HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guidance, standards, EMA Data Quality activities and uses of ADR data

Human and Veterinary

Presented by Tom Paternoster-Howe & Laura Descalzo on 1 March 2024
TDA-HCD & V-SR-PHV

Contents

Guidance

- Human ADR Guidance
- Veterinary AE Guidance

Standards

- Human standards for ICSR creation and transmission
- Veterinary standards for AE creation and transmission

EMA ADR data quality activities

- Human ADR data quality activities
- Veterinary AE data quality activities

EMA uses of ADR data

- Human uses of ADR data
- Veterinary uses of AE data

Guidance

Legislation & guidance concerning ADRs

Legislation relating to human ADRs and data quality

The following legislation governs the reporting of human ADRs within the EEA:

- Regulation (EC) No 726/2004
  - Establishing Eudravigilance, requiring medicinal product information submission
  - Requires EMA to operate "procedures that ensure the quality and integrity of the information collected in the Eudravigilance database" in collaboration with senders of ICSRs
- Directive 2001/83/EC
  - Concern post-marketing ADRs from MAHs and NCAs and PV systems
- Commission Implementing Regulation (EU) No 520/2012
  - Includes minimum requirements for the quality systems for the performance of PV activities, transmission of reports of suspected adverse reactions, use of international standards and formats
- Regulation EU No 536/2014 (Clinical Trials Regulation)
  - Governs safety reporting in the context of a clinical trial

Legislation relating to veterinary AEs and data quality

The following legislation governs the reporting of veterinary AEs within the EEA:

- Regulation (EU) 2019/6 on veterinary medicinal products
  - Establishing Union Pharmacovigilance database for reporting and recording of suspected adverse events, interconnected with Union product database for medicinal product information submission
- Commission Implementing Regulation ((EU) 2021/1281)
  - Includes minimum requirements for the quality systems for the performance of PV activities, transmission of reports of suspected adverse reactions, use of international standards and formats

Guidance relating to human ADR data quality

Good pharmacovigilance practices (GVP) are a set of measures drawn up to facilitate the performance of PV in the EU. GVP apply to MAHs, EMA and NCAs in EU MS. They cover both centrally and nationally authorised medicines

Key modules related to ADR reporting & data quality include:

- GVP Module I – Pharmacovigilance systems and their quality systems
- GVP Module III – Pharmacovigilance inspections
- GVP Module IV – Pharmacovigilance audits
- GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products
  - Including Addendum I – Duplicate management of suspected adverse reaction reports

SUSAR guidance is provided in the Communication from the Commission — Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3')

Guidance relating to veterinary AE data quality

Veterinary good pharmacovigilance practices (VGVP) are a set of measures drawn up to facilitate the performance of PV in the EU. VGVP apply to MAHs, EMA and NCAs in EU MS. They cover both centrally and nationally authorised medicines

Key modules related to suspected adverse event reporting & data quality include:

- Collection and recording of suspected adverse events for veterinary medicinal products (VGVP)
  - Including Appendix – EVV Best practice guide, EU VICH adverse event report implementation guide, VeDDRA
- Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files (VGVP)
- Controls and pharmacovigilance Inspections (VGVP)

Standards

Standards governing the collection, recording & transmission of human ADR reports in the EEA

There are two main standards organisations whose standards govern pharmacovigilance & ADR reports in the EEA:

- ICH – International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
- ISO – International Standards Organisation

Other related standards organisations whose work has contributed to the development of the standards include:

- CIOMS – Council for International Organizations of Medical Sciences
  - CIOMS I form
- HL7 – Health Level 7 International
  - Fast Healthcare Interoperability Resources Specification (FHIR)

Standards governing the collection, recording & transmission of human ADR reports in the EEA

ICH standards directly related to ADR reporting:

- M1: MedDRA Terminology
- E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting
- E2B(R3): Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety reports (ICSRs)
- E2D: Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting

Other ICH standards related to ADR reporting:

- E6(R2): Good Clinical Practice
- E19: Safety Data Collection

Standards governing the collection, recording & transmission of human ADR reports in the EEA

ISO standards directly related to ADR reporting:

- EN ISO 27953-2:2011 Health Informatics, Individual case safety reports (ICSRs) in pharmacovigilance — Part 2: Human pharmaceutical reporting requirements for ICSR

ISO standards related to medicinal products (incorporated in ADR reporting):

