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MAHs access to EudraVigilance

Stakeholders meeting – 02 June 2017

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Content

- Background EU legislation
- Implementation of EV access for MAHs
- Guidelines and training
- Signal detection and validation tools in EV
- Use and analysis of the data – Key elements

Background – EU legislation

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Regulation 726/2004

- The EudraVigilance database shall be fully accessible to the competent authorities in the Member States and to the Agency and the Commission. **It shall also be accessible to MAHs to the extent necessary for them to comply with their pharmacovigilance obligations** [Art 24(2)].

Commission Implementing Regulation 520/2012

- **Minimum requirements for the monitoring of data in the EudraVigilance database (Chapter III):**

➢ MAHs shall monitor the data available in the EudraVigilance database to the extent that they have access to that database [Art 18(2)].

➢ MAHs, NCAs and the Agency shall ensure the continuous monitoring of the Eudravigilance database with a frequency proportionate to the identified risk, the potential risks and the need for additional information [Art 18(3)].

Background – EU legislation

- Signal detection within the EudraVigilance database shall be complemented by statistical analysis, where appropriate [Art 19(2)].
- NCAs, MAHs and the Agency shall determine the evidentiary value of a signal by using a recognised methodology taking into account the clinical relevance, quantitative strength of the association, the consistency of the data, the exposure–response relationship, the biological plausibility, experimental findings, possible analogies and the nature and quality of the data [Art 20(1)].
- The PRAC shall regularly review the methodology(ies) used and publish recommendations, as appropriate [Art 20(3)].

Signal detection support:

- The Agency shall also ensure appropriate support for the monitoring of the EudraVigilance database by MAHs [Art 23].

EudraVigilance access – Implementation

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- Access to EudraVigilance data for MAHs has been implemented in the EudraVigilance Auditable Requirements project established in 2014:
  - New and enhanced EudraVigilance functionalities were agreed by PRAC and endorsed by the EMA Management Board in Dec 2013.
  - 2014 – 2017 Project delivery phase, including testing with stakeholders (NCAs, MAHs).
  - EudraVigilance functionalities, including the level of access and tools provided to MAHs, were subject to an independent audit in February 2017.
  - PRAC issued a recommendation on the audit report – May 2017.
  - Announcement by the EMA Management Board that the database has achieved full functionality – 22 May 2017.

EudraVigilance access – Implementation

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EudraVigilance Access Policy

Stakeholder Group III Marketing Authorisation Holders	
• EVWEB including ICSR Export Manager	• ICSRs electronic (XML) format • ICSR forms
• EVDAS	• e-RMRs and active substance groupings • ICSR line listings • ICSR forms

EVWEB for MAHs

- Tool to manage expedited reporting of ICSRs and provides access to the cases received by the NCAs (permits the centralised reporting)
- Export manager - Electronic download (XML format) of ICSRs
- Level 2a access based on ownership of products containing suspect/interacting substances in ICSRs:
  - Substance level access (active substance high level)
  - Prospective (cases received from Nov 2017)
  - EEA cases
- Level 2b access, includes the narratives.

EVDAS for MAHs

- Tool for monitoring the database, signal detection.
- All MAHs with a medicinal product authorised in the EEA (EVDAS registration for MAHs starts in June 2017).
- Substance level using the highest level of the active substance in the hierarchy of the xEVMPD (active substance high level).
- Cases where the specific substance is coded as suspect/interacting.
- Access to all EVPM cases [*Spontaneous, Reports from* studies *(including 'individual patient use and other studies)*, *Other, Not available to sender].*

Guidelines and Training

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Methodological guideline:

'Screening for adverse reactions in EudraVigilance'

- Describes the use of EudraVigilance for signal detection and the rationale behind the methods based on evidence from research activities (incl IMI PROTECT)
- Provides recommendations for NCAs/EMA and MAHs
- Created by Signal Management Review Technical Working Group (SMART WG) – Work stream 'Methods' (formed by representatives from MSs and EMA)
- PRAC adoption in Nov 2016 and published in Dec 2016

Routine signal detection in EudraVigilance (new)

In December 2016, EMA published **guidance** on routine signal detection methods in EudraVigilance for use by the Agency, national competent authorities and marketing authorisation holders:

Screening for adverse reactions in EudraVigilance

The purpose of this guidance is to provide a **scientific** discussion on the methods recommended and implemented in EudraVigilance for screening for adverse reactions. It does not provide regulatory requirements, which are laid down in good pharmacovigilance practices (GVP) Module IX on signal management.

