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European Medicines Agency

Compliance notifications explanation and Q&A

Background to the compliance calculations & anticipated questions from stakeholders

Executive summary

As described in the Detailed guide regarding the EudraVigilance data management activities by the European Medicines Agency, following a successful pilot programme, the Agency is initiating compliance monitoring based on reporting timelines set out in the pharmaceutical legislation (pharmacovigilance and clinical trials).

Starting from September 2025, EMA has been notifying MAHs, Sponsors & NCAs (sender organisations) about the 7/15/90-day ICSR reporting compliance through automated reports generated by EVDAS. The QPPVs/RPs of all sender organisations will be automatically contacted every month[1] with compliance reports covering the submissions made to EV the previous month.

Legal basis

In accordance with Directive 2001/83/EC, Article 107(3), Marketing Authorisation Holders (MAHs) shall submit to EudraVigilance (EV) reports of serious suspected adverse reactions within 15 days that occur in the Union and in third countries and reports of non-serious suspected adverse reactions occurring in the EEA within 90 days.

In accordance with Directive 2001/83/EC, Article 107(a)(4), national Competent Authorities of EEA Member States (NCAs) shall submit to EudraVigilance (EV) reports of serious suspected adverse reactions that occur in its territory within 15 days and reports of non-serious suspected adverse reactions that occur in its territory within 90 days.

In accordance with Regulation (EU) No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, Article 42(2), Sponsors shall submit to EV reports of fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs) within 7 days and reports of non-fatal or non-life-threatening SUSARs within 15 days.

In accordance with Commission Implementing Regulation (EU) No 520/2012 (IR) on the performance of pharmacovigilance activities (IR), Articles 26(2)(a) and 25(1)(f) of chapter IV ('Use of terminology,

[1] Sender organisations will only be contacted if they submitted at least one valid ICSR to EV in the previous month

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formats and standards'), ICSRs and SUSARs reported to EudraVigilance shall comply with the following ISO standards:

- The Individual Case Safety Report (ICSR) standard (ISO 27953-2:2011) and the modalities on how to implement this standard, as defined in the ICH E2B(R3) guideline;
- terminology on pharmaceutical dose forms and routes of administration (ISO/FDIS 11239:2012), in line with EMA's Referentials Management Service (RMS).

In accordance with Regulation (EC) No 762/2004, Article 24(3), the Agency shall, in collaboration with NCAs and MAHs submitting ICSRs to EV, be responsible for operating procedures that ensure the highest quality and full integrity of the information collected.

In accordance with IR, Article 11(1)(c), specific quality system procedures and processes shall be in place in order to ensure submission of accurate and verifiable data on serious and non-serious suspected adverse reactions to the EudraVigilance database within the 15 or 90-day time frame.

What will you receive?

Sender organisations will receive, via email, one PDF (portable document format) file per month for each type of ICSR[2] that they have submitted to EudraVigilance (EV) in the previous month:

1. Email subject: EudraVigilance Clinical Trial Module (EVCTM) - Notification on adherence to 7/15 days reporting timelines of Individual Case Safety Reports (ICSRs)
   - *File name format: Compliance Reports - <<SENDER ID>> - EVCTM – 7-15 days - <<Month>> <<Year>>.pdf*
2. Email subject: EudraVigilance Post-Authorisation Module (EVPM) - Notification on adherence to 15 days reporting timeline of Individual Case Safety Reports (ICSRs)
   - *File name format: Compliance Reports - <<SENDER ID>> - EVPM - 15 days - <<Month>> <<Year>>.pdf*
3. Email subject: EudraVigilance Post-Authorisation Module (EVPM) - Notification on adherence to 90 days reporting timeline of Individual Case Safety Reports (ICSRs)
   - *File name format: Compliance Reports - <<SENDER ID>> - EVPM - 90 days - <<Month>> <<Year>>.pdf*

This means that, for example, if your organisation submitted to EV both serious and non-serious post-marketing ICSRs, but no SUSARs, in the month of August 2025, then in September 2025 you would receive two emails (as per the second and third bullet points above relating to notifications). Sender organisations will receive a maximum of 3 such email notifications per month.

[2] The term ICSRs includes SUSARs, which are a subset of ICSRs

What do the PDFs contain?

Each PDF will contain 5 different reports. Below are the titles of the reports which would be in the PDF "Compliance Reports - <<SENDER ID>> - EVPM - 15 days - <<Month>> <<Year>>.pdf" [3].

