

The European System for Monitoring Drug Safety, EudraVigilance

(Version 1.0)

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ABSTRACT

Monitoring the safety of medicinal products before and after they receive marketing authorisation is a top priority for regulators and pharmaceutical industry. The new European pharmaceutical legislation makes electronic reporting of adverse drug reactions mandatory from November 2005. In 2001 the European Medicines Agency put in place a system to be used by pharmaceutical industry and national regulators to electronically transmit safety reports in an internationally agreed exchange format, E2B. This system, called EudraVigilance has been continuously improved and extended since. It consists of a secure electronic gateway, a transactional database where all safety reports are stored, a medicinal product dictionary, a pilot data warehouse, and a business intelligence part for reporting and analysing the safety reports received. In addition, two options are provided to national regulators and pharmaceutical companies to send electronic reports to the EudraVigilance system.

After a brief review of the legal basis this paper will describe the functionalities and the architecture of the EudraVigilance system. It will explain the flow of data and their analysis. Finally it will give an outlook over future developments, and in particular, the role of SAS® software for data analysis.

INTRODUCTION

The history of pharmacovigilance is closely linked to the history of drug safety crises. With each crisis, the public and the media have demanded, and the legislators and regulators have provided, improved safety monitoring. The media and the public appear to expect zero-risk medicines. In the real world, zero risk medicines do not exist. For each new drug presented to the regulators for approval, the potential benefits for public health need to be balanced against known safety risks. Information on safety risks at the moment of approval comes from pre-clinical and more importantly, clinical data originating from clinical trials. As the time intervals and the number of patients involved in clinical trials are necessarily limited, the benefit risk balance must be continuously monitored after authorising a new medicinal product. The new medicines legislation also explicitly provides for risk management plans to be submitted by the applicants for marketing authorisation.

It is therefore essential that we have in place systems which will allow us to collect, validate, store and process reports on adverse drug reactions for investigational and authorised medicinal products. The better the data quality and the larger the number of such reports received and processed the earlier will significant signals be detected. In view of the number of adverse drug reactions reported, this has to be carried out using modern tools of information and communications technology.

THE LEGAL REQUIREMENTS

The European legislator created a legal basis for a European database for adverse drug reactions, initially through Regulation 2309/93. This was reinforced through the review of the regulation of pharmaceuticals in the EU, Regulation 726/2004. The legal requirement to electronically report suspected unexpected serious adverse reactions resulting from clinical trials is contained in the Clinical Trials Directive, 2001/20/EC.

1. Council Regulation (EEC) No. 2309/93 as amended

In accordance with **Council Regulation (EEC) No 2309/93** as amended, the EMEA set up a data-processing network and a pharmacovigilance database referred to as EudraVigilance. The provisions are as follows:

▪ **Article 24 (and Article 46)**

The Agency, in consultation with the Member States and the Commission, **shall set up a data-processing network** for the rapid transmission of data between the competent Community authorities in the event of an alert relating to faulty manufacture, serious adverse reactions and other pharmacovigilance data regarding medicinal products marketed in the Community.

- **Article 51, paragraph c**

To this end, the Agency shall undertake the following tasks within its Committees:

The co-ordination of the supervision, under practical conditions of use, of medicinal products which have been authorized within the Community and the provision of advice on the measures necessary to ensure the safe and effective use of these products, in particular by evaluating and making available through **a database information on adverse reactions** to the medicinal products in question (pharmacovigilance).

2. Council Regulation (EC) No 726/2004

With regard to **Regulation (EC) No 726/2004**, the data-processing network and the pharmacovigilance database are referred to as follows:

- **Article 26**

The Agency, in consultation with Member States and the Commission, **shall set up a data-processing network** for the rapid transmission of information to the competent Community authorities in the event of an alert relating to faulty manufacture, serious adverse reactions and other pharmacovigilance data regarding medicinal products authorised in accordance with Article 6 of Directive 2001/83/EC. Such data shall be made publicly accessible, if relevant, after evaluation.

- **Article 57, paragraph d**

Ensuring the dissemination of information on adverse reactions to medicinal products authorised in the Community, by means of a database permanently accessible to all Member States; health-care professionals, marketing authorisation holders and the public shall have appropriate levels of access to these databases, with personal data protection being guaranteed.

3. Directive 2001/20/EC

With regard to **Directive 2001/20/EC**, the provisions for a clinical trial database are as follows:

Article 11, paragraph 1

Member States in whose territory the clinical trial takes place shall enter in **a European database**, accessible only to the competent authorities of the Member States, the Agency and the Commission:

Article 11, paragraph 3

In consultation with the Member States, the Commission shall draw up and publish detailed guidance on the relevant data to be included in this **European database, which it operates with the assistance of the Agency**, as well as the methods for electronic communication of the data. The detailed guidance thus drawn up shall ensure that the confidentiality of the data is strictly observed.

