CBG MEB | MEDICINES EVALUATION BOARD

Best practice for signal assessment

NCA perspective

Stakeholder forum EMA on EV and SD

Presented by: Bianca Mulder (Medicines Evaluation Board)

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Signal Management Process

Article 21

Signal management process

1. The signal management process shall include the following activities: signal detection, signal validation, signal confirmation, signal analysis and prioritisation, signal assessment, and recommendation for action.

What is a signal

- "Information that arises from one or multiple sources (including observations and experiments), which suggests a **new** potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to **justify verificatory action**".

  - Council for International Organisations of Medical Sciences Working group VIII Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010).

- Included in the Commission Implementing Regulation (520/2012) - For the purpose of monitoring data in the EudraVigilance database, only signals related to an adverse reaction shall be considered.

Detection → Validation → Confirmation → Analysis and prioritisation → Assessment → Recommendation for action

Safety databases

Scientific literature

Communications

Potential signals detected

Signal detection and validation in EudraVigilance EMA/NCAs

- Agency takes the lead for monitoring EV, signal detection and validation for CAPs

- NCAs take the lead for monitoring EV, signal detection and validation for NAPs according to the work-sharing list for signal management.

CHAPTER III

Minimum requirements for the monitoring of data in the Eudravigilance database

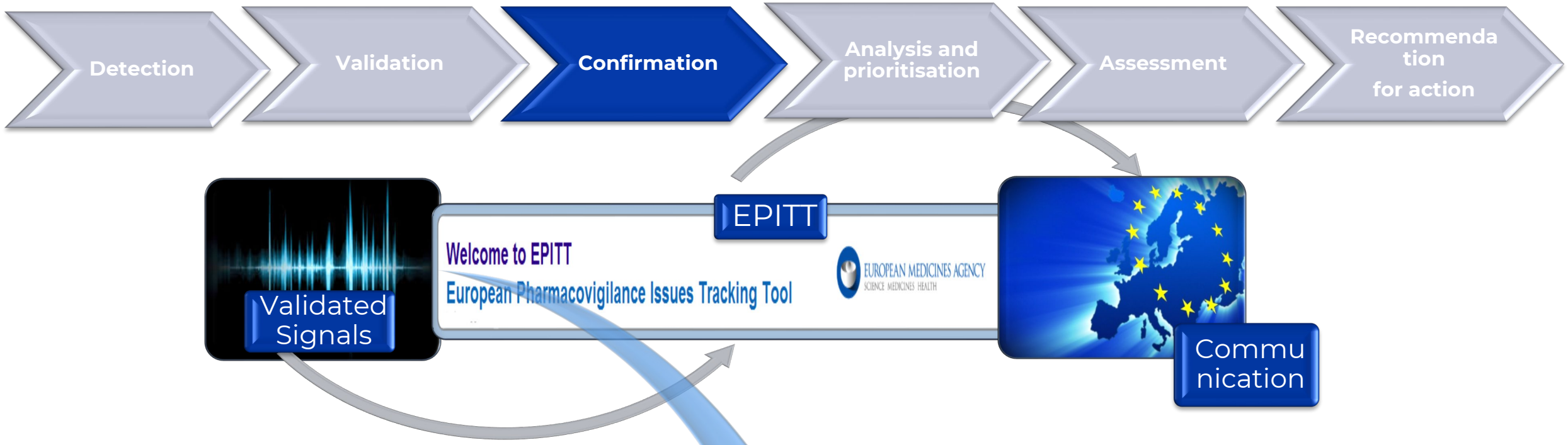
Article 18

General requirements

1. The Agency and national competent authorities shall cooperate in the monitoring of the data available in the Eudravigilance database.

'signal validation' means the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association, or a new aspect of a known association, and therefore justifies further analysis of the signal.