- 5 Standards under the heading of "Health Informatics, Identification of Medicinal Products (IDMP) standard", covering the data elements and structures for unique identification and exchange of:
  - regulated medicinal product information, regulated pharmaceutical product information, regulated information on substances, regulated information on pharmaceutical dose forms, units of presentation and routes of administration and units of measurement
  - These are not yet implemented – presently xEVMPD is product standard & EDQM for dose forms, units, routes of administration

Standards governing the collection, recording & transmission of veterinary AE reports in the EEA

There are two main standards organisations whose standards govern pharmacovigilance & AE reports in the EEA:

- VICH – International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
- ISO – International Standards Organisation

Other related standards organisations whose work has contributed to the development of the standards include:

- HL7 – Health Level 7 International
  - Fast Healthcare Interoperability Resources Specification (FHIR)

Standards governing the collection, recording & transmission of veterinary AE reports in the EEA

VICH standards directly related to AE reporting:

- VICH GL24: Pharmacovigilance of veterinary medicinal products: management of adverse event reports (AERs)
- VICH GL29: Pharmacovigilance: VICH Step By Step Document
- Revised VICH GL35: Pharmacovigilance of Veterinary Medicinal Products: Electronic Standards for Transfer of Data
- Revised VICH GL42: Pharmacovigilance of Veterinary Medicinal Products: Data Elements for Submission of Adverse Events Reports (AERs)

EMA ADR Data Quality Activities

EMA human ADR data quality activities

The data in EudraVigilance is highly heterogenous

- >99.7% of the data in EudraVigilance is submitted by ~3,600 MAHs, NCAs and Sponsors

The Agency is responsible for operating procedures that ensure the quality and integrity of the information collected in EV (Reg 726/2004, Art 24(3)) in collaboration with NCAs & 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

Systematic approach to improving data quality

Consistent, complete, correct and well-structured information submitted in ICSRs and to the XEVMPD is one area of the operation of a quality system and is necessary to perform PV monitoring and evaluation activities including signal detection. These quality assurance activities can be summarised as follows:

a. Adherence to pharmacovigilance legislation and regulatory guidance;
b. Offering of hands-on training courses and the provision of e-learning modules;
c. Pre-production testing with organisations preparing for the electronic submission of ICSRs to EudraVigilance;
d. Application of business rules in EudraVigilance to assist an automatic validation against pre-defined parameters;
e. Duplicate detection and management to address duplicated information of duplicated cases submitted by same or different sender organisations;

Systematic approach to improving data quality

f. Validation of data submitted to the eXtended Medicinal Product Dictionary (XEVMPD) in accordance with Article 57(2) of Regulation (EC) No 726/2004;

g. Automatic and manual reclassification of reported suspect or interacting medicinal product information against the XEVMPD to allow for reliable data retrieval and analysis;

h. EV post-validation database-level checks to assess case validity and report retransmissions;

i. Periodic review of ICSRs submitted by organisations to EudraVigilance based on data sampling;

j. Compliance monitoring based on reporting timelines set out in the pharmaceutical legislation (pharmacovigilance and clinical trials);