- **Article 17, paragraph 3**

Each Member State shall see to it that all suspected unexpected serious adverse reactions to an investigational medicinal product which are brought to its attention are immediately entered in **a European database** to which, in accordance with Article 11(1), only the competent authorities of the Member States, the Agency and the Commission shall have access. The Agency shall make the information notified by the sponsor available to the competent authorities of the Member States.

IMPLEMENTATION OF THE LEGAL REQUIREMENTS

The various legal requirements lead to the following reporting obligations and paths:

1. Investigational Medicinal Products, IMP

Suspected unexpected serious adverse reactions resulting from clinical trials must be reported by the sponsor of the trial to the National Competent Authority (NCA) of the Member State on whose territory the event occurred. It is the responsibility of the National Competent Authority to electronically report the event to the EudraVigilance system. If the event occurred outside the EEA, the sponsor must report the event electronically to the EudraVigilance system. The EudraVigilance Gateway will route the event to the National Competent Authorities.

2. Authorised Medicinal Products

Serious adverse drug reactions to authorised medicinal products must be reported to the EEA Member State on whose territory the event occurred. It is the responsibility of the National Competent Authority to electronically report the event to the EudraVigilance system.

If the event occurred outside the EEA, the marketing authorisation holder must report the event electronically to the EudraVigilance system. The EudraVigilance gateway will route the event to the National Competent Authorities.

If the adverse reaction to an authorised medicinal product results from a post-authorisation clinical trial, the sponsor of that trial is obliged to report the event electronically either to the National Competent Authority if the event occurred on the territory of a Member State, or directly into EudraVigilance, if it happened outside the EEA. As for the other cases, the EudraVigilance Gateway will route events electronically reported by sponsors to the National Competent Authorities.

3. Implementation Issues

The wording of the legal reporting obligations leaves some room for discussions. Pharmaceutical industry and some National Competent Authorities have questioned the need to report a minimum set of product information for inclusion in the EudraVigilance Medicinal Product Dictionary, EVMPD. This problem has been resolved through the conclusion of data exchange agreements with reporting partners.

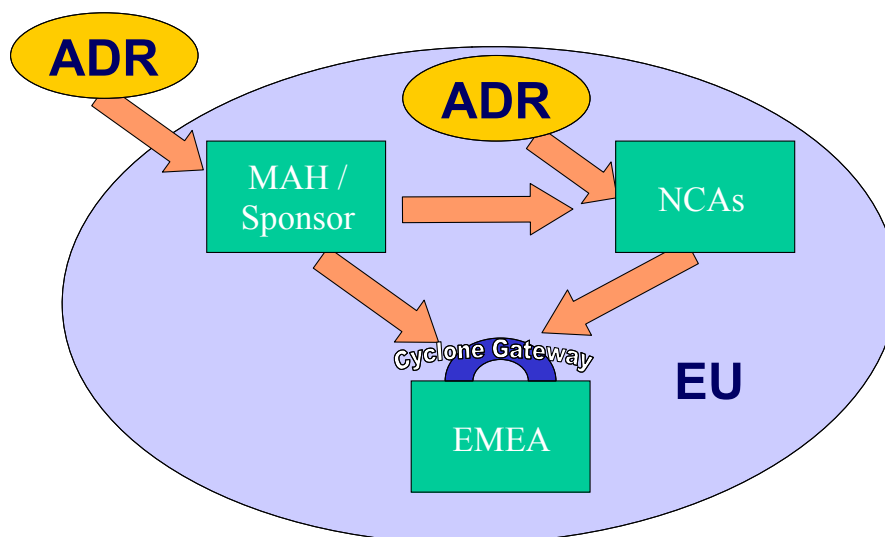


Figure 1: Who Reports What to Whom?

INTERNATIONAL STANDARDS

Drug safety problems are of a global nature. It therefore makes a lot of sense to exchange information about adverse events between the different regions. In 1990, an international body was created, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH. It brings together regulatory authorities from Europe, Japan, and the United States and experts from the pharmaceutical industry in the three regions. Its technical expert working groups have created a number of standards for secure electronic exchange of messages, files and structured data (EDI):

- ICH ESTR1 Gateway: Electronic Standards for the Transfer of Regulatory Information, covering physical media, networks, security, and data interchange formats, and particularly addressing the requirements for confidentiality, integrity, authenticity and non-repudiation.
- ICH E2B message content and format for data elements for transmission of individual case safety reports.
- ICH M5 message content and format for data elements for transmission of essential drug dictionary information required for safety reports

AN OVERVIEW OF THE EUDRAVIGILANCE SYSTEM(S)

