New functionalities in support of the medical literature monitoring service
User manual: EV ICHISCR Export Manager, MLM EVWEB & tracking spreadsheets
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Overview

Article 27 of Regulation (EC) No 726/2004 sets out the provisions for the monitoring of medical literature and the entry of relevant information into the EudraVigilance (EV) database by the European Medicines Agency. A detailed guide (EMA/161530/2014) further defines the scope of the activities and the applicable business processes


The medical literature monitoring (MLM) service covers a range of active substances including herbal active substances as well as designated medical literature based on the use of literature reference databases. All of this information is published on MLM page of the EV website:


The outcome of the screening results is published on a daily basis as "MLM Search Results" at a dedicated area of the EudraVigilance website - Medical Literature Monitoring (MLM) box -


MAHs can access and download the ICSRs from EudraVigilance or a dedicated area of the EudraVigilance website via the ICSR export tool in line with the applicable formats and standards as outlined in Article 25 and 26 of the Commission Implementing Regulation (EC) No 520/2010. A list of ICSRs entered in EudraVigilance is published daily as "MLM ICSRs" at a dedicated area of the EudraVigilance website - Medical Literature Monitoring (MLM) box -


The ICSR export tool allows for filtering based on the following parameters: substance groups, individual substance or substance combinations, dates, pharmaceutical forms and country/region.
1. Pre-requisites

1.1. Eudravigilance Registration

All of the new tools: EV ICHISCR Export Manager, MLM EVWEB & tracking spreadsheets require registration with Eudravigilance (EV). If you are not registered with EV, contact your organisation’s person responsible for Eudravigilance. This is usually the QPPV or head of pharmacovigilance department. If you are unsure who is the relevant person, contact the Eudravigilance Registration team (eudravigilanceregistration@ema.europa.eu) who will be able to assist you.

1.2. Software

The tracking spreadsheets are published as Microsoft Excel 2007+ format spreadsheets. To access the cases, users will require Google Chrome, Mozilla Firefox or Internet Explorer 11 or above. Chrome and Firefox are the recommended options.

1.3. Trusted sites

In order to download the ICSRs from the ICH ICSR Export Manager, you may need to add the Export Manager to the list of trusted sites, especially if you are using Internet Explorer.

To add the Export Manager to the list of trusted sites, follow the steps below:

1. Navigate to the ICH ICSR Export Manager;
2. Go to Tools;
3. Click "Internet Options";
4. Click the "Security" tab;
5. Click "Trusted sites";

6. Click the "Sites" button;

7. Click the "Add" button to add this site to your list of trusted sites.
2. Accessing the MLM functionalities

All functionalities are accessible from the Eudravigilance website:  

In the top-right hand corner click the link "Production" (ringed in red in the image above) and, when prompted, enter your username and password.

This will take you to the secure area.
Welcome to the restricted area of the EudraVigilance website
To continue, please select one of the available functionalities from the menus on the left of the screen.

You will see various menus on the left of the screen. The yellow-ringed link takes you to EVWEB (which is also available directly from https://eudravigilance-human.ema.europa.eu/#/) and the red-ringed menu contains the MLM-specific links.
3. Tracking spreadsheets

Every business day the MLM Service will publish and update the following spreadsheets:

- **MLM Search Results**, which contains the results of the searches and screening of scientific and medical literature that the Agency is monitoring;
- **MLM ICSRs**, which contains the results of the review and assessment of the returned articles and information on the management of the ICSRs created.

Both spreadsheets will be updated daily at 9AM & an article and any related cases will remain in the relevant spreadsheet until the day after it has been completed.

An article is considered completed, and is removed from the sum_screen spreadsheet the following day, once it has been assessed for inclusion/exclusion criteria.

A case is considered completed, and is removed from the sum_ICSR spreadsheet the following day, either:

- until it has been confirmed that there is no case, or once the case has been transmitted to EV and it is assessed that no follow-up is required or that follow-up was received and a follow-up version received or that no follow-up was received by the requested date of reply).

Once an article and/or the cases are completed, they will no longer appear in the daily tracking sheets, and their tracking records will only be the archive, which will be permanently available. However the cases created and transmitted to EV will be permanently available via EVWEB (see Chapter 4).

All dates in the spreadsheets are in the format DD/MM/YYYY. Dates and times are in the format DD/MM/YYYY hh:mm.

### 3.1. MLM Search Results

#### 3.1.1. Accessing the MLM Search results spreadsheet

To access the MLM Search results click on the "MLM Search Results" link to view results in an Excel spreadsheet.

The following message is displayed:

Click "Open" to open the file, or "Save" to save the file locally.
3.1.2. Columns in the MLM Search results spreadsheet

<table>
<thead>
<tr>
<th>Reference</th>
<th>Title</th>
<th>Full text</th>
<th>Conclusion</th>
<th>Progressive</th>
<th>Experimental</th>
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</tr>
</tbody>
</table>
As you can see from the image on the previous page, the spreadsheet has the following columns:

- **Substance group**
  - The substance group for which the search was run that returned this article,
  - If an article is returned in more than one search, then it will appear in the spreadsheet once for each substance group, but duplicate cases will NOT be created,
  - Results are sorted by substance group;

- **Reference database**
  - The database against which the search was run,
    - For daily searches this will be Embase
    - For monthly searches this will be EBSCO;
  - Date & time of search;
  - Literature reference (Vancouver Style: Author(s). Title. Journal. Year;Vol:1st page-last page)
    - The literature reference is entered in accordance with the Vancouver Style, as described in the following article: International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med. 1997; 336:309-15;
  - Primary source country
    - This is the country of the lead author & in accordance with ICH E2B(R2), the two-letter country code will form the first two characters of the WW Case Safety ID. For example, an article by an author based in Paris will see this field populated with FR,
    - In rare circumstances, this country may not correspond to the occurrence country. In such instances, the occurrence country would take precedence for the purposes of reporting;