Validated signal



- Where it is considered that a validated signal requires further analysis, it shall be confirmed
- Confirmation by the PRAC Rapporteur or the lead Member State means communication through EPITT that the signal is valid – 30 days deadline

Confirmed signal

Any confirmed signal shall be entered in the tracking system administered by the Agency and shall be transmitted to the Pharmacovigilance Risk Assessment Committee for the initial analysis and prioritisation of signals

The initial analysis and prioritisation by PRAC is follow-up by a recommendation - 3 main categories of PRAC recommendations:

- No specific action
- Need for additional information – MAHs are involved
- Need for regulatory action - MAHs are involved

Such as:

- Monitoring any relevant emerging information as it becomes available
- Additional data from the MAH in the next PSUR
- Additional analysis in EV or other data sources within signal procedure;
- A PASS conducted by the MAH

PRAC concludes that:

- The assessment of the signal will be performed in the PSUSA. The PRAC recommendation provides clear instructions for the requested data to be submitted as part of the PSUR.
- Following assessment of the data in the signal procedure, the issue needs to be further monitored in the PSURs, GVP Module VII should be followed and MAHs should provide the results in Section 15 even if the assessment does not consider regulatory action or there are no new cases.
    - Review should focus on new data from the reporting period which should be placed in context of what is known (e.g. cumulative data)
    - Following assessment of the data, the PSUR report should indicate whether a new signal is raised (incl. review in section 16), the issue should be kept under monitoring or if routine pharmacovigilance may be more appropriate.

Such as:

- Monitoring any relevant emerging information as it becomes available
- **Additional data from the MAH in the next PSUR**
- Additional analysis in EV or other data sources within signal procedure;
- A PASS conducted by the MAH

Need for additional information

Example:

PRAC agreed that the MAH of [product] should submit by [data] a cumulative review of all cases of [event] associated with [active substance]. This analysis should include a review of the published literature, data from spontaneous reports and reports from studies including all cases in EudraVigilance database, as well as a discussion on possible biological plausibility and mechanism of this association, its causal association, preventability and management. The MAH should also discuss the need for any potential amendment to the product information (PI) and/ or the risk management plan (RMP) and make accordingly a proposal for the changes to the relevant sections within this discussion.

The PRAC will assess the cumulative review within a X-day timetable.

Such as:

- Monitoring any relevant emerging information as it becomes available
- Additional data from the MAH in the next PSUR
- **Additional analysis in EV or other data sources within signal procedure;**
- A PASS conducted by the MAH

Need for additional information – Do's and don'ts

Do's:

- Provide a discussion on possible mechanism (biological and pharmacological plausibility)
- Provide justification for MedDRA strategies → Select best strategies based on the data
- Provide a thorough review/discussion on cases identified from EV and MAH's safety database:
    - Discuss strength of evidence (including, but not limited to)
        - Time to onset (in relation to mechanism)
        - Cases with positive de- or re-challenge (if applicable)
        - Confounders/alternative explanations
        - Confirmation of event/diagnosis
        - Consistency of the evidence across cases (patterns)
- Provide a thorough review on data from RCT's (case reports but also imbalances treatment vs. placebo/comparator), pharmaco-epi studies, literature, non-clinical etc.
- Provide a well balanced overall discussion on causality based on data from all sources
- Provide justification for the need for an update of the product information or any other regulatory action

  → Include frequency calculations, consider the impact of the PI update on clinical practice and which clinical recommendations are warranted (monitoring advices, stopping treatment etc.)

Need for additional information – Do's and don'ts

Don't:

- Focus only on MAH's own safety database

  → Also review Eudravigilance data and other sources of information, such as RCTs, pharmaco-epi studies, literature etc.
- Reject cases without providing sufficient detailed information
- Reject cases simply because a potential confounder has been reported.

  → Look at all information in the case and discuss whether causality can be more likely attributed to the confounder or the suspect.
- Provide solely a causality assessment for each case separately without an overall discussion on causality

  → A good discussion on causality includes a well balanced discussion of all cases and all available sources of information in which strength of evidence is weighed.
- Focus solely on evidence for own product and not on evidence for the class when signal concerns class review

Evaluation of all evidence gathered following initial analysis and prioritisation:

- MAH data, analysis and proposals
- Additional analyses performed by regulators or other stakeholders, in EV or other sources
- Led by Rapporteur appointed by the PRAC
- According to an agreed timetable
- Leads to a further PRAC recommendation

Standard Timetable for the signal assessment

Day	Action
Day 0	Start of the procedure
Day 30	Preliminary PRAC Rapporteur Assessment Report
Day 45	Comments from PRAC member and MAHs
Day 50	Updated PRAC Rapporteur Assessment Report
Day 60	Adoption of PRAC Assessment Report and PRAC Recommendation

Analysis and prioritisation → Assessment → Recommendation for action

🔄 Standard process – MAHs' comments should be provided to the pAR according to the timetable

⚠️ Ad hoc process – When the approach in the uAR differs significantly from the pAR, MAHs are normally given the opportunity to comment within a very short timeframe. In these specific situations, instructions from the EMA Signal Management Lead must be followed.

