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Data Analytics and Methods Task Force

Multi–stakeholder workshop on data quality framework for Adverse Drug Reaction reporting

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Background and Objectives

Following the recent publication of the EU data quality framework (EU DQF) (1) applicable to all data sources used for EU medicine regulation, the European Medicines Regulatory Network (EMRN) is conducting stakeholder consultation with a view to create chapters for specific data domains of medicines regulation. This chapter concerns human and veterinary adverse drug reactions (ADR) arising from all sources (e.g. spontaneous reports, medical literature, non – interventional studies and interventional clinical trials). The chapter should place ADR data quality (DQ) considerations in the context of the overall EU DQF. The main scope is not to 'create' new measurements and rules, but to organise the existing ones in the described framework.

EMRN organized a workshop to obtain input from all stakeholders involved in ADR reporting. The aim of this workshop was to bring together experts in the field to build on their extensive experience and knowledge relating to ADR DQ, in order to:

- Familiarise key stakeholders with the published EU DQF.
- Collect input from experts in the field and learn from existing experiences.
- Discuss important challenges related to measuring, characterising, and improving DQ in the context of ADR data.
- Identify the key topics which should be covered in the EU DQF ADR chapter.

The workshop was attended online by approximately 160 people from various stakeholder groups. This report offers a high-level summary of the workshop presentations, as well as highlights from the discussions with stakeholders.

Welcome and opening remarks

Chair: Paolo Alcini (EMA).

Georgy Genov (EMA, Head of Pharmacovigilance Office) opened the workshop. Pharmacovigilance (PhV) is evolving faster than ever before, making use of a greater range of data sources for signal generation and validation, moving away from individual databases into the world of big data. To characterize, compare and combine various data sources and outputs for regulatory decision making, it is necessary to have an overarching EU DQF.

Anja van Haren (MEB, co– chair EV EWG and PhV BT) shared five important considerations on ADR processes for human medicines. First of all, the human EudraVigilance (EV) post marketing module (EVPM) consists of two types of reports: spontaneous reports of suspected ADRs and solicited reports. Spontaneous reports rely on the initiative of a patient, consumer, or healthcare provider (HCP) to contact a PhV centre or market authorization holder (MAH). Solicited reports are derived from non-interventional studies and other organized data collection systems. The second consideration is that spontaneous reporting systems have limitations, such as underreporting, reporting bias, no denominator data, risk of duplicates, and variable quality of the reported data. However, it should be noted that these systems are intended for signalling, not for complete reporting of all adverse events of all drugs, and therefore these limitations would rather be called characteristics. As a third consideration, it is important to outline that EU legislation drives what is submitted, how it is submitted and when, all defining DQ, and this has changed over time. Fourthly, robust processes are in place, but stakeholders have different practices when it comes to collecting valuable data from primary sources, ensuring that the database reflects the source file, and processing of individual case safety reports (ICSRs). As a fifth point, Anja van Haren poses the question "what makes an ADR report good?". This differs per case, and the necessary details may depend on the context.

James Mount (SEMPA, Vet PhV WP) shared common DQ issues, and strategies to monitor and prevent these. He stressed the impact of poor DQ, which can lead to impaired detection of new risks, negative effects on statistical methods and analysis, and impact on the implementation of new techniques (such as data mining/AI). There is a need for improved data stewardship. Strategies to monitor and prevent DQ issues are a collaborative effort of all stakeholders.

Elke Stahl (BfArM, CTCG) discussed the process of ADR reporting in clinical trials. The investigator records adverse events (AE) and/or ADRs and reports these to the sponsor. The sponsor is responsible for ensuring a positive benefit-risk ratio and has safety reporting responsibilities. Member states cooperate in the assessment of safety reports. The importance of high DQ is emphasized, because ADR reports are the basis of the safety profile of a medicinal product.

Session 1: Overview of EU Data Quality Framework

Chair: Paolo Alcini (EMA).

Ana Cochino (EMA) presented an overview of the EU DQF. The scope is to characterise DQ of any given dataset used for medicine regulation. It sets out the concepts, the definitions, the metrics, and proposes a set of maturity models to describe the quality of a dataset. Its focus is measuring, describing and, where possible, defining standards for what can be considered a 'fit for purpose' dataset. It aims to provide a coherent basis to identify, define and further develop DQ assessment procedures and recommendations for current and novel data types. The DQF dimensions, sub-dimensions and maturity models were presented. The main dimensions of quality outlined in the EU DQF are reliability, extensiveness, coherence, timeliness, and relevance. The EU DQF is applicable to all data used for regulatory purposes.