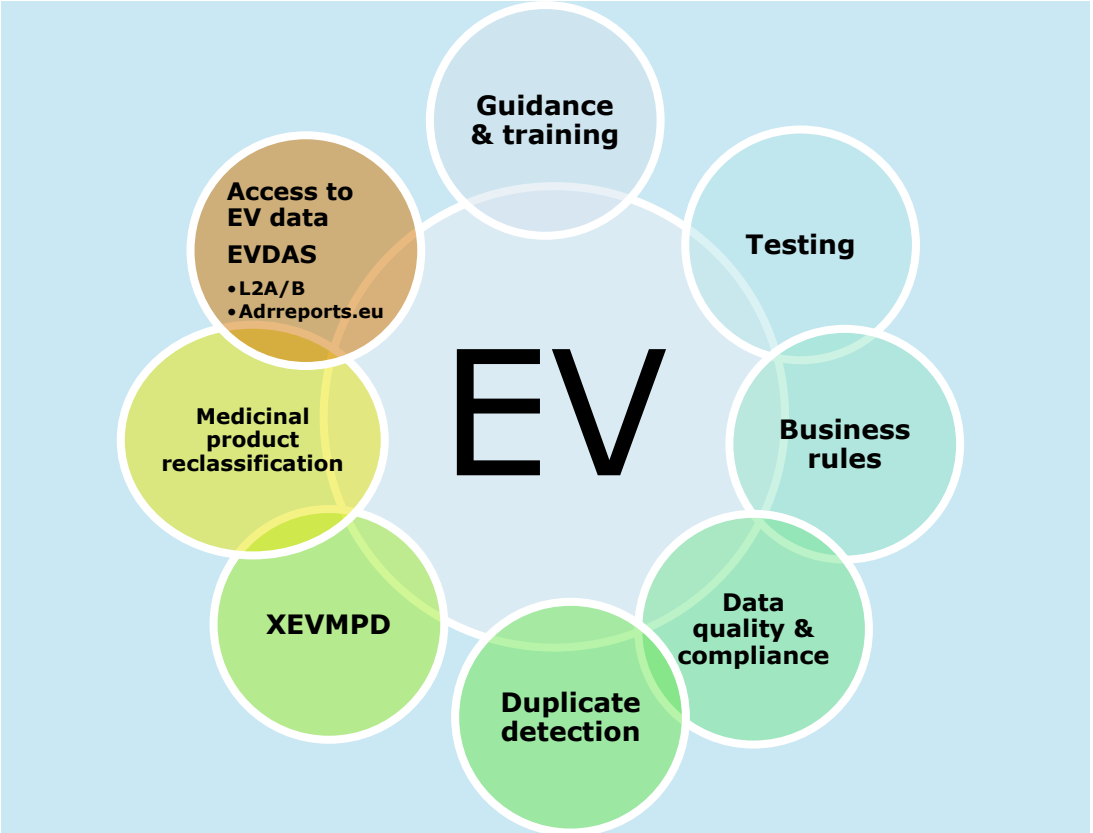
k. Quality audits;

l. Conduct of pharmacovigilance inspections by competent authorities in Member States.

These QA activities are summarised on the next slide and the points c-i described in the document

Elements of the systematic approach to improving data quality

The overlapping circles represent overlapping processes which significantly rely on each other



Pre-production testing

Cases and products transmitted to EV can be created one of two ways:

- Using the organisation's own database (or that of a CRO)
- Using EVWEB

If the organisation is using their own database, before they are granted permission to transmit to EV they have to prove that their database is compliant with the ICH E2B standard (either R2 or R3)

- This is done through the perfect transmission of test cases devised by the EMA to ensure every data field and case type is checked

If the organisation is using EVWEB, then at least one member of their staff has to take the face-to-face EV training course and pass the final exam

Business rules

Demonstrating compliance with ICH E2B(R2) or (R3) standards during testing does not mean that all cases created using a particular database will be correct

Ergo every ICSR transmitted to EV is automatically assessed by the EV parsers against the EV business rules before being loaded into EV and an ACK returned to the sender

EV Business rules cover the following:

- Population of mandatory fields
  - Including data type & field length
- Logical population of fields
  - No future dates, contextual mandating of fields e.g. if reaction is fatal, death section is mandatory

If an ICSR fails the business rules, it is excluded from all PV activities and queries

- Additionally, the expedited compliance clock doesn't stop until a successful ICSR is submitted

Duplicate detection

Duplication of cases in EV can lead to false-positive signals, wasting assessors time, and can also mask true signals. Therefore the Agency detects and merges identified duplicate cases to ensure that each ADR is counted once in EVDAS

The process can be summarised as follows:

1. Duplicate detection algorithms assess all the cases in the database for potential duplication;
2. The potential duplicates are assessed;
3. If duplication is confirmed, a master case is made and transmitted to EV.

The master case is the version of the case used for PV, whilst underlying duplicates remain live in the database for original senders to transmit follow-up & for compliance and audit purposes

Reclassification of products & substances reported in ICSRs

Drug and substance names in ICSRs are NOT based on controlled vocabulary. They are free-text and only the presence of any text in 'Drug name' field (ICH E2B(R3) G.k.2.2) is sufficient for a case to pass business rules

In order to provide usable pharmacovigilance data and to make data available to MAHs and the public, this free-text data needs to be first normalised and reclassified against data from the eXtended EudraVigilance Medicinal Product Dictionary (xEVMPD) and then subsequently grouped by active substance

- Automatic reclassification attempted first overnight on all cases received from 18.00 the previous day until 18.00 that day.
- >99% of drugs/substances successfully automatically reclassified. If drug/substance fails automatic reclassification, then sent for manual reclassification

Database level queries

GVP Module VI sets out 4 minimum criteria for a case to be valid:

a. One or more identifiable reporter;
b. One single identifiable patient;
c. One or more suspected substance/medicinal product;
d. One or more suspected adverse reaction.