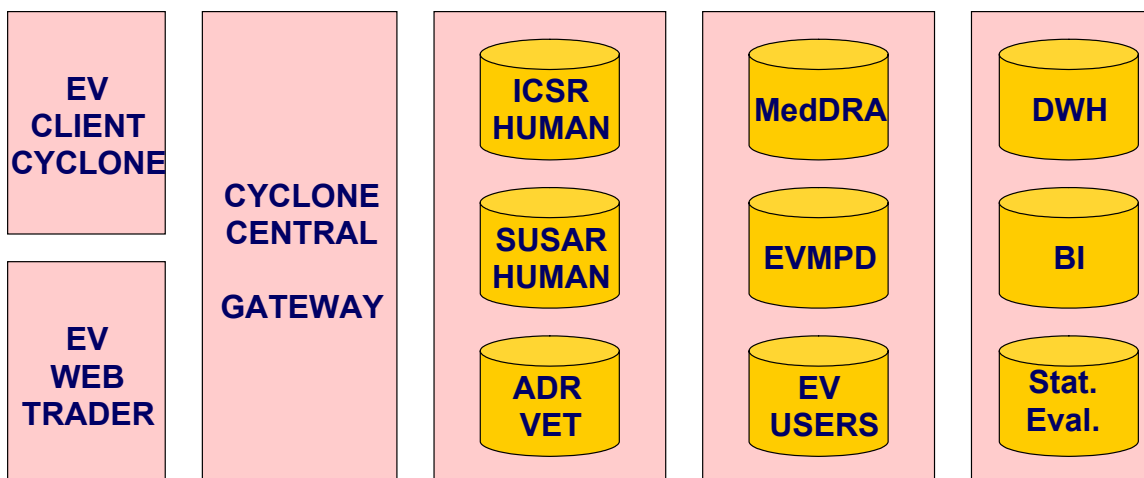


Figure 2: The High-Level Building Blocks of EudraVigilance

EudraVigilance is the European data-processing network and database management system for the exchange, processing and evaluation of safety reports related to authorised and investigational medicinal products in the European Economic Area (EEA).

EudraVigilance is a key component in supporting the European Medicines Agency (EMA) within its Committees in the co-ordination of the supervision, under practical conditions of use, of medicinal products which have been authorised or are being investigated in clinical trials within the European Community, and the provision of advice on the measures to ensure the safe and effective use of these products, in particular by evaluating and making available through a pharmacovigilance database information, on adverse reactions to the medicinal products in question.

EudraVigilance also provides the EEA with a data-processing network for the rapid transmission of safety information between the National Competent Authorities (NCA) in the event of an alert relating to faulty manufacture, serious adverse reactions, and pharmacovigilance data regarding medicinal products marketed in the Community.

The web-based information system is designed to handle the safety report information in full compliance with EU legislation and international specifications (e.g. ICH) featuring:

- Integrated organisation and user management synchronised with the EudraVigilance Gateway profile management
- A fully automated safety and message processing mechanism, using XML-based messaging, supporting both asynchronous data interchange and interactive transactions
- A large reference pharmacovigilance database, that is built by importing and consolidating data from multiple sources, including information on medicinal products and adverse drug reactions
- Extensive query and tracking/tracing capability, both from a scientific and administrative business perspective

The EudraVigilance system is based on a three-tier, light-client based architecture offering remote access to administrative and scientific users in the European Commission, the EMA, Competent Authorities in the EEA and pharmaceutical companies via a secure connection over the Internet.

There is a version of the EudraVigilance system processing medicinal products for human use and one processing products for veterinary use. Both systems are quite similar. In the remainder of this document, we will not distinguish between the two systems. The generic term “safety report” will be used to refer to an individual case safety report (ICSR), a suspected unexpected serious adverse reaction (SUSAR) report or a veterinary adverse drug reaction (ADR) report.

