EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

New EudraVigilance System – Progress update

13th industry stakeholder platform – operation of EU pharmacovigilance

20 March 2018

Presented by Sabine Brosch and Francois Domergue

Agenda

- EudraVigilance in numbers
- EudraVigilance maintenance and hypercare
- Obligations of MAHs to record suspected adverse reactions they access through EudraVigilance
- EVDAS and some important points to note

EudraVigilance in numbers

EudraVigilance – Registrations

- **Registered users**

EudraVigilance	Organisations	Users
MAHs	5,476	18,970
NCAs	78*	1,256

EVDAS	Organisations	Users
MAHs	2,064	6,277
NCAs	65*	878

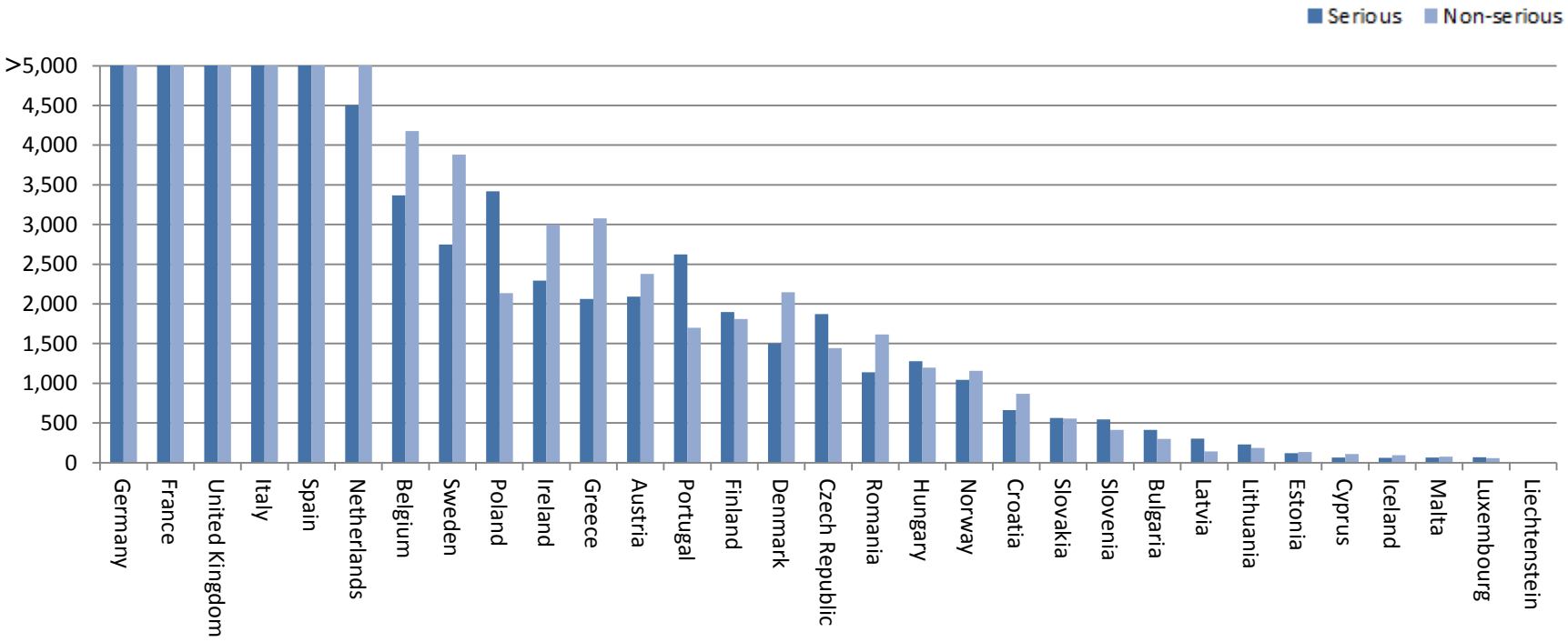
* Includes regional centres

EudraVigilance – Processing of ICSRs

Number of ICSRs processed: 22 November 2017 – 5 March 2018

ICSRs	Total	EEA	Non-EEA
Serious	325,625	142,572	183,053
Non-serious	321,311	315,036	*6,275*

Achievements – Processing of ICSRs



EudraVigilance – Data Quality Activities

Data Quality Processes	Activities Performed	2015	2016	2017	2018
Identifying and managing duplicates	Duplicate couples assessed	31,797	72,655	212,062	20,534
	Master reports generated	40,022	48,111	133,635	17,051, including FU masters
Manual classification of reported medicines and active substances	ADR reports classified (ICSRs)	54,535	64,686	41,124	4,501