The guidance also updates and supersedes the previous guideline on the use of statistical signal detection in EudraVigilance.

Two tools are used in EV for signal detection. The electronic Reaction Monitoring Report (eRMR) is a standard report that provides summarised signal detection data from EV. The EudraVigilance Data Analysis System (EVDAS), which operates on the EudraVigilance Data Warehouse, is used in conjunction with the eRMR to enhance signal detection[1].

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Methodological guideline:

'Screening for adverse reactions in EudraVigilance'

- Disproportionality method: ROR
- Thresholds defining Signal of Disproportionate Reporting (SDR) in EudraVigilance:
  - General population
  - Paediatric population
  - Geriatric population

Implemented recommendation in EudraVigilance

The PRR, which is a very simple calculation, has previously been implemented as the signal detection method in EV. However, the fact that the ROR is an equally simple method, gives the same performance as the PRR, but also forms the basis of more complex statistical models makes it the best choice for future development of the EV system (eRMR and EVDAS) where flexible analytical methods

Implemented recommendation in EudraVigilance

The following criteria are applied in the EV system (eRMR and EVDAS) to define an SDR:

- The lower bound of the 95% confidence interval greater than one;

Implemented recommendation in EudraVigilance

In the EV signal detection system (eRMR), for the paediatric population within-group disproportionality is used defined as follow:

Relative Paed ROR = ROR_{Paed} / ROR_{Rest}

Implemented recommendation in EudraVigilance

In the EV signal detection system (eRMR), for the geriatric population within-group disproportionality is used as follow:

Relative Geriatr ROR = $ROR_{Geriatr}$ / ROR_{Rest}

An SDR is defined when the following criteria are applied:

- The lower bound of the 95% confidence interval of the $ROR_{Geriatr}$ is greater than one;
- The lower bound of the 95% confidence interval of the Relative Geriatr ROR is greater than one;
- The number of individual cases in the geriatric population greater than or equal to

  3 for active substances contained in medicinal products included in the additional monitoring list in accordance with REG Art 23 (see GVP Module X), unless the sole reason for inclusion on the list is the request of a post-authorisation safety study (PASS);

  5 for the other active substances;
- The event belongs to the IME list.

EudraVigilance Stakeholders change management plan

5.2.5.2. Marketing Authorisation Holders

Access will be granted to the EudraVigilance data analysis system to marketing authorisation holders to use signal detection and analytical/reporting functions to the extent necessary to comply with their pharmacovigilance obligations. Such functions will include:

- The electronic Reaction Monitoring Report (eRMR) based on the eRMR used within the EU network and the EMA for signal detection activities;
- The individual case line listing and ICSR form.

The level of access to each ICSR and data elements will be implemented as defined in the revised EudraVigilance access policy. Several safeguards will be put in place in order to ensure compliance with personal data protection i.e. to prevent patient identification.

Guidelines and Training

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EVDAS training for Marketing Authorisation Holders (EV-M5b)

Target audience	Marketing authorisation holders in the EEA
Duration	1.5 hours
Learning outcomes	This module provides information on the EudraVigilance Data Analysis System (EVDAS) functionalities available for MAH users in the EEA in support of their pharmacovigilance obligations. It also provides an overview about how statistical signal detection is implemented in EudraVigilance. At the end of module EV-M5b you should be able to: ▸ Understand the access to EudraVigilance provided via EVDAS; ▸ Be familiar with the EVDAS user interface; ▸ Be able to retrieve electronic Reaction Monitoring Reports (eRMRs), Line Listings, and ICSR forms from EVDAS; ▸ Understand the system functionalities for manipulating report's outputs; ▸ Understand how signal detection is implemented in EudraVigilance; ▸ Understand the outputs of the EVDAS reports.
Availability	▸ Video recordings of the module ▸ EVDAS training for Marketing Authorisation Holders

e-Learning describing the EVDAS access, the tools and the data outputs available since Jan 2017