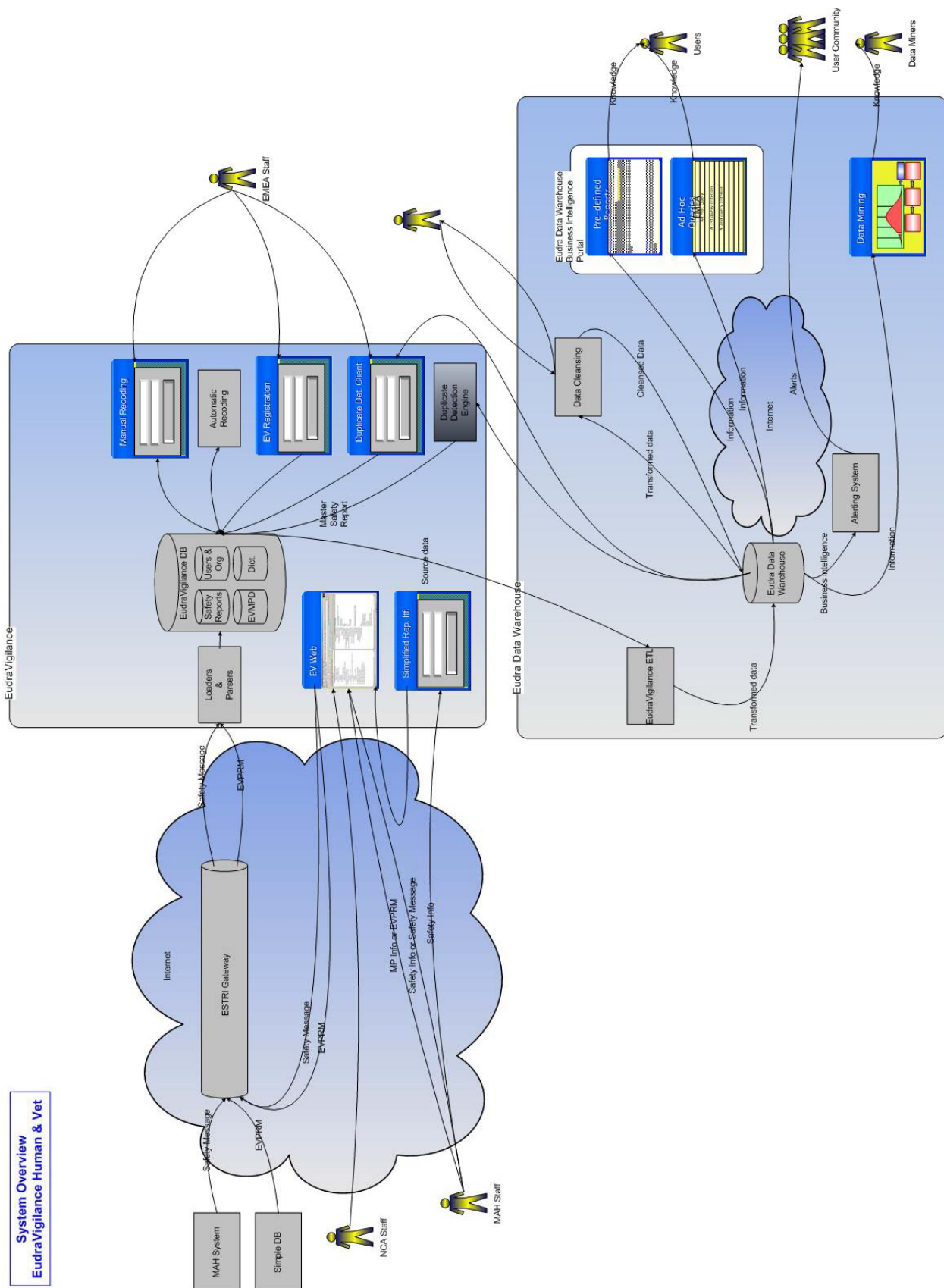


Figure 3: System Overview of EudraVigilance

EUDRAVIGILANCE SAFETY REPORT DATABASE

This database contains all ICRS (1, 2) and SUSARs (3, 4) sent to EudraVigilance.

USER AND ORGANISATION DATABASE

Before being allowed to use EudraVigilance, organisations and users have to be registered within EudraVigilance.

This database contains information on all registered:

- National Competent Authorities
- Regional pharmacovigilance centres
- Marketing authorisation holder
- Affiliates of marketing authorisation holders
- Individual users of the organisations

EUDRAVIGILANCE MEDICINAL PRODUCT DICTIONARY (EVMPD)

The EudraVigilance Medicinal Product Dictionary (EVMPD) has been designed to support in a standardised and structured way the collection, reporting, coding and evaluation of data on authorised medicinal products (1, 1) and investigational medicinal products (3, 4).

The EVMPD offers:

- A distributed and common approach for data collection through user-friendly and easy accessible software solutions available free of charge for pharmaceutical companies
- Integrated standard terminology to code e.g. active ingredients, excipients, pharmaceutical forms, routes of administrations, concentration ranges and units, country codes, marketing authorisation holders and sponsors
- A hierarchical data structure accommodating coding requirements in pharmacovigilance to reliably capture product information in safety reports taking into account the possible vagueness of the reported data by the primary source
- A hierarchical, multi-axial data structure to support scientific data analysis of medicinal product data and grouping of data based on ingredients, strengths and pharmaceutical forms
- Automated data import and systematic workflow with integrated quality control and audit checks
- A standardised XML schema to support the collection and exchange of structured medicinal product information
- Defined data ownership ensuring controlled data update through the respective product owner
- A standardised approach to support updates, variations and withdrawals to medicinal product through the defined responsible product owner
- Traceable and auditable regulatory changes to product information (recording of medicinal product history)

