EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Preparing for the simplified reporting of suspected adverse reactions in the EU

Training Module PhV-M3

Instructions on how to prepare for the simplified reporting of suspected adverse reactions in the EU which becomes effective six months following the announcement of the successful outcome of the audit of EudraVigilance

Sabine Brosch, Monitoring and Incident Management, Pharmacovigilance Department

An agency of the European Union

Version 1.0

Overview Module PhV-M3

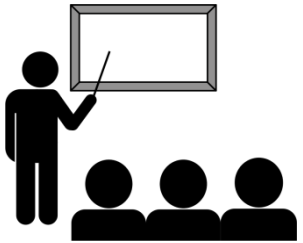
- Introduction to this training module
- What are the legal basis and benefits for the simplified reporting of suspected adverse reactions?
- What are the interim reporting arrangements?
- What are the final arrangements for the simplified reporting of suspected adverse reactions?
- What are key principles that should be taken into account?
- How can I get supporting information?

Overview Module PhV-M3

- Introduction to this training module
- What are the legal basis and benefits for the simplified reporting of suspected adverse reactions?
- What are the interim reporting arrangements?
- What are the final arrangements for the simplified reporting of suspected adverse reactions?
- What are key principles that should be taken into account?
- How can I get supporting information?

Introduction: Context PhV-M3

- Target audience for this training module:
  - National Competent Authorities (NCAs) in the European Economic Area (EEA)
  - Marketing authorisation holders (MAHs)
  - World Health Organisation – Uppsala Monitoring Centre (WHO-UMC)



Introduction: Learning Objectives

- At the end of module PhV-M3 you should be able to:
  - Describe the legal basis and the benefits for the simplification of the reporting of suspected adverse reactions based on the 2010 pharmacovigilance legislation
  - Recognise the current interim arrangements
  - Describe the process of simplified reporting of suspected adverse reactions
  - Recognise important principles in the context of simplified reporting
  - Understand where to obtain supporting information and whom to contact in case of further questions

Overview Module PhV-M3

- Introduction to this training module
- **What are the legal basis and benefits for the simplified reporting of suspected adverse reactions?**
- What are the interim reporting arrangements?
- What are the final arrangements for the simplified reporting of suspected adverse reactions?
- What are key principles that should be taken into account?
- How can I get supporting information?

Session overview: the legal basis and benefits for the simplified reporting of suspected adverse reactions

In this session you will obtain an understanding of:

- The legal background and benefits for the simplification of reporting of suspected adverse reactions for medicines authorised in the EU

Legal Background

- A simplified approach towards the reporting of suspected adverse reactions related to medicines authorised in the EU was introduced with the 2010 pharmacovigilance legislation (Articles 107(3) and 107a(4) of Directive 2001/83/EC)
- The simplified adverse reaction reporting will apply six months following the announcement by the Management Board of the Agency that based on an independent audit report, the EudraVigilance database has achieved full functionality (Article 24(2) of Regulation (EC) No 726/2004)
- Ad interim, the adverse reaction reporting is based on the provisions set out in Article 2(4), Article 2(5) and Article 2(6) of Directive 2010/84/EU and in line with national legislation and guidance where applicable

Legal Background

- The reporting obligations are further detailed in the Guideline on good pharmacovigilance practices: Module VI – Management and reporting of adverse reactions to medicinal products, chapter "VI.C.4.1. Interim arrangements" and chapter VI.C.4.2. "Final arrangements"

HMA Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH

8 September 2014
EMA/873138/2011 Rev 1*

Guideline on good pharmacovigilance practices (GVP)
Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1)

Date for coming into effect of first version	2 July 2012
Draft Revision 1* finalised by the Agency in collaboration with Member States	28 May 2013
Draft Revision 1 agreed by ERMS FG	29 May 2013
Draft Revision 1 adopted by Executive Director	6 June 2013
Released for public consultation	7 June 2013
End of consultation (deadline for comments)	5 August 2013
Revised draft Revision 1 finalised by the Agency in collaboration with Member States	16 July 2014
Revised draft Revision 1 agreed by ERMS FG	31 August 2014
Revised draft Revision 1 adopted by Executive Director as final	8 September 2014
Date for coming into effect of Revision 1 Note: New requirements for non-interventional post-authorisation studies will become mandatory for any new study started after 1 January 2015. Implementation for new or ongoing studies started before that date is optional.	16 September 2014

* Note: Revision 1 contains the following:

- Revisions in VI.A.2.1.1. (Causality), VI.A.2.4. (Seriousness), VI.B.1.2. (Solicited reports), VI.B.3. (Follow-up of reports), VI.B.6.3. (Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure), VI.C.1. (Reporting rules for clinical trials and post-authorisation studies in the EU), VI.C.2.2.2. (Solicited reports), VI.C.6.2.3.7. (Reports of suspected adverse reactions originating from organised data collection systems and other systems);
- Clarifications on the clock start for the reporting of valid ICSRs in VI.B.7.;
- Clarifications on the handling of ICSRs when reported in an official language in VI.C.6.2.2.9.;
- Replacements of tables highlighting interim arrangements applicable to marketing authorisation holders in VI.App.3.1.1.;
- Correction in VI.C.2.2.9. (Period during a public health emergency).

See websites for contact details

European Medicines Agency www.ema.europa.eu
Heads of Medicines Agencies www.hma.eu

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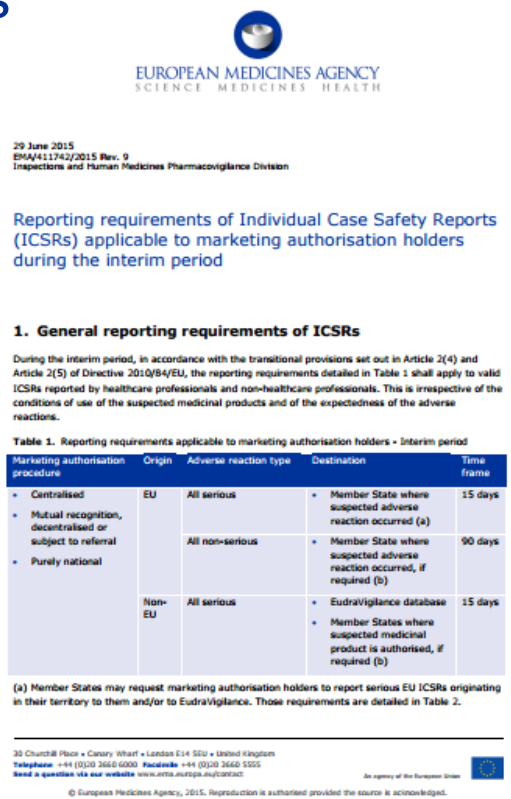
Legal Background –interim arrangements

- The interim reporting obligations are further detailed in the document Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim period (EMA/411742/2015 Rev. 9)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

29 June 2015
EMA/411742/2015 Rev. 9
Inspections and Human Medicines Pharmacovigilance Division

Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim period

1. General reporting requirements of ICSRs

During the interim period, in accordance with the transitional provisions set out in Article 2(4) and Article 2(5) of Directive 2010/84/EU, the reporting requirements detailed in Table 1 shall apply to valid ICSRs reported by healthcare professionals and non-healthcare professionals. This is irrespective of the conditions of use of the suspected medicinal products and of the expectedness of the adverse reactions.

Table 1. Reporting requirements applicable to marketing authorisation holders - Interim period

Marketing authorisation procedure	Origin	Adverse reaction type	Destination	Time frame
• Centralised • Mutual recognition, decentralised or subject to referral • Purely national	EU	All serious	• Member State where suspected adverse reaction occurred (a)	15 days
		All non-serious	• Member State where suspected adverse reaction occurred, if required (b)	90 days
	Non-EU	All serious	• EudraVigilance database • Member States where suspected medicinal product is authorised, if required (b)	15 days

(a) Member States may request marketing authorisation holders to report serious EU ICSRs originating in their territory to them and/or to EudraVigilance. Those requirements are detailed in Table 2.