EudraVigilance – ICSR download requests by MAHs

- **ICSR download requests by MAHs: 22 November 2017 – 5 March 2018**
  - 1,274 MAHs submitted download request to EV
  - 74,070 download requests successfully executed
  - **5,987,253 ICSRs downloaded**

EudraVigilance - Use of EB(R3) ICSR format

- **Organisations sending E2B(R3) ICSRs**
  - Increase of 14 MAHs and 3 Commercial sponsors since January 2018
    - Total:
      - 49 MAHs with gateway profile (including affiliates)
      - 3 commercial sponsors with gateway profile
  - 9 NCAs with gateway profile
  - Other organisations continue to send E2B(R2) files via gateway or are using the new EVWEB

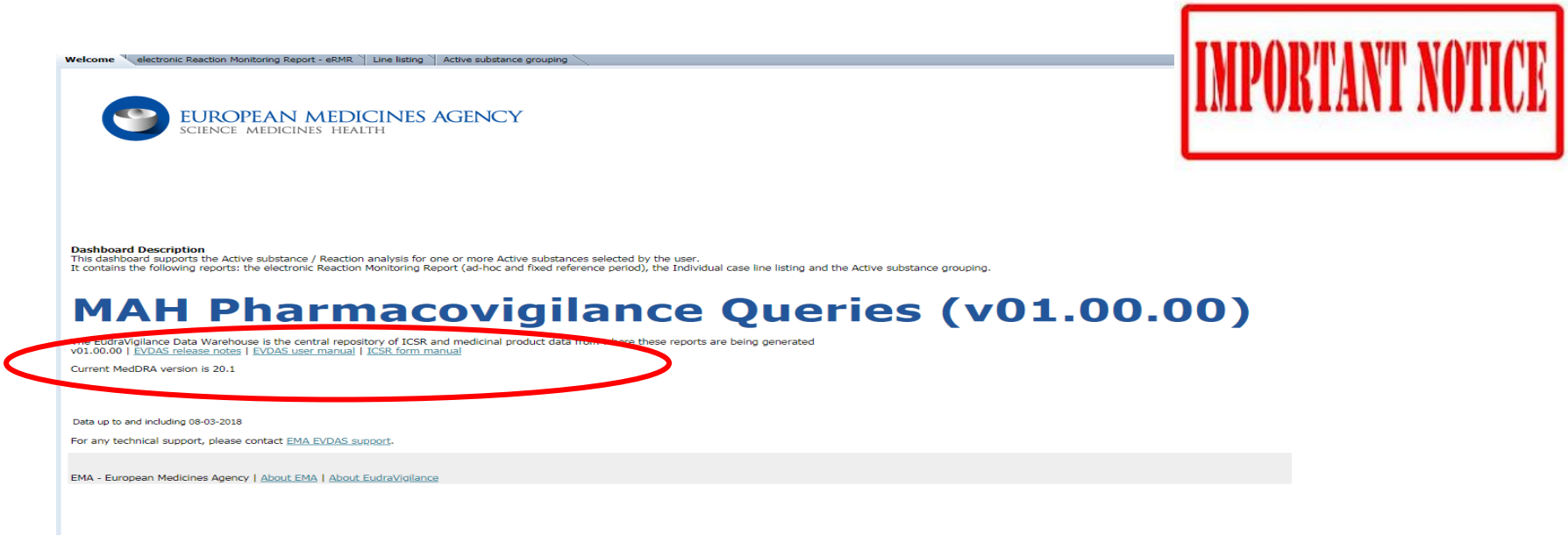
EudraVigilance hypercare and maintenance releases

EudraVigilance - hypercare and maintenance

- **Release 5** of EudraVigilance on **14 February 2018** delivering:
  - ✓ additional improvements
  - ✓ addressing issues identified following go-live on 22 November
- Launch of **MAH fixed eRMRs** launched on **14 February 2018** (following final internal validation)
- Fortnightly maintenance releases during hypercare period until 22 May 2018
- Routine downtime maintenance windows (Mon, Tue, Wed, Thu, 5 to 6 pm UK time)
- Unplanned downtime → emails are sent to users