- **Lead author**;

- **Document Object Identifier**
  - This is a unique identifier for the article & will appear in all spreadsheets to allow easy traceability,
  - If there is no DOI available then a URL for the article will be provided and if there is no URL then the internal tracking number used by the MLM Service will be provided,
  - If there are multiple cases from an article, all will have the same Document Object Identifier or URL;

- **Inclusion/ exclusion criteria**
  - If the cases arising from an article are included, then this is populated with " 5.2.1 - Valid ADR",
  - If an article is definitively excluded, then the first exclusion criterion that it meets, in accordance with those detailed in the inclusion/exclusion criteria document and the flowcharts therein, is assigned,
  - If there are potential cases in an article, then all possible exclusion criteria, in accordance with those detailed in the inclusion/exclusion criteria document, are assigned;
• **Confirmed/ potential ICSRs (C/P)**
  – If the article contains **confirmed** ICSRs, this is populated with "C",
  – If the article contains **potential** ICSRs, this is populated with "P";

• **Serious?**
  – If the case is **serious**, this is populated with "Y",
  – If the case is **not serious**, this is populated with "N";

• **Full text request date**
  – If applicable, this is the date the full-text was requested,
  – The full text will always be requested for a confirmed ICSR;

• **Translation request date**
  – If applicable, this is the date the translation was requested;

### 3.1.3. Cumulative tabs in the MLM Search results spreadsheet

In addition to the daily updates to the MLM Search Results spreadsheet, the MLM Service also provides cumulative tabs:

**Monthly cumulative tabs**

• The full results of the previous month’s screening & reviewing on the first working day of each month
  – Tab name format: MMM YYYY (e.g. Mar 2017)

• The aforementioned monthly tab, filtered to display only special circumstances with no adverse reaction (the exclusion criteria numbered 5.3.2, 5.3.3, 5.3.4, 5.4.2, 5.5.2, 5.6.3 & 5.8.2 in the inclusion-exclusion criteria document) on the first working day of each month
  – Tab name format: MMM YYYY special situation (e.g. Mar 2017 special situation)

**Daily cumulative tabs**

• Running in-month cumulative screening and reviewing results on every other working day of the month
  – Tab name format: "MMM YYYY to date" (e.g. Feb 2017 to date)

• The aforementioned in-month cumulative tab, filtered to display only special circumstances with no adverse reaction (the exclusion criteria numbered 5.3.2, 5.3.3, 5.3.4, 5.4.2, 5.5.2, 5.6.3 & 5.8.2 in the inclusion-exclusion criteria document) on every other working day of the month
  – Tab name format: "MMM YYYY special sit to date" (e.g. Feb 2017 special sit to date)

### 3.1.4. Flow of data into and out of the MLM Search results spreadsheet

Each day the MLM team will run the **search criteria** in Embase against each substance group (and on the first Monday of each month in Ebsco). The results of the searches will be entered into the Agency’s tracking tool.

If a substance returns no articles, this will be recorded as "NO RESULTS RECEIVED".
If an article concerns more than one substance being monitored by the MLM service, then it will be retrieved & recorded for each substance group.

Once the articles are entered into the tracking tool, they will be screened & reviewed to see if they meet the inclusion/exclusion criteria & whether they contain any confirmed or potential ICSRs. The screening & reviewing will take place either the same day as the searching or on the next working day.

At the end of each day, the MLM Service exports the data entered into the tracking tool that day as an Excel spreadsheet & uploads it to the EMA’s system, where it is virus-checked and, at 9AM the following morning, it is made available for download.

The retrieved articles will be presented in the tracking sheet and will remain there until the screening & reviewing is complete. For example, an article was retrieved on 25 August 2015. Later that day the data was extracted & uploaded. The sum_screen spreadsheet with this article was available for download from 9AM on the 26th. Also on the 26th, the article was reviewed & determined not to contain any valid ICSRs. Later that day the data was extracted & uploaded. The sum_screen spreadsheet with this article was available for download from 9AM on the 27th. In the sum_screen spreadsheet available for download the following day did not contain that article.
3.2. **MLM ICSRs**

3.2.1. **Accessing the MLM ICSRs spreadsheet**

To access the MLM ICSRs spreadsheet, click on the "MLM ICSRs" link to view results in an Excel spreadsheet.

The following message is displayed:

![MLM ICSRs Link](image)

Click "Open" to open the file, or "Save" to save the file locally.
### 3.2.2. Columns in the MLM ICSRs spreadsheet

<table>
<thead>
<tr>
<th>Column Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand Name</td>
<td>Name of the brand</td>
</tr>
<tr>
<td>Product Name</td>
<td>Name of the product</td>
</tr>
<tr>
<td>Dose Form</td>
<td>Form of the dose</td>
</tr>
<tr>
<td>Strength</td>
<td>Strength of the dose</td>
</tr>
<tr>
<td>Indication</td>
<td>Indication for use</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>Type of adverse event</td>
</tr>
<tr>
<td>Severity</td>
<td>Severity of the event</td>
</tr>
<tr>
<td>Source</td>
<td>Source of the information</td>
</tr>
<tr>
<td>Date</td>
<td>Date of the information</td>
</tr>
<tr>
<td>Reference</td>
<td>Reference for the information</td>
</tr>
</tbody>
</table>