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Benefits

- Simultaneously receive, access and share pharmacovigilance information for medicinal products for human use authorised in the EU by means of EudraVigilance
- EudraVigilance serves as single point of submission of reports of suspected adverse reactions by marketing authorisation holders
- Same rules on suspected adverse reaction recording and reporting for medicinal products independent of the authorisation procedure of the medicinal product
- Harmonised format and standard for ICSR reporting in the EEA (including business rules)
- Reduced efforts in data management

Session overview: the legal basis and benefits for the simplified reporting of suspected adverse reactions

In this session you obtained an understanding of:

- The legal background and benefits for the simplification of reporting of suspected adverse reactions for medicines authorised in the EU

Overview Module PhV-M3

- Introduction to this training module
- What are the legal basis and benefits for the simplified reporting of suspected adverse reactions?
- **What are the interim reporting arrangements?**
- What are the final arrangements for the simplified reporting of suspected adverse reactions?
- What are key principles that should be taken into account?
- How can I get supporting information?

Session overview: interim reporting arrangements

In this session you will obtain an understanding of:

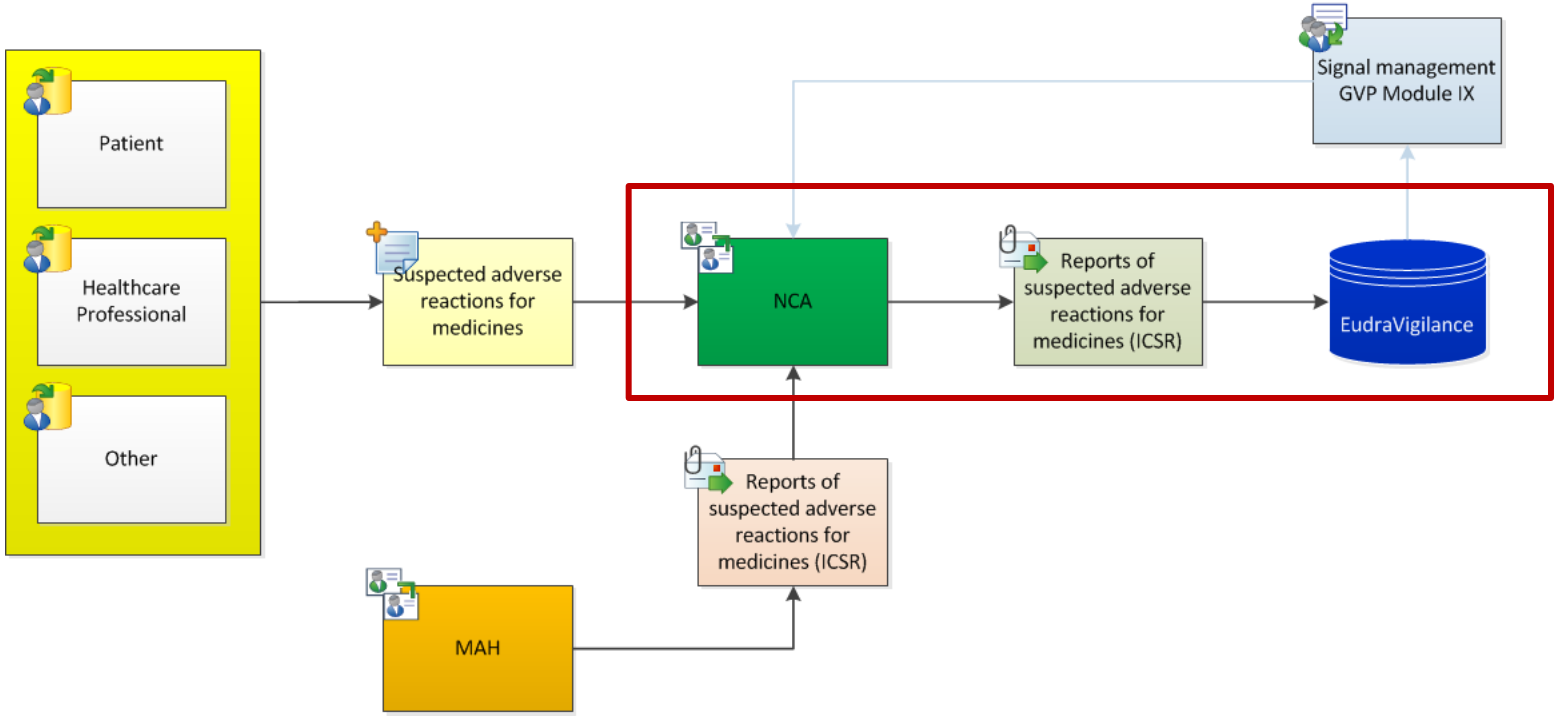
- The current interim reporting arrangements of suspected adverse reactions related to medicines

NCAs - interim reporting arrangements (1a)

- NCAs ensure that all serious ICSRs that occur in their territory and that are reported to them, including those received from marketing authorisation holders, are made available to EudraVigilance within 15 days of the notification of suspected serious adverse reactions

Reference: Article 2(4), Article 2(5) and Article 2(6) of Directive 2010/84/EU
GVP Module VI, chapter VI.C.4.1. Interim arrangements

NCAs - Interim reporting arrangements (1a)

