The key to more efficient risk–benefit analysis

Improving literature monitoring for safety signal detection can positively impact the whole life cycle of a drug. Besides the obvious potential for more efficient and compliant pharmacovigilance reporting, the insights can also translate into vastly better risk–benefit assessments. Here, we look at 5 key steps in improving the efficiency of literature screening workflows.
Why monitor the biomedical literature?

Pharmacovigilance is an essential function in drug development. A strong drug safety strategy goes beyond meeting a legal requirement – it is a commitment to patient safety and has the potential to impact the drug life cycle. Safety signals found in pharmacovigilance activities can translate into crucial insights for understanding the risk–benefit balance of medicinal products. All market authorization holders are familiar with the need for a thorough pharmacovigilance system. It’s vital to capture adverse drug reactions (ADRs) through monitoring spontaneous reporting systems, the biomedical literature, medical forums and even, to a certain extent, social media. Regulatory authorities worldwide require timely reporting of ADRs and pharmaceutical companies are (sometimes painfully) aware of the financial consequences of missing an ADR or a reporting deadline.

The biomedical literature has become a valuable source of information about adverse events and other drug safety signals. In fact, to avoid missing information that might require a report or inform risk–benefit assessments, it’s essential to maintain a comprehensive and efficient system for monitoring literature databases.

Various types of adverse reactions are reported at different rates in spontaneous reporting systems and the literature. For example, gastrointestinal ADRs are consistently more highly reported through spontaneous reporting systems than in peer-reviewed literature. The opposite is true for injury, poisoning and related complications (Table 1). Thus, any comprehensive pharmacovigilance strategy must include monitoring of the biomedical literature.
Boosting the efficiency of biomedical literature screening

The ever-increasing amount of scientific information presents a major challenge as methods need to be put in place to ensure it is reviewed in its entirety to confidently claim that all ADRs have been captured. If the literature databases used are not comprehensive and/or the search strings and literature management processes and workflows are not optimized, there is a risk of missing safety information.

Covering all the bases with traditional methods — in other words, to have more eyes searching for and reviewing the literature from more databases — means increased costs, more working hours and informatics resources, and more complexities in managing workflows.

Based on current industry estimations, on average, only 5% of articles are relevant for ICSRs and less than 1% contain a relevant safety signal. Therefore, the process in identifying relevant safety information needs to become more efficient, rather than simply putting more eyes on journal articles and conference abstracts.

The solution lies in building a comprehensive, efficient and compliant search strategy and review workflow. While it might seem like an impossible task, advances in informatics technologies that have optimized content indexing, text mining, automated searching and alerting make it considerably more straightforward to achieve than it might first appear.

<table>
<thead>
<tr>
<th>Drug substance</th>
<th>System organ class</th>
<th>Percentage of cases reported in the literature</th>
<th>Percentage of cases reported spontaneously</th>
<th>Difference (%)</th>
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</thead>
<tbody>
<tr>
<td>Acetylsalicic acid</td>
<td>Nervous system disorders</td>
<td>25.6</td>
<td>8</td>
<td>17.6</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal disorders</td>
<td>8.4</td>
<td>25.4</td>
<td>17</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Injury, poisoning &amp; complications</td>
<td>35.9</td>
<td>7.5</td>
<td>28.3</td>
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<tr>
<td>Alendronic acid</td>
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<td>21</td>
<td>16.5</td>
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<tr>
<td></td>
<td>Injury, poisoning &amp; complications</td>
<td>28.3</td>
<td>5.4</td>
<td>22.9</td>
</tr>
<tr>
<td>Tamsulosin</td>
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<td>Etoposide</td>
<td>Congenital, familial &amp; genetic disorders</td>
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<td>24.3</td>
<td>24.3</td>
</tr>
</tbody>
</table>

Table 1. A comparison of reporting rates (as a percentage of all cases) in the biomedical literature and through spontaneous reporting systems. Note the lack of consistent favoring of either system. Table reproduced from Klose et al. 2013. Safety information from spontaneous and literature adverse reactions reports: a comparison. Ther. Innov. Regul. Sci., 47, 248–255
Five steps to an efficient strategy

The five steps to follow in building an efficient strategy for monitoring the biomedical literature for ADRs are:

1. **Ensure all literature can be searched simultaneously**

Sources will generally be defined by the regulatory authorities. Consolidated databases that include all the required global and local literature sources are essential for streamlining the process. This is especially important as there can be a requirement to report events reported in non-English literature. For example, market authorization holders operating in France must monitor French-language content. Incorporating screening of local articles into the global process saves time, improves compliance and ensures nothing is missed. Using a platform that can monitor multiple literature databases and alert users of new information is an excellent means of increasing efficiency at this step.