EudraVigilance - hypercare and maintenance

- **EVDAS release notes – eRMR welcome page**



EudraVigilance - hypercare and maintenance

- **EudraVigilance release notes – EV training and support**

User guidance and release notes

User guidance and release notes are available below:

- EudraVigilance EVWEB user manual
- EudraVigilance User Manual - Individual case safety report form
- Marketing authorisation holders' access via the EudraVigilance Data Analysis System (EVDAS) user manual (EV-G1a)
- European database of suspected adverse reactions related to medicines: User manual for online access via the adrreports.eu portal
- XCOMP release note
- EudraVigilance release notes **(updated 20/02/2018)**
- European database of suspected adverse drug reaction reports' website (www.adrreports.eu): release notes v.1.0 (published 19/12/2017)

EudraVigilance - hypercare and maintenance

EudraVigilance and EVDAS Release Notes structure:

- What's New: enhancements (new features)
- Known Issues: reported open issues including recommended workarounds where applicable
- Fixed Issues: reported issues that have been fixed
- Points to Note: important aspects to keep in mind

Users should regularly consult the release notes after each system upgrade

EudraVigilance - maintenance functional updates

- Improvements to the ICSR acknowledgement files, e.g. to increase of readability for end users, e.g.
  - ✓ Parsing error acknowledgements now include the gateway CoreID tracking number, which assists organisations to match the parsing error acknowledgement with the invalid ICSR file submitted.
- EudraVigilance Business rules fixed, e.g. for rare scenario, reporter family name length
- New business rules added for EVPOST function, e.g. maximum file size added, check before posting of invalid file posting
- Improvements to ICSR and acknowledgement message handling

EudraVigilance - maintenance functional updates to come

- **EV transactional system highlights:**
  - User interface improvements/ most address feedback from users, e.g.
    - ✓ If a user's account is locked due to too many failed log in attempts, a notification is displayed on screen to inform users to contact the service desk to re-enable their access.
    - ✓ Additional MLM export search filters have been added to allow for searching by literature references and reporter (name of literature author).
    - ✓ In the Inbox/Outbox area of EVWEB, a new filter has been added to allow searching for a specific "ICSR Batch Number".
    - ✓ In the EVWEB ICSR Search, Webtrader and MedDRA sections, the Excel exports limit has been increased to 1000 rows.
  - **MAH are now able to filter and download ICSRs based on the sender organisation type: National Competent Authorities (EEA Member States), Other sender organisations (excluding NCAs), All sender organisations.**

Obligations of MAHs to record suspected adverse reactions they access through EudraVigilance

EudraVigilance - Operational Aspects

- MAHs are seeking **clarification about their obligations to record suspected adverse reactions they access through EudraVigilance** following the launch of the new and enhanced system on 22 November 2017
- Pharmacovigilance Business Team and the EudraVigilance Expert Working Group reviewed discussion paper putting forward different options at their meetings in February 2018
- Pharmacovigilance Risk Assessment Committee (PRAC) was consulted on the preferred options to proceed at their meeting on 7 March 2018
- Pharmacovigilance Inspectors Working Group (PhV IWG) was consulted at their meeting on 16 March 2018

Two key questions raised by industry- Question I

I. For reports of suspected adverse reactions submitted to EudraVigilance, which are no longer made available by NCAs to MAHs in the EEA based on the simplified reporting rules:

- Are MAHs required to record individual cases related to active substances of medicinal products for which they hold a marketing authorisation in the EEA and for which they cannot exclude ownership when **accessing individual cases by means of the *EudraVigilance download functionality***? ("*ICSRs accessed prospectively*")

Two key questions raised by industry – question 2

II. For reports of suspected adverse reactions that were submitted to EudraVigilance prior to 22 November 2017 and which were not brought to the attention of the MAH previously (hereafter referred also as "retrospective" cases):

- When accessing individual cases in EudraVigilance as part of their **signal management obligations *using the EudraVigilance Data Analysis System*** *(EVDAS)*, are MAHs required to record individual cases related to active substances of medicinal products for which they hold a marketing authorisation in the EEA and for which they cannot exclude ownership?

Some key principles

- In accordance with Article 24 of Regulation (EC) 726/2004, EudraVigilance shall be accessible to MAHs to the extent necessary for them to comply with their pharmacovigilance obligations. **The legislation is silent about the obligations of MAHs as regards the recording of the suspected adverse reactions they become aware of as part of their EudraVigilance access.**
- The legislation puts specific **emphasis on the fact that MAHs should access reports originating from NCAs through EudraVigilance** (Directive 2001/83/EC, Article 107a, paragraph 4, 3rd subparagraph).

