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SCIENCE MEDICINES HEALTH

EV-M5a EudraVigilance Data Analysis System (EVDAS) training for National Competent Authorities

Overview of the EVDAS functionalities and EVDAS outputs to support the pharmacovigilance obligations

Ana Cochino, Andrej Segec, Cosimo Zaccaria and Rodrigo Postigo (EMA)

- Introduction to this training module
- Introduction to EVDAS
- ICH-E2B(R3) EVDAS implementation
- Standard filtering criteria, new approach
- EudraVigilance administrative query library
- Pharmacovigilance query library
- Summary

Version 1.0

- Introduction to this training module
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Introduction: Context EV-M5a

- Target audience for this training module:
  - National Competent Authorities (NCAs) in the European Economic Area (EEA)
    - Personnel in the NCAs that use EVDAS for their pharmacovigilance activities
  - Note: The Art 57 EVDAS dashboard is out of scope of this training module; for this, a dedicated e-learning will be provided.

Introduction: Learning Objectives

- **At the end of this module participants will be able to:**
  - Understand the role of EVDAS as part of the EudraVigilance system.
  - Be familiar with the new EVDAS catalogue of reports.
  - Be able to retrieve EV data using the EVDAS interface.
  - Understand the EVDAS changes triggered by the new ICH-E2B(R3) standard.
  - Understand the main EVDAS reports and outputs.

- Introduction to this training module
- **Introduction to EVDAS**
- ICH-E2B(R3) EVDAS implementation
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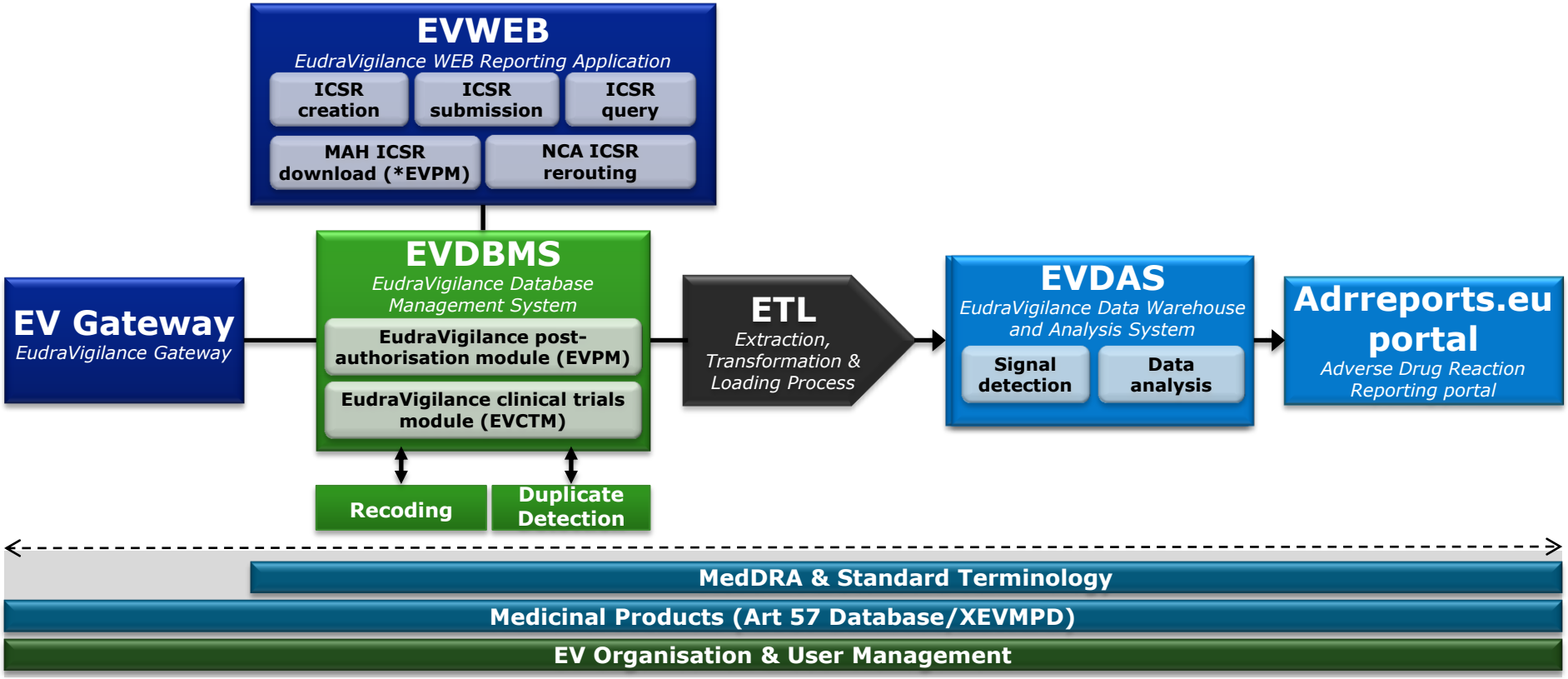
Section overview: Introduction to EVDAS

In this section you will obtain an understanding of:

- EVDAS – a general introduction and terminology used
- How to access EVDAS
- EVDAS welcome page
- EVDAS catalogue

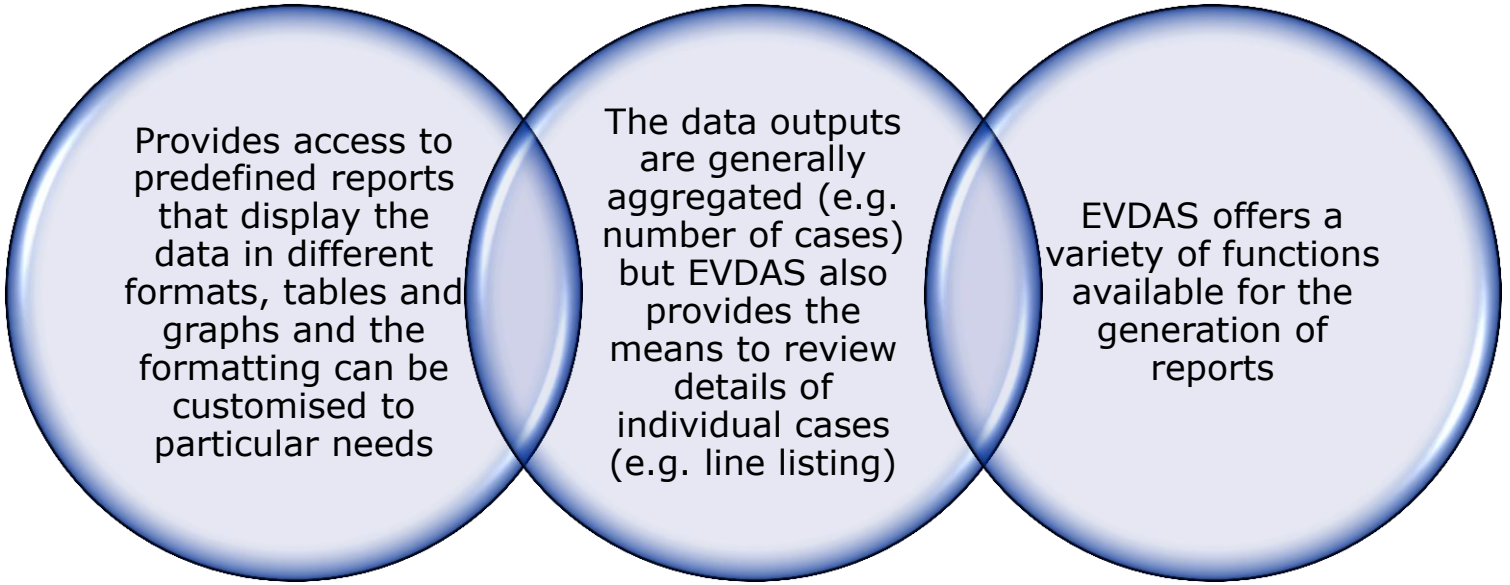
EVDAS


EVWEB
EudraVigilance WEB Reporting Application
ICSR creation
ICSR submission
ICSR query
MAH ICSR download (*EVPM)
NCA ICSR rerouting
EV Gateway
EudraVigilance Gateway
EVDBMS
EudraVigilance Database Management System
EudraVigilance post-authorisation module (EVPM)
EudraVigilance clinical trials module (EVCTM)
Recoding
Duplicate Detection
ETL
Extraction, Transformation & Loading Process
EVDAS
EudraVigilance Data Warehouse and Analysis System
Signal detection
Data analysis
Adrreports.eu portal
Adverse Drug Reaction Reporting portal
MedDRA & Standard Terminology
Medicinal Products (Art 57 Database/XEVMPD)
EV Organisation & User Management

Full description of the EudraVigilance system components and system functionalities are provided in the training module:

EV- M2 Introduction to EV system components and system functionalities

EVDAS


Provides access to predefined reports that display the data in different formats, tables and graphs and the formatting can be customised to particular needs
The data outputs are generally aggregated (e.g. number of cases) but EVDAS also provides the means to review details of individual cases (e.g. line listing)
EVDAS offers a variety of functions available for the generation of reports

EVDAS

The following slides are intended to provide an overview of the main EVDAS features.

This section is intended to be a refresher of the EVDAS interface that could be beneficial for the less experienced users

EVDAS terminology – Objects

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- **Dashboard** is a combination of formats and prompts that when answered and run provides the data in a form of a report.

- The Icon representing a dashboard: 

- The **Report** is the result set of the dashboard that has a defined layout and format.

- The Icon representing a report: 

- **Briefing books** are saved version of reports. These can be saved a snapshot (static version) or as updatable (prompt answers a saved and the report re-runs when the briefing book is opened)

- The icon representing a briefing book: 

Grids and graphs

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a. Medicinal Product Reaction Report (# Individual Cases)

View filter details

No

Recoded Medicinal Product (High Level) OK

Select View Grid

Active Substance (High Level) DABRAFENIB

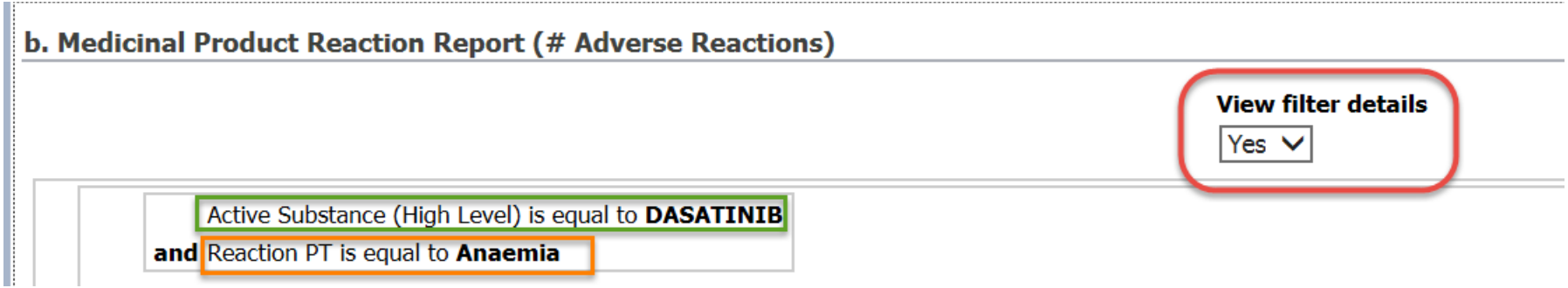
Recoded Medicinal Product (High Level)	DABRAFENIB	TAFINLAR
Reaction SOC		
Blood and lymphatic system disorders	1	3
Cardiac disorders		1
Eye disorders		3
Gastrointestinal disorders	1	4
General disorders and administration site conditions	3	13
Hepatobiliary disorders		1
Infections and infestations		5
Injury, poisoning and procedural complications	1	3
Investigations		11
Metabolism and nutrition disorders		3
Musculoskeletal and connective tissue disorders		1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	14
Nervous system disorders	3	6
Psychiatric disorders	1	2
Renal and urinary disorders	1	1
Respiratory, thoracic and mediastinal disorders	1	6
Skin and subcutaneous tissue disorders	1	5
Social circumstances		1
Surgical and medical procedures		2
Vascular disorders	1	3

10:21:43

Return - Analyze - Refresh - Print - Export - Add to Briefing Book - Create Bookmark Link

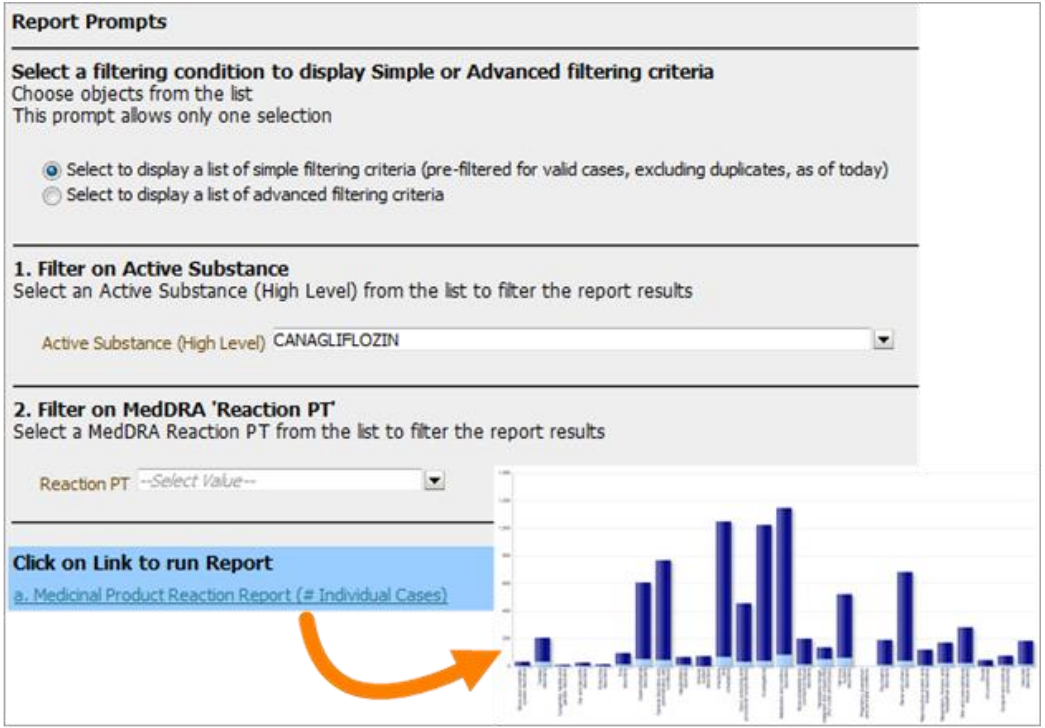
Filters

- Filters define conditions that data must meet to be included in the report results. Only data that meets all the report conditions appears in the final results.
- To see the filters selected together with the report results, the option 'view filters details' should be selected as Yes.



Prompts

- Prompts enable users to select conditions to be included in a report.



Accessing EVDAS

EVDAS can only be accessed via EudraNet. In practice, this means that to access EVDAS users will either need to be in a National Competent Authority (NCA) or the European Commission (EC) or operating from within the firewall of the EC or an NCA, for example via remote log-in.

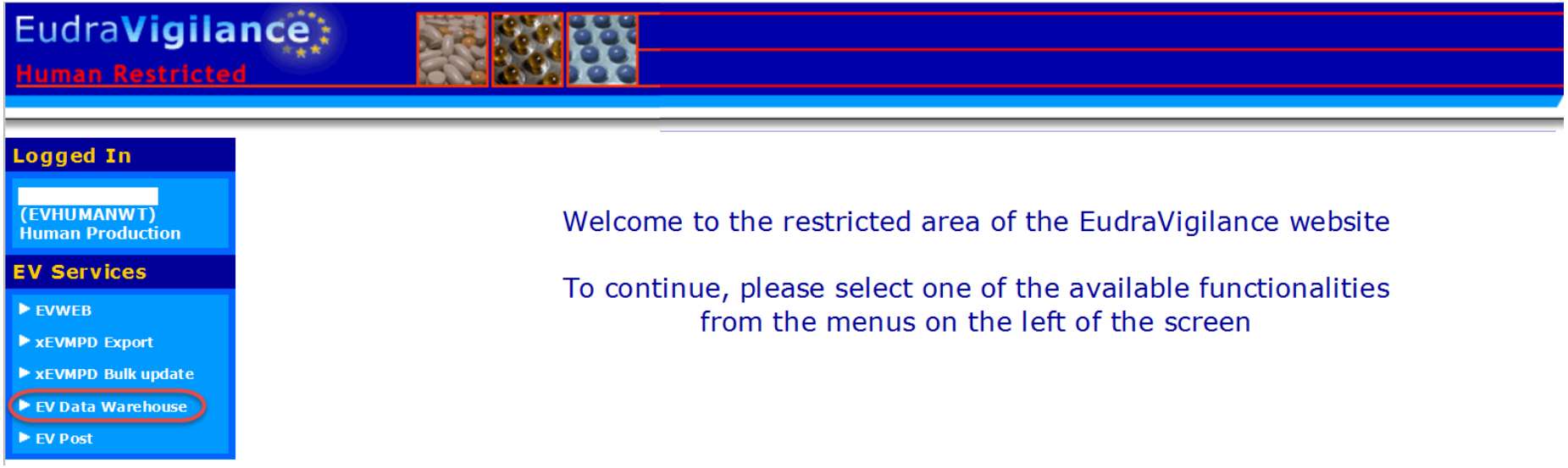
From within EudraNet, there are two methods of accessing EVDAS:

- via the EudraVigilance webpage;
- via the EVDAS welcome page;

Access via the EudraVigilance page

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp&mid=WC0b01ac05800250b5

Access via the EudraVigilance page

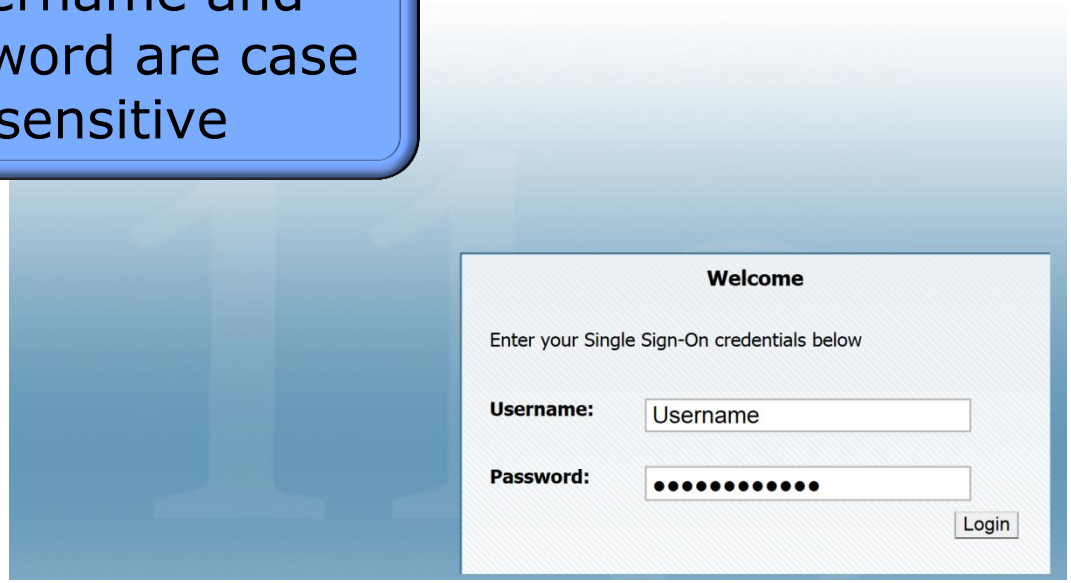


Accessing EVDAS

- Access via EVDAS welcome page:

- http://bi.eudra.org/analytics/saw.dll?dashboard&PortalPath=%2Fshared%2FEudraVigilance%20DWH%20(EVDAS)%2F_portal%2FEudraVigilance%20Data%20Analysis%20System.

Username and password are case sensitive



EVDAS Welcome page

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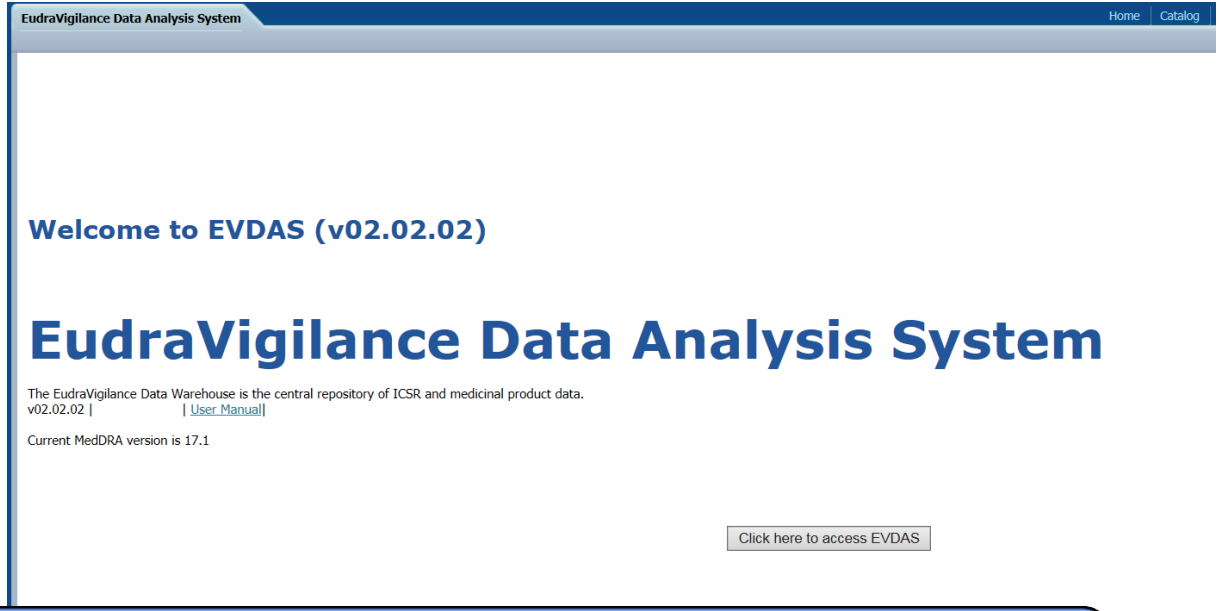
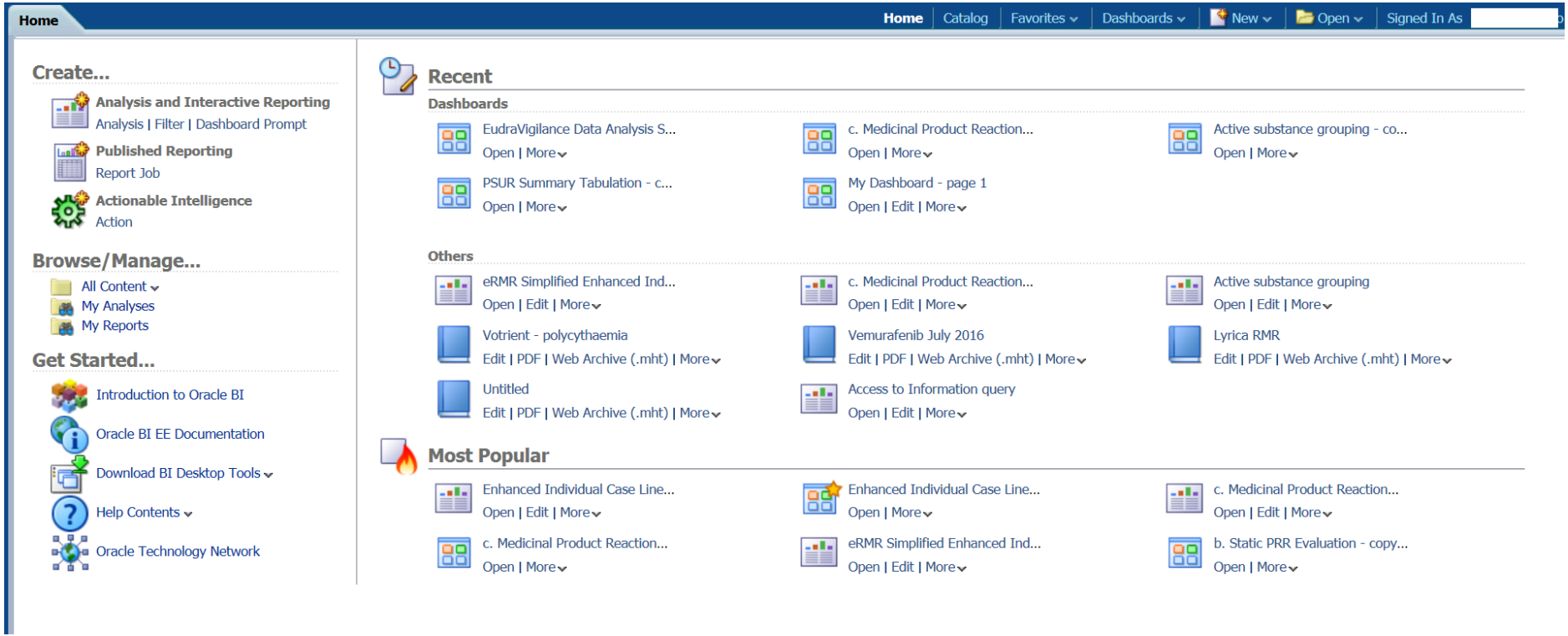
If you access EVDAS via the EV webpage or through the EVDAS page, you will arrive at the EVDAS welcome page

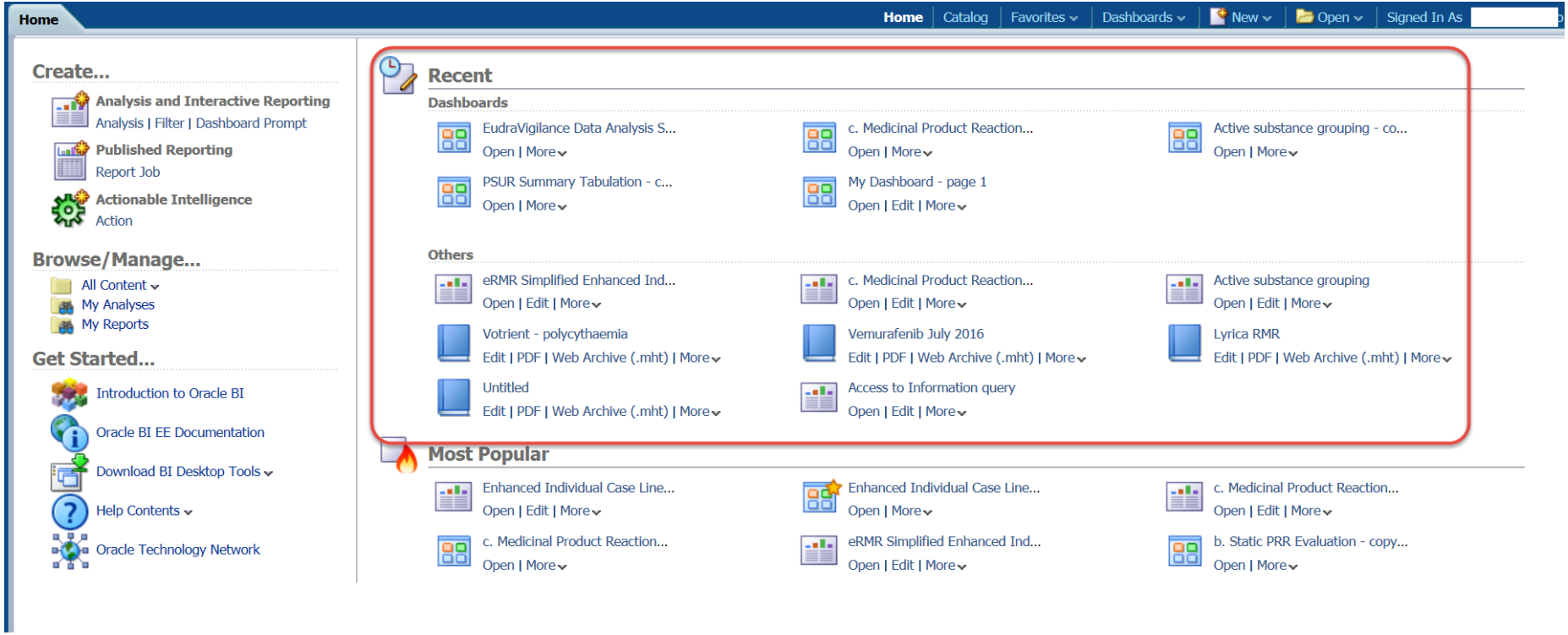


Be aware that in this page you will be able to access the training manuals and also you will know the current MedDRA version implemented in the system

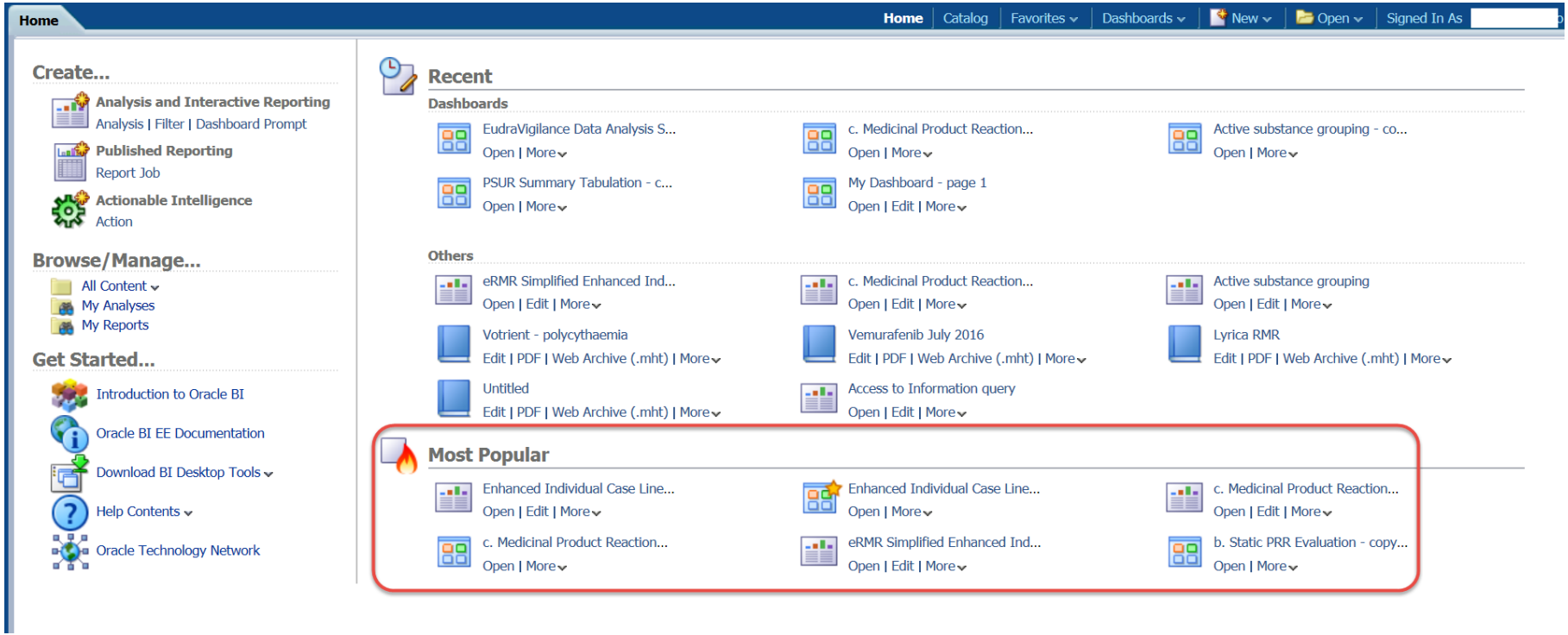
EVDAS home page



EVDAS home page – Recent



EVDAS home page – Most popular



EVDAS home page - Create

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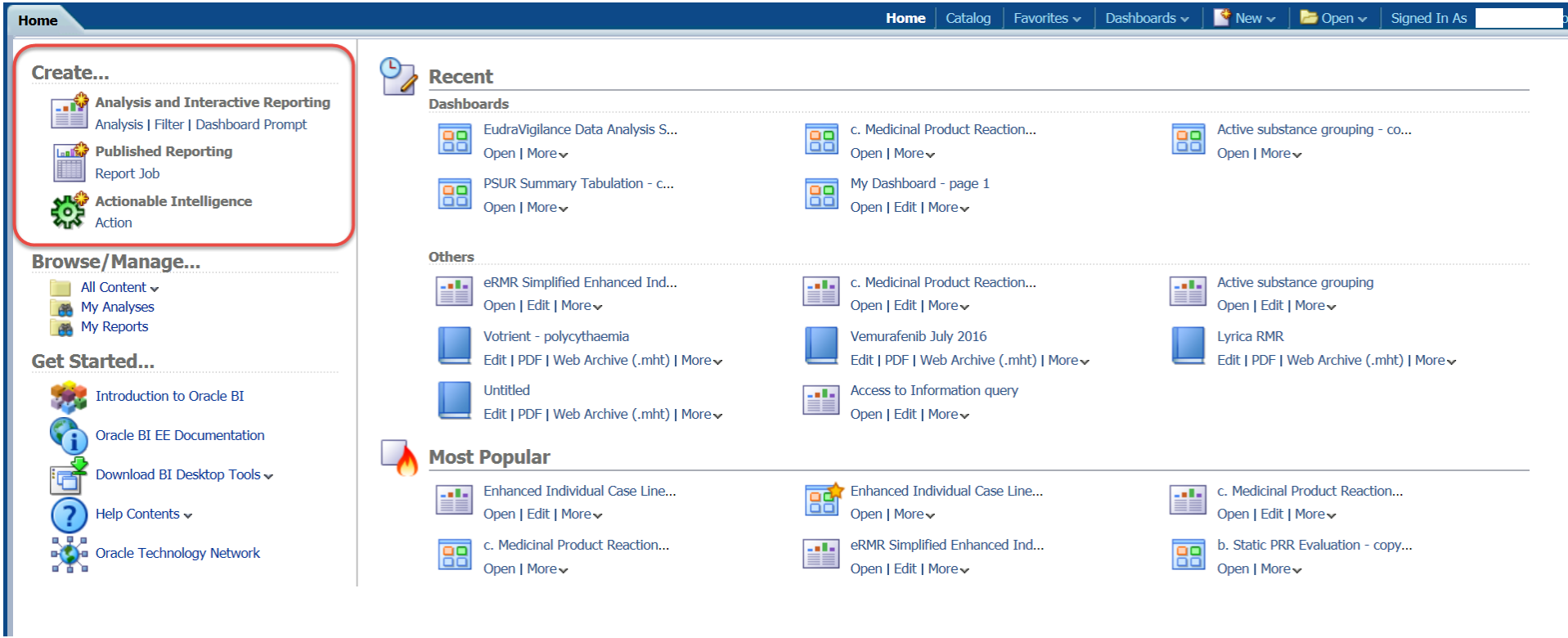

EVDAS home page – Browse/Manage

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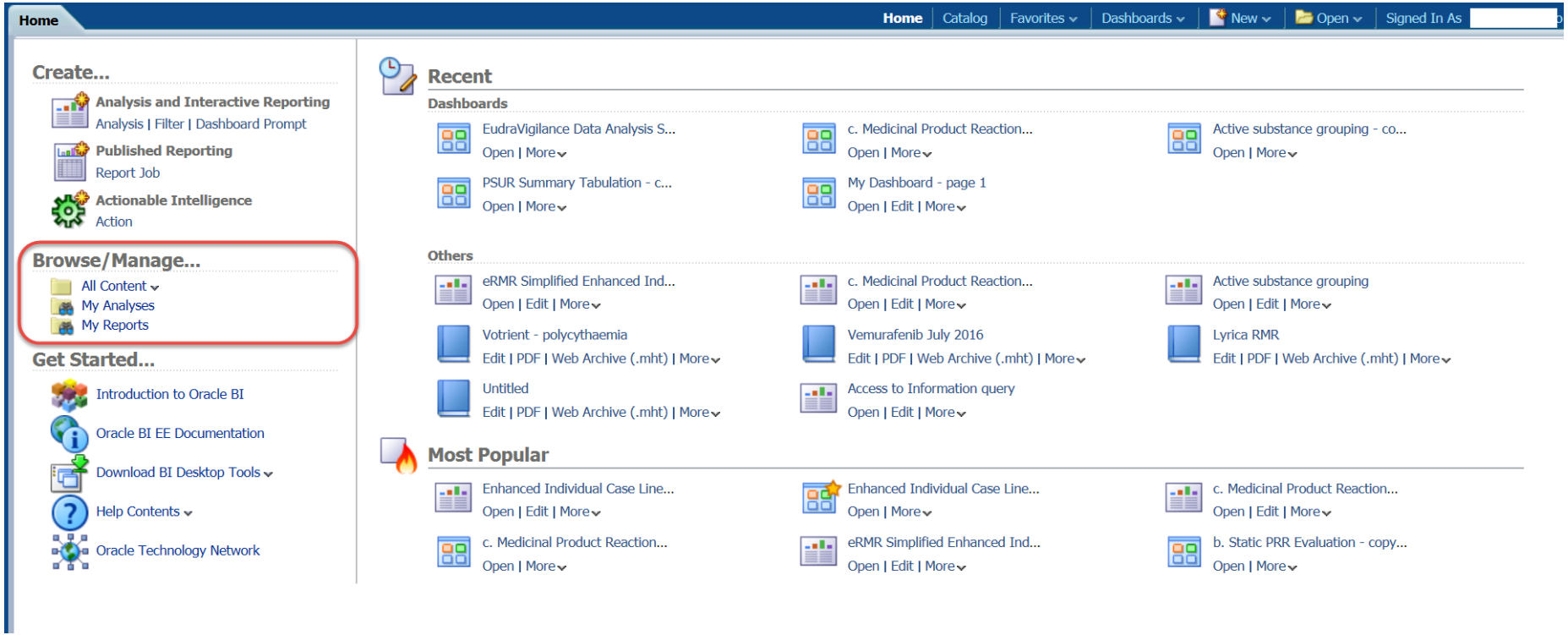
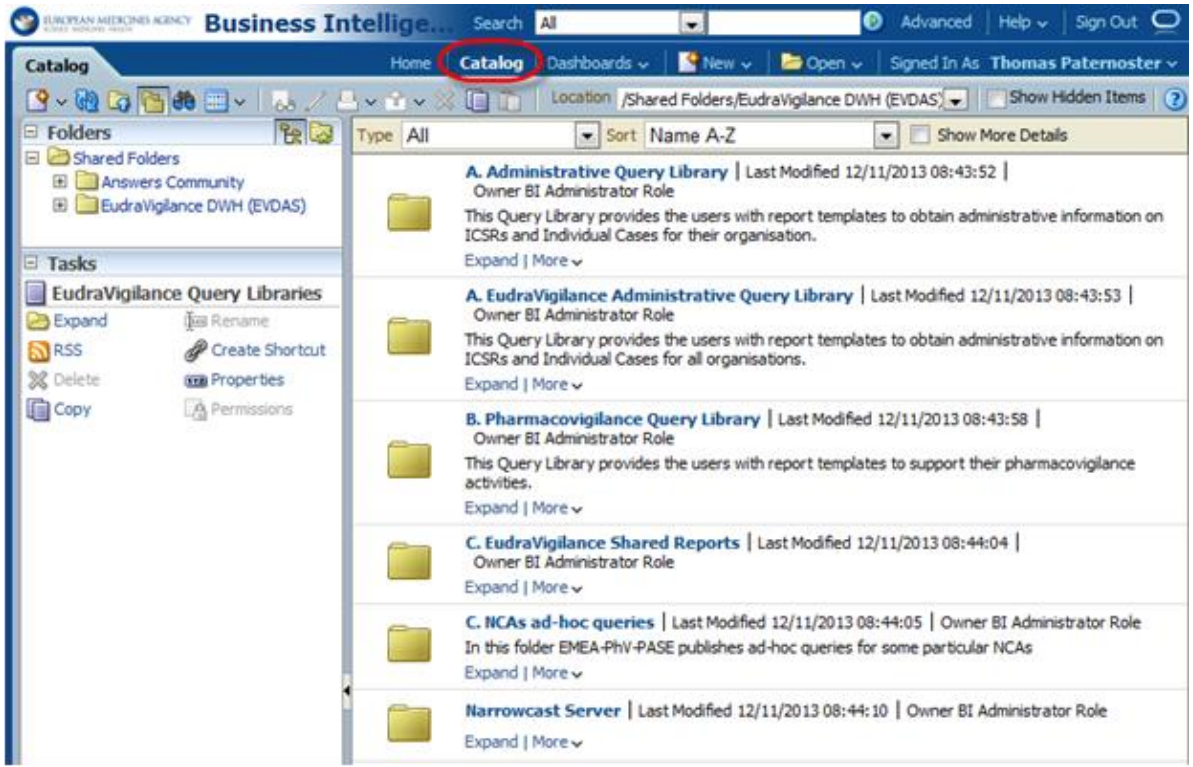


EVDAS Catalogue



EVDAS Catalogue

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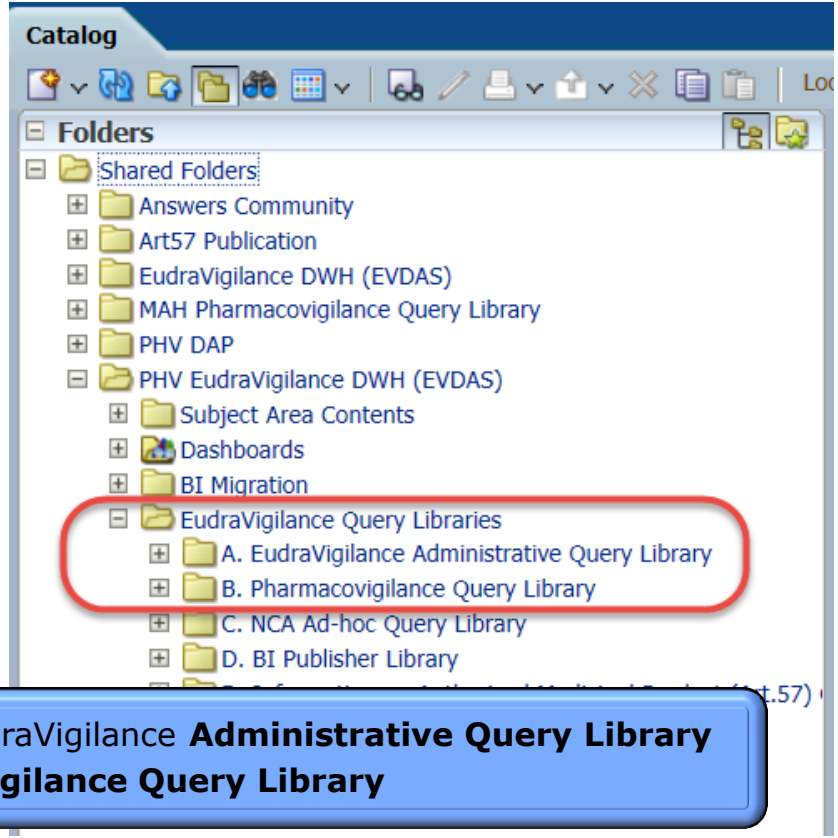
In the folder **EudraVigilance Query Libraries** you will find the new catalogue of reports. Some of the reports are new and other have been enhanced



This training module will focus on the EudraVigilance **Administrative Query Library** and the **Pharmacovigilance Query Library**

Full description of EVDAS and its functionalities is provided in the following training manual:

EV-G2 EVDAS Report Manual

Note: if you are not yet familiar with EVDAS, consult the EVDAS user manual, specifically the chapter on executing queries

Section Summary

In this section you obtained an understanding of:

- What is EVDAS and the different ways to access EVDAS
- General EVDAS terminology
- EVDAS welcome page
- How to access the EVDAS catalogue

- Introduction to this training module
- Introduction to EVDAS
- **ICH-E2B(R3) EVDAS implementation**
- Standard filtering criteria, new approach
- EudraVigilance administrative query library
- Pharmacovigilance query library
- Summary

Section overview: ICH-E2B(R3) EVDAS implementation

In this section you will obtain an understanding of:

- The main fields in the EVDAS reports that are impacted due to the implementation of the ICH-E2B(R3) standard in EudraVigilance
- How the EVDAS filters and outputs have been modified in light of the implementation of the ICH-E2B(R3) standard in EudraVigilance
- The differences in those fields with the previous data structure - ICH-E2B(R2)

Note: this section is not intended to provide a full explanation of the ICH E2B(R3) data elements; it will only outline those that have a direct impact in the EVDAS prompts and therefore triggered changes in the way the database is queried and the data is filtered.
The implementation of some of the new elements in ICH E2B(R3) is also described in this section.