OTHER DICTIONARIES

EudraVigilance contains other dictionaries:

- **MedDRA:** MedDRA is the Medical Dictionary for Regulatory Activities. It was developed in the frame of the ICH M1 activities as a clinically validated international medical terminology for regulatory authorities, and is maintained by the MedDRA's Maintenance and Support Services Organisation (MSSO). MedDRA is used by regulators and pharmaceutical industry for data entry, retrieval, evaluation and presentation during all phases of the drug regulatory process i.e. the pre- and post-authorisation phase. These processes include clinical studies, reports of spontaneous adverse reactions, events, regulatory submissions and regulated product information.
- **VEDDRA**
- **Routes of Administration**
- **Dosage Units**
- **Pharmaceutical forms**
- **ATC**
-

ESTRI GATEWAY

The EMEA has implemented an electronic regulatory submission environment, the EudraVigilance Gateway, which follows the ICH M2 Gateway Recommendation for the Electronic Transfer of Regulatory Information (ESTRI-Gateway).

The purpose of the EudraVigilance Gateway is to operate a single, common, European Economic Area (EEA)-wide Gateway for receiving regulatory information in a fully automated and secure way including all aspects of privacy, authentication, integrity and non-repudiation of all transactions.

The EudraVigilance Gateway allows the pharmaceutical industry to report to a common reporting point within the EEA from where the transactions are re-routed to the addressed Competent Authorities and the EMEA. It provides the Competent Authorities with a secure reporting mechanism to the pharmaceutical industry and to the EMEA. The pharmaceutical industry (i.e. marketing authorisation holders and sponsors) is responsible for implementing at least one of the multiple ESTRi standards in order to ensure electronic communication with any Regulatory Authority

The EudraVigilance Gateway supports two transmission modes:

- The Gateway transmission mode
- The Web Trader transmission mode

The Gateway transmission mode refers to an organization that has a fully ICH compliant pharmacovigilance database available, which permits the generation and receipt of safety reports and the electronic transmission of safety reports via a local gateway solution that meets the ICH M2 standards and that has been successfully tested and connected with the EudraVigilance Gateway.

The Web Trader transmission mode is an integrated component of the EudraVigilance Gateway designed to support small and medium size enterprises (SMEs) or regional pharmacovigilance centres to generate, send and receive in a secure way safety reports to any registered organisation within the EudraVigilance community. This transmission mode is achieved through a specifically developed internet-based tool called EVWeb.

The Web Trader transmission mode is not applicable for national Competent Authorities since they are already connected through the EudraVigilance Gateway but it may be selected as a transmission mode by regional pharmacovigilance centres, if applicable.

EVWEB

The EudraVigilance system also provides a user interface, called EVWeb, to allow for a 'manual' generation and administration via a web browser:

- Safety messages
- Acknowledgement messages
- EudraVigilance product reports messages (EVPRM)

EVWeb can be used by any marketing authorisation holder in the EEA and sponsor of a clinical trial in the EEA. EVWeb is specifically designed for small and medium size enterprises (SMEs), which do not have a fully ICH E2B(M) compliant pharmacovigilance system and / or ESTRi gateway in place. It provides the necessary tool to allow SMEs secure electronic reporting to the EMEA and all National Competent Authorities in the EEA. EVWeb can also be used by regional pharmacovigilance centres to report to their National Competent Authority.

The main functionalities offered by EVWeb are:

- Creation and sending of safety report messages: One of the main functionalities of EVWeb is the possibility to create and send safety reports. Web Trader users may use EVWeb for this purpose by compiling a new message containing one or more safety reports using the specific section of the application. EVWeb will automatically display the complete sections of the hierarchical structure of a typical safety report giving the opportunity to the user to insert the information in the various fields as necessary. The application will also take care of displaying mandatory fields and to detect basic data entry and consistency mistakes before validating the message and sending it. Only Web Trader users are allowed to send safety messages via EVWeb. Gateway users may use the application for all purposes, but safety and acknowledgement messages can only be sent and received via their local gateway.
- Export function: After a safety report has been created, it can be exported in two different formats: XML (which is the typical format for a safety report) and RTF (which is the typical "text" document format).
- ICSR Acknowledgment messages: Acknowledgement messages are used to inform other users that a safety message has been received and processed. They also notify the outcome of the validation of that safety message at the receivers end. EVWeb allows users to create and send acknowledgement messages for received safety messages and to read and store the received acknowledgement messages for the safety messages they sent.
- Follow-up facility: The follow up facility allows the user to view, edit, update and re-send safety reports already stored in the EV DB, taking into account the general access rights of the users.
- Web Trader section: The Web Trader section of the application allows Web Trader users to keep track of sent and received safety messages, acknowledgement messages and rejected messages.