General principles

- The **main requirements for recording and reporting suspected adverse reactions** in the Union and in third countries **is based on the fact that the MAH is the "primary receiver" of the information from the reporter** i.e. *"MAHs shall record all suspected adverse reactions in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study".* (DIR 2001/83/EC, Art 107, par 1).
- **Duplication of efforts** in recording adverse reactions reports **should be limited** ("simplified reporting") thus freeing resources to focus on the monitoring of the safety of medicines.

Some key principles

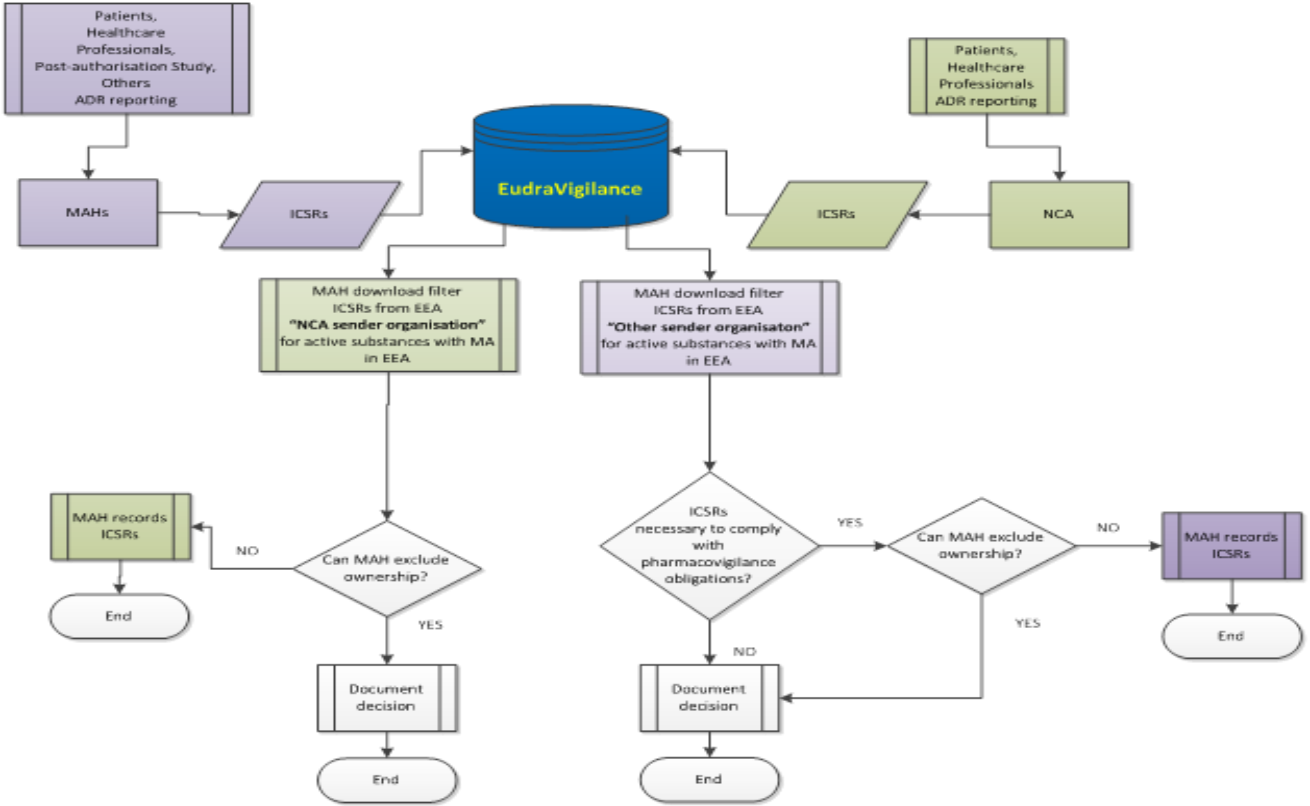
- As part of the signal management process set out in Article 21 of Commission Implementing Regulation (EU) No 520/2012, **MAHs have access in EudraVigilance to electronic Reaction Monitoring Reports (eRMRs), line listings and individual cases related to signals** for active substances of medicinal products, for which they hold a marketing authorisation in the EEA. **MAHs must ensure that they validate and confirm signals, as appropriate**, based on an examination of the data they access in EudraVigilance.
- **Recording of ICSRs** necessary to **"comply with pharmacovigilance obligations"** refers to the **tasks and responsibilities listed in Title IX** of Directive 2001/83/EC and **designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance**.