In the context of ADR reporting there are some points to consider. First of all, the applicability to non-EU data sources and alignment with other DQFs and opportunities for international convergence should be considered, as well as the heterogeneity of different EU systems. Secondly, guidance to implement a maturity model for different regulatory use cases would be beneficial. Thirdly, implications for system owners and data submitters should be well articulated. Moreover, precise measurements of DQ might not always be necessary: in relation to some uses, it might be sufficient to request descriptive documentation on data reliability and relevance. Lastly, primary use of data (data used for the initially designed purpose) is characterized by better control of DQ management, but the secondary use of ADR data (e.g., in the context of real-world data) should also be considered.

Session 2: Regulatory ADR Data Quality activities in Europe

Chair: Chair: Anja van Haren (MEB).

In this session, uses of ADR data, guidance and standards for human and veterinary safety reporting, common identified issues, and regulatory DQ activities were discussed from both EMA and NCA perspective. Tom Paternoster–Howe (EMA) and Laura Descalzo (EMA) presented the human and veterinary regulatory guidance on ADR reporting.
The data in EudraVigilance (EV) is highly heterogeneous: >99.7% of the data is submitted by ~3600 MAHs, NCAs and Sponsors. EMA is responsible for operating procedures to ensure the quality and integrity of the information collected in EV, in collaboration with NCAs and MAHs. To help stakeholders understand the processes the agency operates and to improve their own data quality, EMA published the Detailed guide regarding the EudraVigilance data management activities by the European Medicines Agency.(2) The systematic activities that EMA implements to promote DQ were summarised:

- Adherence to PhV legislation and regulatory guidance;
- Offering of hands-on training courses and the provision of e-learning modules;
- Pre-production testing with organisations preparing for the electronic submission of ICSRs to EV;

- Application of business rules in EV to assist an automatic validation against pre-defined parameters;
- Duplicate detection and management to address duplicated information of duplicated cases submitted by the same or different sender organisations.
- Validation of data submitted to the eXtended Medicinal Product Dictionary (XEVMPD);
- Automatic and manual reclassification of reported suspect or interacting medicinal product information against the XEVMPD to allow for reliable data retrieval and analysis;
- EV post-validation database-level checks to assess case validity and report retransmissions;
- Periodic review of ICSRs submitted by organisations to EV based on data sampling. The findings are classified as high impact (if they affect signal detection), medium impact (if they affect most common signal analysis) and low impact (if they are administrative/typographical findings);
- Compliance monitoring based on reporting timelines set out in the pharmaceutical legislation (PhV and clinical trials);
- Quality audits;
- Conduct of PhV inspections by competent authorities in Member States.

Laura Descalzo presented the systematic approach to improving DQ in EVVET:

- Automatic and manual reclassification of reported veterinary medicinal product information against the Union Product Database (UPD) to allow for reliable data retrieval and analysis;
- EV database-level checks to assess case validity and report retransmissions;
- Conduct of PhV inspections by competent authorities in Member States;
- Pre-production testing with organisations preparing for the electronic submission of ICSRs to EVVET;
- Application of business rules in EVVET to assist population of mandatory fields, and logical population of fields;
- Duplicate detection.

Human ADR reports are used in the following ways by EMA: signal detection and analysis; compliance monitoring; publication of data; non-serious line-listings for PSUR review; setting the submission frequency of PSURs. Veterinary AE reports are used in the following ways by EMA; signal detection and analysis; compliance monitoring; and publication of data.

Elena Rodionova (AGES) presented the perspective of the Austrian NCA. The NCA uses ADR data for routine PhV activities, namely data collection in a national collection system and reporting to EV, monitoring of the national ADRs, and signal detection for substances Austria is responsible for. Examples of DQ issues in signal management are incompleteness or limited quality of the reported cases, noise (duplicates, overreported cases, non-relevant information), data coded incorrectly or insufficiently structured in the pre-existing fields. DQ activities are in place for each of the ADR related activities that the NCA is responsible for. Also, PhV inspections are performed. Examples of common DQ inspection findings are: overreporting, underreporting (e.g. submission of non-valid cases which are then not accounted for), duplicate check ineffective, translation issues, insufficient/inadequate

follow-up, seriousness assessment, third country cases/partner cases not re-evaluated, and coding issues.