ICH-E2B(R3) EVDAS implementation

- EVDAS has been updated and enhanced to support the ICH-E2B(R3) format and new data elements.
- For a period of time MAHs/NCAs will be able to submit ICSRs in R2 format but those will be converted to the new R3 data structure.
- All existing ICSRs in ICH E2B(R2) format have been migrated to the new ICH E2B(R3) standard.
- Users should always be aware that EudraVigilance contains ICSRs submitted in ICH-E2B(R2) and (R3) format and that should be always taken into account when analysing the data (e.g. filtering on new data elements introduced in ICH E2B(R3) standard will not retrieve any case reported under ICH E2B(R2).

Primary source for regulatory purposes

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- New data element introduced in ICH E2B(R3) format (C.2.r.5).
- Identifies which of the primary sources in the ICSR is used for regulatory purposes.
- Based on that, the country of the primary source for regulatory purposes can be identified.

Impact on EVDAS Implementation	
A new filter for "primary source country for regulatory purposes" is created	
R2 data	Use the following algorithm: • occurrence country, • if missing, primary source country • if missing, country code from the Worldwide Unique Case Identification Number
R3 data	Use the country of the primary source for regulatory purposes (C.2.r.5)
EVDAS outputs containing country information (e.g. line listing) are modified to show the primary source country for regulatory purposes	

Primary source country

- This field was provided at case level in ICH E2B(R2) terminology – 'Identification of the country of the primary source' (A.1.1).
- In ICH E2B(R3) can be found under the data element 'Reporter's country code' (C.2.r.3) for each of the reporters and therefore there could be more than one 'Reporter's country' in the same ICSR.

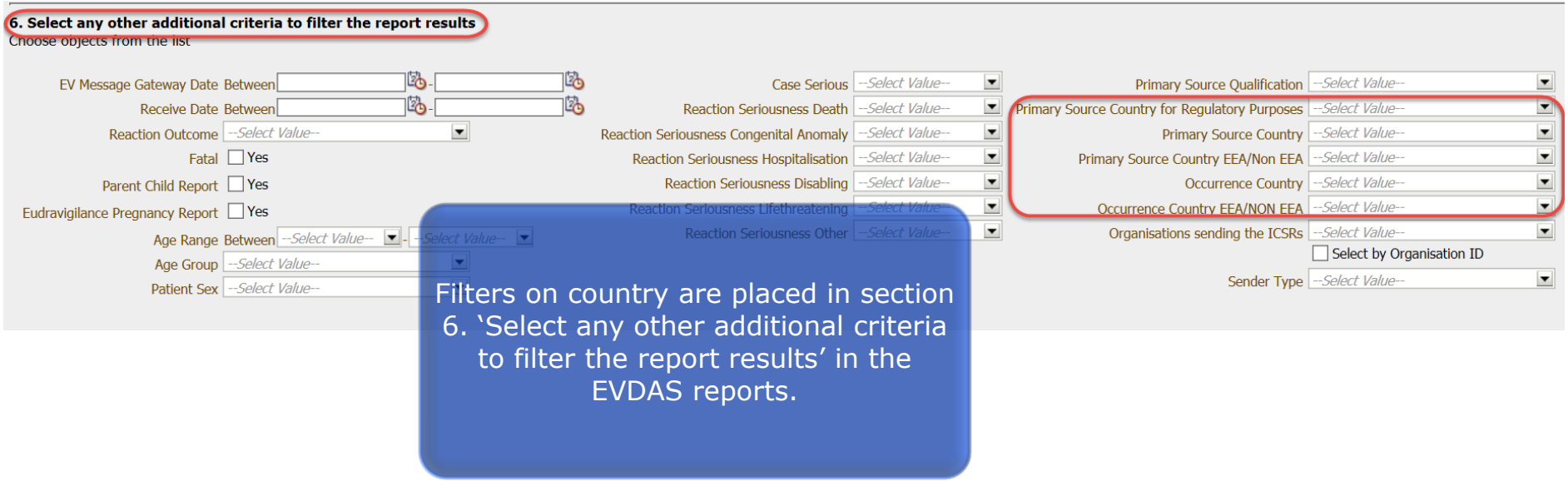
Impact on EVDAS Implementation	
The filter for 'primary source country' is maintained	
R2 data	Use the country of the primary source of the report (A.1.1)
R3 data	Use the primary source country for regulatory purposes (C.2.r.5) in order to harmonise the approach between R2 and R3.

Country where the reaction/event occurred

- This field was provided at case level in ICH E2B(R2) – 'Identification of the country where the reaction/event occurred' (A.1.2).
- In ICH E2B(R3) format, the information is provided in the 'Identification of the country where the reaction/event occurred' (E.i.9) for each of the reactions in the ICSR.

Impact on EVDAS Implementation	
The filter for 'Occurrence country' is maintained	
R2 data	Use the following algorithm when retrieving the data using the EVDAS filter: • occurrence country (A.1.2), • if missing, primary source country (A.1.1) • If missing, country code for the Worldwide Unique Case Identification Number
R3 data	Use the identification of the country where the reaction/event occurred (E.i.9)
Remember, EVDAS outputs containing country information (e.g. Line listing) will use the primary source country for regulatory purposes.	

Country filters



Filters on country are placed in section 6. 'Select any other additional criteria to filter the report results' in the EVDAS reports.

Seriousness Criteria

- This field was provided at case level in ICH E2B(R2) – 'Seriousness criteria' (A.1.5.2.).
- Seriousness criteria are provided at reaction level in ICH E2B(R3) – 'Seriousness criteria at event level' (E.i.3.2 a-f).

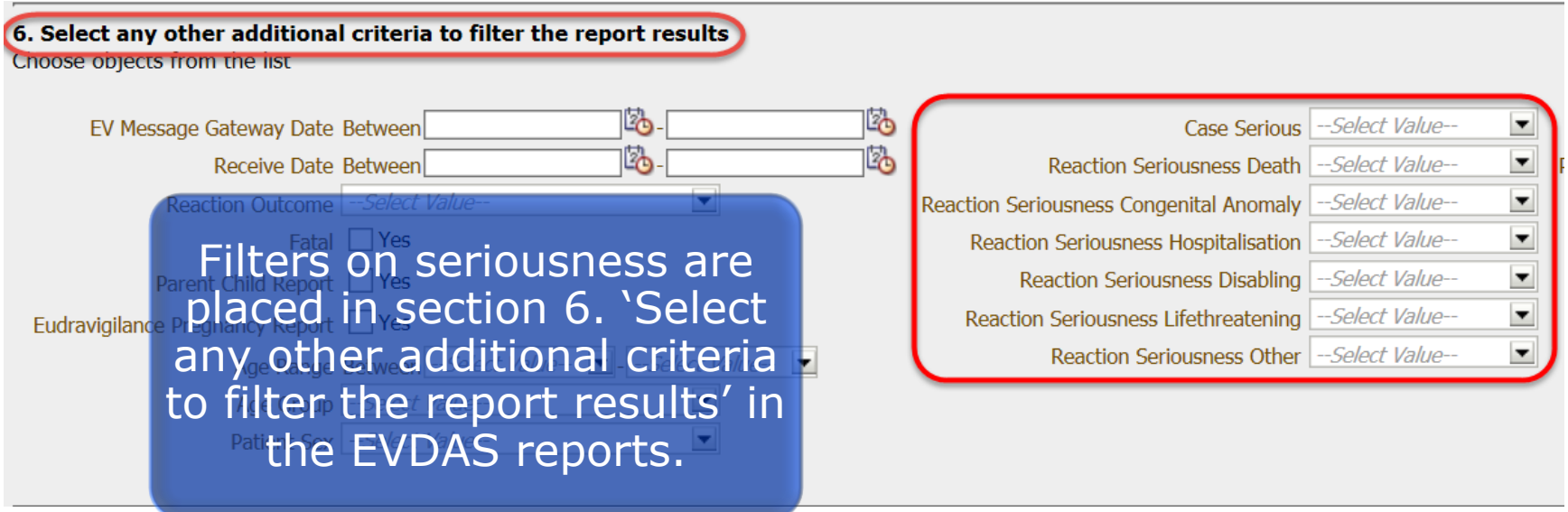
Impact on EVDAS Implementation	
New filters are created to reflect the different seriousness criteria per reaction	
R2 data	For each of the reactions all the seriousness criteria provided at case level are applied at reaction level (A.1.5.2)
R3 data	Use the seriousness criteria at reaction level (E.i.3.2)

Case serious

- The possibility to filter for seriousness at case level is maintained and updated to retrieve ICH-E2B(R2) and ICH E2B(R3) data.

Impact on EVDAS Implementation	
The filter for 'case serious ' is maintained	
R2 data	Use the field "Serious" (A.1.5.1) provided at case level
R3 data	If at least one reaction contains any seriousness criteria marked as "Yes", the case will be considered serious

Seriousness filters

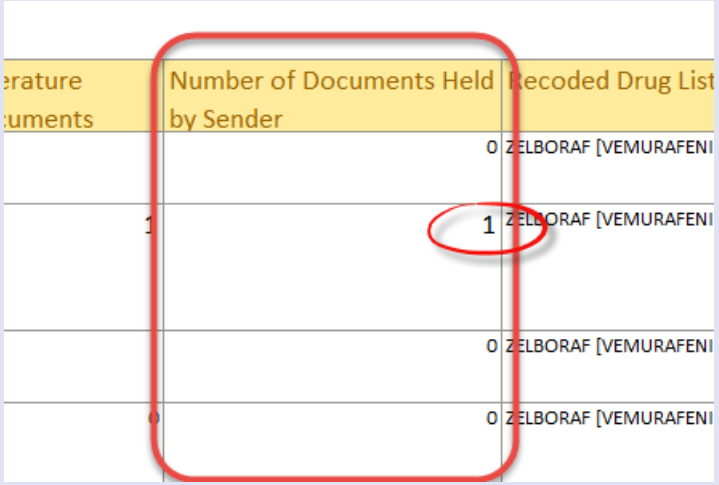


Included documents

- New data element introduced in ICH E2B (R3) - C.1.6.1.r.2.
- Contains the actual content of documents held by the sender (C.1.6.1.r.1) if the sender chooses to send the document (e.g. clinical records, autopsy reports, X-rays).

Impact on EVDAS Implementation	
R2 data	Not applicable
R3 data	The documents are accessible via de individual case line listing

- Line listing hyperlink

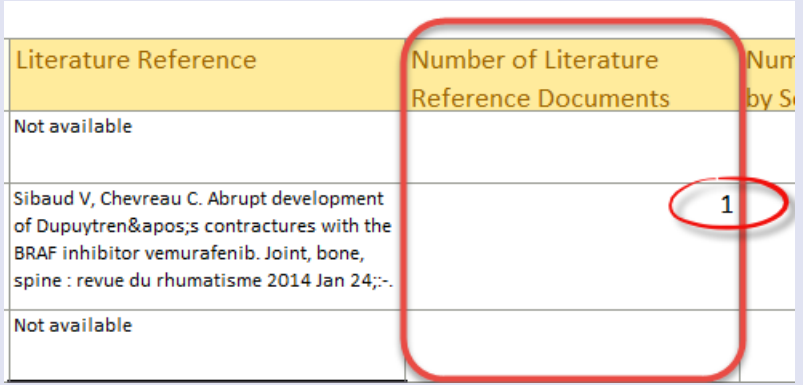


Included documents – Literature articles

- New data element introduced in ICH E2B(R3) - C.4.r.2.
- Contains the actual content referenced in C.4.r.1 ‘Literature reference’ when the sender chooses to send a copy of the literature article.

Impact on EVDAS Implementation	
R2 data	Not applicable
R3 data	The articles are accessible via de individual case line listing

- Line listing hyperlink



Literature Reference	Number of Literature Reference Documents	Num by S
Not available		
Sibaud V, Chevreau C. Abrupt development of Dupuytren's contractures with the BRAF inhibitor vemurafenib. Joint, bone, spine : revue du rhumatisme 2014 Jan 24;:-.	1	
Not available		

Medical Confirmation by a healthcare professional

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- This field was provided at case level in ICH E2B(R2) - A.1.14 'Was the case medically confirmed, if not initially reported from a healthcare professional?'
- In ICH E2B(R3) format, the information is provided for each reaction as part of the data element 'Medical confirmation by healthcare professional' (E.i.8). The field indicates whether the occurrence of the event was subsequently confirmed by a healthcare professional.

Impact on EVDAS Implementation	
R2/R3	No filter is implemented in EVDAS for this data field. To identify cases reported by patients, the filter on primary source qualification (HCP/non-HCP) should be used
The field is populated in the ICSR form.	

Study registration number

- New data element introduced in the ICH E2B(R3) format 'Study registration' C.5.1.r.1
- The field is populated with the study registration number as assigned in a reporting region
- In the EEA the study registration number is the EudraCT number

Impact on EVDAS Implementation	
The previous filter "EudraCT number" is renamed to "Study registration number"	
R2 data	Use the EudraCT number
R3 data	Use the study registration number (C.5.1.r.1)
The EVDAS report B.6.a is renamed to 'EVCTM cases by study registration number'	

Study registration country

- New data element introduced in the ICH E2B(R3) format 'study registration country' (C.5.1.r.2)
- Populated with the country that assigned the study registration number (C.5.1.r.1)
- For studies with EudraCT the study registration country is "European Union"

Impact on EVDAS Implementation	
A new filter for 'study registration country' is created	
R2 data	Use "European Union" for the cases with EudraCT number
R3 data	Use the study registration country (C.5.1.r.2)

Study details filters

Filters on study details are placed in section 6. 'Select any other additional criteria to filter the report results' in the EVDAS reports

Family history

- New data element introduced in ICH E2B(R3) format – 'Family history' (D.7.1.r.6)
- It is set to "Yes" when the medical information provided in the structured information on relevant medical history (D.7.1.r) is reported also to be present in another family member (e.g. hereditary diseases)

Impact on EVDAS Implementation
This field is not implemented as a filter in the EVDAS reports
The information is reflected in the new ICSR form

Relevant Medical History and Concurrent Conditions

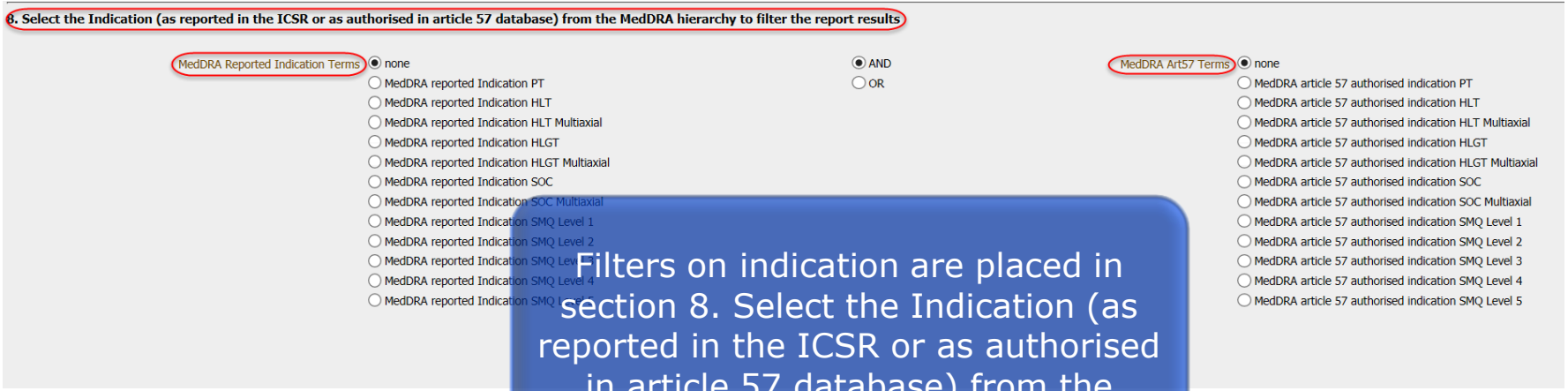
MedDRA LLT	Start Date	End Date	Continuing	Family History	Comments
Atrial fibrillation	10/10/1995		Yes	Yes	The patient was diagnosed with atrial fibrillation in another hospital and no records are in our files
Pneumothorax	04/01/1996		No		The pneumothorax was a spontaneous pneumothorax and the patient had to be intubated for more than a week.

Indication for use

- The ICH E2B(R2) data element ‘indication for use in the case’ (B.4.k.11) becomes a repeatable data element in ICH E2B(R3) within the drug section without the need to repeat the entire drug section (G.k.7.r.2b)

Impact on EVDAS Implementation	
The previous filter for indication placed in the ‘Medicinal Product hierarchy’ section is moved to a new section.	
R2 data	Use indication for use in the case (B.4.k.11)
R3 data	Use the indication for use in case (G.k.7.r.2b) MedDRA code
The indication is shown in the individual case line listing and in the ICSR form	

Filter on the “Indication” for use



Filters on indication are placed in section 8. Select the Indication (as reported in the ICSR or as authorised in article 57 database) from the MedDRA hierarchy to filter the report results

Drug role characterisation

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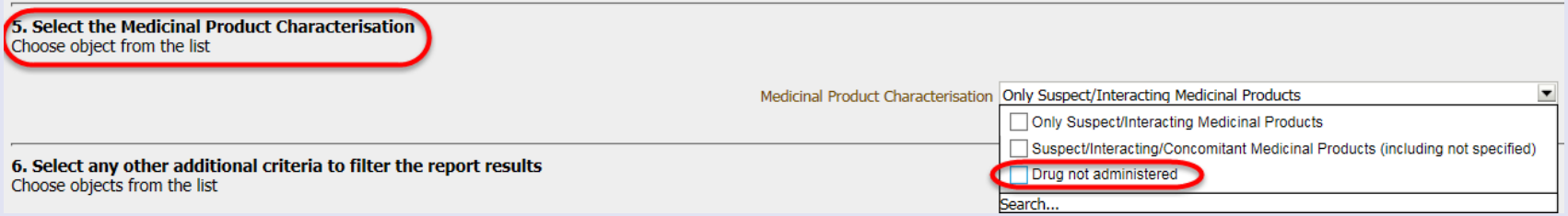
- A new value 'drug not administered' is available in the new ICH E2B(R3) format for the data field 'drug role characterisation' (G.k.1)

Impact on EVDAS Implementation
The EVDAS filter "Medicinal Product Characterisation" has been modified to include the new value
The enhanced individual case line listing is modified to include this new drug role in the "enhance reported drug list" column

- This filter can be found in Section 5. in the EVDAS reports :



Drug Start date, treatment duration, dose and route of administration

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- In the new ICH E2B(R3) format these data elements are repeatable for the same drug

Impact on EVDAS Implementation
These fields are included in the outcome of the individual case line listing under the enhanced 'reported drug list' column. The line listing contains only data of the 1st occurrence of the repeated fields based on the earliest drug start date
The rest of the values can be found in the ICSR form
The line listing is modified to include the string 'more in ICSR' when one of these data fields contains more than one value

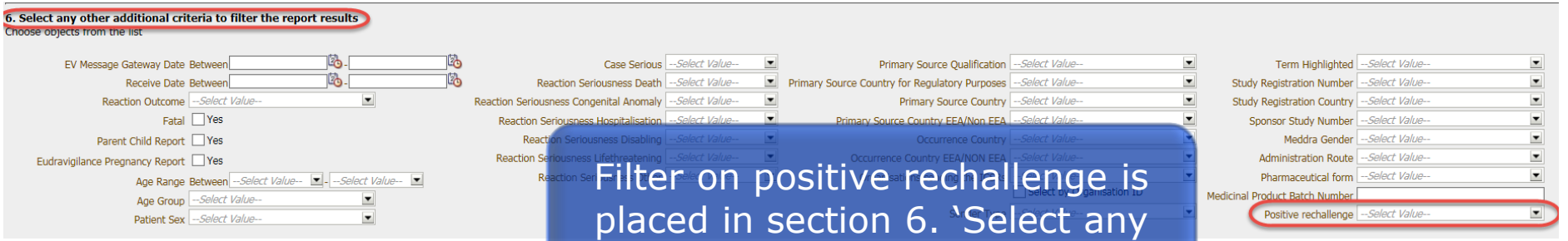
Rechallenge

- New data element introduced in the ICH E2B(R3) format (G.k.9.i.4) 'did the reaction recur on re-administration'. This data element indicates both if the patient was rechallenged with the drug and the known outcome.
- R2 data used the data element 'did reaction recur on readministration?' (B.4.k.17.1) and if yes then 'which reaction(s)/event(s) recurred?' under data element (B.4.k.17.2)

Impact on EVDAS Implementation	
A new filter is created to retrieve the cases with positive rechallenge information	
R2 data	Use only positive rechallenge when the reaction recurred on readministration and the reaction is provided (B.4.k.17.1) & (B.4.k.17.2).
R3 data	Use only positive rechallenge (yes-yes) from the data element "Did the Reaction Recur on Re-administration?" (G.k.9.i.4)

Values allowed in the ICH E2B(R3) data field "Did Reaction Recur on Re-administration?" (G.k.9.i.4)		
1	yes – yes	rechallenge was done, reaction recurred
2	yes – no	rechallenge was done, reaction did not recur
3	yes – unk	rechallenge was done, outcome unknown
4	no – n/a	no rechallenge was done, recurrence is not applicable

Filter on rechallenge



Filter on positive rechallenge is placed in section 6. 'Select any other additional criteria to filter the report results' in the EVDAS reports

NullFlavors

- In the new ICH E2B(R3) format, the concept of “NullFlavor” is introduced
- These are specific values for data elements that can be used in different context

Impact on EVDAS Implementation
NullFlavors are displayed in the EVDAS report outcomes (e.g. line listing) when applicable. However only the code (e.g. MSK, NASK) instead of the full description will be displayed in the concatenated fields of the Enhanced individual case line listing.
In the ICSR form, NullFlavors will not be displayed (value will be left blank), except for the MSK value.

Code Name Definition	Code Name Definition	Code Name Definition
NI	No Information	No information whatsoever can be inferred from this exceptional value. This is the most general exceptional value. It is also the default exceptional value.
MSK	Masked	There is information on this item available but it has not been provided by the sender due to security, privacy or other reasons. There could be an alternate mechanism for gaining access to this information. Note: using this nullFlavor can provide information considered to be a breach of confidentiality, even though no detail data is provided. Its primary purpose is for those circumstances where it is necessary to inform the receiver that the information does exist without providing any detail
UNK	Unknown.	A proper value is applicable, but not known.
NA	Not Applicable	No proper value is applicable in this context (e.g. last menstrual period for a male).
ASKU	Asked But Unknown	Information was sought but not found (e.g. patient was asked but didn't know)
NASK	Not Asked	This information has not been sought (e.g. patient was not asked)
NINF	Negative Infinity	Negative infinity of numbers
PINF	Positive Infinity	Positive infinity of numbers.

Details of the impact of the new ISO/ICH E2B(R3) ICSR standard on ADR reporting and the new business rules in EudraVigilance are provided in the following training module:

PhV-M2a Implementing ISO ICSR/ICH E2B(R3): Key changes for pharmacovigilance

Section summary: ICH-E2B(R3) EVDAS implementation

In this section we have covered

- The main fields in EVDAS that are impacted due to the implementation of the ICH-E2B(R3) standard in EudraVigilance
- How the EVDAS filters and outputs have been modified in light of the implementation of the ICH-E2B(R3) standard in EudraVigilance
- The differences in those fields with the previous data structure - ICH-E2B(R2) guideline
- Where the filters related to those data elements are located in the EVDAS reports

- Introduction to this training module
- Introduction to EVDAS
- ICH-E2B(R3) EVDAS implementation
- **Standard filtering criteria, new approach**
- EudraVigilance administrative query library
- Pharmacovigilance query library
- Summary

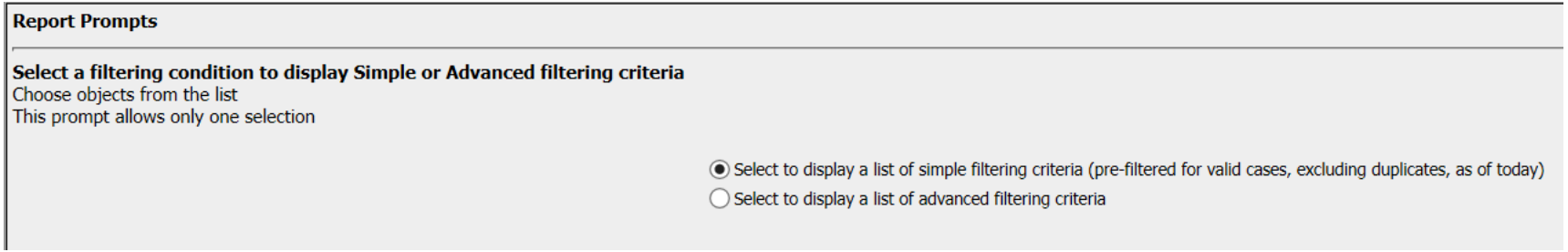
Section overview: Standard filtering criteria, new approach

In this section you will obtain an understanding of:

- The new approach implemented in EVDAS as a standard filtering criteria
- The difference between the simplified and the advanced filtering criteria
- The different filters included in the advance filtering criteria
- Possibilities to further filter the data outputs

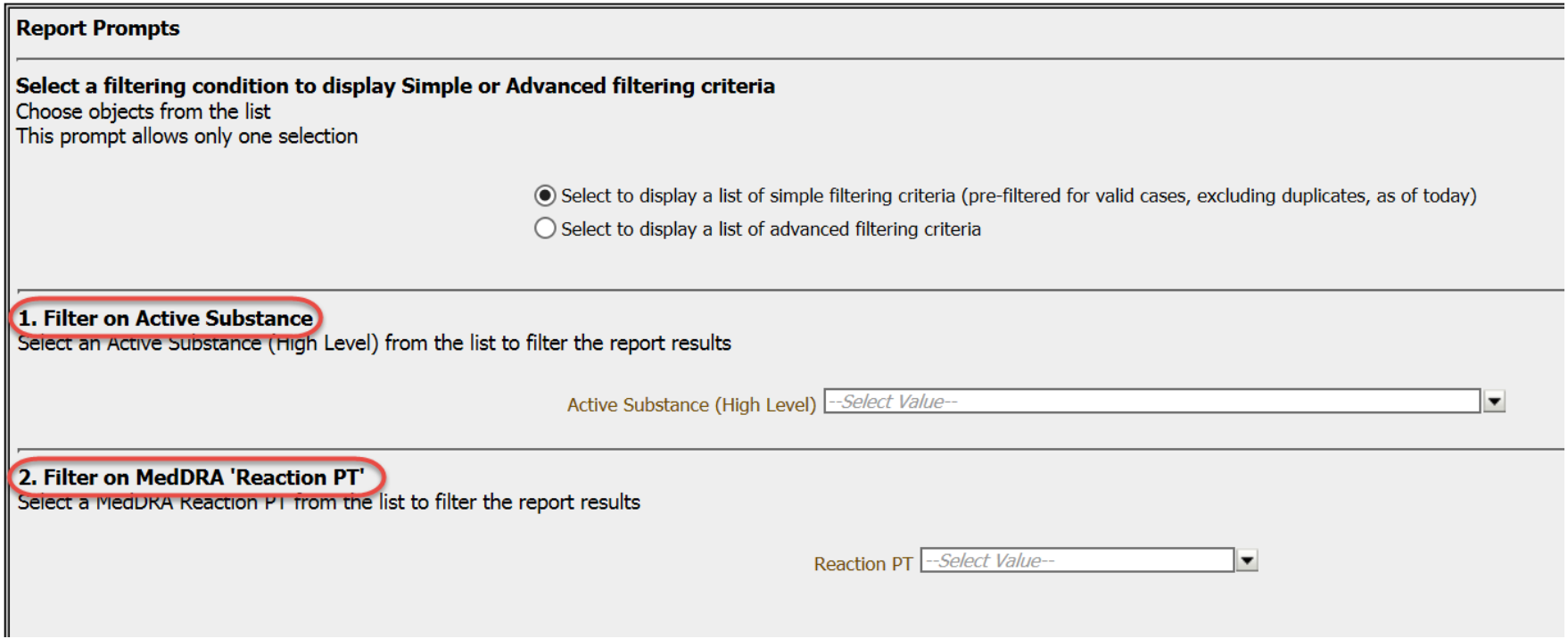
Standard filtering criteria: new approach

- The vast majority of the reports in the Pharmacovigilance query library and some of the reports in the EudraVigilance administrative query library provide the possibility to use a simplified or advanced filtering criteria
- The default option when you open a report with these possibilities is always the simplified filtering criteria
- To move from the simplified to the advance options, select to display a list of the advance filtering criteria



Please be aware that these 2 options are not available in some EVDAS reports. Due to specific characteristics of some reports (eRMR simplified reports, MedDRA dictionary reports) these options are not applicable

Simplified filtering criteria



Active substance (high level) filter

- The active substance high level is based on a manually created hierarchy, grouping similar substances into “groups”
- Most frequently, these groups are formed of various salts (e.g. abacavir succinate; amlodipine maleate) of a particular moiety (abacavir; amlodipine).
- The moiety is also a value within the group.

Active substance (low level)	Active substance (high level)
ABACAVIR	ABACAVIR
ABACAVIR SUCCINATE	
ABACAVIR SULFATE	

Active substance (low level)	Active substance (high level)
AMLODIPINE	AMLODIPINE
AMLODIPINE BESILATE	
AMLODIPINE MALEATE	
AMLODIPINE MESILATE	

High level active substance vs. low level active substance

- The active substance high level is generally used by default; the low level is used when there is an interest in e.g. a particular salt.
- Querying the substance "high level" (e.g. amlodipine) has a different meaning than querying the substance "low level".

Active substance (low level)	Active substance (high level)
AMLODIPINE	AMLODIPINE
AMLODIPINE BESILATE	
AMLODIPINE MALEATE	
AMLODIPINE MESILATE	

High level active substance vs. low level active substance

- "amlodipine" queried at low level will retrieve the reports where only "amlodipine" is reported, in the example only 8,300 cases will be retrieved.

Active substance low level	AMLODIPINE	AMLODIPINE BESILATE	AMLODIPINE MALEATE	AMLODIPINE MESILATE
Number of cases	8,300	10,230	3,230	1,144

- "amlodipine" queried at high level will retrieve reports for the group of substances (e.g.: reports with "amlodipine besilate", "amlodipine maleate" etc.)

Active substance high level	AMLODIPINE
Number of cases	14,600

Simplified filtering criteria

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Run a report by selecting the active substance high level and a MedDRA PT only.

- Multiple entries for substances and PTs are possible

Duplicates are excluded by default

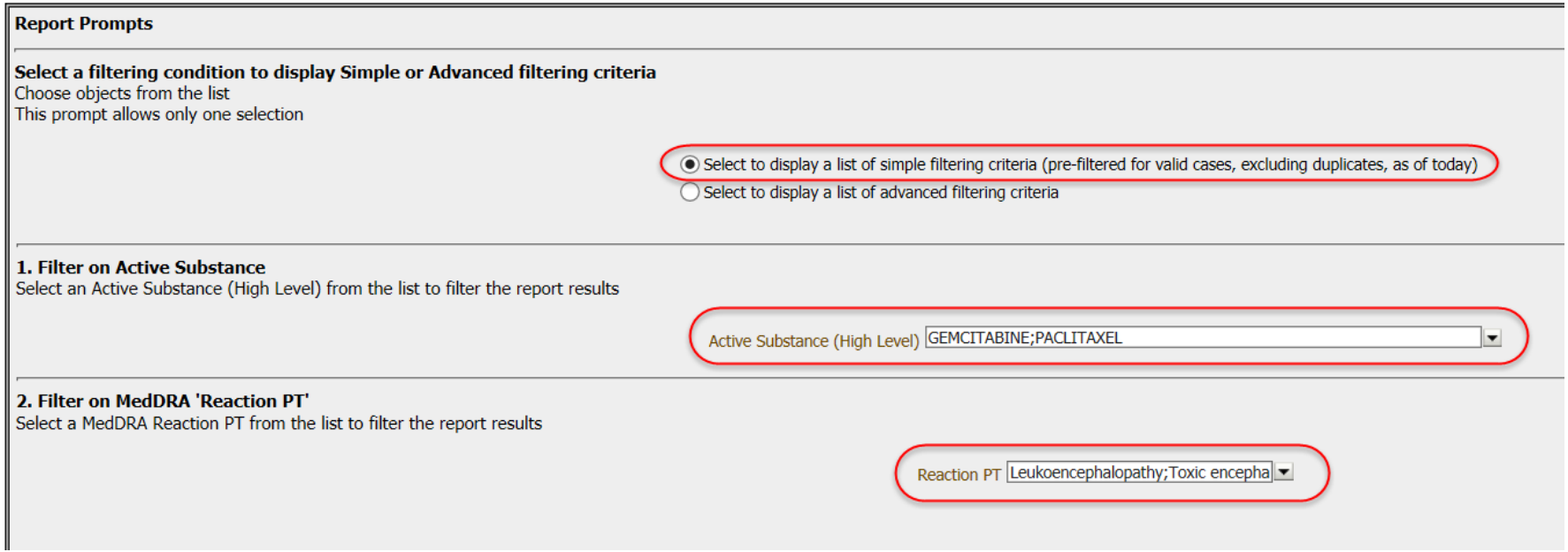
The data displayed is as off today's day

All the cases in EV for the substance and the PT are retrieved when the substance is considered suspect/interacting

- Exemption: ROR reports (only spontaneous, other and not available to sender)

Remember for any other options the user should switch to the advanced filtering criteria.

