



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

# Monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency (MLM Service)

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Who will be impacted and what you need to know



An agency of the European Union





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## Legal background and expected benefits

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Sabine Brosch – Principal Scientific Administrator



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- 1 Legal background and expected benefits
- 2 Detailed guide (scope and key business processes)
- 3 How to prepare (points to be taken into account by MAHs benefiting from the service)
- 4 New functionalities



# Introduction

- Scientific and medical literature remains an important source of information to identify suspected adverse reactions
- MAHs are required to monitor this literature and to report individual cases of suspected adverse reactions for medicinal products, for which they hold a marketing authorisation in the EEA [1]
- This results in duplication of work by MAHs for active substances included in more than one medicinal product as well as duplicated reports in EudraVigilance and National Competent Authorities (NCAs) safety databases



# Introduction – legal basis

Article 27 of Regulation (EC) 726/2004 states the following:

1. The Agency shall monitor selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances. It shall publish the list of active substances being monitored and the medical literature subject to this monitoring.
2. The Agency shall enter into the Eudravigilance database relevant information from the selected medical literature.
3. The Agency shall, in consultation with the Commission, Member States and interested parties, draw up a detailed guide regarding the monitoring of medical literature and the entry of relevant information into the Eudravigilance database.



# Introduction – legal basis

Article 107(3) of Directive 2001/83/EC further states for MAHs:

- For medicinal products containing the active substances referred to in the list of publications monitored by the Agency pursuant to **Article 27 of Regulation (EC) No 726/2004**, marketing authorisation holders **shall not be required to report to the Eudravigilance database** the suspected adverse reactions recorded in the listed medical literature, but
- they **shall monitor all other medical literature and report any suspected adverse reactions.**



## Introduction – expected benefits

The monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency aims to:

- Enhance the **efficiency** of adverse reactions reporting
- Provide a **simplification** for pharmaceutical industry
- **Improve data quality** by reducing the number of duplicates
- Contribute to **resource savings**
- **Support signal detection** activities by NCAs and MAHs





## Introduction – which MAHs will benefit

- The Agency defined a range of active substances including herbal active substances contained in medicinal products for which a high number of marketing authorisations were granted to various MAHs in the EEA
  - More than 3,500 MAHs in the EEA will benefit from the MLM Service for the 300 substance groups [4] selected by the Agency
  - More than 640 MAHs in the EEA will benefit from the MLM Service for the 100 herbal substance groups [5] selected by the Agency
- The list of MAHs benefitting from the service will be published on the [EMA website](#)



## Introduction – summary

- The new MLM Service provides for administrative simplification (and cost saving) mainly for pharmaceutical industry
- The following outlines the scope and detailed arrangements for the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency so marketing authorisation holders can prepare themselves for this beneficial change



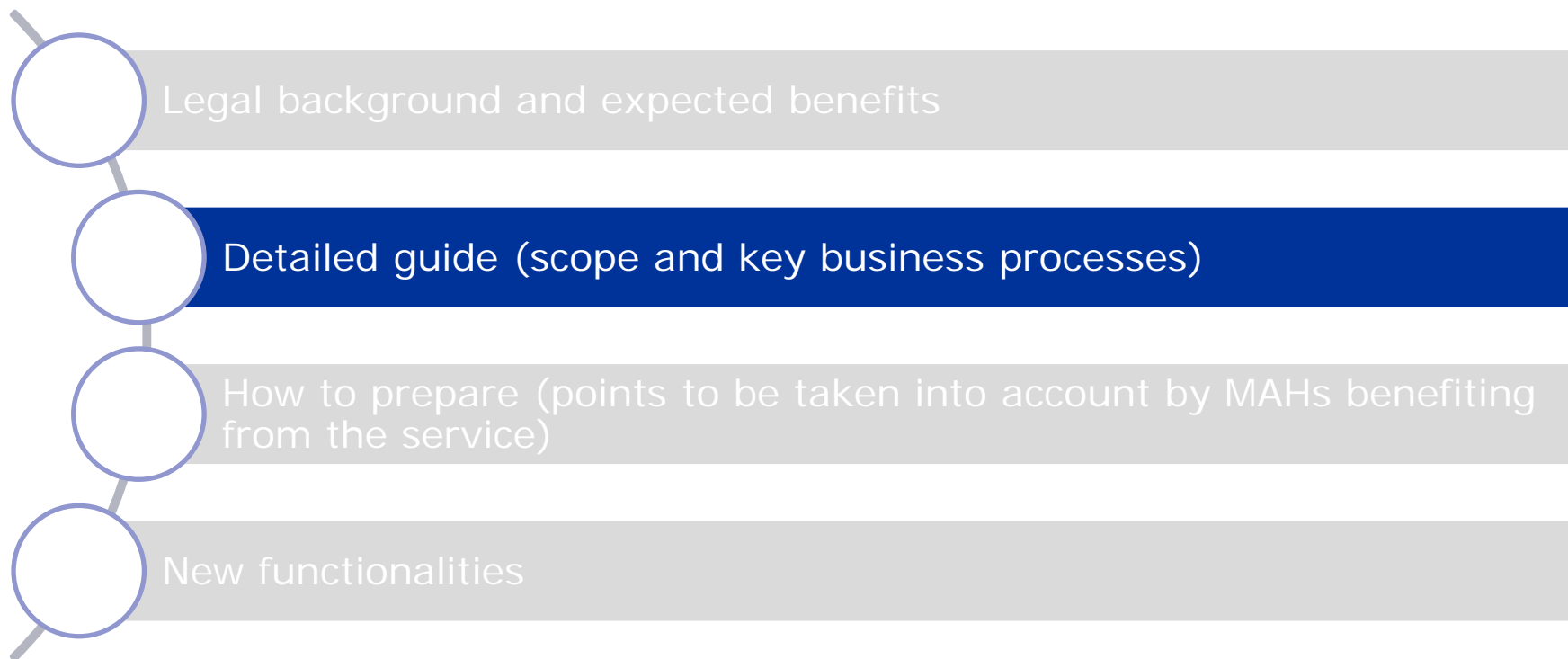
## Detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency [6]

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Sabine Brosch - Principal Scientific Administrator



# Contents





# Active substances the Agency is monitoring



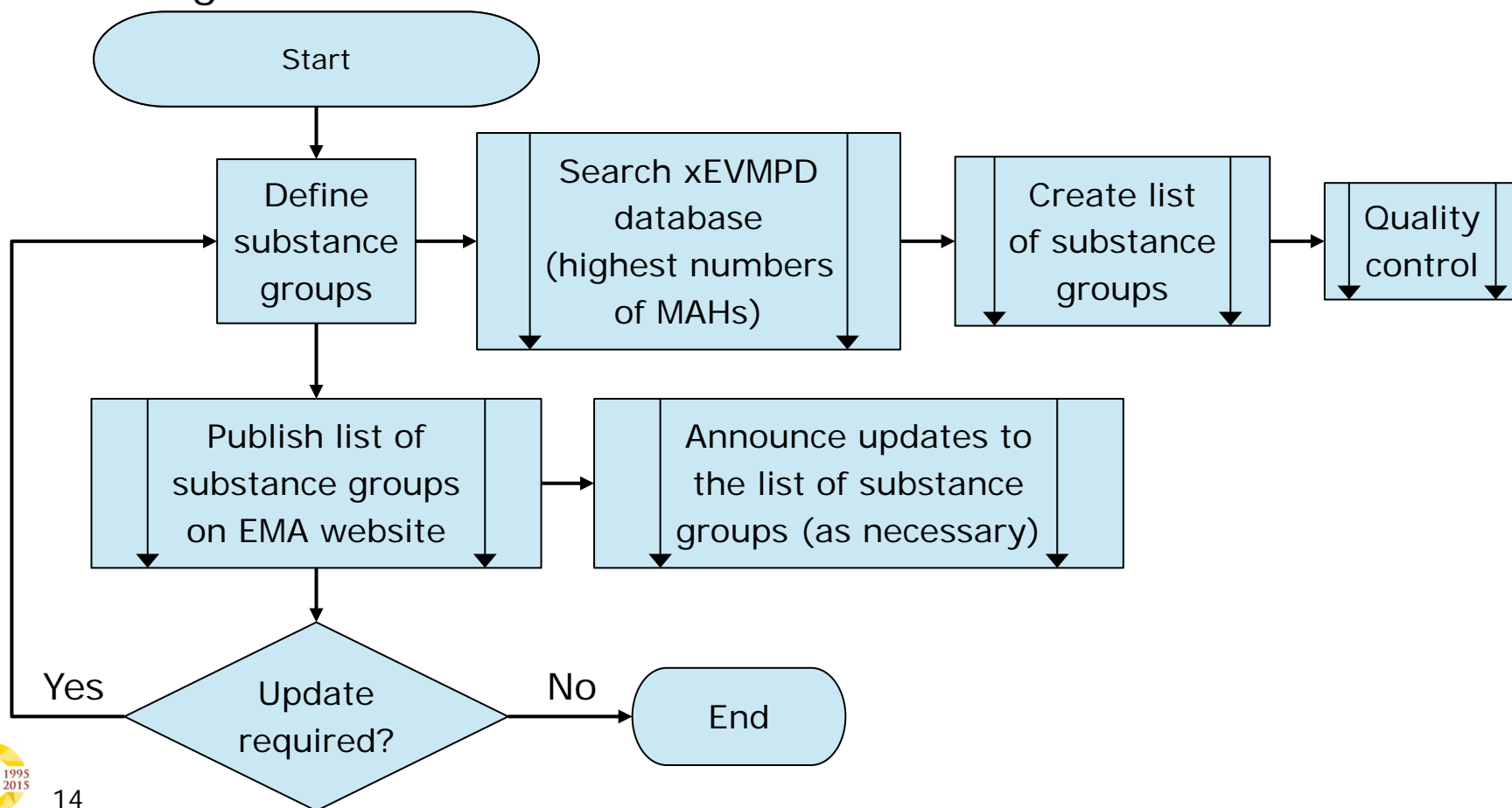
# Active substances the Agency is monitoring (1)

- Active substances including herbal active substances are selected:
  - Based on medicinal product information submitted electronically by MAHs (Article 57(2) of Regulation (EC) No726/2004)
  - For medicinal products with high number of marketing authorisations granted to various MAHs in the EEA
- They are grouped as follows:
  - **300 substances by active moiety** including e.g. salts, esters as well as combinations (referred to as “substance groups”)
  - **100 herbal substances by genus** including combinations (referred to as “herbal substance groups”)
- The lists of substances will be published at the [EMA website](#) **“MLM Substance and Herbal Substance Groups”** [4]



