# Signal Management in Pharmacovigilance

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## Content

- Signal management
- IR 2025/1466 and its impact on signal management
- EU Signal management process
- EU signal management process example (ARBs)
- AI in Signal Management

# Signal Management

## Legislative background

- Regulation (EC) No 726/2004 — Article 28a covers centralised procedures
- Commission Implementing Regulation (EU) No 520/2012 — operational provisions
- Implementing Regulation (EU) 2025/1466
- Directive 2001/83/EC — Article 107h defines signal management obligations
- GVP Module IX – Signal Management — principal guidance for implementation and compliance
- CIOMS VIII Practical Aspects of Signal Detection in Pharmacovigilance
- CIOMS XIV Artificial Intelligence in Pharmacovigilance

# What Is Signal Management?

Definition from GVP Module IX

*"A signal management process is a set of activities performed to determine whether there are new risks associated with an active substance or a medicinal product or whether known risks have changed, and includes any related recommendations, decisions, communications and tracking."*

## Key Components

**1 Identify**
Detect new risks or changes to known risks from safety data sources

**2 Evaluate**
Assess signals to determine clinical significance and regulatory impact

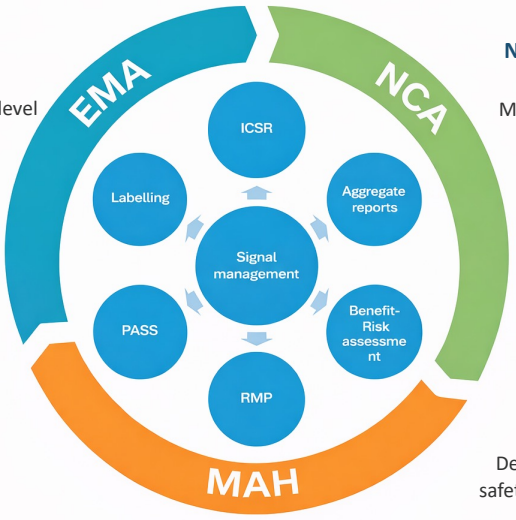
**3 Recommend**
Develop and communicate risk minimisation measures and actions

**4 Track**
Monitor and document all decisions, communications and outcomes

Source: GVP Module IX — Signal Management (Rev 2, Mar 2017)

# Signal Management — Central Part of (EU) Pharmacovigilance

**European Medicines Agency (EMA)**
Coordinates signal management at EU level
Monitors EV for CAPs




**National Competent Authorities (NCAs)**
Monitor and manage signals in MS for NAPs

**Marketing Authorisation Holders (MAHs)**
Detect and manage signals from their own safety databases and all available data sources

Source: EMA Signal Management Overview | GVP Module IX

# IR 2025/1466 & Signal Management

## IR 2025/1466 – Impact on Signal Management

*Commission Implementing Regulation 2025/1466*

**Applicable from 22 July 2025**

1. **Pilot Phase Terminated**
   The pilot phase of signal detection in EudraVigilance (started 22 February 2018, limited to the pilot list of active substances) has now terminated.
2. **No More Standalone Signal Notification to EMA**
   MAHs are no longer expected to submit validated signals to the EMA and NCAs via the standalone signal notification.
3. **Signals Handled via MAH's Own Process**
   All signals, including those from EudraVigilance, should be handled according to the MAH's own signal management process.
4. **PRAC Requests: Include EudraVigilance Data**
   In response to PRAC requests, MAHs must consider and include all relevant data available in EudraVigilance.

Source: Commission Implementing Regulation (EU) 2025/1466 | GVP Module IX update expected Q2 2026

## EudraVigilance Database Monitoring (Art. 18)

*IR 520/2012 Chapter III — Minimum Requirements for Monitoring Data in the EudraVigilance Database*

### What Changed (Art. 18, par. 2 — Replaced)

Effective on 12AUG2025

**Removed:** "to the extent that they have access to that database"

**Now:** MAHs shall monitor the EudraVigilance database **and use it together with data from other available sources.**

**Impact:** EudraVigilance is now a mandatory data source — access limitations/pilot no longer apply as a qualifier.

### What Changed (Art. 18, par. 3 — Replaced)

Effective on 12AUG2025

**Removed:** "Marketing authorisation holders" from the list of parties obliged to continuously monitor EV.

**Now:** NCAs and the Agency shall ensure continuous monitoring of EV, with a frequency proportionate to identified risks.

**Impact:** Continuous monitoring of the EV at system level shifts to EMA/NCAs. MAHs remain responsible for product-specific signal detection using EV data.

### New Clarification — Art. 19(1), 3rd subparagraph:

Effective on 12FEB2026

For the purpose of monitoring data in EudraVigilance, only signals related to a **suspected** adverse reaction shall be considered.

