EMA
EUROPEAN MEDICINES AGENCY

GVP Module IX, Rev.2
Signal management

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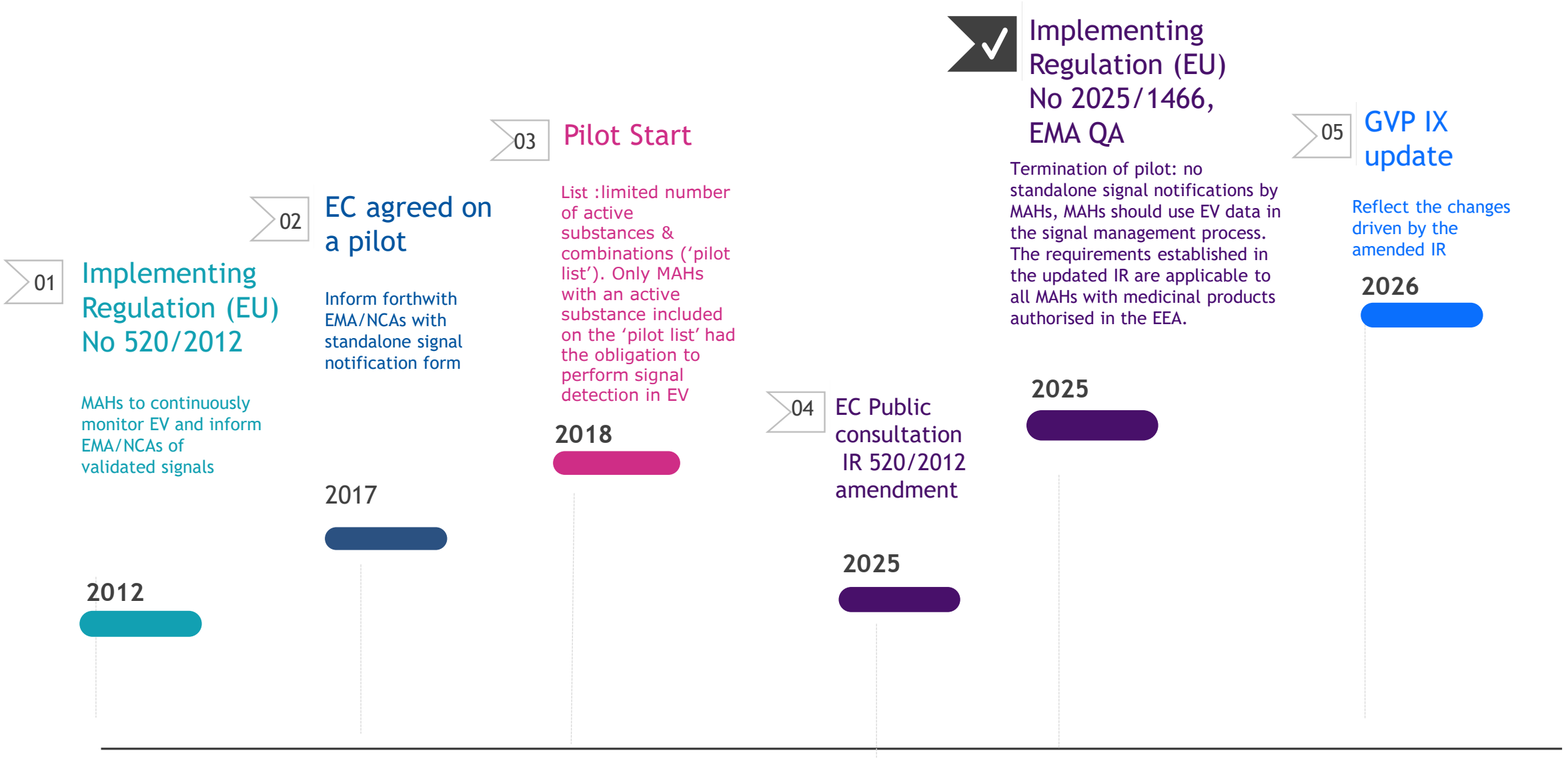
Background to the GVP Rev.2