This image has been cropped to improve legibility. Not all columns are shown.
As you can see from the image on the previous page, the spreadsheet contains more information than the "MLM Search Results" spreadsheet. It contains the following columns (new columns from October 2017 are described in red text):

- **Substance group**
  - The substance group for which the search was run that returned this article,
  - If an article is returned in more than one search, then it will appear in the spreadsheet once for each substance group, but duplicate cases will NOT be created;

- **Reference database**
  - The database against which the search was run,
    - For daily searches this will be Embase
    - For monthly searches this will be EBSCO;

- **Date & time of search**;

- **Literature reference (Vancouver Style: Author(s). Title. Journal. Year;Vol:1st page-last page)**
  - The literature reference is entered in accordance with the Vancouver Style, as described in the following article: International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. N Engl J Med. 1997; 336:309-15,
  - If an article has more than one confirmed or potential case, then the article will appear once for each case, as in the rows highlighted in yellow in the image on the previous page;

- **Primary source country**
  - This is the country of the lead author & the two-letter country code will form the first two characters of the WW Case Safety ID,
  - In rare circumstances, this country may not correspond to the occurrence country. In such instances, the occurrence country would take precedence for the purposes of reporting;

- **Lead author**;

- **Document Object Identifier**
  - This is a unique identifier for the article & will appear in all spreadsheets to allow easy traceability,
  - If there is no DOI available, then a URL for the article will be provided and if there is no URL then the internal tracking number used by the MLM Service will be provided,
  - If there are multiple cases from an article, all will have the same Document Object Identifier or URL;

- **Inclusion/ exclusion criteria**
  - If the cases arising from an article are included, then this is populated with " 5.2.1 - Valid ADR",
  - If an article is definitively excluded, then the first exclusion criterion that it meets, in accordance with those detailed in the inclusion/exclusion criteria document and the flowcharts therein, is assigned,
- If there are potential cases in an article, then all possible exclusion criteria, in accordance with those detailed in the inclusion/exclusion criteria document, are assigned;

- **Confirmed/ potential ICSRs (C/P)**
  - If the article contains confirmed ICSRs, this is populated with "C",
  - If the article contains potential ICSRs, this is populated with "P";

- **Serious?**
  - If the case is serious, this is populated with "Y",
  - If the case is not serious, this is populated with "N";

- **Full text request date**
  - If applicable, this is the date the full-text was requested,
  - The full text will always be requested for a confirmed ICSR;

- **Full text receive date**
  - If applicable, this is the date the full-text was received;

- **Translation request date**
  - If applicable, this is the date the translation was requested;

- **Translation receive date**
  - If applicable, this is the date the translation was received;

- **Suspect or interacting products/substances (semicolon delimited)**
  - This contains the precise names of all substances or combinations of substances are considered suspect or interacting in each case,
  - This may include substances which are not monitored by the MLM Service as long as at least one of the substances,
  - Each different substance or substance combination will be separated by a semicolon,
  - Each substance combination will have a + between the substances,
  - Therefore a case containing both ibuprofen & a combination product containing codeine & paracetamol would see the field populated thus: Ibuprofen; Paracetamol+Codeine;

- **Initial/FU/Amendment**
  - If this is the first version of a case, this is populated with "Initial",
  - If this is a follow-up version of the case based on new information, this is populated with "FU",
  - If this is a follow-up version of a case correcting an error from the previous version, with no new information received, this is populated with "Amendment",
  - If the follow-up is a nullification of the case, then this column will be left blank and the nullification column will be populated instead;

- **WWID (A.1.10.2)**
  - The worldwide unique case safety identifier of the case;

- **Version**
  - If this is the first version of a case, this is populated with "0", 


If this is the first follow-up version of a case, this is populated with “1”,
If this is the second follow-up version of a case, this is populated with “2”,
This pattern continues for all subsequent versions;
• Receive date
  – The day that the minimum criteria for a confirmed case were first received by the MLM Service.
  – If there is a definite case from the initial search, then day zero will be the same as the search date, if not then it will be later,
  – This corresponds to E2B(R2) field A.1.6b and E2B(R3) field C.1.4;
• Latest receipt date (Day zero)
  – The date of receipt of most recent information,
  – This corresponds to E2B(R2) field A.1.7b and E2B(R3) field C.1.5;
• Transmission date (EV)
  – Date the case was first transmitted to Eudravigilance;
• Transmission date (NCA)
  – Date the case was first transmitted to an NCA (as applicable),
  – This column will be removed from December 2017 as all cases will be transmitted only to EV;
• FU to be initiated? (Y/N)
  – If the case does require follow-up (FU), this is populated with "Y",
  – If the case does not require follow-up, this is populated with "N";
• Date FU initiated
  – If applicable, this is the date the follow-up was requested;
• Date reply requested by
  – This is the date by which a reply was requested from the author;
• Reply received? (Y/N)
  – If applicable, if a reply was received, this is populated with "Y",
  – If applicable, if a reply was not received by the date a reply was requested by, this is populated with "N";
• Date FU received
  – If applicable, this is the date the follow-up was received;
• Duplicate? (Y/N)
  – If this case has been confirmed as a duplicate of another case or cases, then this will be populated with "Y"; otherwise it will be blank;
• Master WWID; Other case numbers
- If this case has been merged under a master, then the worldwide case safety ID of the master and/or of all confirmed duplicates will be entered here, separated by a semicolon; otherwise it will be blank;

- Nullified?
  - If this case has been nullified, then this will be populated with "Y", otherwise it will be blank;

- Nullification date

### 3.2.3. Flow of data into and out of the MLM ICSRs spreadsheet

Once an article has been reviewed and been determined to contain one or more confirmed or potential cases, then the article will appear in the MLM ICSRs spreadsheet with one row for each case (confirmed or potential). Each case will have one row for each suspect or interacting substance the subject of monitoring by the MLM Service.