Source: IR 2025/1466, Chapter III — Art. 18, par. 2 & 3 (replaced) | Art. 19(1), 3rd subparagraph (new)

## Signal Management Process (Art. 21)

*IR 520/2012 Chapter III — Minimum Requirements for Monitoring Data in the EudraVigilance Database*

### Art. 21(2) — DELETED

Effective on 12AUG2025

Previously: When a MAH detected a new signal from EudraVigilance, it had to validate it and immediately inform the Agency and NCAs.

**This obligation has been entirely removed.** MAHs no longer need to detect, validate, or submit EV signals to the Agency.

### Art. 21(3) — AMENDED: Signal Validation by NCA/Agency

Effective on 12FEB2026

A validated signal **by a national competent authority or the Agency** that requires further analysis shall be confirmed within 30 days:

- NAP products: confirmed by the NCA of the marketing Member State or lead/co-leader
- CAP products: confirmed by the Agency in collaboration with Member States

### Art. 21(4) — NCA/Agency Responsibilities Retained

Effective on 12FEB2026

NCAs and the Agency shall validate and confirm any signal detected during their continuous EudraVigilance monitoring. Non-confirmed signals require special attention if subsequently followed by new signals for the same product.

Source: IR 2025/1466, Chapter III — Art. 21 (Signal Management Process)

## Practical Implications — Updated Responsibilities

*Update Processes/Procedures for EudraVigilance Monitoring | Art. 23, subpar. 2*

### MAH Responsibilities

- Use EudraVigilance as an **additional data source** (define how EV will be monitored and how data will be used)
- **No longer obliged** to submit validated signals from EV to the Agency
- Handle all signals (including from EV) via the MAH's own signal management process
- In response to PRAC requests, include all relevant EV data

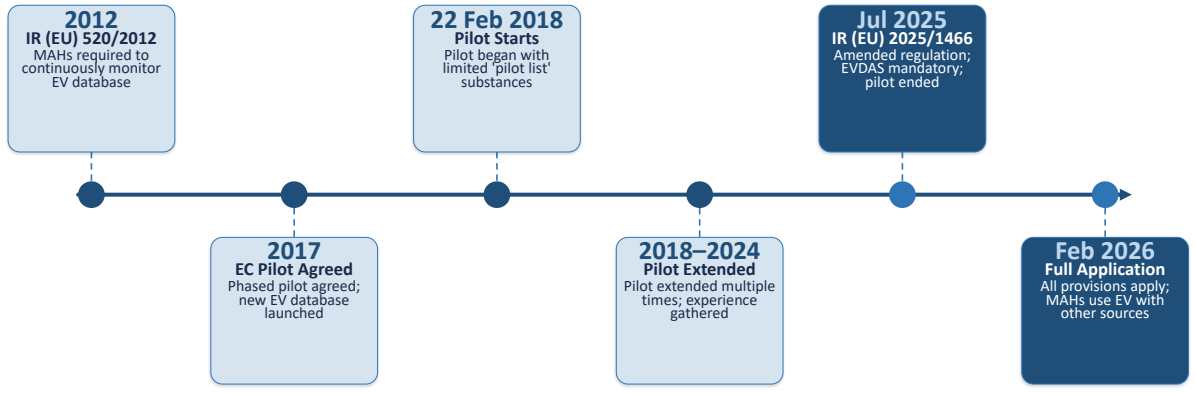
### NCA / Agency Responsibilities

- Continuously monitor EudraVigilance with a **frequency proportionate to the identified risk**, potential risks, and need for additional information
- Shall **validate and confirm** any signal detected during their continuous EV monitoring
- Agency shall ensure appropriate support for the **use** of EudraVigilance by MAHs (changed from "monitoring" to "use")

**An update to GVP Module IX is scheduled for implementation in Q2 2026**

Source: IR 2025/1466, Chapter III | Art. 23, subpar. 2 (Agency support)

## EVDAS Monitoring - Timeline evolution




Dark cards = recent regulatory changes (IR (EU) 2025/1466 amending IR (EU) No 520/2012)

# EU Signal Management Process

## EU Signal Management Process

Role of Regulators

### Regulators

**EMA** — **European Medicines Agency (EMA)**
EudraVigilance monitoring for Centrally Authorised Products (CAPs), together with PRAC Rapporteurs

**MS** — **Member States (NCAs)**
EudraVigilance monitoring for Nationally Authorised Products (NAPs) for NP/MRP/DCP procedures

**LMS** — **Lead Member State**
Appointed for work-sharing on signal monitoring on behalf of other Member States

**PRAC** — **PRAC Committee**
Signal prioritisation, in-depth assessment, and issuing recommendations on regulatory actions