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Legal Framework

Implementing Regulation (EU) No 2025/1466, amending IR (EU) No 520/2012

Minimum requirements for the monitoring of data in the Eudravigilance database

Article 18

~~2. Marketing authorisation holders shall monitor the data available in the Eudravigilance database to the extent that they have access to that database.~~

~~3. Marketing authorisation holders, the national competent authorities and the Agency shall ensure the continuous monitoring of the Eudravigilance database with a frequency proportionate to the identified risk, the potential risks and the need for additional information~~.

in Article 18, paragraphs 2 and 3 are replaced by the following:

2. Marketing authorisation holders shall monitor the data available in the Eudravigilance database and use it together with data from other available sources.

3. National competent authorities and the Agency shall ensure the continuous monitoring of the Eudravigilance database with a frequency proportionate to the identified risks, the potential risks and the need for additional information

Article 21 Signal management process

~~2. Where a marketing authorisation holder detects a new signal when monitoring the Eudravigilance database, it shall validate it and shall forthwith inform the Agency and national competent authorities.~~

In Article 21, paragraph 2 is deleted.

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Scope of GVP IX revision 2

- Revision mainly driven by the Implementing Regulation 520/2012 as amended
- Reflects pilot termination
- Clarifications on roles and responsibilities of the MAHs
- Revised guidance on EV monitoring for MAHs
- No change for the NCAs and EMA to the process , continuously monitoring of EV remains

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Responsibilities of MAHs

- **Continuous EV monitoring / standalone signal notifications to MSs, EMA:** no longer expected for MAHs
- **Signal Management:** MAHs decide at which step EudraVigilance data is used
- **Signal detection:** MAHs may decide to monitor EudraVigilance as a primary source.
- **Assessment:** EudraVigilance data is expected to be used during validation and full signal assessment.

Unchanged:

- validated signals continue to be included in PSURs
- NCAs and EMA continue EV monitoring.

Practical regulatory route: variation, ESI and PSUR remain the regulatory routes for validated signals and proposed risk-minimisation or regulatory actions

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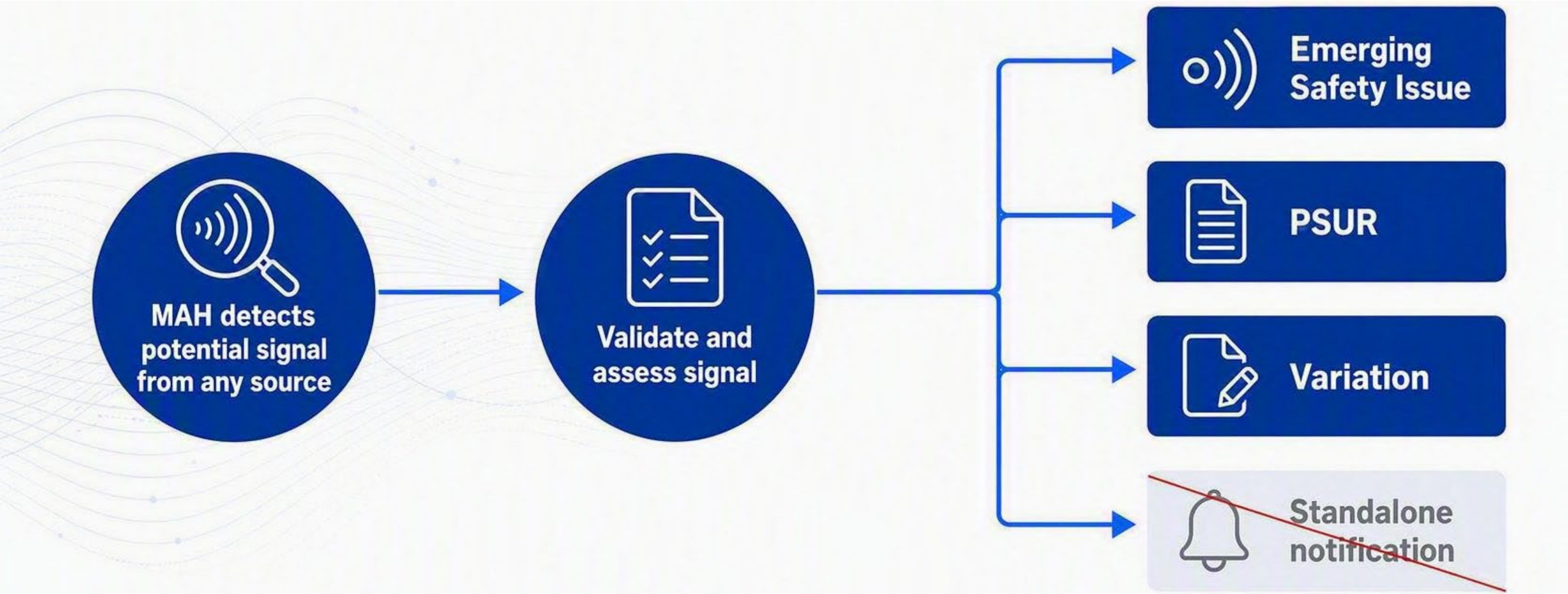
What is changing in regulatory route?