Simplified filtering criteria – Example



Advanced filtering criteria

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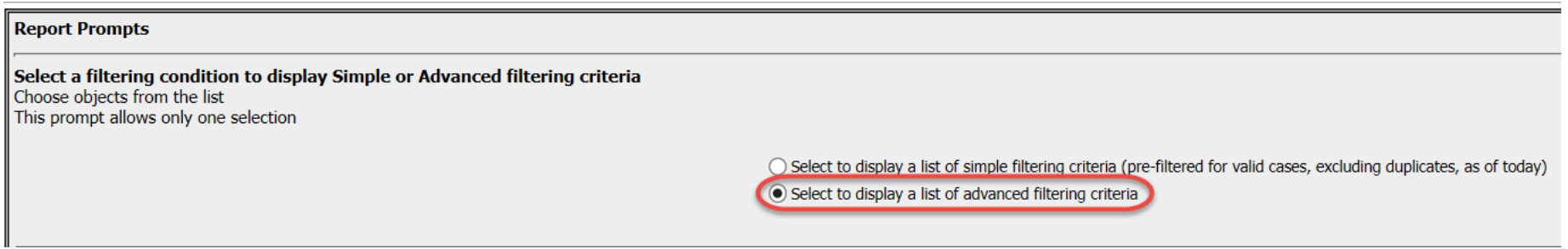
- By switching to the advance filtering criteria from main prompt page, users will be able to filter the data using very different parameters



- The advanced filtering criteria contains 9 prompts
- The following slides will explain the different prompts available for the advanced filtering criteria

Prompt 1 - Medicinal Product hierarchy

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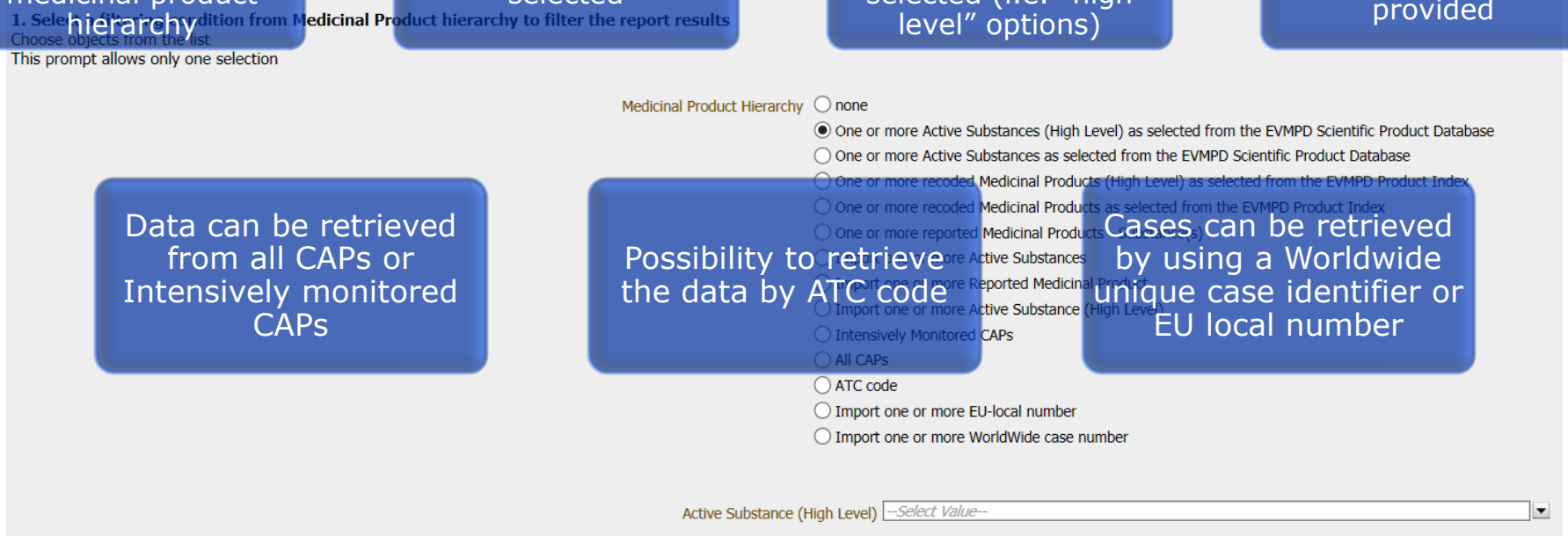
Allows the user to select specific categories of the medicinal product hierarchy

Substances or products can be selected

The highest level in the medicinal product hierarchy can be selected (i.e. "high level" options)

Option to exclude a substance/product from the data is provided



Data can be retrieved from all CAPs or Intensively monitored CAPs

Possibility to retrieve the data by ATC code

Cases can be retrieved by using a Worldwide unique case identifier or EU local number

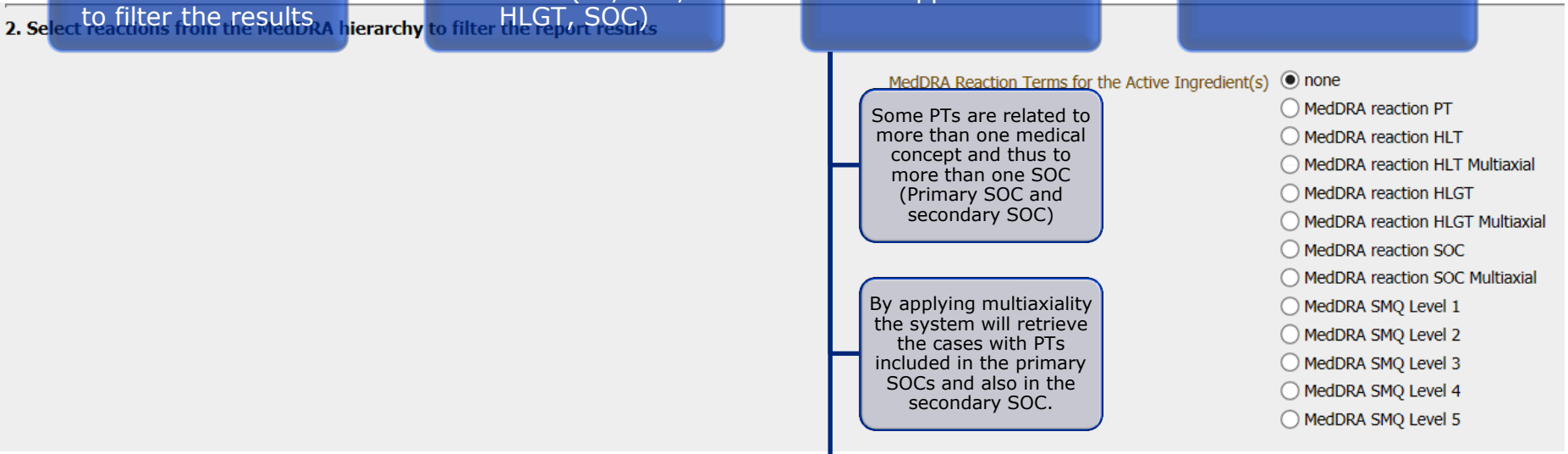
Prompt 2 – Reaction terms

This prompt allows the user to select a MedDRA reaction term to filter the results

Fours levels in the MedDRA hierarchy can be used (PT, HLT, HLGT, SOC)

Multiaxiality can be applied:

Five levels of SMQs can be selected



Some PTs are related to more than one medical concept and thus to more than one SOC (Primary SOC and secondary SOC)

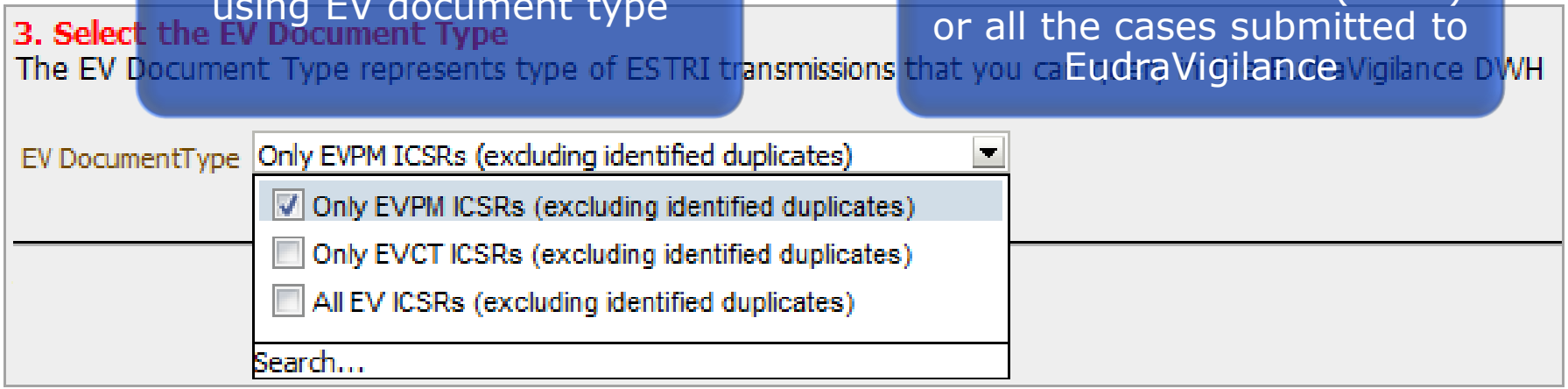
By applying multiaxiality the system will retrieve the cases with PTs included in the primary SOCs and also in the secondary SOC.

The same logic applies when multiaxiality is selected for HLT or HLGT

Prompt 3 - EV document type

This prompt allows the user to select the cases submitted using EV document type

Users can select the cases submitted to the post-authorisation module (EVPM), clinical trials module (EVCT) or all the cases submitted to EudraVigilance



Prompt 4 - Report type

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Allows the user to select a type of report to filter the data

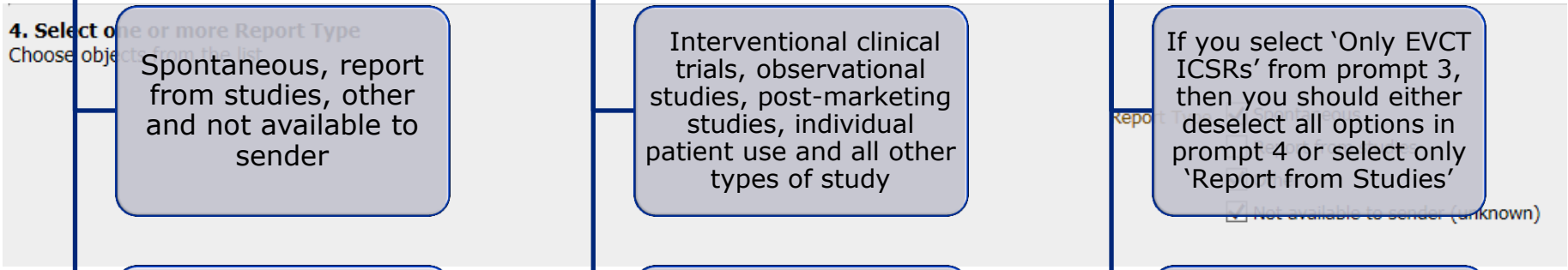
- Spontaneous, report from studies, other and not available to sender
- By default: Spontaneous, other and not available to sender are selected

'Report from Studies' cases can include:

- Interventional clinical trials, observational studies, post-marketing studies, individual patient use and all other types of study
- Cases from patient support programmes are submitted as reports from studies in the EVPM

This prompt needs to be used carefully in combination with prompt 3 'select EV document type'

- If you select 'Only EVCT ICSRs' from prompt 3, then you should either deselect all options in prompt 4 or select only 'Report from Studies'
- All the report types should be selected to retrieve all the cases in the database

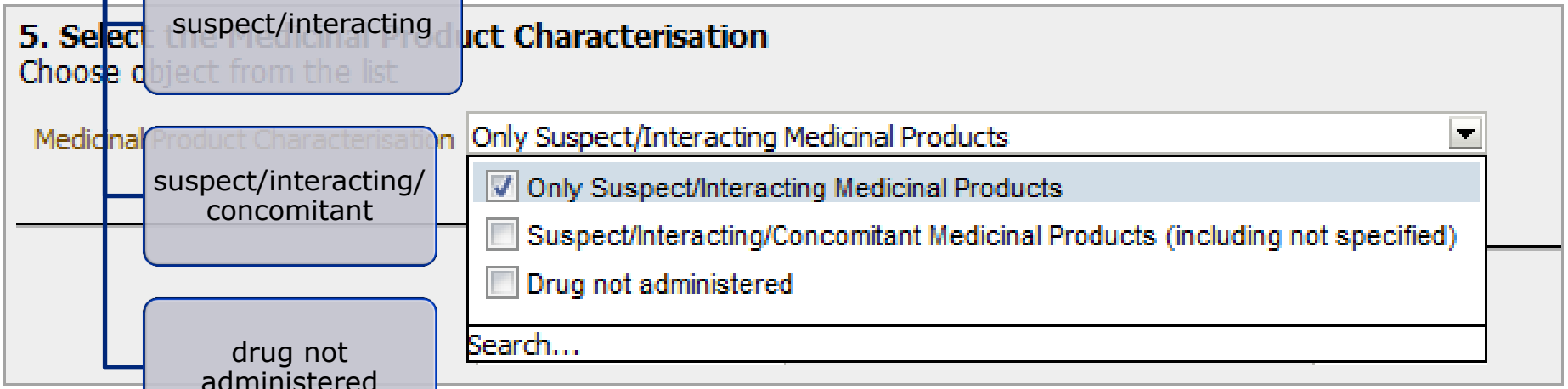


Prompt 5 – Medicinal product characterisation

Allows the user to filter the data by drug role characterisation. The options are:

The default options is only suspect/interacting

- suspect/interacting
- suspect/interacting/ concomitant
- drug not administered



Prompt 6 - Additional criteria to filter the reports

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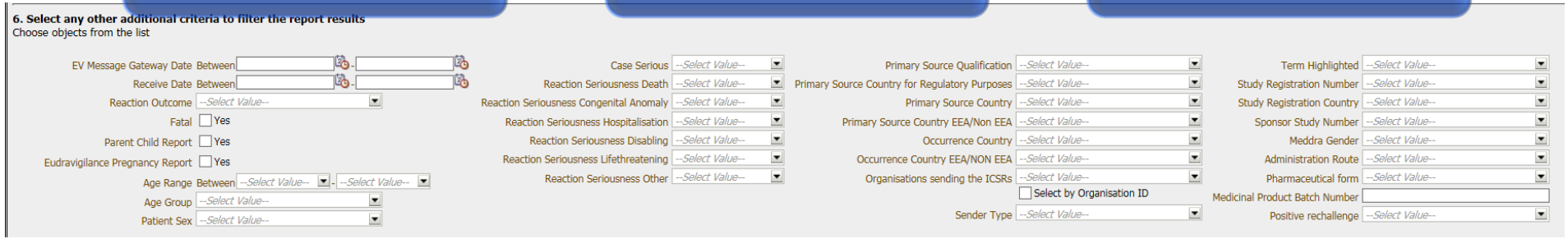
Provides the user with a large variety of options and conditions to filter the data

The combination of more than one filter in this section is applied with an "AND" condition

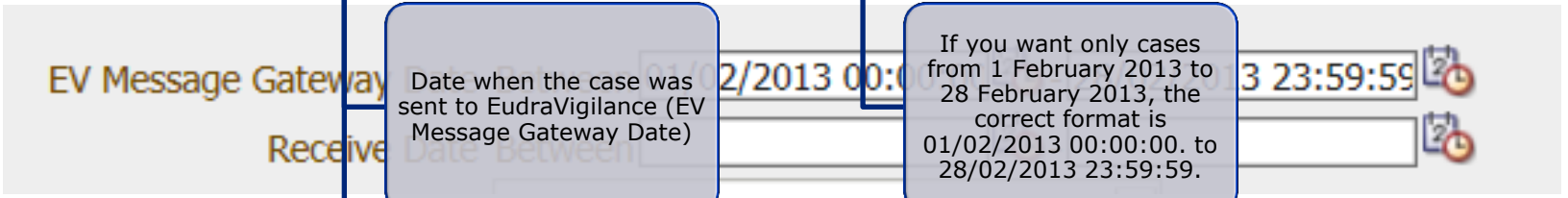
The following slides describe the different filters in this prompt in more detail



Prompt 6 - Additional criteria to filter the reports "Dates"

The "date filters" allow you to filter on a date range. The options are:

Be aware that the filter on dates contain also the time.



Date when the case was sent to EudraVigilance (EV Message Gateway Date)

If you want only cases from 1 February 2013 to 28 February 2013, the correct format is 01/02/2013 00:00:00. to 28/02/2013 23:59:59.

Date the sender received the first information on the case (Receive date).

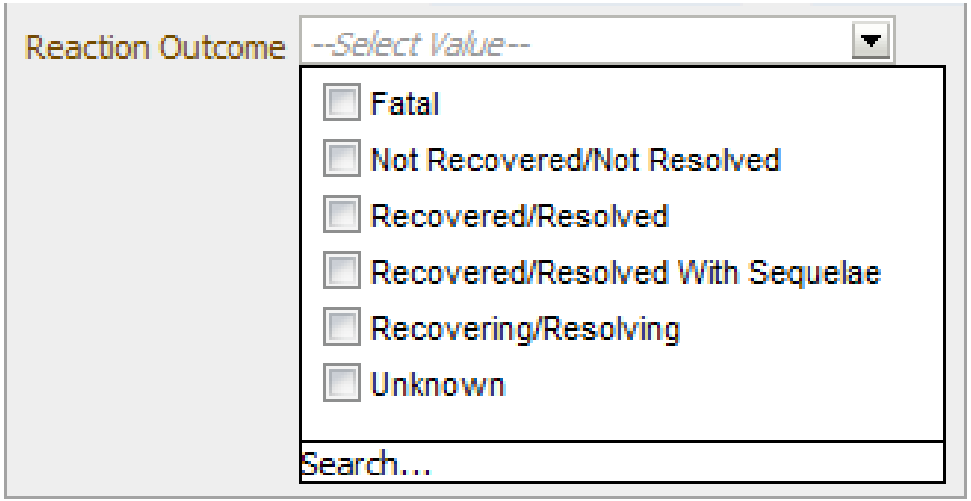
Prompt 6 - Additional criteria to filter the reports

"Reaction outcome"

Filtering on reaction outcome allows the user to select the cases according to the "outcome of the reaction"

Be aware that if you select more than one reaction outcome the system will apply an "OR" condition as we are within the same filter

Like other E2B fields, reaction outcome is not a mandatory field so caution should be exercised when querying the database using this filter



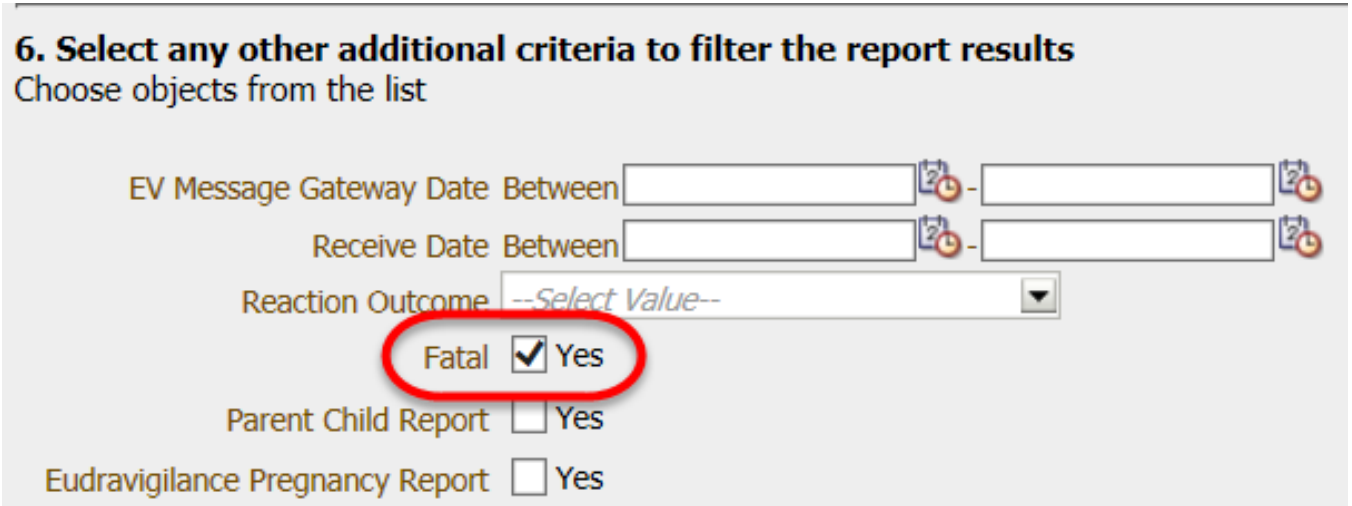
Prompt 6 - Additional criteria to filter the reports

"fatal" filter

Using the "fatal" filter will combine the cases with any reaction outcome fatal plus the cases with seriousness criteria death.

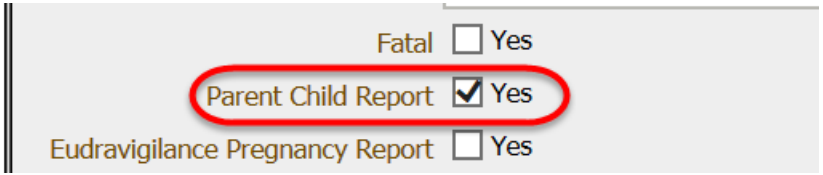
This filter provides with all the fatal cases regardless whether the fatality has been reported in the seriousness criteria or in the reaction outcome

This filter should not be used in combination with reaction outcome or seriousness criteria ('AND' condition will be applied)



Prompt 6 - Additional criteria to filter the reports "Parent-child and pregnancy reports"

By selecting Yes, the system will retrieve all the parent-child reports

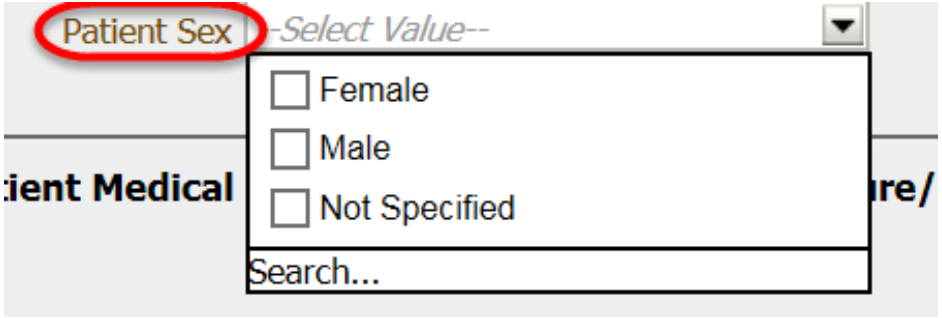


By selecting Yes the system will retrieve all the pregnancy reports

Prompt 6 - Additional criteria to filter the reports

"Patient sex"

This filter allows the user to select cases by "patient sex" (male, female or not specified)



Prompt 6 - Additional criteria to filter the reports

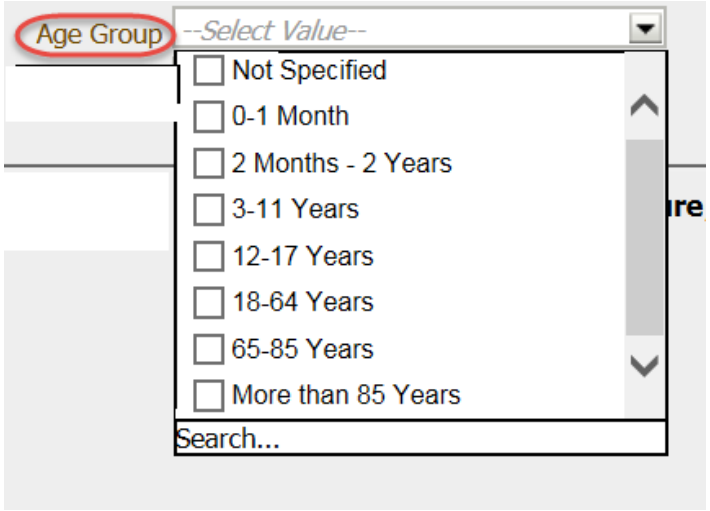
"Patient age"

These filters allow the user to select cases by "patient age"

For "age range" the exact age values in years should be entered

"Age group" provides a selection of predefined groups

These filters should not normally be combined as an "AND" option will applied



Prompt 6 - Additional criteria to filter the reports

"Seriousness criteria"

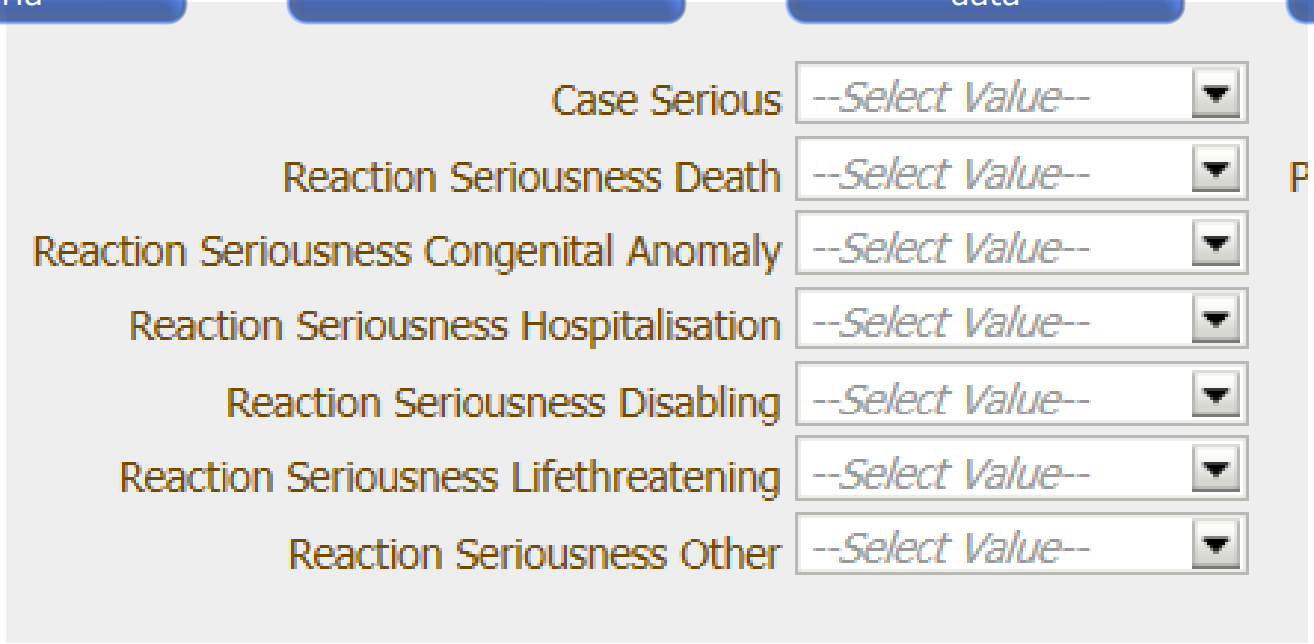
These filters allow the user to select "serious" cases and cases with an specific seriousness criteria

If you select cases serious "Yes" the system will retrieve all the serious cases

Serious criteria were reported at case level in R2 data and at a reaction level in R3 data

The available options in each filter are:

Yes, No and not available



Prompt 6 - Additional criteria to filter the reports

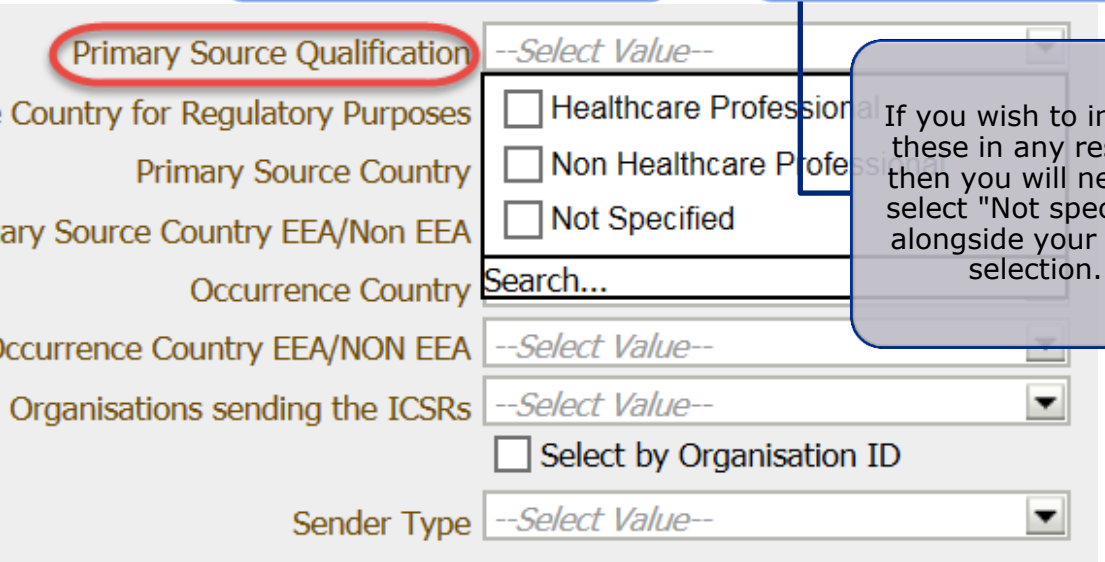
"Primary source qualification"

This filter allows the user to select the cases by primary source qualification of the reporter. The options are:

This can be used to select all the consumer reports

There are >141,000 old cases where no primary source qualification is selected.

- Healthcare professional
- Non-healthcare professional
- Not specified



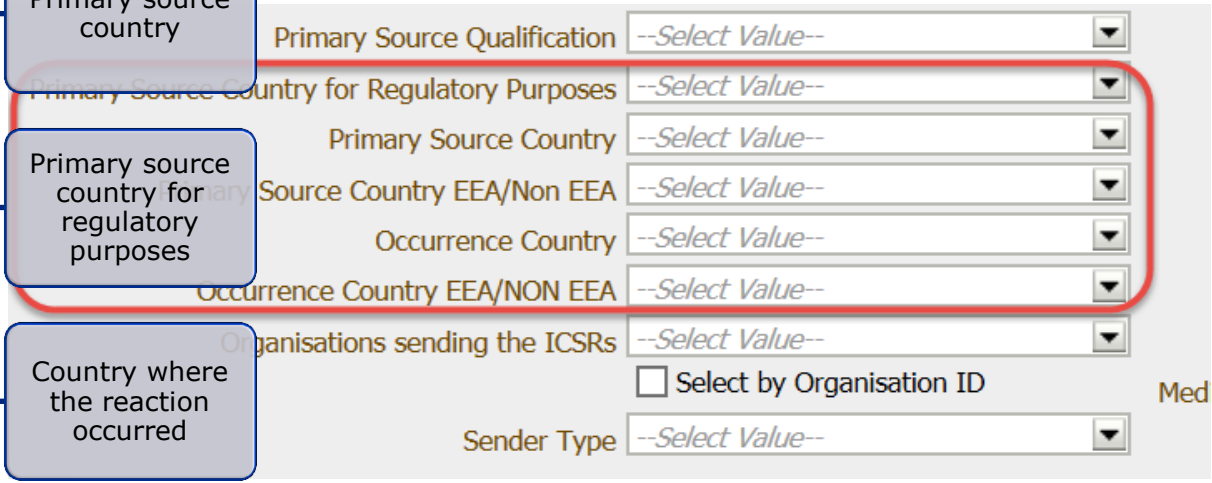
If you wish to include these in any results, then you will need to select "Not specified" alongside your other selection.

Prompt 6 - Additional criteria to filter the reports "Country"

These filters allow the user to select the cases by:

Also options EEA/Non-EEA can be applied

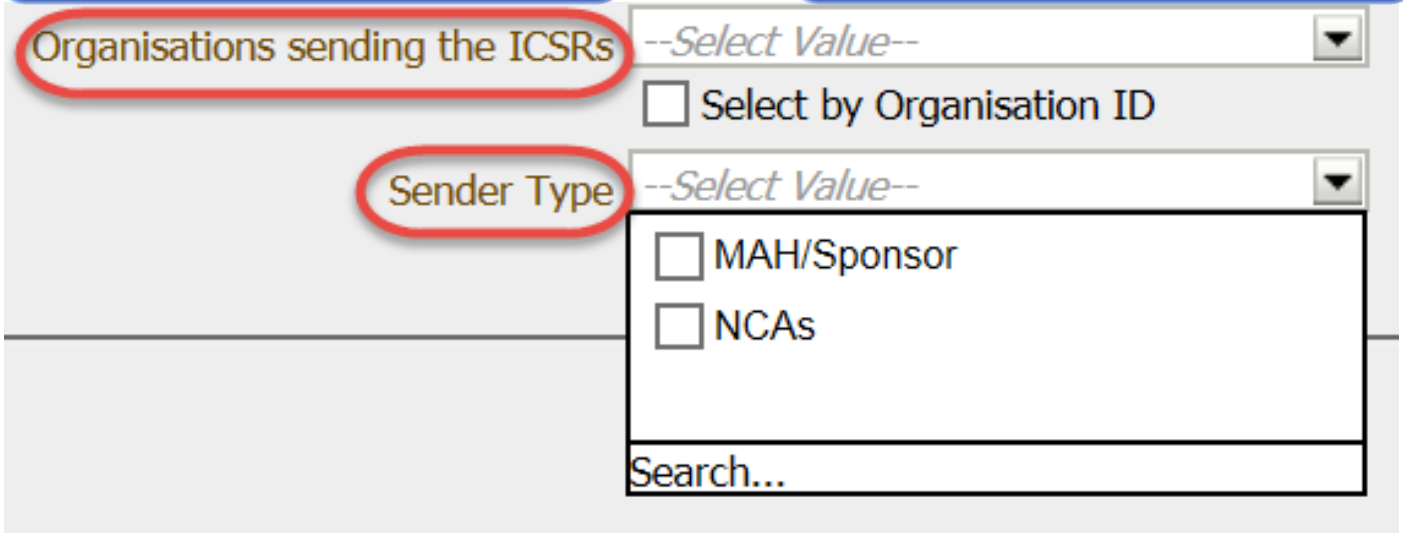
- Primary source country
- Primary source country for regulatory purposes
- Country where the reaction occurred



Prompt 6 - Additional criteria to filter the reports "Organisation and sender type"

These filters allow the users to retrieve cases submitted by a particular sender organisation or sender type (NCAs, MAHs/Sponsor)

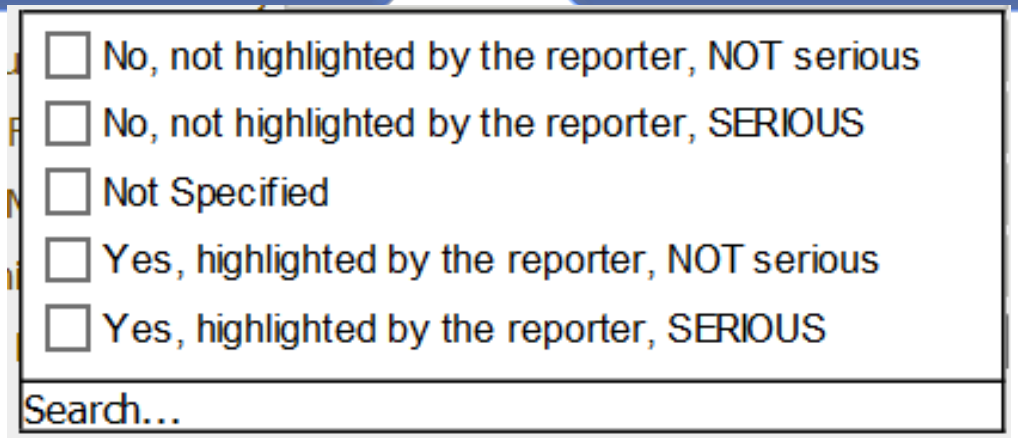
Organisations can be searched by ID rather than the name if desired



Prompt 6 - Additional criteria to filter the reports "Highlighted terms"

This filter allows the user to restrict the search to the term(s) chosen in prompt 2 and which were highlighted by the reporter.

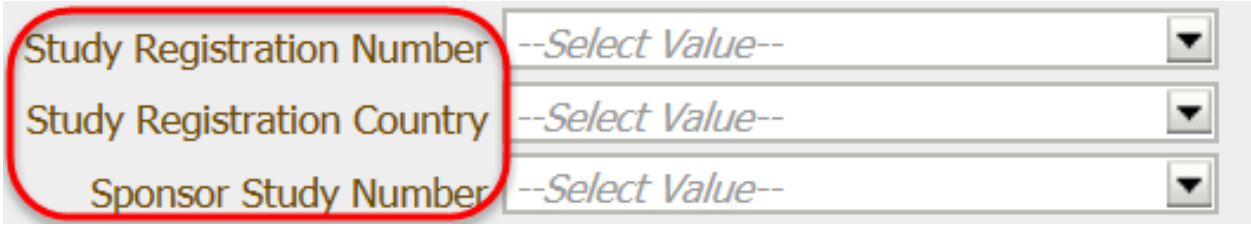
As this field is not mandatory and is not frequently populated, it is not recommended for systematic use; if you do intend to filter on this, always ensure that you include 'not specified' otherwise you miss the majority of cases where no term was highlighted



Prompt 6 - Additional criteria to filter the reports "Study details"

These filters allow the user to select the data based on study registration number, study registration country and sponsor study number

Please remember that in the EEA, the study registration number is the EudraCT number



Prompt 6 - Additional criteria to filter the reports

"Other filters"

Route of administration and pharmaceutical forms

These filters allow the user to select the data according to the route of administration and pharmaceutical form reported in the ICSR

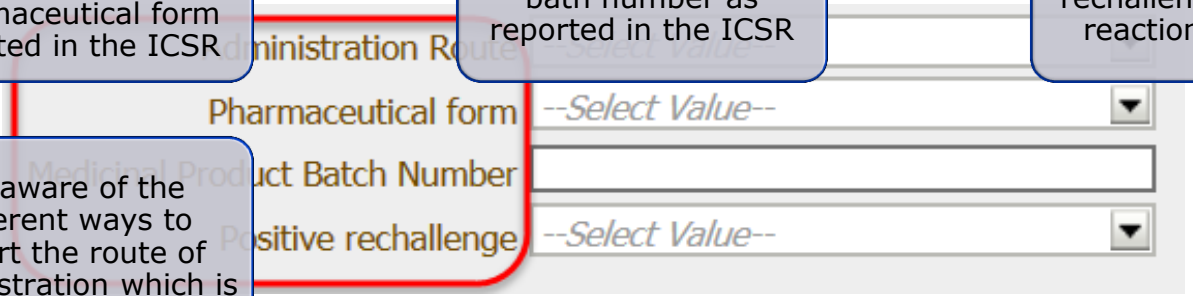
Be aware of the different ways to report the route of administration which is not a mandatory field

Batch number

This filter allows the user to select the cases with an specific bath number as reported in the ICSR

Positive rechallenge

This filter will retrieve the cases when the patient was rechallenged and the reaction recurred.



