EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

# Signal management

Table of contents



**A safety signal is information on a new or known adverse event that may be caused by a medicine and requires further investigation. The European Medicines Agency (EMA), together with the regulatory authorities in the Member States and marketing authorisation holders are responsible for detecting and managing safety signals.**

Safety signals can be detected from a **wide range of sources**, such as spontaneous reports, clinical studies and scientific literature. The EudraVigilance database is an important source of information on suspected adverse reactions and signals.

The presence of a safety signal does not directly mean that a medicine has caused the reported adverse event. An illness or another medicine taken by the patient could also be the cause.

The assessment of safety signals establishes whether or not there is a **causal relationship** between the medicine and the reported adverse event.

The evaluation of safety signals is part of routine pharmacovigilance and is essential to ensuring that regulatory authorities have the most up-to-date information on a **medicine's benefits and risks**.

## Monitoring EudraVigilance: legal basis and guidance

Commission Implementing Regulation (EU) No 520/2012 (article 18) requires EMA, national competent authorities and marketing authorisation holders (MAHs) to continuously monitor the data available in EudraVigilance.

It also requires MAHs to inform EMA and national competent authorities of validated signals detected when monitoring the database.

On 22 November 2017, EMA launched the new EudraVigilance system and enabled MAH access to the system.

**Guidance on regulatory requirements** and on the monitoring and reporting processes for signals is available in good pharmacovigilance practices (GVP) Module IX on signal management.

In line with GVP IX requirements, **standalone notifications of signals** detected in EudraVigilance should be sent to the Agency (MAH-EV-signals@ema.europa.eu) and to the competent authorities in Member States where the medicinal product is authorised using the standalone signal notification form (see also transitional arrangements for MAHs).

- National contact points for standalone signal notifications
- Standalone signal notification form

Guidance on the notification of **emerging safety issues** can be found on the EMA's contact page.

EMA has also published **scientific guidance** on routine signal detection methods in EudraVigilance for use by the Agency, national competent authorities and MAHs. The guidance discusses the methods recommended and implemented in EudraVigilance for screening for adverse reactions. It updates and supersedes the previous guideline on the use of statistical signal detection in EudraVigilance .

## Transitional arrangements for MAHs

EMA and the European Commission have agreed transitional arrangements to streamline the monitoring of EudraVigilance by MAHs.

During a **pilot period** which started on 22 February 2018, MAHs of the active substances included in the following list have to monitor them in EudraVigilance and inform EMA and national competent authorities of validated signals with their medicines.

- List of active substances involved in the pilot on signal detection in EudraVigilance by marketing authorisation holders (updated on 16/09/2021)

**Update August 2022:** EMA and the European Commission have agreed to further **extend the pilot until the end of 2023**.

MAHs with active substances included in the list should continue to monitor them in EudraVigilance for the duration of the pilot.

These transitional arrangements **do not apply** to obligations on simplified reporting and management of individual case safety reports (see Good pharmacovigilance practices (GVP) Module VI and EudraVigilance change management).

**All other MAHs** also have access to EudraVigilance data and can integrate the data into their own signal management processes. However, during the pilot period they will have **no obligation to continuously monitor EudraVigilance** and inform the regulatory authorities of validated signals from EudraVigilance.

The Agency is **supporting MAHs** in using the new EudraVigilance system through targeted e-learning, face-to-face training, webinars and information days. For further information, see EudraVigilance training and support.

## Member State signal management work-sharing

A **lead Member State** may be appointed to monitor data in EudraVigilance, validate and confirm signals on behalf of the other Member States. This applies to active substances contained in medicinal products authorised nationally in more than one Member State.

- List of substances and products subject to worksharing for signal management (last updated 20/07/2022)

For substances with no lead Member State, all Member States have joint responsibility for monitoring those medicines they have authorised.

## Recommendations on signals

The Pharmacovigilance Risk Assessment Committee (PRAC) is responsible for **prioritising and assessing signals** and issuing subsequent recommendations on medicines authorised in the European Union, including nationally and centrally authorised medicines.

The PRAC recommendation may include one or a combination of conclusions, including:

- No need for further evaluation or action at present;
- Need for additional information, including:
  - monitoring any relevant emerging information as it becomes available,;
  - additional analysis in EudraVigilance or other data sources;
  - additional data from the marketing authorisation holder in the next periodic safety update report (PSUR) or submit an ad-hoc PSUR;
  - a post-authorisation safety study conducted by the marketing authorisation holder;
- Need for regulatory action, such as:
  - updating of the product information (summary of product characteristics and package leaflet) and/or risk management plan through a variation;
  - a referral procedure;
  - urgent safety restrictions.

For more information, see:

- Questions and answers on signal management

Marketing authorisation holders should monitor PRAC recommendations on safety signa
Agency publishes on its website and take action accordingly.

As of January 2015, EMA publishes **translations of recommendations** (reviewed by the national competent authorities) for the updating of product information into all official EU languages plus Norwegian and Icelandic. Marketing authorisation holders can use these translations to update their product information. This aims to ensure that consistent and clear information is available to patients in a timely manner in all Member States.

## Designated medical events

EMA has developed a list of designated medical events containing **medical conditions** that are inherently **serious** and often medicine-related:

- EMA designated medical event list

It does not address product specific issues or medical conditions with high prevalence in the general population.

The list contains Medical Dictionary for Regulatory Activities (MedDRA) terms and serves as a **safety net in signal detection.** EMA and Member States use it to focus on reports of suspected adverse reactions that deserve special attention, irrespective of statistical criteria used to prioritise safety reviews.

The designated medical event list is one of the tools the European medicines regulatory network uses and is **not intended as a comprehensive list** of terms for signal detection activities.

EMA has published the list to ensure its approach is transparent. It is subject to review in light of further experience with its use.

## More information

For more information on signal detection and management in the EU and **regulatory requirements** for marketing authorisation holders, see:

- Good pharmacovigilance practices (GVP) - see Module IX on signal management
- Questions and answers on signal management

## Related content

- Pharmacovigilance
- Good pharmacovigilance practices (GVP)
- Pharmacovigilance legislation
- PRAC recommendations on safety signals

## Related documents

Questions and answers on signal management (PDF/336.17 KB)

First published: 04/10/2013
Last updated: 15/01/2021
EMA/261758/2013 Rev 4*

## Related EU legislation

- Directive 2001/83/EC
- Regulation (EC) No 726/2004
- Commission Implementing Regulation (EU) No 520/2012

## Topics

- Data on medicines
- Guidance

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