- Listing of Non-Compliant Individual Cases Submitted to EVPM Outside 15 Days Reporting Period,
  - *A table giving the local report numbers (E2B(R3): ACK.B.r.2) and Worldwide Unique Case Identifier of every late case submitted to EV that month by your organisation*;
- Overview of ICSRs Submission to EVPM Within/Outside 15 Days Reporting Period**,**
  - *A graph showing the percentage of ICSRs (separated into initial and follow-up) which were submitted on-time (Within) or late (Outside) to EV that month by your organisation*;
- Overview of ICSRs Submission to EVPM Within/Outside 15 Days Reporting Period,
  - *A table giving the total number of ICSRs (separated into initial and follow-up) which were submitted on-time (Within) or late (Outside) to EV that month by your organisation*;
- Overview of Submission Timelines of ICSRs to EVPM: 15 Days Reporting Period,
  - *A graph showing the number of ICSRs (separated into initial and follow-up) which were submitted to EudraVigilance for each reporting day (time taken to report measured from day zero) during that month by your organisation*;
- Overview of Submission Timelines of ICSRs to EVPM: 15 Days Reporting Period,
  - *A table giving the number of ICSRs (separated into initial and follow-up) which were submitted to EudraVigilance for each reporting day (time taken to report measured from day zero) during that month by your organisation*.

How is the compliance calculated?

Compliance is calculated as the difference between the data element "Date (of receipt) of most recent information for this report" (ICH E2B (R3) C.1.5) and the "EudraVigilance Gateway date".

ICH E2B (R3) C.1.5 "Date of Most Recent Information for this Report" captures the date each time information (whether initial or follow-up) is received by the sender organisation. However, if the case is amended for any other reason (e.g. after internal review by the sender) this date should not be changed, and the data element C.1.11.1 (report nullification/amendment) should be populated with the value 'amendment,' indicating that the case was amended by the sender, and a reason should be provided on the data element C.1.11.2 (reason for nullification/amendment).

The EudraVigilance Gateway Date is the date of the ICSR-MDN, which is returned to sender organisation by the EV Gateway for each safety report message successfully transmitted[4]. As detailed in the EU Individual Case Safety Report (ICSR) Implementation Guide, Chapter **I.C.2.1.8 Processing and Acknowledgement of Receipt of Safety Messages**, "the date of the ICSR-MDN will serve as the official receipt date of the transmission of the Safety Message by the Gateway and it documents the fulfilment of the reporting timelines as defined in EU legislation."

[3] For each PDF, the referenced module and the number of compliance days will be different according to the calculations being performed
[4] For EVWEB users (WEBTRADERS), the gateway date is visible in the ICHICSR messages area of the ICSRs section of EVWEB (see Q3, below)

As specified in the compliance notification letter, please note that the following types of ICSRs are excluded from the compliance notification:

- "Error reports": ICSRs for which the sender received an acknowledgement code "CR" in data element "Acknowledgment Code for a ICSR Message" (ICH E2B(R3) ACK.B.r.6);
- "Nullification reports": ICSRs where the data element "Report Nullification/Amendment" (ICH E2B(R3) C.1.11.1) is populated with "1";
- "Amendment reports": ICSRs where the data element "Report Nullification/Amendment" (ICH E2B(R3) C.1.11.1) is populated with "2".

However, every other ICSR submitted by every sender organisation will be counted in the reports.

When will the reports be sent?

The report will be sent monthly (usually on the first Wednesday of the month) to the registered EU-QPPVs/RPs of the sender organisations and cover the period of the previous month. If EMA experiences any technical problems the night of report generation, then the reports may be delayed.

Frequently Asked Questions

Q1. What email address will I receive the emails from?

A. The emails will be sent from the address donotreply@ema.europa.eu.

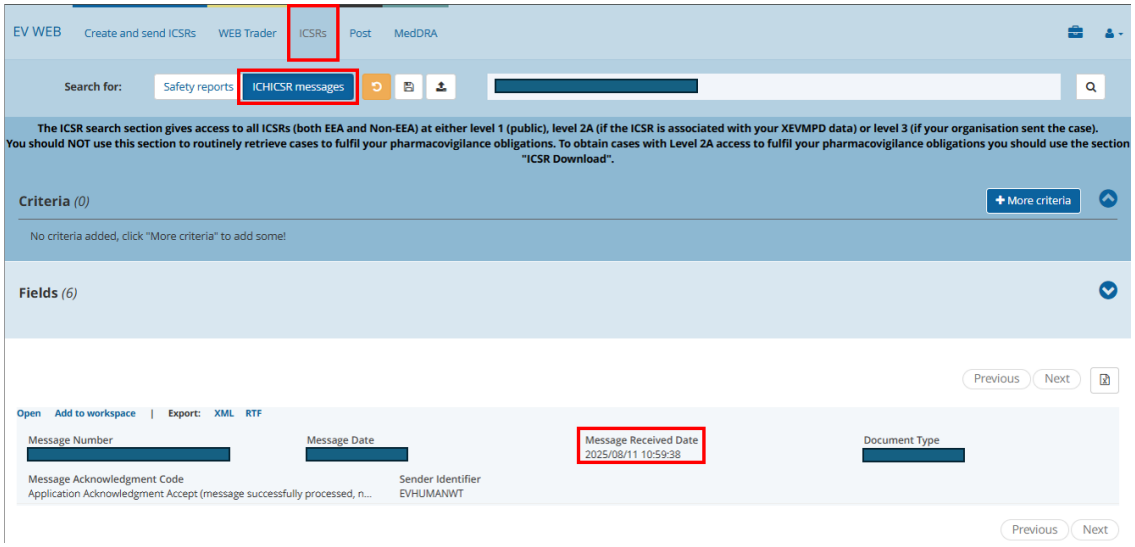
Q2. My organisation has many QPPVs. Who will receive the report?