More training to be released in 2017:

- EVDAS manual for MAHs – Incorporates the user manual on the eRMR
- ICSR form manual – describes the ISCR form in details how the data is included in the form

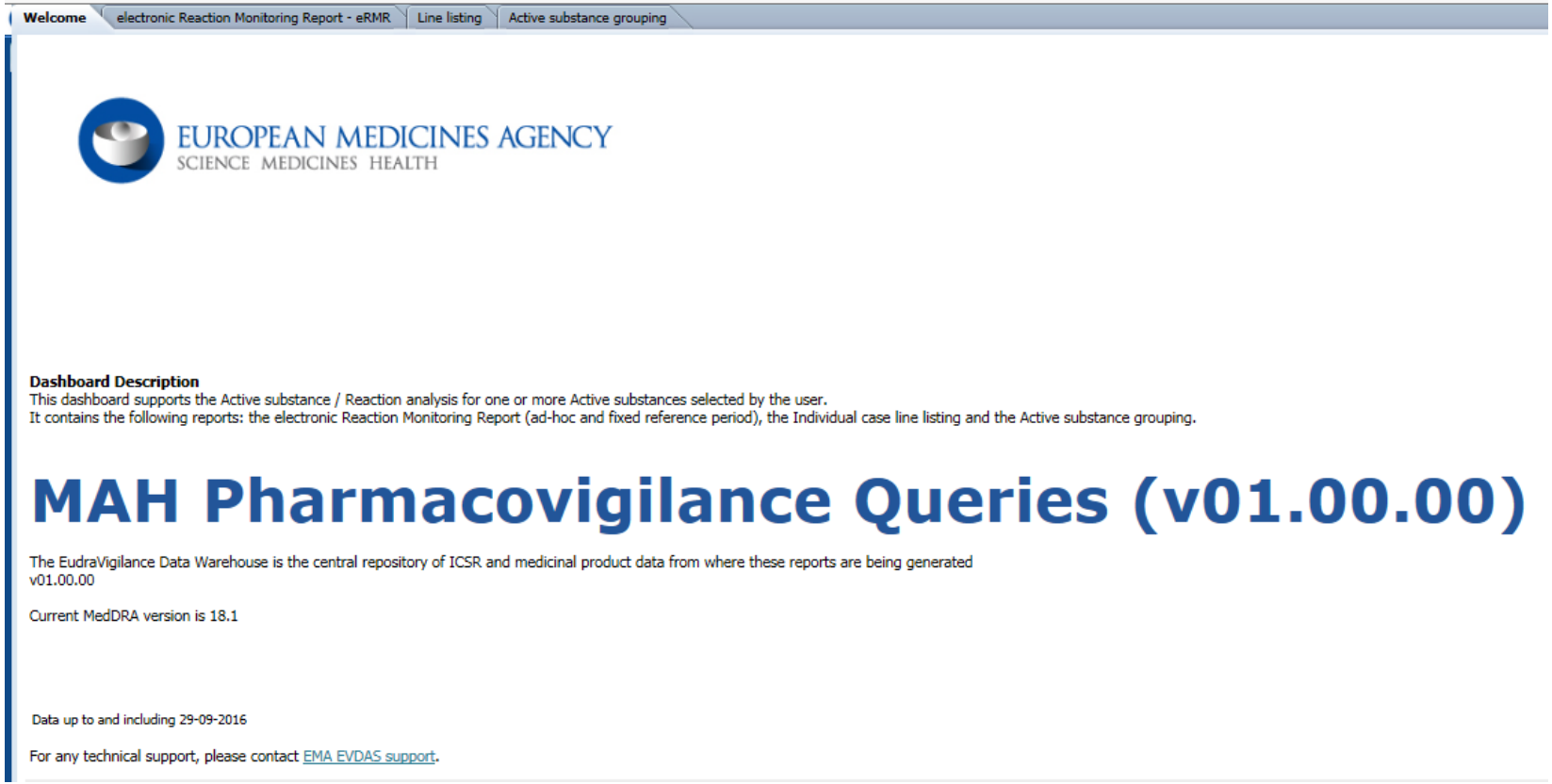
Consult the EudraVigilance training page for the full training programme and updates