# Active substances the Agency is monitoring (2)

- The process of defining active substances that the Agency is monitoring





Scientific and medical literature the Agency is monitoring





# Scientific and medical literature the Agency is monitoring (1)

- The medical literature has been designated in line with the provisions set out in GVP Module VI [1] and is based on the use of the following literature reference databases:
  - **Embase** a large, comprehensive and widely used, daily updated and indexed biomedical reference database covering literature from EEA and non-EEA countries
  - **EBSCO** covering a wide variety of resources, including Medline Plus, International Pharmaceutical Abstracts (IPA) and The Allied and the Complementary Medicine Database (AMED)



# Scientific and medical literature the Agency is monitoring (2)

The journals covered by the reference databases are further described in the document **“Description of the MLM Journal/Reference databases”** [7] published at the [EMA website](#)



Search of scientific and medical literature that the Agency is monitoring



# Search of scientific and medical literature that the Agency is monitoring (1)

- GVP Module VI describes the principles for database searches [1], which are applied as follows:
  - **Daily search of Embase**  
Daily refers to calendar days with the exception of weekends (Saturday and Sunday); bank holidays are considered as calendar days
  - **Monthly search of EBSCO**  
Monthly refers to updates of the database as issued by the database provider every calendar month



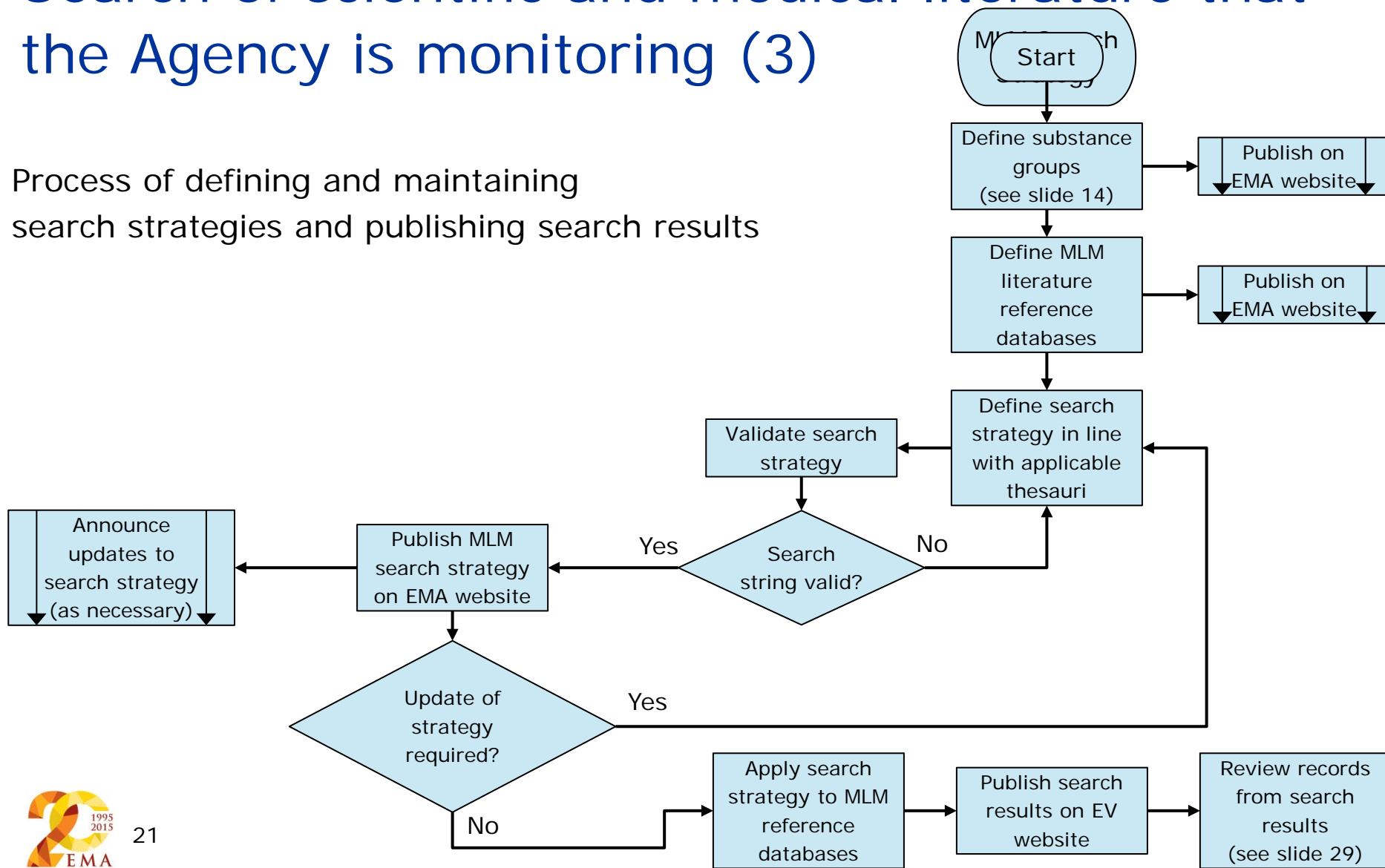
## Search of scientific and medical literature that the Agency is monitoring (2)

- Search **strategies are customised for each substance group** based on key strings [8]
- Search **strategies are applied to the entire dataset** of indexed journals; generally, no other search restrictions apply (e.g. language or sub-headings referring to safety) to achieve the widest possible search coverage
- Search **strings are updated and maintained** where necessary to improve search precision e.g. alignments of substance variants or updates applicable to the thesauri of the reference databases
- **Records of search results are published** at the dedicated area of the EudraVigilance website **“MLM Search Results”** at the next calendar day following execution of the search



# Search of scientific and medical literature that the Agency is monitoring (3)

Process of defining and maintaining search strategies and publishing search results





# Search of scientific and medical literature that the Agency is monitoring (4)

- **MLM Search Results** are presented based on the following parameters and published in Excel format:
  - i. The name of each substance group
  - ii. The name of the reference database(s)
  - iii. The date and time when the search was performed
  - iv. The title of the record, the name of the author(s), the journal title incl. a DOI (or where not available the database reference number) for the record in Vancouver style [9] incl. the primary source country



# Review of medical literature and recording of activities





# Review of medical literature and recording of activities (1)

- The purpose of the screening, review and assessment process is to identify valid ICSRs related to:
  - Suspected adverse reactions originating from **spontaneous reports** and **solicited reports** in humans
  - **Special situations** such as use of a medicinal product during pregnancy or breastfeeding, use of a medicinal product in a paediatric or elderly population, reports of off-label use, misuse, abuse, overdose, medication errors and occupational exposure with suspected adverse reactions
  - **Lack of therapeutic efficacy**
  - Suspected adverse reactions related to **quality defects or falsified medicinal products**
  - **Suspected transmission** via a medicinal product **of an infectious agent**



## Review of medical literature and recording of activities (2)

- **Valid ICSRs** include:
  - Suspected **serious adverse reactions** occurring **in the EEA and in third countries**
  - Suspected **non-serious adverse reactions** occurring **in the EEA**
- The review and initial assessment of each record is performed within one calendar day following the conduct of the search
- **Inclusion/exclusion criteria** [10] are applied to facilitate the screening process, which are regularly reviewed and updated as necessary (published on EMA website)



## Review of medical literature and recording of activities (3)

The steps can be summarised as follows:

- **Search results are exported** to a library management tool
- An **initial review** of the records based on title, citations, key words and abstract (or article if available at this stage) is performed
- Records, which **do not qualify for ICSR reporting**, are archived in an **exclusion group** with the exclusion criteria recorded
- Records, which **could qualify for ICSR reporting**, are moved to an **inclusion group**



# Review of medical literature and recording of activities (4)

The steps can be summarised as follows:

- **Records** are further **screened for possible duplication** since several reference databases are applied to ensure widest possible journal coverage
- **Records** are further **categorised** as those that may refer to potential ICSRs and those that refer to confirmed reports based on the criteria for valid ICSRs
- The **outcome of the screening results** is published at a dedicated area of the EudraVigilance website **“MLM Search Results”** at the next calendar day



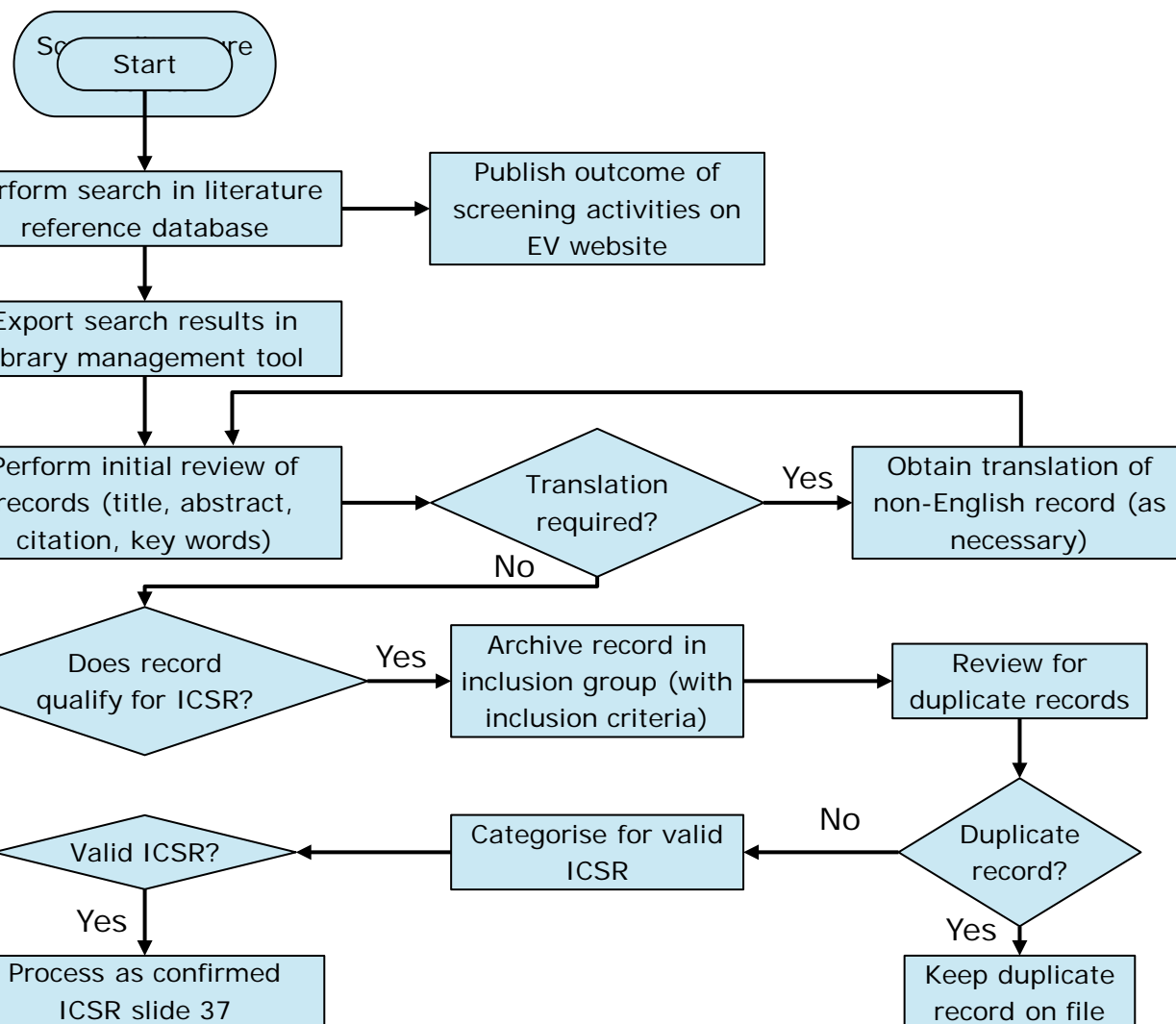
# Review of medical literature and recording of activities (5)