📌 Important note – In both scenarios, a thorough review is expected. No comments should be submitted after the PRAC has discussed and adopted the recommendations, as this interferes with the procedural workflow (e.g., translations, CHMP adoption, publications).

Standard Timetable for the signal assessment

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Advance Notification of signals on the PRAC agenda

- Addressed to all the Qualified Persons Responsible for Pharmacovigilance of the MAHs registered in the Article 57 database
- Communicated the week before the PRAC
- Based on the draft PRAC agenda
- No action required at this stage by the concerned MAHs

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4 July 2025
EMA/221833/2025
Human Medicines Division

To:	Qualified Person Responsible for Pharmacovigilance
From:	[redacted] Head of Pharmacovigilance Office
Re:	Advance notification of signals on the PRAC agenda
Cc:	
Number of pages (including cover sheet):	2

Message

Dear Qualified Person Responsible for Pharmacovigilance,
Please be informed that the following signals are included (on the current draft agenda) for the next PRAC meeting (7-10 July 2025):

New signals

i. Bosutinib – BOSULIF (CAP)

Signal of cutaneous vasculitis

ii. Datopotamab deruxtecan – DATROWAY (CAP)

Signal of anaphylactic reaction

iii. Sulfasalazine (NAP)

Signal of idiopathic intracranial hypertension (Pseudotumor cerebri)

iv. Valproate (NAP) and related substances[1]

PRAC Agenda

- Published on Monday ‘PRAC plenary week’
- Contains all confirmed signals
- Includes initial analysis and follow-assessment
- No action required at this stage by the concerned MAHs

PRAC agendas

Agenda of the PRAC meeting 7-10 July 2025
Draft
Reference Number: EMA/PRAC/202278/2025

English (EN) (874.68 KB - PDF)
First published: 07/07/2025

PRAC recommendations on safety signals

PRAC Recommendations

- A PRAC recommendation is issued each time a signal is discussed at the PRAC
- PRAC recommendations to provide additional data are directly addressed to the concerned MAHs
- PRAC recommendations for regulatory action are submitted to CHMP for adoption (CAPs) and CMDh for information (NAPs)
- Published after CHMP/CMDh week

PRAC recommendations on signals adopted at the 2-5 June 2025 PRAC meeting

Adopted

Reference Number: EMA/PRAC/179172/2025

English (EN) (299.47 KB - PDF)

First published: 30/06/2025

View

1. Recommendations for update of the product information[3]

1.1. Ciltabtagene autoleucel – Immune-mediated effector cell-associated enteritis with CAR T-cell p

Authorisation procedure	Centralised
EPITT No	20133
PRAC Rapporteur	Jo Robays (BE)
Date of adoption	5 June 2025

Recommendation *[see also section 3]*

Having considered the available evidence in EudraVigilance, including by the Marketing Authorisation Holders (MAHs), the PRAC has agreed (Janssen-Cilag International NV) should submit a variation within 2 m PRAC recommendation to amend product information as described b

Summary of product characteristics

4.4 Special warnings and precautions for use

Immune-mediated enterocolitis

Patients may develop immune-mediated enterocolitis, which may emerge several months after Carvykti infusion. Some cases may be refractory to treatment with corticosteroids, and other treatment options may be relevant to consider. There were events of gastrointestinal perforation, including fatal outcomes.

2. Recommendations for submission of supplementary information

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Epcoritamab	Hypogammaglobulinaemia (20174)	Monica Martinez Redondo (ES)	Supplementary information requested (submission by 27 August 2025)	AbbVie Deutschland GmbH & Co. KG
Varicella vaccine (live)	New aspect of the	Jean-Michel	Supplementary	GlaxoSmithKline

3. Other recommendations

INN	Signal (EPITT No)	PRAC Rapporteur	Action for MAH	MAH
Axicabtagene ciloleucel; brexucabtagene autoleucel; ciltabtagene autoleucel; idecabtagene vicleucel; lisocabtagene maraleucel; tisagenlecleucel	Immune-mediated enterocolitis / immune effector cell-associated enteritis with CAR T-cell products (20133)	Jo Robays (BE)	· Ciltabtagene autoleucel: see section 1.1	Janssen-Cilag International NV
			· All other substances: routine pharmacovigilance	Bristol-Myers Squibb Pharma EEIG, Novartis Europharm Limited, Kite Pharma EU B.V.
Omalizumab	Hearing losses (20128)	Mari Thörn	Monitor in PSUR	Novartis

