the body but could not be specific enough for a regulator. The lack of harmonized medical terms and definitions across regions, combined with translation issues, may lead to variations in the standardized terms entered into safety databases, resulting in semantic imprecision and potentially differing clinical assessments and regulatory decisions.

In spontaneous reporting, patients, animal owners and HCPs can be guided on what information should be provided to report an ADR. This can be supported through the use of standardized electronic reporting forms with integrated local dictionaries helping for example on the selection of medicinal products and active substances. Paper forms and the operators of medical information lines can also help to guide reporting of ADRs. Public campaigns about awareness when to report an ADR and the appropriate reporting routes can be useful as well, although this is highly dependent on healthcare systems and local practises.

In clinical trials and some other solicited forms of reporting, investigators and other HCPs involved in the trial should receive thorough training on causality assessments and on the need to provide all available information relevant to the ADR, such as relevant test data and medical history, when first reporting the AE to the sponsor.

6.1.2. Training of data processors, managers and submitters to EV or EVV (MAH, NCA, sponsors)

The entire process of data generation and coding (SOPs, manuals, trainings) should be documented, true, verifiable, and versioned. These aspects should therefore be included in training for submitters to EV, which improves DQ issues in determinants for reliability, extensiveness, coherence and timeliness [1]. After processing, ADRs are thoroughly reviewed by relevant organisations (MAH, NCA, Sponsor) which received the original information from the primary source, based on expectedness, causality, inconsistencies, and corrected as soon as possible. To make the best use of the received information,

1089 these employees need medical/veterinary knowledge, experience and, for collecting additional relevant
1090 information, good communication skills. The information initially available is often insufficient, and
1091 efforts to collect additional follow-up information for spontaneous or literature reports mostly fail. An
1092 important point of improvement for which thorough training is recommended, is inconsistent coding
1093 and to ensure that the same recorded value has the same meaning throughout a dataset. Establishing
1094 a standardised coding manual is recommended to reduce inconsistencies in the coding of
1095 medical/veterinary terms, thereby avoiding misinterpretation of data. Specifically, data
1096 entry/management/submission staff should attend training sessions and regularly refer to the coding
1097 manual and should have access to the training materials outside of the training. As part of the regular
1098 audits as described in GVP Module IV [68] analysts are encouraged to conduct periodic audits of coded
1099 data to identify and rectify inconsistencies.

1100 Furthermore, education on submission rules is pivotal to improve accuracy and to minimise noise. It is
1101 recommended to promote good use of submission rules throughout the network.

1102 **6.1.3. Training of data users and PV-assessors**

1103 As a last step, data users (e.g. regulators, signal detection staff) should be trained to report any
1104 identified incorrect submission either to an internal quality control office or back to the sender
1105 organisation for continuous improvement of DQ.

1106 **6.1.4. Principles of good ADR submission**

1107 What makes a good ADR report? During signal validation, in the human domain ADRs will be evaluated
1108 against the criteria detailed in GVP Module IX [18] chapter IX.B.3. In the veterinary domain AEs will be
1109 evaluated against the criteria detailed in the Guideline on veterinary good pharmacovigilance practices
1110 (VGVP) Module: Signal Management [30]. Consequently, staff processing ADR reports should receive
1111 adequate training to develop an understanding of the information required by pharmacovigilance
1112 assessors to perform signal evaluation based on the data recorded in the database; in this regard the
1113 following principles [73] should be considered:

- 1114 • Submit all valid ADRs to EV/EVV. Record all ADRs and all reports of use in special situations (e.g.
1115 pregnancy or breastfeeding), and ensure that only those ADRs which should be reported are
1116 reported;
- 1117 • Provide accurate non-mandatory¹² details: include patient demographics and relevant medical
1118 history, concomitant medication, ADR description including time-to-onset and what happened after
1119 drug withdrawal and re-administration (dechallenge, rechallenge);
- 1120 • Submit promptly: timely submission enables quick identification of potential safety issues (see
1121 reporting timelines in Table 1);
- 1122 • Causality assessment for solicited reports: causality is related to the concept of change:
1123 “something new or something different”, which typically excludes symptoms that are part of a
1124 chronic illness and pays particular attention to the time-to-onset. Moreover, Causality assessment
1125 can be performed using several methods, such as Bradford-Hill principles, Agence nationale de
1126 sécurité du médicament et des produits de santé (ANSM) imputability, Naranjo algorithm, the
1127 WHO-UMC system or CIOMS criteria or, in the veterinary domain, the ABON system. In general, an
1128 important criterium of causality is: “Time is key”. Given the large number of causality assessment

¹² Although such information is not mandatory for an ADR report to be valid, if the MAH/NCA/Sponsor has received it from the primary source, then it should always be correctly structured in the ADR report

1129 methods, it is recommended that global regulators attempt to harmonise assessment
1130 methodologies for each domain (post-authorisation, clinical trials, veterinary).