ICSRs accessed by MAHs "prospectively" – Option B supported by PRAC

- MAHs should record all individual cases for substances of medicinal products, for which they hold a marketing authorisation in the EEA and **that are submitted by NCAs in EEA Member States to EudraVigilance**.
- As regards individual cases submitted by other MAHs to EudraVigilance, **MAHs should decide if they record individual cases accessed through the EudraVigilance download functionalities**. The decision should be based on the processes necessary to comply with the MAH's pharmacovigilance obligations and should be documented as part of the pharmacovigilance system used by the MAH.
  - PhV IWG would like to have clear criteria developed to be able to objectively assess if "phv obligations" apply

➢ *This applies to all individual cases originating within the EEA and where the MAH cannot exclude ownership (based on GVP VI) of the medicinal product reported (suspect or interacting).*

ICSRs accessed by MAHs "prospectively" – Option B supported by PRAC



ICSRs accessed by MAHs "prospectively" – Option B supported by PRAC

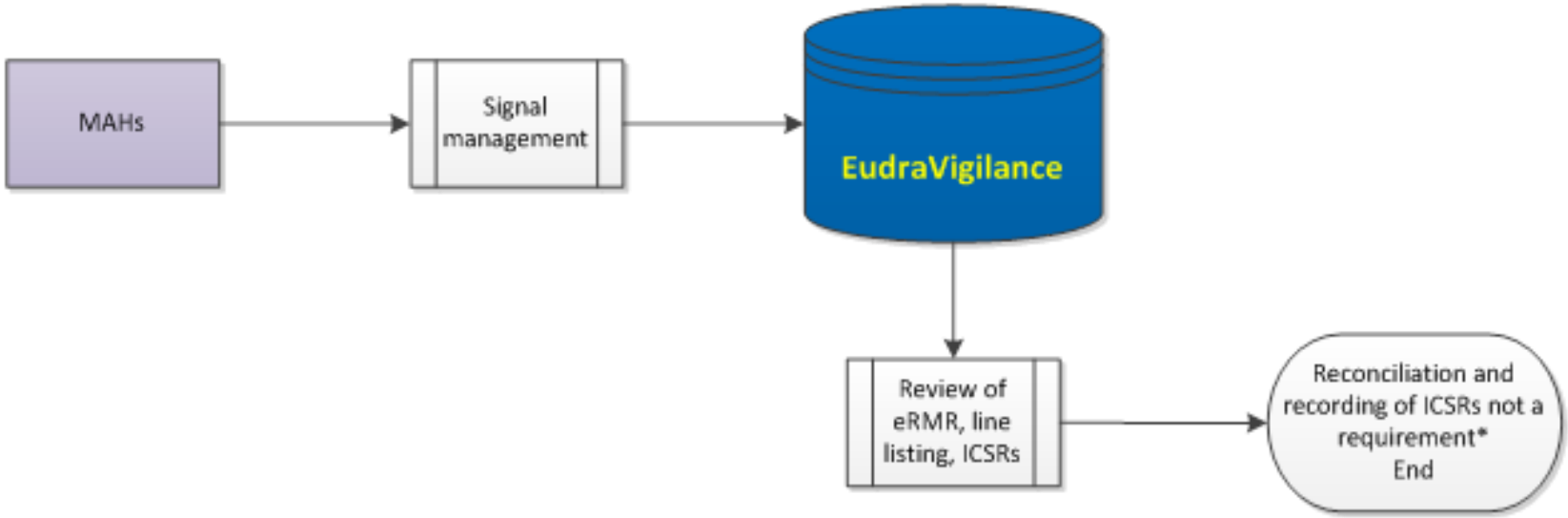
Preferred option because:

- Individual cases originating from NCAs and for which the MAH cannot exclude ownership are routinely processed by the MAH as part of their pharmacovigilance system that they operate.
- ICSRs reported by NCAs and downloaded from EudraVigilance are important as part of the MAHs own signal detection process.
- ICSRs originating from other MAHs can provide relevant information depending on the MAHs' product portfolio and their overall pharmacovigilance obligations.
- A requirement for processing all ICSRs by MAHs as reported by other MAHs to EudraVigilance without putting this in context would create unnecessary burden and duplication of efforts.
- All individual cases are subject to signal management and can be accessed anytime as necessary by MAHs.

