



# Pharmacovigilance literature review in the age of precision medicine

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*Injecting technology solutions into the literature-review  
process*

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Acknowledgement for their support and valuable input: Craig Wylie, Oliver Turnbull and Andrea Solda

# Executive summary

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Over the years, pharmacovigilance (PV) processes have involved PV professionals manually going through high volumes of data to identify, assess and report adverse event (AE) information. This set-up will face increasing challenges, as more and more work needs to be done in fixed amounts of time. The options for addressing the challenges can either be labor intensive or technology enabled. Technology-enabled processes have the advantage of being sustainable over time, with the added benefit of potential savings in time and costs.

Within PV, scientific and medical literature review lends itself to the introduction of natural-language-understanding technology due to the orderliness of the data and the low ratio of AE information found to volume of journal articles reviewed. A simple, three-step approach has been developed to speedily and accurately search through journal articles to identify the ones with reportable AE information using a technology solution. An initial test of the technology solution showed that this new approach could pick up all AE terms with no false-negative results and go on to deliver further benefits.

# 1. Addressing the growing PV burden

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In 1796, Edward Jenner, a local doctor in Gloucestershire, tested the theory that milkmaids did not get smallpox (a potentially fatal disease) because they had suffered from cowpox (a much milder disease). He put pus from a cowpox postule into an incision in the arm of an eight-year old boy. He went on to carry out the same experiment on other people and submitted his results to the Royal Society. This experiment was the basis of vaccination, a cornerstone of modern healthcare.

Thankfully, things have evolved considerably over the years from a patient-safety perspective. Although researchers all around the world continue to test medical theories to discover new ways of treating diseases, robust pharmacovigilance (PV) now exists to make sure the public is safeguarded both at clinical trials and after the medication has been given marketing authorization. Pharmacovigilance is defined as “the science and activities relating to the detection, assessment, understanding and prevention of adverse events (AEs) or any other drug-related problem”<sup>1</sup>. Traditional sources of reported AEs are clinical trials, spontaneous reports from health professionals or patients, and literature reviews of scientific and medical publications. PV functions have the responsibility to collate, evaluate and report adverse events to healthcare regulators.

It is generally accepted that many AEs are not reported. A systematic review of published data from 37 studies worldwide found the median under-reporting rate of adverse events to be 94 percent in spontaneous-reporting systems<sup>2</sup>. As patients become more empowered and avenues such as social media are increasingly used to discuss responses to medication, we should expect increases in the reporting of adverse events. This

means the burden on PV departments will increase, while their regulatory obligated reporting timelines are unlikely to change.

In response to the increasing AE-reporting burden, PV organizations can take a number of approaches to meet their obligations: (i) increase the workload on existing PV staff, (ii) increase the resourcing of the PV department (directly or via outsourcing), or (iii) employ smart working approaches enabled by technology. Of the options above, (i) and (ii) are not sustainable in the long term. That leaves the technology-enabled option, which is often discussed, but has not been explored to any reasonable extent. Injecting technology into the PV process will potentially offer significant benefits over labor-intensive approaches.

## **PV literature review: a starting point for technology-enabled approaches**

In searching for a “beach head” in PV for technology to demonstrate its capabilities, literature review of scientific and medical publications is a good starting point. A PV literature report review involves monitoring a set of journals at least once a week as mandated by regulation to see if any reportable AEs can be identified for a particular drug. This area of PV lends itself to the involvement of technology for a number of reasons; firstly, the articles are written by professionals using standard medical terminology. Secondly, the articles exist in text format and are therefore relatively easy to search. Thirdly, the ratio of AEs found to volume of articles reviewed is very low. These factors make it possible for technology-enabled approaches to show significant benefits in the review of literature reports.