For example, if an article contains 2 cases, the first of which has a suspect drug of paracetamol and the second of which has both paracetamol & ibuprofen as suspect, then there will be one row for the first case & 2 rows for the second case, making a total of 3 rows for the article.

Once assessed as confirmed (C) or potential (P) a case will stay in the MLM ICSRs spreadsheet until the day after it has been completed. A case is considered completed in the following situations:

- Potential cases will always have follow-up sought (including requesting the full-text article if it has not yet been received). Once received, this date will be added to the spreadsheet and the potential case will be reassessed and the status amended to either confirmed or non-valid:
  - For a once-potential case that is now confirmed, the date of receipt of the FU which permitted confirmation is day zero for reporting timelines,
    - A confirmed case stays in the spreadsheet until completed (see below),
  - Once a case is changed to non-valid, the final exclusion criterion must be entered in the tracking tool,
  - The rejected (non-valid) case will appear in the spreadsheet extracted that day with the exclusion criterion,
  - It will no longer be available in the sum_ICSR spreadsheet for the following days, but the previous days’ sheets in the archive will retain the record of the case & the decisions taken;

- The day a confirmed cases is transmitted to EV (and the relevant NCA, if applicable), the following columns are populated for the case:
  - Suspect or interacting products/substances (semicolon delimited),
  - WWID (A.1.10.1),
  - Day zero,
  - Transmission date (EV),
  - Transmission date (NCA),
  - FU to be initiated? (Y/N),
  - Date FU initiated,
  - Date reply requested by;
• This data will be extracted into that day’s spreadsheet, which will be available from 9AM the following day
  - That day’s spreadsheet will be available permanently in the archive;
• If no follow-up was required, then the transmitted case will be considered closed and will not appear in subsequent spreadsheets unless follow-up or duplicates are received or a correction made
  - If a correction was made, then there should be a footnote added to the bottom of the spreadsheet explaining why the case has returned & was corrected;
• A confirmed case transmitted to EV which requires follow-up will stay in the spreadsheet until either:
  - FU has been received, processed & a follow-up version transmitted to EV,
  - FU has been received, but contained no new information,
  - The date by which a reply was requested has passed;
• The day that follow-up is received, the field "Reply received? (Y/N)" will be populated with Y & the field "Date FU received" is populated with that date
  - The tracking sheet for that day will contain this information & it will remain in the tracking sheet with the case for as long as the case remains there;
• If the follow-up contains no new information (an unlikely, but not impossible, scenario), then no follow-up version will be created and the following day the case will disappear from the tracking sheet;
• If the follow-up does contain new information, then a follow-up version will be created & on the day that the follow-up is transmitted the fields "FU creation date", "FU transmission date (EV)" and, if applicable, "FU transmission date (NCA)" will be populated
  - This information will appear in that day’s MLM ICSRs spreadsheet, which will be available the following day from 9AM,
  - Once the follow-up has been sent, the case will not appear in subsequent days’ tracking sheets, but the previous sheets will remain in the archive as a record of what happened;
• If no follow-up is received by the date that FU was requested, then on the following day the field "Reply received? (Y/N)" will be populated with N, thus closing the case. This will appear in that day’s MLM ICSRs spreadsheet, which will be available the following day from 9AM
  - This case will not appear on subsequent days’ spreadsheets, but the record of what happened will remain in the previous days’ spreadsheets in the archive.

3.2.4. Cell highlighting function

In order to improve usability and easily track how long a case is to remain in the ICSRs spreadsheet, the following highlighting rules apply:

1. For new data in sum_ICSR:
   a. When the initial (or any FU version) of a case is transmitted to EV the previous day, the entire row is highlighted in yellow.

2. For cases that are due to leave the ICSRs spreadsheet:
a. When column V “date reply requested by” is 3 working days before the current date, the cell is highlighted in light grey and the text is red.

b. When column V “date reply requested by” is 2 working days before the current date, the cell is highlighted in dark grey and the text is red.

c. When column V “date reply requested by” is 1 working day before the current date, the cell is highlighted in a darker grey and the text is red.

The above screenshot displays the different shades of grey that are used in column V at each stage before a case is removed from the ICSRs spreadsheet.

3.3. Archive

The archive is a record of each day’s tracking sheets, both MLM Search results & MLM ICSRs. The spreadsheets, once archived, are not updated & form a permanent record of the information available to MAHs on each day.

To access the archives of daily sheets, click on the "Archive" link to view results in an Excel spreadsheet.
The following screen will appear

Select the required year...

Select a month to access that month's archive of daily tracking sheets

Archived MLM Search Results spreadsheets will have file names beginning "sum_screen". Archived MLM ICSRs spreadsheets will have file names beginning "sum_icsr".
4. Accessing MLM ICSRs

Since 22 November 2017, all MLM ICSRs have been accessed via the new EVWEB, both for single-case downloads and bulk downloading, which will replace the ICSR Export Manager.

