



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2017
EMA/306740/2017
Information Management Division

EudraVigilance checklist and technical support plan for Marketing Authorisation Holders and Sponsors of Clinical Trials in the EEA

In support of the go-live of the enhanced EudraVigilance System

Agreement by Pharmacovigilance Business Team	16 June 2017
Agreement by the EudraVigilance Expert Working Group	22 June 2017
IT Directors (for information)	26 June 2017
Pharmacovigilance Risk Assessment Committee (for information)	26 June 2017



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1. Introduction

Complimentary to the **EudraVigilance Stakeholder Change Management Plan** adopted through the pharmacovigilance governance (EMA/325783/2016) and published on the dedicated [EudraVigilance change management webpage](#), this document has been prepared to provide general testing instructions as well as a summary of easy to follow steps to assist marketing authorisation holders (MAHs) and sponsors of clinical trials (sponsors) in preparing for the go-live of the new EudraVigilance (EV) system on 22 November 2017.

In addition, **the ICH E2B(R3) Implementation Guide** and the **EU ICSR Implementation Guide** provide important guidance on how to apply the new ISO Individual Case Safety Report (ICSR) standard and how it should be used for the electronic reporting of suspected adverse reactions related to medicines in the European Economic Area (EEA). These documents can be accessed at EudraVigilance change management webpage: "[The new EudraVigilance database, where can I find detailed information and guidance?](#)"

Reference is also made to the **training and support offerings**, which are available at the dedicated [EudraVigilance training and support webpage](#), which provides detailed learnings on how to prepare for the changes to come.

Note:

- ***There will be no changes to the reporting of suspected unexpected serious adverse reactions during clinical trials¹ until the application of the [Clinical Trial Regulation](#).***
- ***Not all steps outlined in this checklist apply to sponsors of clinical trials but will only apply to MAHs in accordance with the new simplified reporting rules set out in the pharmacovigilance legislation.***

2. Technical Checklist

This chapter provides a summary of easy to follow steps to assist MAHs and sponsors in preparing for the technical changes in relation to the go-live of the new EudraVigilance (EV) system on 22 November 2017.

2.1. IT changes for the exchange of ICSRs and Acknowledgements

2.1.1. Gateway users

MAHs/sponsors that are using a local gateway connection to receive safety and acknowledgement messages electronically should prepare for the following:

- **June 2017:** Update the local pharmacovigilance/safety TEST system with the receiver identifiers that should be used in sending ICSR messages for processing by EVPM and EVCTM as described in section I.C.3.1.2 EudraVigilance Message Receiver Identifiers of the EU Individual Case Safety Report (ICSR) Implementation Guide.
- **June 2017:** Update the local pharmacovigilance/safety TEST system to be able to accept additional message types used for ICSRs that are downloaded from EudraVigilance for further

¹ 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 (OJ L 311, 28.11.2001, p. 67).

import into your local system as described in section I.C.3.1.1 Message Type of the EU Individual Case Safety Report (ICSR) Implementation Guide.

- **By 26 June 2017:** Update the gateway configuration in the XCOMP test environment based on the instructions provided below to ensure ICSRs can be transmitted to the new EudraVigilance system.

To set the destination of the safety and acknowledgement messages as the EudraVigilance gateway, you may need to include in your gateway configuration one of the following two XPATHs (direct or relative path) to be able to process E2B(R3) files correctly:

- Direct path:
Sender /MCCI_IN200100UV01/sender/device/id/@extension
Receiver /MCCI_IN200100UV01/receiver/device/id/@extension
- Relative path:
Sender /*/sender/device/id/@extension
Receiver /*/receiver/device/id/@extension

IMPORTANT:

- **These paths need to be added in addition to the existing E2B(R2) XPATHs so that you are able to process both E2B(R2) and E2B(R3) ICSRs.**
- There is **no change needed to the EV gateway certificates.**
- Note that the **E2B(R3) ICSRs file size can be up to 20Mb.**
- **Email servers used for AS1 connections might need their configurations updated in order to be able to process 20Mb ICSRs.**
- **June to November 2017:** Test your pharmacovigilance/safety system to receive ICSRs in the new ICH E2B(R3) format (via the download function of EVWEB):
 - a. Refer to the following e-learning modules:
 - ISO ICSR standard implementation for IT system developers (IT-M1):
<https://www.youtube.com/watch?v=pwA9nYO2VDQ>
 - ISO ICSR (E2B(R3)) system implementers workshop:
<https://www.youtube.com/playlist?list=PL7K5dNgKnawY00IFuSmY4V2zJFehB1BvT>
 - b. Refer to the ICH backwards and forwards conversion (BFC) tool available on the dedicated [EudraVigilance change management webpage](#) and the e-learning module:
 - [Implementing ISO ICSR/ICH E2B\(R3\): Backwards and forwards conversion](#) (PhV-M2b)