➤ EVMPD functionalities: These sections of EVWeb allow users to navigate, browse and perform analytical queries throughout the EudraVigilance Medicinal Product Dictionary (EVMPD). Users are able to insert specific key words and/or combinations of elements to run complex queries on the EVMPD. Results are displayed on screen. Users can use EVWeb to create and send electronic messages called EudraVigilance Product Report Message (EVPRM). This function allows the creation of a new medicinal product entry, an update, a variation or a nullification of any information already present in the EVMPD.

➤ MedDRA functionalities: The user is able to browse and query the complete MedDRA terminology. MedDRA is fully integrated in the EVWeb application.

DATA QUALITY ENHANCEMENT

EudraVigilance contains several components aimed at enhancing the quality of the received data (a.k.a “Data Cleansing”). The most important are:

➤ Loaders & Parser: While loading the safety reports and medicinal product information in the database, the different loader and parser processes perform multiple validations against the business rules.

➤ Recoding: A process that attempts to look up the contents of free texts fields in lookup tables (a.k.a. dictionaries) and store the lookup code next to the free text. Some of the fields that are re-coded are: Active substance name, Parent drug name, Medicinal product, Indication fields, Reaction fields, Species, Breeds, There is an automatic and a manual recoding process. The automatic process processes automatically every night all reports. The manual process enables EMEA staff to manually “modify” a free text field and run the automatic process on selected safety reports.

➤ Duplicate detection: Duplicate reports are safety reports that refer to the same case of adverse reaction. The duplicated reports are unwanted because their presence can cause several unpredictable and undesired effects such as, for example, to distort the statistics based on the safety reports. Duplicate detection is done in EudraVigilance by a complex automated process to discover potential duplicated reports and a user interface to analyse and manage the automatically discovered duplicates.

➤ ETL: The ETL process transports daily information from the transactional database, that receives data directly from the companies and member states, to the data warehouse, that is used for data analysis. The ETL process performs several data cleansing operations (e.g. calculation of missing fields from other information in the report) and normalisation operations (e.g. normalisation of the measurement units)

DATA WAREHOUSE

The Eudra(Vigilance) data warehouse is a database where the data from the transactional DB is re-structured for the sole purpose of easy and high-performance data analysis.

Its main features will be:

- A semantically consistent pharmacointelligence data store
- The data will be sourced from all of the databases described above and other databases in other systems (e.g. EudraCT).
- The data will be cleansed and formatted in line with the appropriate international standards

WEB REPORTING AND SIMPLE DATA ANALYSIS

Users will access the information in the data warehouse via the Eudra(Vigilance) Data Warehouse Portal that will offer access to a wide range of pre-defined standard reports and allow the users to define and execute ad-hoc queries on the data available in the data warehouse.

The main features will be:

- Sort reports and query result sets
- Export reports and query results
- Refine query results
- Store query results
- View the source data
- Perform historical queries
- Scheduling of user-created reports
- Roll-up operations (or drill up operations), which allow aggregation on a data cube, either by climbing up the relevant concept hierarchy for a dimension or a dimension reduction.
- Drill down operation as a reverse of the roll up operation to allow the user to navigate from less detailed

data to more detailed data.

- Slice and dice operation
- Pivot (rotate) operation
- Drill across operation allowing the user to execute queries (i.e. across) more than one fact table
- Drill through operation
- Alerts: The system allows to create product specific alert queries and risk profiles including the possibility to define thresholds that can trigger automatic alert messages and mechanisms

STATISTICAL ANALYSIS AND SIGNAL DETECTION

Highly specialised statistical analysis and signal detection will be done via the EudraVigilance data mining component.

The following statistical techniques will be used:

- Linear models (ANOVA, ANCOVA, simple or multiple regression)
- Generalised linear models
- Analysis of dependent data (random and mixed-effect models, analysis of spatial data)
- MANOVA
- MANCOVA
- Exploratory multivariate techniques and clustering techniques (cluster analysis, factor analysis, principal component analysis)
- Classification methods (discriminant analysis, neural networks tree bases methods)
- Analysis of time series (univariate and multivariate, including analysis on the spectral domain)
- Survival analysis (univariate and multivariate techniques)
- Quality control methods.

In addition, the data mining system / statistical software will support methodologies based on:

- Association rules
- Classification and regression methods (e.g. decision trees, Bayesian classification, Bayesian networks)
- Regression and interpolation methods (e.g. regression trees, regression splines, radial basis functions)
- Cluster analysis (using different clustering methods e.g. partitioning methods, hierarchical clustering methods).