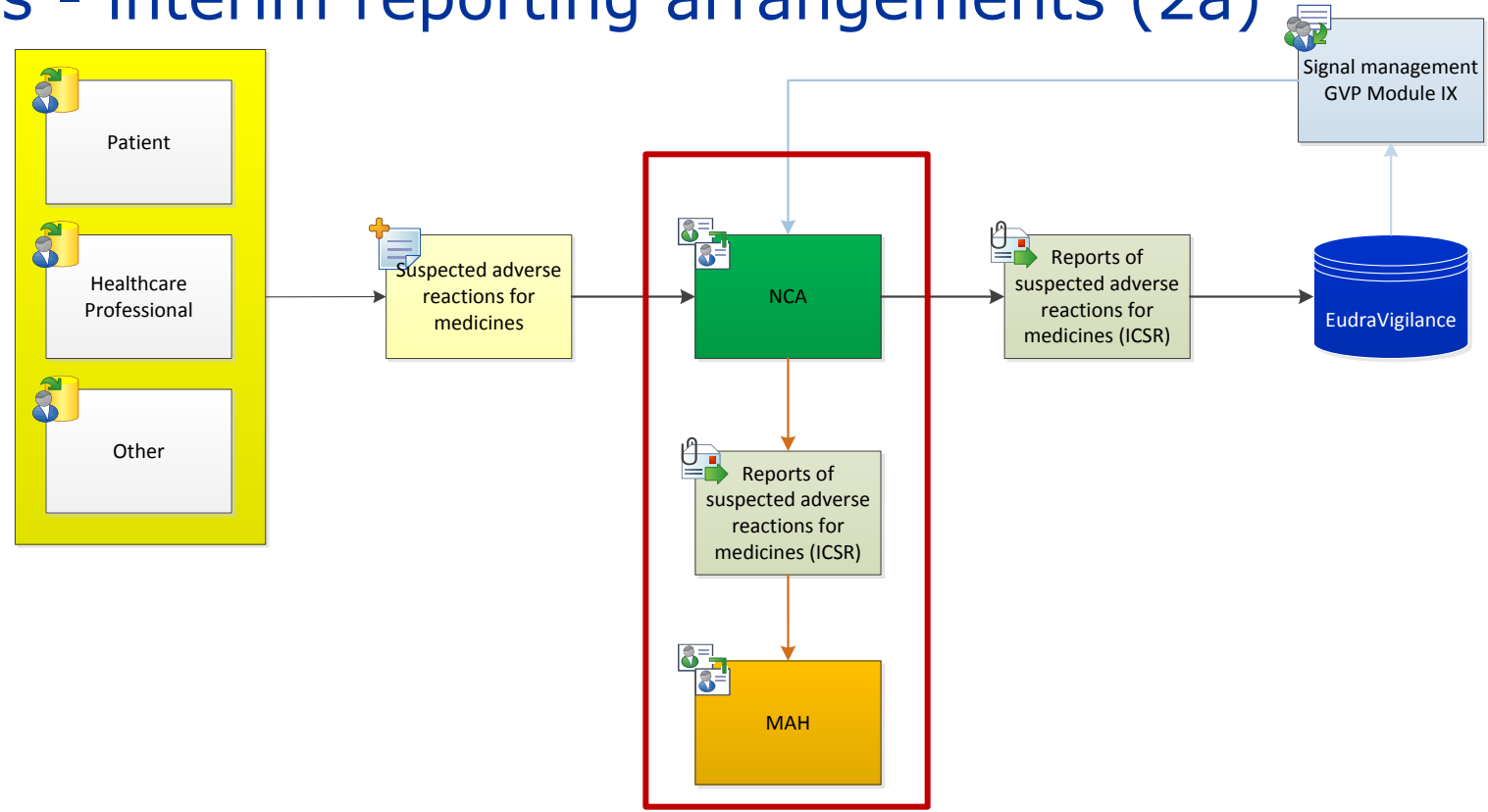


NCAs - interim reporting arrangements (2a)

- Competent authorities in Member States make available, to the marketing authorisation holders of the suspected medicinal products, all serious ICSRs reported directly to them

Reference: Article 2(4), Article 2(5) and Article 2(6) of Directive 2010/84/EU
GVP Module VI, chapter VI.C.4.1. Interim arrangements

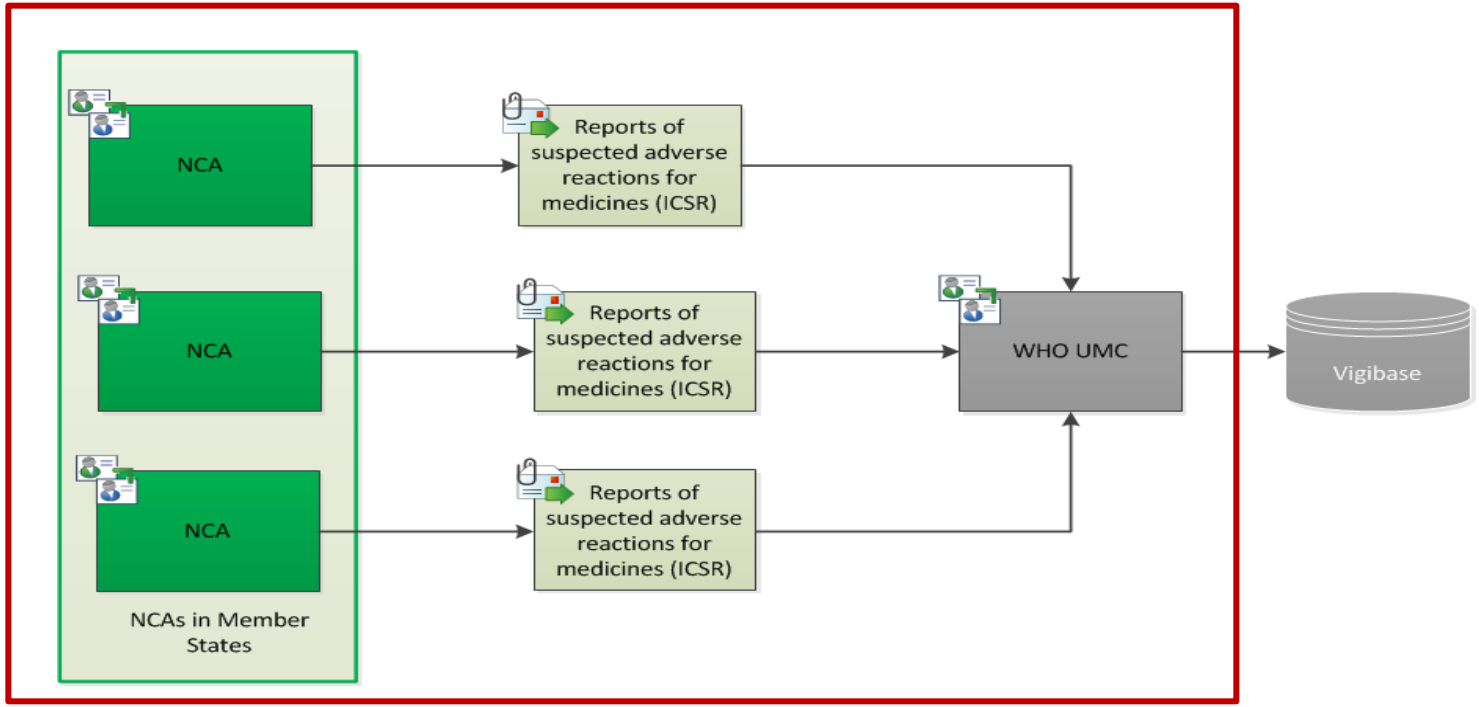
NCAs - interim reporting arrangements (2a)



NCAs - interim reporting arrangements (3a)

- NCAs make reports of suspected adverse reactions that occur in their territory and that are reported to them to the WHO UMC

NCAs - interim reporting arrangements (3a)

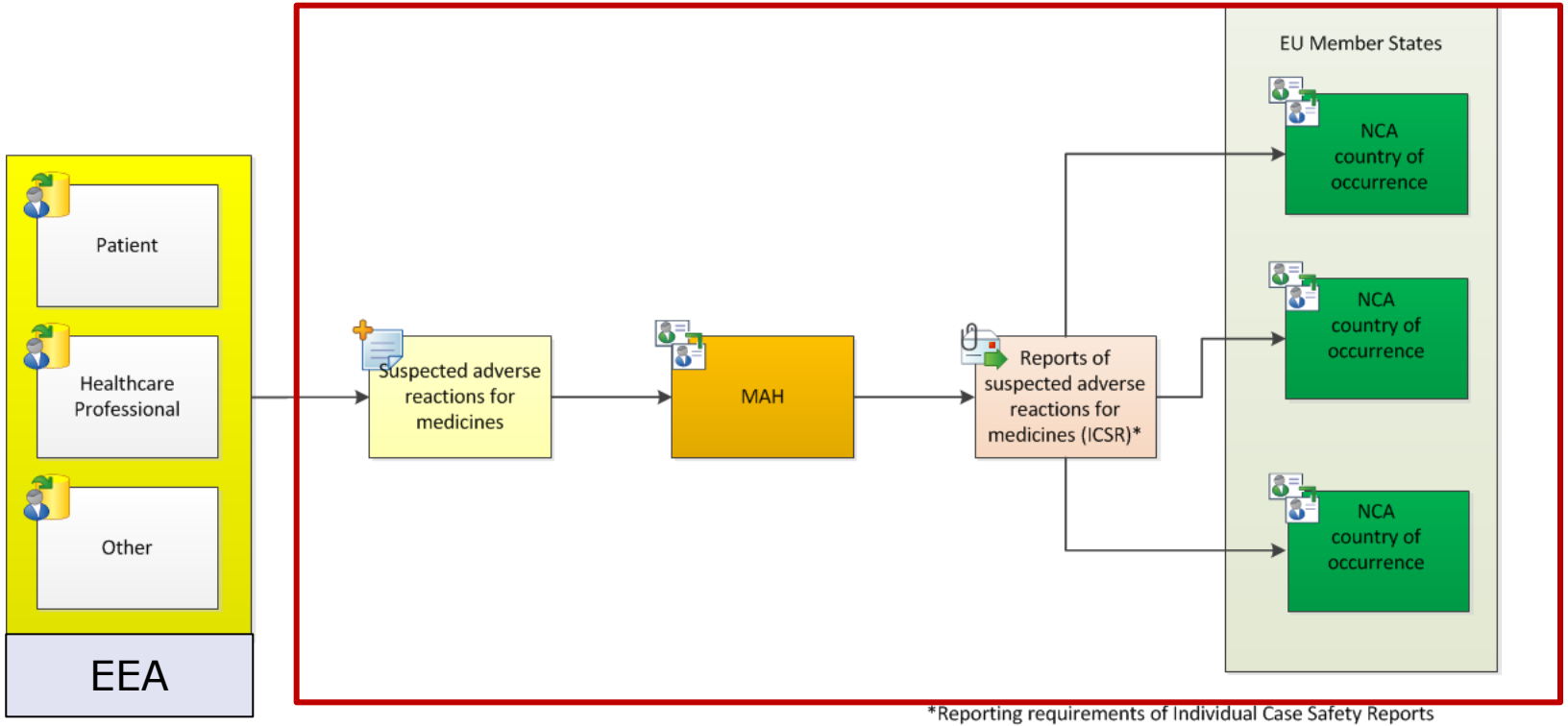


MAHs - interim reporting arrangements (4a)