**CHMP** — **CHMP / CMDh**
CHMP endorses PRAC recommendations for CAPs; CMDh is informed of outcomes for NAPs

Source: EMA Q&A on Signal Management (Rev 5, Jan 2026)

# EU Signal Management Process

Role of Marketing Authorisation Holders (MAHs)

## Marketing Authorisation Holders (MAHs)

**EV — Continuous EudraVigilance Monitoring**
Mandatory since 2025 – MAHs must routinely monitor EudraVigilance data alongside other safety data sources

**SD — Signal Detection & Validation**
Perform signal detection and validation per GVP Module IX using EVDAS and other sources

**60d — Data Submission Upon PRAC Request**
Provide requested data and assessments to PRAC within a 60-day deadline following signal confirmation

**PI — Product Information Updates**
Keep product information (SmPC, PIL) up to date in line with PRAC recommendations and signal outcomes

**ESI — Validated Signals & Safety Issues**
Report validated signals in PSURs and notify via Emerging Safety Issue (ESI) mechanism when applicable

Source: EMA Q&A on Signal Management (Rev 5, Jan 2026)

# Signal Detection

## Signal Sources

**MAHs must monitor many data sources:**

- ICSRs / non-valid cases (drug-event pairs)
- EudraVigilance database
- RMP (summary of safety concerns)
- Aggregate data
- Literature (global and local)
- Product quality complaints
- Manufacturing deviations
- Websites and media (incl. social media)
- Clinical and non-clinical studies, PASS
- Regulatory authorities (PRAC, CAs, FDA)

## MAH Monitoring Obligation

**Regular monitoring is mandatory**

Frequency must be proportionate to risk and documented with justification. Recommended intervals range from 2 weeks to 6 months.

## Frequency Considerations

**Key criteria for setting frequency:**

- Time since initial marketing authorisation
- Patient exposure
- Potential risks and missing info (RMP)
- PSUR submission frequency
- Monitored safety topics
- EVDAS monitoring frequency

**MAH must continuously monitor all signal sources**
Risk-proportionate frequency (2 wks – 6 mo) — documented & justified

# Signal Validation

Verifies that available documentation contains **sufficient evidence of a new potentially causal association** or a **new aspect of a known association** that justifies further analysis

### 1 Previous Awareness

- ADR in product labelling
- ADR in labelling of other products with same active substance
- Addressed in RMP/PSUR

### 2 Strength of Evidence

- Number and quality of cases
- Temporal association, dechallenge/rechallenge
- Related MedDRA terms
- Consistency, possible mechanism

### 3 Clinical Relevance

- Seriousness/severity
- Outcome and reversibility
- Vulnerable populations
- Misuse, off-label, med. errors

### 4 Additional Sources

- Clinical trial data
- Literature cases
- Class effect analysis
- Non-clinical findings

**Note:** A known association may give rise to a new signal if its frequency, duration, severity or outcome changes (e.g. new fatality) compared to SmPC information.

# Signal Evaluation & Confirmation

**Validation** → **Evaluation** → **Confirmation**

*Is this a new signal?* | *Full analysis of evidence* | *PRAC confirms signal*

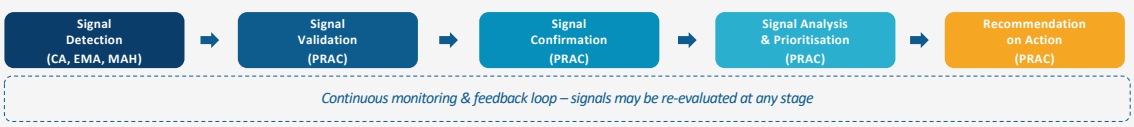
## Signal Evaluation

- Further analysis of validated signal
- Assessment of causal relationship
- Propose actions: PI changes &/or risk minimisation measures
- Communication as appropriate
- Update safety reference (SmPC, RMP)

## Signal Confirmation (PRAC only)

- Within **30 days** from signal validation
- Does **not** mean causality confirmation of individual cases
- Verification of known information (SmPC, PSURs, previously assessed signals)
- PRAC decides on need for further evaluation

**Figure IX.1** – Signal Management Process (GVP Module IX)



# Signal Assessment & Recommendation

**Validation** — *Is this a new signal?*

**Evaluation** — *Full analysis of evidence*

**Assessment** — *PRAC assessment of signal*

## Signal Assessment (PRAC Rapporteur)

- Confirmed signal referred to PRAC Rapporteur
- 60 days for MAH to submit data (cumulative review of cases, studies, literature)
- 60 days for PRAC assessment of submitted data
- Assessment of causal relationship