- The Excel file MLM Search Results with the **outcome of the screening results** are presented based on the following parameters:
  - i.– iv. Parameters outlined on slide 22
  - v. The criteria upon which the record was excluded or included for further case processing and creation of ICSRs in EudraVigilance and reporting to concerned NCA(s)
  - vi. A flag if the record refers to confirmed or potential ICSRs
  - vii. A flag if the records refer to serious and/or non-serious adverse reactions
  - viii. The primary source country
  - ix. The date when full text article (and translation where applicable) is requested



# Review of medical literature and recording of activities (6)

Process of defining and maintaining search strategies and publishing search results





# Processing of confirmed ICSRs



# Processing of confirmed ICSRs (1)

The steps can be summarised as follows:

- For records of confirmed ICSRs, the **full text article** (and where necessary, an English translation) **is obtained**; this is where the full text article is not immediately available from the reference database
- Following **review of the full text article**, the number of valid ICSRs referred to in the article is determined including seriousness of the suspected adverse reactions
- Prior to the ICSR creation, a **duplicate check** is performed in EudraVigilance; this focuses primarily on identifying ICSRs that might originate from the same article





## Processing of confirmed ICSRs (2)

The steps can be summarised as follows:

- Where one or more **duplicates are identified**, the world-wide unique case identifier is recorded (for notification of the Agency and to be used in the ICSR “Other case identifiers in previous transmissions”)
- A **further duplicate check** is conducted once the ICSRs are processed in EudraVigilance with the aim to identify duplicates originating from the literature screening and other sources than the literature



## Processing of confirmed ICSRs (3)

For the creation of the ICSRs the following applies:

- Use of **English** for free text data elements
- Compliance with **EU personal data protection legislation and copyright law**
- Compliance with **GVP Module VI and Articles 26, 27, 28 and 29 of the Commission IR (EU) No 520/2012**
- Recording of a **literature reference in Vancouver Style** together with a DOI
- Preparation of **a case narrative** for all individual cases summarising all relevant information required for the medical assessment of the case
- **No** specific **case narrative** is prepared **for non-serious adverse reactions**
- **Causality assessment** and suspected relatedness of each medicinal product to the adverse reaction(s) in accordance with the provisions of GVP Module VI



## Processing of confirmed ICSRs (4)

- ICSRs are created within the following timelines:
  - **Suspected serious adverse reactions** originating from the EEA or in third countries **immediately and no later than seven calendar days** from day zero
  - **Non-serious adverse reactions** originating from the EEA **within 21 calendar days** from day zero
- Day zero refers to the date on which the Agency's service provider becomes aware of a record containing the minimum information for a valid ICSR
  - Where a full text article (and translation where applicable) cannot be obtained within a timeframe that would allow for compliance with the aforementioned reporting timelines, the ICSRs are processed based on the minimum information available in the initial record; new information resulting from the full text article is processed as follow-up



## Processing of confirmed ICSRs (5)

### Timelines for processing confirmed ICSRs

- ICSRs related to **serious and non-serious adverse reactions** are submitted **within one calendar day** to the concerned NCA in accordance with the reporting requirements of ICSRs as outlined in GVP Module VI
- **MAHs can access and download the ICSRs from EudraVigilance** in line with the applicable formats and standards as outlined in Article 25 and 26 of the Commission IR (EC) No 520/2010
- A list of ICSRs entered in EudraVigilance is published daily at a dedicated area of the EudraVigilance website **“MLM ICSRs”**



## Processing of confirmed ICSRs (6)

- The Excel file **MLM ICSRs is published daily** including the following parameters:

i.– ix. Parameters outlined on slide 28

x. The date when full text article (and translation where applicable) is received

xi. The name of medicinal products/substances (suspect, interacting)\*

xii. The world-wide unique case identifier for each valid ICSR

xiii. The date when the initial ICSR was created and transmitted to EudraVigilance and concerned NCA(s)

xiv. The follow-up status (follow-up to be initiated Yes/No)

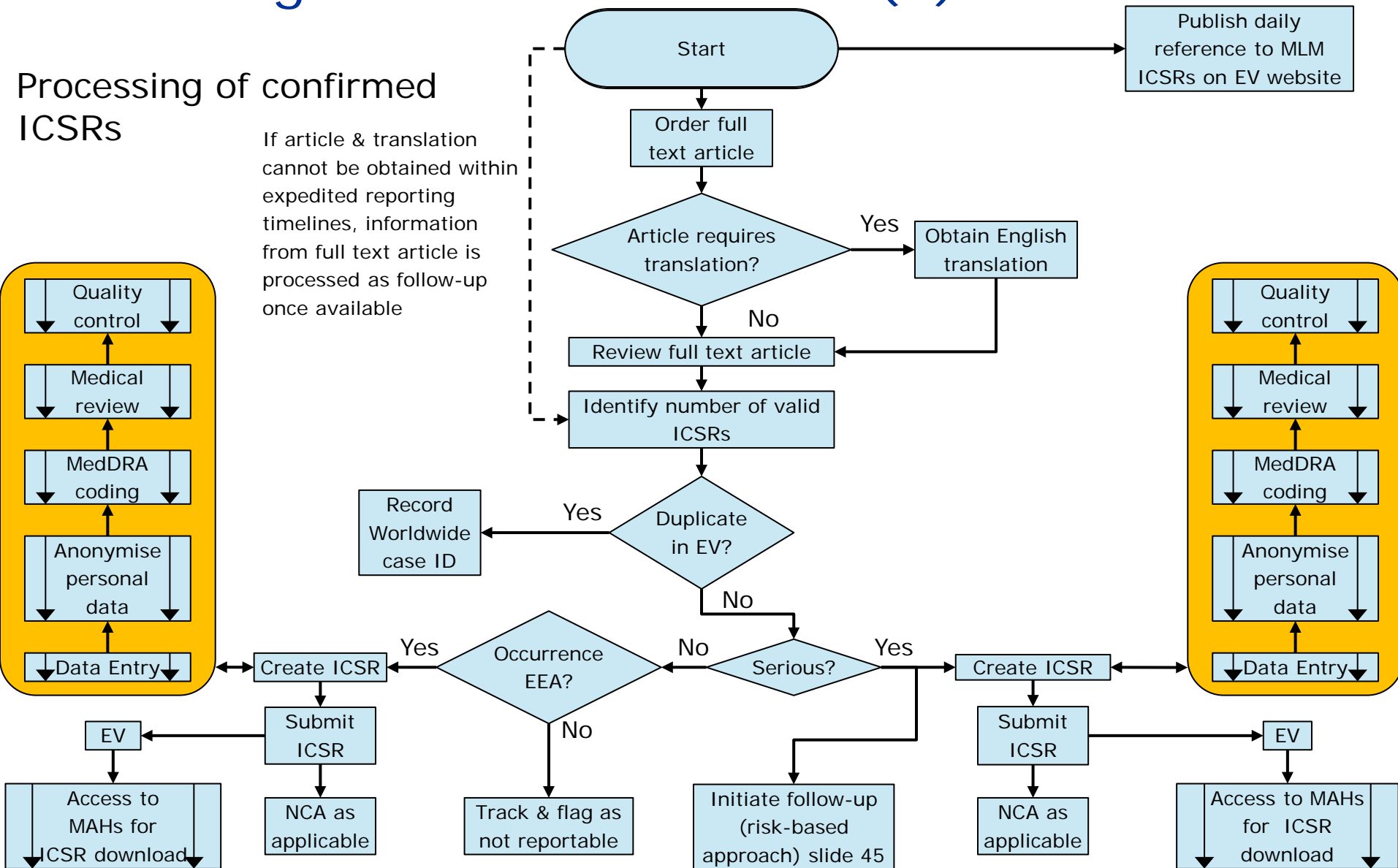
\* Note: For ICSRs which refer to suspect or interacting medicinal products/substances other than the substance groups subject to the monitoring by the Agency, MAHs should not report those ICSRs to the concerned NCA(s) in the EEA or the Agency as applicable to avoid duplication of reports.



# Processing of confirmed ICSRs (7)

## Processing of confirmed ICSRs

If article & translation cannot be obtained within expedited reporting timelines, information from full text article is processed as follow-up once available





# Processing of potential ICSRs



# Processing of potential ICSRs (1)

The steps can be summarised as follows:

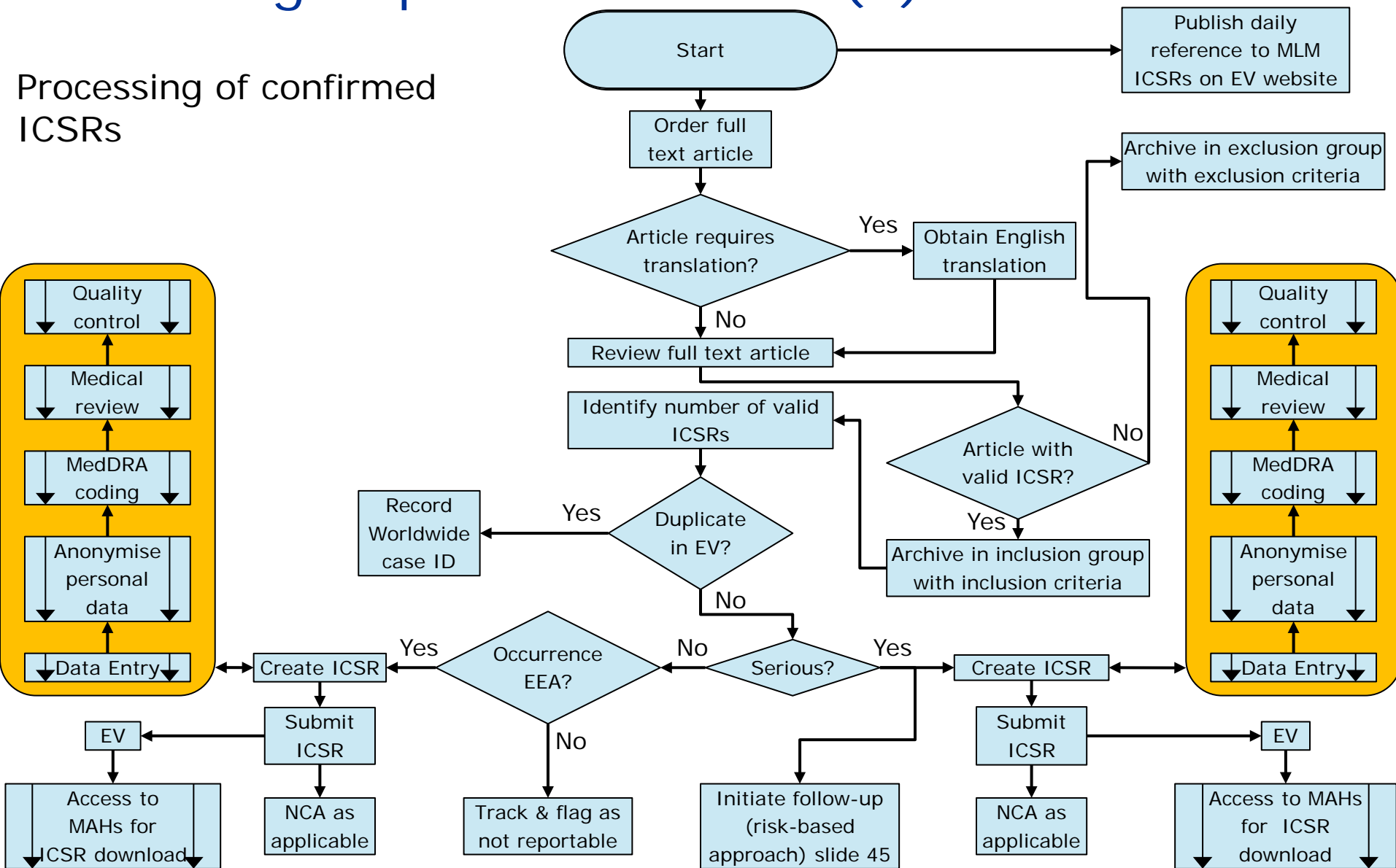
- For records of potential ICSRs, the **full text article** (and where necessary, an English translation) **is obtained**
- The **full text article is reviewed** in line with the inclusion/exclusion criteria [10]
- Articles which **do not qualify for a valid ICSR** are archived in an **exclusion group** with the exclusion criteria recorded
- Articles which refer to **one or more valid ICSRs** are archived in the **inclusion group** with the inclusion criteria recorded
- The **outcome** of the screening of the full text article and the processing of potential ICSRs is recorded in **“MLM ICSR”**
- **Valid ICSRs** are processed





# Processing of potential ICSRs (2)

## Processing of confirmed ICSRs





# Follow-up of individual cases



## Follow-up of individual cases (1)

- Individual case reports are **followed-up with the publication author(s)** as necessary to obtain supplementary detailed information, which is important for the scientific evaluation
- This is in addition to any effort to collect missing minimum information (potential ICSRs)
- In principle, one attempt to follow-up with the primary author is made for suspected **serious adverse reactions** based on a **risk-based approach**:
  - where the **outcome is not known**
  - where pre-defined **clinical information is missing** as regards important medical events [11] or for both and
  - where **not all of the minimum reporting criteria are available** for a valid ICSR



## Follow-up of individual cases (2)

- Where follow-up is pursued, the status is recorded in the Excel “**MLM ICSRs**” with the following parameters:
  - i.– xiv. Parameters outlined on slide 36
  - xv. The date when the follow-up was initiated
  - xvi. The date by which a response is requested
  - xvii. A flag, if a response is received (no response, response with new information, response with no additional information)
  - xviii. The date when follow-up information is received
  - xix. The date when the follow-up ICSR was created and transmitted to EudraVigilance and concerned NCA(s)



## Follow-up of individual cases (3)

### Processing of follow-up information

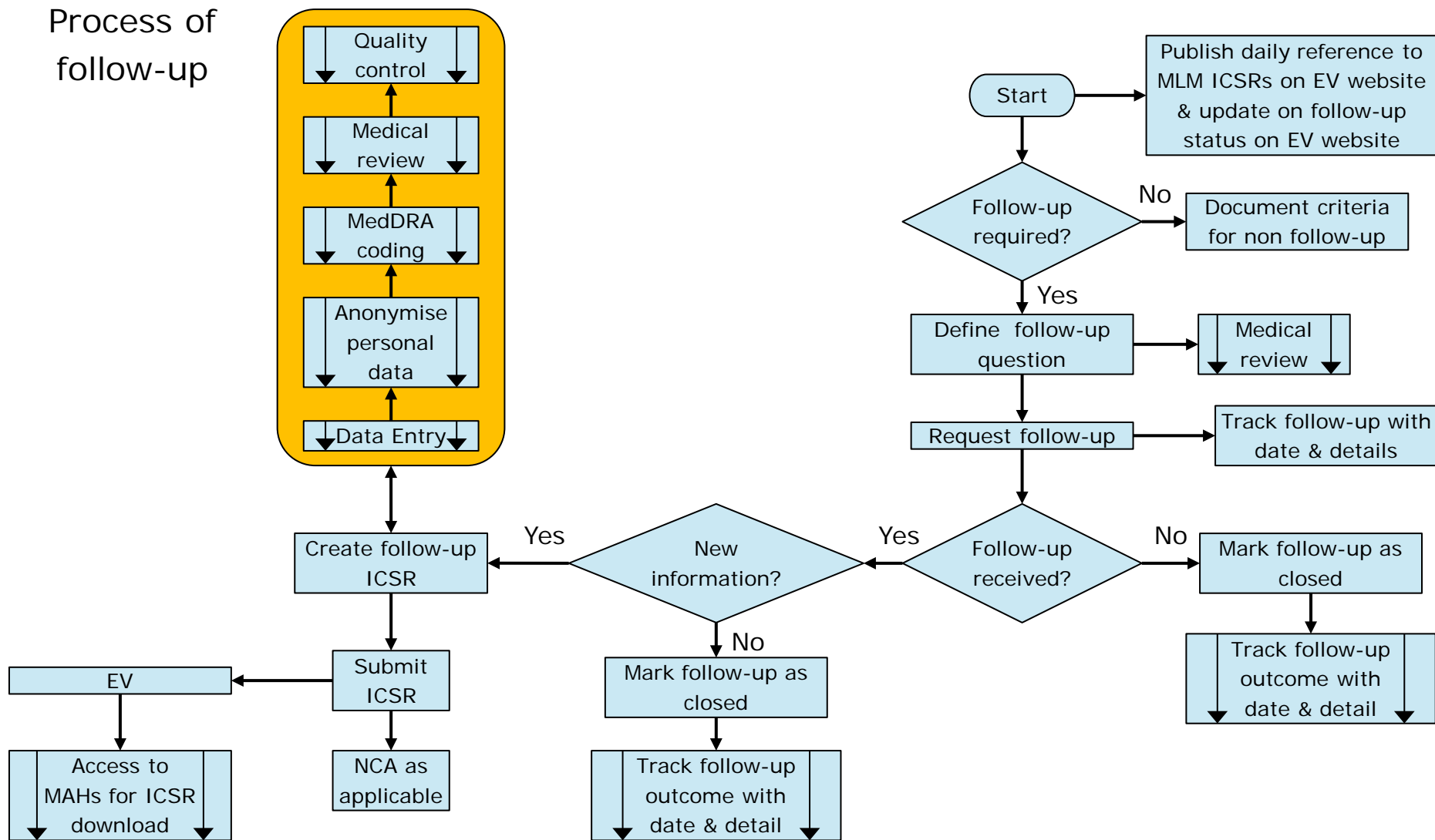
- ICSRs are created within **seven calendar days** following **receipt of new information** related to suspected **serious adverse reactions**
- Day zero refers to the date of receipt of any new follow-up information by the Agency's service provider

Note: in instances, where a MAH/NCA obtains new information outside the follow-up process operated by the Agency e.g. in the context of the validation of a signal, the MAH/NCA should send a follow-up report in accordance with the reporting requirements of ICSRs as outlined in GVP Module VI.



# Follow-up of individual cases (4)

Process of follow-up





# Quality management (1)

- **Audited quality management practices** are put in place to ensure that the service provider operates to consistently high levels of quality, efficiency and cost-effectiveness
- Business processes are based on **SOPs and WINs** prepared and maintained by the service provider, which are subject to approval and publication by the Agency [12]
- **Performance monitoring** and improvement measures are further defined as part of a Service Level Agreement between the Agency and the service provider



## Quality management (2)

- **Surveys are conducted at six monthly intervals** of MAHs and NCAs in EEA Member States to aid the identification of potential areas of improvement and to enhance performance if required
- The Agency also initiates **two yearly audits** of the service provider's internal quality management and control systems and of the services provided to assess their effectiveness with a view to bringing about continuous improvement
- The audits are to be performed by **an independent auditor** appointed by the Agency
- The **first audit** of the literature screening process will be conducted within **three months following the successful completion of a pre-production pilot**





## Interaction with stakeholders (1)

- A **service desk** is operated to assist in dealing with enquiries from MAHs and NCAs in EEA Member States
- The working language of the service desk is English
- The **working hours are those of the business hours of the Agency** [13]
- The contact details of the service desk are published at a dedicated area of the EMA website



## How to prepare: An outline of the necessary preparatory steps

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Sabine Brosch – Principal Scientific Administrator