ACCESS TO EUDRAVIGILANCE AND EVWEB

Only registered organisations and their registered individual users are granted access to EudraVigilance. When registering with EudraVigilance, all organisations need to specify their transmission mode.

National Competent Authorities should always specify their transmission mode as gateway transmission mode. Regional pharmacovigilance centres can choose to use the gateway or the Web Trader transmission mode.

MAHs need to specify their transmission mode at the level of the headquarters and at the level of the affiliates if the safety reports management is not centralised within a company. Different transmission modes may be used at each level. For MAHs, the chosen transmission mode determines the default access rights to EudraVigilance.

Individual users of National Competent Authorities have access to all safety reports stored in EudraVigilance.

MAHs have currently only restricted access to EudraVigilance. Individual users of a pharmaceutical company can only view the safety reports that have been submitted by this company to the EMEA. MAHs may also define specific user rights for their affiliates, and their individual users during the registration process.

Access to EVWeb is personal and non-transferable for each user of each organisation. It is achieved through entering a personal login ID and password and a security certificate obtained following registration with EudraVigilance.

FLOW OF DATA THROUGH EUDRAVIGILANCE

This section shows how the different components of the system, as described above, collaborate in processing data on safety and medicinal products. The example taken is that of an adverse reaction related to a medicinal product for human use authorised in the EEA where the marketing authorisation holder (MAH) has an IT system that can generate and process ICH E2B messages and is connected to the ESTRIM Gateway.

1. An adverse reaction occurs in relation to a medicinal product of the MAH. Typically, the issue shows up somehow in the pharmacovigilance IT system of the MAH and, after verification by the pharmacovigilance department, the ICSR report is created automatically, wrapped in an ICSR message and submitted to the ESTRIM Gateway.
2. The ESTRIM Gateway encrypts the ICSR message and transports it across the Internet.
3. The ESTRIM Gateway will deliver the ICSR message in the inbox of all addressees. These include the EMEA and all concerned (cf. supra) NCAs in the EEA.
4. Upon delivery, the ESTRIM Gateway automatically generates a message disposition notification (MDN) at the receiver's end and sends this back to the sender over the ESTRIM Gateway.
5. The EudraVigilance Loader picks the ICSR message out of the EMEA's ESTRIM Gateway inbox and loads it into the system.
6. Upon loading, the report included in the message is verified against a set of business rules.
7. Depending on the outcome of the verification of the message against the business rules:
 - 7.1 If the message conforms to the business rules, an acknowledgement message is automatically generated in line with the ICH E2B specifications and is sent back via the ESTRIM Gateway to the sender of the original message.
 - 7.2 If the message does not conform to the business rules, the information will still be stored in the database, but flagged as erroneous. An acknowledgement message listing the errors is automatically generated in line with the ICH E2B specifications and is sent back via the ESTRIM Gateway to the sender of the original message.
8. The data re the safety issue is now entered in the EudraVigilance database.
9. Overnight, the data in the database passes various data quality enhancement processes:
 - 9.1 Recoding
 - 9.2 Extraction from the EudraVigilance transactional database, transformation and loading by the ETL process in the Eudra(Vigilance) data warehouse
 - 9.3 Duplicate detection: The detection of duplicates results in a new master report being re-injected in the EudraVigilance transactional database.
10. Loading the new data in the data warehouse might set off one or more alerts, resulting in the appropriate group of users being warned immediately.
11. The next day, the information is available in the data warehouse for:
 - 11.1 Consultation in pre-defined reports
 - 11.2 Ad hoc queries
 - 11.3 Data mining
12. The Eudra(Vigilance) users can now connect to the Eudra(Vigilance) Data Warehouse Portal to turn the information stored in the data warehouse into knowledge on safety in the EEA. More advanced users will perform data mining.

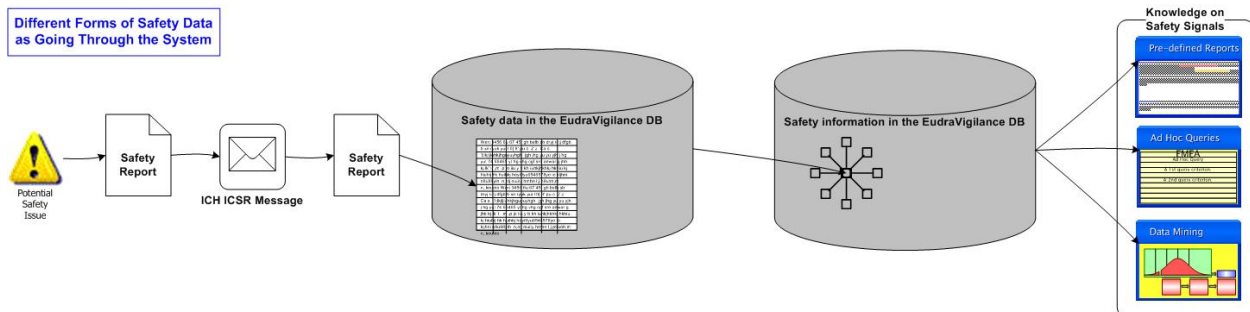


Figure 4: Different forms in which safety "data" travels through EudraVigilance

SOFTWARE ARCHITECTURE

THE TRANSACTIONAL SYSTEM

The EudraVigilance system architecture is mostly 3-tiered: database layer, application layer and the presentation layer.