- MAHs report all serious ICSRs that occur in the EU to the competent authority of the Member State on whose territory the suspected adverse reactions occurred, within 15 days of the day on which the holder concerned gained knowledge
- If required by Member States, marketing authorisation holders report all non-serious ICSRs that occur in the EU to the competent authority of the Member State on whose territory the suspected adverse reactions occurred

Reference: Article 2(4), Article 2(5) and Article 2(6) of Directive 2010/84/EU
GVP Module VI, chapter VI.C.4.1. Interim arrangements

MAHs - interim reporting arrangements (4a)



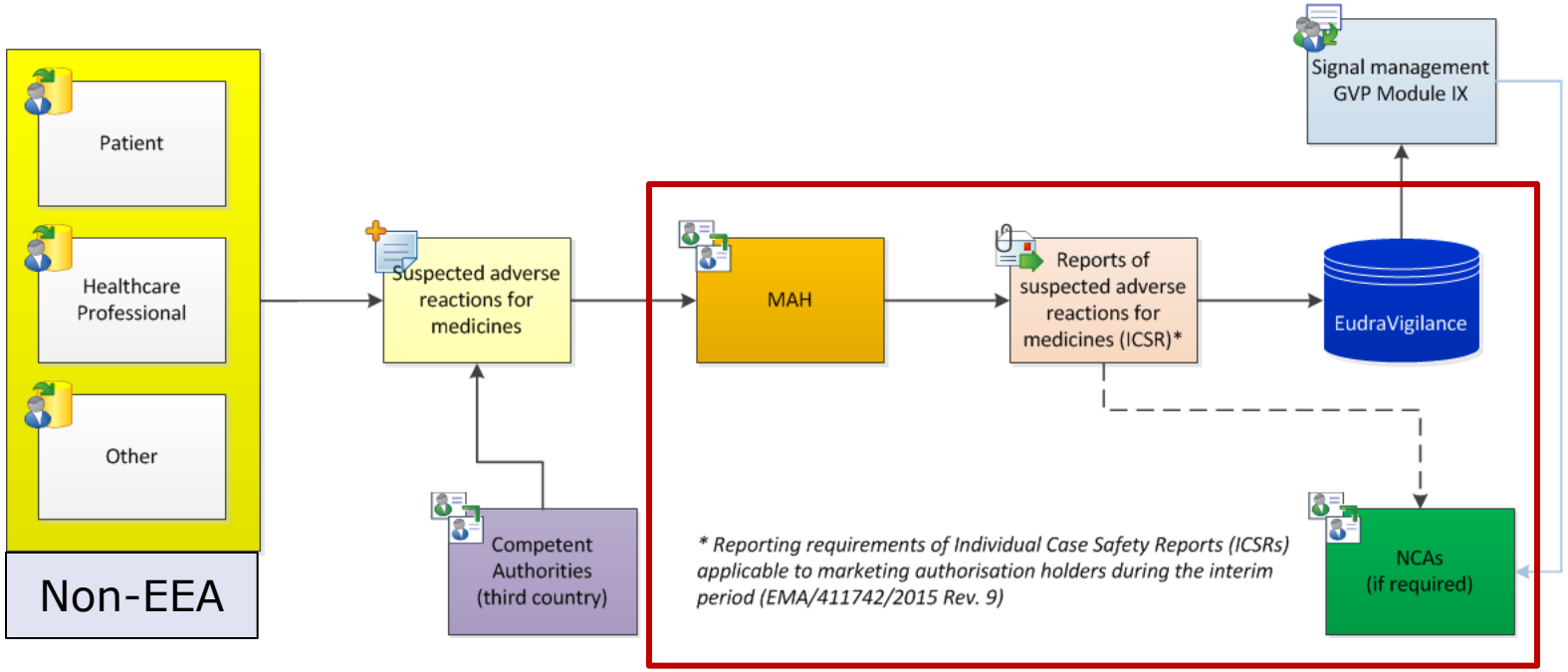
*Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim period (EMA/411742/2015 Rev. 9)

MAHs - interim reporting arrangements (4b)

- MAHs to report to the EudraVigilance database all serious ICSRs that occur outside the EU, including those received from competent authorities, within 15 days of the day on which the holder concerned gained knowledge
- Note: if required by Member States, those reports shall also be submitted to the competent authorities in the Member States in which the medicinal product is authorised

Reference: Article 2(4), Article 2(5) and Article 2(6) of Directive 2010/84/EU
GVP Module VI, chapter VI.C.4.1. Interim arrangements

MAHs - interim reporting arrangements (4b)

