Industry perspective on signal management

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1st EMA/HMA multi-stakeholder forum on EudraVigilance and signal detection

EU Regulation Changes

End of the EVDAS Pilot Phase

- The EudraVigilance Data Analysis System (EVDAS) pilot program, which ran from February 2018 to July 2025, has officially concluded with the entry into force of Regulation 2025/1466 on August 12, 2025.

Key Regulatory Changes Under Commission Implementing Regulation (EU) 2025/1466

- **Article 18, Paragraph 2 and 3 Revision**:
  - MAHs monitor and use EudraVigilance data alongside other available sources, representing a shift from routine monitoring to integration.
  - EMA and NCAs will assume responsibility for continuous, risk-based monitoring, this will no longer be performed by MAHs
- **Article 21, Paragraph 2 Deletion**: The standalone signal notification form has been eliminated, requiring MAHs to handle all signals through their internal signal management processes according to GVP Module IX

Implementation Timeline

- **August 12, 2025**: EudraVigilance monitoring and signal management changes
- **February 12, 2026**: Remaining provisions including PSMF documentation, subcontracting requirements, and PSUR updates
- **GVP Module IX Update:** Scheduled for Q2 2026 to reflect new regulatory framework

Q&A on IR (EU) 2025/1466

- **3. What are the expectations for MAHs regarding the implementation of Article 18, paragraph 2 of Implementing Regulation (EU) No 520/2012?**

MAHs should describe the changes driven by the updated IR 520/2012 in their signal management and pharmacovigilance procedures. In relation to Art 18, paragraph 2, MAHs should describe how the data in EudraVigilance will be monitored and how those data will be used in conjunction with other available sources.

During the signal management activities, MAHs shall monitor the data available in EudraVigilance in conjunction with those from other available data sources within their established processes with a frequency proportionate to the risk, the known safety profile of the product and the characteristics of the product.

During the assessment of signals led by the PRAC, and in response to PRAC requests for cumulative reviews, analyses, and proposed actions, MAHs are expected to consider and include all relevant data available also in EudraVigilance. This should be done in accordance with the specific context of the substance on the market (e.g. different indications, formulations, or routes of administration) and the scope of the signal.

Tier-Based Signal Management

Definition:

A tier-based approach in signal management is a risk-proportionate strategy where products are grouped into categories (tiers) based on their safety profile, regulatory status, and other risk factors. Each tier is assigned a different frequency and intensity of signal detection activities.

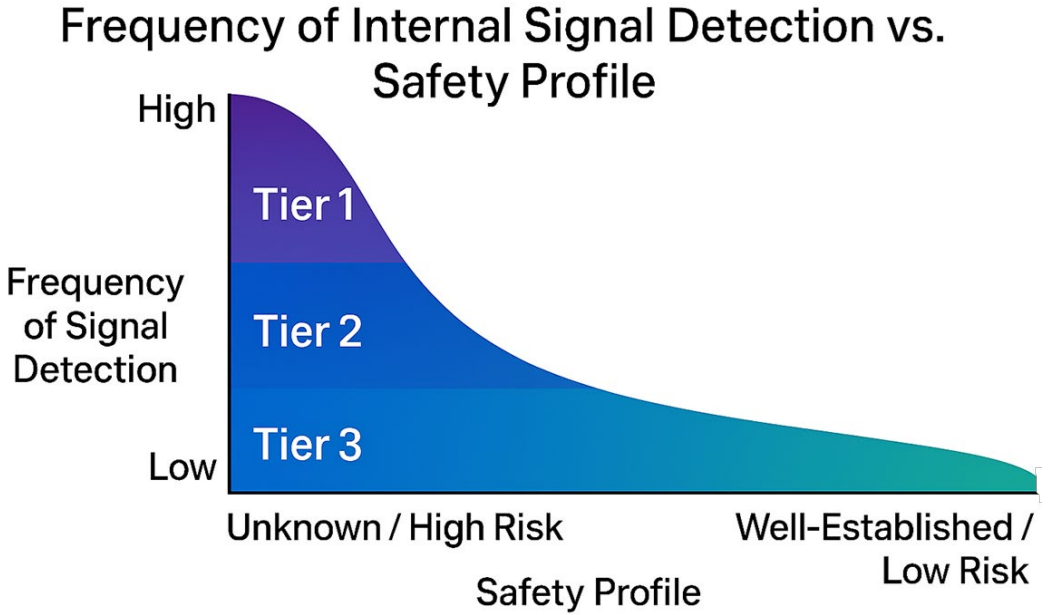
Purpose:

- Focus resources on higher-risk products
- Ensure timely identification of safety concerns
- Align with regulatory expectations for risk-based pharmacovigilance

Outcome:

- Efficient signal management

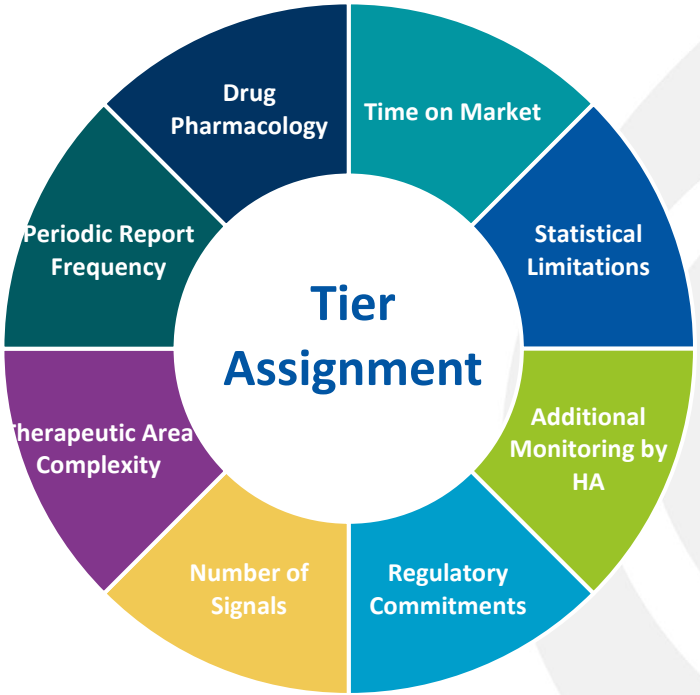
Tier-Based Signal Management



Disclaimer:

This diagram is provided solely as an illustrative example to explain the concept of a risk-based approach to signal detection. It does not represent a regulatory requirement or a standardized practice. The number of tiers, monitoring frequencies, and other parameters may vary across Marketing Authorization Holders (MAHs) depending on their internal processes and product portfolios.

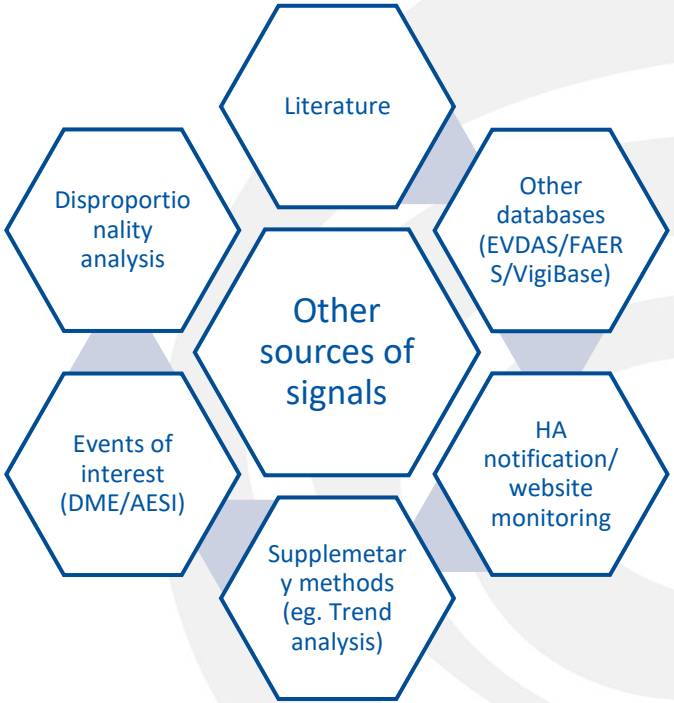
Criteria for Tier Assignment – Multi-Factorial Approach



Disclaimer: *This slide is provided as an illustrative example. The criteria listed for tier assignment may vary across different MAHs and are not exhaustive or limited to those shown here.*

Tier-Based Signal Management

- **Proportionate monitoring:**
  - Higher-risk products (e.g., new chemical entities, products under additional monitoring, or with known risks/regulatory commitments) are monitored more frequently and may involve additional sources or methods compared to lower-risk products (eg. mature products, generics, biosimilars).
- **Beyond disproportionality analysis:**
  - Tier-based approach also may influence which additional sources (eg. FAERS) and methods (eg. trend analysis) are considered and when they are used.
- **Flexible application:**
  - Principles are risk-based and adaptable



This concept is not prescriptive; practices vary across organizations

Experience of EVDAS Data Use

- EVDAS, including eRMRs with statistical disproportionality results, provides MAHs, EMA, and NCAs access to one of the largest pharmacovigilance databases and signal detection tool.
- Strengths of EVDAS continue to be leveraged by EMA and NCAs (new EU regulation).
- MAHs use EudraVigilance data alongside other available sources
- MAHs continue to leverage EVDAS for validation or evaluation of signals
- Use of EVDAS data to support signal analysis:
  - The volume and complexity of data require pragmatic review and resource prioritization
  - Experience with EVDAS:
    - Operational complexities with deduplication management,
    - Line listing review requires additional information from cases for assessment
    - Case download format requires conversion for readability via EVWEB or xml viewer
    - Case reports quality (for completeness and accuracy) require collaborative efforts

Risk-Based Signal Management

Risk-Based Signal Management

- Proportionate analysis
- Flexibility
- Data-drive prioritization

Risk based approach transforms challenges into strategic advantage

Benefits

- Improve efficiency
- Fit for purpouse
- Adaptable to different product types (generic/biosimilar, innovative)

Perspectives Across the Industry

- Regulatory expectations and compliance obligations are consistent across MAHs
- Resource availability and capability differences within industry

Leverage strategic advantages in signal detection approaches

Generic/Biosimilar MAH Strategies:

- **Reference Product Monitoring:** Systematic surveillance of innovator safety updates and regulatory actions
- **Collaborative Approaches:** Industry consortium participation and shared surveillance platforms
- **Formulation-Specific Focus:** Targeted monitoring for formulation-related adverse events

Innovator MAH Strategies:

- **Proprietary Data Access:** Comprehensive safety databases from clinical development and post-marketing surveillance
- **Research Integration:** Seamless incorporation of preclinical, clinical, and epidemiological data sources
- **Regulatory/Scientific Engagement:** Proactive engagement with regulatory authorities and scientific advisory committees

Q&A