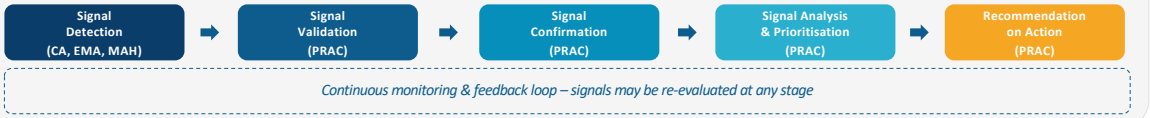
## PRAC Recommendation for Action

**No need for further evaluation or action:**
- Routine pharmacovigilance

**Need for additional information:**
- MAH should submit additional data, address in the next PSUR / ad-hoc PSUR
- MAH should sponsor PASS
- EMA/MS should collect further information, perform further analysis

**Need for regulatory action:**
- Update of product information, implement aRMM
- MS/Commission should initiate a referral procedure

**Figure IX.1** – Signal Management Process (GVP Module IX)

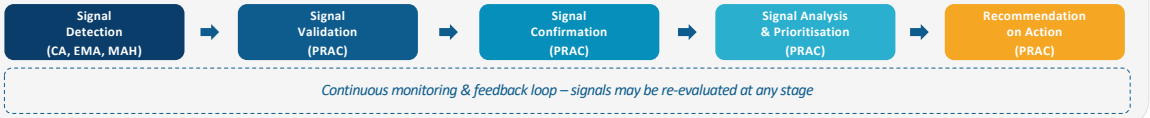



# EPITT & EMA Communication on Signals

Tracking and transparency mechanisms

- EPITT (European Pharmacovigilance Issues Tracking Tool) — tracking signals in the EU
- Only regulatory authorities can enter signals in EPITT
- MAHs receive advance notice of confirmed signals before each PRAC meeting
- Confirmed signals reflected in draft PRAC agenda on EMA website
- All PRAC recommendations published on EMA Signal Management webpage within 1 month
- PI update wording published in English + all EU official languages
- MAHs have legal obligation to continuously monitor the EMA website

**Figure IX.1** – Signal Management Process (GVP Module IX)




Source: EMA Q&A on Signal Management (Rev 5, Jan 2026)

# EU Signal Management Process Example

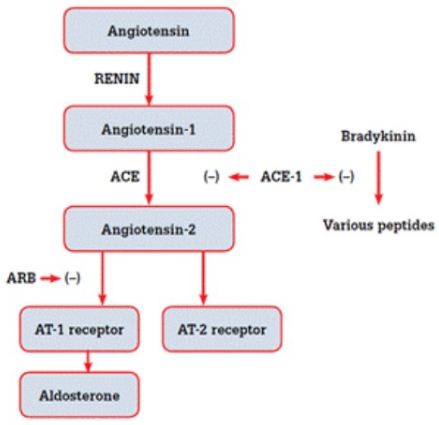
## ARBs & Intestinal Angioedema

## Angiotensin II receptor blockers (ARB)

*Signal of intestinal angioedema, EPITT 20104*

- **ARBs are indicated** for the treatment of hypertension, heart failure or asymptomatic left ventricular dysfunction, secondary prevention of coronary artery disease, diabetes mellitus and diabetic nephropathy, subject to certain conditions.
- **Intestinal angioedema is characterised** by fluid extravasation in the submucosal space of the intestinal wall, leading to symptoms such as chronic abdominal pain,diarrhea, nausea and vomiting.
- Intestinal angioedema known to be associated with other renin-angiotensin acting agents (e.g., ACEI)

Angiotensin II receptor blockers: azilsartan - EDARBI (CAP), NAP; irbesartan - APROVEL (CAP); IFIRMASTA (CAP); IRBESARTAN TEVA (CAP); IRBESARTAN ZENTIVA (CAP); KARVEA (CAP), NAP; irbesartan, hydrochlorothiazide - COAPROVEL (CAP); IFIRMACOMBI (CAP); IRBESARTAN HYDROCHLOROTHIAZIDE ZENTIVA (CAP); IRBESARTAN/HYDROCHLOROTHIAZIDE TEVA (CAP); KARVEZIDE (CAP), NAP; telmisartan - KINZALMONO (CAP), MICARDIS (CAP), PRITOR (CAP), TELMISARTAN ACTAVIS (CAP), TELMISARTAN TEVA PHARMA (CAP), TOLURA (CAP), NAP; telmisartan, amlodipine – TWYNSTA (CAP), NAP; telmisartan, hydrochlorothiazide - ACTELSAR HCT (CAP), KINZALKOMB (CAP), MICARDISPLUS (CAP), PRITORPLUS (CAP), TOLUCOMBI (CAP), NAP; valsartan, sacubitril – ENTRESTO (CAP), NEPARVIS (CAP); valsartan, amlodipine – COPALIA (CAP), DAFIRO (CAP), EXFORGE (CAP), NAP; valsartan, amlodipine, hydrochlorothiazide - COPALIA HCT (CAP), DAFIRO HCT (CAP), EXFORGE HCT (CAP), NAP; other fixed-dose combinations containing angiotensin II receptor blockers (NAP)