The new EVWEB user manual explains all the functions for downloading cases, whether as single cases, as a listing in an Excel spreadsheet or as bulk downloading:

- Chapters 1.7, 1.8, 2.7, 2.11.1 & 2.11.2 of the new EVWEB user manual explain search methods, loading data and exporting data, which are analogous to the single case downloading that was available in EVWEB until 8 November 2017;
  - Chapter 1.7.1 explains simple queries,
  - Chapters 1.7.2 & 1.7.3 explain performing advanced queries,
  - Chapter 1.8 explains how to load data into EV for further processing or exporting if desired,
  - Chapter 2.7 explains the functions of the ICSR single case download screen,
  - Chapter 2.11.1 explains the Excel list export,
  - Chapter 2.11.2 explains the single item export (exporting cases as XML files or as human-readable ICSR forms, RTFs or HTML documents);
- Chapter 2.11.3 of the new EVWEB user manual explains the ICSR download functionality, which is analogous to the bulk downloading that was previously performed using the ICSR Export Manager. This is also covered in Chapter 4.3 of this manual
  - Tips on creating filters and amending existing filters are covered in Chapter 4.4 of this user manual

4.1. Log in

There are two methods to access the ICSR Export Manager: Either you can click on the EVWEB link in the restricted area, as described in Chapter 2 or you can go directly to EVWEB via the following URL: https://eudravigilance-human.ema.europa.eu/#/.

This will take you to the entry page of EVWEB.

Click the "Login" button and a login dialogue will appear.
### 4.2. Main Menu

Once you have logged-in, you will be presented with the main menu.

EVWEB’s main menu will vary in available options, depending on the user’s account access rights. In this user manual we will describe the menu entries and system functionality available to regular MAH users (i.e. non-administrators) of the interface. Depending on your account’s rights, you may see all of these options or a limited set of them.

**Note:** Additional locked features are available, such as tools for administrators of the EVWEB system, but these will only be available to user accounts that have the necessary permissions.

A typical EVWEB main menu consists of the following links:

<table>
<thead>
<tr>
<th>Menu Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Create and send ICSRs</td>
<td>Allows access to the part of the application dedicated to the creation and sending of ICH E2B(R3) Safety messages.</td>
</tr>
<tr>
<td>WEB Trader</td>
<td>Allows access to review your own messages, both sent and received. You will be able to see messages sent to you and by you, in the &quot;Inbox&quot; and “Outbox” views. The &quot;Inbox&quot; and “Outbox” view options will only be available to WEB Trader users. Users sending information via their locally established Gateway will not see these view options.</td>
</tr>
<tr>
<td>ICSRs</td>
<td>Allows you to view, browse and query ICSRs and Safety messages located in the EVDBMS.</td>
</tr>
<tr>
<td>Post</td>
<td>Provides a quick method to upload and send either ICH E2B(R3) or ICH E2B(R2) compliant Safety messages to the system.</td>
</tr>
<tr>
<td>MedDRA</td>
<td>This area of the application allows you to browse and perform searches at all levels of MedDRA.</td>
</tr>
<tr>
<td>ICSR Download</td>
<td>Allows the bulk export of ICSRs and Safety messages based on predefined criteria options.</td>
</tr>
</tbody>
</table>

The **Workspace screen** is a new addition to EVWEB’s supported functions. It acts as a temporary, centralised area where multiple EVWEB items (Safety and Acknowledgement messages, ICSRs) can be added to for better review and management.
**Note:** The EVWEB interface has been designed to utilise the latest WEB user interface (UI) approach called responsive UI. This approach automatically adjusts the EVWEB interface to the best possible viewing layout based on the size of your screen or web browser window. For example, if the screen or window is too small, the main menu may be hidden within the following menu icon: ![Menu Icon].

Main menu: Normal screen/window size

Main menu: Small screen/window size

The link corresponding to the currently active screen of EVWEB will have a darker background.

This user manual will describe the functions of the “ICSRs” link and the “ICSR Download” link. For all other functions, please see the [EVWEB user manual](#).

### 4.3. ICSR Download

EVWEB offers a dedicated screen that allows the bulk export of ICSRs and Safety messages. To access this screen, click on the **ICSR Download** link in the main menu.

You will be presented with the **ICSR Download** interface as shown in the following screenshot.

![ICSR Download Interface Screenshot]
To perform a bulk export procedure, you first define a set of criteria which will return a set of matches; then you export all of them as a single compressed (.zip) file.

**Note:** The exported items contained in the single compressed file are in ICH E2B(R3) XML format.

To proceed with the bulk export process, you need to follow the steps outlined in the below table (the numbers reference the screenshot above):