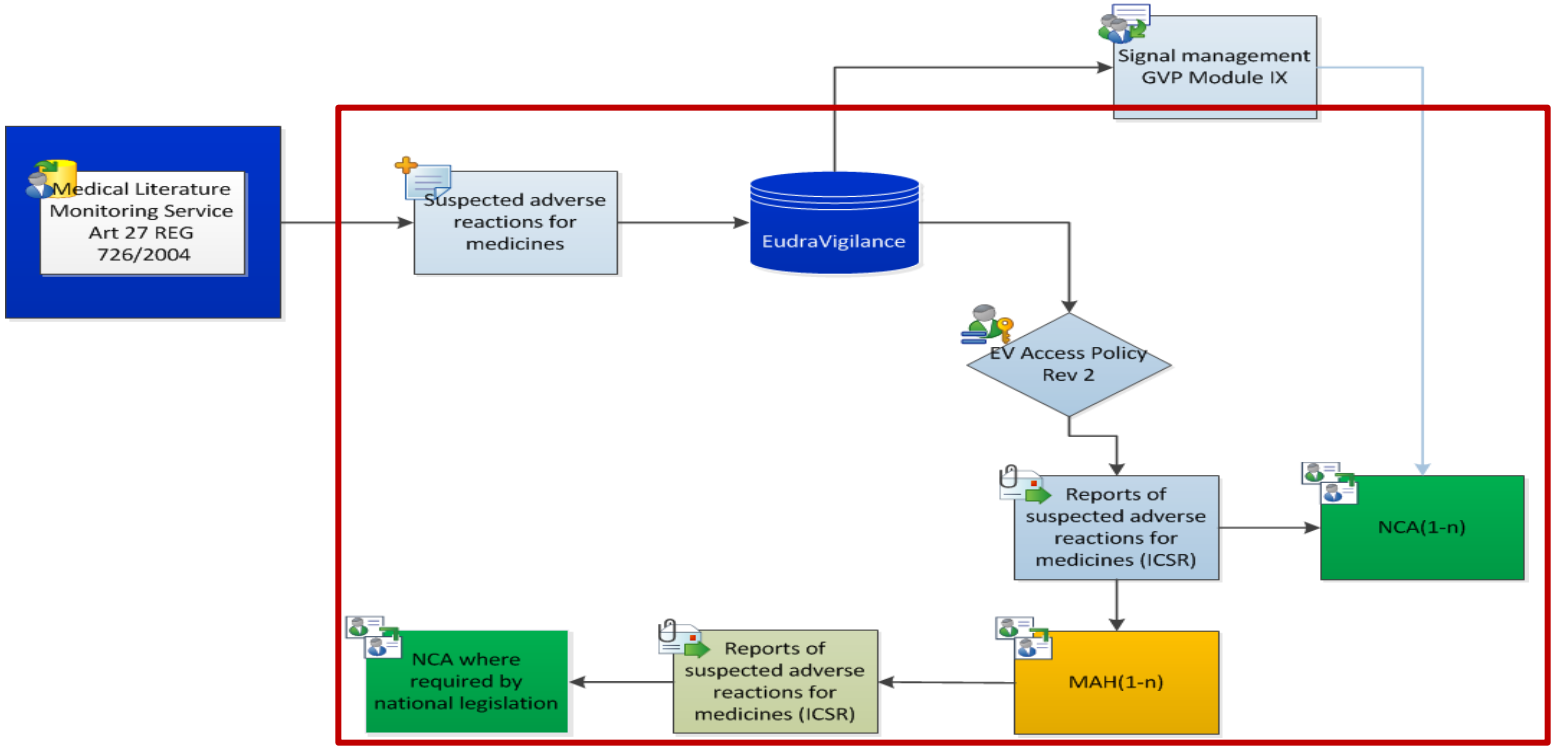


MAHs interim reporting arrangements (5a)

- 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.
- *Unless otherwise specified by national legislation and guidance*, concerned marketing-authorisation holders should not submit the ICSRs resulting from the medical literature monitoring service to the concerned national competent authorities in the EEA.

Reference: Article 27 of Regulation 726/2004

MAHs interim reporting arrangements (5b)



Session overview: interim reporting arrangements

In this session you obtained an understanding of:

- The current interim reporting arrangements of suspected adverse reactions related to medicines

Overview Module PhV-M3

- Introduction to this training module
- What are the legal basis and benefits for the simplified reporting of suspected adverse reactions?
- What are the interim reporting arrangements?
- **What are the final arrangements for the simplified reporting of suspected adverse reactions?**
- What are key principles that should be taken into account?
- How can I get supporting information?

Session overview: final reporting arrangements

In this session you will obtain an understanding of:

- The simplified reporting arrangements of suspected adverse reactions related to medicines

Note: simplified reporting applies to all EEA Member States, including Iceland, Liechtenstein and Norway.

NCAs final reporting arrangements (1a)

- Within 15 days following the receipt of reports of serious suspected adverse reactions, Member States need to submit the reports electronically to EudraVigilance
- Within 90 days from the receipt of reports of non-serious suspected adverse reactions, Member States need to submit the reports electronically to EudraVigilance
- Marketing authorisation holders have to access those reports through EudraVigilance

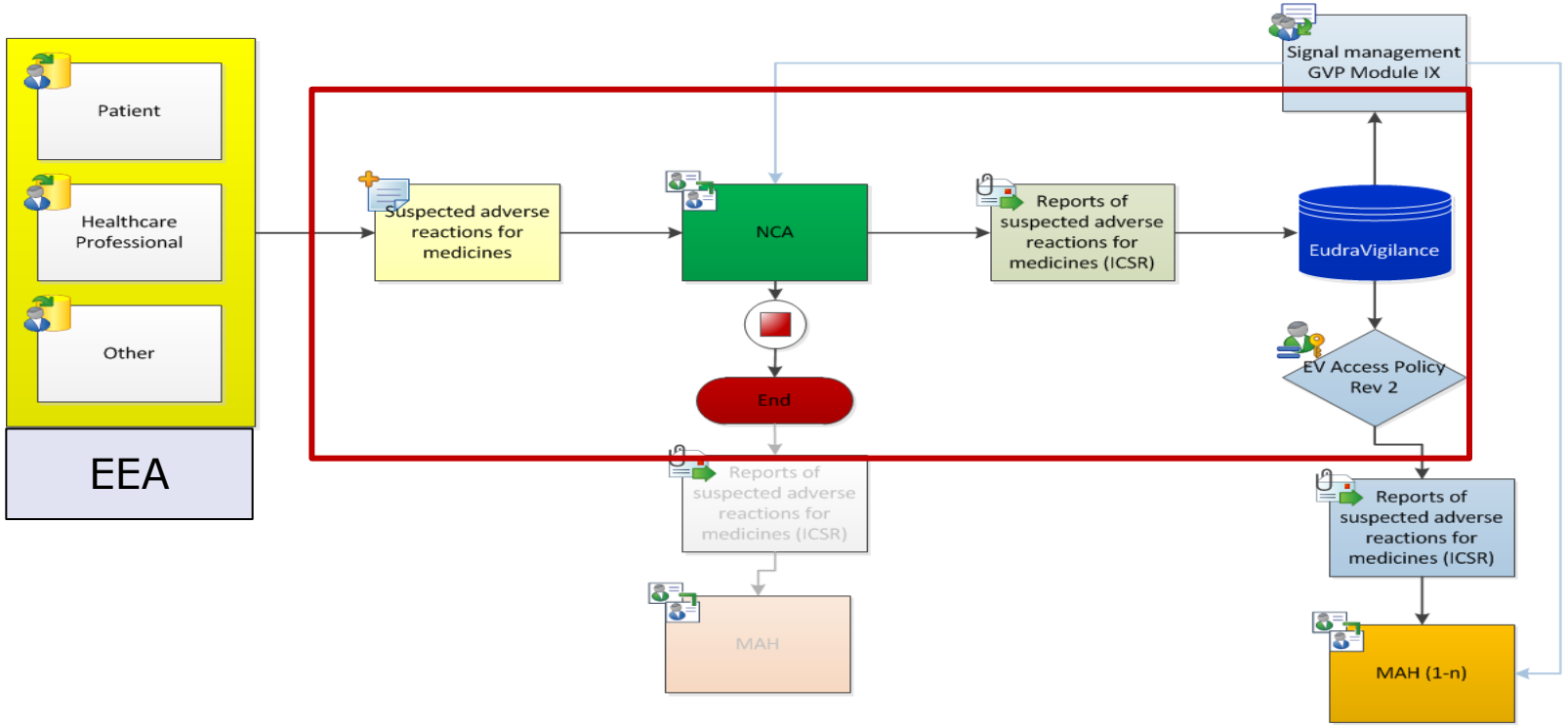
Reference: Article 107(4) of Directive 2001/83/EC

NCAs final reporting arrangements (1a contd)

- Member States shall ensure that reports of suspected adverse reactions arising from an error associated with the use of a medicinal product that are brought to their attention are made available to EudraVigilance…..

Reference: Article 107(5) of Directive 2001/83/EC

NCAs final reporting arrangements (1a)

