Succeeding with Revised GVP Module IX: Seizing the Opportunity and Managing the Challenges

Regulatory & Safety

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Signal management remains a cornerstone of ensuring patient safety. The release of the revised Good Pharmacovigilance Practices (GVP) Module IX – Signal Management on 16th October 2017, which updates the June 2012 version, brings further clarification and additional regulatory requirements for the marketing authorisation holder (MAH). From 22nd February 2018, MAHs with an active substance on the EMA pilot additional monitoring list are obliged to monitor the EudraVigilance Data Analysis System (EVDAS) for new and existing signals with a frequency proportionate to the identified risk, potential risks and need for additional information. The pilot will last one year, after which the EMA will release further guidance based on the information gained through the pilot. This update to the EudraVigilance (EV) system aims to provide better detection of new or changing safety issues by giving users access to data on their products and the ability to customise reports in various formats, and is one of the main driving forces behind the update of GVP Module IX.

This article summarises the changes in the Module IX revision and provides insights on how industry can seize the opportunity to meet the associated challenges through improvement of signal management processes and technology.

Module IX revision presents an opportunity to review Signal Management

The update to Module IX is a major revision which impacts Pharmacovigilance, regulatory (i.e. labeling), and quality functions. The main changes are summarized below:

EudraVigilance Data Analaysis System (EVDAS)

- Legal requirement for MAH's to monitor EudraVigilance at least every six months and inform the European Medicines Agency (EMA) and National Competent Authorities (NCAs) of any new validated signals.
- Signals identified and validated through continuous monitoring of EVDAS should be reported to the EMA via Standalone Notifications within 30 days.

Terminology

- Emerging Safety Issues (ESIs), which require the urgent attention of the Competent Authorities, were previously detailed in GVP Module VI, have now been re-defined in Module IX.
- A new sub-chapter on terminology has been introduced in order to clarify key definitions such as 'signal', 'signal validation' and 'signal confirmation'. Some terms apply only to the EU signal management process.

Roles and Responsibilities

- The roles and responsibilities of all stakeholders involved including the MAH, Competent Authorities of member states, the Pharmacovigilance Risk Assessment Committee (PRAC) and the EMA, have been further clarified to reduce ambiguity.
- Signals detected through the continuous monitoring of EudraVigilance will undergo a specific process of prioritization and assessment by the PRAC.

Timelines

- For signals detected through EV monitoring which are subsequently validated, a Standalone Notification should be submitted to the EMA within 30 days, unless the substance is on the EURD list and the PSUR is due within 6 months.
- For signals detected through the monitoring of EV data which require an update to the product information and/or the RMP, a variation application is required to be submitted to the Competent Authorities within 3 months for important risks and 6 months for adverse reactions or risks not considered important.

New Addendum I

- "Methodological Aspects of Signal Detection from Spontaneous Reports of Suspected Adverse Reactions" provides detailed guidance on statistical signal detection methods, and monitoring of designated medical events (DMEs), specific patient populations and other special situations.

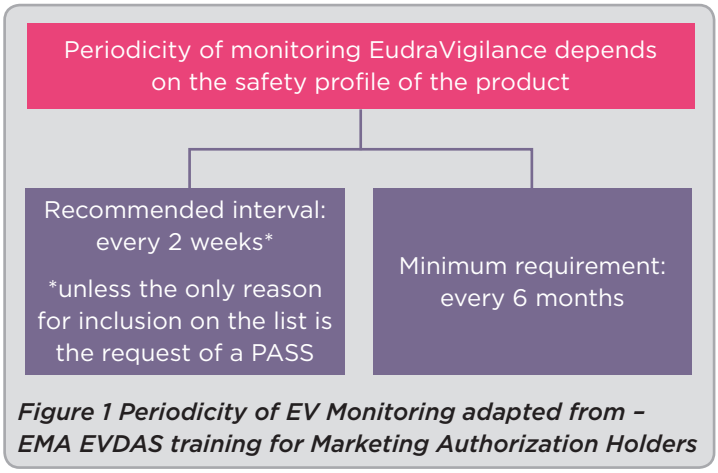

Figure 1 Periodicity of EV Monitoring adapted from – EMA EVDAS training for Marketing Authorization Holders

The changes required to comply with revised Module IX present an opportunity for review and improvement of a company's signal management process. We will explore four aspects of signal management: fit-for-purpose detection; timely informed assessment and action; oversight and tracking; and future readiness. For each aspect, we will review where the revised Module IX brings challenges and opportunities including: improved signal identification, better signal tracking, a narrowing of the gap from signal to patient, and greater operational efficiency.