Source: EMA/PRAC Signal Recommendations – July & October 2024 Meetings

## Signal Management Process – Real-World Example

Part 1: Signal Detection & Review | ARBs & Intestinal Angioedema | Jul–Aug 2024

| Process Step | Date | What Happened | Outcome / Decision |
|---|---|---|---|
| 1 **Signal Detection** | Before Jul 2024 | EMA routine signal detection activities identified 45 EV cases of intestinal angioedema across multiple ARBs | *Signal flagged for PRAC review* |
| 2 **Prioritisation** | 8–11 Jul 2024 | PRAC agreed that intestinal angioedema can be considered a class-effect for ARBs and that further evaluation is warranted.<br><br>60-day timetable | *Rapporteur appointed; signal prioritised for assessment* |
| 3 **Data Gathering** | 28 Aug 2024 | Based on July PRAC signal recommendations, MAHs requested to comment on proposed PI updates | *MAH input deadline set (28 Aug 2024)* |

*Continued on next slide*

Source: EMA/PRAC Signal Recommendations – July & October 2024 Meetings

## Signal Management Process – Real-World Example

Part 2: Decision & Implementation | ARBs & Intestinal Angioedema | Oct–Nov 2024

| Process Step | Date | What Happened | Outcome / Decision |
|---|---|---|---|
| 4 **Assessment** | 28–31 Oct 2024 | PRAC reviewed all evidence including MAH responses; confirmed causal association | *SmPC §4.4/4.8 and PL updates recommended* |
| 5 **Recommendation** | 28-31 Oct 2024 | PRAC formally recommended MAHs submit variation to implement PI changes | *2 months for MAH for variation submissions (4.4. & 4.8.)* |
| 6 **Publication** | 25 Nov 2024 | October PRAC signal output and new SmPC/PL wording extracts published | *Implementable wording available in all languages (EMA/PRAC/499604/2024)* |

*Signal closed – PI update implementation complete*

Source: EMA/PRAC Signal Recommendations – July & October 2024 Meetings

## Recommended wording

**Summary of product characteristics**

4.4. Special warnings and precautions for use

*For olmesartan, irbesartan, valsartan, losartan and candesartan:*

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists, [including <INN>] (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, <INN> should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

*For azilsartan, eprosartan and telmisartan:*

Intestinal angioedema

Intestinal angioedema has been reported in patients treated with angiotensin II receptor antagonists (see section 4.8). These patients presented with abdominal pain, nausea, vomiting and diarrhoea. Symptoms resolved after discontinuation of angiotensin II receptor antagonists. If intestinal angioedema is diagnosed, <INN> should be discontinued and appropriate monitoring should be initiated until complete resolution of symptoms has occurred.

4.8. Undesirable effects

*For olmesartan, irbesartan, valsartan, losartan, and candesartan: addition within the table of adverse reactions for the respective ARB. For losartan, olmesartan and irbesartan the frequency should be "rare". For valsartan and candesartan, the frequency should be "very rare":*

SOC Gastrointestinal disorders

Intestinal angioedema

*For azilsartan, eprosartan and telmisartan:*

Description of selected adverse reactions:

Cases of intestinal angioedema have been reported after the use of angiotensin II receptor antagonists (see section 4.4).

**Package leaflet**

For all ARBs (olmesartan, azilsartan, candesartan, eprosartan, irbesartan, valsartan, losartan and telmisartan):

2. What you need to know before you take X

Warnings and precautions

Talk to your doctor if you experience abdominal pain, nausea, vomiting or diarrhoea after taking <X>. Your doctor will decide on further treatment. Do not stop taking <X> on your own.

4. Possible side effects

*For olmesartan, irbesartan, valsartan, losartan and candesartan addition within the table of adverse reactions for the respective ARB. For losartan, olmesartan and irbesartan the frequency should be "rare". For valsartan and candesartan, the frequency should be "very rare":*

Intestinal angioedema: a swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting and diarrhoea

*For azilsartan, eprosartan and telmisartan:*

Frequency 'not known': Intestinal angioedema: a swelling in the gut presenting with symptoms like abdominal pain, nausea, vomiting, and diarrhoea has been reported after the use of similar products.