Kathrin Schirmann (BVL) presented DQ activities for AE data by the veterinary German NCA. The use of veterinary ADR data was described as well as the process for reporting pre-and post-EU regulation 2019/6. Common DQ issues include database incompatibilities, data entry errors, insufficient data coding, and incomplete case narratives. These DQ issues are handled by several actions: to inform and liaise with the MAH on the detected DQ issue, entry in the BVL internal list for record keeping, and entry in EU list (PhVWP-V DQ Subgroup was initiated to discuss DQ issues, draft solutions, and facilitate exchange to inspectors). Examples of DQ checks performed on all received reports were discussed, namely minimum data entry criteria, and completeness of case narrative.

Q&A

Different interpretations of underreporting were discussed, specifically a case where an MAH has received ADR information but doesn't submit it to EV as an ICSR, and an example of a primary source not informing NCAs or MAHs of a suspected ADR.

Session 3: Stakeholder ADR DQ activities in Europe

Chair: Elke Stahl (BfArM)

Jim Nickas (EUCOPE) presented the human medicines MAH perspective on practices to improve DQ in ADR reporting. Challenges in measuring and improving ADR DQ are underreporting and reporting biases (e.g. serious or newest reports more likely to be reported, difficult to estimate the true denominator), incomplete and inconsistent data, variations across data sources, signal detection challenges (to detect signals across the noise and also measuring the performance of signal detection algorithms is challenging), evolving data standards and practices, and lack of harmonisation at global level. Incomplete or inconsistent data is an important issue, so to communicate what makes a report "complete" should be part of the efforts to improve DQ. There are different ADR reporting routes which all have challenges. Addressing these challenges requires collaborative efforts among all stakeholders, such as harmonizing data standards, implementing quality control (QC) processes, integrating data from multiple sources, applying advanced analytical techniques and leveraging AI to help improve the measurement characterisation and overall quality of ADR data.

Zurab Koberidze (EUCROF) presents the Clinical Research Organisation (CRO) perspective on ADR DQ, in the context of solicited reports. At the study site, the variability in experience between employees is challenging for DQ assurance, which is managed by providing training, adequate plans and guidance. There could be discrepancies between the electronic data capture (EDC) system and the safety database, which is managed by implementing automatic checks, requesting approvals on critical steps, and reconciliation. For the safety group, who reviews data, the trial complexity can be an issue, as well as quickly adapting to regulatory changes. This is managed by handling a four-eye principle in case processing, standardized coding dictionaries, the use of templates, trainings, and company deviation

management. To improve DQ in the submission process, a four-eye principle or gateway submission is implemented. Potential technical solutions, such as AI or wearables, could play a role in improving DQ. However, the quality of the methodology should first be improved.

Magali Quetin (Animalhealth Europe) presented the view of the industry for veterinary medicinal products. The AE reports in animals are very diverse, it involves multiple species with different requirements for reporting, and special types of collected AEs. The reports are mainly spontaneous, usually triggered by customer care activities and often reported by animal owners, vet nurses or animal health technicians. It is challenging to have standardized rules for quality for the diversity of reports. Additionally, it should be considered that business drives the reporting, e.g. decrease in production performance (growth, milk production), and increase in mortality will trigger ADR reporting. Limitations to the system of AE reporting were discussed. The biggest challenge is the handling of duplicate reports which require communication between the different MAHs as the nullification is based on receipt date, requiring reconciliation to try to get the case as most complete as possible. Moreover, there is limited possibility for capturing details. Also, cases are not forwarded to other MAHs/NCAs, but manual download is required. In particular, it is challenging to report products used for diagnostic reasons and also when different products (from different MAHs) are administered at the same time. Only the case originator can submit follow-up, so additional information needs to be transferred outside the system. The (re-)coding of products can lead to wrong assignments of the product name and handling of third country products are difficult in the system. Lastly, different requirements from different agencies bring challenges as well. In conclusion, PhV practices need to be adapted to the veterinary business. The veterinary PhV teams are much smaller than in the pharmaceutical industry for human medicines. Also, the requirements of multiple agencies need to be accommodated with the same report. Any initiative on DQ for ADR reporting requires a harmonization at Veterinary International Conference on Harmonization (VICH) level.