The solution should automatically de-duplicate the results. This spares pharmacovigilance team members from having to review items twice. Similarly, the system should flag literature that has been or will be reviewed by the European Medicines Agency’s Medical Literature Monitoring (MLM) system and a clear history is needed to indicate where deduplication has occurred.

Results that are not relevant for a given search (e.g., from a country where the drug is not marketed) should also be flagged to save valuable time when reviewing.

2. **Ensure the full text can be thoroughly monitored**

It is essential to ensure that the database comprehensively indexes the full content of the article, not just the abstract. ADRs are not always mentioned in abstracts and even an optimized search string cannot find what is not indexed.
3. Use a search with ~100% recall and high precision

Recall measures how many of all existing records known to be relevant for the search are retrieved by the search formula. It’s the measurement of quality for literature screening. Precision measures how many of the records in the search results are relevant to the searcher’s needs. High precision means that few records will be irrelevant. Precision impacts productivity: the higher the precision, the fewer irrelevant records are being retrieved. However, in pharmacovigilance, it is often the case that precision is sacrificed to ensure 100% recall as this is the most important metric.

Since regulatory bodies can audit the literature monitoring process of any market authorization holder, everything must be well documented, including the process of search formula creation and revision. The expectation from the EMA and FDA is that the literature monitoring process will consistently reveal 100% of ADRs so that ICSRs can be filed on time and drugs can be kept safe for patient consumption.

Optimizing a search strategy consists of running and adjusting the strategy multiple times against a database with a known set of documents that represent 100% recall and high precision (the so-called GOLD set). The documentation of this process gives clear evidence of the quality of the search string and can be provided to regulatory bodies.

4. Automate a regular search with alerts for new results

Modern informatics solutions allow automation of searches once the string has been designed. At defined times, the search should run and alert the pharmacovigilance team if new results have been found. De-duplication of results is important to keep the workload manageable.

5. Have a triage and review strategy for the items retrieved

Even with 100% recall and high precision for adverse events for a given drug, the pharmacovigilance team is still potentially dealing with a huge number of items that are not relevant for ICSRs. Up to 95% of articles identified can contain adverse events that don’t need an ICSR, although they still need to be reviewed at a later date for aggregate reporting.

Therefore, it’s important to identify and prioritize the ICSR-relevant articles to meet the tight deadline on this type of report. This means flagging articles that meet the 4 pharmacovigilance criteria for ICSRs: an identifiable patient, an adverse event, a suspect drug and an identifiable reporter.

A system that supports this flagging, along with a clear review process and oversight of articles as they move through the workflow, enables the pharmacovigilance team to quickly deal with items needing most urgent attention and then proceed to review and analyze other items for other safety information that can inform risk–benefit assessments.

Case study: the impact of optimizing a search string

A CRO was hired by the market authorization holder, a mid-size pharma company, to screen 139 products for ICSRs. They used an open search strategy for a weekly screening with 7 full-time employees involved in the process. The strategy retrieved around 2,800 articles per week.

Search string optimization was performed by Elsevier and validated against a GOLD set. Thereafter, the CRO had a 44% reduction in the volume of articles retrieved (higher precision, no compromise on recall). Only 3 full-time employees were needed for a cost savings estimated at $2,500 per week, or $129K per annum.
Introducing QUOSA™ PV

QUOSA PV is a GxP-compliant workflow management tool that provides a complete audit trail and oversight of the literature management process. It helps to organize and automate the monitoring and triage of biomedical literature in a scalable environment. QUOSA PV centralizes the discovery of critical adverse event information in various types of literature, helping pharmacovigilance groups address all the challenges of literature screening workflow. It also allows PV teams to easily manage information from the EMA’s MLM program.

QUOSA PV enables users to:

- Consolidate a broad spectrum of literature resources
- Automate the import of alerts from other databases and the de-duplication of results
- Review literature and monitor the article pipeline through a single browser-based interface
- Leverage flexible workflows and user roles so literature review can be performed in a manner consistent with existing processes
- Capture, validate and search for signal information from literature
- Rapidly assess information with automated literature review and triage
- Export case data and other safety information in the correct format for reporting systems and aggregate reports
- Improve oversight and efficiency with workload management tools and dashboard views
- Quickly capture all data needed for an audit, saving considerable time when inspections occur

There are plans to add more features to QUOSA PV in the near future, including the possibility to flag articles with the criteria relevant for ICSRs.