Fit-for-purpose signal detection

A phrase often heard in relation to the revised GVP Module IX and signal management is 'no one size fits all'. What exactly does this mean?

As signal management processes become more granular, there has been a shift towards bespoke designs for signal detection, tailored to the benefit-risk profile of specific products, rather than taking the same approach for every product in the entire portfolio. It is no longer sufficient to apply the same methodology for signal detection company-wide, as regulators request evidence that the benefit-risk profile of a product is continually reviewed. The same process operating at the same frequency is unlikely to fit both a mature, low-risk product and a new-to-market product with important identified risks.

Fit-for-purpose signal detection can be achieved through the implementation of a signal surveillance process tailored to the benefit-risk profile of the products concerned. Using degree of risk to prioritize effort allows PV teams to strategically manage the allocation of resources. For example, a very low-risk product may only require EVDAS monitoring every three to six months, whereas higher risk products may require more frequent monitoring and data analysis. Better defined timelines in Module IX enable industry to achieve a greater level of consistency of communication regarding signals both internally and externally within their organizations, but for some, the obligation to monitor EV triggers concerns with resourcing the workload increase and questions about whether this additional source of data is a duplication of efforts.

The EMA recommend that the following factors should influence how often to monitor EudraVigilance: time since first authorization, patient exposure, potential risks, PSUR frequency, and any safety concern of interest in

specific situations. Periodicity of signal detection activities is a key element to the signal surveillance strategy, not just for EVDAS monitoring but also for other routine quantitative and qualitative signal detection. Using a tier-based approach is one way that some companies have distinguished between levels of priority and can determine source of signal detection, activities and frequency of monitoring. Core sources could include ICSR review and literature. Non-core sources could include statistical analysis and EVDAS. Not all signal surveillance activities are suitable for all products. An approach that has been tailored to the benefit-risk profile of a product can be successfully used by companies to prioritize the key signal detection activities necessary for that product. Figure 2 provides an example of a tier-based approach.

	Tier 1	Tier 2	Tier 3
Product profile	New Product with evolving safety profile <2 years since IBD	Young Product with stabilising safety profile 2-5 years since IBD	Mature Product with established safety profile >5 years since IBD
Signal detection sources	ICSR Literature Statistical detection EVDAS: every 2 weeks	ICSR Literature Statistical detection EVDAS: every month	ICSR Literature EVDAS: every 3-6 months
Signal detection activities	ICSR review Literature review DME's Special situations Data mining EVDAS review	ICSR review Literature review Data mining EVDAS review	ICSR review Literature review EVDAS review
Frequency of monitoring	Every Month	Monthly to Quarterly	Semi-Annually

Table 1: An example of fit for purpose detection in a tier-based approach

Timely informed assessment and action

The duration of time 'from signal to patient' is an area of focus and has been highlighted by regulatory inspections in recent years. Pharmaceutical companies are having to justify length of time taken from evaluating a signal to communicating new safety information to the patient via a label update or other methods, especially for serious risks which impact public health. For signals identified and validated through continuous monitoring of EudraVigilance, there will be three separate requirements to report to the EMA:

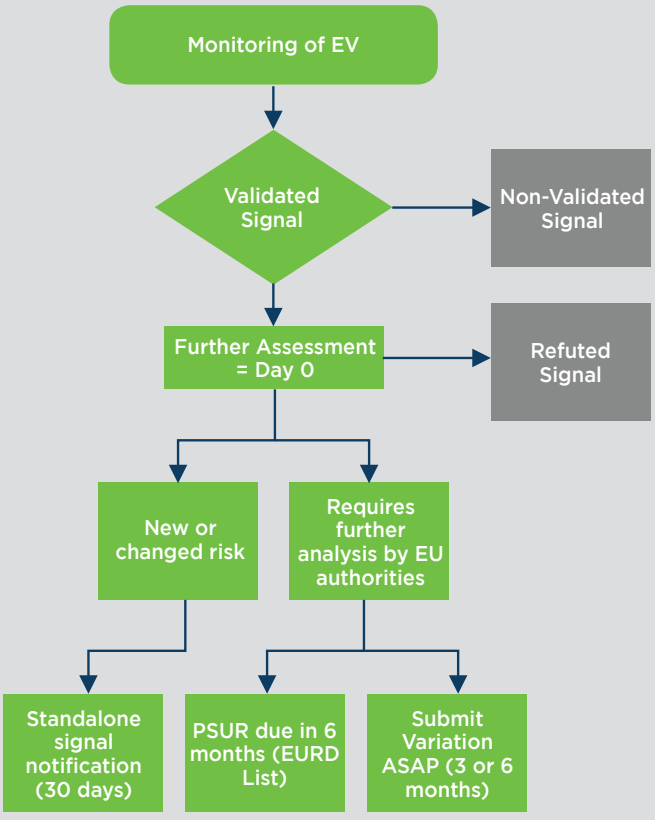

Figure 2: Handing of Signals detected through monitoring of EudraVigilance

- If the signal has been validated and requires further analysis, a Standalone Notification must be submitted to the EMA within 30 days of signal validation, unless the signal is included in the PSUR and that PSUR is due within 6 months
- If the signal is included in the PSUR, and is due within 6 months this needs to be submitted as per the usual process
- For signals which require an update to the RMP or product information, a variation application will need to be submitted to the EMA as soon as possible, within 3 months for important identified risks, and 6 months for risks not considered important.

These updates reinforce the need for clearly defined internal timelines throughout the entire process from the point of signal detection to completion of a recommended action. In our experience, we have observed that companies differ in their preference of setting internal timelines, some preferring to track the process from the identification of a safety observation until recommended actions are completed, whilst others opting only to set a timeline from the point in which a signal is validated, until a decision

is made (i.e. confirmed or refuted). Whichever internal timelines you choose, it is imperative that these are clearly documented, and all necessary employees trained, especially with the EMA defined timelines for signals identified through EudraVigilance. It should be clearly identifiable from company SOPs which signal process will be followed, regardless of source of data. There are clear benefits to maintaining the same timelines for both signals detected through EudraVigilance, as opposed to 'other sources', as with any consistent process – this avoids confusion and is a more conservative approach, but the impact on capacity, capability and cost need to be considered. With no regulatory obligation (yet) to adhere to the EMA timelines for signals from 'other sources', some may choose to only do what is 'necessary', for now.

Cross-functional teams support the timely informed assessment of signals throughout their lifecycle. The management of a signal depends on prioritization, but timelines that fall outside the realm of safety become much harder for the safety team to track. For that reason, it is essential for cross-functional teams to be effective and efficient, utilizing safety and medical governance structures to meet deadlines and achieve key milestones. The opportunity to involve a cross-functional team such as a benefit-risk team (BRT) can occur at several points in the process from signal detection and validation, to assessing and prioritizing the signal, to the implementation of the action to address the signal.

As products undergo routine data mining to identify signals, it is likely that members of the BRT will already be aware of signals 'under the microscope' which have not been validated yet, based on knowledge of the safety profile of the product, known risks, and information in aggregate reports. This early involvement of key cross-functional stakeholders (e.g. medical safety physicians, epidemiology, safety scientists, QPPV, risk management, and labeling) can lead to efficiency and transparency right from the start, especially with the new requirement to submit applications for variations to product information within three months for important risks. As this requirement affects labeling just as much as safety, the earlier communication channels open, the better. For example, if labeling is involved in the BRT meetings during signal validation and assessment, a decision to update the label later would not be a 'surprise', and resources can be ready when action is needed. In parallel, safety can work alongside labeling to carry out the Pharmacovigilance necessary tasks such as author a signal evaluation report, update the risk management plan (RMP) or periodic safety update report (PSUR), all within the three-month timeframe.

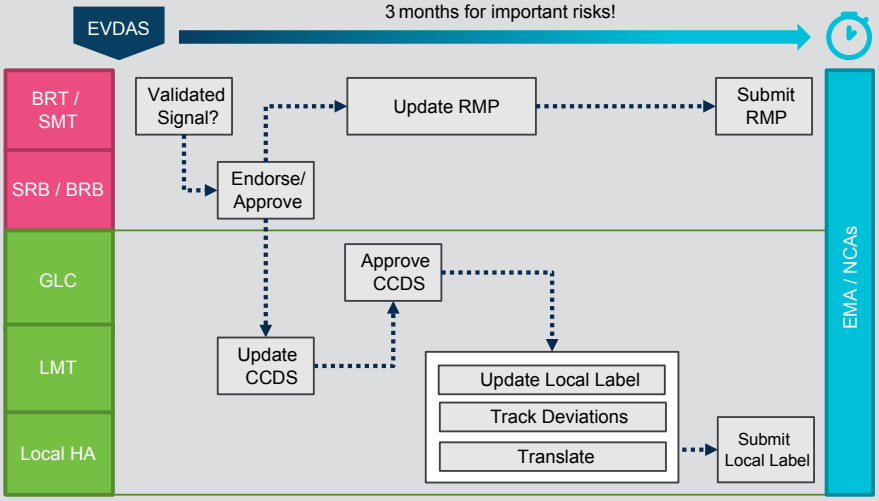

Figure 3: An example of how cross-functional teams must work together with the new EMA timeline