1131 For clinical trials, the investigator has more training and obligations than reporters of spontaneous
1132 reports and the data is generated in a controlled environment. Therefore, more information than the
1133 bare minimum should be available and reported by the investigator. In particular, investigators should
1134 report (and sponsors should submit) clinically meaningful data for each SUSAR, including time-to-
1135 onset, action taken with the suspect drug, the outcome of the reaction (at the time of reporting and
1136 follow-up) and relevant medical history and test data. If this information is not immediately available,
1137 follow-up should be expedited to provide it and to update the ADR report as necessary (which is true
1138 for all ADR reports across all domains).

1139 **6.2. Integration of clinical pharmacology in ADR processes**

1140 Identification, reporting, analysis, management, submission, and public awareness of ADRs should
1141 become a more integrated system from clinical trials to post-authorisation. To integrate the system,
1142 clinical pharmacology should be at the base of ADR reporting.

1143 It starts with profiling of all potentially relevant pharmacological activity, starting in the early phases of
1144 drug development. Most ADRs can be predicted from the pharmacological and preclinical profile: one
1145 can predict in which dose ranges they might occur, what risk factors increase their occurrence,
1146 interactions or organ failure. Therefore, the pharmacology of the medicine, potential ADRs, and
1147 characteristics of a patient population should be acknowledged when writing the common technical
1148 document and the development risk management plan, that later on inform the risk management plan.
1149 This could improve identification of (relevant) ADRs, and the quality of the reported ADRs in terms of
1150 reliability, causality assessment and coherence. This is of high importance, because when the safety
1151 analysis is misguided, e.g. by incorrect specification of the patient population in a clinical trial, this may
1152 lead to unnecessary hazard to patients and risks that a good medicine (or even a drug class) is
1153 discontinued in the drug development process or post-marketing.

1154 Furthermore, clinical pharmacology, together with pharmaco-epidemiology and clinical judgement,
1155 plays an important role in signal detection and signal assessment. Statistical and quantitative methods
1156 provide valuable tools for identifying potential safety signals; however, interpretation of these findings
1157 is strengthened by an understanding of the pharmacology of the medicine, biological plausibility, and
1158 the overall clinical context. The integration of these complementary approaches can support the timely
1159 identification and evaluation of emerging safety concerns. A challenge in signal detection is to
1160 recognise causality. This decision can be hampered by lack of knowledge on the pharmacology of the
1161 medicine. If a signal is only raised after a number of events, mainly based on pharmaco-epidemiology
1162 this may lead to a delay in recognition and consequent risk of casualties.

1163 Ultimately, integration of all ADR processes as described above could lead to a more Bayesian
1164 approach to PV by predicting ADRs and mitigating risks, informing (development) risk management
1165 plans and product safety information.

1166 **6.3. Improvement of standard implementation**

1167 Standardisation is key to improve DQ of ADR reports. This includes standardisation of the process, but
1168 also of the data itself (e.g. data fields and terminology).

1169 **Data collection forms**

1170 It is recommended that standardised templates for all types of data collection form (webforms, paper
1171 forms and forms for medical information phone lines) is developed for data collection at the primary

1172 source, which should be used by all stakeholders (MAHs, NCAs, and sponsors of clinical trials). It is
1173 recommended that, as much as possible, these data collection forms support the ISO ICSR/ICH
1174 E2B(R3)/VICH GL35 electronic format. These standardised forms should be simple and should guide
1175 the primary source to report the most important and useful information for a high-quality ADR report,
1176 in particular clinical data in order to help the scientific evaluation. Overcomplete reports and extremely
1177 lengthy narrative are certainly not necessary to provide a good ADR report. In the human domain, the
1178 Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Work Package 4
1179 Paper ADR Reporting Forms template [74] provides a basis for such forms.

1180 Data collection tools should also be developed to allow/encourage the direct electronic reporting of
1181 ADRs from hospital, veterinary surgery and other medical/veterinary health records.