Introducing Embase®

Embase is a highly versatile, multipurpose and up-to-date biomedical database, covering the most important international literature from 1947 to present. All articles are indexed in full using Elsevier’s life science thesaurus Emtree®. Recommended by the EMA in their Guideline on Good Pharmacovigilance Practices Module IV, Embase offers tools specifically designed to support comprehensive literature monitoring.

Key among these is PV Wizard, which is available exclusively through Embase.com. This intuitive query builder has a pre-coded PV search strategy designed in consultation with pharma industry partners. It simplifies the creation and optimization of search strategies so that any user can quickly build complex search strategies with close to 100% recall and high precision.

PV Wizard guides the user through a 5-step process of adding terms that are connected automatically to create the search string. In turn, the user defines the drug name, alternative drug names, adverse drug reactions, and special situations (pregnancy, compassionate use, etc.), and then limits the data and results to humans. Note that the search queries run by EMA for their MLM searching are available to review and run through PV Wizard, adding another layer of important utility.

A full search string can be built in less than 30 seconds. This is a huge streamlining of this critical step. The searches can be automated to run regularly and send alerts through to the team directly or via QUOSA PV and can also be used as a basis for optimizing search strategies.

Search strategies produced with PV Wizard can be exported for audits with no need to spend time creating auditable documents.

The Embase database contains more non-English biomedical literature than any other database. Elsevier continually works to improve the search power for this content.

The first of these advancements is the French Local Language Module, which allows users to search and identify adverse drug reactions in a selection of French literature chosen based on industry recommendations. The literature is curated and translated to maximize its utility to international users. It mitigates the risk of being non-compliant, increases efficiency, and reduces the time and error that may result from manual screening of local language content.

More local language modules are planned for Embase in the future, ensuring it continues to improve support for compliant, efficient and comprehensive literature monitoring.
Elsvier and efficient literature monitoring

Elsevier’s pharmacovigilance solutions have been specifically developed to enable pharmaceutical companies ensure better drug safety, including through the creation of an efficient literature monitoring strategy.

Here are 5 specific ways where we help:

1. Our solutions ensure all literature can be searched simultaneously to save time.
   QUOSA PV is designed to consolidate a broad spectrum of literature resources, including Embase with its French Local Language Module, other Elsevier and non-Elsevier literature databases, journal RSS feeds, and internal company databases.

2. Embase ensures the full text can be thoroughly monitored.
   Embase’s comprehensive indexing covers the full text of all content, not just the abstracts. Therefore, adverse events mentioned in the main body of an article will always be captured.

3. Elsevier supports the optimizing and validating of searches.
   PV Wizard is specifically designed to enable rapid creation and optimization of high-recall, high-precision searches. Our Professional Services team helps customers to validate searches.

4. Automated searches can be set to run regularly and alert for new results.
   Both Embase and QUOSA PV offer automatic email alert functions. On Embase, users can set which search strings they wish to run and define the frequency and who should receive the alerts.

5. QUOSA PV supports a triage and review strategy for the items retrieved.
   When QUOSA PV imports content from all assigned databases and RSS feeds, it automatically de-duplicates results. It automates the literature review and triage process for rapid identification of case, signal and drug-specific data. In addition, the solution will soon offer support for ICSR-relevant flagging of content.

Efficiency gains translate to improved patient safety, cost savings and risk–benefit assessments

The efficiency gained through improved literature monitoring for ADRs goes beyond confidence in the level of compliance with regulatory requirements. It represents improved patient safety as pharmaceutical companies are better able to capture the signals and respond to them. It means cost savings as fewer full-time employee hours are taken up with the process of literature monitoring and review. It also means deeper insights into drug safety that can translate into improved risk–benefit assessments — and that can have huge impact on the life cycle of the drug.
QUOSA PV

QUOSA PV helps customers promote efficiency and compliance by centralizing the discovery of adverse event information in various types of literature, and automating information monitoring and triage in a scalable environment that supports detailed audit trails.

Embase

Embase helps customers improve literature monitoring for adverse events with the world’s most comprehensive biomedical literature database.

For more information about QUOSA PV and Embase, visit elsevier.com/pharmacovigilance

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