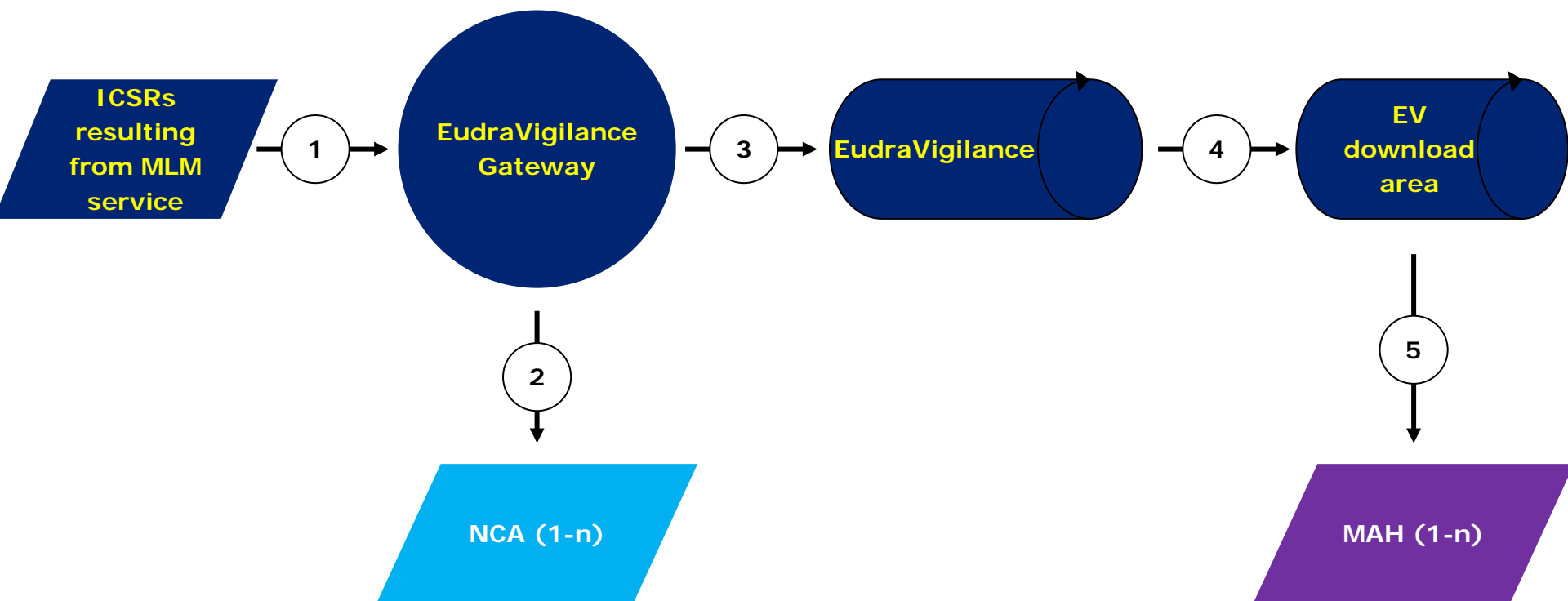


# Contents

- Legal background and expected benefits
- Detailed guide (scope and key business processes)
- **How to prepare (points to be taken into account by MAHs benefiting from the service)**
- New functionalities



# I. EudraVigilance functionalities - How will it work?





## 1. EudraVigilance functionalities - How will it work?

1. ICSRs resulting from the MLM service refer to the selected medical literature subject to the monitoring by the Agency and the identified reports of suspected adverse reactions to medicinal products containing active substances identified as part of the scope of the Agency's activities
2. ICSRs resulting from the MLM service are transmitted electronically via the EudraVigilance Gateway to NCAs in EEA Member States in accordance with the reporting requirements of ICSRs applicable during the interim period
3. ICSRs resulting from the MLM service are transmitted electronically to EudraVigilance



# 1. EudraVigilance functionalities - How will it work?

4. ICSRs resulting from the MLM service are made available for download by the MAHs concerned (EudraVigilance download area or EVWEB). This refers to ICSRs of suspected serious adverse reactions occurring within and outside the EEA and non-serious adverse reactions from within the EEA
5. Concerned MAHs can download the ICSRs resulting from the MLM service in XML format in compliance with the “Note for guidance: EudraVigilance Human – Processing of safety messages and individual case safety reports (ICSRs)” (EMA/H/20665/04/Final Rev. 2)

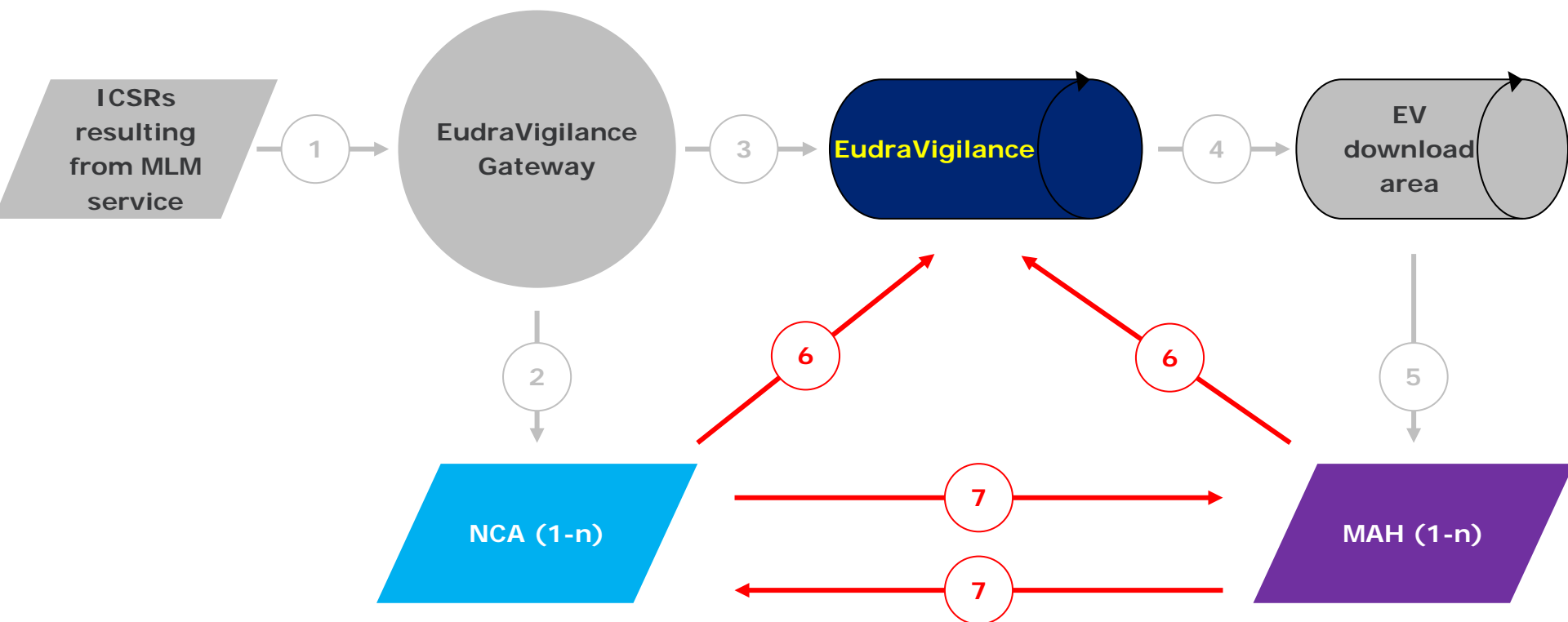


## II. Change Management - Technical Preparations

- **MAH WEB Trader user**
  - Access to EVWEB environment: no changes for users registered in the EVWEB environment
  - The existent requirements and browser restrictions for EVWEB apply (preferable IE 8, to communicate in case a newer version of IE is used)
- **EudraVigilance download area for MAHs**
  - Test and production environment :
    - ✓ System configured to accept ICSRs with the **Sender identifier** **“MLMSERVICE”**



## II. Change Management – Processes to be discontinued







## II. Change Management – Processes to be discontinued

6. Member States should not re-submit the ICSRs resulting from the MLM service to EudraVigilance
6. Member States should no longer forward/provide the ICSRs resulting from the MLM service to the concerned MAHs, since MAHs can download those ICSRs from the EudraVigilance Download Area
7. Concerned MAHs should not re-submit the ICSRs resulting from the MLM service to EudraVigilance (suspected serious adverse reactions from outside the EEA)
7. *Unless otherwise specified by national legislation and guidance,* concerned marketing authorisation holders should not submit ICSRs resulting from the medical literature monitoring service to the concerned national competent authorities in the EEA



# Acronyms

Acronym	Description
AMED	Allied and Complementary Medicine Database
DOI	Document Object Identifier
EEA	European Economic Area
ICSR	Individual Case Safety Report
IME	Important Medical Event
IPA	International Pharmaceutical Abstracts
IR	Implementing Regulation
MAH	Marketing Authorisation Holder
MLM	Medical Literature Monitoring
NCA	National Competent Authority



# Acronyms

<b>Acronym</b>	<b>Description</b>
SOP	Standard Operating Procedures
WIN	Work Instructions



# References

Document	Link
[1] Guideline on good pharmacovigilance practices: Module VI – Management and reporting of adverse reactions to medicinal products	<a href="http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf">http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf</a>
[2] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Consolidated version: 05/06/2013)	<a href="http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf">http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf</a>
[3] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Consolidated version : 16/11/2012).	<a href="http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf">http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf</a>



# References

Document	Link
[4, 5] MLM Substance and Herbal Substance Groups	<a href="#">Published on MLM service pages of EMA website</a>
[6] Detailed guide regarding the monitoring of medical literature and the entry of relevant information into the EudraVigilance database by the European Medicines Agency	<a href="#">Published on MLM service pages of EMA website</a>
[7] Description of the MLM Journal/Reference databases	<a href="#">Published on MLM service pages of EMA website</a>
[8] MLM Search Strategies	<a href="#">Published on MLM service pages of EMA website</a>
[9] Vancouver Style	<a href="http://www.lib.unimelb.edu.au/recite/citations/Vancouver/ref444-elecSourceArticleWithDOI.html?style=4&amp;type=2&amp;detail=4">http://www.lib.unimelb.edu.au/recite/citations/Vancouver/ref444-elecSourceArticleWithDOI.html?style=4&amp;type=2&amp;detail=4</a>



# References

Document	Link
[10] MLM inclusion/exclusion criteria	<a href="#">Published on MLM service pages of EMA website</a>
[11] MedDRA Important Medical Events	Available from <a href="https://eudravigilance.ema.europa.eu/human/textforIME.asp">https://eudravigilance.ema.europa.eu/human/textforIME.asp</a>
[12] Procedures	<a href="http://www.ema.europa.eu/ema/index.jsp?url=pages/about_us/general/general_content_000338.jsp">http://www.ema.europa.eu/ema/index.jsp?url=pages/about_us/general/general_content_000338.jsp</a>
[13] Agency business hours and holidays	<a href="http://www.ema.europa.eu/ema/index.jsp?url=pages/about_us/general/general_content_000247.jsp&amp;mid=WC0b01ac05800293ff">http://www.ema.europa.eu/ema/index.jsp?url=pages/about_us/general/general_content_000247.jsp&amp;mid=WC0b01ac05800293ff</a>



## New functionalities

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Thomas Paternoster-Howe - Scientific Administrator



# Content







# Eudravigilance Related functionalities

Daily spreadsheets

- MLM Search results
- MLM ICSRs

Archives

ICSR Export Manager

EVWEB MLM



# Landing page

From the restricted area of the EudraVigilance website, you will see new features for medical literature monitoring

- MLM search results
- MLM ICSRs
- Archive
- ICSR Export
- Substances
- Further MLM info





## Using the new functionalities

All of the functionalities described in the following slides require you to be registered with EudraVigilance to be able to access them

Contact your person responsible for EV (usually the QPPV or head of PV department) or their trusted deputy to be registered.