Prompt 7 – Patient medical history

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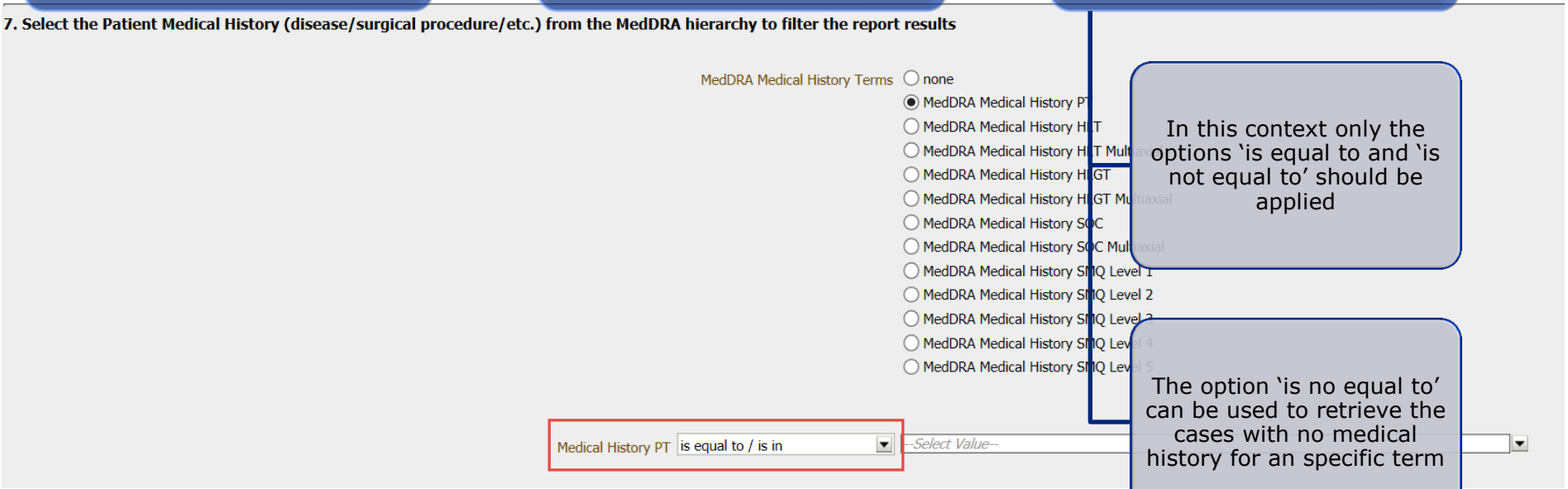
Users will be able to filter the data based on the medical history reported in the ICSR when reported as structured data

MedDRA hierarchy and multiaxiality can be applied

When selecting a term, an operator will be displayed with different options



In this context only the options 'is equal to and 'is not equal to' should be applied

The option 'is no equal to' can be used to retrieve the cases with no medical history for an specific term

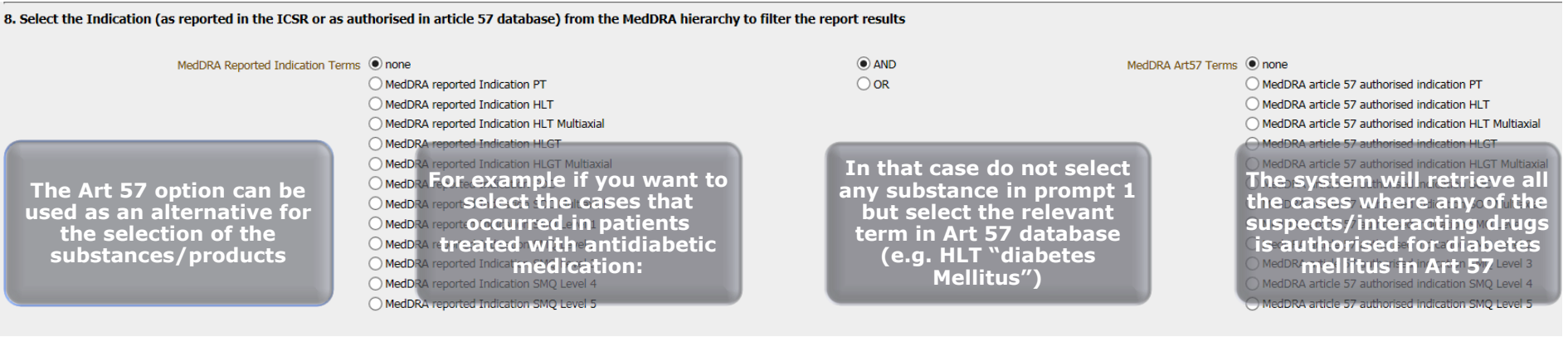
Prompt 8 – Indication for use

This prompt allows the user to select the data according to the indication for use of the medicinal products

The indication can be selected as reported in the ICSR or as per the Art 57 database (only for recoded ICSRS)

MedDRA hierarchy and multiaxiality can be applied

If the Art 57 indication option is selected the system will give you the options of indications included in the Art 57 database



The Art 57 option can be used as an alternative for the selection of the substances/products

For example if you want to select the cases that occurred in patients treated with antidiabetic medication:

In that case do not select any substance in prompt 1 but select the relevant term in Art 57 database (e.g. HLT "diabetes Mellitus")

The system will retrieve all the cases where any of the suspects/interacting drugs is authorised for diabetes mellitus in Art 57

Prompt 9 – Cut-off date

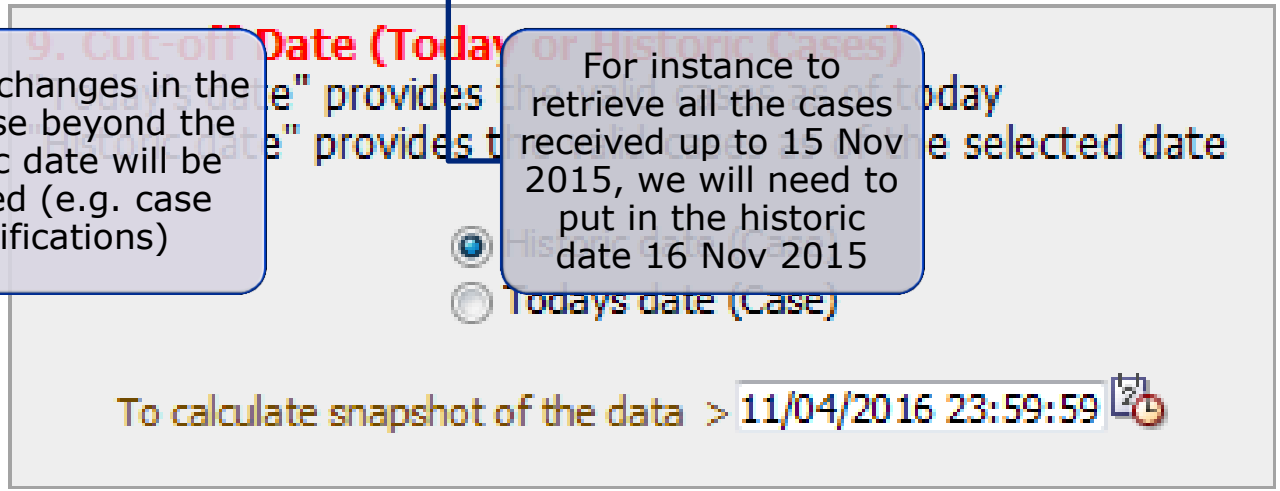
This prompt allows the user to retrieve the information in EV at a particular moment in time by selecting an specific "historic date"

Note the EV is updated overnight, so the data retrieved on a given date will contain the cases received up to the date before

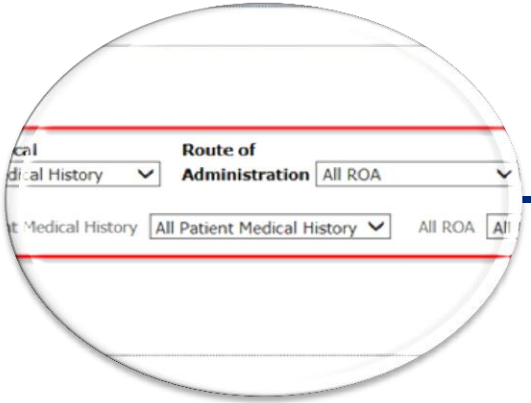
The default value of the prompt is today's day

Further changes in the database beyond the historic date will be omitted (e.g. case nullifications)

For instance to retrieve all the cases received up to 15 Nov 2015, we will need to put in the historic date 16 Nov 2015



Further filtering the data



One of the novelties of the new EVDAS catalogue is the possibility of further filter the data after the report has run and you have the results in the EVDAS interface

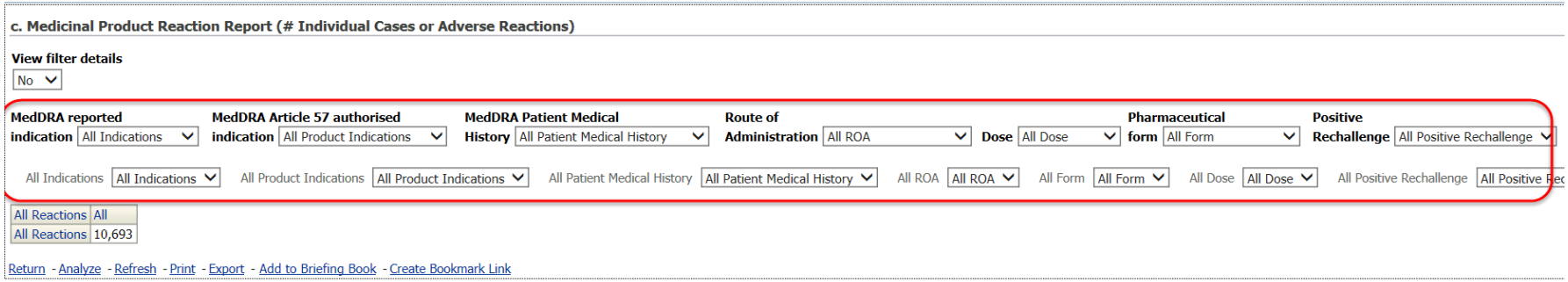
- Indication
- Medical history
- Route of administration
- Dose
- Pharmaceutical form
- Positive rechallenge

Further filtering the data

These extra filters are placed at the top of the reports results

Remember these filters do not have to be applied necessarily

The same filters can be also introduced in the previous prompt pages



Further filtering the data – how does it work?

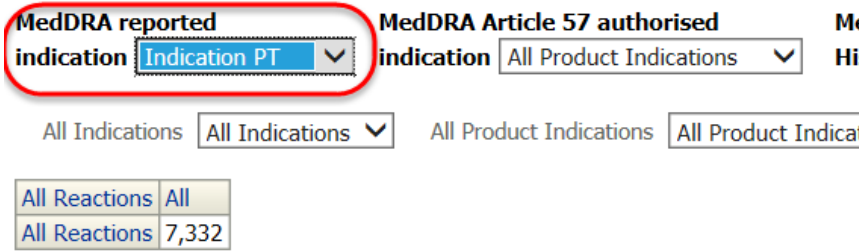
- In other to apply the extra filtering criteria, you need to activate first the filter you want to apply and let the report to run.
- Then you will be ready to filter the data according to the previous selection criteria.

See example in the following slides:

Further filtering the data - Example

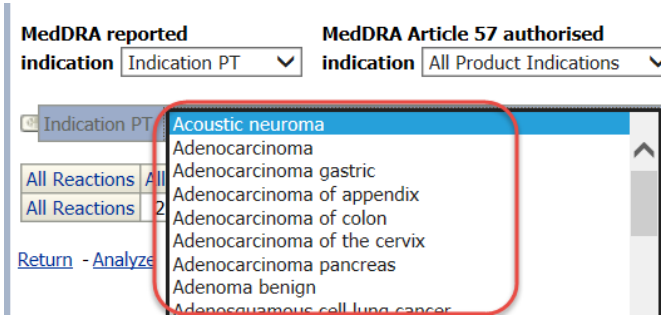
- The system has retrieved 7332 cases with bevacizumab in the gastrointestinal SOC

- To further filter this number based on the indication, select *MedDRA reported indication PT*



Further filtering the data - Example

- The system will run and display a list of the indications reported in those 7,332 cases for bevacizumab and gastrointestinal SOC



- Then you can select the specific indication PT to filter the number of cases
  - In the example, 22 of the 7,332 cases contain the indication PT 'gastrointestinal carcinoma'

Section summary: Standard filtering criteria

In this section we have covered:

- The new approach implemented in EVDAS as standard filtering criteria
- The difference between the simplified and the advanced filtering criteria
- The different filters included in the advanced filtering criteria
- Possibilities to further filter the data outputs

- Introduction to this training module
- Introduction to EVDAS
- ICH-E2B(R3) EVDAS implementation
- Standard filtering criteria, new approach
- **EudraVigilance administrative query library**
- Pharmacovigilance query library
- Summary

Section overview: EudraVigilance Administrative query library

In this section you will obtain an understanding of:

- The different categories of reports included in the EudraVigilance administrative query library
- Principles and instructions for running reports within the Library
- Output examples of the main reports in the Library

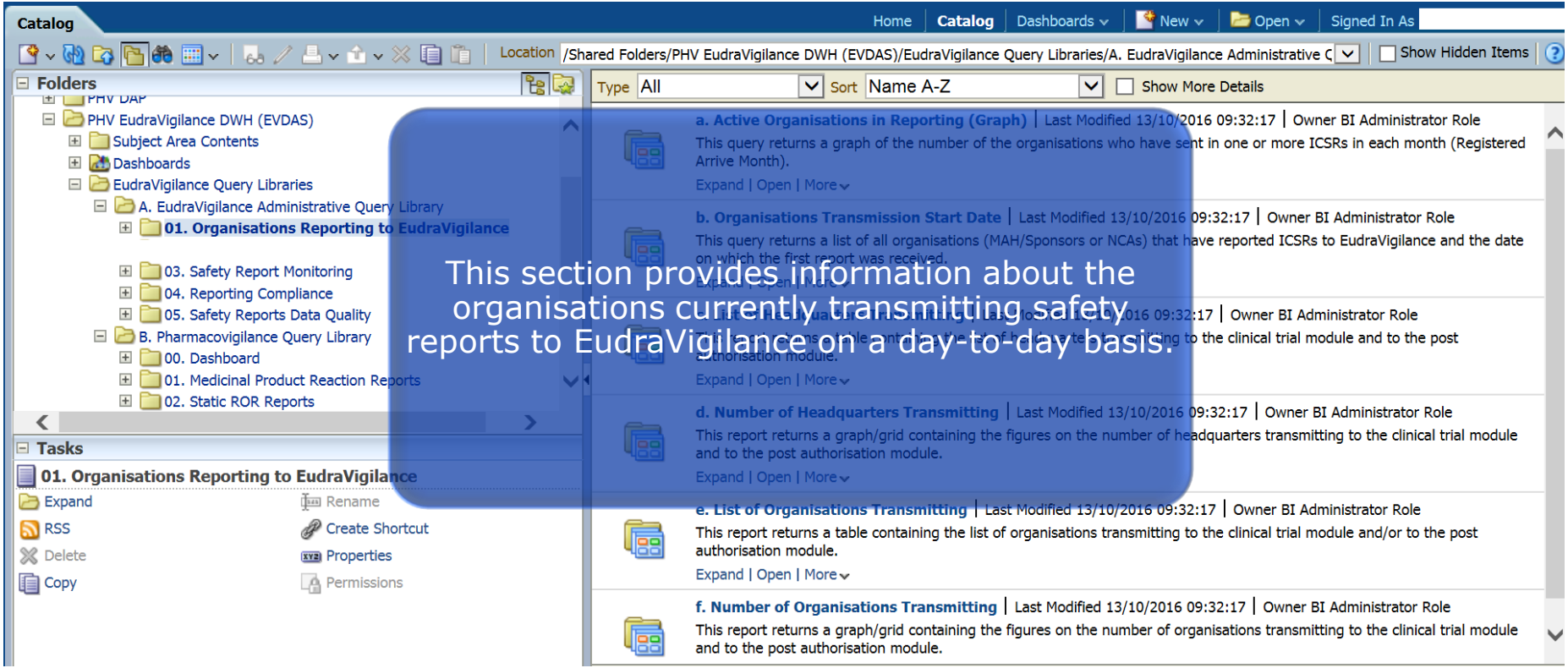
EudraVigilance administrative query library

- This library contains reports designated to support analysis of compliance with the reporting rules and quality of the data transmitted by MAHs to EV.
- The majority of the reports retrieve information on all ICSRs transmitted, which will include all versions of the cases.
- The library is subdivided in 4 folders.

Filter options

- The prompts and filter options within the reports included in this library vary depending on the report.
- Some reports provide the standard simplified and advanced filtering options.
- Other reports provided a simplified filter options driven by the type of output are intended to retrieve.

A01 - Organisations Reporting to EudraVigilance



This section provides information about the organisations currently transmitting safety reports to EudraVigilance on a day-to-day basis.

A01c. List of Headquarters transmitting

This report returns a table containing the list of headquarters transmitting to the EVCT and EVPM

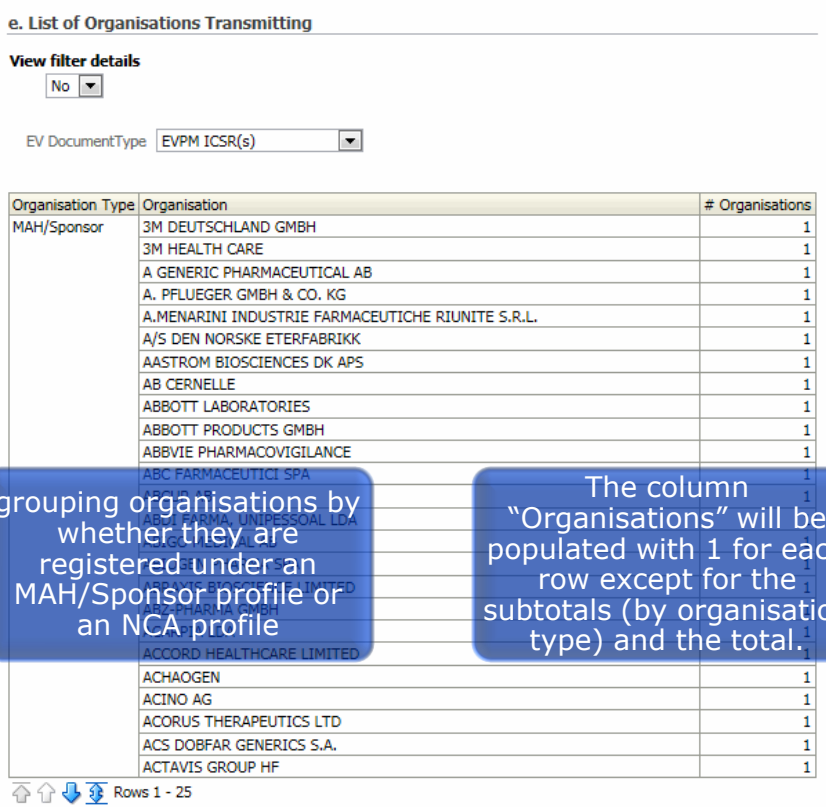
The report returns as a table with various additional filtering options

Organisations registered in EV are either registered as headquarters or as affiliates grouped under a headquarters.

Organisation Type	Headquarter	# Headquarters
MAH/Sponsor	BELUPO HRVATSKA	1
	JGL	1
	MaxPharma d.o.o.	1
	PharmaS d.o.o.	1
	mibe GmbH Arzneimittel	1
MAH/Sponsor Total		**5**
NCAs	Agency for Medicinal Products and Medical Devices	1
NCAs Total		**1**
Grand Total		**6**

If multiple affiliates under the same headquarters have each transmitted ICSRs to EV they will only be counted once in this query

A01e. List of organisations transmitting



e. List of Organisations Transmitting

View filter details

No

EV DocumentType: EVPM ICSR(s)

Organisation Type	Organisation	# Organisations
MAH/Sponsor	3M DEUTSCHLAND GMBH	1
	3M HEALTH CARE	1
	A GENERIC PHARMACEUTICAL AB	1
	A. PFLUEGER GMBH & CO. KG	1
	A.MENARINI INDUSTRIE FARMACEUTICHE RIUNITE S.R.L.	1
	A/S DEN NORSKE ETERFABRIKK	1
	AASTROM BIOSCIENCES DK APS	1
	AB CERNELLE	1
	ABBOTT LABORATORIES	1
	ABBOTT PRODUCTS GMBH	1
	ABBVIE PHARMACOVIGILANCE	1
	ABC FARMACEUTICI SPA	1
	[illegible]	1
	[illegible]	1
	[illegible]	1
	[illegible]	1
	[illegible]	1
	[illegible]	1
	ACCORD HEALTHCARE LIMITED	1
	ACHAOGEN	1
	ACINO AG	1
	ACORUS THERAPEUTICS LTD	1
	ACS DOBFAR GENERICS S.A.	1
	ACTAVIS GROUP HF	1

Rows 1 - 25

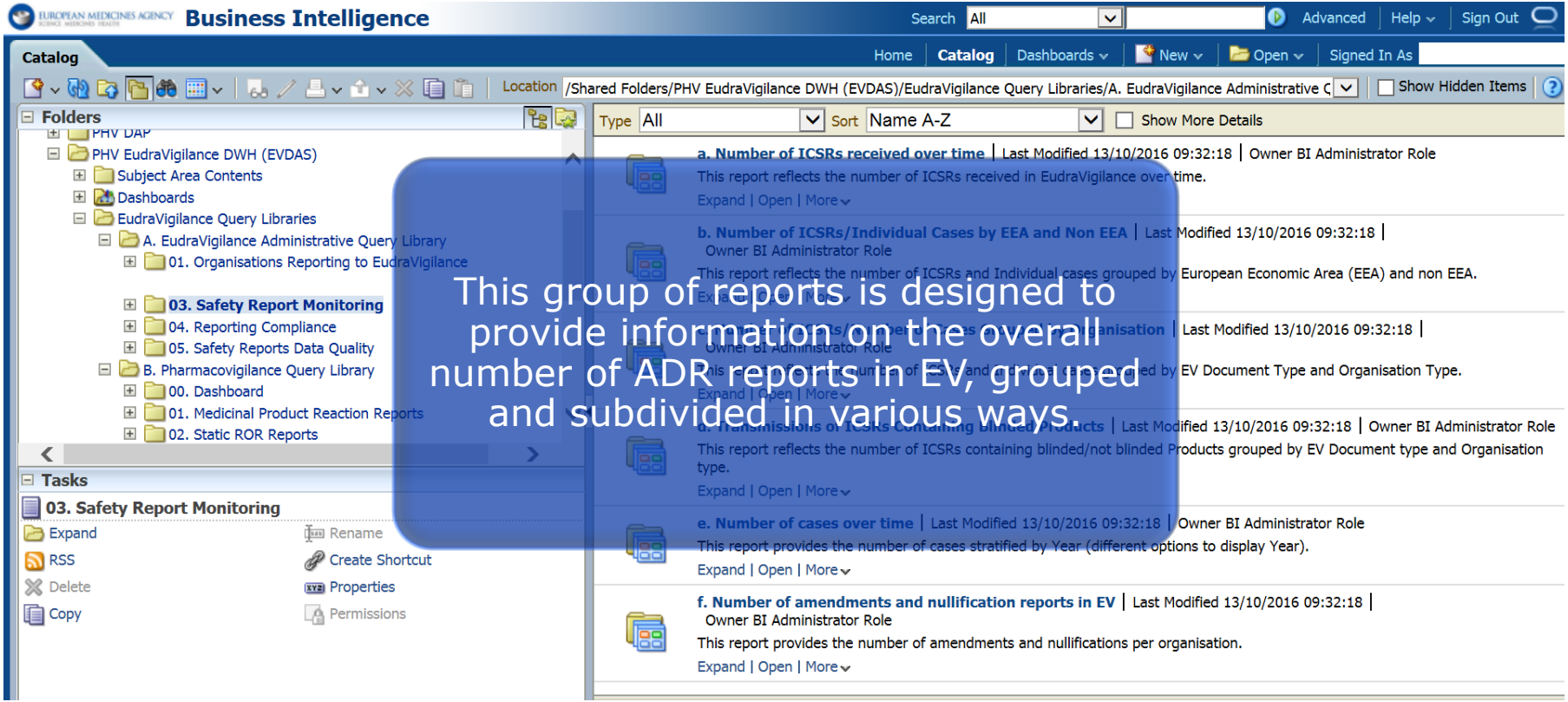
list of organisations (whether headquarters, affiliates or 3rd party service providers) transmitting to EV

grouping organisations by whether they are registered under an MAH/Sponsor profile or an NCA profile

The column "Organisations" will be populated with 1 for each row except for the subtotals (by organisation type) and the total.

Once the report has been run and the results returned, you can filter by EV Document Type

A03. Safety Report Monitoring



This group of reports is designed to provide information on the overall number of ADR reports in EV, grouped and subdivided in various ways.

A03a. Number of ICSRs Received Over Time

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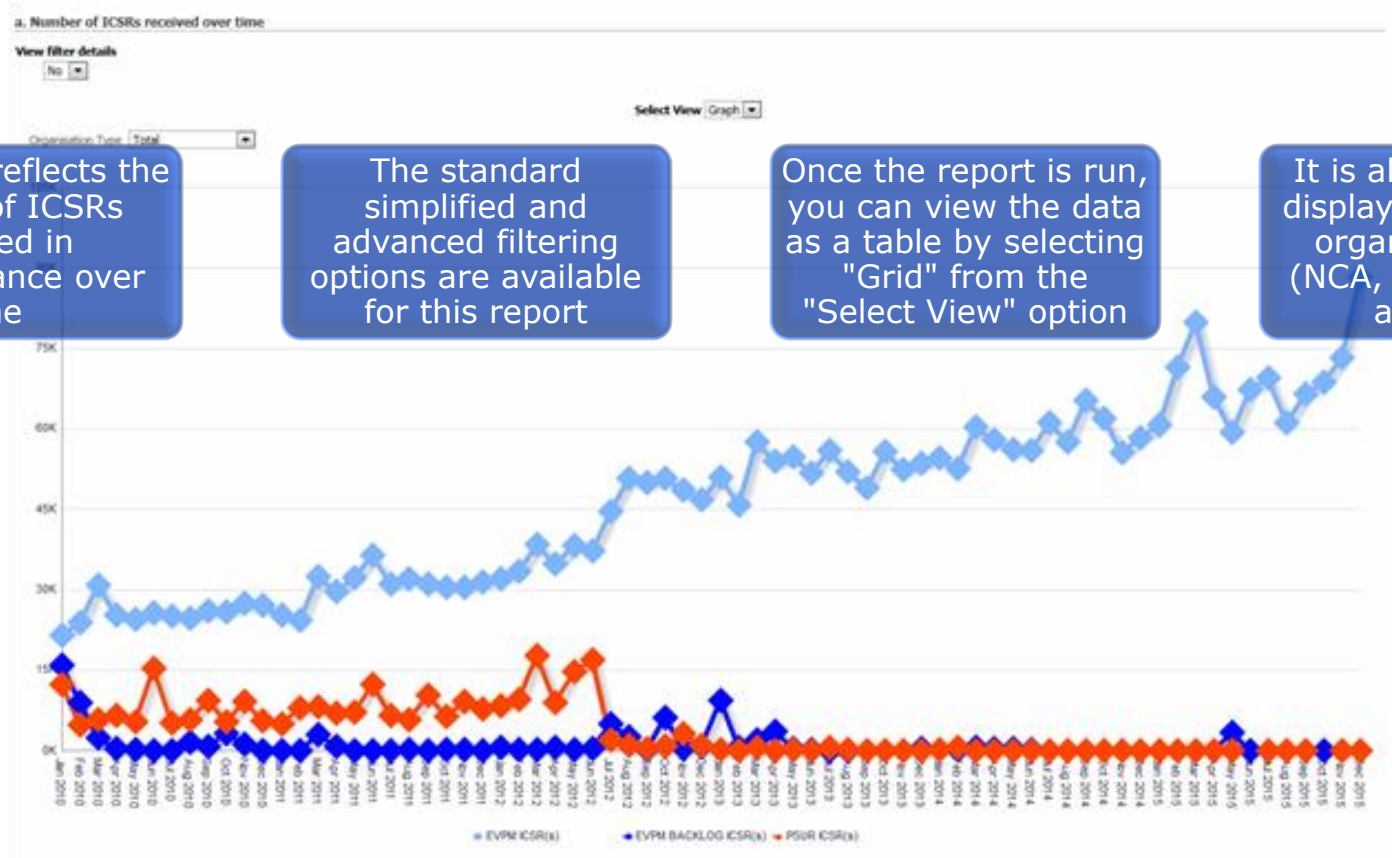
This report reflects the number of ICSRs received in EudraVigilance over time

The standard simplified and advanced filtering options are available for this report

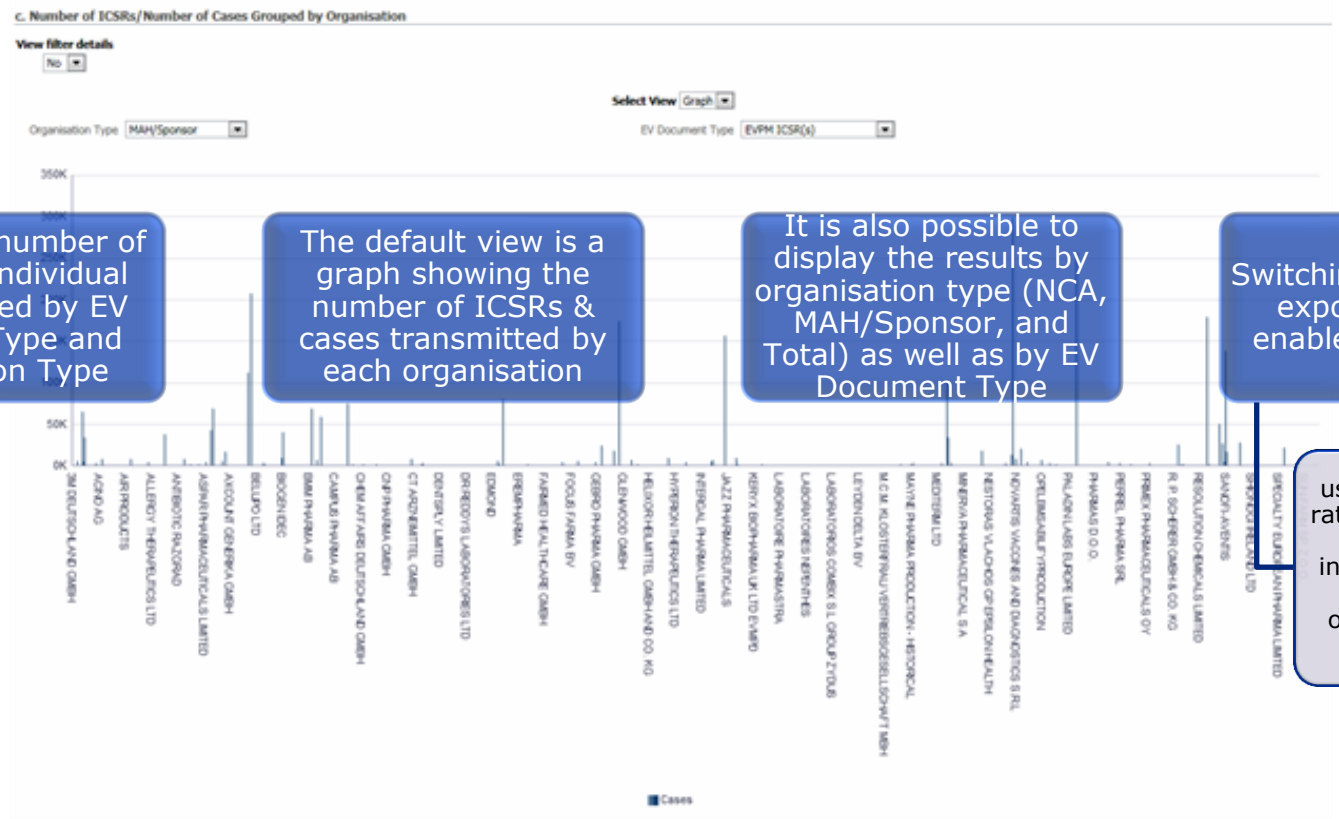
Once the report is run, you can view the data as a table by selecting "Grid" from the "Select View" option

It is also possible to display the results by organisation type (NCA, MAH/Sponsor, and Total)



A03c. Number of ICSRs/Number of Cases Grouped by Organisation

EUROPEAN MEDICINES AGENCY



Displays the number of ICSRs and Individual cases grouped by EV Document Type and Organisation Type

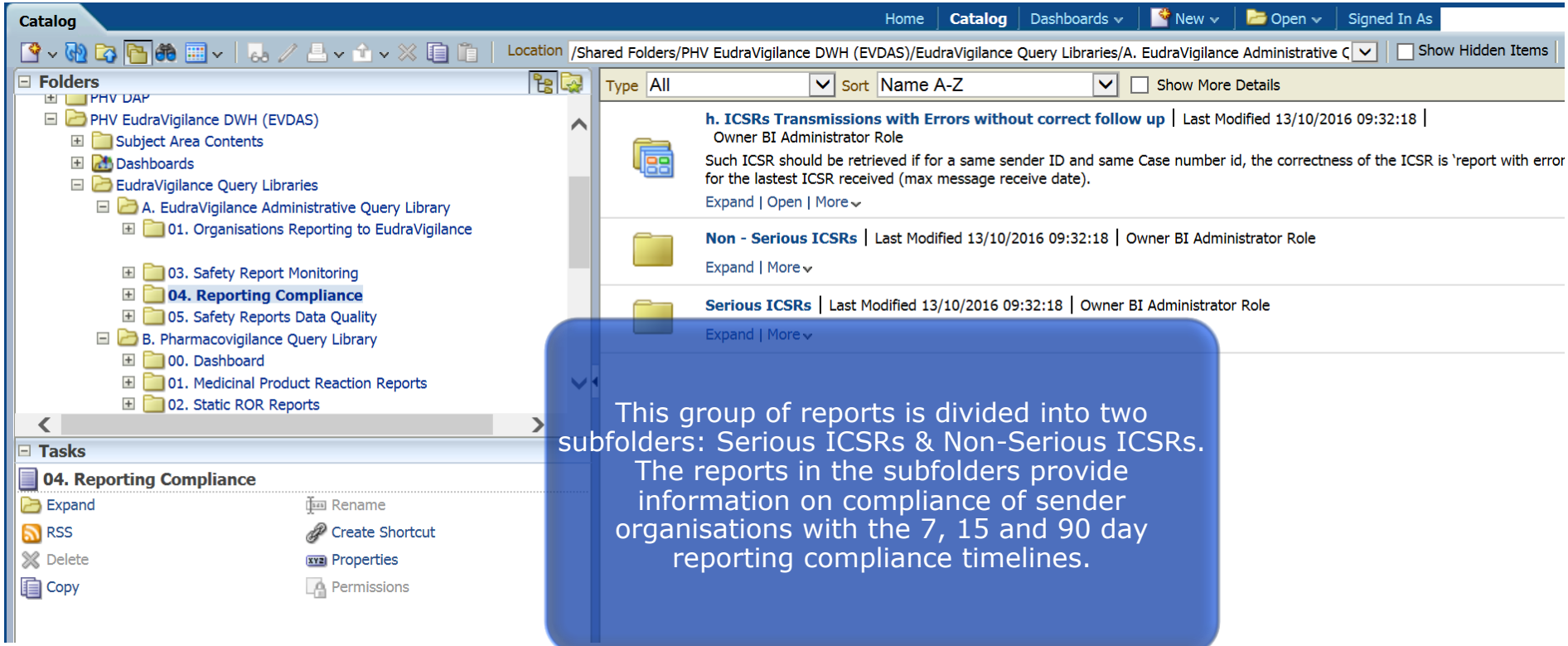
The default view is a graph showing the number of ICSRs & cases transmitted by each organisation

It is also possible to display the results by organisation type (NCA, MAH/Sponsor, and Total) as well as by EV Document Type

Switching view to grid & exporting to Excel enables data analysis

users could compare the ratio of ICSRs to cases for the organisation of interest compared to the average or to other organisations of similar size

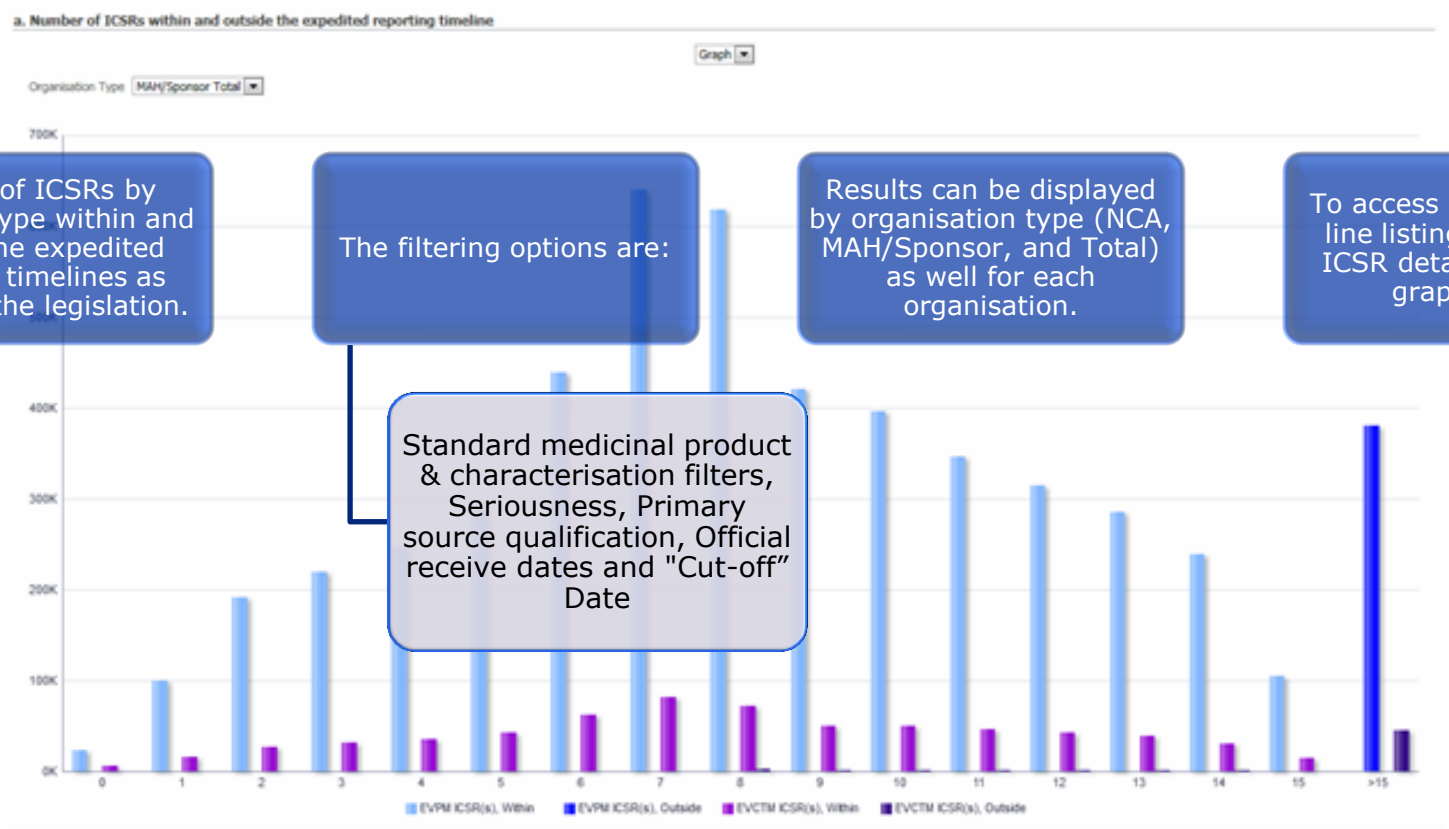
A04. Reporting compliance



This group of reports is divided into two subfolders: Serious ICSRs & Non-Serious ICSRs. The reports in the subfolders provide information on compliance of sender organisations with the 7, 15 and 90 day reporting compliance timelines.

A04.a Number of ICSRs Within or Outside the Expedited Reporting Timeline

EUROPEAN MEDICINES AGENCY



Number of ICSRs by document type within and outside the expedited reporting timelines as defined in the legislation.

The filtering options are:

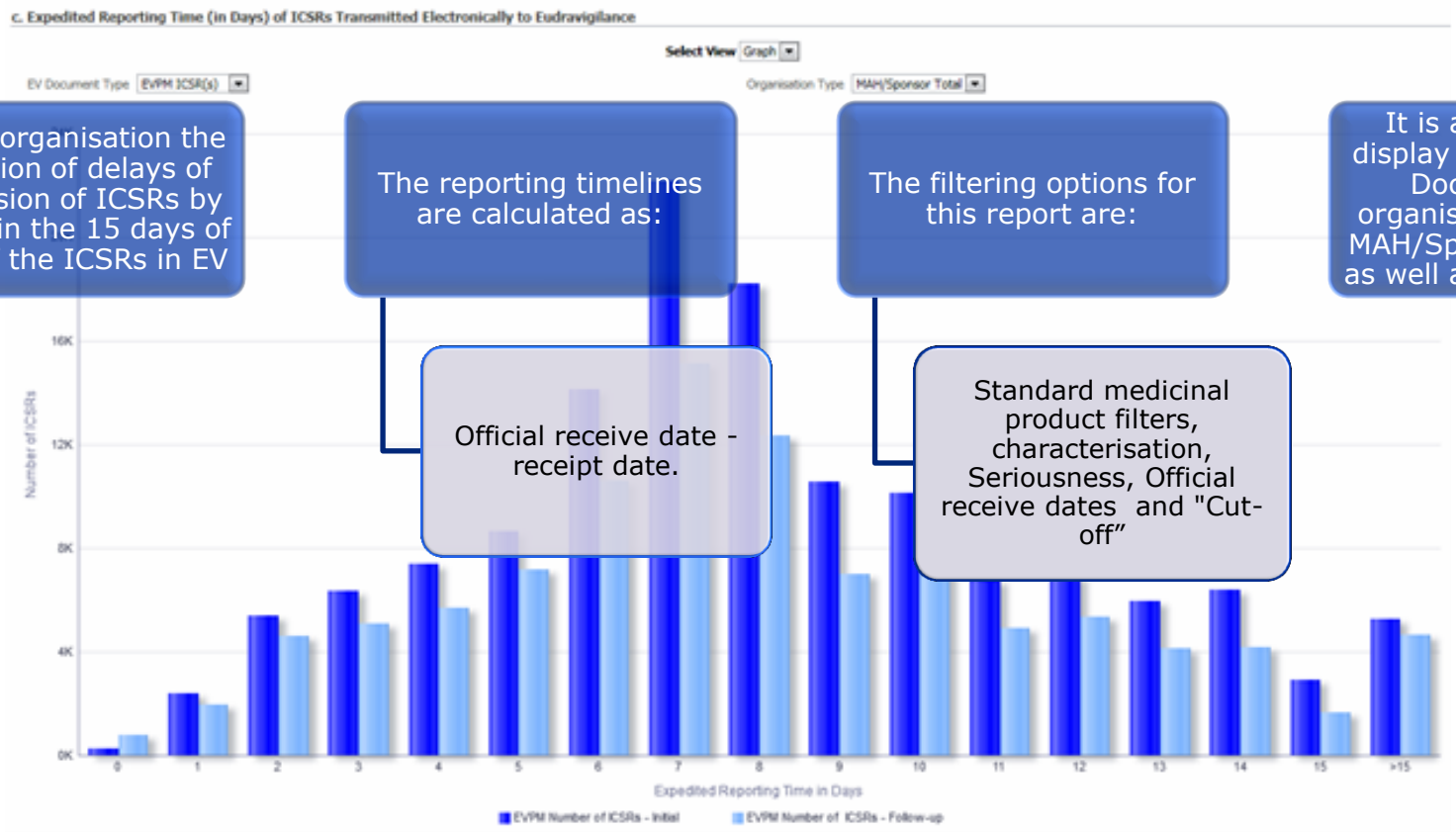
Standard medicinal product & characterisation filters, Seriousness, Primary source qualification, Official receive dates and "Cut-off" Date

Results can be displayed by organisation type (NCA, MAH/Sponsor, and Total) as well for each organisation.