Tuula Ikonen (EORTC) presented the ADR DQ activities of a non-commercial sponsor, with a focus on clinical trials. First it was discussed what DQ activities are performed: review of data, timeliness, and the correct functioning in the database. Specific DQ activities for SAEs are described, which include database validation, individual safety case quality reviews, QC of Development Safety Update Reports (DSUR) or Annual Safety Reports (ASR), reconciliation activities, QC of PhV documents in the Trial Master File, and data timeliness (receipt and query response and compliance with submission timelines). Furthermore, the specific approach of EORTC for safety DQ activities was highlighted. First, it is considered if a full quality check is required versus a risk-based approach. If the latter, the focus is on related cases e.g. SUSARs, SARs; fatal and life-threatening case reports; and DSURs. The priority is in high-risk trials and in new medicinal products. There are internal processes in place for DQ activities, such as process reviews and internal guidelines. From a technology point of view, it is moving towards automated checks, but findings require review and action management by experts. Important to consider, is that non-commercial sponsors are a diverse group of stakeholders with different operation modes (one center, national, with one or few investigators, vs. multi-center, international, network of investigators), protocols (single- vs multi-arm, in all phases, ranging from complex trials to pragmatic trials, different size of trials, with different data collection approaches), and multiple sources of funding. Non-commercial sponsors are not MAHs and have no commercial ownership of medicinal

products. The current situation with guidance for DQ activities, is that multiple guiding documents are available, but when it comes to details, it may take effort to translate guidance to operational activities. In terms of training of DQ activities, it is difficult to find suitable trainings for non-commercial sponsors.

Q&A

It is discussed to what extent AI is used by various stakeholders (NCAs, MAHs, EMA). In general, AI is not implemented yet, but its use is (cautiously) being investigated in multiple areas and pilots are ongoing.
The implementation of GDPR legislation complicated duplicate checking, and also impacts many aspects of the ADR reporting system because it results in difficulties of follow-ups and obtaining complete information. The legislation tends to result in over-implementation, where too much is redacted, even though it is not identifiable information.
Anne Tobin (HPRA) commented on the submission of reports for medical monitor cases, where there is a duplication of effort on behalf of the MAH for active substances that are covered by the EMA system.

Session 4: Panel discussion on high–quality ADR data

Chair/moderator: James Mount (SEMPA)

This session starts with an introduction by Tom Paternoster– Howe (EMA) on the challenges of recording, measuring, characterising, analysing, and improving ADR DQ. He presented a visualisation of the pipeline routes by which different organisations obtain and submit their ADR data to EV. For non-EEA ICSRs, the pipeline is long, and many stakeholders are involved: EMA can be the fifth or sixth step from the primary source. When EMA receives an ICSR, there are various unknowns: what was the source information? Is all the reported information in the case file? Is the sender permitted to include all reported information? Was it accurately entered? Was it correctly structured? How many copies of the same ADR are in different cases? Additionally, the scale of PhV makes it difficult to comprehensively assess DQ: EV receives ~10,000 ICSRs a day of ~5000 unique senders of ICSRs per year and there could be different ways to prioritise the assessments (e.g. risk-based). The EMA does not have the ability to change (non-master) cases in EV: the sender is the owner of the case and is the only one who can nullify or change it. Ergo, EMA must request senders to make changes, which can lead to concerns such as conflicting demands, company policies that clash with EMA requests, fear of messing with data from regulators, or the MAH has sold their product and has no longer access to these cases.

In this session, the panellists discussed how to tackle the challenges related to recording, measuring, characterising, analysing and improving ADR DQ. The panellists are introduced: Paolo Porcelli (AIFA, Inspector), Rodrigo Postigo (EMA, PhV Office), David Lewis (EFPIA), Magali Quetin (AnimalhealthEurope), Joop van Gerven (CCMO Committee), Boukje Raemaekers (WHO-UMC).

The first discussion is on the most significant challenges for organisations to address ADR DQ:

- Paolo Porcelli discusses the Inspector's point of view.
- From MAH perspective David Lewis summarized the biggest challenge as the medical integrity of the report, which must remain faithful to the source data.
- Joop van Gerven indicated that for an ethics committee and NCA, the biggest challenge is the quality of SUSARs reported by the primary source, because healthcare providers (HCP) are not used to having to structure their findings in the required reporting format which is unnatural to them, and MAHs have a fear to be incomplete or directive so send the maximum detail provided, which may mask the relevant insights to understand the case. It is questioned why the report of HCPs and MAHs should all be in one document.
- Magali Quetin added that the lack of harmony between Europe and other regions is a challenge in the veterinary industry, as well as the divergent preferences and interpretations between the agencies in Europe. A potential solution would be harmonization at VICH level.
- For UMC (Boukje Raemaekers) the most important challenge with DQ is missing information, either not reported at start or after follow-up, or lost in the journey (not intentional, or intentional to protect privacy for example when implementing GDPR).
- The view of the signal management group at EMA, presented by Rodrigo Postigo, faces duplicates as a large challenge given that reaching the threshold for detection is more likely. He suggested putting efforts into avoiding submission of those duplicates from the beginning. The main sources of duplicates are the literature and the publications of data by other regulators worldwide. Another challenge is the lack of information in the cases, which especially for signal validation is disappointing. It was also noted that patient support programme cases add numbers for the statistical signal detection perspective but they are not that useful from a validation perspective, as they normally do not contain full description of the events and diagnosis. In addition, follow-up information is very important and necessary, especially as it often provides more information on diagnosis, but can be challenging to get, emphasizing the importance of collecting as much information as possible at the first report. The narratives should always include follow-up information integrated in the narrative by correcting the information entered in the first version of the narrative that is not applicable anymore, instead of including one narrative after another once the follow-ups are received. Also, the narrative and electronic fields should be consistent, otherwise the case may be invalid from the analysis perspective as it is challenging to assess controversial information. Moreover, cases of drug interactions, medication errors, misuse, etc. are sometimes coded in MedDRA but the information in the case do not explain the issue . Lastly, the senders' comments which should reflect the MAH assessment, are taken into account when considering raising a signal, but the quality is sometimes insufficient. The senders' comments are sometimes very high level and do not differ much from other cases with different reactions, there is sometimes a tendency to consider almost everything confounded by the disease and the sender states that the case is not considered related without an explanation. A more in-depth discussion of the case and thoughtful consideration should be put in place, suggesting a better engagement of the MAHs with case assessment. David Lewis responded to Rodrigo Postigo that from a MAH perspective, follow-up can be difficult: he surveyed 1,000 literature articles, all 1,000 authors have been contacted for follow-up, but the MAH only received 3 replies. The follow-up is

approximately 30-40%, so the majority of cases are lost to follow-up. Magali Quetin added that for vets in the US, there is reimbursement for the efforts of providing follow-up, but this is not allowed in all countries.

- Joop van Gerven noted that there are large differences in the level of supported information. It ranges from highly detailed and sophisticated in early phase clinical trials, to poor quality in post-marketing registration PhV. It is unknown how this level of detail is accounted for in the analysis of an ADR report.

Q&A

Are there already regular interactions between authorities and stakeholders on DQ on the human side, apart from on individual case basis? Joop van Gerven answered that for The Netherlands this has been desired for years, but it is difficult because there are different organisations responsible for different parts of data collection. David Lewis contributed by highlighting an interaction between regulators across Europe and the industry, focusing on the potential value of social media case reports.
In terms of spontaneous reporting for human medicinal products, which message should be adopted: quantity or quality? Considering that a report is valid with only four minimum criteria, is this not an "open door" for low-quality reports? David Lewis responded that both quality and quantity is desired. Boukje Raemaekers agreed, mentioning that quality is necessary to evaluate a signal of disproportionate statistical reporting. Paolo Porcelli confirmed and added that with drugs that have been on the market for a long time, the focus should be mainly on quality.
Joop van Gerven asked, how much do we use information from medicines that never make it to the market? These often fail because of ADRs, so if those ADRs can be related to a pharmacological mechanism of action, or drug class, this can be highly relevant information to consider when assessing safety of marketed medicinal products.

Session 5: Key topics for the development of the ADR chapter of the Data Quality Framework

Discussion

Moderator: Anne Tobin (HPRA)

This session provided a voice to all participants, speakers, panellists, and listeners. It is focused on what should be the key elements of the ADR DQF chapter. The following questions were posed in the poll.

1. Do you think that the EU DQF ADR chapter should include a section on the impact of duplication of cases on PV databases? 96% of 68 respondents voted "yes".
2. Do you think that the EU DQF ADR chapter should link the processes detailed in ICH guidelines & GVP modules to the overarching DQF? 94% of 47 respondents voted "yes".
3. Do you think that the EU DQF ADR chapter should consider the different uses of ADR data separately? 41% of 54 respondents voted "yes", 48% voted "no", 11% voted "not sure".