## MLM Search results

The “MLM search results” spreadsheet details the results of the searches of the literature as described on slides 21 & 22 and in Chapter 2.3 of the detailed guide on literature monitoring

This will be published within one calendar day of performing the search

The published data will contain, as a minimum:

- The name of each substance group
- The name of the reference database(s)
- The date and time when the search was performed
- The literature reference and a Document Object Identifier
- The country of the primary author



## MLM ICSRs (1)

The “MLM ICSRs” spreadsheet details the outcome of the screening and reviewing of the search results, as described in slides 24-29 and in chapter 2.4 of the detailed guide on literature monitoring

This will be published within one calendar day of performing the reviews

The records will be updated daily and an ICSR shall remain in the daily spreadsheet until it has been closed



## MLM ICSRs (2)

The published data will contain, as a minimum (1):

- The name of each substance group
- The name of the reference database(s)
- The date and time when the search was performed
- The literature reference and a Document Object Identifier
- The country of the primary author
- The date when the record was screened
- The criteria upon which the record was excluded or included for further case processing and creation of ICSRs in EudraVigilance and reporting to concerned NCA(s)



## MLM ICSRs (3)

The published data will contain, as a minimum (2):

- A flag if the record refers to confirmed or potential ICSRs
- A flag if the records refer to serious and/or non-serious adverse reactions
- The primary source country
- The date when full text article (and translation where applicable) is requested



# Archive

The archives contain records of all daily activities and provide a full & permanent record of this work

Click on the link, then select the year, month and then date of interest

All spreadsheets in the archive and the daily spreadsheets are downloadable for all users





# ICSR Export

All MAHs are entitled to access all ICSRs created by the MLM service

For ease of access, the EMA has created a specific tool (the ICSR Export Manager) for downloading batches of ICSRs swiftly and easily

The ICSR Export Manager allows MAHs to download all ICSRs created by the MLM service or to filter ICSRs in accordance with the exclusion criteria detailed in GVP Module VI, Chapter VI.C.2.2, so that only those ICSRs relating to substances where ownership cannot be excluded are returned



## ICSR Export Manager (1)

The ICSR Export Manager allows for filtering on the following criteria as a primary means of exclusion:

- Active substance name of suspect or interacting drugs
- Date of case transmission to EV
- Country of occurrence of the adverse reaction or, if this is not specified, Primary source country
- Pharmaceutical form

## Filters

Click the filter name to display / hide the filter.  
The Filter Name is highlighted once a selection is made.  
The selection will be filtered-on only when it is highlighted in the list.

[Save Filters](#)  
[Load Filters](#)

username (AAA)  
HUMAN PRODUCTION V. 7.11.5.1

Active Substance Group

Active Substance Combination

### Start Date (\*)

Clear

Official Receive Date  
(Date the ICSRs were entered into EV)

2015-02-24

### End Date (\*)

Clear

Official Receive Date  
(Date the ICSRs were entered into EV)

2015-03-11

Country of Occurrence

Country of Occurrence (Groups)

Dosage Form

## Active Filters

Click on the Name of the Filter to  
disable/enable it.

### Start Date End Date

Request Name

- Initial  
 Case

Count

Count

Request

Refresh List

## Request Name

Size

Status

Requested on 06/03/2015 10:16, ICHCSR	280 (822 KB)	Completed	<a href="#">Download</a>	<a href="#">Archive</a>
Requested on 04/03/2015 17:10, ICHCSR	16 (75 KB)	Completed	<a href="#">Download</a>	<a href="#">Archive</a>
Requested on 04/03/2015 10:28, ICHCSR	1 (5 KB)	Completed	<a href="#">Download</a>	<a href="#">Archive</a>
Requested on 27/02/2015 11:24, ICHCSR	2157 (7.7 MB)	Completed	<a href="#">Download</a>	<a href="#">Archive</a>
15-23jandosagefrm (on 27/02/2015 10:23), ICHCSR	6 (3 KB)	Completed	<a href="#">Download</a>	<a href="#">Archive</a>



# ICSR Export Manager – mandatory filters

Mandatory filters are marked with an asterisk

**Start Date (\*)**

Official Receive Date  
(Date the ICSRs were entered into EV)

ICSR Export Manager

username (AAA)  
HUMAN PRODUCTION V. 7.11.5.1

Save Filters  
Load Filters

Country of Occurrence (Groups)

Dosage Form

Active Filters Click on the Name of the Filter to disable/enable it.

Request Name

Initial  Case

Count Count Request Refresh List

Request Name Size Status



# ICSR Export Manager – active filters

Active filters have the title in bold blue text

And are listed in the “Active Filters” bar

The screenshot shows the ICSR Export Manager interface. On the left, a list of filters is displayed. The filter 'Start Date (\*)' is highlighted with a red box, and its description 'Official Receive Date (Date the ICSRs were entered into EV)' is shown below it. On the right, the 'ICSR Export Manager' control panel is visible, including 'Save Filters' and 'Load Filters' links, a username field, and two 'Clear' buttons. At the bottom, the 'Active Filters' bar is shown, containing the text 'Click on the Name of the Filter to disable/enable it.' and a filter 'Start Date End Date' which is also highlighted with a red box. Below the bar, a table header is visible with columns for 'Request Name', 'Size', and 'Status'.





# ICSR Export Manager – show/hide filters

Inactive filters are hidden by default

Click the filter name and it will be displayed

Filters		Click the filter name to display / hide the filter. The filter name is highlighted once a selection is made. The selection will be filtered on only when it is highlighted in the list.		<a href="#">Save Filters</a>	<a href="#">Load Filters</a>	username (AAA)
						HUMAN PRODUCTION V. 7.11.5.1
<b>Active Substance Group</b>	<input type="text"/>			<input type="button" value="Copy"/>	<input type="button" value="New"/>	<input type="button" value="Delete"/>
Substance Group (one or more Substance Combinations) referenced in Safety Reports.				<input type="button" value="Refresh"/>	<input type="button" value="Clear"/>	
You may make multiple selection in this list.				Order: <input type="checkbox"/> Text		
<b>Active Substance Combination</b>						
<b>Start Date*</b>				<input type="button" value="Clear"/>		
Official Receive Date (Date the ICSRs were entered into EV)	<input type="text" value="2015-03-02"/>					
<b>End Date*</b>				<input type="button" value="Clear"/>		
Official Receive Date (Date the ICSRs were entered into EV)	<input type="text" value="2015-03-17"/>					
<b>Country of Occurrence</b>						
<b>Country of Occurrence (Groups)</b>						
<b>Dosage Form</b>						



# ICSR Export Manager – active substance group (1)

Enter the name of the desired substance into the search box and press Enter

When the substance is returned, click the name to select & activate the filter



## Eudravigilance ICHICSR Export Manager

Filters Click the filter name to display / hide the filter.  
The Filter Name is highlighted once a selection is made.  
The selection will be filtered-on only when it is highlighted in the list. [Save Filters](#) [Load Filters](#) username (AAA)  
HUMAN PRODUCTION V. 7.11.5.1

**Active Substance Group**

Substance Group (one or more Substance Combinations) referenced in Safety Reports.

You may make multiple selection in this list.  Text

PARACETAMOL

Note how the filter name is now in bold blue, because it has been activated



# ICSR Export Manager – active substance group (2)

To filter on multiple groups, click “New” and another group section will appear



## Eudravigilance ICHCSR Export Manager

Filters Click the filter name to display / hide the filter.  
The filter name is highlighted once a selection is made.  
The selection will be filtered on only when it is highlighted in the list. [Save Filters](#) [Load Filters](#) username (AAA)  
HUMAN PRODUCTION V. 7.11.5.1

<b>Active Substance Group</b> Substance Group (one or more Substance Combinations) referenced in Safety Reports. You may make multiple selection in this list.	paracetamol <b>PARACETAMOL</b>	<input type="button" value="Copy"/> <input type="button" value="New"/> <input type="button" value="Delete"/> <input type="button" value="Refresh"/> <input type="button" value="Clear"/>
<b>Active Substance Group</b> Substance Group (one or more Substance Combinations) referenced in Safety Reports. You may make multiple selection in this list.	PARACETAMOL	<input type="button" value="Copy"/> <input type="button" value="New"/> <input type="button" value="Delete"/> <input type="button" value="Refresh"/> <input type="button" value="Clear"/>

Order:  Text

To remove a filter, click “Delete”







## ICSR Export Manager – active substance group (3)

The Active substance groups, as described in Chapter 1 of the detailed guide on literature monitoring, include all substances including various salts, and includes substance combinations under the group

For example, the Paracetamol substance group contains paracetamol on its own, and paracetamol in combination with everything that it is in combination with in the xEVMPD



# ICSR Export Manager – active substance combination (1)

Filtering on the active substance combinations is performed in the same manner as for active substance groups

Filters		Click the filter name to display / hide the filter. The filter name is highlighted once a selection is made. The selection will be filtered on only when it is highlighted in the list.		<a href="#">Save Filters</a>	<a href="#">Load Filters</a>	username (AAA)
HUMAN PRODUCTION V. 7.11.5.1						
<b>Active Substance Group</b>	paracetamol	PARACETAMOL		Copy	New	Delete
Substance Group (one or more Substance Combinations) referenced in Safety Reports.				Refresh	Clear	
You may make multiple selection in this list.				Order: <input type="checkbox"/> Text		
<b>Active Substance Combination</b>	paracetamol	PARACETAMOL, ACETYLSALICYLIC ACID, ANHYDROUS CAFFEINE		Copy	New	Delete
Substance Combination referenced in Safety Reports.		PARACETAMOL, ACETYLSALICYLIC ACID, ANHYDROUS CAFFEINE, CHLORPHENIRAMINE MALEATE		Refresh	Clear	
You may make multiple selection in this list.		PARACETAMOL, ACETYLSALICYLIC ACID, CAFFEINE		Order: <input type="checkbox"/> Text		
		PARACETAMOL, ACETYLSALICYLIC ACID, CAFFEINE, CODEINE PHOSPHATE HEMIHYDRATE				
		PARACETAMOL, ACETYLSALICYLIC ACID, CAFFEINE, ETHYLMORPHINE HYDROCHLORIDE				

You may filter on multiple combinations or multiple groups within the same search window



## ICSR Export Manager – active substance combination (2)

If a substance is included as part of a combination with another monitored substance, then the specific combination will be found under the earliest combination group

The substance groups are ranked by the greatest number of MAHs that hold MAs for a product containing this substance

For example paracetamol + codeine is under the Paracetamol substance group

If selecting only combinations, you will need to carefully select from the list of substances

You can save selections, so that the substance group/combinations do not need to be selected every time



# ICSR Export Manager – Start & End Dates

You must select a date range for your request

<b>Start Date (*)</b>		<input type="button" value="Clear"/>
Official Receive Date (Date the ICSRs were entered into EV)	<input type="text" value="2015-02-24"/>	
<b>End Date (*)</b>		<input type="button" value="Clear"/>
Official Receive Date (Date the ICSRs were entered into EV)	<input type="text" value="2015-03-11"/>	

The Start Date and End Date cannot be more than 15 days apart

To change dates, double-click the entered date & a calendar will pop up from where you can select your date



# ICSR Export Manager – occurrence country

You can also filter on country of occurrence

If the occurrence country is not populated, then the filter will search for Primary Source country, which is a mandatory field

<b>Country of Occurrence</b>		<input type="button" value="Refresh"/> <input type="button" value="Clear"/>
Filter on Occurrence Country (A.1.2) or, if not populated, Primary Source Country (A.1.1)	<ul style="list-style-type: none"><li>AF - Afghanistan</li><li>AL - Albania</li><li>DZ - Algeria</li><li>AS - American Samoa</li><li>AD - Andorra</li></ul>	Order: <input type="checkbox"/> Code
You may make multiple selection in this list.		