To access directly a case line listing and see the ICSR details, click on a graph value.

A04.c Expedited Reporting Time (in Days) of ICSRs Transmitted Electronically to EudraVigilance

EUROPEAN MEDICINES AGENCY



For each organisation the distribution of delays of transmission of ICSRs by time within the 15 days of receipt of the ICSRs in EV

The reporting timelines are calculated as:

Official receive date - receipt date.

The filtering options for this report are:

Standard medicinal product filters, characterisation, Seriousness, Official receive dates and "Cut-off"

It is also possible to display the results by EV Document Type, organisation type (NCA, MAH/Sponsor, and Total) as well as by organisation

EUROPEAN MEDICINES AGENCY

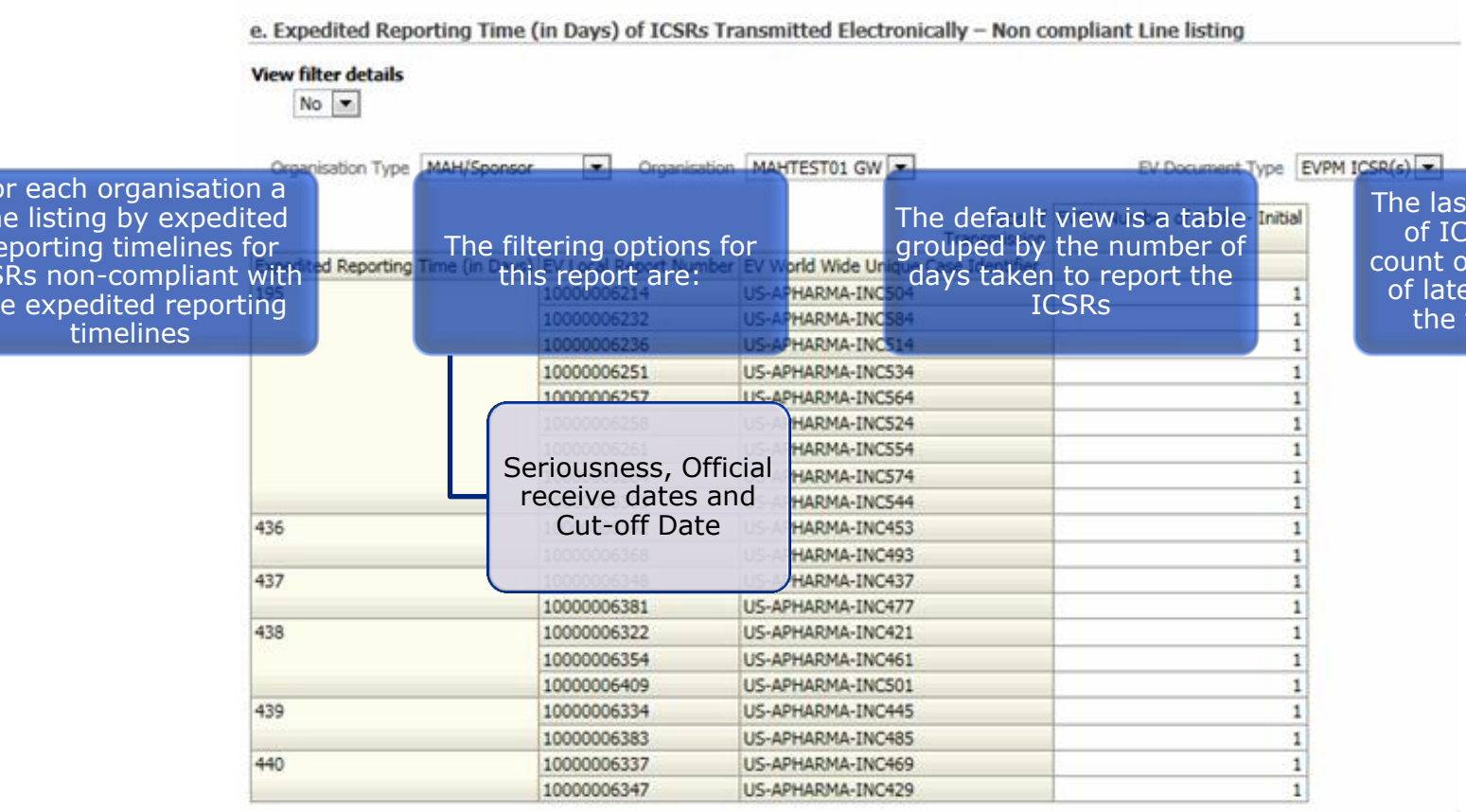
For each organisation a line listing by expedited reporting timelines for ICSRs non-compliant with the expedited reporting timelines

The filtering options for this report are:

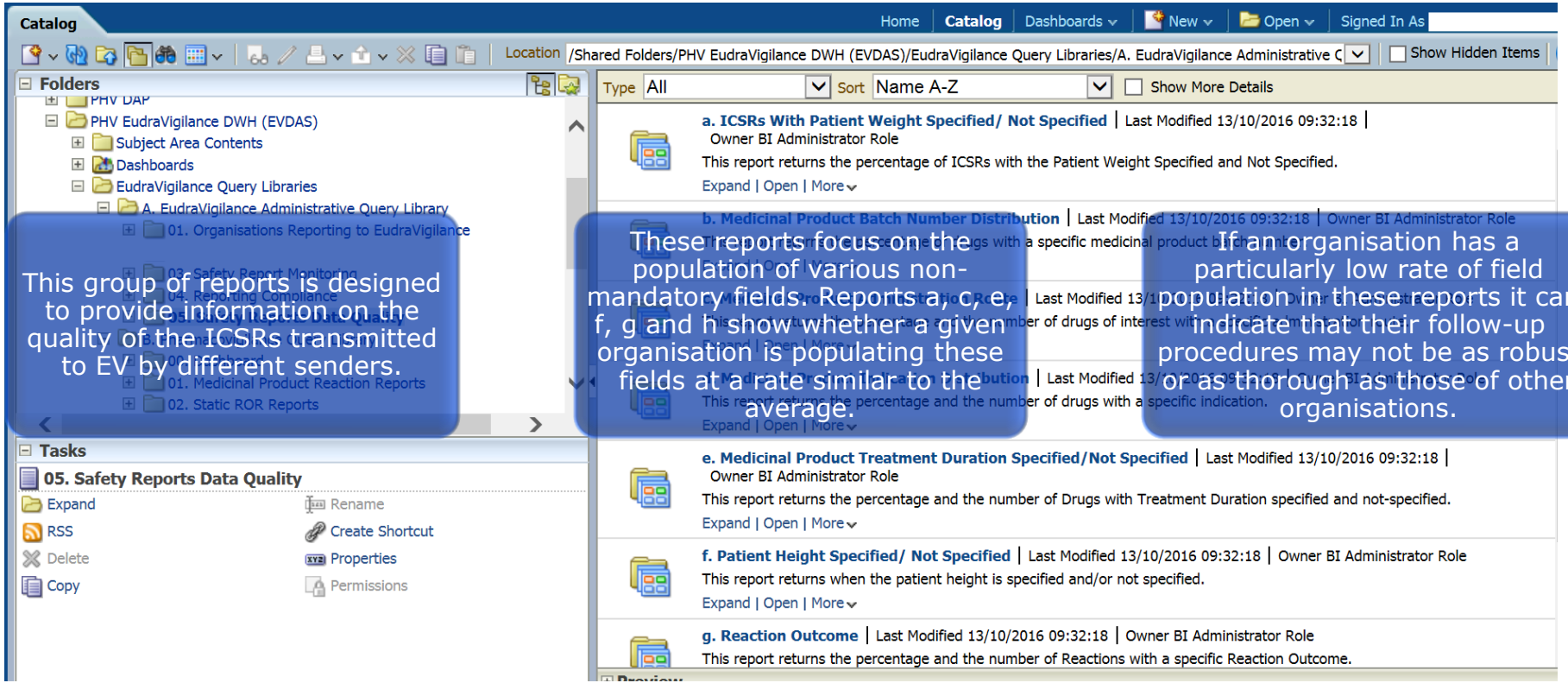
Seriousness, Official receive dates and Cut-off Date

The default view is a table grouped by the number of days taken to report the ICSRs

The last column "Number of ICSRs" provides a count of the total number of late cases that meet the filtering criteria



A.05 Safety Reports Data Quality



This group of reports is designed to provide information on the quality of the ICSRs transmitted to EV by different senders.

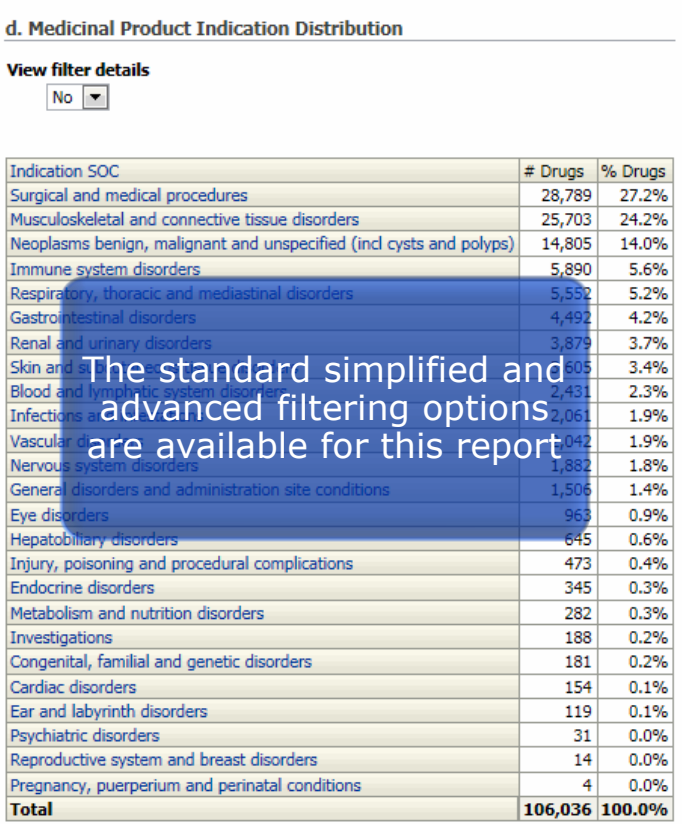
These reports focus on the population of various non-mandatory fields. Reports a, c, e, f, g and h show whether a given organisation is populating these fields at a rate similar to the average.

If an organisation has a particularly low rate of field population in these reports it can indicate that their follow-up procedures may not be as robust or as thorough as those of other organisations.

A.05d. Medicinal Product Indication Distribution

EUROPEAN MEDICINES AGENCY

This report returns the percentage and the number of drugs with a specific indication



d. Medicinal Product Indication Distribution

View filter details

No

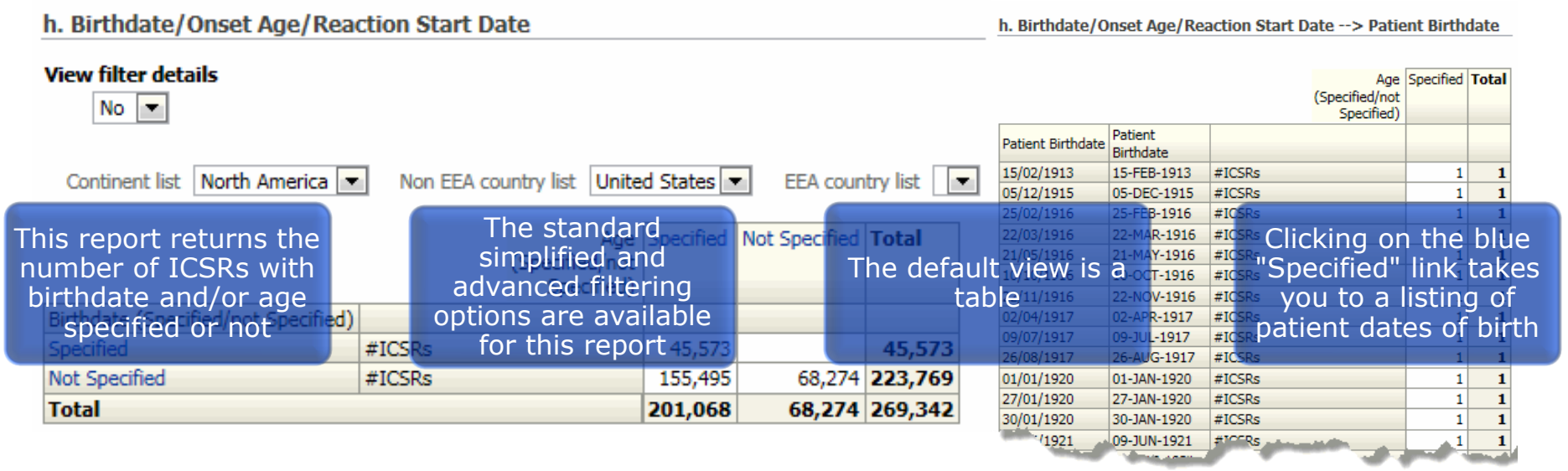
Indication SOC	# Drugs	% Drugs
Surgical and medical procedures	28,789	27.2%
Musculoskeletal and connective tissue disorders	25,703	24.2%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	14,805	14.0%
Immune system disorders	5,890	5.6%
Respiratory, thoracic and mediastinal disorders	5,552	5.2%
Gastrointestinal disorders	4,492	4.2%
Renal and urinary disorders	3,879	3.7%
Skin and s	605	3.4%
Blood and lymphatic system disorders	2,431	2.3%
Infections a	2,061	1.9%
Vascular d	042	1.9%
Nervous system disorders	1,882	1.8%
General disorders and administration site conditions	1,506	1.4%
Eye disorders	963	0.9%
Hepatobiliary disorders	645	0.6%
Injury, poisoning and procedural complications	473	0.4%
Endocrine disorders	345	0.3%
Metabolism and nutrition disorders	282	0.3%
Investigations	188	0.2%
Congenital, familial and genetic disorders	181	0.2%
Cardiac disorders	154	0.1%
Ear and labyrinth disorders	119	0.1%
Psychiatric disorders	31	0.0%
Reproductive system and breast disorders	14	0.0%
Pregnancy, puerperium and perinatal conditions	4	0.0%
Total	**106,036**	**100.0%**

The standard simplified and advanced filtering options are available for this report

Click an Indication SOC to view it at a lower-level. Clicking once displays HLGT for that SOC & then clicking the HLGT displays HLT

A.05h Birthdate/Onset Age/Reaction Start Date

EUROPEAN MEDICINES AGENCY



This report returns the number of ICSRs with birthdate and/or age specified or not

The standard simplified and advanced filtering options are available for this report

The default view is a table

Clicking on the blue "Specified" link takes you to a listing of patient dates of birth

Please note that the Safety Report Data Quality reports within the EudraVigilance Administrative Query Library will be updated and enhanced during 2017.

This training module will be updated accordingly

Section summary: EudraVigilance administrative query library

- **In this section we have covered:**
  - The different categories of reports included in the EudraVigilance administrative query library
  - Principles and instructions for running reports within the Library
  - Output examples of the main reports in the Library

- Introduction to this training module
- Introduction to EVDAS
- ICH-E2B(R3) EVDAS implementation
- EudraVigilance administrative query library
- **Pharmacovigilance query library**
- Summary

Section overview: Pharmacovigilance query library

In this section you will obtain an understanding of:

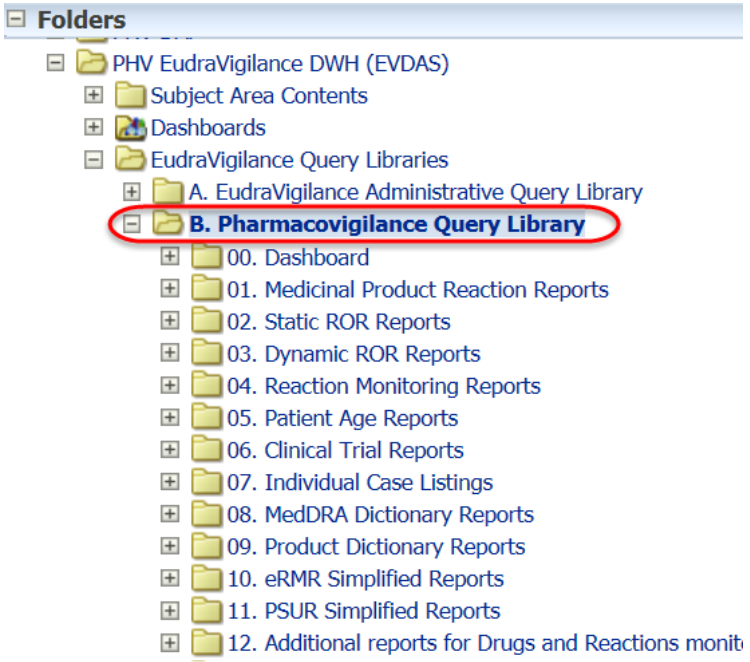
- **The main reports included in the pharmacovigilance query library catalogue**

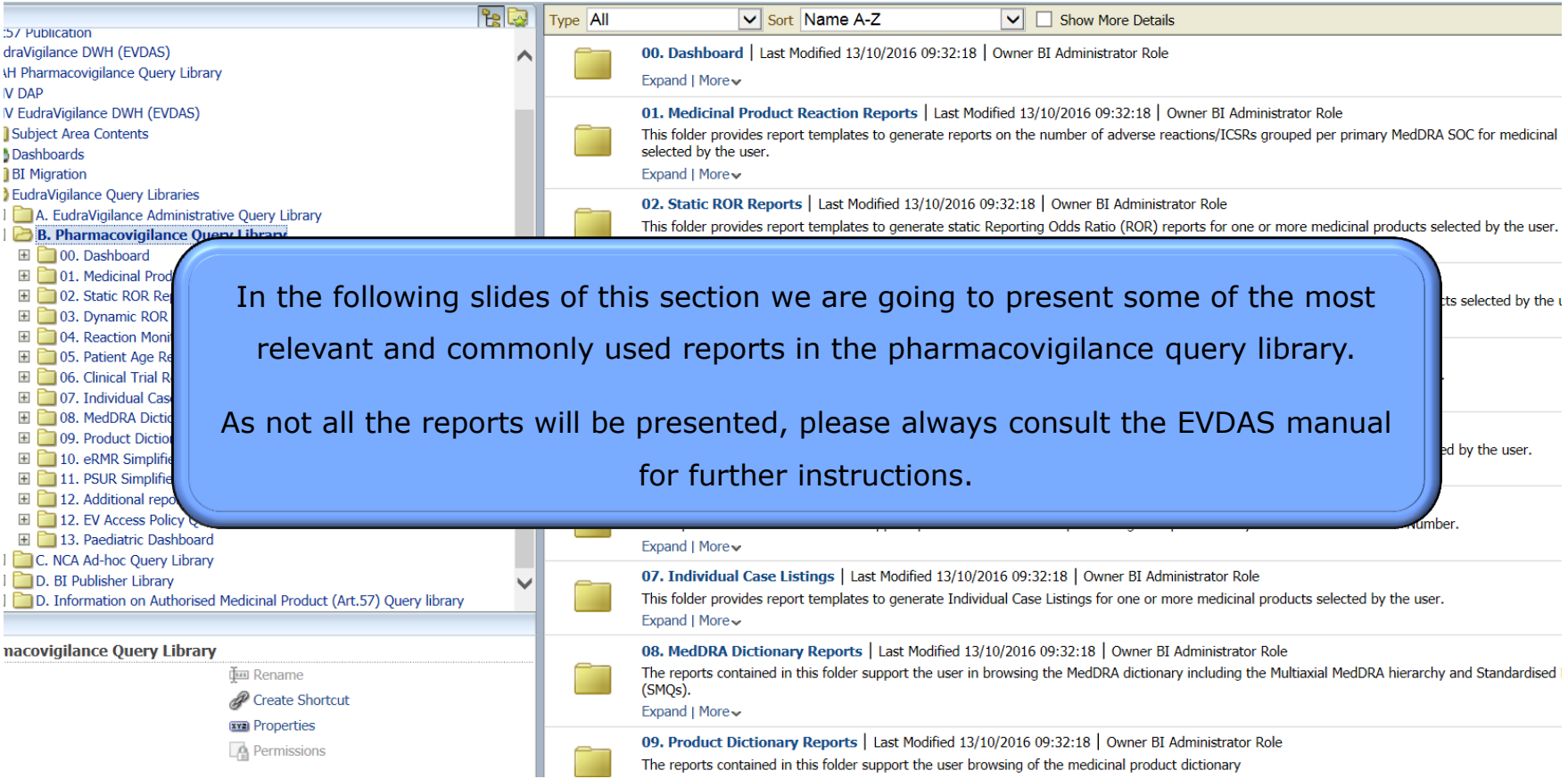
Pharmacovigilance query library

The pharmacovigilance query library contains dashboards and reports that are used for the analysis of safety data, for signal detection and validation as well as assessments during other pharmacovigilance procedures.

The reports provide aggregated data outputs as well as details of the individual cases.

To access the Pharmacovigilance query library, click 'catalog' on the global header, then in the folder pane, expand EudraVigilance DWH (EVDAS), then EudraVigilance Query Libraries then B. Pharmacovigilance Query Library.





In the following slides of this section we are going to present some of the most relevant and commonly used reports in the pharmacovigilance query library.

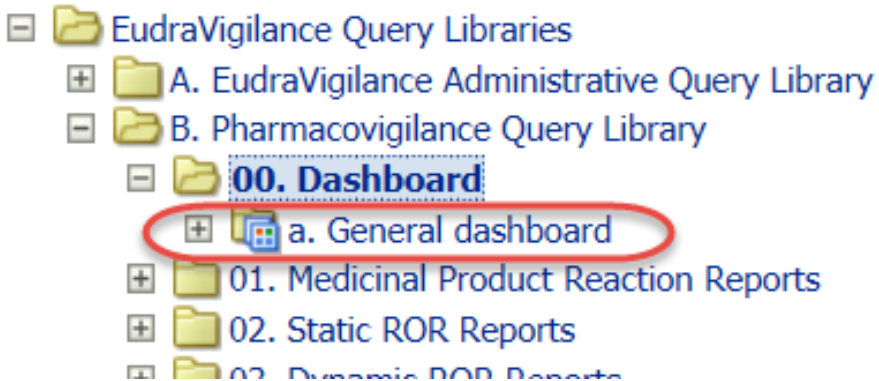
As not all the reports will be presented, please always consult the EVDAS manual for further instructions.

General dashboard

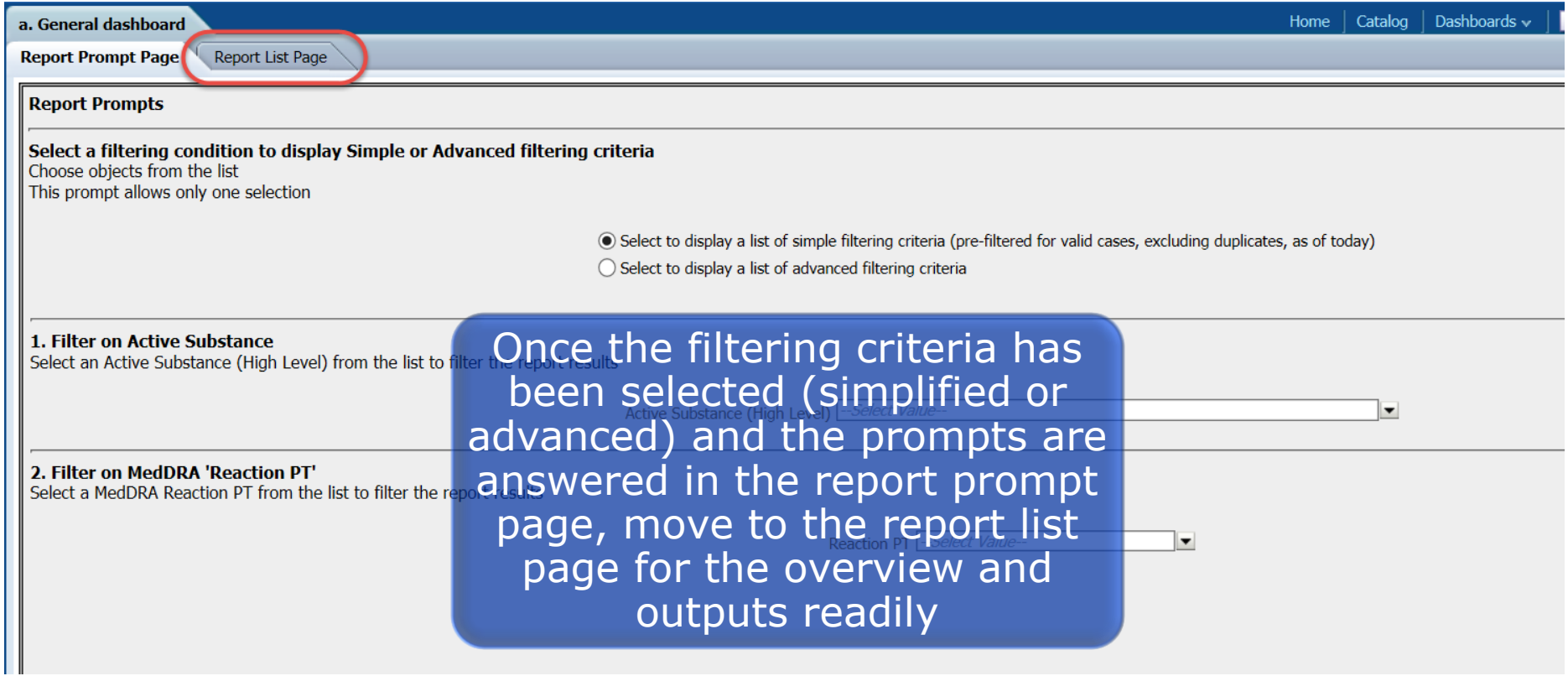
General dashboard

- A general dashboard has been created to simplify the data analysis in EVDAS.
- By entering the filter criteria only once on the prompt page of the dashboard (which follows exactly the same prompt structure as all other reports), you will then be able to run several reports simply by clicking on the links corresponding to these reports on the 'Report list page'.
- As before, you can choose to use the simplified or advanced filtering criteria.
- All the report results you will obtain from the next window will correspond to these criteria.

General dashboard

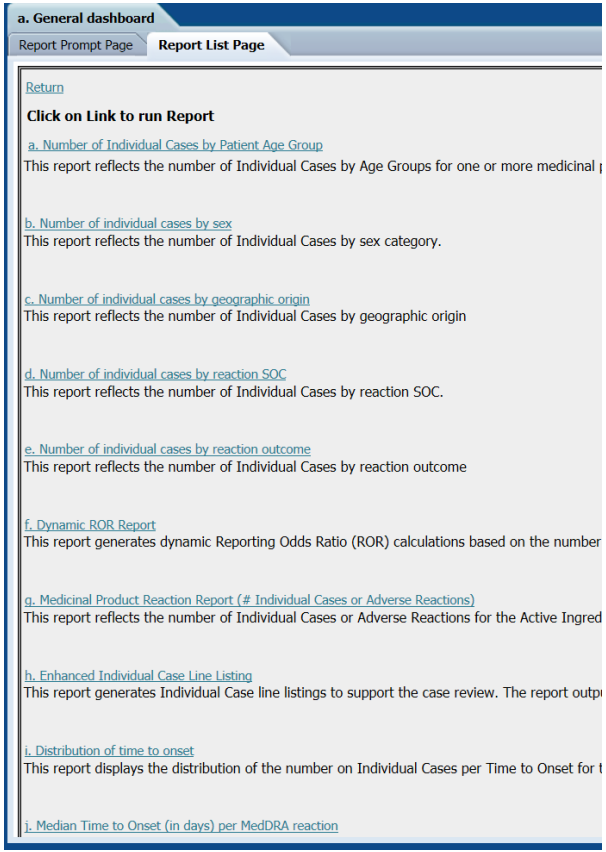


General dashboard



Once the filtering criteria has been selected (simplified or advanced) and the prompts are answered in the report prompt page, move to the report list page for the overview and outputs readily

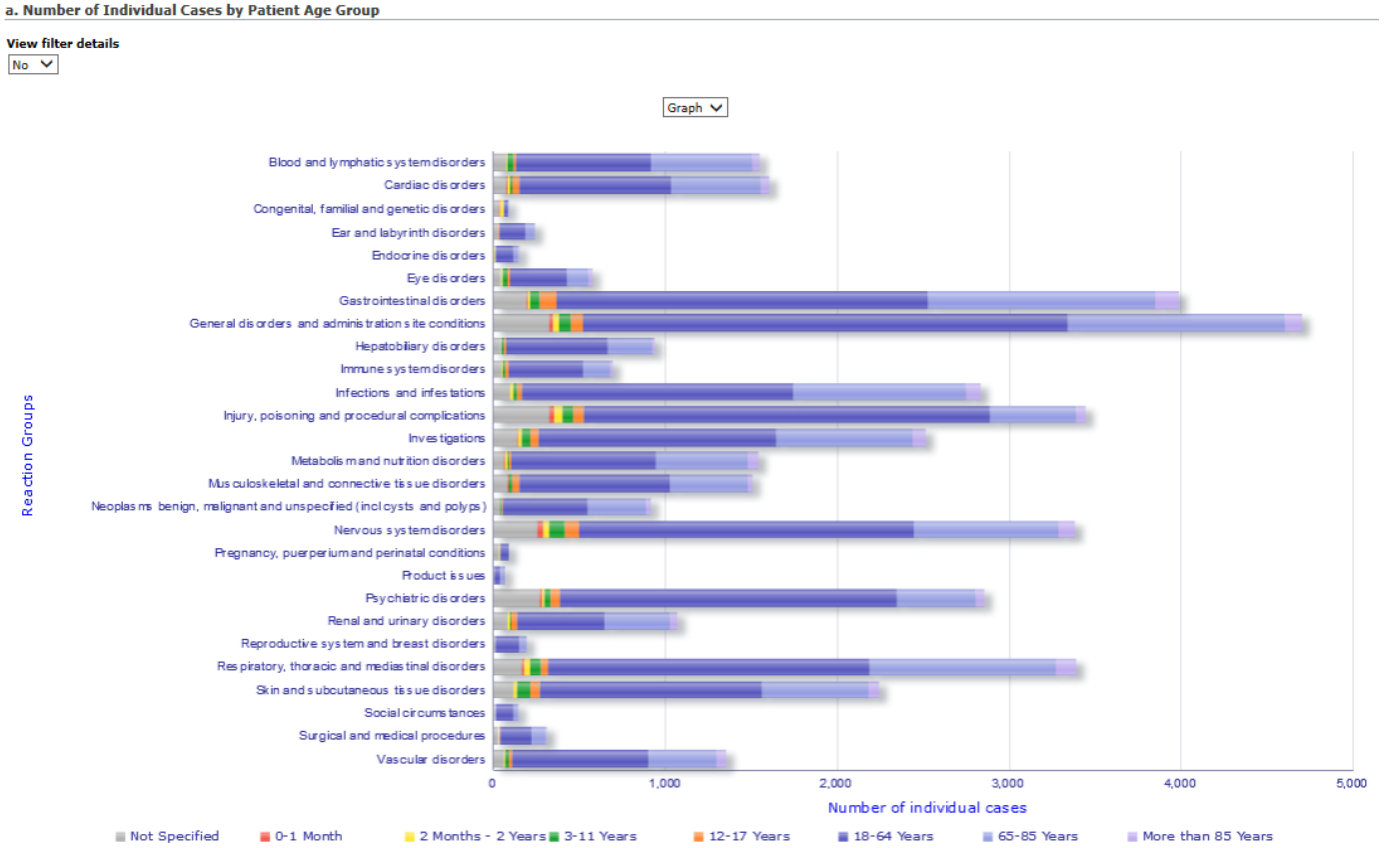
Reports links



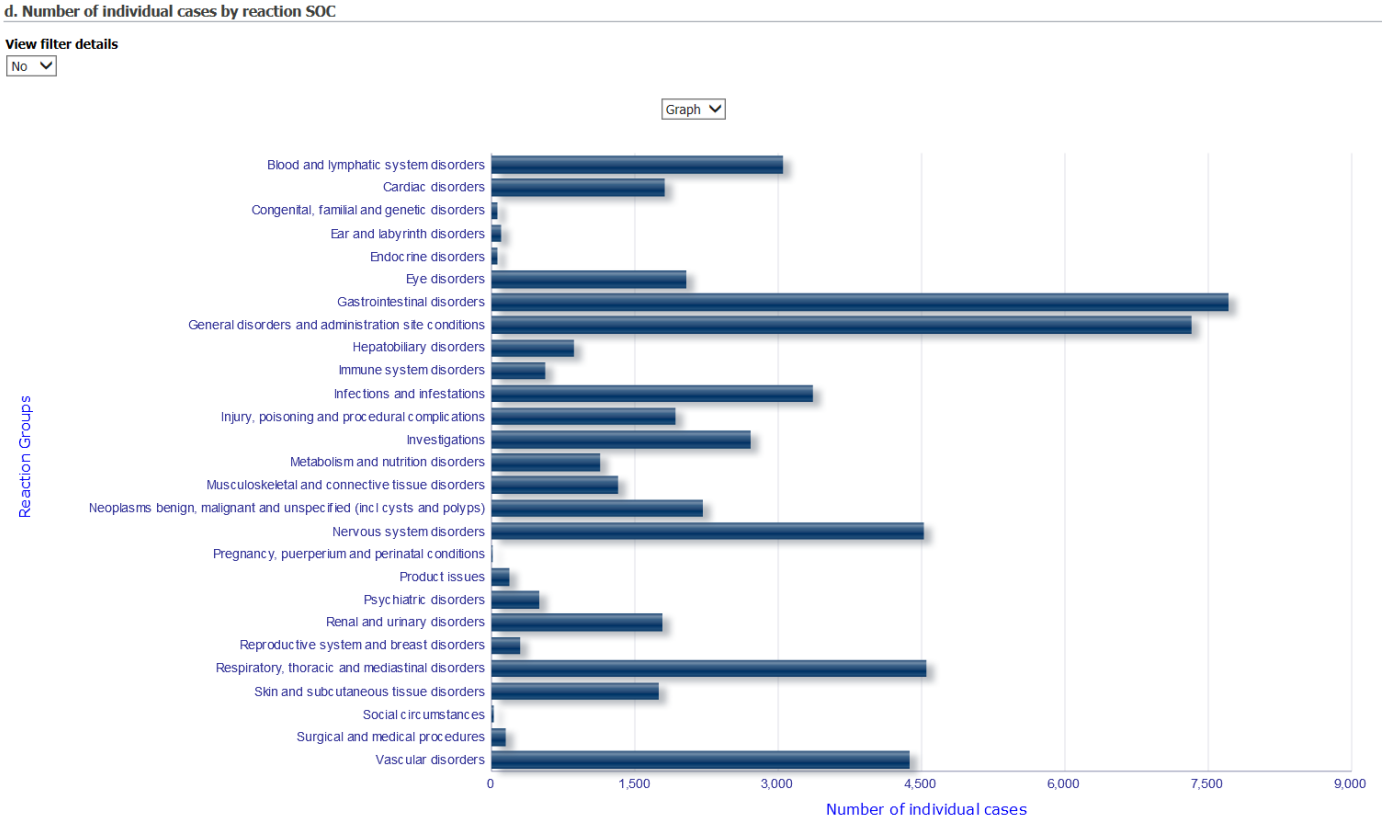
Clink on any link to open the reports and get the data

General dashboard example: number of cases by age

EUROPEAN MEDICINES AGENCY



General dashboard example: Number of cases by reaction



General dashboard example: Number of cases by sex

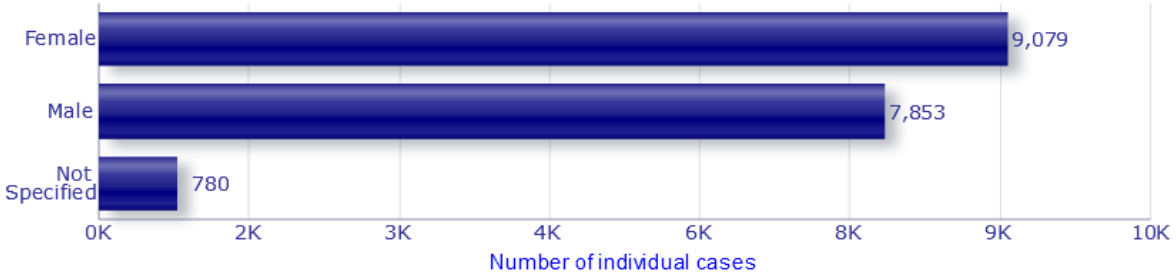
EUROPEAN MEDICINES AGENCY

b. Number of individual cases by sex

View filter details

No

Sex	Cases	%
Female	9,079	51.3%
Male	7,853	44.3%
Not Specified	780	4.4%
Total	**17,712**	**100.0%**



General dashboard example: Number of cases by geographic distribution

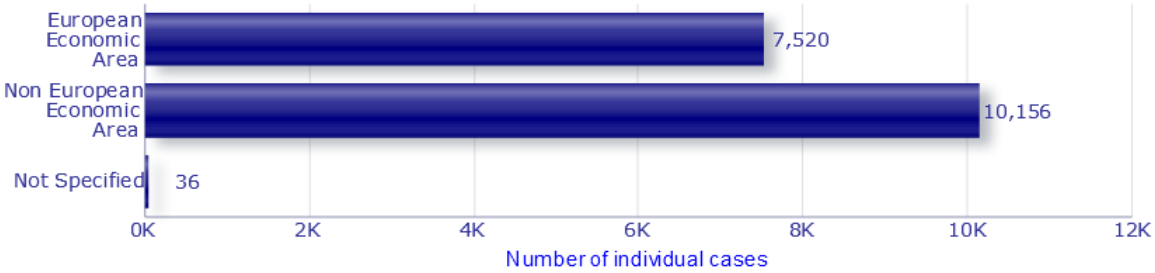
EUROPEAN MEDICINES AGENCY

c. Number of individual cases by geographic origin

View filter details

No

Primary Source Country fo Regulatory Purposes	Cases	%
European Economic Area	7,520	42.5%
Non European Economic Area	10,156	57.3%
Not Specified	36	0.2%
Total	**17,712**	**100.0%**



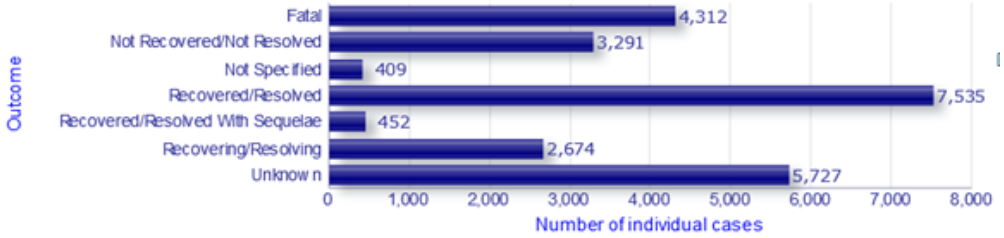
EUROPEAN MEDICINES AGENCY

e. Number of individual cases by reaction outcome

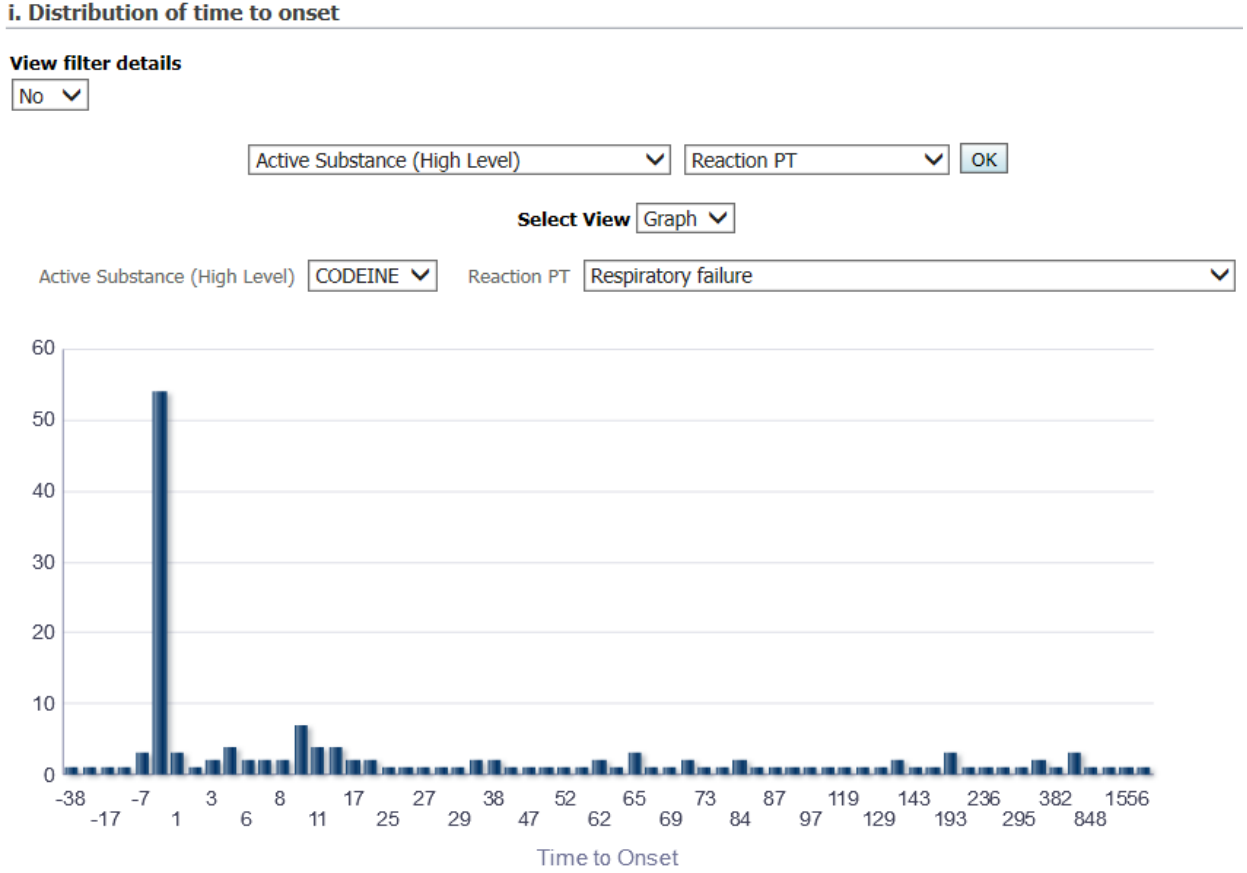
View filter details

No

Outcome	Cases	%
Fatal	4,312	24.3%
Not Recovered/Not Resolved	3,291	18.6%
Not Specified	409	2.3%
Recovered/Resolved	7,535	42.5%
Recovered/Resolved With Sequelae	452	2.6%
Recovering/Resolving	2,674	15.1%
Unknown	5,727	32.3%
Total	**17,712**	**100.0%**



General dashboard example: Time to onset distribution



Medicinal Product Reaction Reports

Medicinal product reaction reports

- The medicinal product reactions reports provide an overview of the number of cases/reactions submitted to the database.
- These reports can be used to have an overview of the cases reported for specific substance and an overview of which substances contain cases for a specific ADR.
- The data can be filtered according to the simplified or advanced filtering criteria previously explained.
- The outcomes are provided in grid or graphs formats.