A. The emails will be sent to the person registered in EudraVigilance as the EU Qualified Person for Pharmacovigilance (QPPV) or Responsible Person (RP). Details on EudraVigilance Access Management can be found in the EMA EudraVigilance Registration Manual, chapter 5.

Q3. I have a question about the report I received. What steps should I take?

A. Firstly, you should double-check the submissions that your organisation made to EV – look in your Gateway outbox and check the Receipt Dates (ICH E2B (R3) C.1.5 *Date of Most Recent Information for this Report*) & Gateway Dates of each case of concern. Check also the ACK messages for the ICSR(s) that you have questions about.

If you are an EVWEB user, you can search for your cases in the "ICHICSR messages" area of the **ICSRs** section of EVWEB (see image below), where you will be able to see the Receipt Dates and Gateway Dates of the ICSRs registered in EV. The EV's official gateway date is visible under the section "Message Received Date".



If you still have a question, then you should submit it via the EMA Service Desk: ICSR compliance notification question form.

Q4. My organisation did not submit any ICSRs last month, will I receive a compliance letter this month?

A. No. EMA will not generate or send any automated compliance letters to your organisation if no cases have been received in EVCTM nor in EVPM from your organisation for the concerned period.

Q5. My case has been counted twice. Is this a mistake?

A. The compliance is per ICSR. If within the same month two ICSRs are received for the same case (e.g. initial + follow-up), then each ICSR will be counted individually for reporting compliance calculations.

Q6. I nullified/amended this case, yet it appears to have been counted. Is this a mistake?

A. The compliance is per ICSR. If, within the same month, an ICSR is received in EudraVigilance and another ICSR for the same case is then received with the data element "Report Nullification/Amendment" (ICH E2B(R3) C.1.11.1) populated with 1 or 2, the compliance report will not include the nullification/amendment ICSR; but it will still consider the previously submitted (non-nullification/non-amendment) ICSR(s) for that case.

Q7. In the case narrative my organisation made it clear that an ICSR we submitted was a correction report, but it has been counted as late in the compliance reports. Why is this?

A. All ICSRs submitted to Eudravigilance are included in the 7/15/90 days reporting calculations unless either the data element "Report Nullification/Amendment" (ICH E2B(R3) C.1.11.1) is populated with "1" (Nullification report) or "2" (Amendment report) in a report, or if the ICSR receives a negative ("CR") ACK.

Q8. I submitted a follow-up ICSR, but I forgot to change the date of receipt of most recent information (ICH E2B(R3) C.1.5), making my case appear late even though it was really transmitted within 15 days of receipt of follow-up. I then submitted another ICSR with the correct date. Will my case be counted as being late?

A. As the compliance is per ICSR, the version with the incorrect date will appear to be late in the generated reports. The other version, if submitted on-time will not appear to be late. It is not possible to change the compliance of an already-submitted ICSR.

Q9. I submitted a case, but it is not listed in the automated report. Why is that?

A. There are some reasons that could explain this scenario. Firstly, please check the case submission date to ensure that submission was made during the period covered by the automated report. If the submission was made outside the period, then it will not be included in the report.

Alternatively, if the submission was made during the relevant month, then you will need to understand what acknowledgement you got for your case:

- If the acknowledgement was negative ("CR" – see the EU ICSR Implementation Guide, section **I.C.2.1.8 Processing and Acknowledgement of Receipt of Safety Messages** for further guidance), then the case was not accepted by the EV system, meaning that the regulatory timeline clock has not stopped and the ICSR should be corrected and retransmitted;
- If the case was submitted to EV but no acknowledgment was received after 48 hours, it means that an error occurred. The ICSR should be resubmitted and, as described on page 17 of the EudraVigilance Support Guide, you should notify the EV Service Desk by reporting an incident via this link).

Q10. I submitted an ICSR on day 14, but it was originally rejected (negative acknowledgment). Then, I corrected the ICSR, re-submitted on day 16 it and got a positive acknowledgement. Will the case be regarded as being on-time or as late?