Every one of these elements can be populated in order to make a case appear valid even when the sender lacks the relevant information to make the case valid. This may mask true signals by inflating the denominator used in ROR (and similar) calculations

- Examples: Patient initials populated only with “UNKNOWN” or MedDRA LLT “Adverse event” entered as reaction

EMA has created queries to identify such cases within EV

Periodic individual case review

In addition to the database level queries, periodic reviews of samples of ICSRs are performed by the EMA, based on the parameters for the content of an ICSR as set out in Article 28 of the Commission Implementing Regulation (EC) 520/2012

Process can be summarised as follows:

- 10-20 senders selected for assessment each month
- 10-25 recent cases from sender selected, including variety of different case types
- Agency prepares report
  - Findings classified as high impact, medium impact, low impact depending on effect of error on PV activities
    - High: affects signal detection. Medium: affects most common signal analyses. Low: administrative/typographical
- Sender organisation to fix cases, implement CAPA, comment on report
  - If apparently erroneous data entry was justified and not an error, then EMA will amend the report

Systematic approach to improving data quality

Consistent, complete, correct and well-structured information submitted in ICSRs and to the XEVMPD is one area of the operation of a quality system and is necessary to perform PV monitoring and evaluation activities including signal detection. These quality assurance activities can be summarised as follows:

- Adherence to pharmacovigilance legislation and regulatory guidance;
- Pre-production testing with organisations preparing for the electronic submission of AEs to EudraVigilance;
- Application of business rules in EudraVigilance to assist an automatic validation against pre-defined parameters;
- Duplicate detection and management to address duplicated information of duplicated cases submitted by same or different sender organisations;

Systematic approach to improving data quality in EVVET

- Automatic and manual reclassification of reported veterinary medicinal product information against the UPD to allow for reliable data retrieval and analysis;
- EudraVigilance database-level checks to assess case validity and report retransmissions;
- Conduct of pharmacovigilance inspections by competent authorities in Member States.
- QA activities are summarised on the next slides

Pre-production testing

Cases and products transmitted to EVVET can be created one of two ways:

- Using the organisation's own database (or that of a CRO)
- Using EVWEB

If the organisation is using their own database, before they are granted permission to transmit to EVVET they have to prove that their database is compliant with the VICH standards.

- This is done through the correct transmission of test cases devised by the EMA to ensure that data fields and case types are checked

Business rules

Demonstrating compliance with VICH standards during testing does not mean that all cases created using a particular database will be correct

Ergo every AE transmitted to EVVET is automatically assessed by the EV parsers against the EVVET business rules before being loaded into EV and an ACK returned to the sender

EV Business rules cover the following:

- Population of mandatory fields
  - Including data type & field length
- Logical population of fields
  - No future dates, contextual mandating of fields
  - If an AE fails the business rules, it is excluded from all PV activities and queries

Reclassification of products & substances reported in AEs

Product and substance names in AE can be submitted as controlled vocabulary or as free-text, and just the presence of any text in 'Registered Name or Brand Name' field (B.2.1) is sufficient for a case to pass business rules

In order to provide usable pharmacovigilance data and to make data available to MAHs and the public, this free-text data needs to be first normalised and reclassified against data from the Union Product Database (UPD)

- Automatic reclassification attempted first overnight on all cases.
- If drug/substance fails automatic reclassification, then sent for manual reclassification

Duplicate detection

Duplication of cases in EVVET can lead to false-positive signals, wasting assessors time, and can also mask true signals. Therefore the Agency detects and merges duplicate cases to ensure that each AE is counted once in EVVET DWH

The process can be summarised as follows:

1. Duplicate detection algorithms assess all the cases in the database for potential duplication;
2. The potential duplicates are assessed;
3. If duplication is confirmed, one of the reports is designated as the principal report and the other marked as the duplicate.

The principal report is the version of the case used for PV, whilst underlying duplicates remain live in the database for audit purposes. Process related to follow-up to duplicate reports currently being defined.

EMA uses of ADR data

EMA uses of ADR data

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
- Publication of data

Any questions?

Further information

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Telephone +31 (0)88 781 6000
Send us a question Go to www.ema.europa.eu/contact

Follow us on **@EMA_News**