1182 For reports from organised data collection systems, the template should include questions that require
1183 the reporter to provide a causality assessment. For clinical trials reporting forms, investigators should
1184 be encouraged to document the reasoning supporting the causality assessment, including key elements
1185 such as temporal relationship, alternative explanations, dechallenge/rechallenge information and
1186 relevant medical history

1187 Moreover, webforms should have drop-down lists or suggested names for medicines, medical terms
1188 and other data elements that have controlled vocabularies when transmitting the report as an ICSR,
1189 while still allowing reporters to enter terms not on the suggested lists. This would increase coherence
1190 and decrease incorrect coding. It would also improve precision at the time of reporting. A clear
1191 explanation and/or automated notifiers will guide the primary source (patients, animal owners and
1192 HCPs) to provide the critical data elements resulting in higher DQ.

1193 **Product/substance coding terminologies**

1194 There are many different product/substance coding terminologies and implementations of rules
1195 regarding product names in stakeholder databases, and these are free-text fields in EV & EVV. To
1196 improve semantic coherence, it is recommended that one standard coding terminology for each
1197 domain (human/veterinary) for product and substance names is applied to all systems and stakeholder
1198 databases. Moreover, training for data entry/management/submission staff to EV & EVV, and one
1199 standardised coding manual for each domain (implementation rules), is recommended to reduce
1200 coding inconsistencies and improve coherence.

1201 **Medical and veterinary terminology coding**

1202 Correct, accurate, consistent coding of medical and veterinary terms is essential to allow for consistent
1203 analysis of potential signals. MAHs, Sponsors and NCAs should all ensure that MedDRA and VEDDRA
1204 coding principles [75, 76] are implemented in their systems and are followed by data entry and
1205 medical/veterinary review staff.

1206 **Harmonised processes**

1207 Lastly, it is recommended that global regulators adopt harmonised approaches to sharing data with
1208 MAHs to try and maintain the coherence as much as possible.

1209 **6.4. Early implementation of data validation processes**

1210 Automated checks to improve DQ should be integrated in PV databases, e.g. age should not be <0
1211 years, and a check for the number of completed fields. Ideally, automated data validation should be
1212 performed as early as possible, upon data collection. These could be implemented through e.g.
1213 automated notifications upon data entry in the webform for data collection, to reduce errors, stimulate
1214 completeness of the minimum required fields (Section 4.4.) and encourage collection of other data

1215 elements for scientific evaluation. Another example would be the use of code lists for dates, which
1216 could improve format coherence.

1217 During the data management and processing step of the data life cycle, it is recommended that data
1218 validation is performed for structured fields. This could include metrics of completeness. It is
1219 recommended that MAHs develop a metric that is specific for a certain product or reaction, because
1220 key-data elements may differ for each product.

1221 **6.5. Implementation of feedback mechanisms to allow for data corrections.**

1222 Data lineage (or traceability) describes the history of data, detailing its origins, the sources it came
1223 from and the transformations it underwent before reaching its current state [1]. The pipeline for safety
1224 data collection and ADR reporting can be extensive with many stakeholders involved in the same case.
1225 Traceability and data ownership as the ADR travels through the pipeline could improve reliability and
1226 could reduce duplication.

1227 Good feedback across the ADR pipeline in all steps of the data lifecycle will improve DQ. These
1228 activities are recurring and should be monitored on a continuous basis. Therefore, information on the
1229 organisation that submitted each ADR report is mandatory in EV and EVV to provide the possibility for
1230 contacting sender organisations regarding the quality of the data in an ICSR. Furthermore, information
1231 on the primary source is stored in the database of the organisation contacted by them so that they can
1232 be contacted to request follow-up information. It is important that the original receiver of an ADR
1233 report (MAHs/sponsors/regulators) contacts the primary source when they find a problem with the
1234 data in an ADR report. Therefore, it is important to implement oversight activities such as defined and
1235 quantifiable metrics to enable MAHs, Sponsors and Regulators to objectively assess if data is fit for
1236 purpose. In addition, regular medical review discussions or regular compliance monitoring meetings
1237 should be held in each organisation across the ADR pipeline. This is especially important when certain
1238 data management or data submission activities are outsourced to third parties, or when collaborating
1239 with business partners. With these mechanisms in place, it is easier to reach out to other stakeholders
1240 and come to an agreement to make data corrections.