<table>
<thead>
<tr>
<th>ICSR Download Screen Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Criteria</td>
<td>Define the criteria that will narrow down the items you wish to bulk export. The default, pre-selected criteria available in the ribbon are:</td>
</tr>
<tr>
<td></td>
<td>- <strong>Reports:</strong> Select &quot;MLM reports&quot;. See Chapter 4.3.1 for more information;</td>
</tr>
<tr>
<td></td>
<td>- <strong>Start Date:</strong> Select the start date of a date range on which messages containing ICSRs are received;</td>
</tr>
<tr>
<td></td>
<td>- <strong>End Date:</strong> Select the end date of date range on which messages containing ICSRs are received,</td>
</tr>
<tr>
<td></td>
<td>- Start and end-dates are mandatory and cannot be more than 15 days apart;</td>
</tr>
<tr>
<td></td>
<td>To further fine-tune the results, the user can select a series of criteria options available from the &quot;More criteria&quot; button:</td>
</tr>
<tr>
<td></td>
<td>- <strong>Active Substance:</strong> Insert one or more active substances that should be present in the matching items;</td>
</tr>
<tr>
<td></td>
<td>- <strong>Reporter Country:</strong> Select the country of the primary source for regulatory reporting purposes,</td>
</tr>
<tr>
<td></td>
<td>- Only one country can be selected;</td>
</tr>
<tr>
<td></td>
<td>- <strong>World Wide Case Id:</strong> Insert the worldwide unique case ID number,</td>
</tr>
<tr>
<td></td>
<td>- Multiple WWIDs can be entered;</td>
</tr>
<tr>
<td></td>
<td>- <strong>Active Substance Group:</strong> Select the active substance group;</td>
</tr>
<tr>
<td></td>
<td>- <strong>Active Substance Combination:</strong> Select the active substance combination;</td>
</tr>
<tr>
<td></td>
<td>- <strong>Active Substance MLM Group:</strong> Select the active substance MLM group,</td>
</tr>
<tr>
<td></td>
<td>- You should use the Active Substance MLM Group or combination when searching for MLM reports;</td>
</tr>
<tr>
<td></td>
<td>- <strong>Active Substance MLM Combination:</strong> Select the active substance MLM combination,</td>
</tr>
<tr>
<td></td>
<td>- <strong>NOTE:</strong> These filters are combined with an AND. If you select both 'Active Substance MLM Group' AND 'Active substance MLM Combination', then only ICSRs which have suspect drugs meeting both criteria will be returned. See Chapter 4.5 &quot;Active substances&quot; for more information;</td>
</tr>
<tr>
<td></td>
<td>- <strong>Serious:</strong> Select whether you want only serious or non-serious cases.</td>
</tr>
<tr>
<td>ICSR Download Screen Option</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td>(2) “Count”, “Reset”, “Save Criteria” (:flexbox) &amp; “Load Criteria” (:flexbox) Buttons</td>
<td>The buttons available in this area provide additional actions that help the user with the overall bulk export process.</td>
</tr>
<tr>
<td></td>
<td>- <strong>Count</strong>: Click on this button to see the number of items that match the defined criteria.</td>
</tr>
<tr>
<td></td>
<td>- <strong>Reset</strong>: Clears all changes (including criteria options) and initiates a new count process.</td>
</tr>
<tr>
<td></td>
<td>- <strong>Save Criteria (:flexbox)</strong>: Saves the applied criteria options to a file, allowing you to perform a future bulk export process using the same criteria settings.</td>
</tr>
<tr>
<td></td>
<td>- <strong>Load Criteria (:flexbox)</strong>: Loads criteria options that were saved using the “Save Criteria” button.</td>
</tr>
<tr>
<td>(3) “Request” Field &amp; Button</td>
<td>Enter a ‘request name’ to distinguish the bulk export process that will initiate when clicking on the “Request” button. It also provides the filename to the compressed file that becomes available for download.</td>
</tr>
<tr>
<td>(4) ICSR Download Status</td>
<td>This area offers information regarding running (“Pending”) and completed (“Resolved”) bulk export processes.</td>
</tr>
<tr>
<td></td>
<td>The common feedback fields are:</td>
</tr>
<tr>
<td></td>
<td>- <strong>Requested on</strong>: Indicates the date on which the bulk export process was requested.</td>
</tr>
<tr>
<td></td>
<td>- <strong>Completion status</strong>: Provides metrics on the succeeded (S) and total (T) number of matches processed for bulk exporting (S/T).</td>
</tr>
<tr>
<td></td>
<td>- <strong>Request name</strong>: The name of the process and resulting compressed file. Originates from the “Request” field.</td>
</tr>
<tr>
<td></td>
<td>- <strong>File size</strong>: The size of the resulting compressed file.</td>
</tr>
<tr>
<td></td>
<td>- <strong>Status</strong>: Indicates the status of the bulk export process. The available conditions are:</td>
</tr>
<tr>
<td></td>
<td>- <strong>STARTED</strong>: A bulk export request has just been initiated and is in progress.</td>
</tr>
<tr>
<td></td>
<td>- <strong>COMPLETED</strong>: A bulk export request has been successfully processed and resolved.</td>
</tr>
<tr>
<td></td>
<td>- <strong>COMPLETED_WITH_ERROR</strong>: A bulk export request has been resolved but one or more reports failed to be exported.</td>
</tr>
<tr>
<td></td>
<td>- <strong>ARCHIVED</strong>: A resolved bulk export request that has passed the 5th day from its creation date.</td>
</tr>
<tr>
<td></td>
<td>- <strong>Exported Reports</strong>: The number of exported reports originating from the resolved bulk export request.</td>
</tr>
<tr>
<td><strong>Note</strong>: The rounded arrows icon (:flexbox) next to “History”, when clicked, refreshes the status area and displays the latest information updates.</td>
<td></td>
</tr>
</tbody>
</table>
**Note:** The filters in EVWEB do not exactly match those from the previous ICSR Export Manager. There are three significant changes:

- **Reporter country,**
  - Previously this allowed multiple selections. Presently it only allows a single selection. This will be resolved in a future release of EVWEB;

- **Worldwide case safety Identifier,**
  - Previously the bulk download did not permit searching using WWID. This is now possible and you may select many WWIDs in a single search,
  - WWIDs can be typed or pasted into the search box or into a filter;

- **Pharmaceutical form,**
  
  Previously users could filter on pharmaceutical form, but this is not possible in the first release of EVWEB because until mid-November 2017, ICH had not agreed which code or term list to use for pharmaceutical forms. This meant that it could not be implemented in the new system in time for go-live. This, in turn, meant that the free-text data could not be used for a filter. This will be remedied in a future release, which will permit the building of filters based on pharmaceutical form,

  From 22 November 2017 the MLM Service will use the EDQM pharmaceutical form list, which was adopted by the ICH, when entering pharmaceutical forms. This means that when the filters are built, all MLM Service cases will be retrievable when they should be.