Source: EMA/PRAC Signal Recommendations – July & October 2024 Meetings

ivigee services

# Artificial Intelligence in PV

# Artificial Intelligence in Pharmacovigilance (PV)

Opportunities and Responsibilities – CIOMS XIV

## Why AI is Emerging in PV

### 1 Increasing Data Volume & Complexity

- Rapid growth of ICSRs and safety databases (e.g., EV, VigiBase, FAERS)
- Expansion of data sources: literature, electronic health records, registries, social media, RWD
- Increasing regulatory expectations and shorter timelines

### 2 AI Use Cases Across the PV Lifecycle

- Case intake & processing (extraction, coding, triage)
- Signal detection & prioritisation
- Literature screening and document review
- Translation and structured query generation
- Summarisation of safety information

## Potential Benefits

**Efficiency**

Improved efficiency and scalability of PV operations

**Speed**

Faster detection of emerging safety signals

**Consistency**

Enhanced consistency in repetitive tasks

**Evidence Synthesis**

Support for evidence synthesis from large unstructured datasets

**Important:** AI supports decision-making — it does not replace medical or regulatory judgment.



Source: CIOMS XIV Working Group – Artificial Intelligence in Pharmacovigilance

# Artificial Intelligence in Pharmacovigilance (PV)

Opportunities and Responsibilities – CIOMS XIV (continued)

## Important Caveats

**Probabilistic, Not Infallible**

AI outputs are probabilistic — results must always be critically reviewed before use in safety decisions

**Context-Dependent Performance**

Performance depends on context of use and the quality of input data — biased data leads to biased results

**Human Judgment First**

AI supports decision-making — it does not replace medical or regulatory judgment in PV

## Key Takeaways

### 1 AI is Transformative for PV

- PV data volumes are growing exponentially
- AI addresses scalability and efficiency challenges across the lifecycle
- Use cases span case intake, signal detection, literature review, and summarisation
- Enables faster detection of emerging safety signals

### 2 Responsible Implementation is Essential

- Human oversight remains essential at every stage of the PV process
- AI augments, but does not replace, expert medical and regulatory judgment
- Context of use, data quality, and governance are critical success factors
- Outputs must be validated and critically reviewed before safety decisions



Source: CIOMS XIV Working Group – Artificial Intelligence in Pharmacovigilance

## Core Principles for Implementation

CIOMS XIV – Artificial Intelligence in Pharmacovigilance

| | | |
|---|---|---|
| 1 | **Risk-Based Approach** | Assess model influence and decision consequences; oversight proportional to patient and regulatory impact |
| 2 | **Human Oversight** | Human-in-the-loop or human-on-the-loop; clear accountability and defined responsibilities |
| 3 | **Validity & Robustness** | Fit-for-purpose validation; real-world performance monitoring; continuous re-evaluation |
| 4 | **Transparency & Explainability** | Document model purpose, inputs, and outputs; communicate limitations; enable auditability |
| 5 | **Data Privacy** | Protect personal health information; comply with data protection regulations; caution with generative AI |
| 6 | **Fairness & Equity** | Avoid bias amplification; ensure representative training data; evaluate subgroup performance |
| 7 | **Governance & Accountability** | Defined ownership; lifecycle oversight; ongoing risk management |

Source: CIOMS XIV Working Group – Artificial Intelligence in Pharmacovigilance

## AI — Which One?

Comparing AI Types: From Rule-Based Automation to Autonomous AI

| Characteristic | Automation (Rule-Based) | Predictive AI / ML | Generative AI | Agentic AI | Autonomous AI |
|---|---|---|---|---|---|
| Core Principle | Predefined rules (if-then logic) | Statistical learning from historical data | LLMs generating new content | LLM + tools + multi-step planning | Self-directed decision-making |
| Data Learning | No learning from data | Yes | Yes (pre-trained + fine-tuned) | Yes | Yes |
| Unstructured Text / Reasoning | Very limited / No reasoning | Limited / Limited | Strong / Moderate | Strong / Yes | Strong / Advanced |
| External Tools / Autonomy | Scripted only / Low | Typically no / Low-Moderate | With integration / Moderate | Core capability / High (bounded) | Fully integrated / Very High |
| Explainability | High (transparent rules) | Moderate (model-dependent) | Moderate | Lower (complex workflows) | Potentially low |
| Regulatory Suitability (GxP) | High | Moderate (validated models needed) | Moderate (requires grounding, verification against real data sources) | Complex (strong governance) | Very challenging |

## 1. Automation

AI applications across signal management activities

**Automation (Rule-Based)**

**Characteristics**

- Rules if-then defined by human, predefined repetitive workflows, RPA

**Use in Signal Management**

- **Standardization od data**: MedDRA/WHO mapping, check of mandatory fields, duplication detection
- **Periodic calculations**: Planned disproportionality calculations, defined reports
- **Rule-based triage & prioritization**: product + serious PT + pediatric -> high priority
- **Generation and maintenance of evidence**: automated signal tracking, audit trail, comments