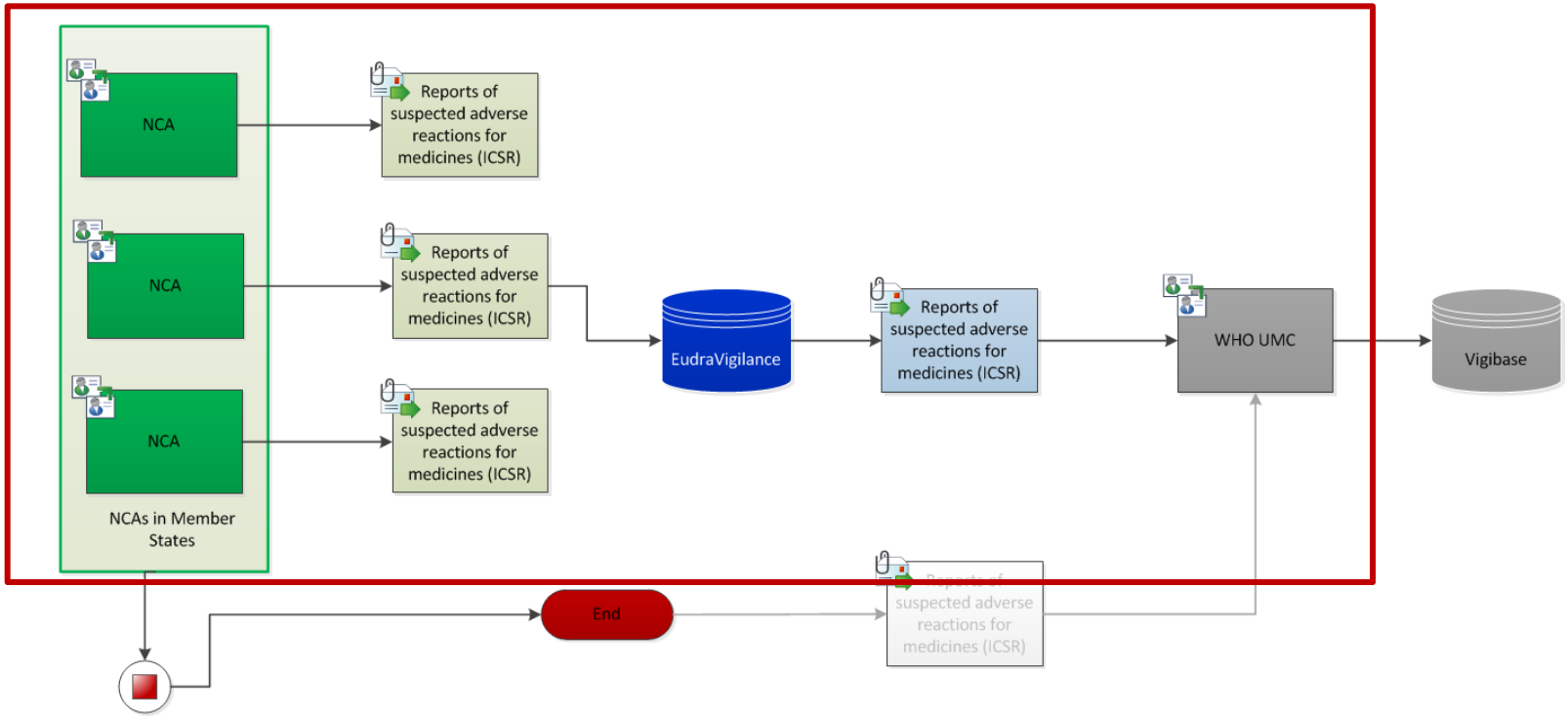


WHO-UMC final reporting arrangements (2a)

- The Agency has to make available promptly all suspected adverse reaction reports occurring in the Union to the World Health Organisation.

Reference: Article 28c(1) of Regulation 726/2004

WHO-UMC final reporting arrangements (2a)

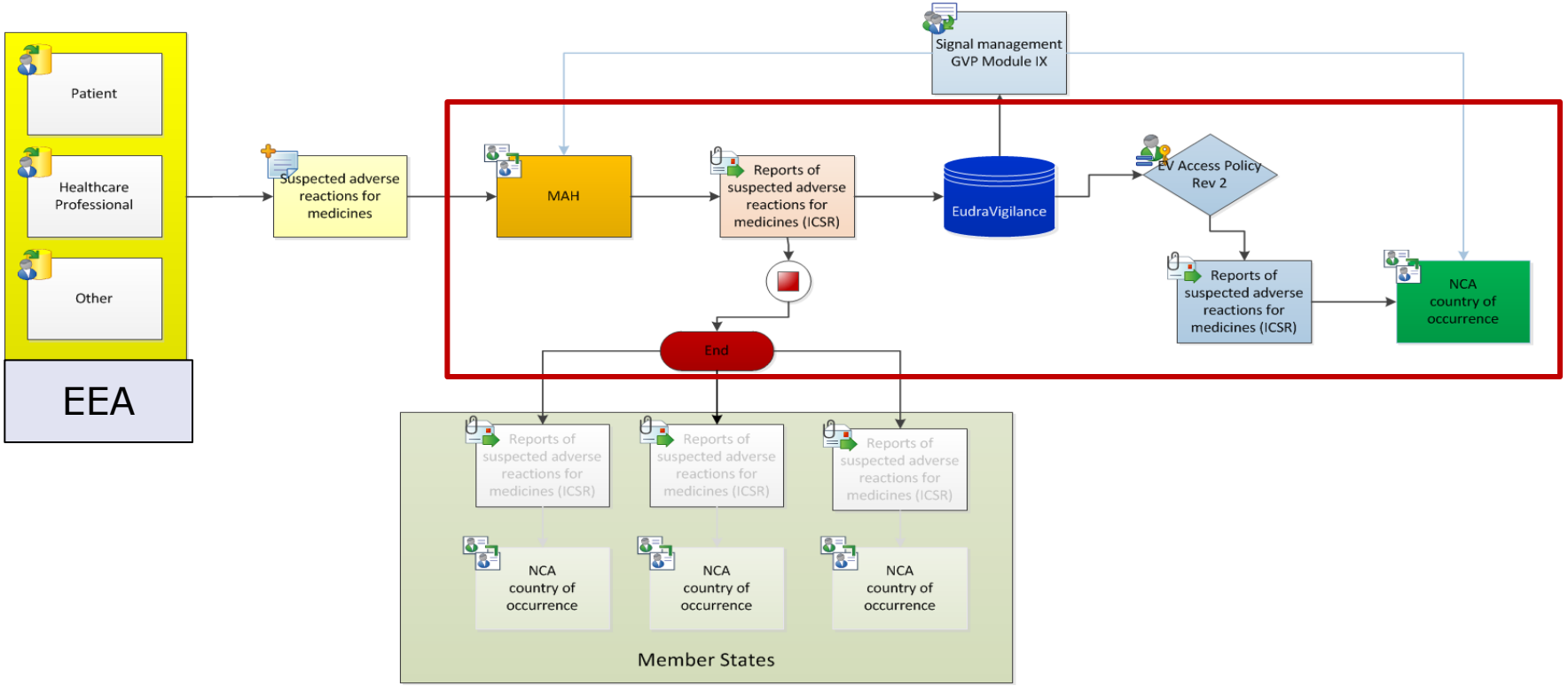


MAHs final reporting arrangements (3a)