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1 World Health Organization. Essential medicines and health products: pharmacovigilance. 2016. [http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/pharmvigi/en/](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/)

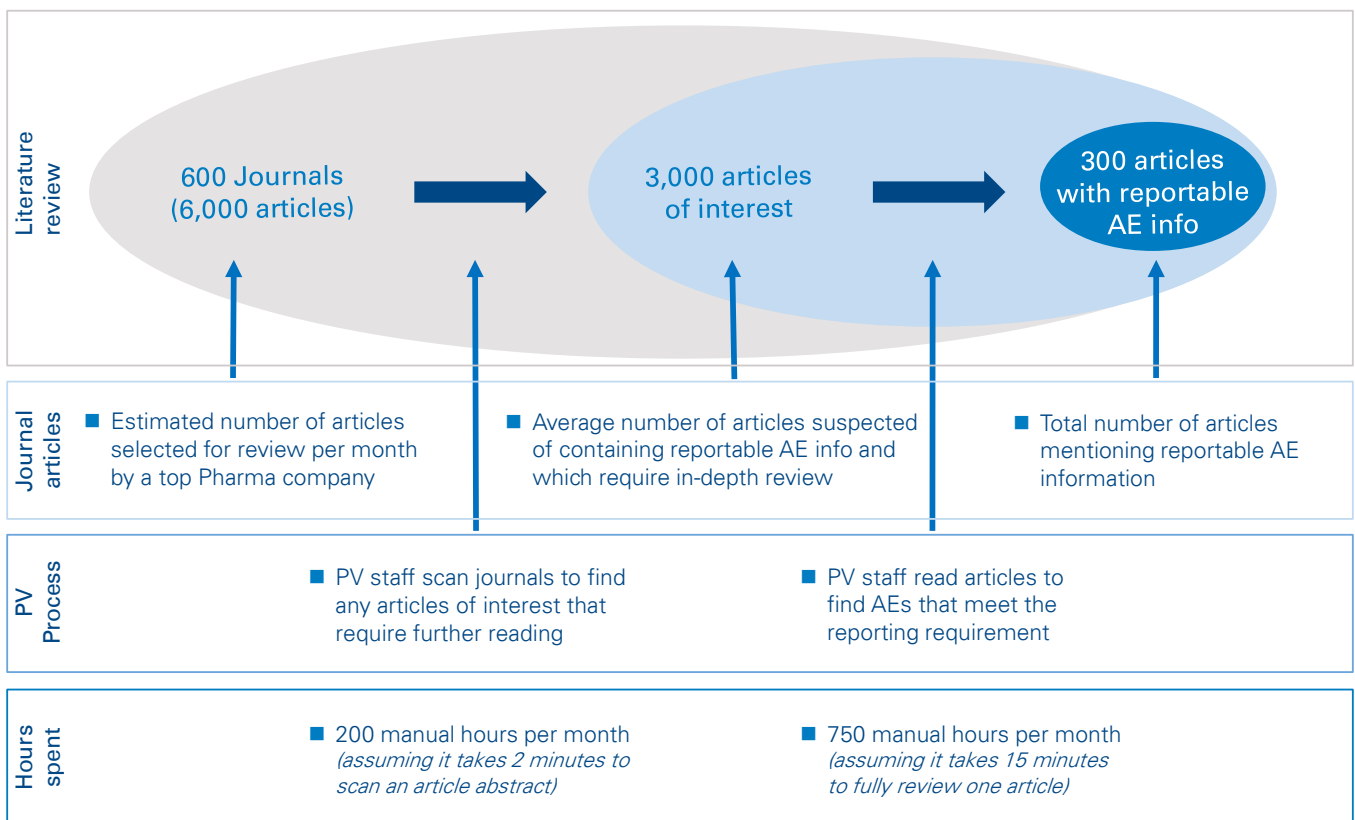
2 Mittmann N, Knowles SR, Gomez M, et al. Evaluation of the extent of under-reporting of serious adverse drug reactions: the case of toxic epidermal necrolysis. *Drug Saf* 2004;27:477–87. doi:10.2165/00002018-200427070-00004