- http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000162.jsp&mid=WC0b01ac0580a1a1fb

Stakeholders support:

- MAHs support webinars
- Engagement with Inspectors Working Party and inspectors training to aim for consistency in the approaches

Signal detection and validation tools in EV



Signal detection and validation tools in EV

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eRMR:

- Aggregated summary tabulation of the number of cases with statistical analysis.
- Incorporates a 'reporting period' so new cases (from last screening) are highlighted - that allows for **continuous monitoring** of the database **(IR Art 18).**
- Possibility to retrieve eRMRs with reporting period from 1 day to 6 months to allow monitoring with a **frequency proportionate to the risks (IR Art 18).**
- Incorporates the ROR for **statistical analysis (IR Art 19).**
- It is developed according to the **recognised methodology (IR Art 20).**

Signal detection and validation tools in EV

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1st part of the eRMR: Drug-event combination using the MedDRA hierarchy with information on IME/DME

Active Substance	SOCs	HLGTs	HLTs	SMQ Broad	SMQ Narrow	PTs	IME / DME
Gefitinib	Gastr	Exocrine Pancreas Conditions	Acute And Chronic Pancreatitis	Drug reaction with eosinophilia and systemic symptoms syndrome	Acute Pancreatitis	Pancreatitis	Ime / Dme
Gefitinib	Gastr	Exocrine Pancreas Conditions	Acute And Chronic Pancreatitis	Drug reaction with eosinophilia and systemic symptoms syndrome	Acute Pancreatitis	Pancreatitis Acute	Ime / Dme

2nd part of the eRMR: Number of cases in the EVPM

New EVPM	Total EVPM	New EEA	Tot EEA	New HCP	Tot HCP	New Serious	Tot Serious	New Obs	Tot Obs	New Fatal	Tot Fatal	New Med Err	Tot Med Err	New + RC	Tot + RC	New Lit	Tot Lit
0	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	0
0	2	0	2	0	2	0	2	0	0	0	2	0	0	0	0	0	0
0	1	0	1	0	1	0	1	0	0	0	1	0	0	0	**0**	0	0

Signal detection and validation tools in EV

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3rd part of the eRMR: disproportionality as per the methodological guideline

New Paed	Tot Paed	Ratio ROR (-) Paed vs Others	Paediatric SDR	New Geriatr	Tot Geriatr	Ratio ROR (-) Geriatr vs Others	Geriatrics SDR	ROR (-) All	SDR
0	11	2.96	Y	0	30	0.19	N	5.30	Y
0	3	1.28	N	0	2	0.09	N	3.63	N
0	1	99.00	Y	0	**0**		N	0.46	Y

Signal detection and validation tools in EV

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Line listing and ICSR form:

- Provide access to details of the individual cases.
- Line listing (Level 1 access – 53 fields) – Overview of the cases.
- ICSR form – Level 2a (228 fields) provided to all the MAHs with a product authorised in the EEA for a specific suspect/interacting substance (regardless of the product) - allows for full assessment of the EV data for signals in conjunction with the case narratives.
- ICSR form – Level 3 (272 fields) for the cases MAHs have previously submitted and MLM cases.

Reaction / Event

MedDRA LLT	Start Date	Stop Date	Duration	Outcome	Seriousness*
Drug reaction with eosinophilia and systemic symptoms	01/08/2002	31/08/2002		not recovered/not resolved/ongoing	death, life threat., hospital., congen.
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	05/06/1980			not recovered/not resolved/ongoing	death, life threat., congen.
End stage liver disease	20/08/2002			fatal	death, disability, other
B-immunoblastic lymphoma (Kiel Classification) refractory				recovered/resolved	life threat., other

Drug Information

Role†	Drug	Start Date	Stop Date	Duration	Dose	Units in Interval	Action taken
S	Avastin 25 mg/ml [bevacizumab]	15/01/1992	01/02/1992		10 mg/kg	1 per 2w	Drug withdrawn
C	Epilim Chrono 200 mg [valproic acid]						Dose reduced