Other publications (not specific to signals)

Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 7 – 10 July 2025

Share

11 July 2025

Ixchiq: temporary restriction on vaccinating people 65 years and older to be lifted

News | Human | Pharmacovigilance

Page contents

Vaccine to be used only when there is a significant chikungunya risk and after careful consideration of the benefits and risks

EMA's safety committee (PRAC) has completed its review of Ixchiq, a live attenuated chikungunya vaccine, following reports of serious side effects.

The temporary restriction on vaccinating people aged 65 years and above, which was put in place during the review, will now be lifted.

However, PRAC concluded that, for people of all ages, the vaccine should only be given when there is a significant risk of chikungunya infection and after a careful consideration of the benefits and risks.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

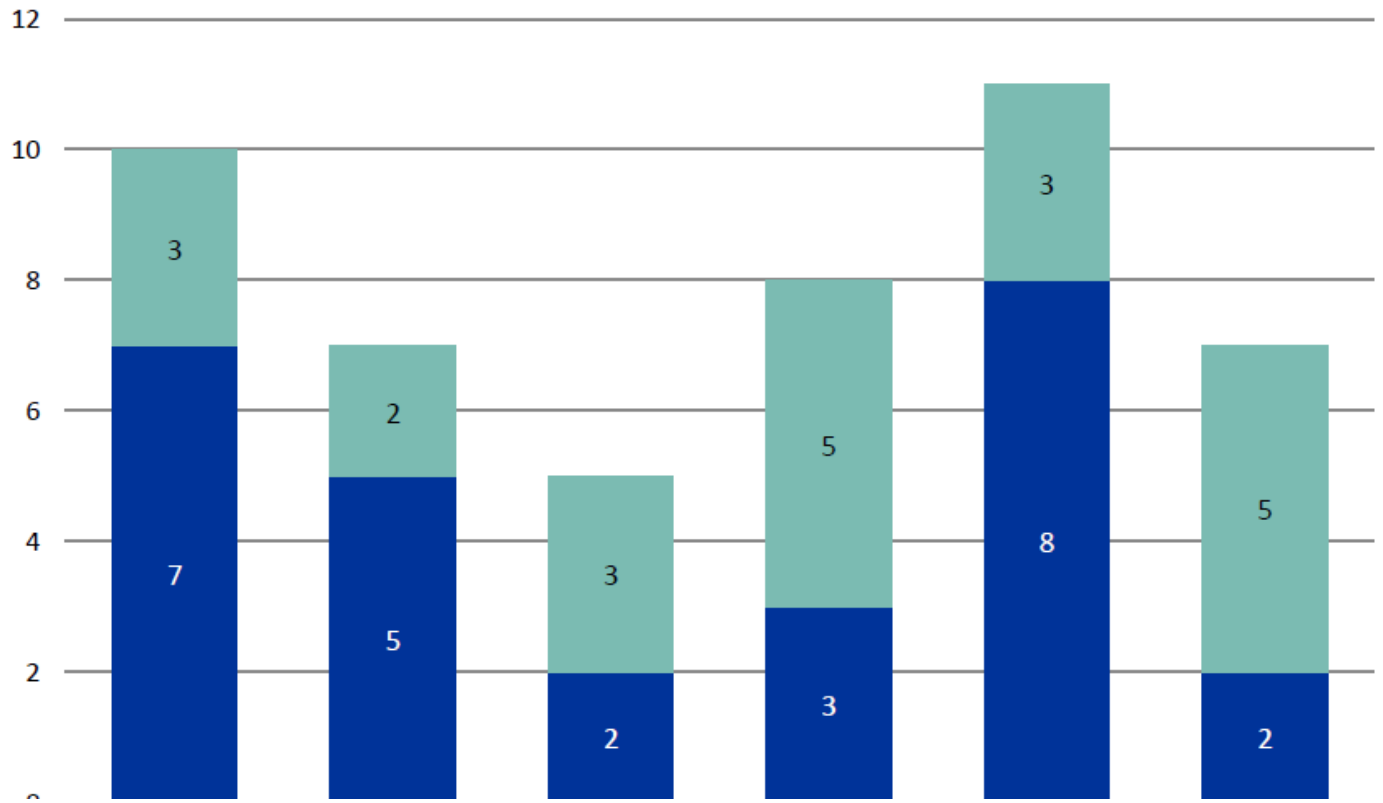
25 June 2025
EMA/PRAC/199835/2025
Human Medicines Division