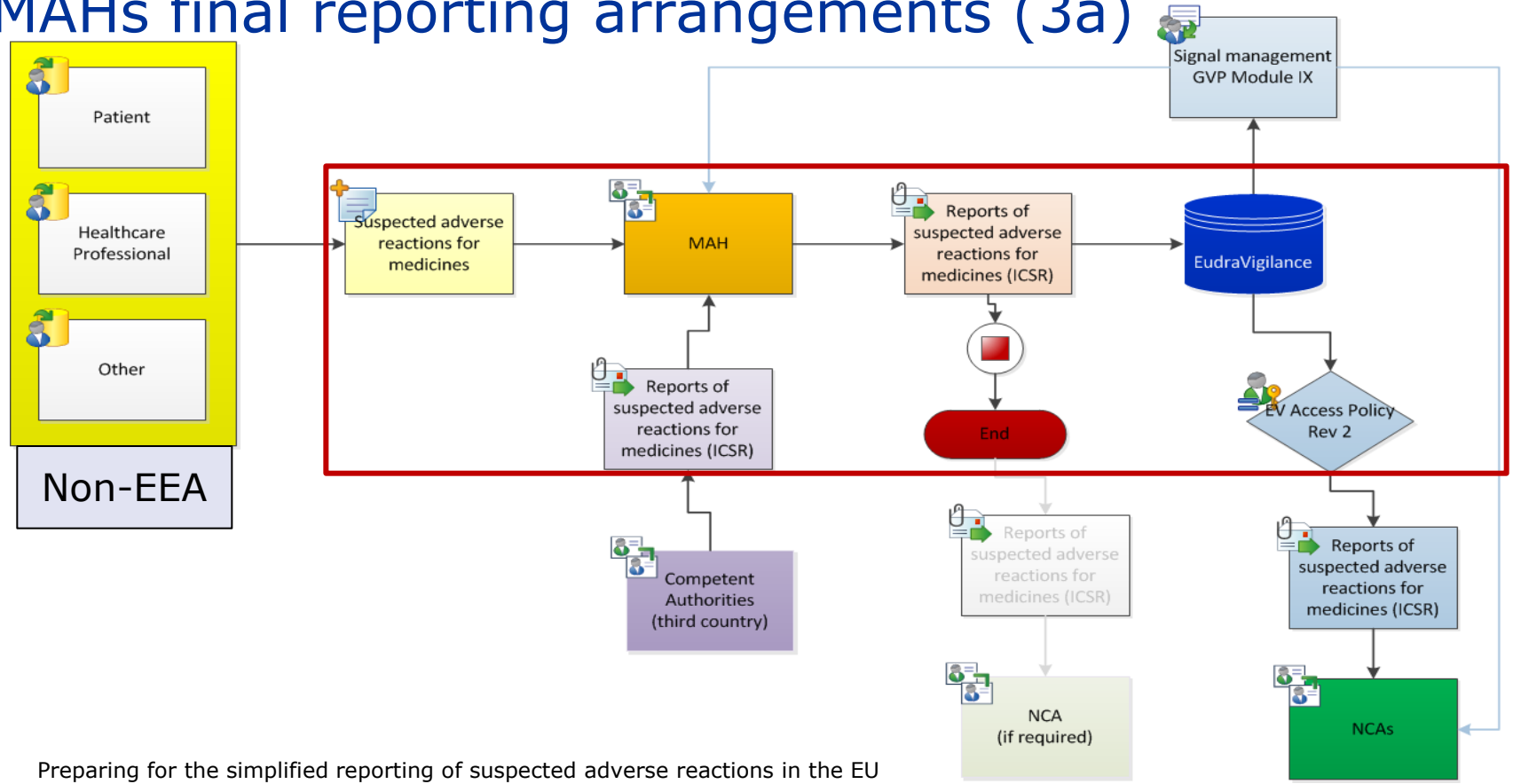
- Marketing authorisation holders need to submit electronically to EudraVigilance information on all serious suspected adverse reactions that occur in the Union and in third countries within 15 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.
- Marketing authorisation holders need to submit electronically to EudraVigilance information on all non-serious suspected adverse reactions that occur in the Union, within 90 days following the day on which the marketing authorisation holder concerned gained knowledge of the event.

Reference: Article 107(3) of Directive 2001/83/EC

MAHs final reporting arrangements (3a)



MAHs final reporting arrangements (3a)

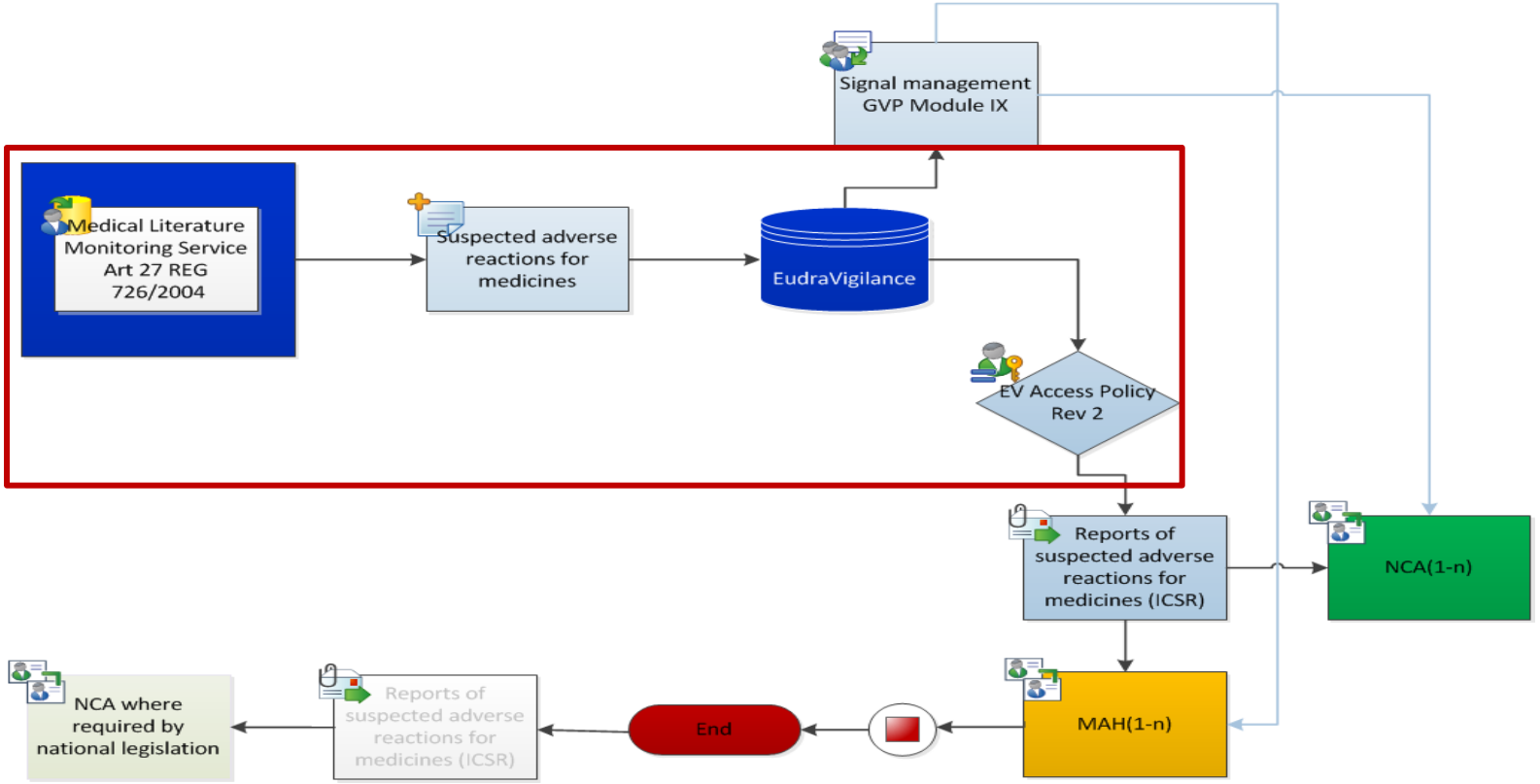


MAHs final reporting arrangements (4a)

- 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.

Reference: Article 27 of Regulation 726/2004

MAHs final reporting arrangements (4a)



Session overview: final reporting arrangements

In this session you obtained an understanding of:

- The simplified reporting arrangements of suspected adverse reactions related to medicines

Overview Module PhV-M3

- Introduction to this training module
- What are the legal basis and benefits for the simplified reporting of suspected adverse reactions?
- What are the interim reporting arrangements?
- What are the final arrangements for the simplified reporting of suspected adverse reactions?
- **What are key principles that should be taken into account?**
- How can I get supporting information?

Session overview: key principles that should be taken into account

In this session you will obtain an understanding of:

- Some of the key principles that should be taken into account when moving to the simplified reporting

Key principles to be taken into account (1)

As part of the simplified adverse reaction reporting the following key principles should be taken into account:

- EudraVigilance should be based on the highest internationally recognised data quality standards, which requires NCAs and MAHs to adhere to the:
  - electronic reporting requirements as defined in EU legislation
  - concepts of data structuring, coding and reporting in line with EU legislation, guidelines, standards and principles referred to in GVP Module VI, chapter VI.C.6.2.2.1

This is a pre-requisite to maintain a properly functioning EudraVigilance database intended to fully support the protection of public health.