1241 Another mechanism for data correction could potentially be the use of **Artificial Intelligence** (AI) to
1242 aid human data management activities. Technology and automation become more and more common
1243 as seen by the rise of AI for PV activities such as data entry and scoring of disease severity [77]. These
1244 PV applications should allow a flexible approach to AI modelling and deployment as these increase in
1245 terms of precision over time due to incremental learning and enhanced models for classification and
1246 severity scoring. These AI tools may be helpful for initial validation by automated data corrections
1247 regarding data entry, adverse reaction coding, diagnosis checking and scoring of disease
1248 severity/seriousness; but these should always be suggestions and a humans should always be taking
1249 the final decisions. It should be noted that the MAH/NCA/Sponsor remains responsible to validate,
1250 monitor and document model performance and include regular reviews of AI operations in the PV
1251 system to mitigate risks related to algorithms and models used. The Report of CIOMS Working Group
1252 XIV "Artificial Intelligence in Pharmacovigilance" contains many recommendations regarding the use of
1253 AI in human PV [78], and these should be taken into account before using AI in PV (and these are also
1254 broadly applicable to the use of AI in veterinary PV). Another important consideration before using AI
1255 in PV, or any health data, is ensuring compliance with the AI Act (Regulation (EU) 2024/1689).

1256 **6.6. Maintain immutability of data at the point of transmission**

1257 One of the issues with ADR reporting can be the apparent lack of immutability. Data immutability
1258 refers to the principle that data is never deleted or modified. Once data is recorded (e.g. once entered
1259 into a database), it can only be supplemented with additional information that may invalidate or

replace the previous data, but it cannot be removed. In other words, once data is entered into a system (and potentially relied upon by other data or actions), it cannot be altered without explicitly noting a new state of the information while preserving the knowledge of the previous state. Data used for regulatory purposes should be immutable. This does not mean that evidence cannot be updated; but any update should be treated as a separate, though related dataset. This principle is fundamental to many frameworks, such as ALCOA++ [79] and FAIR [80] and underpins the EMA guideline on computerised systems and electronic data in clinical trials [79]. A general rule is that aspects of DQ should be addressed as early as possible in the data collection and generation process. The further data travels from the original context, the harder it becomes to correct issues [1]. In ADR collection, management and reporting, this should be through the creation of different versions of a case, with a full audit trail for each version and the case as a whole. If any versions require transmission to another party, they should be transmitted, stored and managed as separate ICSRs under the same case.

Applying the concept of immutability to ADR data could improve reliability. It is critical that in all versions of a case, the case number (ICH E2B(R3) C.1.8.1/VICH GL35 A.4.1) remains the same. Ideally in the case narrative, there should be an amendment version date to match the last received date recorded in the case (or the date the information was amended if a correction is made with no new information). Follow-up information should be clearly identifiable, and from the perspective of signal detection it would be ideal if it were integrated in the narrative by correcting the information entered in the first version of the narrative that is not applicable anymore. All the changes should also, where applicable, be reflected in the appropriate structured E2B(R3) data elements. At the bottom of the narrative, there would ideally be a note highlighting the changes, so assessors can easily see the changes. However, there is no clear recommendation on how to include follow-up information in case narratives in the existing guidance. It is recommended to include such recommendations in future guideline updates. Because of the challenges with obtaining follow-up information, it is of importance to collect as much relevant information as possible upon first receipt of the ADR. For stakeholders, it is critical to maintain an audit trail to be able to see the different versions of the case. For the data procurement step, it is also important to pay attention to data immutability as removal of identifiable information on patient/reporter might impact the information in the case narrative.

6.7. Routine duplicate detection and elimination by databases

The detection of duplicates remains a challenge (Section 5.3.1.) despite tremendous efforts across the ADR pipeline [81]. It is clear that duplicate reports should be removed from PV databases before statistical analyses are conducted; however, the applicable submission rules cannot completely avoid duplicate submission. For example, in the human domain GVP Module VI states that when one party is made aware that the primary source(s) may also have reported the ADR to another concerned party, the report should still be considered as a valid ADR report [17].

Multiple approaches are in place for duplicate detection such as probabilities, comparing the likelihood of specific combinations of country, medicines, ADRs, sexes, ages, species etc. occurring on a given pair of reports based on background reporting rates. Databases should be routinely screened to detect and eliminate duplicate reports by collaboration of stakeholders across the ADR pipeline (NCA, MAH, sponsors, EMA and WHO-UMC). The detection and handling of duplicates by these stakeholders form an important element of good case management and in the human domain collaboration between MAHs, NCAs in Member States and EMA in the detection of duplicates in EV is mandated by Directive 2001/83/EC [33]. In the veterinary domain, Commission Implementing Regulation (EU) 2021/1281 [32], Article 4(f) mandates that MAHs are responsible for the management of duplicates in EVV.