Medicinal product reaction reports

The medicinal product reaction reports folder contain 3 different reports

1.a Medicinal product reaction report – Individual cases

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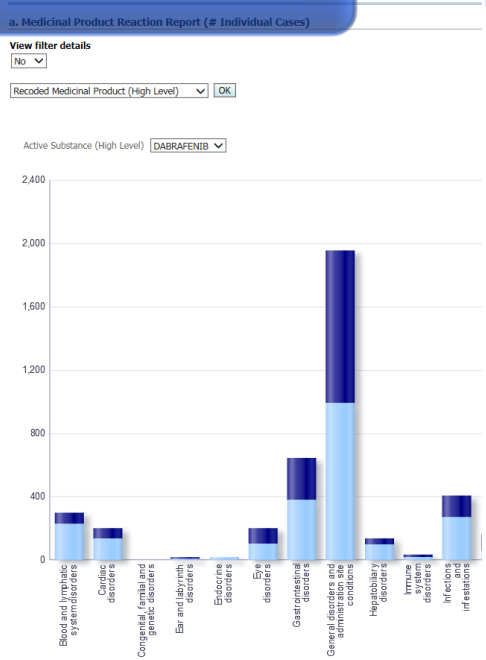
This report reflects the number of individual cases for a substance/product

It is possible to change the level of the substance/product to display the results

By clicking on the chart or table on a reaction will drill down in the MedDRA hierarchy



a. Medicinal Product Reaction Report (# Individual Cases)

View filter details

No

Recoded Medicinal Product (High Level) OK

Select View Grid

Active Substance (High Level) DABRAFENIB

Recoded Medicinal Product (High Level)		DABRAFENIB	TAFINLAR
Reaction SOC	Reaction HLGT		
Congenital, familial and genetic disorders	Chromosomal abnormalities and abnormal gene carriers	1	
	Hepatobiliary disorders congenital		1
	Musculoskeletal and connective tissue disorders congenital		1
	Renal and urinary tract disorders congenital		1

17:47:34

Return - Analyze - Refresh - Print - Export - Add to Briefing Book - Create Bookmark Link

1.b Medicinal product reaction report – Adverse reactions

The Medicinal product reaction report – Adverse reactions provides with the number of reactions according to the selected criteria

Remember one individual case may contain more than one reaction

b. Medicinal Product Reaction Report (# Adverse Reactions)

View filter details

No

Recoded Medicinal Product (High Level) OK

Select View Grid

Active Substance (High Level) DABRAFENIB

Recoded Medicinal Product (High Level)	DABRAFENIB	TAFINLAR
Reaction SOC		
Blood and lymphatic system disorders	319	100
Cardiac disorders	163	82
Congenital, familial and genetic disorders	1	3
Ear and labyrinth disorders	7	9
Endocrine disorders	16	7
Eye disorders	139	140
Gastrointestinal disorders	639	447
General disorders and administration site conditions	1,716	1,509
Hepatobiliary disorders	132	54
Immune system disorders	19	17
Infections and infestations	365	180

- The Medicinal product reaction report – Individual cases or adverse reactions provides the user the possibility to count either number of cases or adverse reactions.
- Count of cases or reactions can be changed once the report has run and the results are obtained.

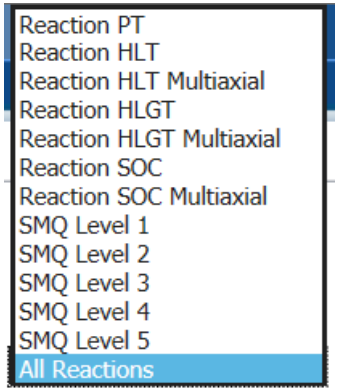
EUROPEAN MEDICINES AGENCY

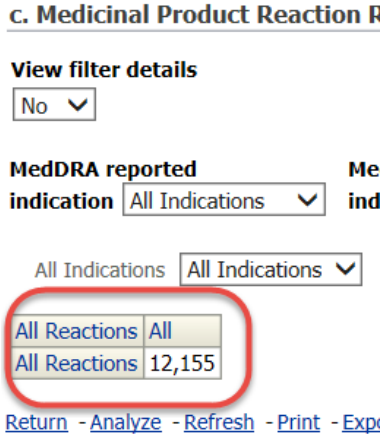
The report gives you an overview of the number of cases per MedDRA PT

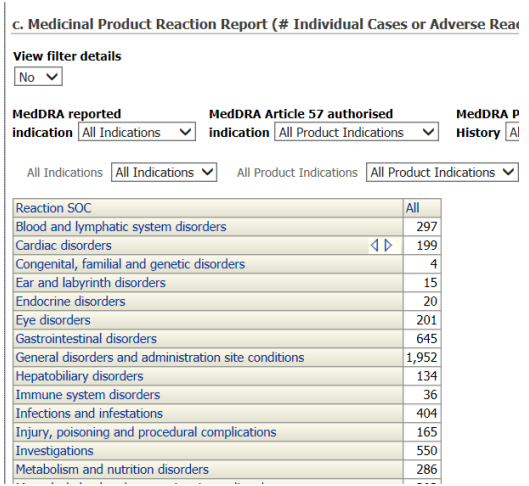
The report offers the possibility to view the total number of all the cases/reactions

And also offers the possibility to view the number of cases/reactions per MedDRA hierarchy (SOC in the example)

Reaction PT	All
Abdominal adhesions	5
Abdominal compartment syndr	3
Abdominal discomfort	29
Abdominal distension	43
Abdominal hernia	9
Abdominal hernia perforation	1
Abdominal mass	3
Abdominal pain	481
Abdominal pain lower	25
Abdominal pain upper	108
Abdominal rigidity	7
Abdominal strangulated hernia	1







- Remember: to change the view between cases and reactions, substance/product hierarchy and MedDRA hierarchy, select you preference in the corresponding prompts and click OK

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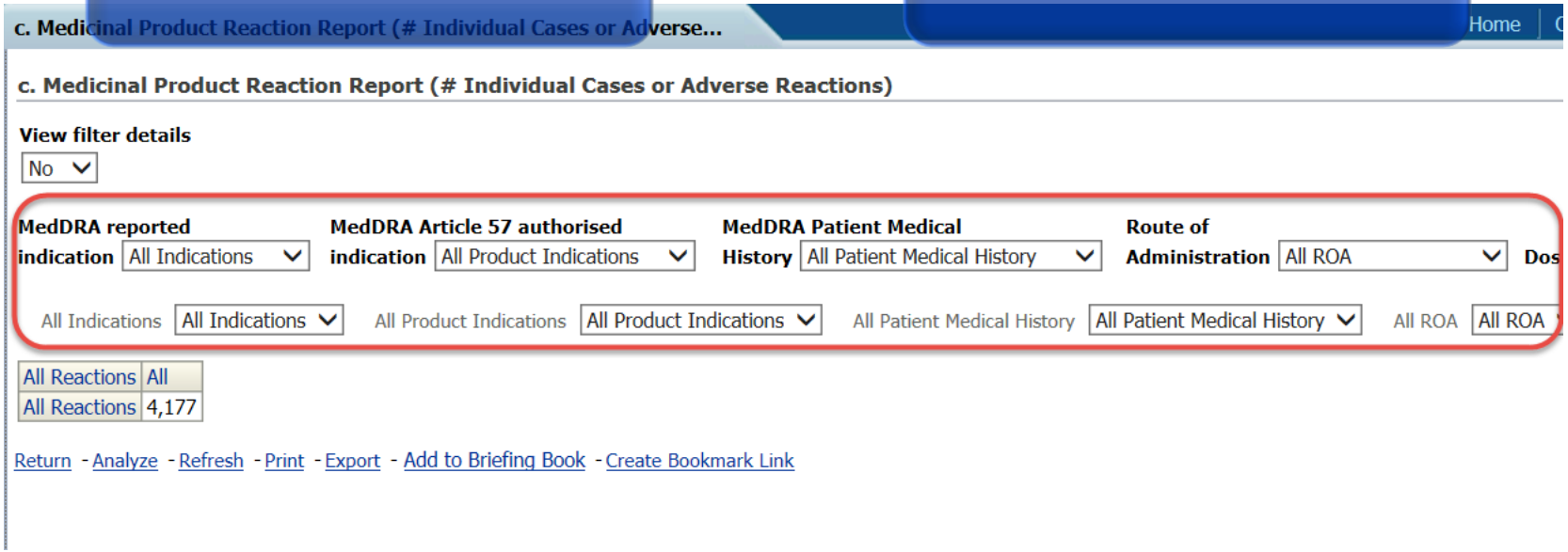
This report also offers the possibility to further filter the data once you get preliminary results.

Please be aware that report 1a and 1b do not have this possibility



Disproportionality analysis and ROR reports

Disproportionality analysis

- Disproportionality in *reporting* of ADRs rather than difference in *risk* with the medicinal products.
- The underlying principle of this method is that a drug–event pair is reported more often than expected, this is based on:
  - the frequency of cases on the reported drug and a specific adverse event
  - and the frequency of the same event reported for all the other drugs in the database

- EV criteria for Signals of disproportionality (SDRs):
  - ROR- > 1 AND the number of cases >=3 (if on additional monitoring list), otherwise n >=5 AND event is an IME

Measures of disproportionality

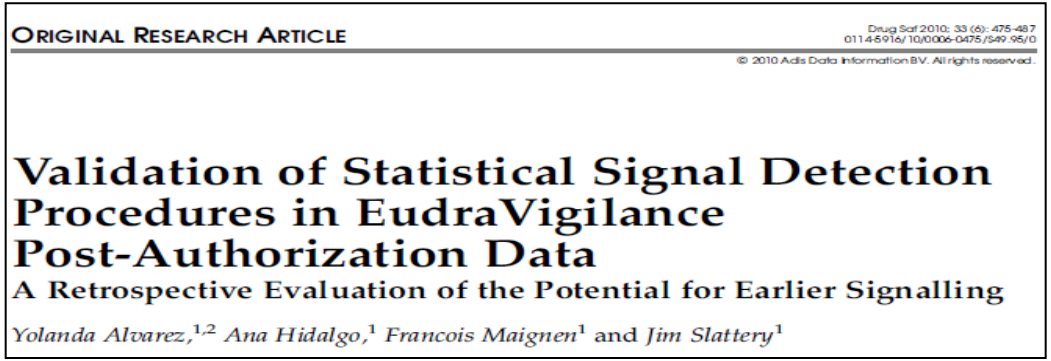
- Reporting odds ratio (ROR) – used in EV
- Proportional reporting ratio (PRR)
- Yule's Q
- Poisson probability
- Empirical Bayes Geometric Mean (EBGM, EB05)

	Event R	All other events
Medicinal product P	a	b
All other products	c	d

$$ROR = \frac{a/b}{c/d}$$

➢ *Similar estimates; concordance increases with rising number of reports (Van Puijenbroek et al. Pharmacoepidemiology and drug safety. 2002; 11: 3-10; Candore et al. Drug Safety. 2015;38(6):577-87)*

Benefits of using disproportionality analyses



ORIGINAL RESEARCH ARTICLE

Drug Saf 2010; 33 (6): 475-487
0114-5916/10/0006-0475/$49.95/0

Validation of Statistical Signal Detection Procedures in EudraVigilance Post-Authorization Data

A Retrospective Evaluation of the Potential for Earlier Signalling

Yolanda Alvarez,[1,2] Ana Hidalgo,[1] Francois Maignen[1] and Jim Slattery[1]

- Statistical methods can lead to earlier detection of safety signals – approx. 54% signals were detected earlier (mean time saved 2.45 years)
- 20% signals are however detected earlier by traditional methods
- 26% are not detected by statistical methods → established pharmacovigilance methods and disproportionality analyses are complementary

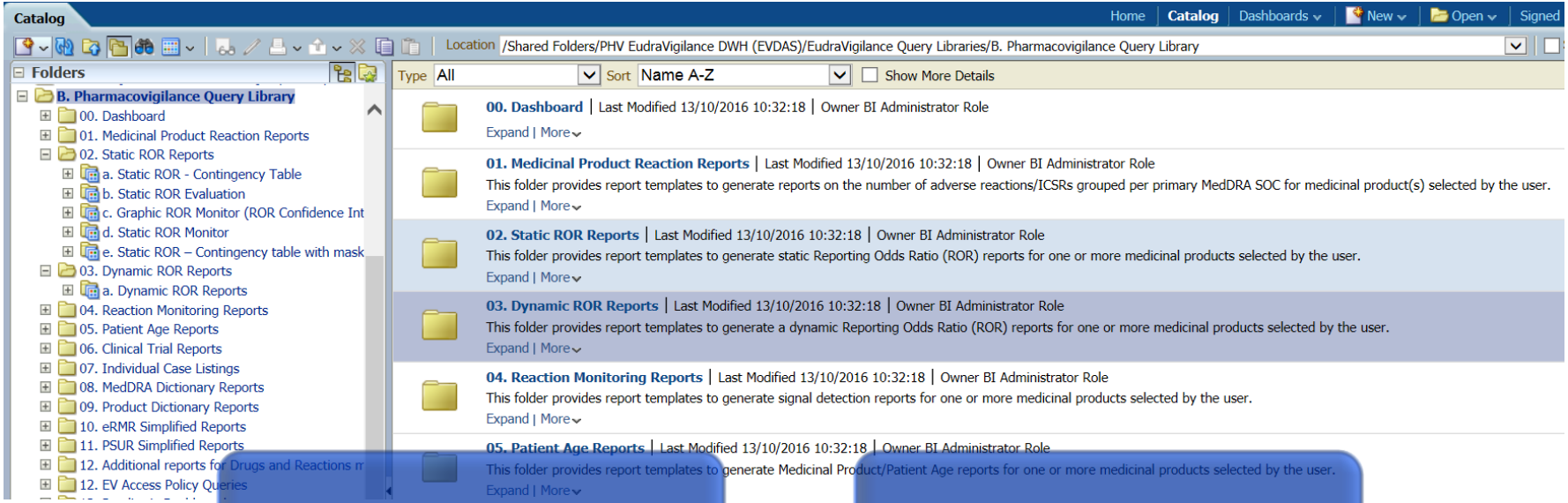
Caveats in disproportionality analyses

- The disproportionality analysis is not an inferential exercise.
- Disproportionality in reporting may arise due to a number of biases (underlying disease, artefacts due to reporting practices/ medical terminologies/coding/duplicates, type of medicinal products/source of data etc.).
- This statistical association does not imply any kind of causal relationship between the administration of the drug and the occurrence of the adverse event.
- False positives – where there is no causal association but SDR is present.
- False negatives (masking effect*) - the absence of an SDR does not exclude an association.
  - **Maignen et al. Pharmacoepidemiology and drug safety. 2014; 23(2): 208-217*
- Consequently, there is a scientific consensus that SDRs from quantitative methods should always be medically assessed.

Principles and methods for statistical signal detection in EudraVigilance are developed in the EMA guideline 'Screening for adverse reactions in EudraVigilance'

ROR reports

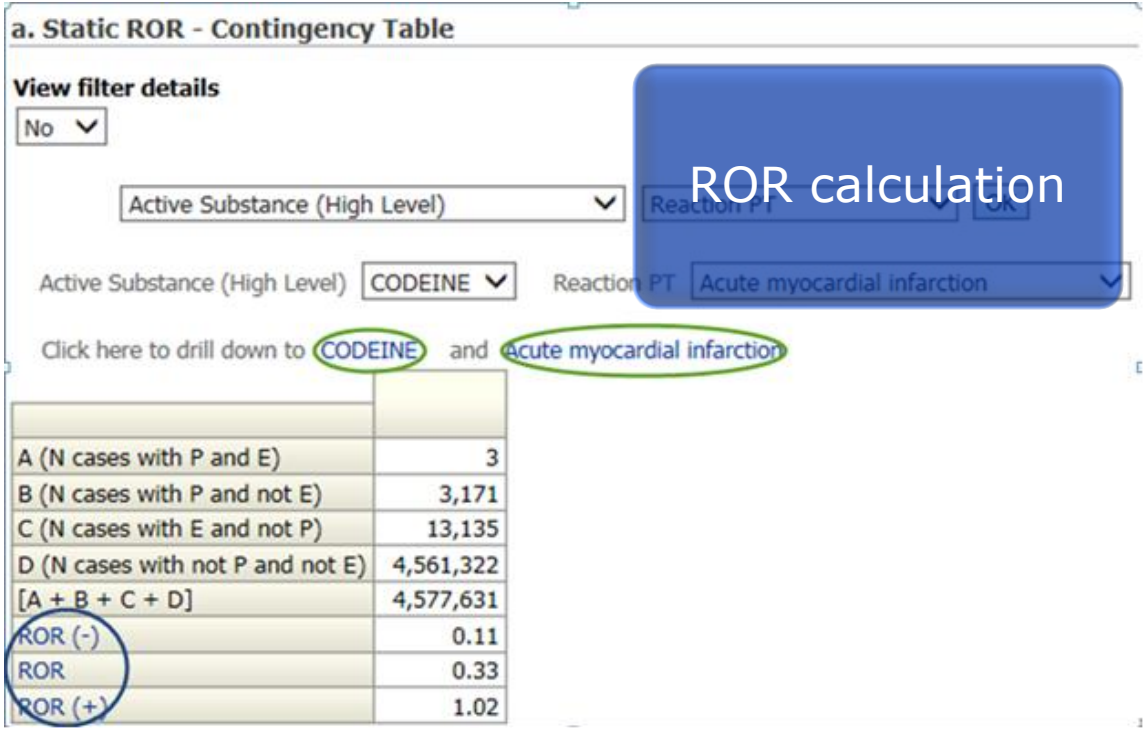
5 reports for static ROR and 1 for dynamic ROR



Static: ROR at a point in time, now or in the past

Dynamic: ROR over time

ROR report B.2.a Static ROR – Contingency Table



a. Static ROR - Contingency Table

View filter details

No

Active Substance (High Level)

Active Substance (High Level) CODEINE

Reaction PT Acute myocardial infarction

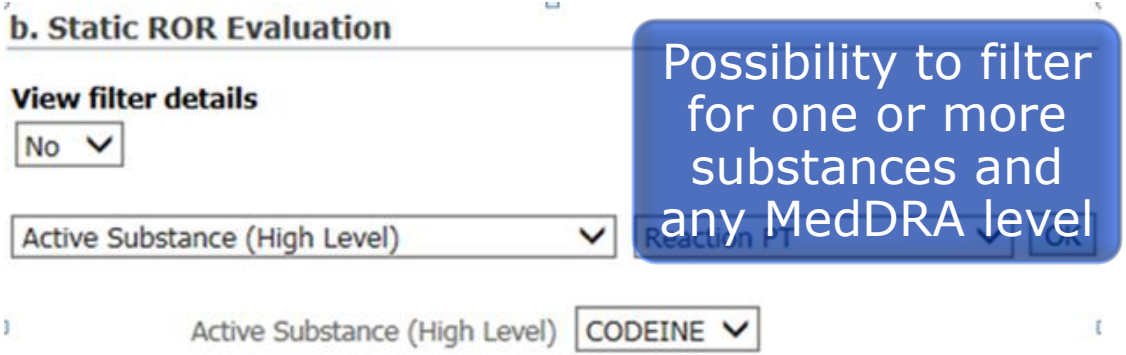
Click here to drill down to CODEINE and Acute myocardial infarction

A (N cases with P and E)	3
B (N cases with P and not E)	3,171
C (N cases with E and not P)	13,135
D (N cases with not P and not E)	4,561,322
[A + B + C + D]	4,577,631
ROR (-)	0.11
ROR	0.33
ROR (+)	1.02

ROR calculation

ROR confidence interval

ROR report B.2.b Static ROR Evaluation



Reaction PT	ROR (-)	ROR	ROR (+)	# Cases
Cardiac disorder	0.11	0.28	0.76	4
Cardiotoxicity	0.18	1.31	9.30	1
Cardiovascular disorder	0.71	1.43	2.86	8
Cardiovascular insufficiency	0.24	1.67	11.89	1

Possibility to filter for one or more substances and any MedDRA level

The results show the MedDRA term, the ROR and its confidence interval

ROR report B.2.b Static ROR Evaluation – subgroup analysis

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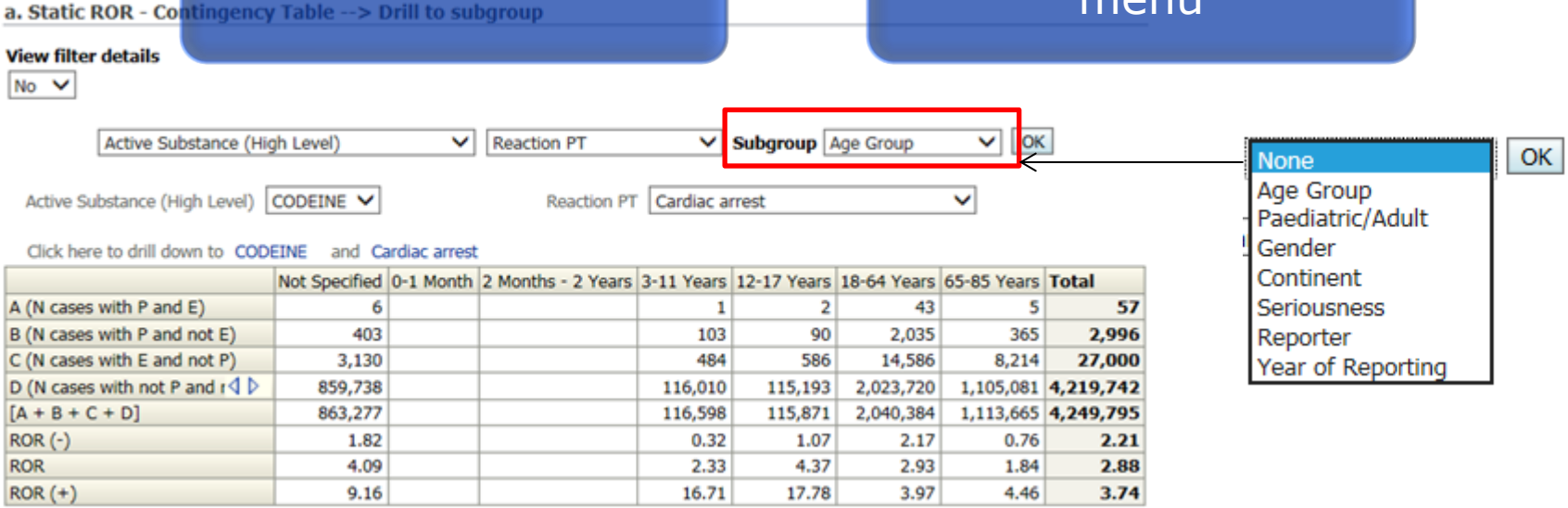
Drill down to predefined subgroups by clicking on the ROR

Subgroups can be selected in the age group drop-down menu

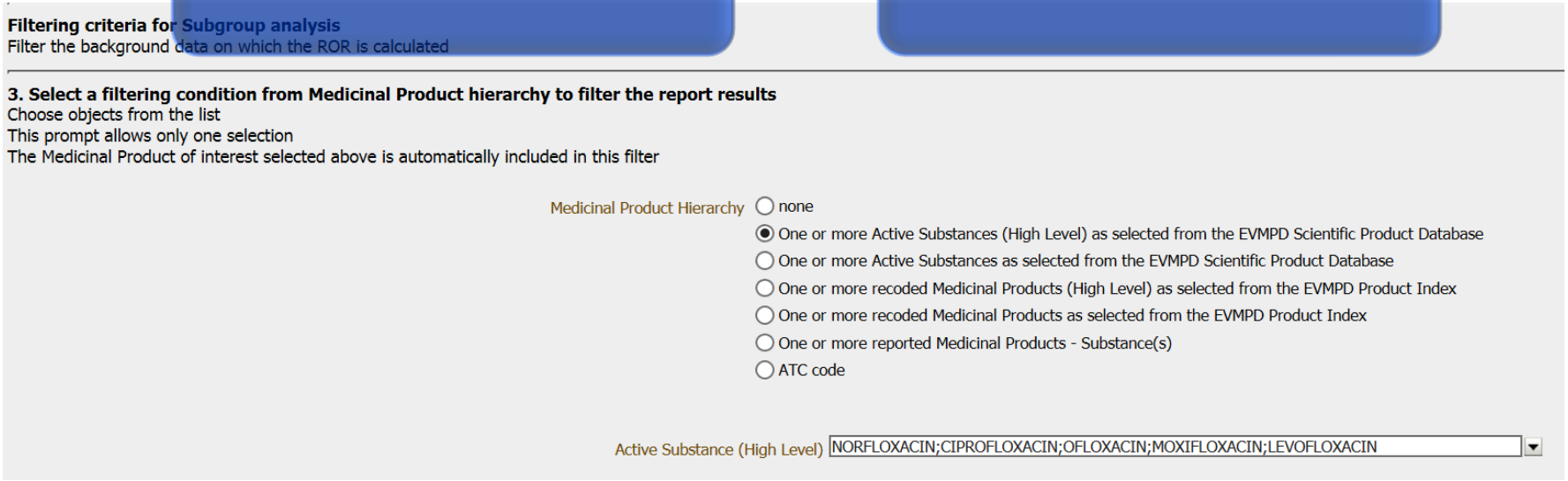


	Not Specified	0-1 Month	2 Months - 2 Years	3-11 Years	12-17 Years	18-64 Years	65-85 Years	Total
A (N cases with P and E)	6			1	2	43	5	**57**
B (N cases with P and not E)	403			103	90	2,035	365	**2,996**
C (N cases with E and not P)	3,130			484	586	14,586	8,214	**27,000**
D (N cases with not P and r	859,738			116,010	115,193	2,023,720	1,105,081	**4,219,742**
[A + B + C + D]	863,277			116,598	115,871	2,040,384	1,113,665	**4,249,795**
ROR (-)	1.82			0.32	1.07	2.17	0.76	**2.21**
ROR	4.09			2.33	4.37	2.93	1.84	**2.88**
ROR (+)	9.16			16.71	17.78	3.97	4.46	**3.74**

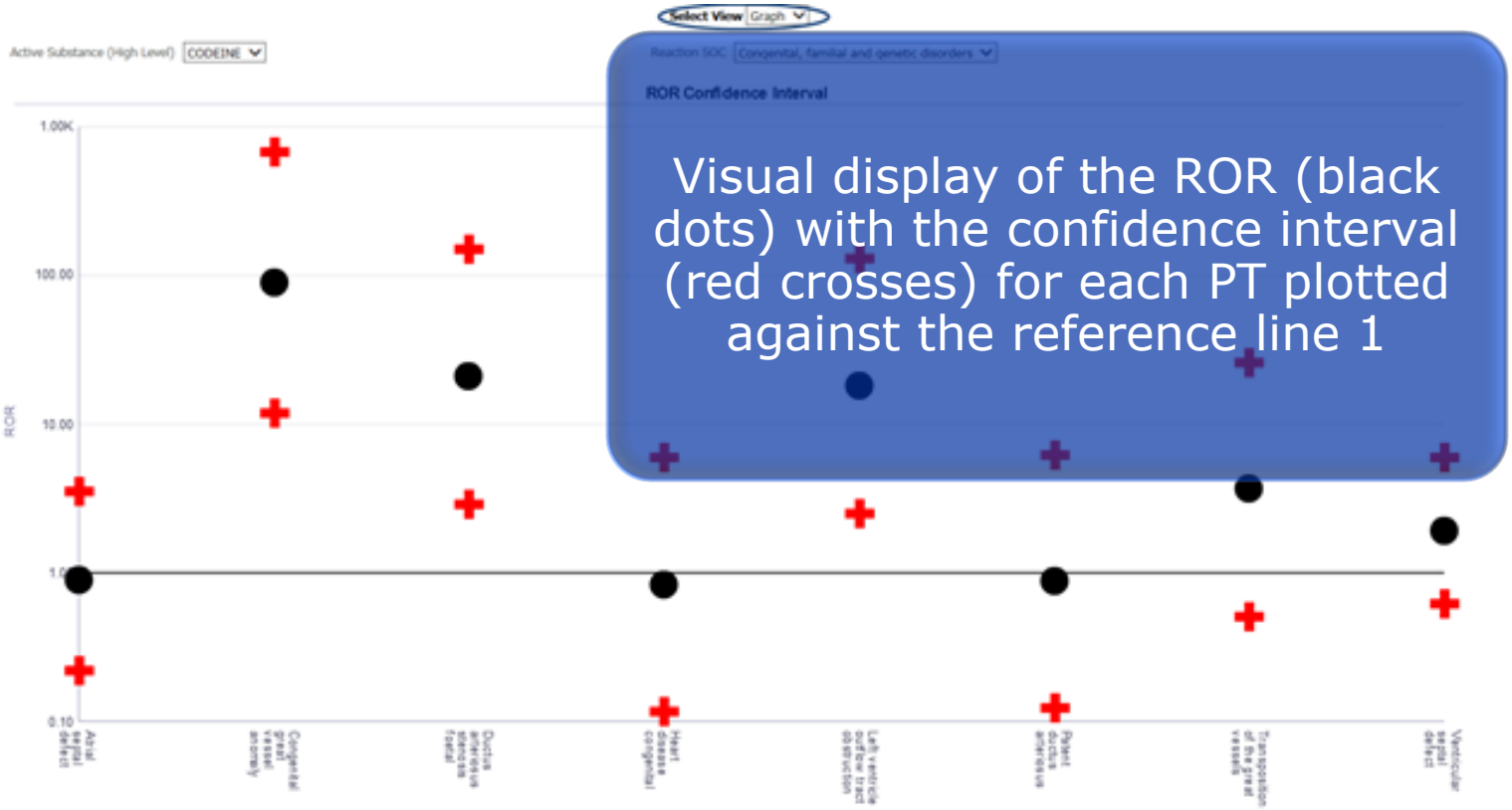
ROR report B.2.b Static ROR Evaluation – subgroup analysis

The dataset for the calculation of the ROR can be selected upfront

In the example, the ROR will be calculated against data for other fluoroquinolones



ROR report B.2.c Graphic ROR Monitor (ROR Confidence Interval)



ROR report B.2.d Static ROR Monitor

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Calculates the value of the ROR at the levels of MedDRA SOC, HLGT, HLT and PT

d. Static ROR Monitor

View filter details

No

Active Substance (High Level) CODEINE

Reaction SOC	Reaction HLGT	Reaction HLT	Reaction PT	ROR (SOC)	ROR (-) (SOC)	ROR (HLGT)	ROR (-) (HLGT)	ROR (HLT)	ROR (-) (HLT)	ROR (PT)	ROR (-) (PT)
Blood and lymphatic system disorders	Anaemias nonhaemolytic and marrow depression	Anaemias NEC	Anaemia	1.99	1.58	1.49	0.97	1.41	0.81	1.58	0.91
		Marrow depression and hypoplastic anaemias	Aplastic anaemia	1.99	1.58	1.49	0.97	1.57	0.78	3.17	0.44
			Bone marrow failure	1.99	1.58	1.49	0.97	1.57	0.78	2.78	1.04
			Pancytopenia	1.99	1.58	1.49	0.97	1.57	0.78	1.05	0.34
	Coagulopathies and bleeding diatheses (excl thrombocytopenic)	Coagulopathies	Coagulopathy	1.99	1.58	2.00	1.04	2.73	1.42	1.88	0.47
			Disseminated intravascular coagulation	1.99	1.58	2.00	1.04	2.73	1.42	5.80	2.75
	Haematological disorders NEC	Haematological disorders	Haemoconcentration	1.99	1.58	1.61	0.40	1.61	0.40	75.63	9.45
			Histiocytosis haematophagic	1.99	1.58	1.61	0.40	1.61	0.40	2.60	0.36
	Haemolyses and related conditions	Anaemias haemolytic NEC	Haemolytic anaemia	1.99	1.58	2.41	0.90	2.50	0.62	2.52	0.63
		Anaemias haemolytic mechanical factor	Haemolytic uraemic syndrome	1.99	1.58	2.41	0.90	3.17	0.44	3.93	0.55
		Haemolyses NEC	Haemolysis	1.99	1.58	2.41	0.90	7.27	2.33	5.58	1.38
			Intravascular haemolysis	1.99	1.58	2.41	0.90	7.27	2.33	26.30	3.55
	Platelet disorders	Thrombocytopenias	Heparin-induced thrombocytopenia	1.99	1.58	1.98	1.22	2.05	1.27	2.37	0.59
			Thrombocytopenia	1.99	1.58	1.98	1.22	2.05	1.27	2.13	1.25
			Thrombocytopenic purpura	1.99	1.58	1.98	1.22	2.05	1.27	4.17	0.58
	Red blood cell disorders	Polycythaemia (excl rubra vera)	Polycythaemia	1.99	1.58	20.31	10.43	7.76	1.08	8.07	1.12
		Red blood cell abnormal findings NEC	Erythropenia	1.99	1.58	20.31	10.43	25.37	12.48	55.11	16.87
			Macrocytosis	1.99	1.58	20.31	10.43	25.37	12.48	74.06	29.21
	Spleen, lymphatic and reticuloendothelial system disorders	Lymphatic system disorders NEC	Lymph node pain	1.99	1.58	0.95	0.40	0.88	0.33	3.90	0.55
			Lymphadenopathy	1.99	1.58	0.95	0.40	0.88	0.33	1.00	0.37
		Spleen disorders	Splenic infarction	1.99	1.58	0.95	0.40	1.25	0.18	12.87	1.77
	White blood cell disorders	Eosinophilic disorders	Allergic eosinophilia	1.99	1.58	2.46	1.75	4.34	2.16	99.90	99.90
			Eosinophilia	1.99	1.58	2.46	1.75	4.34	2.16	3.83	1.82
		Leukocytoses NEC	Leukocytosis	1.99	1.58	2.46	1.75	1.63	0.61	2.20	0.82
			Lymphocytosis	1.99	1.58	2.46	1.75	1.63	0.61	4.23	0.59

ROR report B.2.e Static ROR – Contingency Table with Masking Calculation

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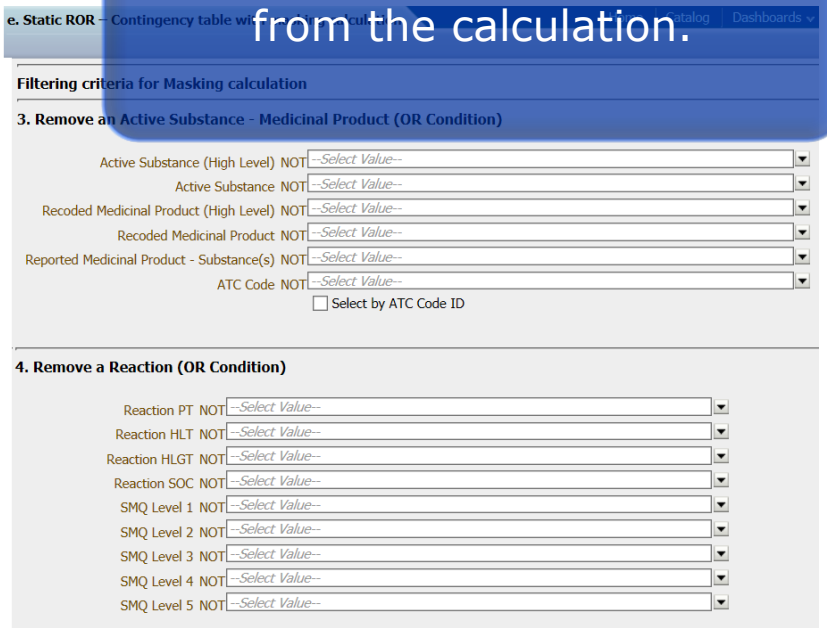
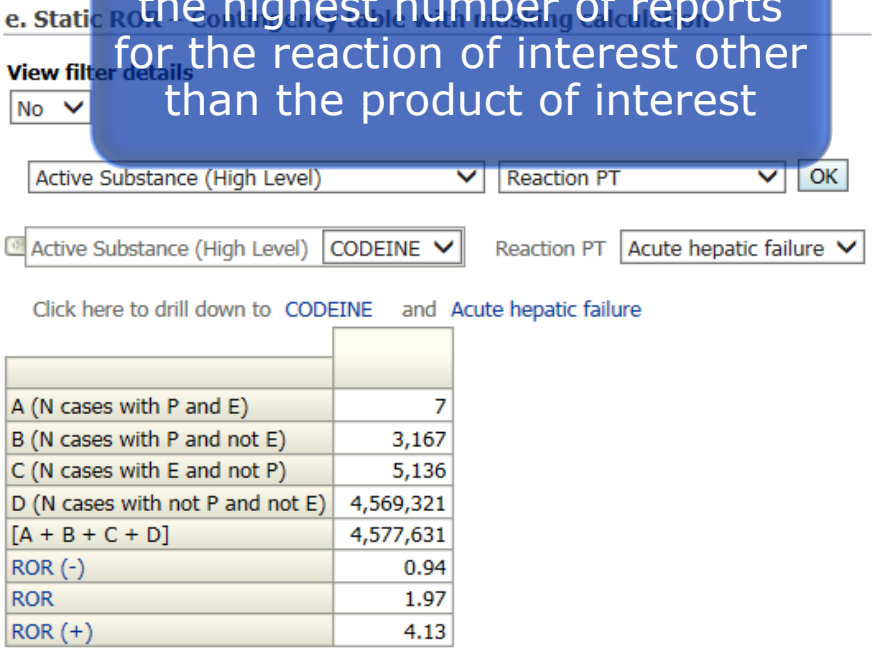
Display the results of the contingency and permits to remove substances or reactions from the calculation.