## 2. Technology is now sufficiently mature to play a role in PV literature review

Pharmacovigilance processes are usually carried out by big teams of well-trained PV professionals, and the general feeling is that the work requires a manual approach due to its intricacies. The recent advances in machine learning and natural-language processing require this consensus to be revisited, particularly in the area of scientific and medical literature review. Machine learning is increasing the impact of technology, particularly in work processes that were previously considered complex. The current process of literature review involves manual scanning

of articles in a set of journals to select those of interest for further investigation. The selected articles are then reviewed by a trained PV professional for AE information that meets the reporting criteria. Finally, the articles with reportable AEs are then forwarded to the PV case-processing and -reporting team. This process is very time consuming, with a low percentage of AEs found for each review cycle.

Figure 1: The current literature report review process in many PV departments

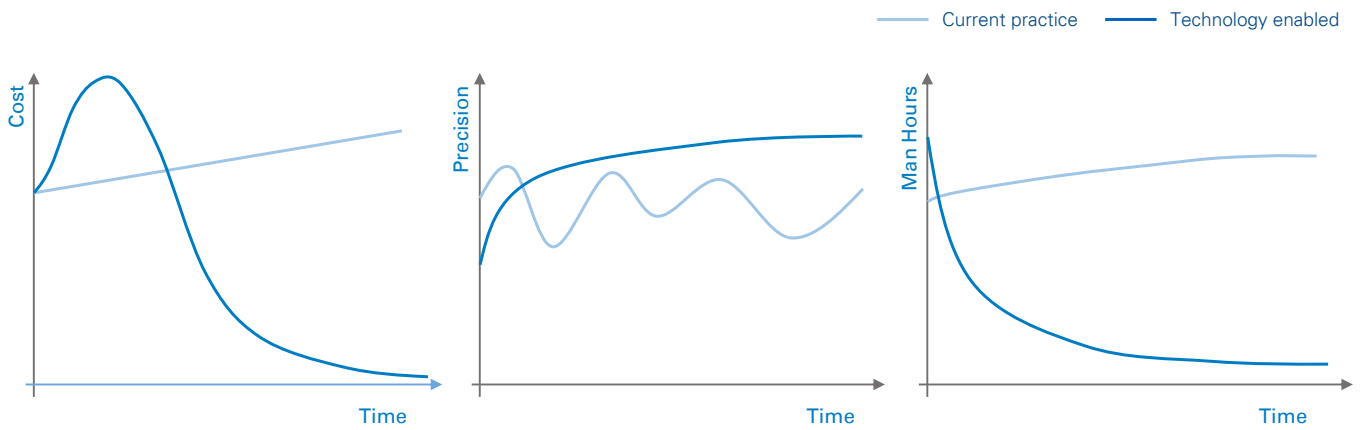


Source: Arthur D. Little

By embedding technology (natural-language processing) within the literature-review process, the time taken to do the work can be significantly reduced, saving the expert intervention to focus on those parts of the process on which it will have the most productive impact. In addition, the solution can be relied upon to be accurate every time (within a predictable margin of error), as the technology is not subject to environmental factors that can

affect manual performance. Furthermore, while the full cost of a technology-enabled process needs to be evaluated, it is safe to hypothesize that in the long term, the initial set-up costs will be offset by relatively low operations costs (licenses, maintenance costs, etc.), which will make it a cheaper option than the labor-intensive approach.

Figure 2: Hypothesis curves of the benefits of technology-enabled PV literature review vs the current practice over time



Source: Arthur D. Little

### 3. Experimenting with technology solutions

There are three simple steps to carrying out a literature review of scientific and medical journals using existing technology. **Firstly**, the search foundations need to be established by ensuring that all the relevant AE search terms are uploaded, as well as all the journals that are regularly searched. This involves loading the MedDRA dictionary, names of medicines, commonly used AE terms, and journal articles onto the technology solution. The uploaded information can always be updated to include new search terms or journals.