If desired, you can also search by region, including or excluding the EU or EEA

<b>Country of Occurrence (Groups)</b>		<input type="button" value="Clear"/>
Country Codes of Occurrence (Groups). Single selection list.	<ul style="list-style-type: none"><li>EU</li><li>EEA</li><li>Non EU</li><li>Non EEA</li></ul>	



## ICSR Export Manager – pharmaceutical form

Users can also filter on pharmaceutical form of the suspect or interacting drugs as an exclusion or inclusion criterion

Dosage Form	<input type="text"/>	<input type="button" value="Copy"/> <input type="button" value="New"/> <input type="button" value="Delete"/>
Dosage Forms referenced in Safety Reports.	<input type="text"/>	<input type="button" value="Refresh"/> <input type="button" value="Clear"/>
You may make multiple selection in this list.		Order: <input type="checkbox"/> Text

For example if you only hold MAs for tablets for, then you can limit the search to return only tablets

Since pharmaceutical form is not always specified in articles, this search also returns ICSRs where the pharmaceutical form is not populated



## ICSR Export Manager – disabling filters

The Active Filters bar shows which criteria have been filtered on

Active Filters Click on the Name  
disable/enable it. ~~Active Substance Group~~

Request Name

Case  Count

If you wish to disable a filter, rather than having to delete or clear all iterations of it, you can simply click the filter name in the Active Filters bar

Disabled filters are marked by strikethrough text

The selections made in the filter remain, but they are not filtered-on



# ICSR Export Manager – counting & requesting (1)

To view how many ICSRs your filter selections will return click “Count”

**Active Filters** Click on the Name of the Filter to disable/enable it.

Request Name

**Active Substance Group Start Date End Date**

Initial  Case

**Count** Count **Request** Refresh List

Request Name	Size	Status	
Requested on 06/03/2015 10:16, ICHICSR	280 (822 KB)	Completed	<a href="#">Download</a> <a href="#">Archive</a>
Requested on 04/03/2015 17:10, ICHICSR	16 (75 KB)	Completed	<a href="#">Download</a> <a href="#">Archive</a>
Requested on 04/03/2015 10:28, ICHICSR	1 (5 KB)	Completed	<a href="#">Download</a> <a href="#">Archive</a>
Requested on 27/02/2015 11:24, ICHICSR	2157 (7.7 MB)	Completed	<a href="#">Download</a> <a href="#">Archive</a>
15-23jandosagefrm (on 27/02/2015 10:23), ICHICSR	6 (3 KB)	Completed	<a href="#">Download</a> <a href="#">Archive</a>

The request appears in the requests list





# ICSR Export Manager – counting & requesting (2)

If you do not enter a request name, then the name will be populated with the date and time of the request

**Active Filters** Click on the Name of the Filter to disable/enable it. **Active Substance Group** **Start Date** **End Date**

Request Name   Initial  Case **Count** Count **Request** **Refresh List**

Request Name	Size	Status
Requested on 06/03/2015 10:16, ICHICSR	(B)	Completed
Requested on 04/03/2015 17:10, ICHICSR		Completed
Requested on 04/03/2015 10:28, ICHICSR	MB)	Completed
Requested on 27/02/2015 11:24, ICHICSR		Completed
15-23jandosagetm (on 27/02/2015 10:25), ICHICSR		Completed

**Download**

Download Archive

Download Archive

To download the ICSRs, click the Download button





# ICSR Export Manager – initial vs case (1)

Users can choose to download either the initial or latest version of the cases which meet the filtering criteria

The screenshot displays a web interface for the ICSR Export Manager. On the left, under the heading "Active Filters", there is a text input field labeled "Request Name". Above this field, a tooltip reads "Click on the Name of the Filter to disable/enable it." In the center, a dropdown menu is open, showing two radio button options: "Initial" (with a selected radio button) and "Case". On the right, under the heading "Date", there are two buttons: "Request" and "Refresh List".

To switch between these options, select the appropriate radio button



## ICSR Export Manager – initial vs case (2)

Active Filters	Click on the Name of the Filter to disable/enable it.	Active Substance Group	Start Date	End Date		
Request Name	<input type="text"/>	<input checked="" type="radio"/> Initial <input type="radio"/> Case	<input type="button" value="Count"/>	Count	<input type="button" value="Request"/>	<input type="button" value="Refresh List"/>

“Initial” brings back the **first** versions of valid cases. This means that cases which have since been nullified will be **excluded** from the results

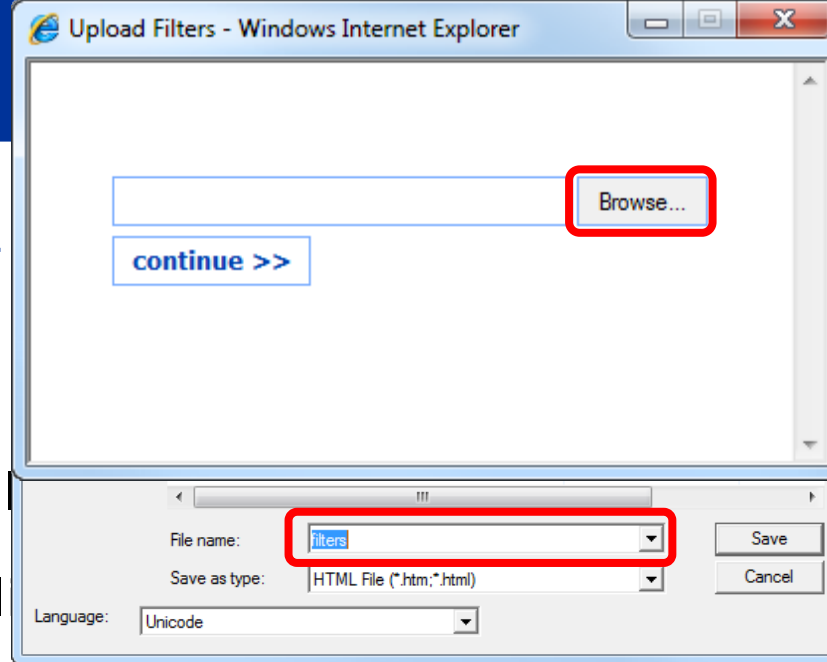
Case brings back the **latest** versions of all cases. This means that cases which have been nullified will be **included** in the results

To find the initial versions of nullified cases, search on the case number in EVWEB MLM (see slides 94-101)



# ICSR Export

# Loading filters



Users can save filters

whenever needed

To save filters, click the 'Browse...' button at the top of the screen

bar towards the



## Eudravigilance ICHICSR Export

### Filters

Click the filter name to display / hide the filter. The filter name is highlighted once a selection is made. The selection will be filtered on only when it is highlighted in the list.

Save Filters  
Load Filters

username (AAA)

AN PRODUCTION V. 7.11.5.1

Active Substance Combination

Start Date (\*)  
Original Receipt Date (Date the ICSRs were entered into EV) 2015-03-11

End Date (\*)  
Original Receipt Date (Date the ICSRs were entered into EV) 2015-03-11

Country of Occurrence

Country of Occurrence (Groups)

Message Form

---

Active Filters  Start Date End Date

A save box will open and you can then enter a relevant name for this filter selection

Once saved the filters can be stored in the user's own systems and shared with colleagues

To load saved filters, click "Load filters" and locate the filters by clicking the **Browse** button in the load filters box that will open



# Substances

This link takes you to the list of substances monitored by the MLM service

The process of defining the substances is described in slides 12-14



## Further MLM info

This link takes you to the MLM page of the EMA website, where you will find:

- User manuals
- The substances being screened
- The journals & databases being screened
- Search strings
- helpdesk links

And other information on the MLM service





## EVWEB MLM (1)

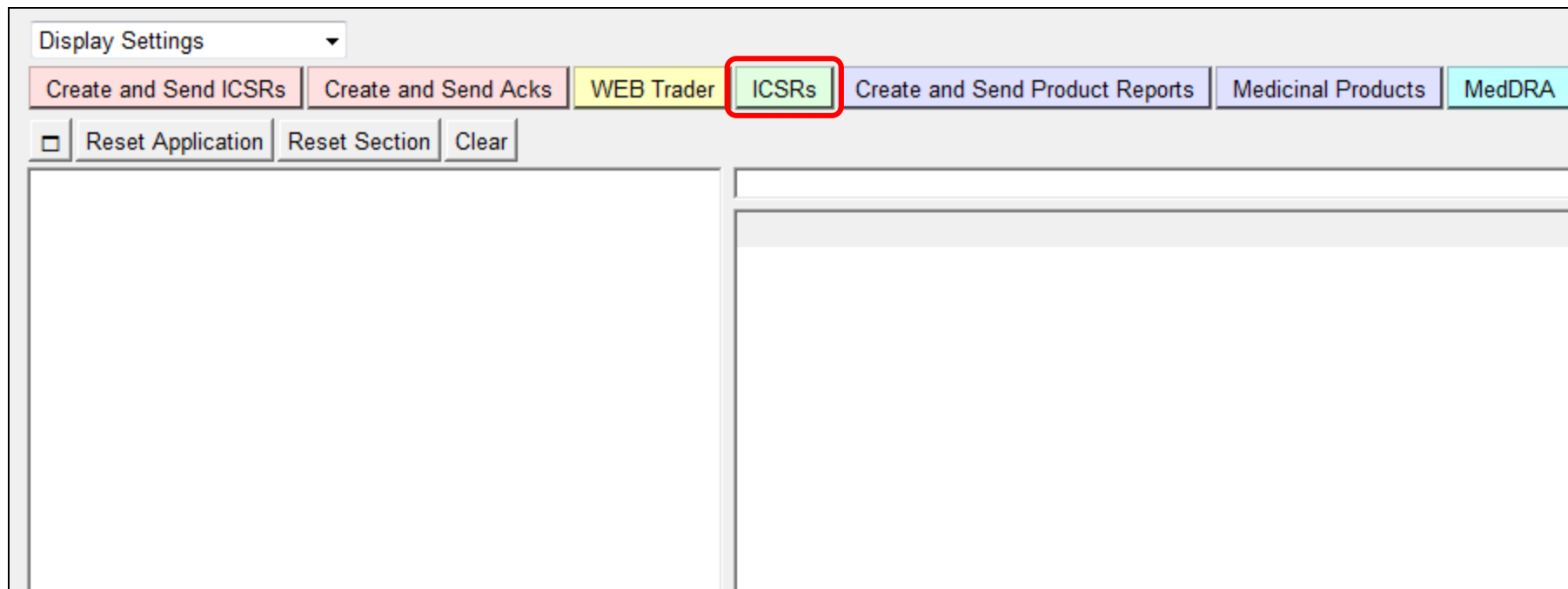
In addition to the ICSR Export Manager, MAHs & NCAs can access and download ICSRs via EVWEB