The EV system uses a combination of worldwide unique (case) identification number and sender identification for each ADR report and has a built-in deduplication mechanism to identify and eliminate

1306 duplicate reports by creating master cases to merge the information from duplicate cases [81]. The
1307 EVV system has similar deduplication mechanisms in place to ensure that duplicate cases are removed
1308 from the pharmacovigilance analyses.

1309 ***6.8. Effect of recommendations on DQ per DQ dimension***

1310 These seven recommendations to improve DQ in ADR collection and reporting have been categorised
1311 per step in the data lifecycle in Table 2. The stakeholders involved in each data lifecycle step are
1312 indicated in each column heading. The recommendation numbers correspond with the numbers in
1313 Section 6.

1314 Table 2: Implementation of recommendations organised along the ADR data lifecycle.

1315

	Definition of data requirements (NCA, MAH, sponsor of clinical trials)	Data collection or generation (primary source: patients, animal owners, HCPs, lawyers, investigators)	Data management and processing (NCA, MAH, sponsor of clinical trials)	Data submission (EMA)	Data procurement and aggregation (EMA, NCA, MAH, WHO-UMC)	Delivery for consumption (EMA, WHO-UMC, MAH, NCA)
Education ¹³ (section 6.1)		Training of primary source (investigators) Context-specific explanations in data collection forms	Training of data managers			Training of PV-assessors
Integrating clinical pharmacology (section 6.2)		Knowledge of pharmacology for improved causality assessment (investigators and sponsors)	Knowledge of pharmacology for MedDRA & VedDRA coding and causality assessment			Knowledge of pharmacology for improved signal detection
Improved standard implementation (section 6.3)	Design standardised data collection forms		Standard coding terminology for drug names			
Data validation processes (section 6.4)	Design validation checks e.g. age ≤150y	Checks during data entry	Data validation after collection by metrics of completeness			
Implementation of feedback mechanisms (section 6.5)		Gather high DQ from follow-up information at the primary source	Feedback among stakeholders for data corrections	Feedback among stakeholders for data corrections and fitness for purpose of data	Return cases to the sender for further follow-up	Feedback among stakeholders e.g. MAH-MAH
Maintain immutability (section 6.6)	Allow immutability for all data elements in a version and versioning within a case Update guidelines regarding the incorporation of follow-up information into case narratives	Investigators, immutability when providing follow-up information	Apply immutability and version management		QC for removal of identifiable information	
Routine duplicate detection (section 6.7)			Perform routine duplicate detection in own databases	Perform routine duplicate detection in EV		Perform duplicate detection after downloading cases

¹³ Education impacts all activities in the ADR pipeline, but most impact is expected in the highlighted steps in the data lifecycle.

7. Concluding remarks

This chapter is an extension of the EMRN DQF for medicines regulation, specifically on human ADR and veterinary AE reporting². The DQF application to ADR data provides a background on the impact of DQ for ADR reporting. It provides insights into the larger ADR ecosystem, the stakeholders and their role in ADR collection, management and submission. It further outlines the main challenges for ADR collection, management and submission organised by the five DQ dimensions and provides recommendations for the characterisation of systems and processes underpinning data and for all stakeholders in the ADR ecosystems. These parts provide actionable and focused recommendations for assessing DQ of ADR reporting with the goal of improving the usefulness of ADR reporting to support regulatory decision making.

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9. Glossary

1330 This glossary addresses the main terms and definitions that have been used in this DQF application to
1331 ADR reporting and submission for regulatory decision making.