**Secondly**, a search must be run to identify any articles that contain the names of drugs (branded and generic) for which the Marketing Authorization Holder (MAH) has PV responsibility. For articles containing references to the specific drugs, another search must be conducted to identify those that contain predetermined AE search terms.

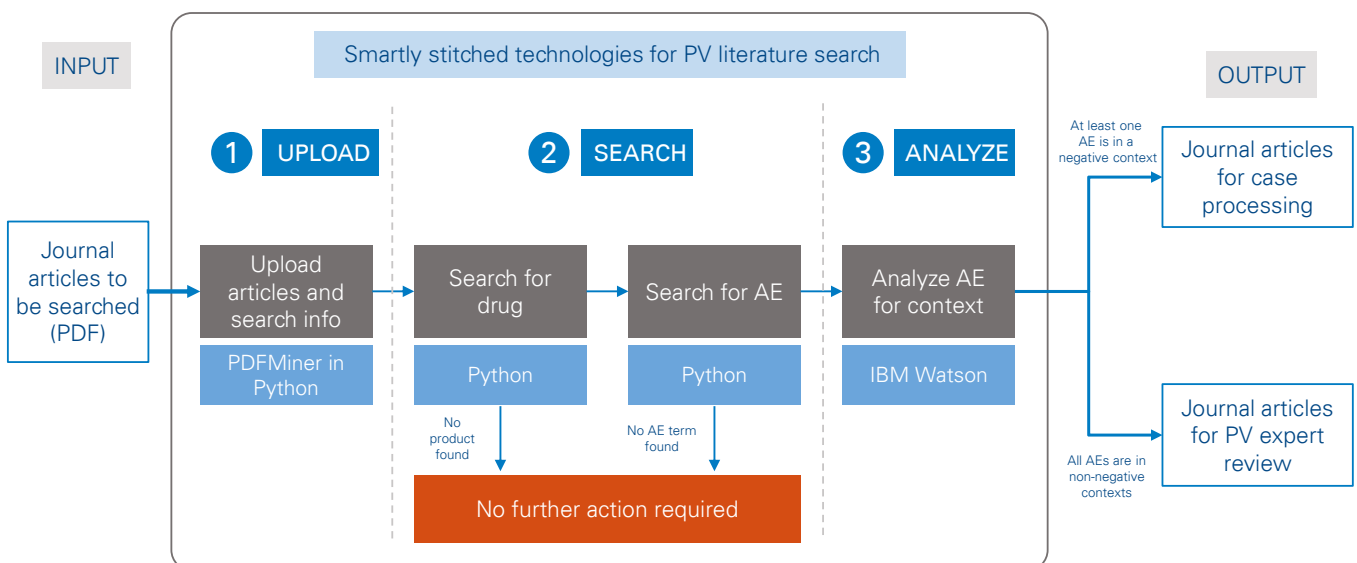
The **third** step involves analyzing the output of search runs. For articles that have the names of drugs and at least one identified AE, a context analysis can be performed to better understand the nuance around the identified AE term; for example, the word

“headache” (possibly negative) may have been identified, but the context analysis may reveal that the full statement was, “the patient did not experience any headache” (most likely positive).

The articles from the process that refer to reportable AEs can then be reviewed by PV professionals, with priority given to articles with negative AE contexts. Outputs with no drug names and no AEs identified (usually making up the bulk of journal articles reviewed) will require no further action. After a search cycle, a quick review can be done to see if any adjustments need to be made to the search infrastructure (additional AE terms, better context analysis, etc.), so the next run produces even better results.