After initiating a bulk export process the user waits for it to complete which, in turn, will force it to move from the “Pending” group section to that of the “Resolved” group section. Once in the “Resolved” section, the user can proceed to export the compressed file by selecting the bulk export process row, and then clicking on the “Download” option that appears at the top left.

**Note:** All completed bulk export processes remain in the “Resolved” group section, and do not get deleted. However, after 5 days from the date of their creation they acquire the status of “ARCHIVED” and cannot be downloaded again.

### 4.3.1. “Reports” Criteria

The “Reports” criteria item is used to filter-down the results of a bulk export request, based on the type (i.e. EMA/NCA, MAH etc.) and assigned access rights of the logged-in user. For MAH users, this criterion is mandatory.

As you can see from the screenshot below, there are 4 options:

- PV obligations reports (L2A);
- Case narrative requests (L2B);
- MLM reports;
- PV obligations reports (L2A) & MLM reports.
To download MLM cases, you should select “MLM reports”. Unless you want to download all MLM service cases, do **NOT** select the option “PV obligations reports (L2A) & MLM reports” as this report will either lead to you downloading too many MLM cases if you do not filter on substances or too few L2A reports if you do.

### 4.4. Active substances being monitored

The Active Substance Groups, as described in Chapter 1 of the detailed guide on literature monitoring, are available from the [dedicated MLM Service page](#) of the EMA Website and from the Medical Literature Monitoring menu on the Eudravigilance website.

Each Substance Group includes all substances including various salts, and substance combinations under the group. The Substance Groups are ranked by the greatest number of MAHs that hold MAs for a product containing this substance.

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; however 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. Therefore the combination of paracetamol & codeine is under the Paracetamol substance group, and not the Codeine group, because the Paracetamol Substance Group is ranked before the Codeine Substance Group. Therefore, if you are searching using the Substance Groups and you want a case with codeine as a suspect or interacting drug, whether alone or in combination, you will need to select the Codeine substance group & in a separate query, all substance combinations containing codeine from higher-ranked groups. You should do this as two separate filters, since selecting the CODEINE active substance group & the PARACETAMOL, CODEINE active substance combination in the same query will return only cases where both a substance under the codeine group **AND** the combination product were considered suspect or interacting.
Conversely, when selecting only multiple active substance groups or only multiple active substance combinations, an "OR" operator is applied. Therefore, if you select active substance group PARACETAMOL and then active substance group CODEINE, the search will return all cases containing either paracetamol or codeine.

If selecting only combinations, you will need to carefully select from the list of substances before entering your filtering criteria, taking into account how information is likely to be reported in articles. You should generally ensure that you include a substance or substance combination which matches the substance group since salts or specific grade are unlikely to be reported in an article. For example, the Paracetamol active substance group includes the following substances:

- PARACETAMOL;
- PARACETAMOL COMPAP PVP 3;
- PARACETAMOL DC;
- PARACETAMOL PH. EUR.

If you are an MAH for a product containing "Paracetamol DC" as the active substance, your filter should include both "Paracetamol DC" and "Paracetamol", since you cannot reasonably exclude the possibility that the cases reported as having "Paracetamol" as the active substance refer to your product; but you would not need to include "Paracetamol compap PVP 3" or "Paracetamol Ph. Eur", since if those were reported then they would clearly not be your product.

You will not need to select substances every time, since, as described in Chapter 4.4, above, you can save & load filters.

4.4.1. Active Substance Group

Searching on Active Substance Groups is optional. If you wish to retrieve cases concerning all substances, do not filter of this criterion.

To search on an active substance group, select the criterion from the "More criteria" menu.
A text box will appear. Enter the name, or part of the name, of the desired substance group into the search box (ringed in red in the image below)

As you type the system will offer you options, as in the image below.

Once your desired substance group is presented, click on it and it will be added to the filter.

Even if only one active substance group is returned, you still need to click it to select it.

To remove a substance group, click on the x, ringed in red in the image above. To add more substance groups, click on the typing area and being to type the name as before.

Click "Update" to save the filtering criterion.

To amend a saved filtering criterion, click on the saved criterion, to remove it click on the X to the right of the criterion, ringed in green in the image above.

4.4.2. Active Substance Combination

Searching on active substance combinations is performed in the same manner as for active substance groups; however there are many more combinations than groups and so you may need to use more iterations of the field to be able to select all of your substance combinations.
While it is technically possible to combine searches for groups and combinations at the same time, it is very strongly recommended **NOT** to do so. If you search for both a substance group & a substance combination, then only ICSRs containing both will be returned.

To return ICSRs containing either a substance group (or groups) or a specific substance combination (or combinations), you would need to make two or more different queries.

### 4.4.3. Interaction between “Active Substance Group”, “Active Substance Combination” and the “Medical literature monitoring: substance and herbal substance groups” spreadsheet

All the substance groups and combinations covered by the MLM Service are listed in the document “Medical literature monitoring: substance and herbal substance groups” published on the MLM webpage.