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Risk-based monitoring for MAHs

- **General recommendation on EV frequency for MAHs removed:** no recommended EV frequency as at least 6-month period
- **Monitor risk-proportionately:** MAHs to monitor the data available in the EudraVigilance database in a risk proportionate manner and use EudraVigilance data with other sources as part of pharmacovigilance responsibilities.
- **MAHs set periodicity:** The frequency of monitoring should be proportionate to the identified risk, the potential risks and the need for additional information on medicinal products or active substances (e.g. time since first authorisation, patient exposure, target population)
- **Documentation:** MAHs to record the monitoring strategy in the Pharmacovigilance System Master File.

Key takeaway: MAHs choose the monitoring frequency in a risk-based approach and document

Unchanged: for NCAS and EMA

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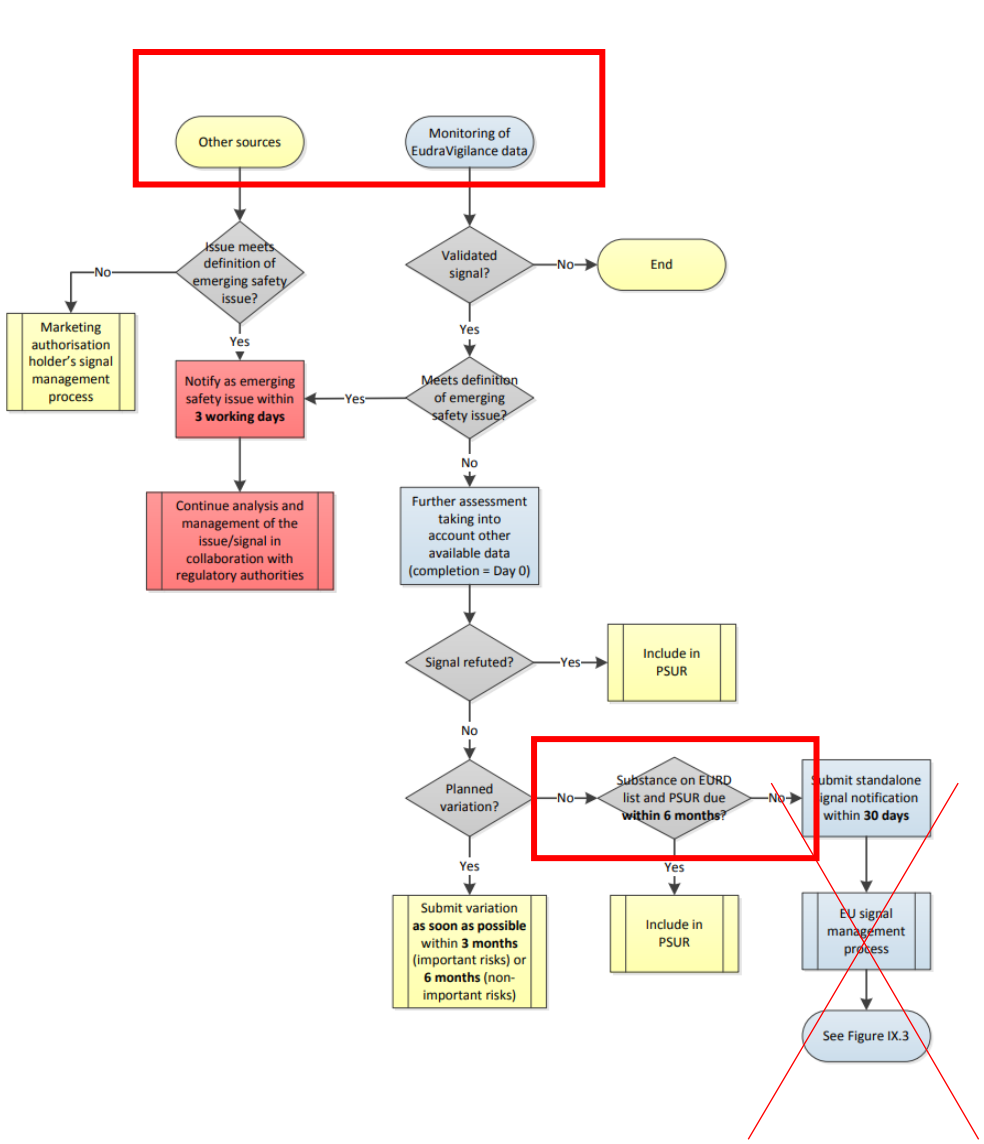
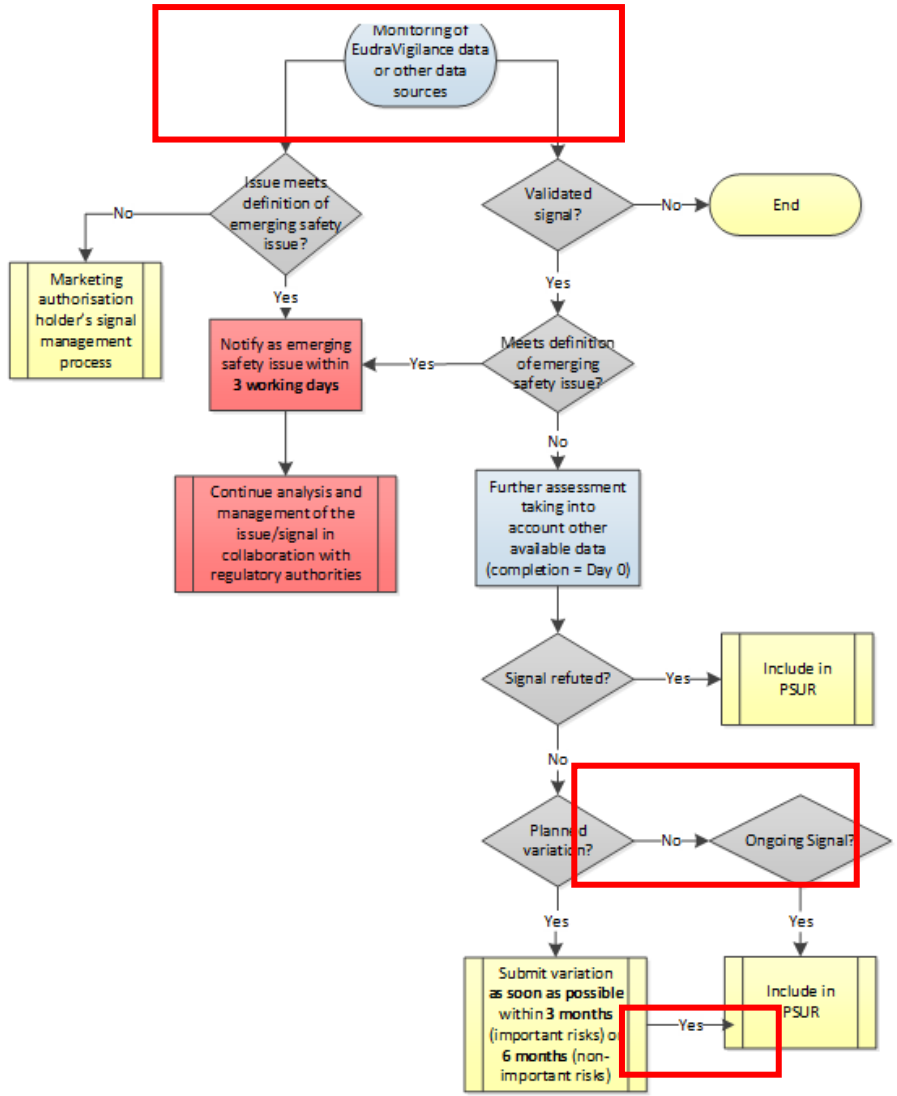
Flowchart on EU Signal Management Process