We performed an experiment to examine the proposed three-step approach (upload-search-analyze), the details of which can be found in our paper entitled “Finding the needle in the PV haystack.” [www.adl.com/automating-medical-literature-review](http://www.adl.com/automating-medical-literature-review) We built a technology solution by combining pre-existing technology services, including IBM Watson’s Natural Language

Figure 3: Technology-enabled literature review of scientific and medical publications



Source: Arthur D. Little

Understanding and the PDFMiner library for the Python coding language. We then loaded journal articles, some of which mentioned a drug name and AE terms, to the solution and searched and analyzed. The results indicated that:

1. All the articles with the drug name were correctly identified.
2. All the articles with the drug name and AE terms were correctly identified, i.e., no false-negative results.

3. A small percentage of articles were wrongly identified as containing reportable AE information; these false positives were due to the technology highlighting AE terms, which were not reportable.

The upload-search-analyze steps were conducted within a fraction of the time it would have taken a PV professional to achieve the same results.

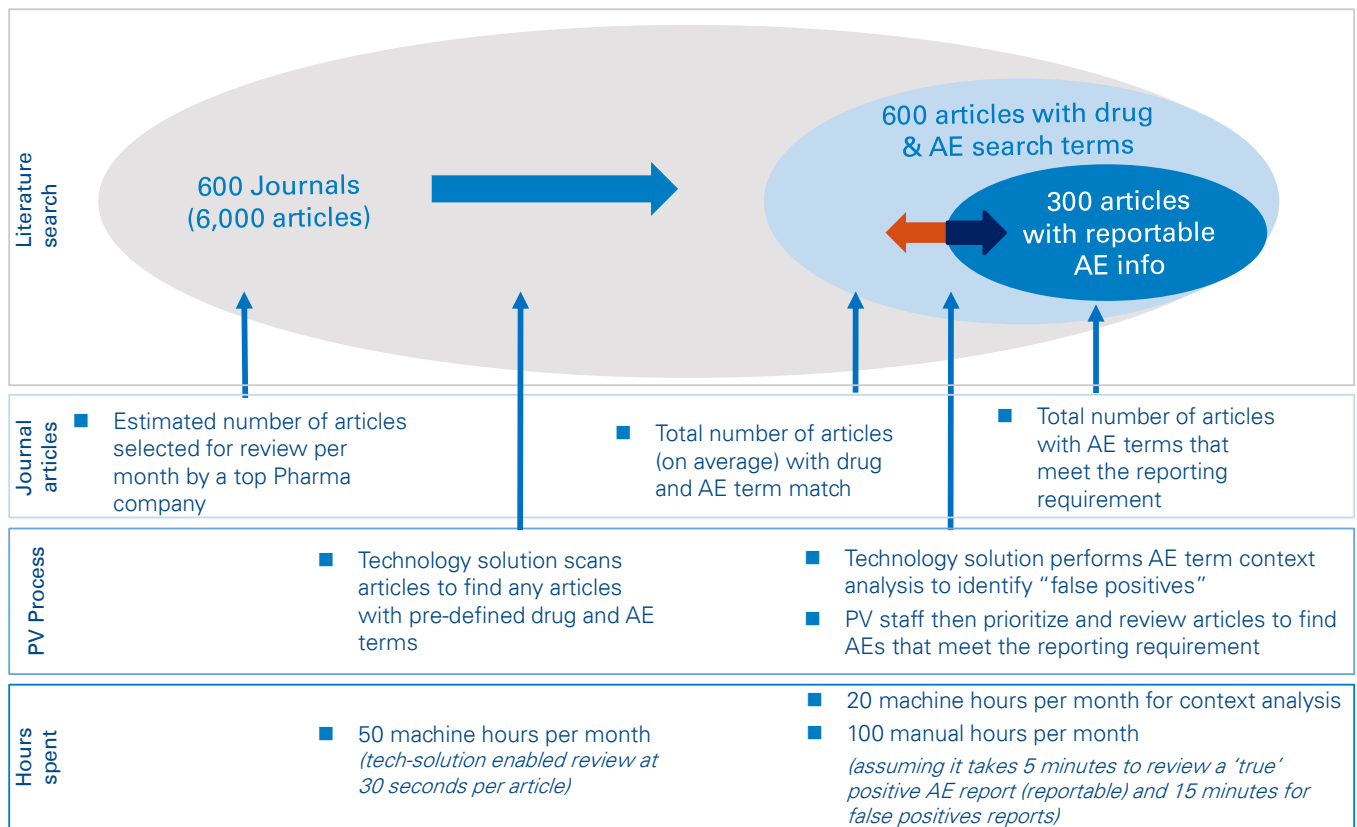


# 4. Technology addresses the increasing PV burden and then goes the extra mile

Incorporating technology solutions into the existing PV literature-review process has led to the creation of a new proposed process for carrying out literature-report reviews. This new process shows that significant savings in manual hours can be accrued by employing technology-enabled approaches. The model makes a very liberal assumption that if Y=number of articles with AE references, a technology solution will present

2Y for manual review after a search cycle. Comparing the current labor-intensive approach to literature review with the proposed technology-enabled approach, it is clear that the introduction of technology can create a lot of savings in manual hours and focus manual input on the aspects of the work that require the attention of a highly trained PV professional. All this can be done while preserving the accuracy of the PV process.

Figure 4: Proposed literature review process using a technology-enabled approach



Source: Arthur D. Little

Figure 5: Potential time-savings with proposed literature review approach

PV literature-review approaches	Total PV professional time spent per month (hrs)	PV professional time (%)
Current approach (labour intensive)	950	100
Technology-enabled approach	100	10.5
Potential savings	850	89.5

Source: Arthur D. Little