Definitions	Explanation
ADR pipeline	The sequence of steps of an ADR through the data lifecycle from data collection to delivery for consumption.
Adverse Drug Reaction	An ADR is characterised by at least a reasonable possibility of a causal relationship between a medicinal product and an adverse event
Adverse Event	Any untoward medical occurrence that may present during treatment with a medicinal product, but which does not necessarily have a causal relationship with this treatment.
Healthcare Professional (HCP)	In this document the term Healthcare Professional, abbreviated to HCP, refers to professional providers of healthcare in both the human and veterinary domains. Examples of such persons include doctors, nurses, pharmacists and veterinarians.
Immutability	Data immutability refers to the principle that data is never deleted or modified. Once data is entered into a system, it can only be altered with new information while preserving the knowledge of the previous state.
Individual Case Safety Report	Individual Case Safety Report (ICSR) refers to the format and content for the submission of an individual report of adverse reactions in relation to a medicinal product that occur in a single patient at a specific point of time [17]
Pharmacovigilance	The process of detecting, evaluating, understanding, and preventing adverse effects of medicines is defined as pharmacovigilance.
Reporting	The process of a primary source informing a Sponsor, MAH or NCA about an ADR. Throughout this document “ADR reporting” is used to refer to the entire process of ADR collection, management and submission
Sender organisation	An organisation which collects ADR data from primary sources and submits ICSRs to EudraVigilance
Submission	The process of a Sponsor, MAH or NCA submitting an ICSR to EV or EVV (or to another receiver’s pharmacovigilance database)
Suspected Unexpected Serious Adverse Reaction	A serious adverse reaction which occurred in a clinical trial, of which the nature, severity or outcome is not consistent with the reference safety information.
Unexpected events	Events that affect the benefit-risk balance of a clinical trial that were unforeseen, e.g. an unexpected increase in the incidence of expected serious adverse reactions or new non-clinical data that may be clinically important. Unexpected events do not include SUSARs. These should be reported via the Clinical Trials Information System (CTIS)

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Appendix I – Overview of guidelines

1334 Overview of guidelines and frameworks for ADR reporting

Human ADR reporting		
EMA	Access to EudraVigilance data webpage [39]	ADR reporting platform EudraVigilance
EMA	Detailed guide regarding the EudraVigilance data management activities by the European Medicines Agency, 2020 [16]	Data management and quality assurance activities performed by EMA for ADRs submitted to EudraVigilance.
EMA	EU Individual Case Safety Report (ICSR) Implementation Guide, 2021 [20]	Implementation guide
EMA	Good practice guide on recording, coding, reporting and assessment of medication errors [19]	Good practice guide
EMA	Guideline on computerised systems and electronic data in clinical trials [79]	CT Guideline
GVP	Guideline on good pharmacovigilance practices (GVP) Module IV – Pharmacovigilance audits (Rev 1), 2015 [68]	Good Vigilance Practices
GVP	Guideline on good pharmacovigilance practices (GVP) - Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2) [17]	Good Vigilance Practices
GVP	GVP Module IX on signal management [18]	Good Vigilance Practices
GVP	Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations III: Pregnant and breastfeeding women and their children exposed in utero or via breastmilk	Good Vigilance Practices
ICH	ICH Harmonised Tripartite Guideline: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A [8]	Scientific guideline
ICH	ICH E2B Implementation Working Group Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs) - E2B(R3) Data Elements and Message Specification [4]	Scientific guideline
ICH	ICH Harmonised Tripartite Guideline: periodic benefit-risk evaluation report (PBRER) E2C(R2) [9]	Scientific guideline
ICH	ICH Harmonised Guideline: Post-approval safety management: definitions and standards for management and reporting of individual case safety reports E2D(R1) [10]	Scientific guideline
ICH	ICH Harmonised Tripartite guideline: Development Safety Update Report E2F [11]	Scientific guideline
MedDRA	Best practices for MedDRA – Recommendations for Implementation and use of MedDRA [76]	Best practices MedDRA
MedDRA	Introductory Guide for Standardised MedDRA Queries (SMQs) Version 23.1 [72]	MedDRA guide
WHO	Safety of Medicines - A guide to detecting and reporting adverse drug reactions [82]	High-level guide

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Veterinary AE reporting		
EMA	Combined Veterinary Dictionary for Drug Regulatory Activities (VeDDRA) list of clinical terms for reporting suspected adverse events in animals and humans to veterinary medicinal products (EMA/CVMP/PhVWP/10418/2009 Rev.16)	VeDDRA guideline
EMA	Guidance notes on the use of VeDDRA terminology for reporting suspected adverse events in animals and humans [28]	Best practices VedDRA
EMA	EU VICH adverse event report implementation guide [29]	Implementation guide
EMA	Veterinary Union pharmacovigilance database best practice guide (BPG) (EMA/371192/2021) [27]	Best practice guide
VGVP	Guideline on veterinary good pharmacovigilance practices (VGVP) - Module: Collection and recording of suspected adverse events for veterinary medicinal products (EMA/306663/2021)	VGVP practice
VGVP	Guideline on veterinary good pharmacovigilance practices (VGVP) - Module: Signal Management (EMA/522332/2021)	VGVP practice
VICH	VICH Pharmacovigilance of veterinary medicinal products: management of adverse event reports (AERs) [33]	PV guidelines for veterinary products

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