An example of a free to download program is MSXSL.exe. This program requires the use of a command line:

msxsl <file to be converted> <XSLT location> -o <file name of converted file>

Example:

msxsl "E2B(R3)_file.XML" downgrade-icsr.xsl -o "E2B(R2)_file_convert.xml"

- c. Refer to the 'EU reference instances' and 'EU example instances' available on the dedicated [EudraVigilance change management webpage](#) (see chapter 4.2. of this document) to obtain sample ICSRs for testing E2B(R3) transmissions to the EudraVigilance system.
- **By 26 June 2017:** Make sure that your technical experts are registered with EudraVigilance to have access to the XCOMP (test) environment. Existing users of the current EudraVigilance system will be automatically migrated to the new EudraVigilance system. However, existing users should check that their XCOMP userid and password are still valid by accessing the current XCOMP test environment. If the login credentials are no longer valid, the EudraVigilance Registration team should be contacted at EudraVigilanceRegistration@ema.europa.eu.
- **26 June 2017:** Start using the XCOMP test environment to access the new EudraVigilance functionalities and to start testing the processing of ICH E2B(R2) or(R3) messages as applicable. The new URL for the XCOMP environment is <https://eudravigilance-human-xcomp.ema.europa.eu>.
- **By 22 November 2017:** Update your local pharmacovigilance/safety PRODUCTION system with the receiver identifiers that should be used for sending ICSR messages for processing by the different EV modules, as described section I.C.3.1.2 EudraVigilance Message Receiver Identifiers of the EU Individual Case Safety Report (ICSR) Implementation Guide.
- **By 22 November 2017:** update your local pharmacovigilance/safety PRODUCTION system to accepted additional message types used for ICSRs that are downloaded from EudraVigilance for further import into your local system, as described section I.C.3.1.1 Message Type of the EU Individual Case Safety Report (ICSR) Implementation Guide.
- **By 22 November 2017:** Make sure that your experts are registered with EudraVigilance have access to the PRODUCTION environment. For the registration of new users in PRODUCTION, please follow the registration steps as outlined at the dedicated webpage [EudraVigilance: how to register](#). Existing users of the current EudraVigilance system will be automatically migrated to the new EudraVigilance system. However, existing users should check that their userid and password are still valid by accessing the current PRODUCTION environment. If they are no longer valid, the EudraVigilance Registration team should be contacted at EudraVigilanceRegistration@ema.europa.eu. Please also check that the functional e-mail address and e-mail address of the Qualified Person for Pharmacovigilance (QPPV) or appointed deputy are still correct.
- **22 November 2017 onwards:** Use the new EVWEB functionalities in the EudraVigilance PRODUCTION environment. The new URL for the PRODUCTION environment is <https://eudravigilance-human.ema.europa.eu>.
- **22 November 2017 onwards:** ensure compliance with security and confidentiality principles as published on the dedicated webpage [EudraVigilance: security principles and responsibilities](#).

2.1.2. EVWEB users

MAHs that are using EVWEB to receive safety and acknowledgement messages electronically should prepare for the following:

- **By 26 June 2017:** Make sure that your experts are registered with EudraVigilance to have access to the XCOMP (test) environment. For the registration of new users in the XCOMP test environment, follow the registration steps as outlined at the dedicated webpage [EudraVigilance: how to register](#). Existing users of the current EudraVigilance system will be automatically migrated to the new EudraVigilance system. However, existing users should check that their XCOMP userid and password are still valid by accessing the current XCOMP test environment. If the login credentials are no longer valid, the EudraVigilance Registration team should be contacted at EudraVigilanceRegistration@ema.europa.eu.
- **26 June 2017:** Use the XCOMP (test) environment to access the new EudraVigilance functionalities in EVWEB. The new URL for the XCOMP environment is <https://eudravigilance-human-xcomp.ema.europa.eu>.
- **By 22 November 2017:** Make sure that your experts are registered with EudraVigilance have access to the PRODUCTION environment. For the registration of new users in PRODUCTION, please follow the registration steps as outlined at the dedicated webpage [EudraVigilance: how to register](#). Existing users of the current EudraVigilance system will be automatically migrated to the new EudraVigilance system. However, existing users should check that their userid and password are still valid by accessing the current PRODUCTION environment. If they are no longer valid, the EudraVigilance Registration team should be contacted at EudraVigilanceRegistration@ema.europa.eu. Please also check that the functional e-mail address and e-mail address of the Qualified Person for Pharmacovigilance (QPPV) or appointed deputy are still correct.
- **22 November 2017 onwards:** Use the new EVWEB functionalities of the EudraVigilance PRODUCTION environment. The new URL for the PRODUCTION environment is <https://eudravigilance-human.ema.europa.eu>.
- **22 November 2017 onwards:** ensure compliance with security and confidentiality principles as published on the dedicated webpage [EudraVigilance: security principles and responsibilities](#).