## 5. Conditions are perfectly aligned for technology-enabled approaches

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The move from the current labor-intensive approach to a more technology-enabled approach in literature review can be made by any company regardless of the number of drugs or devices it monitors. A number of health-related disciplines that do very complex work are already deploying technology to improve their processes. For example, the Nature Journal reported in 2016 that artificial intelligence had been tested in a study and was able to detect skin cancer to the same accuracy as a board-certified dermatologist<sup>3</sup>. We are in an age of precision medicine in which some expensive drugs are only given to people who have been tested and shown to have high probability of response to the medication. Surely, this same approach can be applied to the use of expensive PV resources.

Closer to home, some companies are starting to explore ways of introducing technology-enabled working into PV. A paper published in 2017<sup>4</sup>, looked at using technology to support the FDA's work in PV. This suggests willingness on the regulatory side to accept the involvement of technology in replacing certain manual processes.

As a first step to making the transition from manual to technology-enabled PV literature review, a strategic-analysis team (advised by PV and technology experts) needs to be assembled to prepare a business case for the transition. The

strategic-analysis team will have to fully outline both the existing process and the proposed technology-enabled process. Using an agreed time horizon and considering costs and time savings, the team must then estimate the potential benefit of transitioning to a technology-enabled approach. The business case will consider all important factors, from technology licenses and maintenance regimes to procedural documentation updates.

When Edward Jenner decided to take the leap and conduct the vaccination experiment in the late 1700s, he had a lot less to work with. He took a big risk to his reputation to promote the idea of vaccination, as there was real doubt in the scientific community even after he had published positive results of his experiment. With technology-enabled PV literature review, the technology is accessible and affordable, and has been applied in several areas of medicine. The need is present in PV, and the situation is crying out for an alternative to the current labor-intensive way of doing things. If Edward Jenner was alive today and presented with the situation in PV, what would he say? Considering that we are in the age of precision medicine, it is likely that he would demand an injection of technology into the PV process, perhaps, starting with PV scientific and medical literature review.

3 Andre E, et al. Dermatologist – level classification of skin cancer with deep neural networks. Nature Vol 542. February 2nd, 2017

4 Sorbello A, et al. Prototype software analytical tool development and usability testing. Harnessing Scientific Literature Reports for Pharmacovigilance. Appl Clin Inform. 2017; 8(1): 291–305. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5373771/>

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