4. My organisation has robust processes in place to ensure good quality ADR data. 28% of 54 respondents voted "strongly agree", 54% voted "agree", 17% voted "neither agree nor disagree", 2% voted "disagree", 0% voted "disagree strongly".
5. The ADR reports that I have seen from other organisations, would suggest that they apply robust processes to ensure good quality ADR data. 0% of 49 respondents voted "strongly agree", 16% voted "agree", 63% voted "neither agree nor disagree", 20% voted "disagree", 0% voted "disagree strongly".
6. Are you aware of the detailed guide regarding the EV data management activities by the EMA (https://www.ema.europa.eu/en/documents/other/detailed-guide-regarding-eudravigilance-data-management-activities-european-medicines-agency_en.pdf)?(2) 55% of 47 respondents voted "yes".
7. Do you perform database-level analysis of all of the ADRs you hold to search for systematic or frequent errors? 59% of 39 respondents voted "yes".
8. Do you agree or disagree with the following statement: MedDRA/VedDRA coding is a significant challenge regarding ADR DQ? 37% of 35 respondents voted "strongly agree", 26% voted "agree", 17% voted "neither agree nor disagree", 9% voted "disagree", 11% voted "disagree strongly".
9. How often do your ADR data entry staff receive MedDRA/VedDRA coding refresher training? 14% of 28 respondents voted "Every 6 months when a new version is released", 21% voted "Whenever the Term selection Points to Consider document is updated", 14% voted "Whenever there is a significant update to the Term selection Points to Consider document", 46% voted "Another predetermined frequency", 4% voted "Never".
10. Do you use a methodology for the classification of errors in ICSRs similar to that in Annex 1 of the Detailed guide? e.g. High: affects signal detection Medium: affects most-common signal analyses Low: administrative/typographical errors. 30% of 40 respondents voted "Yes – same as or similar to Annex 1", 25% voted "Yes – different to Annex 1 (please describe in the Webex chat)", 45% voted "No".

Q&A

Would a document with instructions to support consistent safety case processing be of interest to the EMA? EMA is working on a document that focusses on overall DQ practices, rather than on more granular details (e.g. how to code cases). However, it would be interesting to consider setting up such a document. David Lewis highlighted a paper by Van Stekelenborg, *et al.* (3) on a newly recognized phenomenon namely case replication: the same case is processed by 2-3 different companies resulting in different reports. On average, one patient report is replicated four times. As a result, case replication removal will also play an important role in DQ improvement.

Is there an analysis showing the main sources of duplicates? David Lewis explained that there are many causes for duplicates. One cause is that there can be multiple MAHs responsible for the same active substance (especially in literature cases where the brand name is not reported). Another cause is that submission of ADR reports by both patients, pharmacists, and HCPs, is actively encouraged resulting that the same case is reported by both the patient and the HCP.

Do you think the ADR DQF would benefit from a section related to the effects of GDPR? Anne notes that from a NCA point of view, while GDPR is welcomed, it does bring challenges in terms of increased redaction of information. In her opinion it would be helpful if the ADR DQF would describe this.
The integrity of the individual ICSR is brought forward as important topic in the DQF. David added that the Worldwide Case Unique Identifier is a crucial field and stressed that this should always be provided by the primary source. Also, information provided by the patient should be checked with an HCP. Tom Paternoster–Howe asked if WHO-UMC performs database (Vigibase) checks for inconsistencies within a case, Boukje Raemaekers answered that there is no process at this moment.

Closing remarks

Paolo Alcini (Head of Healthcare Data, EMA) ended the session with closing remarks and next steps. The workflow of developing a DQF chapter progresses in the following steps:

- review of existing practices, processes, documents on DQ in the given domain (landscape analysis);
- organisation of this workshop with stakeholders;
- drafting the document, which is expected by November 2024.

A public consultation on the EU DQF chapter is expected early 2025. After that, a final version of this ADR DQ chapter will be released. The valuable feedback provided in this workshop will enable EMA to draft a robust DQF chapter covering the whole landscape of ADRs and will help to establish a framework to support DQ of all stakeholders.

References

1. EMA. Data Quality Framework for EU medicines regulation. 2023.
2. EMA. Detailed guide regarding the EudraVigilance data management activities by the European Medicines Agency. 2020.
3. van Stekelenborg J, Kara V, Haack R, Vogel U, Garg A, Krupp M, et al. Individual Case Safety Report Replication: An Analysis of Case Reporting Transmission Networks. Drug Saf. 2023;46(1):39-52.