Drug Information *(cont.)*

Info†	Drug	Indication	Cumul. dose to 1st Reaction	Pharm. Form	Route of Admin.	Parent Route of Admin.	Batch / Lot #
	Avastin 25 mg/ml [bevacizumab]	Non-small cell lung cancer	1200 mg	Concentrate for solution for infusion	transplacental	intravenous	AO852369
	Epilim Chrono 200 mg [valproic acid]	Clonic seizures	15 g	Prolonged Release Tablets			123654PP

Additional Information on Drug
This was an unfortunate medication error

Signal detection and validation tools in EV

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Case Narratives:

- Provided in EVWEB [level 2b access (230 fields)] and this provides the possibility to download XML files to incorporate the data in the MAHs databases.
- Access is provided to all the MAHs with a product authorised in the EEA for the specific substance of interest (regardless of the product and regardless of the marketing authorisation route).
- Access is provided for all the EVPM cases where the specific substance is coded as suspect/interacting.
- Therefore, all MAHs with a product authorised in the EEA for the substance of interest will have the possibility to retrieve Level 2b (incl narratives) for all the cases included in the eRMR.

Case Narratives:

- The request for Level 2b is 'automated' in EVWEB – No stand alone request and no documentation should be submitted to the EMA.
- MAHs should confirm in the system the following:
  - ✓ Confirm that L2B access is required due to pharmacovigilance obligations in line with the published Good Vigilance Practice Modules
  - ✓ Select the reason for the request, from the options provided in the system
  - ✓ Confirm agreement to comply with the terms related to the protection of personal data
- Level 2b will be provided within minutes (depends on the number of cases requested)

Use and analysis of the data – Key elements

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Periodicity of EudraVigilance monitoring:

- MAHs should determine the monitoring frequency for each of their substances using a risk-based approach considering the known safety profile.
- GVP IX rev. 1 recommends at least every 6 months (longer intervals not possible with current system).
- Elements that may be considered: time since first authorisation, patient exposure, potential risks in RMP, PSUR frequency (…).
- The frequency should be documented according to the MAH's internal procedures.

Use and analysis of the data – Key elements

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eRMR screening:

- The eRMR provides the data and the disproportionality analysis, but it does not state which DECs should be further analysed.
- MAHs should exercise scientific rationale when deciding which DECs from the eRMR deserve further analysis, this should be based on the knowledge of the safety profile of the product (including closely related terms that are labelled), exposure, patient population, previous assessments etc.
- Statistical signal detection has to be complemented with clinical and scientific assessment and judgement.
  - **A SDR is not the same as a validated signal.**
  - There could be real safety signals that do not show as SDRs (~ 50% of the signals raised from the EV screening did not appear as SDRs).

Use and analysis of the data – Key elements

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Signal validation:

- MAHs should fully analyse all the data available in EudraVigilance (including the narratives), taking into account the strength of evidence from the cases and clinical relevance.
- Other data available to the MAHs should be included during the validation (e.g. literature).
- The definition of 'signal' should always be considered: a signal should provide 'new information'.
- It may be useful to consult information on the class and product information for other products containing the same substance (e.g. generic products vs innovators).
- The signal management procedure is not a tool to harmonise SmPCs.
- PRAC recommendations on signals and EMA advanced notifications should be considered.

Final key remarks - Opportunities

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- Since the establishment of the EudraVigilance Gateway in November 2001, the database has reached over 6 million cases in the EVPM.
- One of the largest spontaneous reporting systems worldwide.
- Disproportionality methods have demonstrated advantages for signal detection, and this information can be used during signal assessments.
- The statistical analysis implemented in EudraVigilance follows a methodology which is developed and explained in the guidelines available to the stakeholders.
- Extended access to details of the individual cases provides the opportunity to fully assess the data and provides transparency within the decision making.
- EudraVigilance data is provided to all the stakeholders in real time.
- The data is subject to quality control and duplicate detection.
- The good use of the data is key to benefit from the database without overloading the EU system unnecessarily.

Thank you for your attention

Further information

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