ICSRs accessed by MAHs "retrospectively" – Option B supported by PRAC

- MAHs should not be required to process individual cases of which they gained knowledge retrospectively by accessing EudraVigilance as of 22 November 2017.
- This does not preclude a MAH to reconcile and record ICSRs identified in EudraVigilance taking into account the end-point of the signal management or safety monitoring activities i.e. the discovery of a new risk/ADR or change in the status of a risk/ADR as part of a validated signal.

ICSRs accessed by MAHs "retrospectively" – Option B supported by PRAC



ICSRs accessed by MAHs "retrospectively" – Option B supported by PRAC

Preferred option because:

- The intended purpose of the provision of safety data from EVDAS to MAHs is signal management. All the individual cases are subject to safety monitoring and accessible in EudraVigilance as required by the MAH.
- MAHs should not be required to retrospectively enter reports of suspected adverse reactions, which were previously not made available to them. A reconciliation of individual cases as part of the pharmacovigilance system operated by the MAH based on the individual cases identified in EudraVigilance every time an e-RMR or a line listing is reviewed would imply major workload for the MAH without additional benefits as regards the safety monitoring of medicines.

Obligations of MAHs to record suspected adverse reactions they access through EudraVigilance

Next steps:

- EMA will consult the European Commission (EC) on the legal interpretation of the proposed options in the context of the EU pharmacovigilance legislation
- EMA will issue further guidance following consultation with the EC
- Industry is invited to nominate volunteers to work with the EudraVigilance Expert Working Group on the development of criteria to determine "pharmacovigilance obligations" and the subsequent recording of cases
- In the meantime, proceed in accordance with your currently established processes

Tips in working with EVDAS

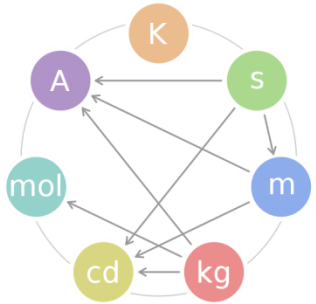
Number of cases in the eRMR and line listing

- A "2 day processing window" should always be considered in the Extract Transformation Loading (ETL) process for ICSRs in EVDAS
- This is due to the fact that the safety message processing is paused at 6 p.m. UK time to allow for other processes to operate over night (e.g. classification process, duplicate detection algorithm)
  - This means e.g. for the ad hoc eRMR, all ICSRs with the gateway date 1/4/2018 will be available on 4/4/2018 (instead of the 2/4/2018)
- **If you need all cases from a day, you will always need to wait an extra day before they are processed**

Number of cases in the eRMR and line listing

- A fix is planned for the ad-hoc eRMR by end of March 2018
- This is to reconfigure the ETL for the ad-hoc eRMR so it is executed with a "2-day delay" e.g. the ad hoc eRMR for the 16 April 2018 will only be available on the 19 April 2018
  - Note that the user can only select from the prompts, if a day hasn't been created yet in the ETL, it cannot be selected.
- The ad-hoc eRMR is therefore always what the user selects as date range.
- Similarly, the monthly fixed eRMR will be made available in future with a "2-day delay"
- The line listings always reflect the latest data up to the previous day i.e. 6 p.m

Line listings and E2B(R3) dose units



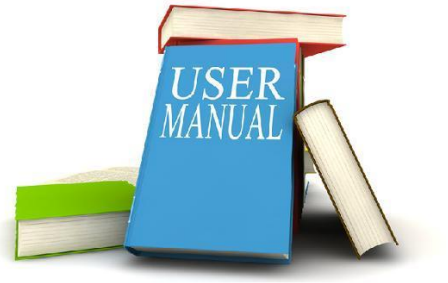
- For ICSRs submitted in E2B(R3) format: the dose unit does not display in the drug columns of the line listing.
- A fix is expected by the end of March.
- This does not affect the ICSR form, and the dose unit is available there.

Active substance groupings

- A fix will be implemented in May to ensure that the active substance grouping report will display only the latest version of validated medicinal product information based on the Article 57 submissions.
  - Currently all product information is shown also the non-validated one.

Tips in working with EVDAS

- These aspects will be addressed in detail as part of the next version of the EVDAS user manual



Any questions?

Further information

[Insert relevant information sources or contact details as applicable.]

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Follow us on **@EMA_News**