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes for PRAC meeting on 05-08 May 2025

Chair: Ulla Wändel Liminga – Vice-Chair: Liana Martirosyan

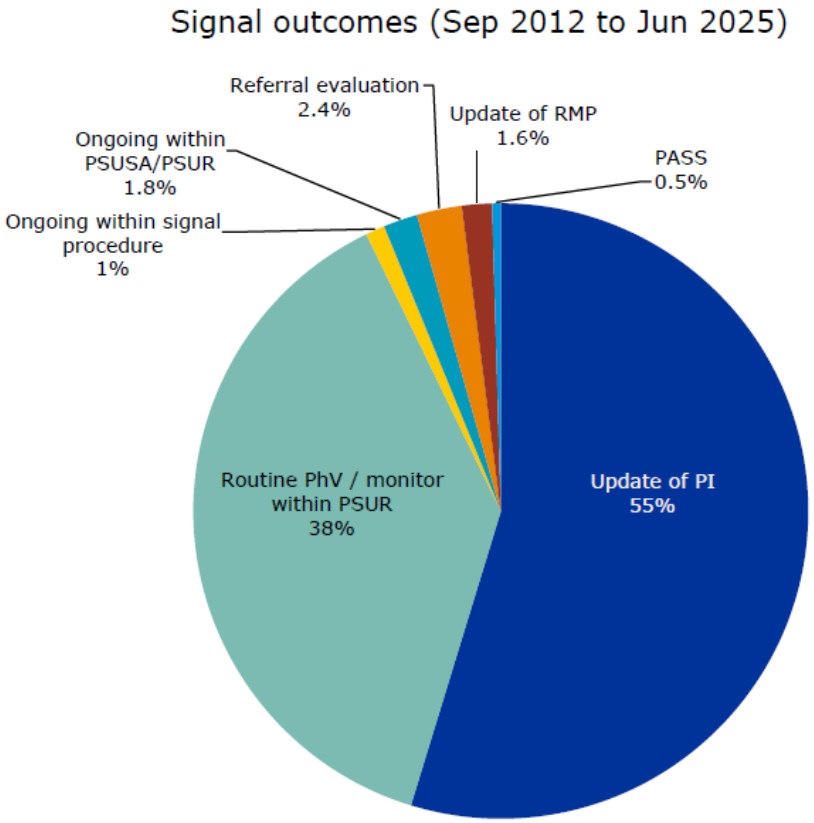
PRAC Signals

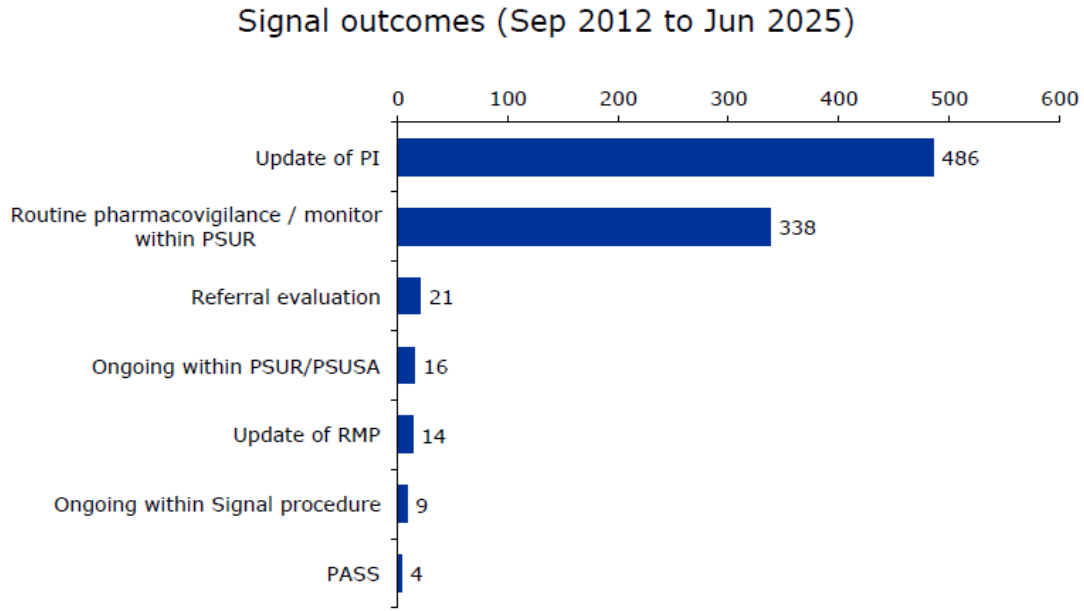


Sep 2012 – Jun 2025
888 signals
1588 signal discussions

Median for Q1-Q2 2025:
7.5 signals per month

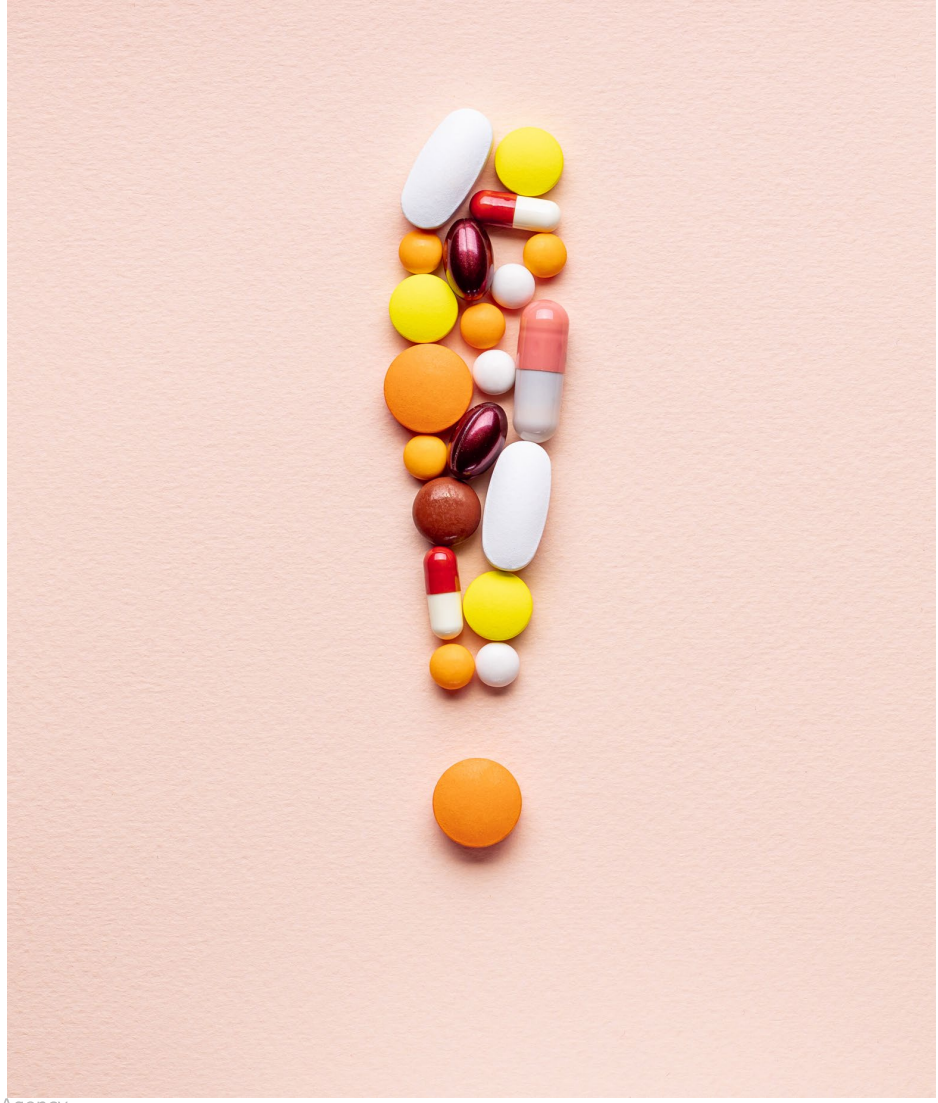
PRAC Signals Outcomes





Always remember…..

The MAH shall ensure that the product information is kept up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations made public by means of the European medicines web-portal established in accordance with Article 26 of Regulation (EC) No 726/2004. [DIR Art 23 (3)]



Reminder:

The most frequently asked questions and answers are published in EMA's Q&A on signal management

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