2.2. Signal Management and Data Analysis

2.2.1. EVDAS users (MAHs only)

- **22 November 2017 onwards:** Use the new EVDAS functionalities in the PRODUCTION environment. The URL for the EVDAS Production environment is <https://bi.ema.europa.eu>.
- **By November 2017:** Make sure that you have registered your EVDAS users within the allocated time slot.
 - Follow the phased registration approach and the registration steps as outlined on the dedicated webpage [EudraVigilance: how to register](#).
- **22 November 2017 onwards:** Start using EVDAS in line with the principles set out in the pharmacovigilance legislation and the [Guideline on good pharmacovigilance practices \(GVP\)](#) module IX "Signal Management".

- **22 November 2017 onwards:** ensure compliance with security and confidentiality principles as published on the dedicated webpage [EudraVigilance: security principles and responsibilities](#).

3. Business process checklist

This chapter provides a summary of easy to follow steps to assist MAHs in preparing for the business process changes in relation to adverse reaction reporting and/or signal management as of 22 November 2017.

There will be no changes to the reporting of suspected unexpected serious adverse reactions during clinical trials until the application of the Clinical Trial Regulation.

As of 22 November 2017 onwards, the following business process changes apply:

- MAHs need to submit electronically to EVPM information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the MAH concerned gained knowledge of the event. In practice this applies to the reporting of serious suspected adverse reactions of which the MAH gained knowledge on 22 November 2017 and thereafter. MAHs should therefore stop sending ICSRs to the national competent authorities (NCAs) as of 22 November 2017. Detailed guidance will be provided as part of the go-live plan.
- MAHs need to submit electronically to EVPM information on all non-serious suspected adverse reactions that occur in the Union, within 90 days following the day on which the MAH concerned gained knowledge of the event. In practice this applies to the reporting of non-serious suspected adverse reactions that occur in the EEA and of which the MAH gained knowledge on 22 November 2017 and thereafter. Detailed guidance will be provided as part of the go-live plan.
- MAHs need to use EVWEB functionalities to obtain access and to download reports of suspected adverse reactions which are reported by NCAs to EudraVigilance.
- MAHs need to access EVDAS to the extent necessary to comply with their pharmacovigilance obligations.
- MAHs need to comply with the provisions set out in [Guideline on good pharmacovigilance practices](#): Module VI – Management and reporting of adverse reactions to medicinal products. Revision 2 is planned to be adopted and published on the EMA website in July 2017.
- MAHs need to comply with the provisions set out in [Guideline on good pharmacovigilance practices](#): Module IX – Signal management Revision 1 is planned to be adopted and published on the EMA website in October 2017.
- MAHs and sponsors need to ensure they comply with [security and confidentiality principles](#) that stakeholders using EudraVigilance need to comply with, as published on the EV webpages on EMA website.

Ongoing and continuing:

- MAHs and sponsors of clinical trials need to ensure that the medicinal product data recorded in the Article 57 (XEVMPD) database are correct and kept up to date.

4. Testing instructions

In accordance with the implementation roadmap (chapter 5.1 of the [EudraVigilance Stakeholder Change Management Plan](#)), the release of the new XCOMP (test) environment will take place on 26 June 2017.

From this date onward, the XCOMP environment can be used by MAHs or sponsors for testing of their local pharmacovigilance/safety IT system and the interoperability with the new EudraVigilance system or for familiarisation with the new EVWEB interface.

4.1. Testing of electronic exchange of ICSRs in E2B(R2) format

Where the electronic submission of ICSRs to EudraVigilance is already established, it is important to perform the Gateway configuration and communication testing (refer to chapter I.C.2.1.5.2 of the EU ICSR Implementation Guide) in advance of the go-live of the new EudraVigilance system on 22 November 2017.