Key principles to be taken into account (2)

- The Agency in collaboration with stakeholders that submit ICSRs to EudraVigilance, are *jointly responsible to contribute to the quality and integrity of the data* as defined in legislation:
  - The Agency shall, in collaboration with the stakeholder that submitted an ICSR to the EudraVigilance database, be responsible for operating procedures that ensure the highest quality and full integrity of the information collected in the EudraVigilance database [REG Art 24(3)]. This includes as well the monitoring of use of the terminologies referred to in chapter IV of the Commission Implementing Regulation (EU) No 520/2012 [IR Art 25(3)]
  - Specific quality system procedures and processes shall be in place in order to ensure the 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 [IR Art 11 (1) (c)]

Key principles to be taken into account (3)

- The Agency in collaboration with stakeholders that submit ICSRs to EudraVigilance, are *jointly responsible to contribute to the quality and integrity of the data* as defined in legislation:
  - Specific quality system procedures and processes shall be in place in order to ensure the quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions [IR Art 11 (1) (d)]
  - Marketing authorisation holders shall collaborate with the Agency and the Member States in the detection of duplicates of suspected adverse reaction reports [DIR Art 107(5)]
  - Member States shall collaborate with the Agency and the marketing authorisation holders in the detection of duplicates of suspected adverse reaction reports [DIR Art 107a (3)]

Details are provided in GVP Module VI, chapter VI.C.6.2.4.

Key principles to be taken into account (4)

- MAHs and NCAs should have in place *an audit system*, which ensures the highest quality of the ICSRs transmitted electronically to EudraVigilance within the correct time frames, and which enables the detection and management of duplicate ICSRs in their system.
- Those transmitted ICSRs should be complete, entire and undiminished in their structure, format and content.
- For the purpose of a systematic approach towards quality in accordance with the quality cycle as outlined in GVP Module I, managerial staff (i.e. staff with management responsibilities) in any organisation should be responsible for ensuring that adequate resources are available and that training is provided.

Details are provided in GVP Module VI, chapter VI.C.6.2.4.

Key principles to be taken into account (5)

Follow-up information

- EudraVigilance *will provide access to initial reports as well as follow-up reports* to marketing authorisation holders from the time when the simplified reporting will become applicable – this in accordance with the EudraVigilance Access Policy (revision 2)
- *There is no need for marketing authorisation holders to contact NCAs in EEA Member States to check if new information on the case is available/was obtained*; any new case information will be reported by NCAs to EudraVigilance, where the information is accessible to the marketing authorisation holders for the medicinal products for which they hold a marketing authorisation in the EU

Session overview: key principles that should be taken into account

In this session you obtained an understanding of:

- Some of the key principles that should be taken into account when moving to the simplified reporting

Overview Module PhV-M3

- Introduction to this training module
- What are the legal basis and benefits for the simplified reporting of suspected adverse reactions?
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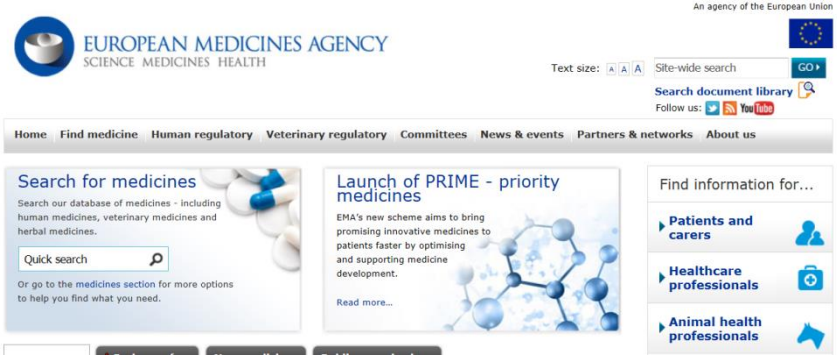
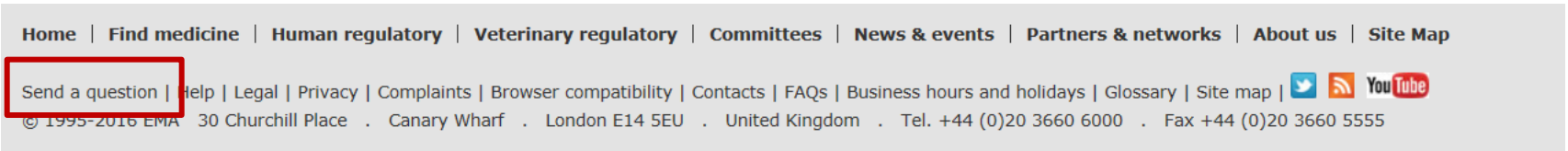
- What are the final arrangements for the simplified reporting of suspected adverse reactions?
- What are key principles that should be taken into account?
- **How can I get supporting information?**

Where can I get support if needed?

Pharmacovigilance operations

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





Reference Documents (1)

Reference	Document title
Regulation 726/2004	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)
Directive 2001/83/EC	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)
Commission Implementing Regulation 520/2012	COMMISSION IMPLEMENTING REGULATION (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council

Reference Documents (2)

Reference	Document title
EMA/411742/2015 Rev. 9 29 June 2015	Reporting requirements of Individual Case Safety Reports (ICSRs) applicable to marketing authorisation holders during the interim period
EMA/873138/2011 Rev 1*	Guideline on good pharmacovigilance practices: Module VI – Management and reporting of adverse reactions to medicinal products
EMA/827661/2011	Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management

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Summary of PhV-M3

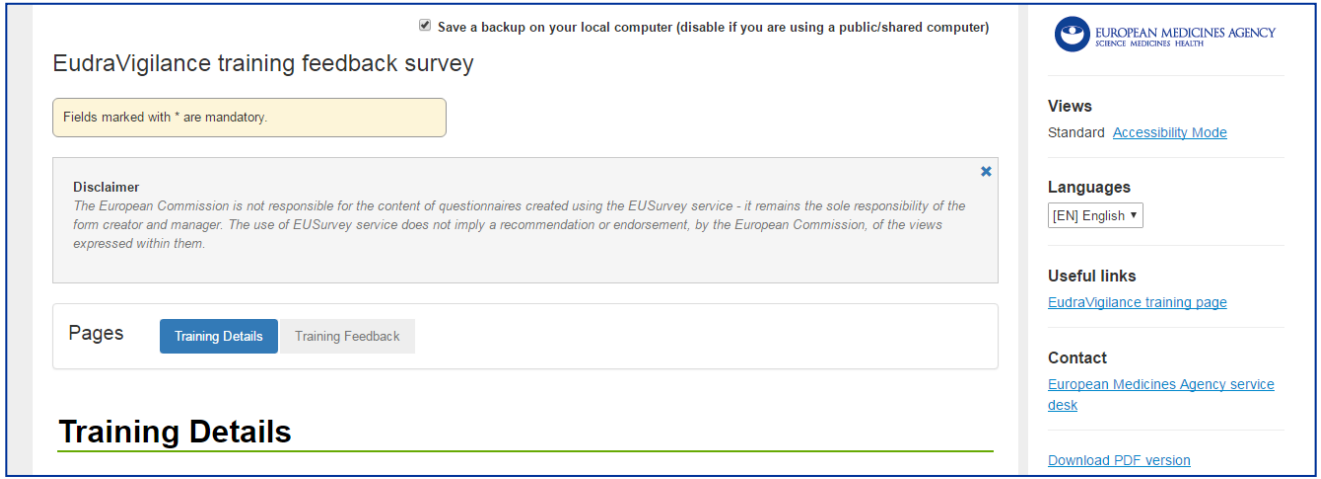
We are now at the end of the training module PhV-M3, which allows you to:

- Describe the legal basis and the benefits for the simplification of the reporting of suspected adverse reactions based on the 2010 pharmacovigilance legislation
- Recognise the current interim arrangements
- Describe the process of simplified reporting of suspected adverse reactions
- Recognise important principles in the context of simplified reporting
- Understand where to obtain supporting information and whom to contact in case of further questions

Feedback

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

- The survey is accessible via this link.



Acronyms (1)

Acronym	Description
EEA	European Economic Area
EU	European Union
EV	EudraVigilance
GVP	Guidelines on good pharmacovigilance practices
ICSR	Individual Case Safety Reports

Acronyms (2)

Acronym	Description
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National competent authority
PhV	Pharmacovigilance
WHO UMC	World Health Organisation Uppsala Monitoring Centre

Thank you for your attention

Further information

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