**Figure 1. Medical literature monitoring: substance and herbal substance groups spreadsheet**

<table>
<thead>
<tr>
<th>ID</th>
<th>Substance Group</th>
<th>Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PARACETAMOL</td>
<td>ACETYLCYSTEINE, PARACETAMOL</td>
</tr>
<tr>
<td>1</td>
<td>PARACETAMOL</td>
<td>ACETYLSALICYCLIC ACID, ANHYDROUS CAFFEINE, PARACETAMOL</td>
</tr>
<tr>
<td>1</td>
<td>PARACETAMOL</td>
<td>ASCORBIC ACID, CHLORPHENAMINE, PARACETAMOL</td>
</tr>
<tr>
<td>1</td>
<td>PARACETAMOL</td>
<td>ASCORBIC ACID, PARACETAMOL</td>
</tr>
<tr>
<td>1</td>
<td>PARACETAMOL</td>
<td>ASCORBIC ACID, PARACETAMOL, ACETYLSALICYCLIC ACID</td>
</tr>
<tr>
<td>1</td>
<td>PARACETAMOL</td>
<td>ASCORBIC ACID, PARACETAMOL, ANHYDROUS CAFFEINE</td>
</tr>
<tr>
<td>1</td>
<td>PARACETAMOL</td>
<td>ASCORBIC ACID, PARACETAMOL, CAFFEINE</td>
</tr>
<tr>
<td>1</td>
<td>PARACETAMOL</td>
<td>ASCORBIC ACID, PARACETAMOL, CODEINE PHOSPHATE HEMIHYDRATE</td>
</tr>
<tr>
<td>1</td>
<td>PARACETAMOL</td>
<td>ASCORBIC ACID, PARACETAMOL, PHENYLEPHRINE</td>
</tr>
</tbody>
</table>

Note how even though only the substance group Paracetamol is displayed, column C, “Substances”, contains combinations of paracetamol with other substances monitored by the MLM Service, e.g. ascorbic acid. These combinations are only displayed under the paracetamol group because all fixed drug combinations are displayed under the first substance group in which they appear.

The column “Substance Group” corresponds to the ICSR Export Manager filter option “Active Substance Group”. As mentioned in Chapter 4.5, combination products containing multiple substances monitored by the MLM Service are grouped under the earliest substance group and not necessarily under the substance you expect.

The column “Substances” corresponds to the ICSR Export Manager filter option “Active Substance Combination” and only exact matches of these combinations will be indexed by the export manager (although the order the substances are entered in the active substance field (ICH E2B(R2) B.4.k.2.2, ICH E2B(R3) G.k.2.3.r.1) is irrelevant because they are entered as separate substances & the EudraVigilance ICSR Export Manager indexing tool combines them to match the list).

The substance combinations and groups are created based on the data entered in the xEVMPD (also known as the Article 57 database); but in the literature substances might be described only by the active moiety and not include the salt form, so when you are creating filters to search for reportable cases you should include the forms both with and without the salts.
4.5. Saving, amending, validating & loading filters

4.5.1. Saving filters

Once you have created your filter, you can save it for re-use at a later date. To do this, click the “Save criteria” button and follow your browser’s normal process for downloading and saving files.

Whereas the previous bulk download system’s filters were saved as XML files, the EVWEB filters are stored as JSON (JavaScript Object Notation) files. Because of this the previous filters that you used will not be reusable and you will need to rebuild them using the new system.

4.5.2. Amending filters

If you have a pre-existing filter used for the previous system, or have a list of the active MLM substance combinations that you need to search for, then you can add the substances into the filter offline by editing a saved file using a programme such as Notepad++ or similar. If you are doing this, you will need to pay particular attention to the syntax used. You may find it easiest to create a filter containing 3 or more of the criterion on which you wish to filter so that you can base the editing on the syntax therein.

Within an individual filter, any selections you make will expand your search (an "OR" operator is applied), so if you select both Paracetamol & Codeine as the Active Substance MLM Groups, then cases containing either Paracetamol or Codeine will be returned.

Among different filters, any selections you make will contract your search (an "AND" operator is applied), so if you select the country of occurrence as Spain and the active substance group as Paracetamol, then only ICSRs occurring in Spain where paracetamol was the suspect or interacting drug will be returned.

Note: There is a filter limit of approximately 1000 selections in total for any given search. If you require more than 1000 selections you will need to perform another query.

4.5.3. Validating filters

Once you have built and saved a filter, you may need to validate it to ensure that it returns the same data as you would have received previously. You can either use the data that you previously downloaded & compare the same date range, or you can compare the data in XCOMP that was sent from 2-6 October 2017. This matches the data in production from 2-4 October 2017.

4.5.4. Loading filters

To load a saved filter, click the “Load criteria” button and select the filter to upload following your browser’s normal process for uploading files.

You will need to amend the start and end dates, ringed in red in the image below, to fit the time period that you need to search for, since they will be the dates you had entered the last time you saved your filters.

**Note:** Start & End dates cannot be more than 15 days apart.
5. List of acronyms used in the document

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>EV</td>
<td>Eudravigilance</td>
</tr>
<tr>
<td>EVWEB</td>
<td>Eudravigilance Web application</td>
</tr>
<tr>
<td>FU</td>
<td>Follow-up</td>
</tr>
<tr>
<td>HTML</td>
<td>Hypertext Markup Language</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>ICSR</td>
<td>Individual case Safety Report</td>
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<tr>
<td>JSON</td>
<td>JavaScript Object Notation</td>
</tr>
<tr>
<td>MLM</td>
<td>Medical Literature Monitoring</td>
</tr>
<tr>
<td>NCA</td>
<td>National Competent Authority of an EEA Member State</td>
</tr>
<tr>
<td>RTF</td>
<td>Rich Text Format</td>
</tr>
<tr>
<td>XCOMP</td>
<td>The EudraVigilance External Compliance environment, used for QA testing</td>
</tr>
<tr>
<td>XML</td>
<td>Extensible Markup Language</td>
</tr>
</tbody>
</table>