E2B(R2) test files should be submitted to the XCOMP environment to ensure that the files can be received and processed correctly by EudraVigilance. In addition, the acknowledgement messages returned by the XCOMP environment should be reviewed by MAHs or Sponsors of clinical trials to ensure that there are no errors.

If MAHs or sponsors continue to use established E2B(R2) systems, they should use the E2B(R3) test files available for download from the XCOMP environment and test the upload of the files in their local pharmacovigilance/safety system with a BFC solution.

MAHs or sponsors do not need to contact the EMA for the purpose of this testing. EMA should only be contacted if issues are encountered (see chapter 7).

E2B(R2) test files are made available by the EMA for reference, the sample files and scripts for E2B(R2) ICSRs/ACKs testing include the following scenarios:

1. Fatal report with cause of death and autopsy sections filled in
2. A follow up report (sent in after the initial report)
3. A report including patient medical and drug history
4. A parent child report
5. A nullification report
6. A report where the worldwide unique safety report number (A.1.10) is either a Regulatory authority's case report number (A.1.10.1) or a Other sender's case report number (A.1.10.2) that is different from the sender's safety report unique identifier (A.1.0.1)
7. A non-intervention study (observational) report sent to EVPM (Receiver ID EVTEST)
8. If applicable to the organisation an interventional study (Clinical Trial phase I-IV) report sent to EVCTM (Receiver ID EVCTMTEST)
9. A case reported in the literature
10. A report with the section report duplicate (A.1.11.1) completed

Test files are published on the dedicated webpage [EudraVigilance: electronic reporting](#) (Step 5a: XML test phase for organisations using the E2B(R2) format).

If the electronic submission of ICSRs to EudraVigilance is to be initiated for the first time by MAHs or sponsors still using the E2B(R2) format, the instructions published on the webpage [EudraVigilance: electronic reporting](#) should be followed.

A specific testing time slot can be booked from 26 June 2017 by contacting EMA at gattesting@ema.europa.eu.

4.2. Testing of electronic exchange of ICSRs in E2B(R3) format

MAHs or Sponsors of Clinical trials should perform testing in line with chapter I.C.2.1.5 System testing requirements of the EU ICSR Implementation Guide.

As the electronic submission of ICSRs to EudraVigilance will be initiated for the first time by MAHs or sponsors using the E2B(R3) format, the instructions published on the webpage [EudraVigilance: electronic reporting](#) should be followed. A specific testing time slot can be booked from 26 June 2017 by contacting EMA at gattesting@ema.europa.eu.

However, ahead of this dedicated testing with EMA, MAHs or Sponsors of Clinical trials can already perform preliminary testing of the electronic submission of ICSRs to the EudraVigilance XCOMP test environment in E2B (R3) format. E2B(R3) test files are being made available below by the EMA for reference, the sample files and scripts for E2B(R3) ICSRs/ACKs testing include the following scenarios:

1. Initial and follow-up
2. Patient death
3. Parent/child
4. Past drug / past medical history / Test results
5. Advanced therapies (device component)
6. Product name parts
7. Clinical trial SUSAR
8. Observational studies
9. Literature report with article attached

Test files are published on the dedicated webpage [EudraVigilance: electronic reporting](#) (Step 5b: XML test phase for organisations using the E2B(R3) format).

5. Stakeholder Communication

- Establish internal and external communication plans to facilitate the communication within your organisation and business/contractual partners, who will be affected by the changes to come.

6. Training and support

- MAHs/sponsors should follow the learning pathway recommended by EMA:
 - **Introduction to EMA's training offering (PhV-M0):**
(<https://www.youtube.com/watch?v=qvHZrmfZj80&feature=youtu.be>)
- MAHs/sponsors should consider attending face to face trainings and Information Days organised by EMA as applicable to them and as announced at the dedicated webpage [EudraVigilance training and support](#).
- MAHs/sponsors should attend support webinars organised by EMA as announced at the dedicated [EudraVigilance training and support](#) webpage.

7. Questions and enquiries

- If you have pharmacovigilance/clinical trials reporting questions and other general enquiries: [Send a question to the European Medicines Agency](#)
- If you require technical support using EudraVigilance and the gateway/web client contact the: [EMA IT Service Desk](#) Tel. +44 (0)20 3660 7523