For every MAH, there are a number of decision points which must be established. For example, once a signal is confirmed, will it automatically form part of the RMP? What are the criteria for whether or when a signal becomes an important identified risk? Who makes the decision when day zero begins? The natural connection between signal management and risk management is strengthened through well-defined processes and established governance. If the validated signal is an important identified risk, and requires an update to the RMP, key players such as risk management and labeling can work together to ensure oversight and adherence to the three-month regulatory timeline. With labeling playing a key role in the BRT, they can inform on the status of local health-authority (HA) submission and approval. One further point of consideration is that establishing clear Key Performance Indicators (KPIs) across signal management activities provides cross-functional teams with oversight, allowing companies to stay on top of tracked signals and prioritise products with higher risk.

Oversight and tracking

In order to meet new demands from the EMA in Module IX, existing signal management processes will likely need to be created, updated, or refined. How do teams effectively coordinate, if signals are being validated and confirmed, the PSUR is due within two months, and the product label requires an update by the end of the quarter? Furthermore, how will industry ensure that compliance is maintained and timelines are met? There are several ways to enhance oversight of these processes and the use of available tools and technology can play a key role. Though there are several tools available that support signal management, the fit-for-purpose solution will depend on factors such as your product portfolio, size and scale of business and overall strategy.

Navitas Life Sciences Model for Success

Fit for purpose detection

With varying product portfolios, there is no one-size-fits-all. It is important to have a strategy in place that is fundamentally benefit-risk driven and considers prioritization and activity periodicity.

Timely informed assessment and action

Early engagement of the BRT and use of clearly defined timelines throughout the entire process from the point of a safety observation to completion of a recommended action is an efficient and collaborative approach to signal management.

Oversight and tracking

A single centralized system to track the complete 'lifecycle' of a signal through label implementation strengthens oversight and reduces the likelihood of inspection findings.

Future Readiness

Pro-active monitoring and utilization of EVDAS as well as maintaining insight on the latest regulatory intelligence is the key to staying on the right side of compliance and being prepared for the future.

The latest revision of GVP Module IX presents an opportunity for Pharmaceutical Companies to review and improve impacted signal management processes and technology. Navitas Life Sciences is a global life sciences company with a combined total of over 100 years Pharmacovigilance consulting experience. If a further discussion about any of the insights within this paper would be helpful, then please contact us using the details below and one of our subject matter experts will be happy to have a conversation in the context of your specific needs.

The benefits of a single centralized system to track the lifecycle of a signal from the moment that an ICSR trend such as increased frequency or severity is detected (safety observation) through to the update of a label or other recommended action are clear. An integrated, end-to-end tool which works in sync with the safety database to review ICSRs, as well as other sources for statistical detection (e.g. Vigibase and FAERS) simplifies the signal tracking process, as all data are visible in one place. The tool should allow tracking throughout the potential validation of signals, through to creation of signal evaluation reports, signal decisions, actions and closing of signals, regardless of source. It is better still if that tool also tracks label updates to the point of health authority approval and subsequent implementation in the market to HCPs and patients, although the choice of tools such as this are currently limited.

Setting timelines and responsibilities within the tool, according to established processes, will allow for better collaboration with team members also working on upcoming aggregate reports. Being able to easily extract data from the tool supports the creation of summary tabulations for aggregate reports and data mining, and provides justification to an inspector why a signal might not have been validated at a particular time. Several tools for signal detection currently exist on the market, but changes are expected in this space due to emerging technologies. The EMA have not currently announced any plans for integration between EVDAS and signal detection software platforms, so EudraVigilance data will have to be 'manually' added for the time being.

Future Readiness

The long-awaited update of GVP Module IX is a positive step towards improving global patient safety, and a key expectation from one of the leading worldwide regulatory bodies, but it will not be the last. Signal management is a continually evolving process – and the question remains: how will industry adapt to be able to manage the future state? The newly released EudraVigilance 8 system, and the requirement to monitor EVDAS is a significant change which aspires to improve the speed and accuracy with which signals are detected and the way that signals are managed overall. With a larger repository of case data, and better tools to identify signals, plus the evolving regulatory requirements, workload for Pharmacovigilance teams and cross-functional collaborators could significantly increase. As the global volume of data grows, new tools and automation within existing tools to decipher adverse events and signals are imperative. With this in mind, companies must have the infrastructure necessary to continually show their products are maintaining a favourable benefit-risk balance in dynamic therapeutic landscapes. Updates to this process will undoubtedly be released over time, and maintaining insight on the latest regulatory intelligence is the key to staying on the right side of compliance.

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