A. The compliance is calculated per ICSR as the difference between the data element "Date (of receipt) of most recent information for this report" (ICH E2B(R3) C.1.5) and the EMA's official gateway date (see Q3) for the ICSRs that received a positive acknowledgement ("CA"). In this example, only one ICSR was successfully submitted, and it was submitted on day 16. If it is a serious ICSR, then it will be regarded as being late.

Q11. I submitted a case on/before the regulatory due date, but the acknowledgment message was received after the due date. Why isn't my case listed as late in the report?

A. If the case was submitted on/before the regulatory due date and received positive acknowledgment, then it will be considered as "on time" even if the acknowledgment message was received after the due date.

Q12. I am based in the USA, and I submitted a case on close of business of the regulatory due date (e.g. Day 15) but the case is listed as late in the report. Why is that?

A. Please be mindful of potential time zone differences when submitting a case to EV, as close of business in your location could mean the deadline has already passed for EMA. The official EV gateway date should be checked. In ICSR submissions you can include the time zone from which you are making your submissions and this will be taken into account for compliance. See the EU ICSR Implementation Guide, section **I.C.4.1 Business Rule Notes**, Table 35, Item 5 for further guidance.

Q13. I have received a report detailing a number of late cases. What action is expected of me?

A. As described in GVP Module I[5], Chapter **I.B.9.1. Compliance management by marketing authorisation holders**

"For the purpose of compliance management, marketing authorisation holders shall have specific quality system procedures and processes in place in order to ensure the following:

…

the submission of accurate and verifiable data on serious and non-serious adverse reactions to the competent authorities within the legally required time-limits [IR Art 11(1)(c)] (see Modules VI and IX);"

You should follow your usual structures and processes regarding compliance monitoring established in accordance with GVP Module I.

You are **not** expected to routinely reply to the EMA regarding each monthly report. EMA or NCAs will contact you if there are particular issues which require further discussion.

Q14. My organisation submits ICSRs under various different profiles. Will these all be grouped under the Headquarter, or will each profile receive its own report?

A. The reports are sent to each organisation as defined by the batch sender identifier (N.1.3) in a message. Therefore, if an EV Head Quarter profile uses multiple affiliates with their own organisation IDs to submit ICSRs, then each sender will each receive their own set of reports.

Q15. Are you planning to extend this monitoring to other process indicators in the future (other than ICSR submissions)?

A. At this point time there are no plans to include other indicators in the automated compliance reports.

Q16. What actions will be taken by EMA if the submission compliance is seen to be inadequate?

A. The information that the Agency is now sharing with stakeholders has always been available to both EMA and NCAs. It is routinely used by NCAs and EMA to monitor the quality and

[5] GVP Module I – Pharmacovigilance systems and their quality systems

regulatory compliance of the information in EudraVigilance, in line with the legal obligations referenced above, and can be used by pharmacovigilance inspectors of the Member States.

Q17. We noted several reports listed as late. These reports contained both serious and non-serious adverse events, but only the non-serious adverse event(s) qualified the ICSR for submission to EV. Therefore, we considered these reports to be on-time.

A. If an ICSR contains serious and non-serious reactions, then it will be classed as a serious case. If you have events which are not related to the administration of the suspect/interacting drug, then they should not be reported in the Reaction section of an ICSR.

Q18. Should we be measuring downgrades in seriousness on receipt of follow up according to the 90-day timeline for post-marketing ICSRs?

A. As per GVP Module VI, chapter VI.C.3. Submission time frames of ICSRs in EU

"According to Article 107(3) and 107a(4) of Directive 2001/83/EC,

- serious valid ICSRs shall be submitted by the competent authority in a Member State or by the marketing authorisation holder within 15 days from the date of receipt of the reports;
- non-serious valid ICSRs shall be submitted by the competent authority in a Member State or by the marketing authorisation holder within 90 days from the date of receipt of the reports

This is referring to ICSRs, and so a downgraded non-serious ICSR is measured against a 90-day clock

Q19. Do we still need to report significant non-compliance (such as reporting obligations to EV which might impact on the safety profile of an authorised MP) now that the reporting compliance reports are being submitted?

A. Yes, you do still need to inform EMA about significant non-compliance, as detailed in the section "Compliance issues with pharmacovigilance obligations" on the Contacts at the European Medicines Agency webpage.

Q20 My MAH/Sponsor has not received any reports yet, why not?

A. For September, October & November 2025, only the 20 MAHs who sent the most ICSRs to Eudravigilance during the 12 months to May 2025, and all NCAs, will receive the notifications. This will be extended to cover all organisations from December 2025. If you have still not received a report from December 2025, see questions 2 & 4 of this document.