**Benefits**

- Speed, consistency, auditability

**Limits**

- Needs exact rules, cannot work with unclarity or unstructured information

## Predictive AI/ML

AI applications across signal management activities

**Predictive AI / ML**

**Characteristics**

- Models trained on historical structured data and predict the result (risk, probability, trends, etc.)
- No text generation, only numbers, scores

**Use in Signal Management**

- **Detection of anomalies**: proactive detection (or even prediction) of ”unusual” increase of PT/SMQ, country, batch, age group etc.
- **Prioritization**: identified probability of actionable signal based on defined characteristics (seriousness, new, consistency, biologic plausibility, class effect etc.)
- **De-duplication, case linking:** probabilistic pairing of similar cases across data sources
- **Quality of data sources**: prediction of missing data, detection of inconsistencies (e.g., age vs indication vs dosage)

**Benefits**

- Improved triage and speed, less false alarms

**Limits**

- Depends on quality (and quantity) of training data, need for continuous re-validation, risk of bias

## Generative AI

Generative AI

AI applications across signal management activities

**Characteristics**

- LLMs, can created text and prepare new content (summarization, extraction, classification)
- Conversational, work with natural language (e.g., ChatGPT, Claude, Gemini, Mistral)

**Use in Signal Management**

- **Triage from narratives or literature**: quick summary of key information from ICSRs (time relevance, dechallenge/rechallenge, comorbidities, concomitant medication).
- **Semantic grouping**: identification of similar naratives/events (although different verbatim)
- **Document drafting**: Signal validation reports, draft of communication, drafts for presentation in PSUR/DSUR
- **Extract, normalize**: pre-fills structured fields from free text
- **Intelligent search**: e.g., show me all cases of X + Y + time relevance + pediatric across all provided data sources

**Benefits**

- Speed of work with text, improved transparency, clarity

**Limits**

- Halucination -> human oversight necessary

## Agentic AI

Agentic AI

AI applications across signal management activities

**Characteristics**

- Generative AI + ability to perform multiple steps (plan, decide, call tools, create ticktes, workflows)
- Can divide the task, decide, use other tools, check mistakes, continues until task is finished, finds own ways

**Use in Signal Management**

- **Orchestration**: find case series -> run analysis (disproportionality, trends, stratification) -> prepare tables and charts -> draft assessment, list open questions -> create/update signal in tracking system -> divide tasks
- **Continuous monitoring**: regularly assess pre-defined hypothesis, monitors thresholds
- **Evidence assembly**: collects relevant information from multiple sources (ICSRs, SDB, HER, literature, AE connected with MI/PQC)

**Benefits**

- Huge savings in time, less manual steps, improved consistency of process

**Limits**

- Governancy (what can do without human), access rights, audit trail, robust testing / validation

## Autonomous AI

AI applications across signal management activities

**Autonomous AI**

**Characteristics**

- Independent, defines goals, changes stragies, acts without human involvement

**Use in Signal Management (theoretical)**

- **Autonomous screening & recommendations**: independently maintains the list of signal candidates, changes thresholds per season and reporting dynamics, suggests priorities
- **Autonomous planning of work:** divides workload, suggests deadlines, escalation if risk of non-compliance
- **Closing of "low-risk signals":** decides, what is "low-risk"

**Benefits**

- The highest effectivity

**Limits**

- Decisions about humans not done by humans

## Use in Pharmacovigilance & Signal Management

How Each AI Type Applies to Signal Management Activities

| Activity | Automation | Predictive AI / ML | Generative AI | Agentic AI | Autonomous AI |
|---|---|---|---|---|---|
| Data Processing | Rule-based filtering, MedDRA checks | Data quality scoring | Extraction from narratives | Orchestrates validation workflows | Self-adjusting monitoring logic |
| Signal Detection | Fixed disproportionality thresholds | Anomaly detection, trend prediction | Contextual interpretation of results | Runs analyses + interprets outputs | Dynamic threshold adaptation |
| Case Triage | Prioritization by seriousness, product, etc. | Predicts actionable signal likelihood | Summarizes ICSRs, clusters narratives | Full triage package generation | Self-prioritization of pipeline |
| Signal Validation | Checklist enforcement | Predictive plausibility scoring | Draft validation report, literature summary | Evidence collection + structured dossier | Proposes validation decision (human review req.) |
| Signal Assessment | Template-driven documentation | Comparative statistical modeling | Draft assessment rationale | Multi-source evidence integration | Suggests regulatory action |
| Documentation | Auto-generation of tracking records | Forecasting reporting burden | Draft PSUR/DSUR signal sections | End-to-end document assembly | Continuous auto-updated safety report |
| Monitoring | Reminder systems, SLA tracking | Predictive workload modeling | Periodic executive summaries | Continuous monitoring + task allocation | Autonomous lifecycle management |
| Human Oversight | Low | Moderate | High (content verification) | Very High (decision control) | Mandatory at all critical decisions |