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Terminology

1 IX.A.1.2 — Terminology specific to the EU signal management process with oversight of the Pharmacovigilance Risk Assessment Committee (PRAC)

Addition of defined term

PRAC Lead

Definition

PRAC representative appointed by the PRAC for assessment of a signal concerning nationally authorised products. The PRAC Lead should usually be from the Lead Member State that has confirmed the signal.

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1 IX.B.5 Quality requirements:

[…]A system of quality management (see GVP Module I) should be applied to all signal management processes. Detailed procedures for this quality system should be developed, documented and implemented. This includes the rationale for the method and periodicity of signal detection activities. Timelines for signal management activities including for submitting any required variations resulting from signal evaluation should be defined and documented […]

2 IX.C.4.1. Variation of the terms of marketing authorisation

A marketing authorisation holder may conclude, based on their assessment of a signal detected through the monitoring of EudraVigilance data or other available sources, that the product information and/or the RMP should be updated through a variation.
In such cases, the marketing authorisation holder should submit the variation application to the relevant competent authorities as soon as possible and no later than 3 months after completing the assessment of the signal (‘Day 0’) if it corresponds to an important risk (see GVP Annex I), or within 6 months for other risks […]

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GVP Rev. 2 comments addressed

1 IX.C.1.1 — MAH responsibilities

[…] Marketing authorisation holders shall monitor the data available in the EudraVigilance database and use it together with data from other available sources. [IR Art 18 (2)]
To implement this requirement, marketing authorisation holders should determine at which step in the signal management process EudraVigilance data will be used. For instance, marketing authorisation holders may decide to monitor the EudraVigilance database for signal detection purposes as a primary source. It is expected that all marketing authorisation holders use EudraVigilance data during the evaluation of validation and the full signal assessment a signal as described in section I.X.B.3. […]

2 IX.C.3 — Monitoring of EV data

[…] For the Marketing authorisation holders that decided to monitor regularly and with specific periodicity the EudraVigilance database for signal detection purposes as a primary source, the frequency of monitoring should be proportionate to the identified risk, the potential risks and the need for additional information on medicinal products or active substances.
Each organisation should determine the appropriate frequency for each active substance or medicinal product they monitor in the EudraVigilance database, taking into account the considerations below. The monitoring frequency (including any changes) and the justification thereof should be documented in accordance with the organisation's internal procedures (see also IX.B.5.) […]

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3 IX.C.4. Procedural options for signals detected by the marketing authorisation holder in the EU

[…] The marketing authorisation holder who has detected a signal should consider and use the EudraVigilance data in the validation and the full signal assessment when applicable (see IX.B.3. and IX.C.3.2.) […]

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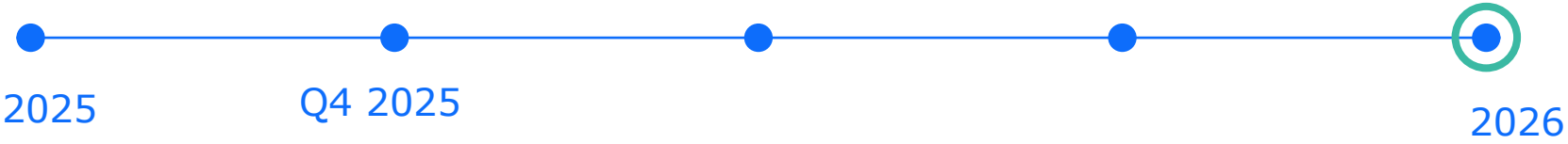
Timelines

EC IR(EU) 2025/1466 amending IR (EU) No 520/2012 — Review Process → Anticipated Publication GVP IX Rev.2



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