EVWEB offers more filtering options (56 different filters), but is not optimised for batch downloading, unlike the ICSR Export Manager

On accessing EVWEB, you will see the following screen



## EVWEB MLM (2)



Click on the green “ICSRs” button





# EVWEB MLM (3)

The screenshot displays the EVWEB MLM interface. At the top, there is a 'Display Settings' dropdown menu. Below it is a horizontal navigation bar with several buttons: 'Create and Send ICSRs', 'Create and Send Acks', 'WEB Trader', 'ICSRs', 'Create and Send Product Reports', 'Medicinal Products', and 'MedDRA'. Underneath the navigation bar is a secondary row of buttons: 'Reset Application', 'Reset Section', 'Clear', and a refresh icon. The main interface is divided into two sections. On the left is a tree-view navigation menu with the following items: 'Safety Reports (-)', 'ICHICSR Messages (-)', 'Queries', and 'Statistics'. On the right is a large empty rectangular area, with the word 'Empty' written in the top-left corner of this area.

The tree-view area will be populated



# EVWEB MLM (4)

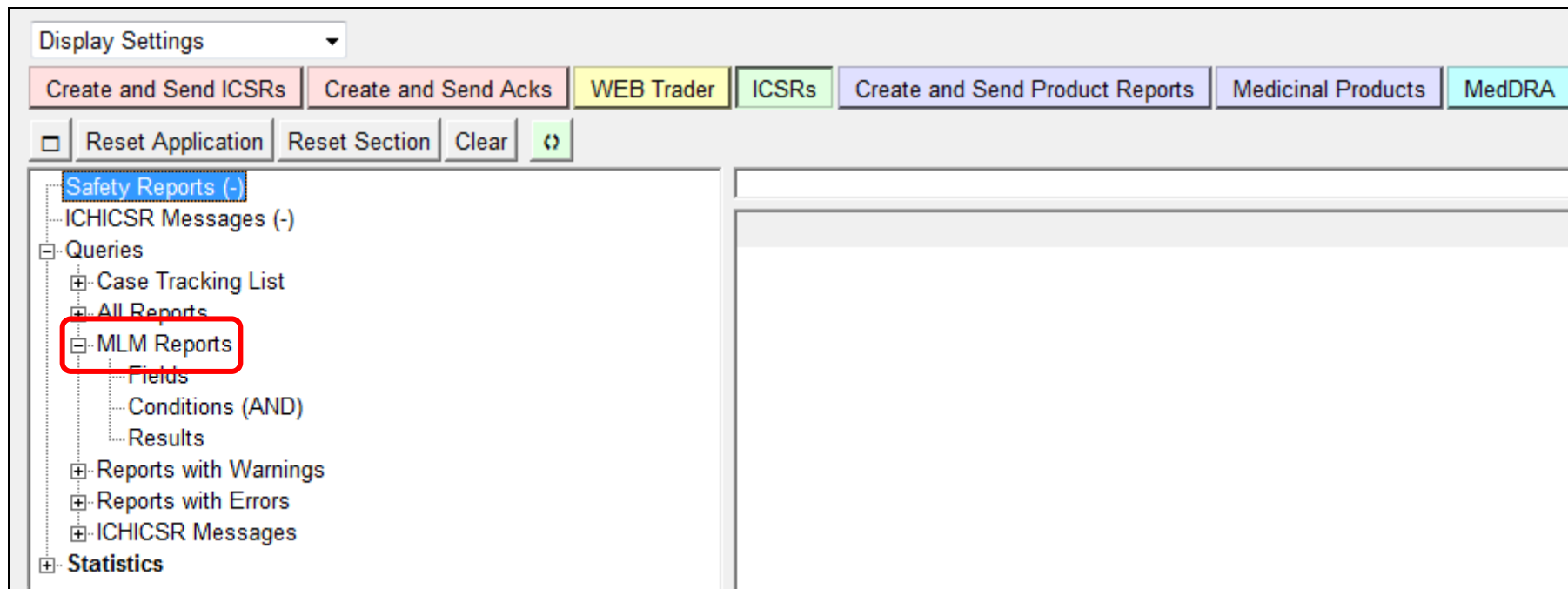
The screenshot displays the EVWEB MLM interface. At the top, there is a 'Display Settings' dropdown menu. Below it, a series of colored buttons are arranged horizontally: 'Create and Send ICSRs' (pink), 'Create and Send Acks' (pink), 'WEB Trader' (yellow), 'ICSRs' (green), 'Create and Send Product Reports' (blue), 'Medicinal Products' (blue), and 'MedDRA' (cyan). Underneath these buttons is a row of utility buttons: 'Reset Application' (with a square icon), 'Reset Section' (with a square icon), 'Clear' (with a square icon), and a green circular refresh icon. The main interface is split into two panes. The left pane contains a tree-view menu with the following items: 'Safety Reports (-)' (highlighted in blue), 'ICHICSR Messages (-)', 'Queries' (with a red bracket on its left), 'Case Tracking List', 'All Reports', 'MLM Reports', 'Reports with Warnings', 'Reports with Errors', 'ICHICSR Messages', and 'Statistics'. The right pane is currently empty, showing the word 'Empty' at the top.

Click on the + next to “Queries”  
The tree-view menu expands





# EVWEB MLM (5)



Click on the + next to “MLM Reports”  
The tree-view menu expands further





# EVWEB MLM (6)

Display Settings ▾

Create and Send ICSRs   Create and Send Acks   WEB Trader   ICSRs   Create and Send Product Reports   Medicinal Products   MedDRA

Reset Application   Reset Section   Clear   E   R   Run   Run to Excel  

- Safety Reports (-)
- ICHICSR Messages (-)
- Queries
  - Case Tracking List
  - All Reports
  - MLM Reports
    - Fields
    - Conditions (AND)
    - Results
  - Reports with Warnings
  - Reports with Errors
  - ICHICSR Messages
- Statistics

Description	Name/Value
Reporting Type	<input type="checkbox"/>
Local Report Number (Matches)	<input type="checkbox"/>
Blinded Suggestion	<input type="checkbox"/>
Blinded	<input type="checkbox"/>
Blinded (Manual Recode Status)	<input type="checkbox"/>
Message Receive date	<input type="checkbox"/>
Message Receive date (From)	<input type="checkbox"/>
Message Receive date (Up to)	<input type="checkbox"/>
Transmission date	<input type="checkbox"/>
Transmission date (From)	<input type="checkbox"/>
Transmission date (Up to)	<input type="checkbox"/>
Primary Source Country	<input type="checkbox"/>
Occurrence Country	<input type="checkbox"/>
Reporter Country	<input type="checkbox"/>
Study Name (Matches)	<input type="checkbox"/>
Study Number (Matches)	<input type="checkbox"/>
Study Type	<input type="checkbox"/>
Medicinal product (Matches)	<input type="checkbox"/>
Active substance (Matches)	<input type="checkbox"/>
Drug characterization	<input type="checkbox"/>
Product Scientific Name (Matches)	<input type="checkbox"/>
Drug Indication (code)	<input type="checkbox"/>



# EVWEB MLM (7)

Display Settings

Create and Send ICSRs   Create and Send Acks   WEB Trader   ICSRs   Create and Send Product Reports   Medicinal Products   MedDRA

Reset Application   Reset Section   Clear   E   R   Run   Run to Excel

- Safety Reports (-)
- ICHICSR Messages (-)
- Queries
  - Case Tracking List
  - All Reports
  - MLM Reports
    - Fields
    - Conditions (AND)
    - Results
  - Reports with Warnings
  - Reports with Errors
  - ICHICSR Messages
- Statistics

Description	Name/Value
Reporting Type	<input type="checkbox"/>
Local Report Number (Matches)	<input type="checkbox"/>
Blinded Suggestion	<input type="checkbox"/>
Blinded	<input type="checkbox"/>
Blinded (Manual Recode Status)	<input type="checkbox"/>
Message Receive date	<input checked="" type="checkbox"/>
Message Receive date (From)	<input type="checkbox"/>
Message Receive date (Up to)	<input type="checkbox"/>
Transmission date	<input type="checkbox"/>
Transmission date (From)	<input type="checkbox"/>
Transmission date (Up to)	<input type="checkbox"/>
Primary Source Country	<input type="checkbox"/>
Occurrence Country	<input type="checkbox"/>

To select an option, tick the box next to the required option  
Then double-click the blue box which appears next to it





# EVWEB MLM (8)

Display Settings

Create and Send ICSRs   Create and Send Acks   WEB Trader   ICSRs   Create and Send Product Reports   Medicinal Products   MedDRA

Reset Application   Reset Section   Clear   E   R   **Run**   Run to Excel

- Safety Reports (-)
- ICHICSR Messages (-)
- Queries
  - Case Tracking List
  - All Reports
  - MLM Reports
    - Fields
    - Conditions (AND)
    - Results
  - Reports with Warnings
  - Reports with Errors
  - ICHICSR Messages
- Statistics

Description	Name/Value
Reporting Type	<input type="checkbox"/>
Local Report Number (Matches)	<input type="checkbox"/>
Blinded Suggestion	<input type="checkbox"/>
Blinded	<input type="checkbox"/>
Blinded (Manual Recode Status)	<input type="checkbox"/>
Message Receive date	<input checked="" type="checkbox"/> 07/04/2015
Message Receive date (From)	<input type="checkbox"/>
Message Receive date (Up to)	<input type="checkbox"/>
Transmission date	<input type="checkbox"/>
Transmission date (From)	<input type="checkbox"/>
Transmission date (Up to)	<input type="checkbox"/>
Primary Source Country	<input type="checkbox"/>
Occurrence Country	<input type="checkbox"/>

Enter or select your filtering option

Then click "Run" to run the query and retrieve the data





# Thank you for your attention

Any queries, please email:

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