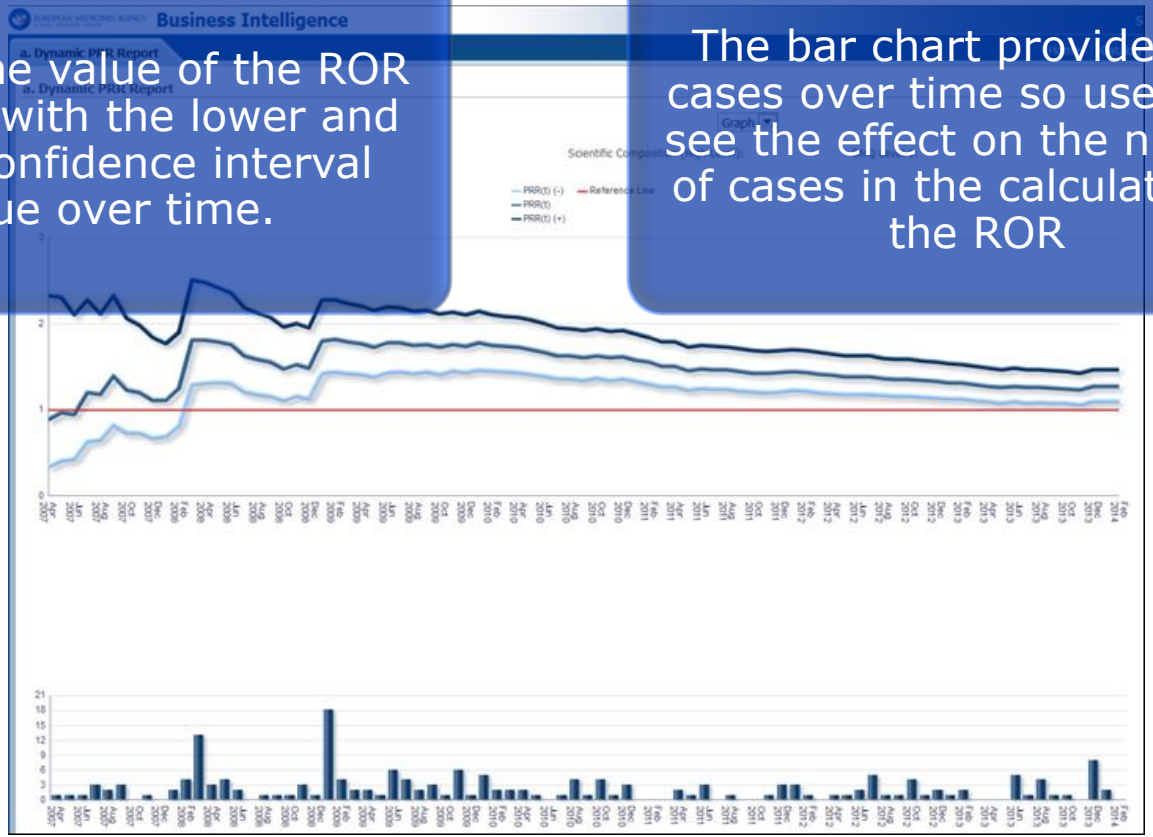
It is estimated that the highest masking effect is due to the product (or produts0 which has the highest number of reports for the reaction of interest other than the product of interest



A (N cases with P and E)	7
B (N cases with P and not E)	3,167
C (N cases with E and not P)	5,136
D (N cases with not P and not E)	4,569,321
[A + B + C + D]	4,577,631
ROR (-)	0.94
ROR	1.97
ROR (+)	4.13

ROR report B.3 Dynamic ROR Reports

Display the value of the ROR together with the lower and upper confidence interval value over time.



The bar chart provides the cases over time so users can see the effect on the number of cases in the calculation of the ROR

eRMR and eRMR simplified reports

eRMR: a tool for signal detection in EV

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Active Substances	SOCs	PTs	IME / DME	New EV	Tot EV	Tot Fat	AM OM C	Tot + F	Tot Li	Priority Paed	Priority Geriat	Tot Spontaneou	PRR (-) All	Priority All	Changes	Signal Status
Active substance	Blood	Cytopenia	Ime	1	21	7	---	0	0			4	4.25	2-IME SDR	Increased	linked
Active substance	Blood	Thrombocytopenia	Ime	2	109	26	---	0	2	1-TME		41	3.36	2-IME SDR	Increased	linked
Active substance	Card	Cardiac Disorder		1	20	4	---	0	0			6	0.77		Increased	linked
Active substance	Card	Arteriosclerosis Coronary Artery		1	5	1	---	0	2			3	1.80		Increased	linked
Active substance																linked
Active substance																closed
Active substance																linked
Active substance																linked
Active substance																linked
Active substance														SDR	(fatal)	other
Active substance	Genrl	Condition Aggravated		2	8	1	---	0	0			6	0.49		Increased	disease
Active substance	Genrl	Peripheral Swelling		3	19	1	---	0	0			3	0.19		Increased	linked
Active substance	Genrl	Chest Discomfort		2	19	1	---	0	0			6	0.64		Increased	linked
Active substance	Genrl	Pain		1	61	7	---	0	0			10	0.32		Increased	other
Active substance	Genrl	No Therapeutic Response		1	6	1	---	0	1			5	2.39		Increased	Other
Active substance	Immun	Drug Hypersensitivity		1	5	1	---	0	0			2	0.23		Increased	closed

Electronic Reaction Monitoring Report (eRMR) is a formatted Excel file used as a tool for monitoring the safety of drug use, facilitating prioritisation, detection, evaluation and documentation of suspected adverse drug reactions in EudraVigilance.

EV monitoring for Nationally Authorised Products

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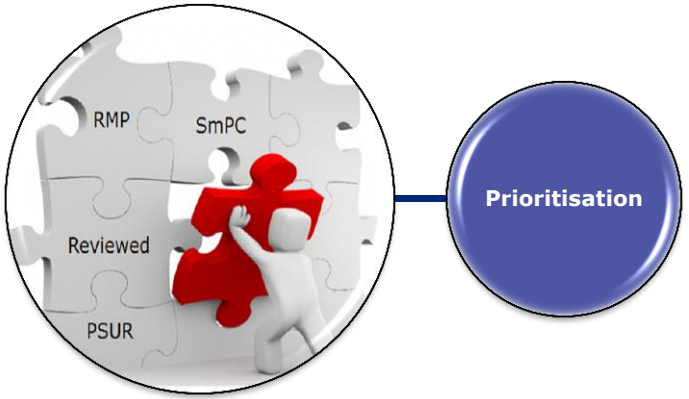
- The EMA routinely provides eRMRs to NCAs for monitoring of EV according to the work-sharing list for signal management.
- One file per active substance is provided
- The eRMR file contains built-in simplified queries that allows for direct access to EVDAS (e.g. Line listings and statistical analysis) facilitating signal validation and evaluation.

eRMR – Goal

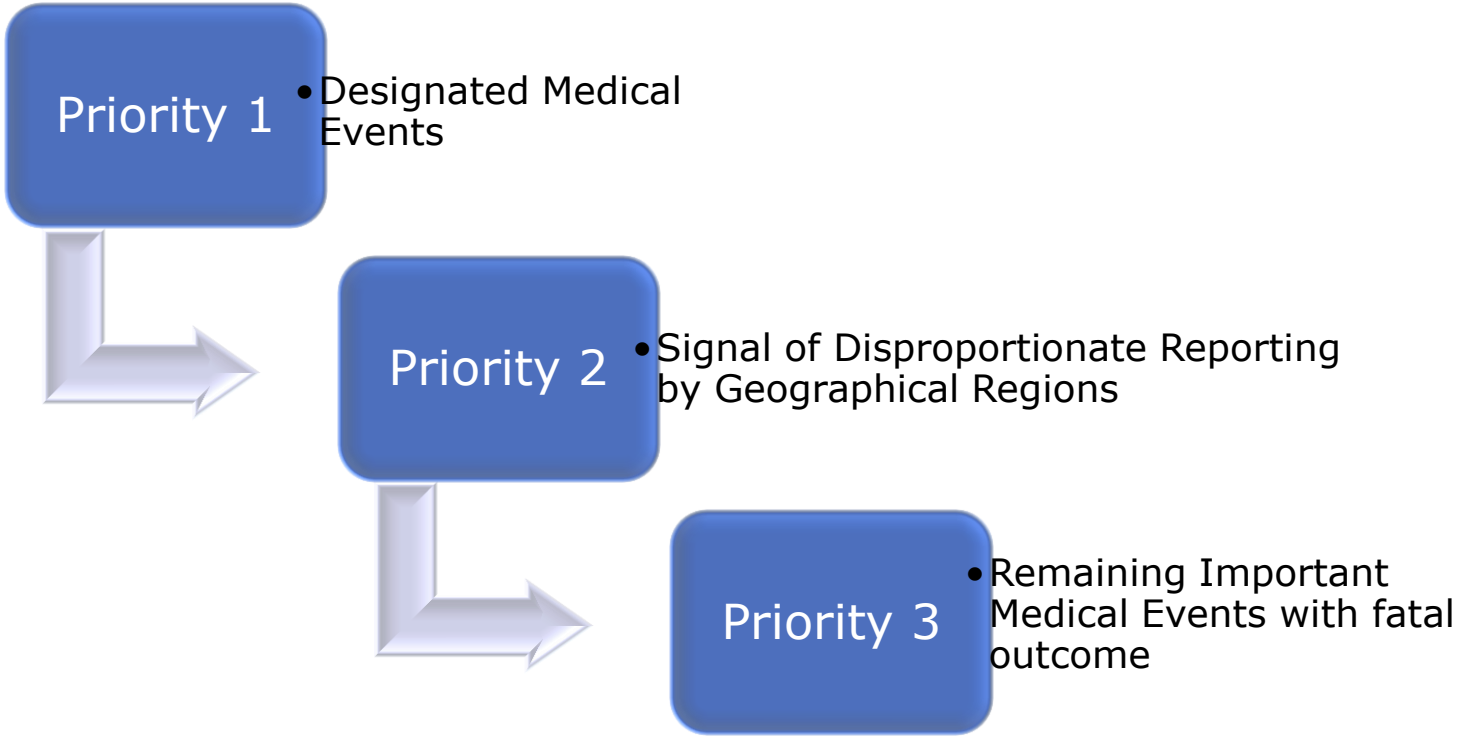
Detection of signals by monitoring new and historical data in EudraVigilance

Evaluation of the new safety information in relation to previous awareness

Tracking all reviews to build knowledge overtime assigning a signal status



Priorities – General population



Designated medical events list

Designated medical events (updated)

EMA has developed a list of designated medical events containing **medical conditions** that are inherently **serious** and often medicine-related:

EMA designated medical event list

It does not address product specific issues or medical conditions with high prevalence in the general population.

The list contains Medical Dictionary for Regulatory Activities (MedDRA) terms and serves as a **safety net in signal detection.** EMA and Member States use it to focus on reports of suspected adverse reactions that deserve special attention, irrespective of statistical criteria used to prioritise safety reviews.

The designated medical event list is one of the tools the European medicines regulatory network uses and is **not intended as a comprehensive list** of terms for signal detection activities.

EMA has published the list to ensure its approach is transparent. It is subject to review in light of further experience with its use.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp&mid=WC0b01ac0580727d1b

Important medical events

Important medical event list

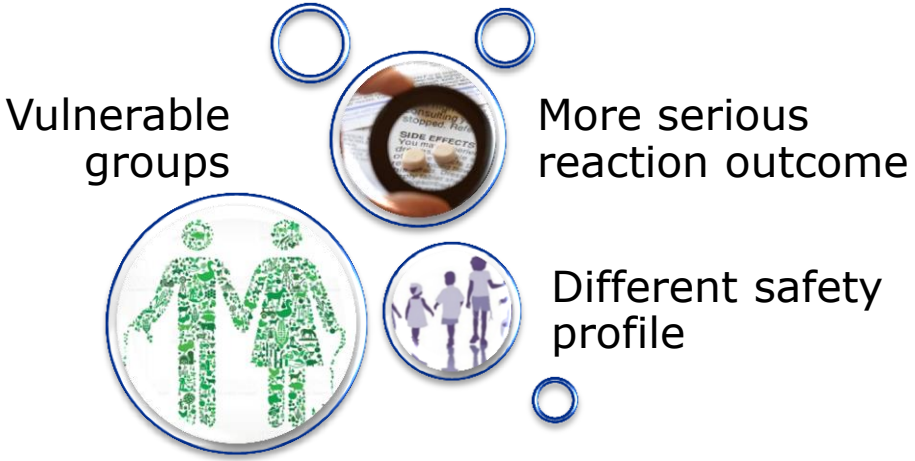
The EudraVigilance Expert Working Group has coordinated the development of a list of important medical event (IME) terms, together with the criteria to facilitate its maintenance.

The list aims to facilitate the classification of suspected adverse reactions as well as aggregated data analysis and case assessment for the day-to-day pharmacovigilance activities of stakeholders in the EU. The list is for guidance purposes only. To submit any comments on the IME list, send an email to: medraimelist@ema.europa.eu.

- Important medical event terms list (MedDRA version 19.1)
- Inclusion and exclusion criteria for the "Important Medical Events" list

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000166.jsp&mid=WC0b01ac0580a68f78

Focussed Signal Detection in sub-groups



Data presented by sub-groups

- Separate presentation of data in the eRMR based on new/cumulative number of cases for paediatrics and geriatrics

Targeted medical events

- Flag in the eRMR targeted medical terms with an increased interest in the subpopulation

Relative ROR

- New statistical method: Relative ROR which identifies a subgroup imbalance

eRMR Excel file: Structure

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eRMR

EVDAS

Legend

DME	Paediatric TME
Acute hepatic failure	Cardiac arrest
Acute kidney injury	Overdose
Agranulocytosis	Drug ineffective
Anaphylactic reaction	Respiratory arrest
Anaphylactic shock	Dyspnoea
Anaphylactoid reaction	Brain oedema
Anaphylactoid shock	Cardiac failure
Angioedema	Respiratory distress
Aplasia pure red cell	Off label use
Aplastic anaemia	Accidental overdose
Autoimmune haemolytic anaemia	Intentional overdose
Autoimmune hepatitis	Pulmonary oedema
Autoimmune pancreatitis	Pulmonary haemorrhage
Azotaemia	Septic shock
Blindness	Thrombocytopenia
Bone marrow failure	Apnoea
Deafness	Drug Abuse
Deafness neurosensory	Neutropenia
Deafness permanent	Haemorrhage intracranial
Deafness transitory	Pulmonary embolism
Dermatitis exfoliative	Hypertension
Dermatitis exfoliative generalised	Anaemia

eRMR_03Oct2016_06Nov2016 | EVDAS | Legend

Structure used and type of information

- Used of the Agreed Terminology (MedDRA) to Report a Drug Event Combination (DEC) and to group cases by different medical concepts

Active Substances	SOCs	HLGTs	HLTs	SMQ Narrow	PTs
Active Substances	Neopl	Miscellaneous And Site Unspecified Neoplasms	Neoplasms Malignant Site Unspecified	Malignancies	Neoplasm Malignant
Active Substances	Neopl	Respiratory And Mediastinal Neoplasms	Non-Small Cell Neoplasms Malignant Of	Malignancies	Lung Adenocarcinoma
Active Substances	Neopl	Skin Neoplasms Malignant And	Skin Melanomas (Excl Ocular)	Malignancies - - Skin Neopl, Malig & Unspec	Lentigo Maligna
Active Substances	Nerv	Neurological Disorders Of The Eye	Neurologic Visual Problems Nec		Hemianopia Homonymous
Active Substances	Resp	Pulmonary Vascular Disorders	Pulmonary Thrombotic And Embolic Conditions	Embolic And Thrombotic Events	Pulmonary Embolism

Structure used and type of information

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- Defined Categories in EV used to display the most relevant information for the screening

New EV	Tot EV	New EEA	Tot EEA	New HCP	Tot HCP	New Serious	Tot Serious	New Obs	Tot Obs	New CT	Tot CT	New Fatal	Tot Fatal	AMOMO	Tot + RC	Tot Lit
1	11	0	7	1	11	1	11	0	2	0	1	0	5	---	0	0
1	7	1	6	1	6	1	7	0	0	0	2	0	0	---	0	0
1	13	1	9	1	13	1	13	0	4	0	1	0	0	---	0	3
1	75	0	22	1	74	1	75	0	33	0	4	1	18	---	0	0
1	23	1	10	1	9	1	23	0	16	0	0	0	0	---	0	0

AMOMO stands for: Abuse, Misuse, Overdose, Medication Error, and Occupational Exposure data

eRMR structure: Priorities

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- Priorities Total population
- Priorities Paediatrics
- Priorities Geriatrics

Active Substances	SOCs	SMQ Narrow	PTs	Priority Paed	Priority Geriatr	Priority All
Active Substances	Resp	Convulsions - - Gen-Conv-Seiz Following Immunisatio	Dyspnoea	1. TMEs		
Active Substances	Immun	Depress & Suicide/Self-Inj	Anaphilactic shock		2-IME SDR	1. DME
Active Substances	Immun		Transplant Rejection	2 - IME SDR		3. IME Fatal
Active Substances	Inj&p		Transplant Dysfunction			2-IME SDR
Active Substances	Blood	Haematopoietic Cytopenias	Leukopenia			

Additional useful information

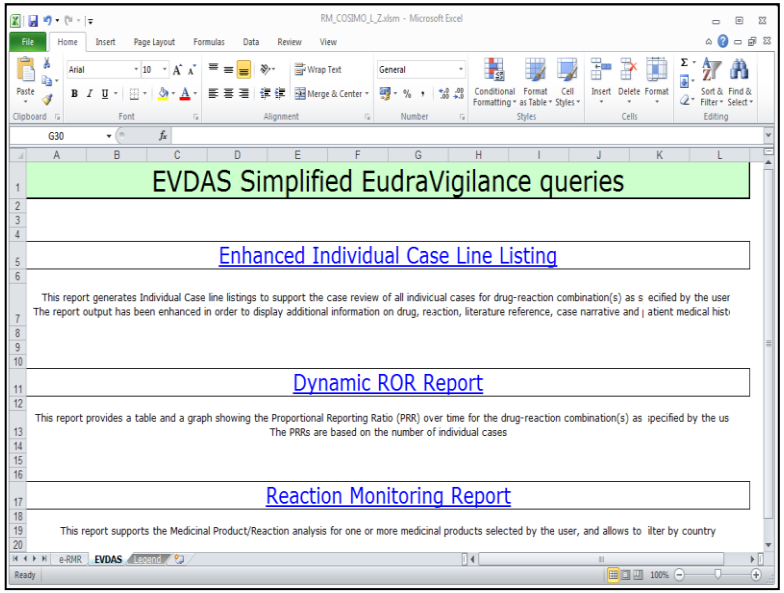
- Positive Re-challenge
- Literature Reports
- Most reported Route of Administration (RoA)
- Most reported Indication (HLGT)

Tot + RC	Tot Lit	Roa 1	Tot Roa (n/a)	Indic.1 (HLGT)	Tot Indic. (n/a)
0	5	Oral Use	18	Seizures (Incl Subtypes)	13
0	0	Oral Use	8	Seizures (Incl Subtypes)	1
1	33	Intravenous Use	34	Therapeutic Procedures And Supportive Care Nec	6
0	3	Intravenous Use	9	Therapeutic Procedures And Supportive Care Nec	5
8	3	Oral Use	55	Demyelinating Disorders	159

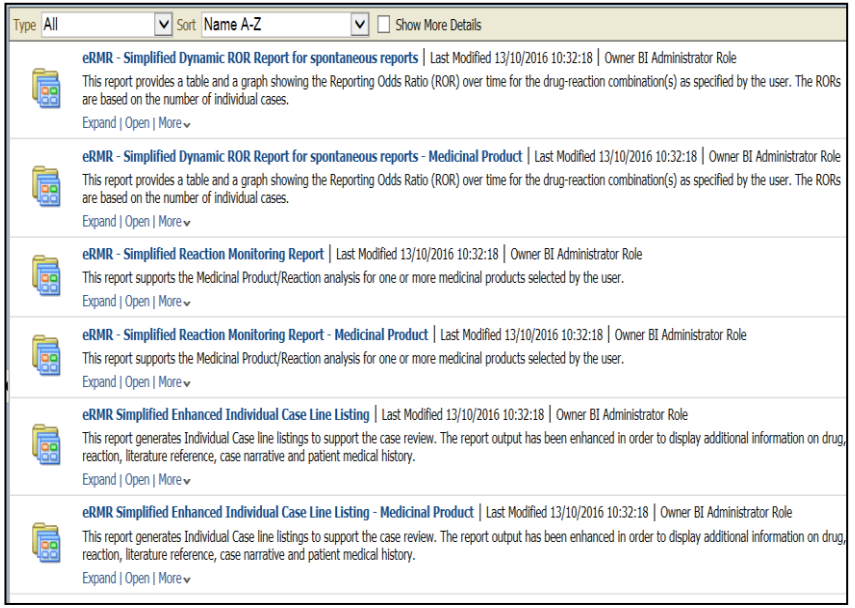
Accessing the queries via the e-RMR

EUROPEAN MEDICINES AGENCY

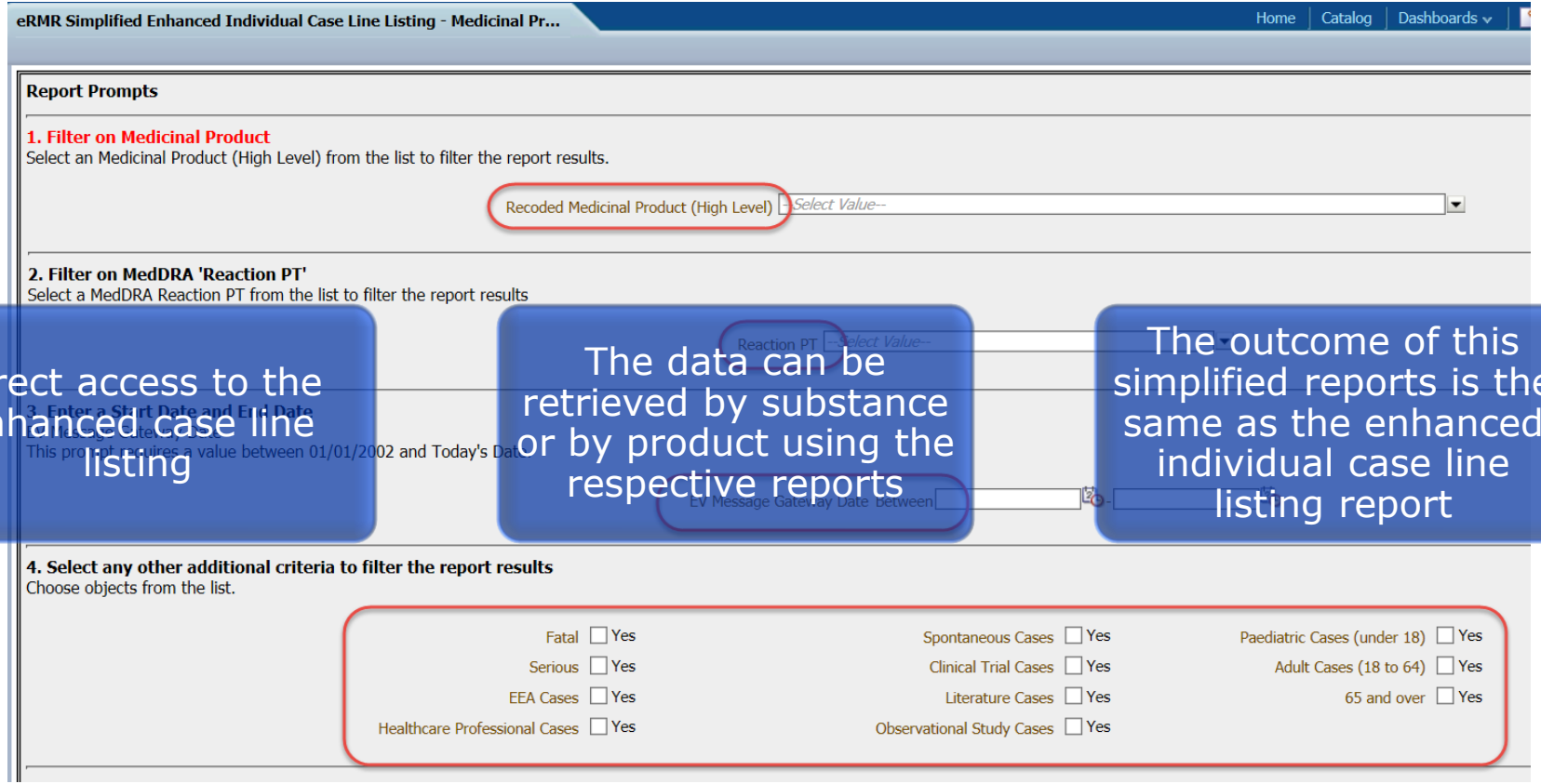
eRMR



EVDAS



eRMR Simplified Enhanced Individual Case Line Listing

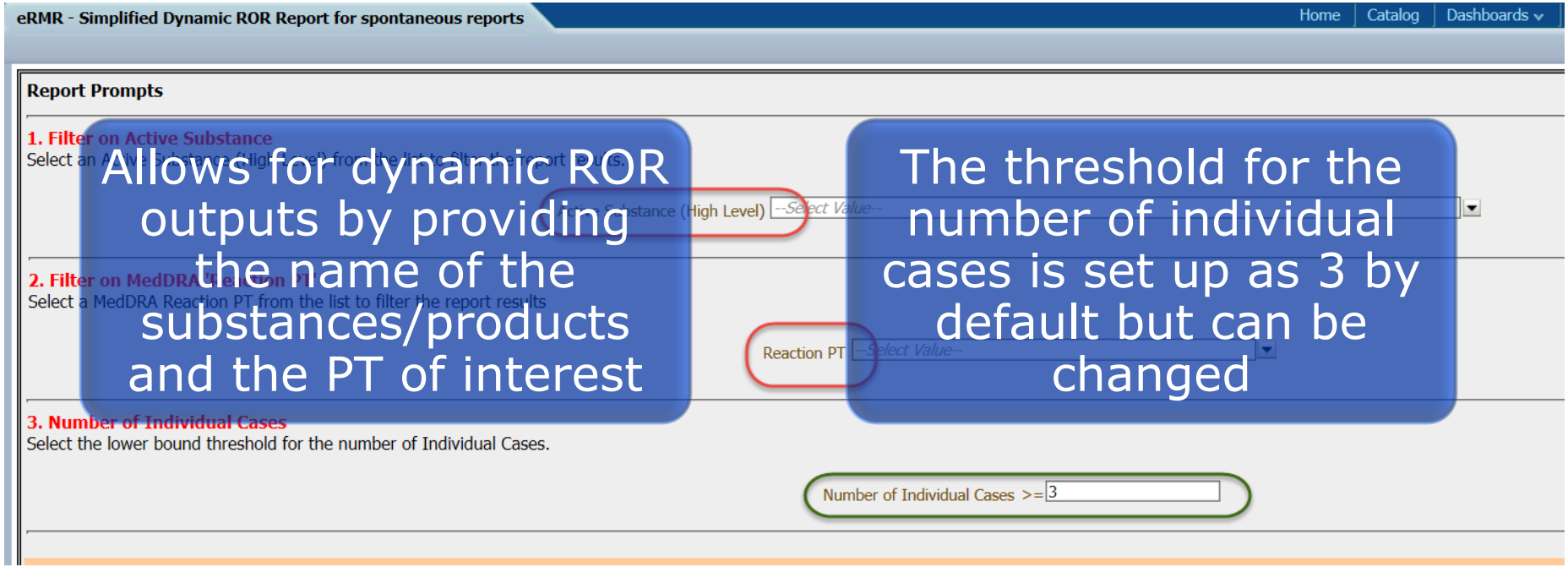


Direct access to the enhanced case line listing

The data can be retrieved by substance or by product using the respective reports

The outcome of this simplified reports is the same as the enhanced individual case line listing report

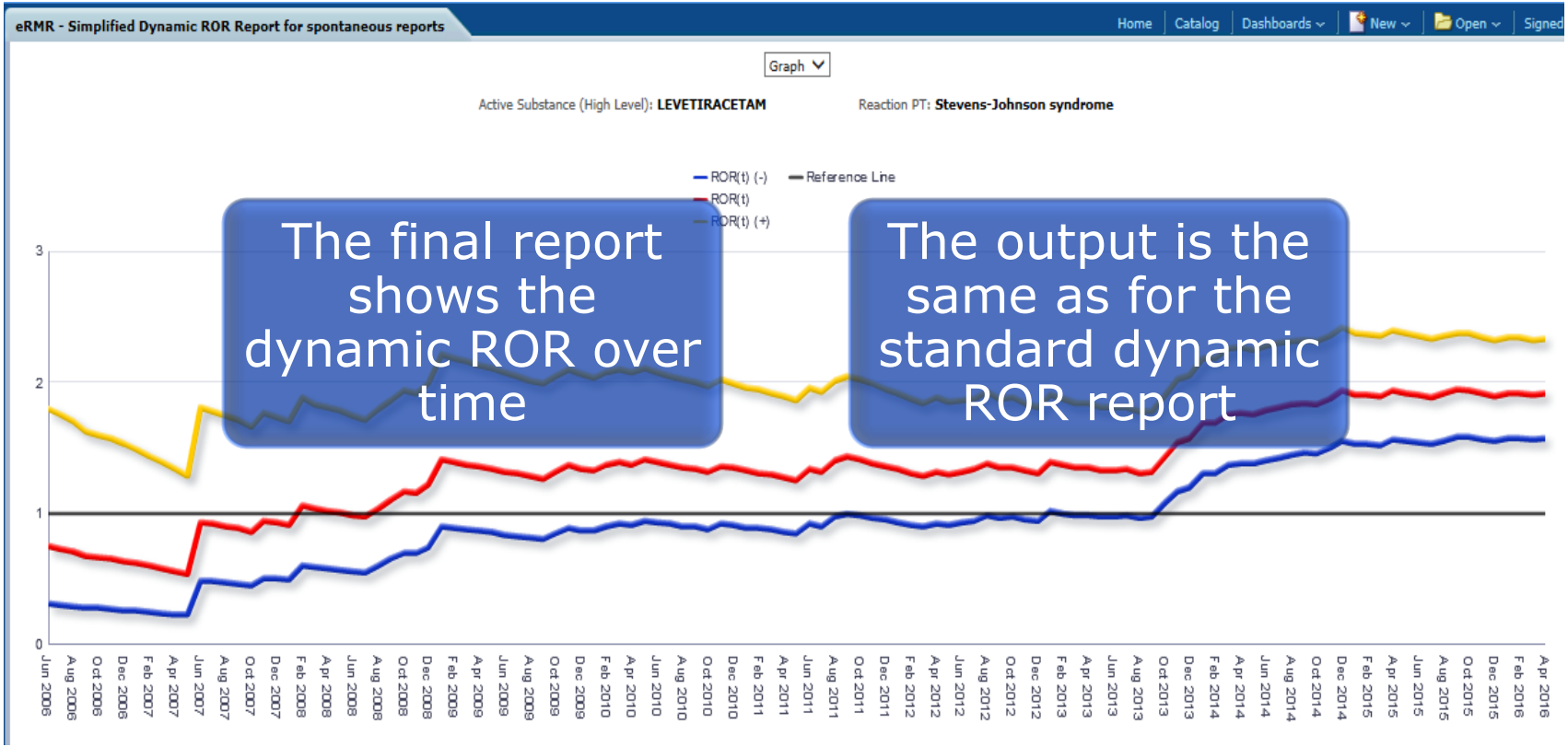
eRMR Simplified Query – Dynamic ROR Report



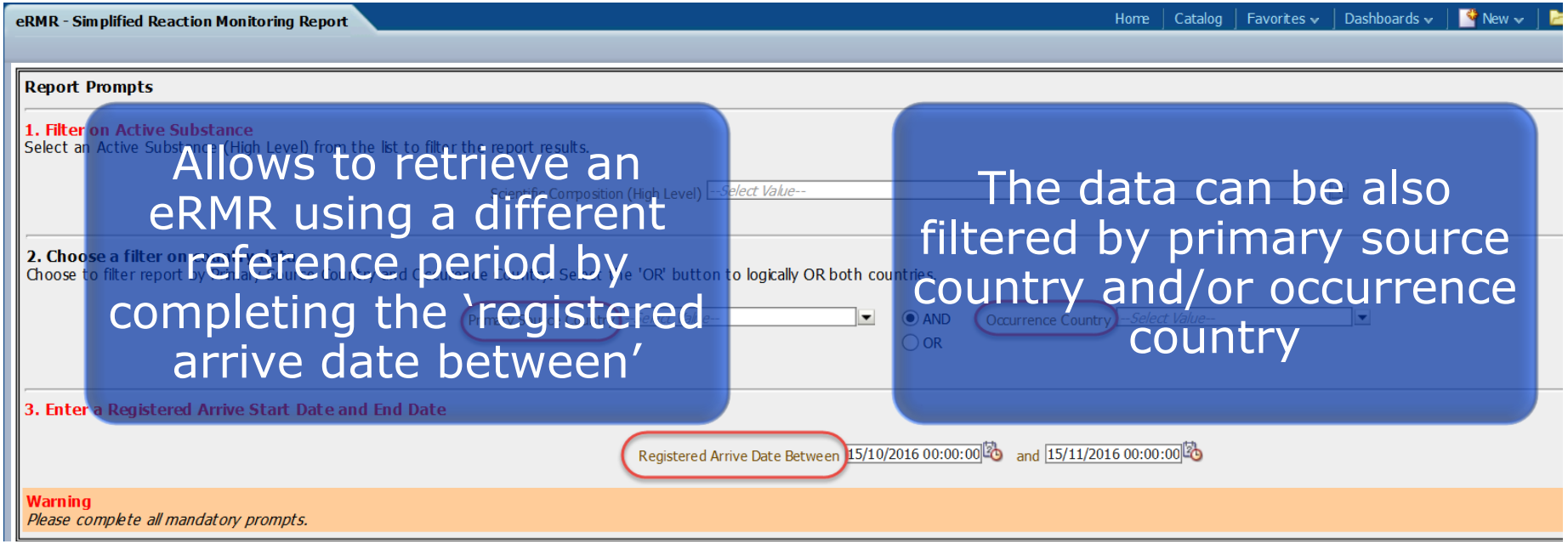
Allows for dynamic ROR outputs by providing the name of the substances/products and the PT of interest

The threshold for the number of individual cases is set up as 3 by default but can be changed

Dynamic ROR report



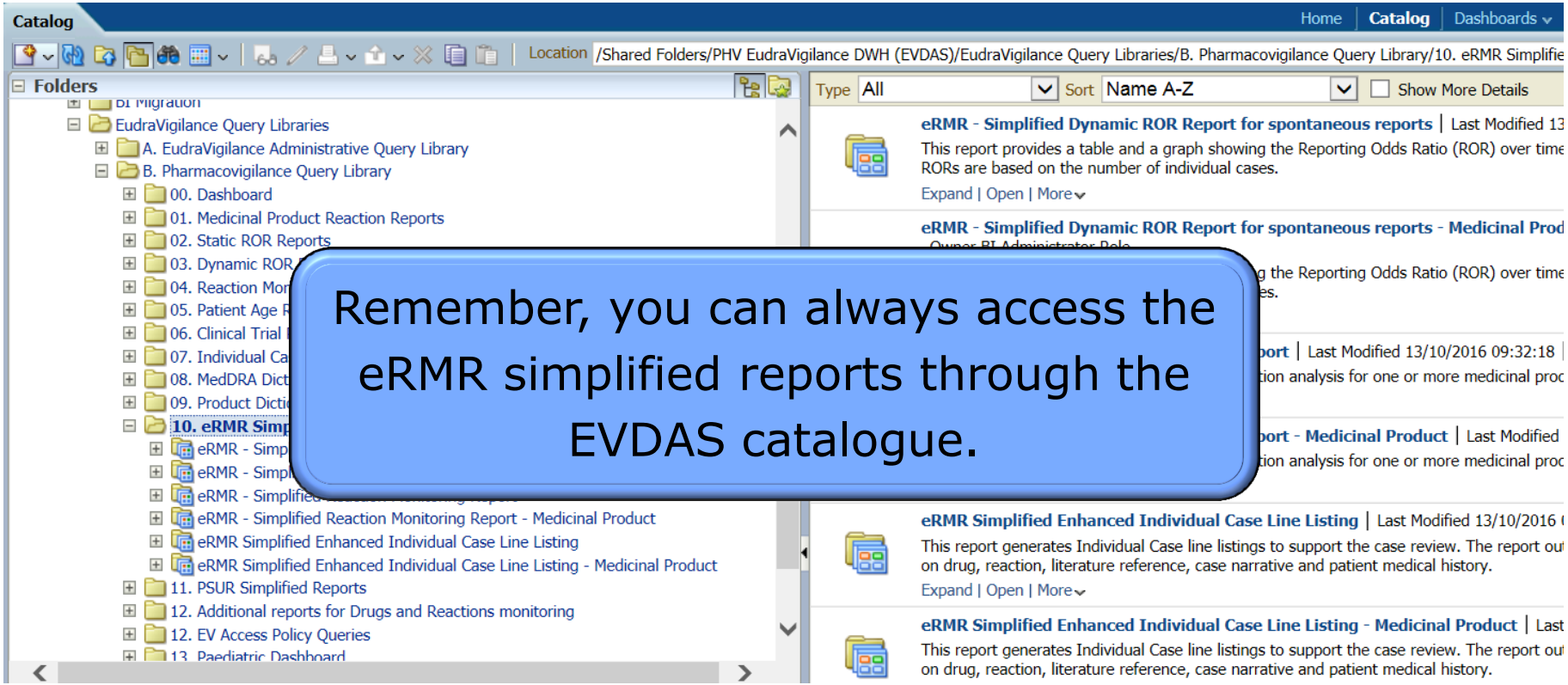
Simplified query – Reaction Monitoring Report



Allows to retrieve an eRMR using a different reference period by completing the 'registered arrive date between'

The data can be also filtered by primary source country and/or occurrence country

eRMR simplified reports



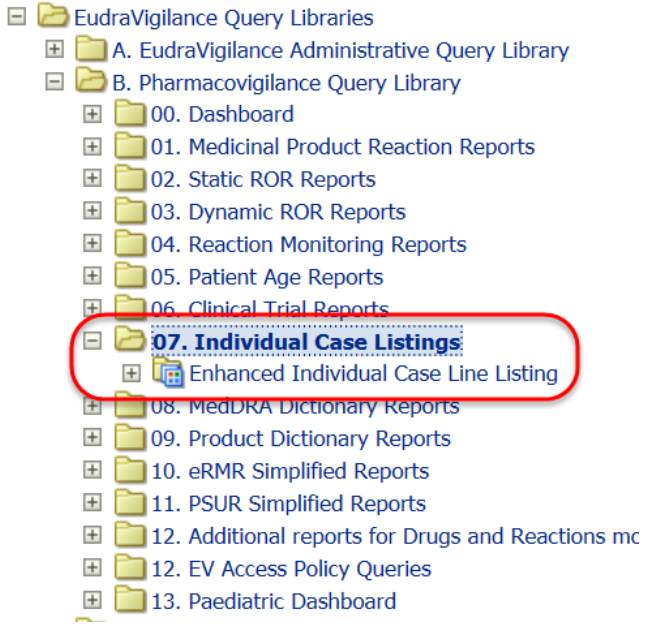
Individual Case Line Listing

Enhanced individual case line listing

- This EVDAS report permits a creation of line listing containing details of the individual cases.
  - One of the main tools from EVDAS to support the safety assessment of individual cases.
  - It has been enhanced to include all relevant information.
  - Provides links to the narrative, ICSR forms and E2B forms.
  - It can be accessed from the action links in other outputs within the EVDAS catalogue.