## Examples of solutions

CIOMS XIV examples

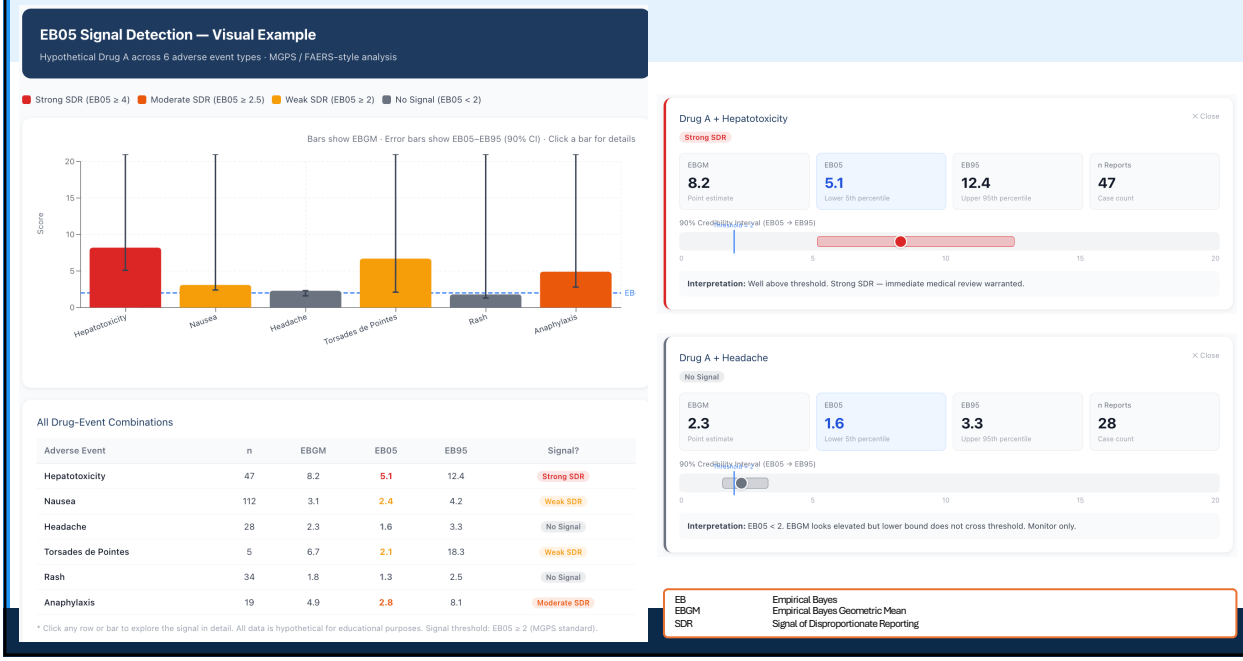
**Table 1: Examples of deployed artificial intelligence solutions in pharmacovigilance described in the public domain**

*Source: CIOMS XIV working group*

| AI solution | Pharmacovigilance context / database |
|---|---|
| Automated coding of medicinal products | VigiBase[21] |
| Duplicate detection | FAERS,[98] VigiBase[15] |
| Automated triages of individual case reports | Swedish Medical Products Agency[34], pharmaceutical companies[99] |
| Automated triages for quantitative signal detection | Databases of various regulatory authorities, international organisations, and pharmaceutical companies |
| Predictive models for quantitative signal detection | VigiBase,[56,100] Netherlands pharmacovigilance centre Lareb[101] |
| Adverse event cluster analysis for signal detection and assessment | VigiBase[80,102] |
| Literature surveillance for safety data | EudraVigilance[103] Netherlands pharmacovigilance centre Lareb[104] |

Source: CIOMS WG XIV – AI in Pharmacovigilance (2025)

## Examples of solutions



## Future of AI in Signal Management

From detection to prediction and prevention

- Real-time / near-real-time signal detection at unprecedented speed and scale
- Shift from post-approval to early-stage development signal detection
- PV evolves from reactive reporting → proactive prediction and prevention
- Expert AI systems tailored to therapeutic areas (oncology, immunology, vaccines)
- Integration of multi-modal data: electronic health records, genomics, internet of things, wearables
- Advanced systems may develop refined medical judgement — but human oversight remains crucial
- Signal management is one of the “critical” PV processes – any AI element in PV system must comply with GVP
- Human oversight: HIC – HITL – HOTL
- Safety of AI
- Regulatory environment (e.g., The EMA Reflection Paper on the Use of Artificial Intelligence (AI) in the Medicinal Product Lifecycle, 9 Sep 2024)

# Thank you.

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