Post meeting notes

Conclusions

Key stakeholders

The pipeline for ADR reporting is long. The most important stakeholders in ADR DQ management are:

- Patients
- Healthcare professionals
- Researchers
- Regulators
- Medical coders
- Drug safety committees
- Pharmaceutical companies
- CROs
- Non-commercial sponsors

Important challenges

Important challenges related to measuring, characterising, and improving DQ include:

- The (medical) integrity of the individual ICSR: limited quality of documentation, including incomplete case narratives, data entry errors, incomplete use of structured fields, incomplete and inconsistent data, translation issues (with the use of automatic tools);
- Insufficient/inadequate follow-up;
- Noise (**duplicates**, overreported cases, underreporting, reporting biases);
- Missing/incorrect coding;
- Variations across data sources;
- Evolving data standards and practices.

Important challenges specific to veterinary AE reporting in EVVet include:

- Missing/incorrect coding of species/breed, active substance vs brand name, and VeDDRA coding
- Limited possibility for capturing details in the EVVet data model (e.g. concomitant products, diagnostic products);
- Cases not automatically forwarded to other stakeholders;
- Lack of harmony between Europe and other regions, and different requirements from different agencies.

Key topics in EU DQF ADR chapter

The scope of the EU DQF is to characterise DQ of any given dataset used for medicine regulation. It sets out the concept, the definitions, the metrics, and proposes a set of maturity models to describe the quality of a dataset. The chapter focussing on ADR reporting should place ADR DQ considerations in the context of the overall EU DQF. It should be assessed how the DQ dimensions and subdimensions

(presented in Session 1 of this workshop) can be best applied to the ADR data domain, also given the main challenges for ADR DQ, as listed above.

The EU DQF ADR chapter would benefit from including a description of the different ADR reporting pipelines and activities of stakeholders, including (S)AE/ADR reports from clinical trials and ADR reporting from EV post-marketing modules (spontaneous reports of suspected ADRs and solicited reports). Additionally, the chapter should link the processes detailed in legislation and guidance (ICH guidelines & GVP modules), as presented in Session 2 of this workshop, to the overarching EU DQF.

There are several points to consider when focussing on ADR reporting DQ in this chapter:

- The applicability to non-EU data sources and alignment with other DQFs and opportunities for international convergence, as well as the heterogeneity of different EU systems.
- Guidance to implement a maturity model for different regulatory use cases (including signal detection, study of safety in clinical trials prior to authorisation, study of safety in the context of observational studies).
- Implications for system owners and data submitters.
- Precise measurements of DQ might not always be necessary: in relation to some uses, it might be sufficient to request descriptive documentation on data reliability and relevance.
- Primary use of data is characterized by better control of DQ management, but the secondary use of ADR data (e.g., in the context of real-world data) should also be considered.

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List of abbreviations

Abbreviation	Definition
(S)AE	(Serious) Adverse event
ADR	Adverse Drug Reaction
AI	Artificial intelligence
AIFA	Italian Medicines Agency
AGES	Österreichische Agentur für Gesundheit und Ernährungssicherheit GmbH
AEMPS	Spanish Agency of Medicines and Medical Products
ASR	Annual safety report
BfArM	Federal Institute for Drugs and Medical Devices
BVL	Federal Office of Consumer Protection and Food Safety
CCMO	Central Committee on Research Involving Human Subjects
QC	Quality Control
CRO	Clinical Research Organisation
CTCG	Clinical Trials Coordination Group
DQ	Data quality
DSUR	Development Safety Update Reports
EU DQF	European Data Quality Framework
EMA	European Medicines Agency
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMRN	European Medicines Regulatory Network
EORTC	European Organisation for Research and Treatment of Cancer
EUCOPE	European Confederation of Pharmaceutical Entrepreneurs
EUCROF	European CRO Federation
EV	EudraVigilance
EV EWG	EudraVigilance Expert Working Group
HCP	Healthcare Professional
HPRA	Health Products Regulatory Authority
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
NCA	National Competent Authority
PhV	Pharmacovigilance
PhV BT	Pharmacovigilance Business Team
PhV WP	Pharmacovigilance Working Party
PSUR	Periodic Safety Update Report
SEMPA	Swedish Medical Products Agency
XEVMPD	eXtended Medicinal Product Dictionary
WHO -UMC	World Health Organization, Uppsala Monitoring Centre