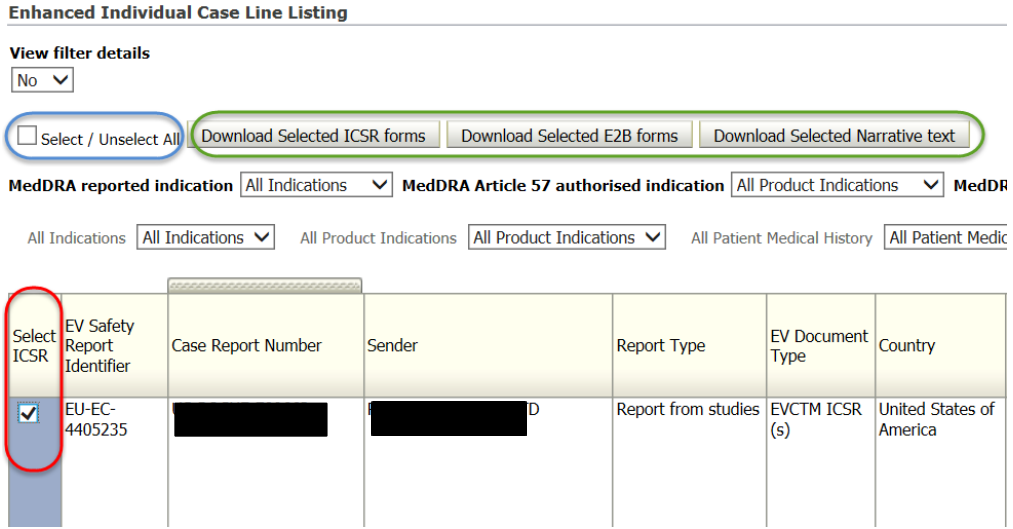
Enhanced individual case line listing

- The line listing is placed in folder 7 in the pharmacovigilance query library.
- To retrieve a line listing, complete the prompts by using the simplified or advanced filtering criteria



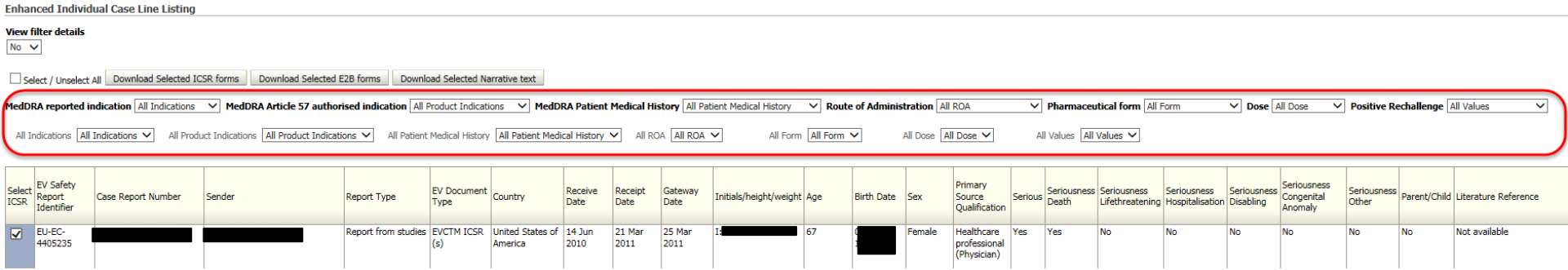
Enhanced individual case line listing

- The EVDAS outcome of the line listing gives the users the possibility to select specific cases of interest and based on that selection, the ICSR form, the narrative or the E2B form can be downloaded.
- The possibility to select or unselect all the cases also exist.



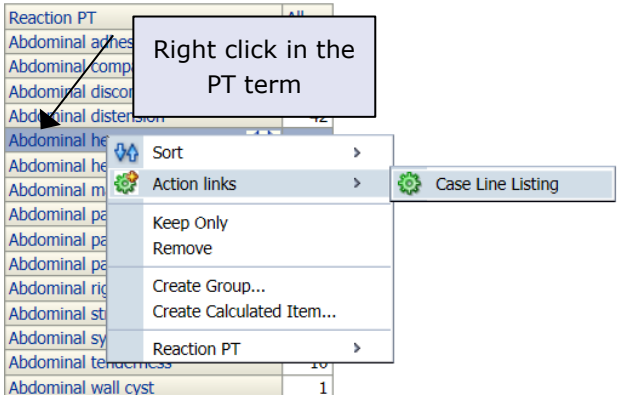
Enhanced individual case line listing

Remember the line listing can be further filtered by using the filters at the top according to the instructions provided in section “standard filtering criteria, new approach”



Enhanced individual case line listing

- The line listing can be also retrieved from the action links in other EVDAS outputs including the eRMR



Click on the links to get a line listing

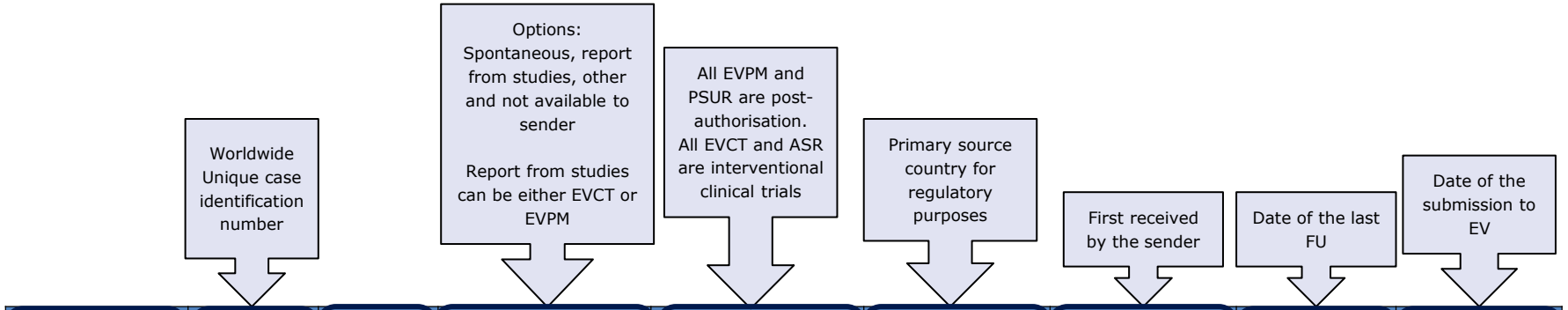
Active Substances	SOCs	PTs	IME / DM	New EV	Tot EV	Tot Fatal	AM OM C	Tot + PC
Gefitinib	Metab	Decreased Appetite		2	245	56	---	1
Gefitinib	Renal	Cystitis Haemorrhagic	Ime	1	51	3	---	2
Gefitinib	Renal	Haematuria		1	72	4	---	2

Enhanced individual case line listing

- The following slides will explain the different fields and columns provided in the enhanced line listing
  - The screenshots are based on a line listing exported in Excel
  - The listing can be divided in the following sections:
    - ICSR characteristics
    - Patient and reporter characteristics
    - Seriousness criteria
    - Parent-child
    - Literature and documents included
    - Drug list
    - Indication, rechallenge reaction and medical history
    - Narrative, ICSR form, E2B form, reporter and sender comments

Enhanced individual case line listing

'Case characteristics'



EV Safety Report Identifier	Case Report Number	Sender	Report Type	EV Document Type	Country	Receive Date	Receipt Date	Gateway Date
EU-EC-6589666	US-MAH-11111111	MAH PRODUCTS	Spontaneous	EVPM ICSR(s)	United States of America	24 Oct 2012	24 Oct 2012	26 Oct 2012
EU-EC-6589321	US-MAH-99999	MAH PRODUCTS LTD	Report from studies	EVPM ICSR(s)	United States of America	06 Sep 2012	06 Sep 2012	20 Dec 2012
EU-EC-7896523	FR-MAH-123456	EEA regulatory authority	Spontaneous	EVPM ICSR(s)	France	30 Aug 2013	27 Aug 2013	03 Sep 2013

Enhanced individual case line listing

'Patient and reporter characteristics'

As reported or calculated by the system based on date of birth and 1st reaction start date

"Healthcare professional" if at least one of the primary sources is a healthcare professional, otherwise "non health professional"

Initials/height/weight	Age	Birth Date	Sex	Primary Source Qualification
I: XX H:n/a W:n/a	26	31-FEB-1973	Female	Healthcare professional (Physician)
I: XX H:n/a W:86.26	67	31-NOV-1995	Female	Non Healthcare professional (Consumer or other Non-Health Professional)
I: UNKNOWN H:n/a W:n/a	69	Not Specified	Male	Healthcare professional (Physician)

Enhanced individual case line listing

'Seriousness criteria'

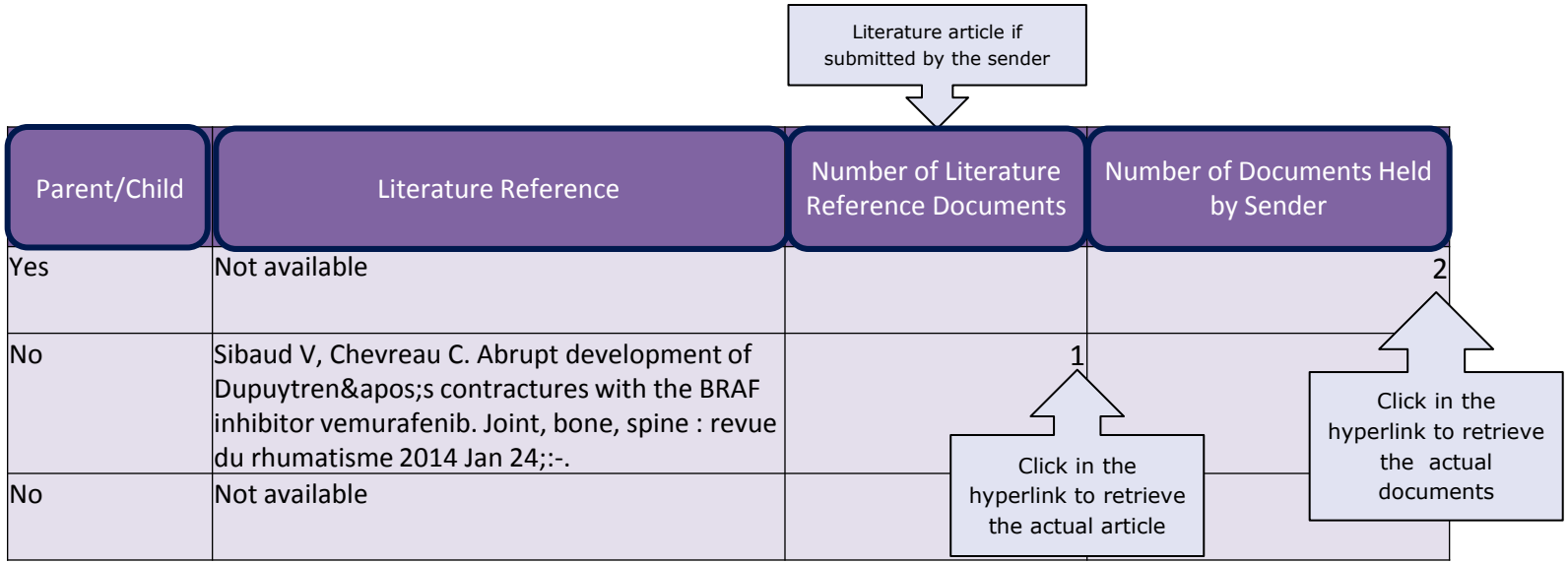
Case level

R3 data: Seriousness criteria provided at reaction level
R2 data: displays all the seriousness criteria reported at case level

Serious	Seriousness Death	Seriousness Life-threatening	Seriousness Hospitalisation	Seriousness Disabling	Seriousness Congenital Anomaly	Seriousness Other
Yes	Not Available	Not Available	Not Available	Yes	Not Available	Yes
Yes	Not Available	Yes	Not Available	Yes	Not Available	Yes
Yes	Yes	Not Available	Not Available	Not Available	Not Available	Not Available

Enhanced individual case line listing

‘Parent-child; Literature and documents included’



Enhanced individual case line listing

'Drug list'

As recoded in the xEVMPD "brand name [substance]"

Drug characterisation is abbreviated to:
Suspect: S, Interacting: I, Concomitant: C, Drug not administered: N

Therapy duration is populated using the field duration of drug administration (G.k.4.r.6a/b) but if that is not available, then it is calculated from the therapy start date (G.k.4.r.4) and therapy stop date (G.k.4.r.5) when those dates are provided in a complete format (DDMMYYYY).

Recoded Drug List	Number of Suspect/ Interacting Drugs	Suspect/Interacting Enhanced Reported Drug List (Drug Char - Indication PT - Action taken with drug - [Start Date - Duration - Dose - Route])	Concomitant/Not Administered Enhanced Reported Drug List (Drug Char - Indication PT - Action taken with drug - [Start Date - Duration - Dose - Route])	Indication(s) PT of the drug of interest as reported in the ICSR
[DEXKETOPROFEN, [VEMURAFENIB]	1	[VEMURAFENIB] (S - Malignant melanoma - Unknown - [01/01/1900 - n/a - n/a - UNKNOWN])	[DEXKETOPROFEN (C - n/a - Not Available - [01/05/2019 - n/a - n/a - UNKNOWN])	VEMURAFENIB - Malignant melanoma

Enhanced individual case line listing

'Rechallenge, reaction and medical history'

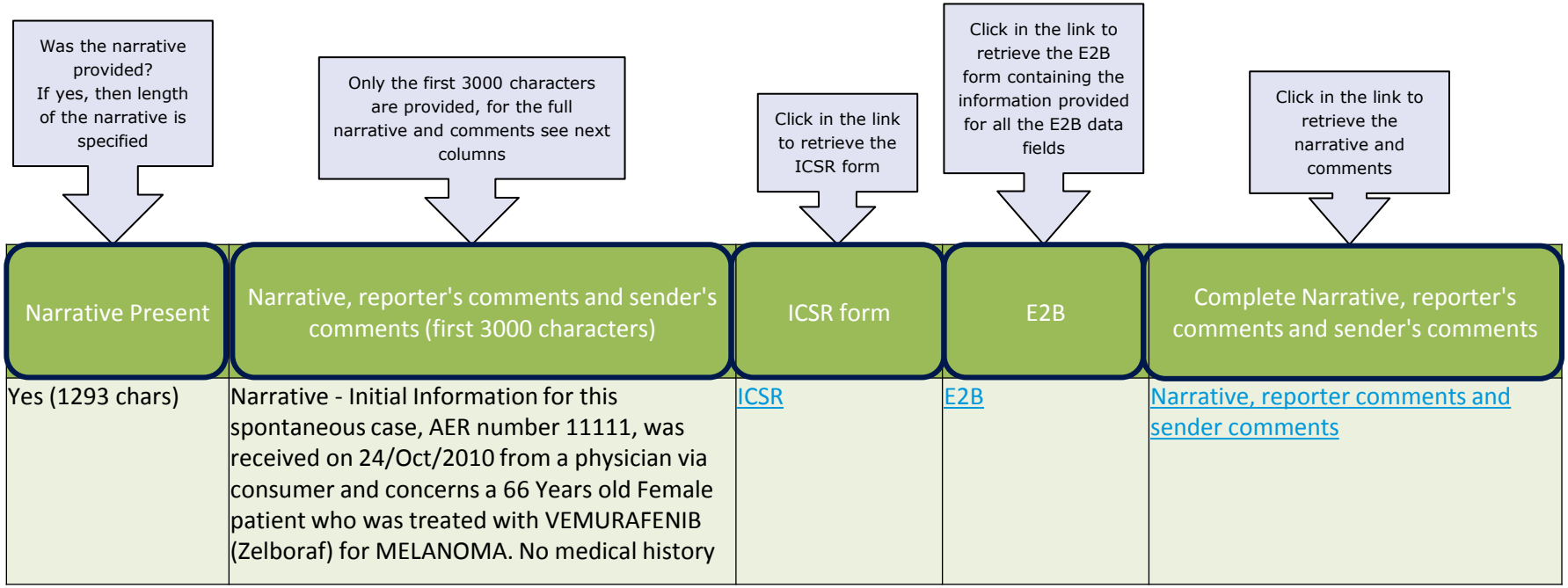
Drug/reaction combination for which the reaction recurred following drug administration

If available, states if the condition was continuing at the time of the report and also comments provided

Positive rechallenge for suspect/interacting drugs	Reaction List PT (Outcome - Date - Duration - Time to onset)	Structured Medical History (Continuing - Text)
Zelboraf- neutropenia	Neutropenia (Recovered/Resolved - 01/09/2011 - n/a - 31d)	Actinic keratosis (Not available - Not available) Pruritus (Not available - Not available) Prostatic specific antigen increased (Not available - Not available)

Enhanced individual case line listing

‘Narrative, ICSR form, E2B form, reporter and sender’s comments’



Narrative Present	Narrative, reporter's comments and sender's comments (first 3000 characters)	ICSR form	E2B	Complete Narrative, reporter's comments and sender's comments
Yes (1293 chars)	Narrative - Initial Information for this spontaneous case, AER number 11111, was received on 24/Oct/2010 from a physician via consumer and concerns a 66 Years old Female patient who was treated with VEMURAFENIB (Zelboraf) for MELANOMA. No medical history	ICSR	E2B	Narrative, reporter comments and sender comments

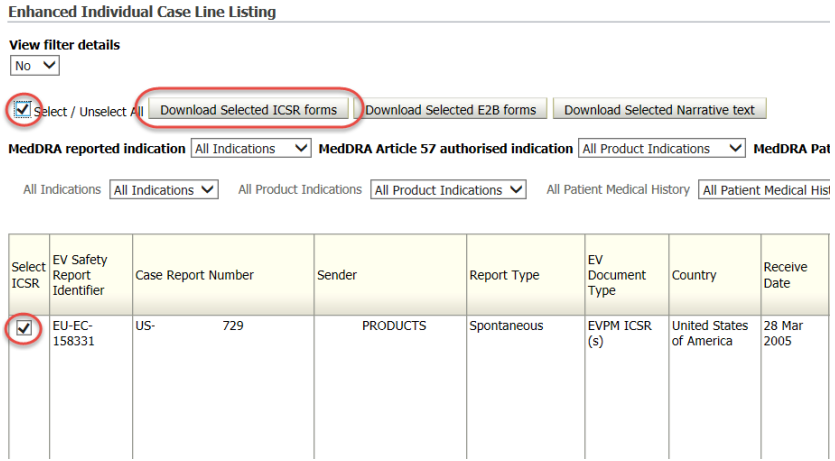
ICSR form

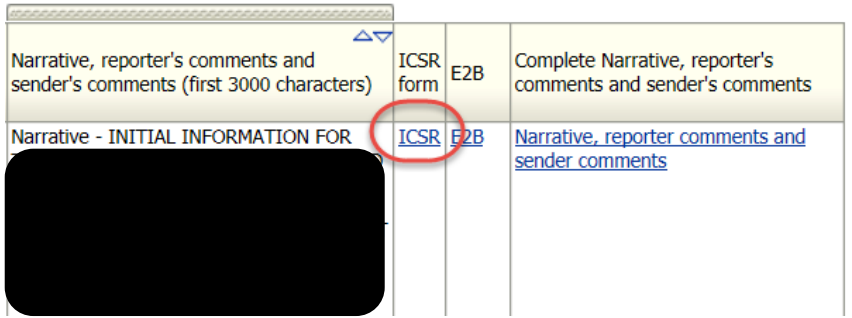
ICSR Form

- Following the implementation of the ICH-E2B(R3) format in EV, the new ICSR form has been created to provide a readable format for the E2B(R3) data elements.
- The ICSR form replaces the CIOMS I previously retrieved from the database under R2 format.
- The ICSR form does not contain the reported information for all possible E2B data fields but rather a selection of fields considered most relevant for safety assessment.
- When necessary to consult fields not included in the form (e.g MedDRA versions), the E2B form retrievable from the line listing should be consulted.
- In general the data elements are populated in the form in the same way (text, numbers) as they have been reported, sometimes abbreviations are used. Moreover some fields are populated following a calculation of specific fields following the same rules as in the line listing (e.g. therapy duration).
- The ICSR is provided in PDF format.

Access to the ICSR form

- EVDAS access to the ICSR form is provided from the line listing either by downloading the forms in bulk for the selected cases or by clicking in the link for the specific cases





ICSR Form – Format

- The data fields provided in the ICSR form are structured and displayed in a way that facilitates the analysis of the data and provides the user with the key elements to assess the temporal and causal association between the drugs and the ADRs. Fields in the form are grouped into logical sections (e.g. drug, reaction, medical history), so that the user can easily visualise all the available information for a specific topic.

- All the ICSR forms follow the same format regardless of cases submitted under ICH E2B(R2) or (R3) but users should consider when analysing the data that legacy cases were migrated to the new ICH E2B(R3) format.

ICSR Form – Dynamism

- The are some core sections in the form that will always be present. This is to make the form consistent and recognisable by the users; these sections are: general information, Patient, Reaction, Drug and Case narrative.

- The rest of the sections follow a specific dynamism. That means that if no data has been provided for the entire section, that section is not populated in the form. This is to avoid having completely empty sections.
  - Example: If the case is not fatal and therefore no information is provided in the data elements related to death, the section “Death” is not populated.

ICSR form – Sections

The following slides provide a general overview of the sections populated in the ICSR form.

The data populated in the slides is for the purpose of training and it is not real data.

ICSR form
General Information

General Information	
Worldwide Unique Case Identification Number	JP-Beta-lactam-3462832
Sender type	Pharmaceutical Company
Sender's Organisation	Beta-lactam antibiotics S.L.
Date Report Was First Received from Source	10/11/2002
Date of Most Recent Information	10/11/2002
Type of Report	Report from study
Primary source country	JP
Study registration number	983200163
Study Name	Open-label trial and randomiz ontrolled, crossover trial of hydrogen-enriched water for mitochond athies
Study Type	Clinical trials
Reporter's qualification	Physician, Consumer
Case serious?	Yes
Medically confirmed?	Yes

Fields on the study details do not appear in the spontaneous cases

ICSR form

Patient

Patient						
Initials	**Date of Birth**	**Age**	**Age Group**	**Sex**	**Weight**	**Height**
KD	15/11/1972	43 years	Adult	Female	53.25 kg	102 cm

ICSR form

Reaction/event

As serious criteria is reported as reaction level in R3 format, the cases migrated from R2 will populate the seriousness criteria (reported at case level) for all the reactions reported in the case

Reaction / Event					
MedDRA LLT	**Start Date**	**Stop Date**	**Duration**	**Outcome**	**Seriousness***
Drug reaction with eosinophilia and systemic symptoms	01/08/2002	31/08/2002	30d	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

ICSR form

Drug information

Dynamic field: The column is not populated if no data is reported

Dynamic field: Only for Parent/child reports

Based on R3 data elements G.k.10.r and G.k.11 (free text) to capture additional information not covered by other section [e.g. 1=counterfeit, 7=Medication error]

Drug Information

Role†	Drug	Start Date	S	uration	Dose	Uni	Action taken
S	Avastin 25 mg/ml RECODED	15/01/1992	0	15d	10 mg/kg		Drug withdrawn
C	Epilim Chrono 200 mg RECODED						Dose reduced

Drug Informat

Info‡	Drug		n	Cumul. dose to 1st Reaction	Pharm. Form	Route of Admin.	Parent Route of Admin.	Batch / Lot #
7	Avastin		cell er	1200 mg	Concentrate for solution for infusion	transplacental	intravenous	AO852369
	Epilim Chrono 200 mg RECODED	Clonic seizures		15 g	Prolonged Release Tablets			123654PP

Additional Information on Drug
This was an unfortunate medication error

ICSR form
Temporal association

Reaction / Event					
MedDRA LLT	**Start Date**	**Stop Date**	**Duration**	**Outcome**	**Seriousness***
Drug reaction with eosinophilia and systemic symptoms	01/08/2002	31/08/2002	30d	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 RECODED	15/01/1992	01/02/1992	15d	10 mg/kg	1 per 2w	Drug withdrawn
C	Epilim Chrono 200 mg RECODED						Dose reduced

Time to onset and rechallenge

Calculation of the Time to Onset:

- Difference between the reaction start date (E.i.4) and earliest therapy start date (G.k.4.r.4).
- If the earliest therapy start date is not provided, or it is not provided in a valid format, but there are subsequent therapies valid dates provided, then the calculation of TTO will not take into account those consecutives dates, otherwise the information provided will not be a real TTO.
- If TTO cannot be calculated as above, the value for G.k.9.i.3.1a/b 'Time Interval between Beginning of Drug Administration and Start of Reaction / Event' is used to populate this field.

Time-to-Onset and Rechallenge matrix table

Reaction/Event (MedDRA LLT)	Drug	TTO	Rechallenge?/Reaction recurred?
Drug reaction with eosinophilia and systemic symptoms	Avastin 25 mg/ml Epilim Chrono 200 mg	187d 186d	No/NA Yes/Yes
Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes	Avastin 25 mg/ml Epilim Chrono 200 mg	125d 140d	Yes/No No/NA
End stage liver disease	Avastin 25 mg/ml Epilim Chrono 200 mg	20d 123d	Yes/No No/NA
B-immunoblastic lymphoma (Kiel Classification) refractory	Avastin 25 mg/ml Epilim Chrono 200 mg	20 hours 123d	Yes/No No/NA

Medical history, concurrent conditions and past drug history

Relevant Medical History and Concurrent Conditions

MedDRA LLT	Start Date	End Date	Continuing	Family History	Comments
Atrial fibrillation	10/10/1995		Yes	Yes	The patient was diagnosed with atrial fibrillation in another hospital and no records are in our files
	04/01/1996		No		The pneumothorax was a spontaneous pneumothorax and the patient had to be intubated for more than a week.
Varicella		05/10/1999	No		It was unknown if the patient had been immunised against the virus

Dynamic field: captures information about other medical history that cannot be coded

Text for Relevant Medical History and Concurrent Conditions (not including reaction / event)
Unclear if the patient had surgeries in the past

Past drug history

Drug	Start Date	End Date	Indication	Reaction
Cotrimoxazole	01/08/1994	31/09/1994	Acute pulmonary histoplasmosis	Eye disorder
Acetylsalicylic acid	05/05/1993		Headache	Gastrointestinal disorder

ICSR form
Death

Data elements D.9.2.r.1b [reported cause of death (MedDRA code)] and D.9.2.r.2 [reported cause of death (free text)] are combined in one cell

Data elements D.9.4.r.1b [autopsy determined cause of death (MedDRA code)] and D.9.4.r.2 [autopsy determined cause of death (free text)]. are combined in one cell

Death			
Date of Death	**Reported Cause**	**Autopsy done?**	**Autopsy-determined Cause of Death**
31/08/2002	Pancreatic cancer	Yes	Pancreatic cancer resectable

Narrative, literature and comments

Case Narrative

"Multis post annis respiciebat ...no Buendia eratMeminerit ut perspiciantur distant pater eius diei cum glacie flumen equi... luto Canabrava uiginti domibus limpidae aquae fluminis ripa tutaquod lectum decurrent p... vaprehistoric. Multa nomina tam recenti re mundi, etseñalarías

When no data is provided, the following verbatim is displayed: *"Case narrative has not been submitted to EudraVigilance"*.

Literature Reference

Mudalel ML, Dave KP, Humme JP, Solga SF. N-acetylcysteine treats intravenous amiodarone induced liver injury. World Journal of Gastroenterology 21: 2816-2819, No. 9, Mar 2015

Trikudanathan G, Arain M, Mallery S, Freeman M, Attam R. Endoscopic necrosectomy in children. Journal of Pediatric Gastroenterology and Nutrition 59: 270-273, No. 2, Aug 2014

Additional documents are included

Article accessible through the Line listing .

Reporter's Comments

"Gloria statuitque simul uenarum finem castellum ad ostium tabernaculi. Byquinis reales, videre possent gypsy at digitis uenarum inspicere.""Removeatur Science has distantias», super Melquiades. ""Mox homoVides quid usquam gentium domi relicto. ""A meridieDemonstratio magnificantes vitrum cum giganteas incendio miram fecit: multum illiin medio plateae et paleas videlicet radios succenderuntsolar. José Buendía Arcadio qui ad consolacionem inriti magnetesIpse armatus Inuentionem multumque fatigatus noua belli usu. Melquiades rursus temptaret";

Sender's Diagnosis / Syndrome / or Reclassification of Reaction / Event (MedDRA LLT)

hepatic failure

Sender's Comments

hepatic failure

Laboratory test

populated using data elements F.r.3.2 [Test Result (value / qualifier)] combined with element F.r.3.2. [Result Unstructured Data (free text)] which is provided in brackets.

Laboratory Test

Test Name	Test Date	Results	Normal High Value	Normal Low Value	Comments
blood pressure	01/01/2009	90/170 mm[Hg]	70 mm[Hg]	140 mm[Hg]	hormally the blood pressure well controlled
Drug-induced lymphocyte stimulation test	15/08/2002	positive for bevacizumab			The test was done in another lab
Bilirubin conjugated	25/08/2002		17 umol/L	5 umol/L	
Platelet count	10/08/2002		410 10*9/L	150 10*9/L	maybe this could be a reaction to chemotherapy but we don't have baseline values

ICSR form
Parent-child

Information Concerning the Parent for a Parent-Child/Foetus Report

Parent						
Initials	**Date of Birth**	**Age**	**Weight**	**Height**	**Sex**	**Last Menstrual Period Date**
JD	22/06/1937	30 years	65 kg	169 cm	Female	08/08/2001

Relevant Medical History and Concurrent Conditions of the Parent				
MedDRA LLT	**Start Date**	**End Date**	**Continuing**	**Comments**
Malignant hypertension	01/06/1956		Yes	The mother had uncontrolled hypertension for several years
White coat hypertension	05/06/1980	18/09/1980	No	

Past Drug History of the Parent				
Drug	**Start Date**	**End Date**	**Indication (MedDRA Term)**	**Reaction (MedDRA LLT)**
Alimta	01/01/2009	01/01/2009	Asbestosis	Breast external beam radiation therapy
Amiodarone tablets	15/12/1986	15/12/1989	Borderline hypertension	Pericoronitis
Avloclor 250 MG				

Text for Relevant Medical History and Concurrent Conditions of the parent (not including reaction / event)
Unclear if the parent had surgeries

ICSR form
Related reports

Related Reports	
Relation	**Case Identifier**
Duplicate	Hospital La Princesa
Duplicate	Red Cross International
Duplicate	FDA
Linked	GB-London- 987654
Linked	ES-Madrid-789456
Linked	IT-Rome-741258

ICSR form – training

Full description of the ICSR form is provided in the User Manual:

EV-G6 - ICSR form

Other EVDAS reports

Patient age reports

- This folder provides reports to generate Medicinal Product/Patient Age reports for one or more medicinal products selected by the user.

Clinical trial reports

- The reports contained in this folder support queries on clinical trial reports using the Sponsor Study Number or the EudraCT Number.

MedDRA Dictionary reports

- The reports contained in this folder support the user in browsing the MedDRA dictionary including the Multiaxial MedDRA hierarchy and Standardised MedDRA Queries (SMQs).

Product Dictionary Reports

- The reports contained in this folder support the user browsing of the medicinal product dictionary

PSUR simplified reports

- These reports provide the possibility to retrieve line listings and summary tabulations to support the assessment of the PSURs and also contains the active substance grouping report

Section summary: Pharmacovigilance query library

- **In this section we have covered:**
  - General dashboard
  - Medicinal Product reaction reports
  - Disproportionality analysis and ROR reports
  - eRMR and simplified eRMR reports
  - Individual case Line Listing
  - ICSR Form
  - Other EVDAS reports

- Introduction to this training module
- Introduction to EVDAS
- ICH-E2B(R3) EVDAS implementation
- Standard filtering criteria, new approach
- EudraVigilance administrative query library
- Pharmacovigilance query library
- Summary

Summary of EV-M5a

- We are now at the end of the training Module EV-M5a, which provided you the basis for:
  - EVDAS and its role in the EudraVigilance system.
  - New EVDAS catalogue of reports.
  - How to retrieve EV data using the EVDAS interface.
  - Understand the EVDAS changes triggered by the ICH-E2B(R3).
  - Understand the main EVDAS reports and outputs.

Supporting Documents (1)

Documentation	Description
EV-G2 - EVDAS Report Manual	Detailed guide to support EVDAS users and describing EVDAS functionalities (run, save, export reports in EVDAS) and key EVDAS functionalities. The manual will describe functionality common to every report in EVDAS as well as information specific to individual reports covered in annexes
EV-G1b - eRMR for NCA; structure and key activities in screening	Describe the eRMR as a signal detection tool for signal detection in EV and how to use the tool.

Supporting Documents (2)

Documentation	Description
Screening for adverse reactions in EudraVigilance	Describes the methods of statistical signal detection in EudraVigilance
EV-G6 - ICSR form	Full description of the ICSR form

Supporting Documents (3)

Documentation	Description
European Union individual case safety report (ICSR) implementation guide	• This guidance describes the EU-specific requirements to generate a valid ICSR safety and acknowledgment messages in the international format EN ISO ICSR 27953-2:2011 in accordance with ICH E2B(R3) guidance. • This guidance should be read in conjunction with the ICH E2B(R3) implementation guide and related materials published on the ICH website.

Where can I get support if needed?

EudraVigilance Registration

- Email - eudravigilanceregistration@ema.europa.eu
- Tel - 44 (0) 20 3660 7523

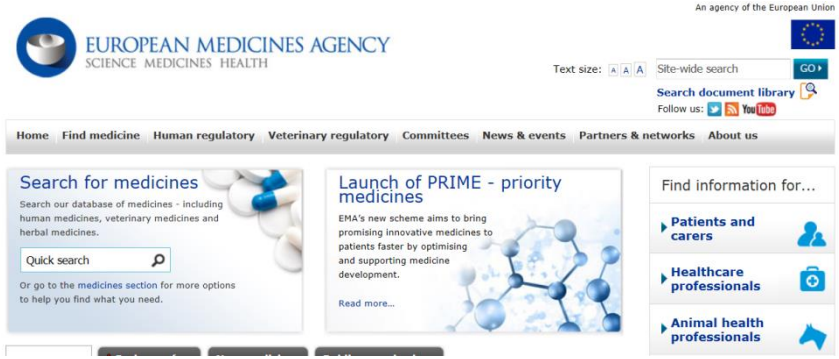
EudraVigilance Operations and IT Operations

- Visit the EMA Service Desk portal: https://servicedesk.ema.europa.eu
- Urgent helpline for technical enquiries: +44 (0)20 3660 8520

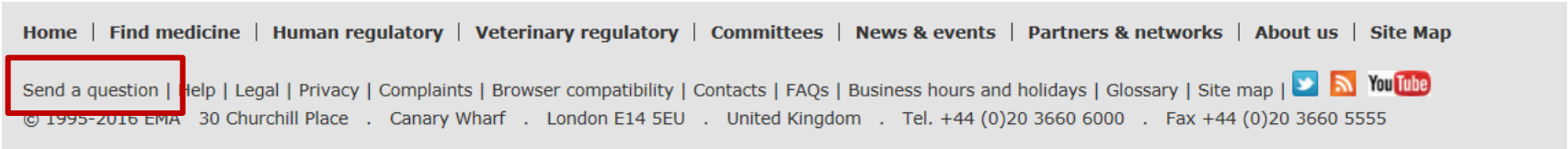
Where can I get support if needed?

Pharmacovigilance operations

- Send a question to EMA (accessible from the EMA homepage)



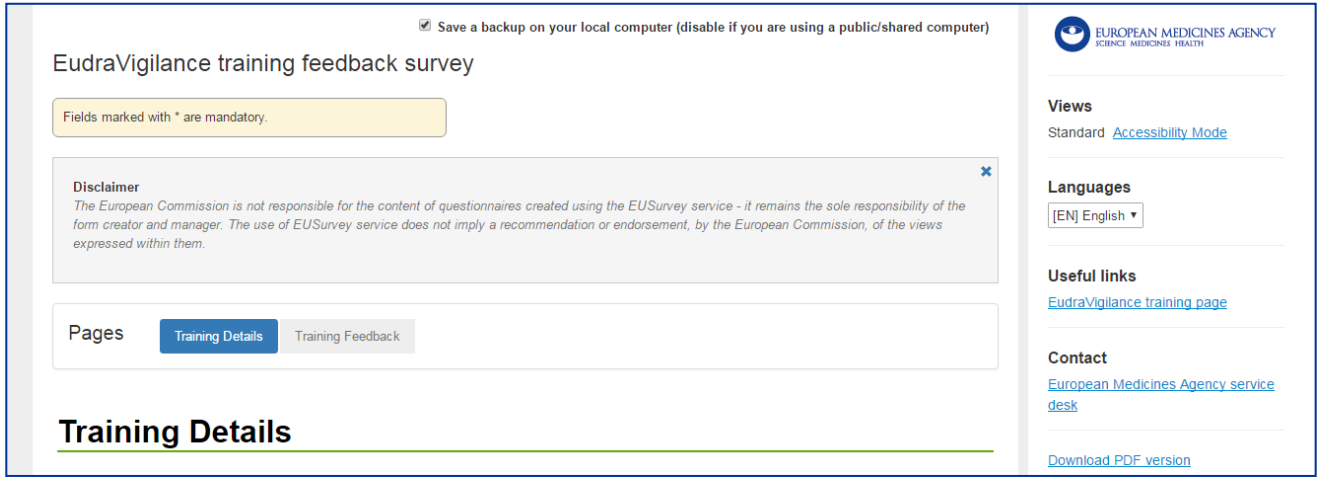
Web address:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/landing/ask_ema_landing_page.jsp&mid=WC0b01ac05806499f0



Feedback

- Please provide us with feedback on this E-learning module and any attendant guidance documents you have viewed by taking the EMA training survey.

- The survey is accessible via this link.



Acronyms

Acronym	Description
ADR	Adverse Drug Reaction
AMOMO	Abuse, Misuse, Overdose, Medication error and Occupation exposure
CIOMS	Council for International Organizations of Medical Sciences
DEC	Drug Event Combination
DEM	Designated Medical Event
EEA	European Economic Area
EMA	European Medicines Agency

Acronyms

Acronym	Description
eRMR	Electronic Reaction Monitoring Report
ETL	Extraction, transformation and loading process
EU	European Union
EV	EudraVigilance
EVCT	EudraVigilance Clinical Trials Module
EVDAS	EudraVigilance Data Analysis System
EVDMS	EudraVigilance Database Management System

Acronyms

Acronym	Description
EVPM	EudraVigilance Post-authorisation Module
EVWEB	EudraVigilance Web Application
Geriatr	Geriatric
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Professional
HLGT	High-Level Group Terms
HLT	High-Level Terms

Acronyms

Acronym	Description
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICSR	Individual Case Safety Report
IFU	Indication for Use
IME	Important Medical Event
IR	Commission implementing Regulation 520/2012
Lit	Literature
MAH	Marketing Authorisation Holder

Acronyms

Acronym	Description
Med Err	Medication error
MedDRA	Medical Dictionary for Regulatory Activities
MSK	Masked
NASK	Not asked
NCA	National Competent Authority
OBIEE	Oracle Business Intelligence Enterprise Edition
Obs	Observational

Acronyms

Acronym	Description
Paed	Paediatric
PASS	Post-authorisation Safety Study
PROTECT	Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium
PSUR	Periodic Safety Update Report
PT	Preferred Term
QPPV	Qualified Person for Pharmacovigilance
RC	Rechallenge

Acronyms

Acronym	Description
ROA	Route of Administration
ROR	Reporting Odds Ratio
SDR	Signal of disproportionate reporting
SMQ	Standardised MedDRA Query
SOC	System Organ Class
Sp	Spontaneous
TTO	Time to Onset

Thank you for your attention

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