Database Layer

The database layer consists of an Oracle 9.2 database management system (DBMS) hosting the data and the business and application logic implemented as PL/SQL packages and triggers.

The DBMS is configured as a Real Application Cluster (RAC) and runs on Intel servers with the Linux operating system.

Application Layer

The application layer consists of Visual Basic components in COM+ and of Microsoft Windows Services (e.g. the Loader).

The application layer also contains the main components of the ESTR1 gateway, implemented with Cyclone Central.

Presentation Layer

The presentation layer is implemented with ASP with VB Scripting.

The EVWeb consists of DHTML pages with JavaScript and of ActiveX components.

THE DATA WAREHOUSE

The system architecture of the Eudra data warehouse is a mixture of 3-tiered and 2-tiered:

Database Layer

The database layer consists of an Oracle 9.2 database management system (DBMS).

The data for use of SAS is not stored in this layer, but in the application layer in the SAS libraries.

The DBMS is configured as a Real Application Cluster (RAC) and runs on Intel servers with the Linux operating system.

Application Layer

The application layer consists of:

- For web reporting and basic data analysis: MicroStrategy Intelligence Server 8 and MicroStrategy NarrowCast Server
- For advanced statistical analysis: SAS Enterprise Guide and SAS Data Miner.

Presentation Layer

The application layer consists of:

- For web reporting and basic data analysis: MicroStrategy Web Server
- For advanced statistical analysis: SAS Client

EUDRAVIGILANCE AND SAS

The data mining functionality as described in the sections above is being implemented entirely with SAS functionality.

On a daily basis, the transactional information will be transferred to the SAS libraries for data analysis with SAS Enterprise Guide and SAS Data Miner.

Scoring results will be fed back to the transactional DB and the data warehouse.

CURRENT STATUS OF IMPLEMENTATION AND A VIEW TO THE FUTURE VERSIONS

CURRENT STATUS OF THE SOFTWARE DEVELOPMENT ACTIVITIES

EudraVigilance Human 7.0 and EudraVigilance Vet 2.1 are currently in production and offer most of the functionality as described above.

FUTURE SOFTWARE RELEASES

Future versions of EudraVigilance Human will provide:

- Data warehouse functionality (incl. Web reporting, Simple data analysis, Statistical analysis and Signal detection) as described above
- More advanced duplicate detection
- Access to other stakeholders
- In general, more functionality aimed at further automating the pharmacovigilance workflow and supporting the regulatory activities in the EEA
- Further integration in and inter-operability with the other EU Telematics systems
- Update EudraVigilance to future evolution of the legislation, standards and guidelines (e.g. ICH E2B(R)).
- Interfaces to other health databases

Future versions of EudraVigilance Veterinary will provide:

- Data warehouse functionality (incl. Web reporting, Simple data analysis, Statistical analysis and Signal detection) as described above
- Duplicate detection
- Access to other stakeholders
- General functionality aiming at an improved user experience

- In general, more functionality aimed at further automating the pharmacovigilance workflow and supporting the regulatory activities in the EEA
- Further integration in and operability with the other EU Telematics systems
- Update EudraVigilance to future evolution of the legislation, standards and guidelines.

A version of EudraVigilance Human and Veterinary specifically tailored for use at and by the National Competent Authorities, will be provided beginning 2006.

CURRENT STATUS OF THE DATA PROCESSING ACTIVITIES

Data Processing Figures (on 31/Aug/05)	
Transactions (incl. MDNs) processed by the ESTR1 Gateway since Nov/01:	> 1 200 000
EV Human	
Pharmaceutical companies in production:	47
Sponsors of clinical trials in production:	32
National Competent Authorities in production:	14
Safety reports reported:	> 130 000
Cases reported:	> 40 000
Presentations for medicinal products:	> 3 500
EV Veterinary	
National Competent Authorities in production:	21
Safety reports reported:	± 3 000

CONCLUSION

- EudraVigilance is a powerful tool for monitoring the safety of medicinal products
- Once the complete feed of data has been established, it will be the largest database of its kind in the world
- It will become an extremely useful resource for academic and commercial research once full access to data mining and statistical evaluation can be provided.

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