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Review Article

Artificial Intelligence Applied to Pharmacovigilance: Evaluation of Critical Issues in Relation to Real Opportunities

Bianca Maria Salvatore[1]*, Marcella Falcone[1], Duccio Micela[2] and Marco Giacomelli

[1]*DOC Generici, Italy*

[2]*JSB Solutions, Italy*

***Corresponding Author:** Bianca Maria Salvatore, DOC Generici, Italy.

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Abstract

Pharmacovigilance (PhV) detects, assesses and prevents adverse events (AEs) and other drug-related problems by collecting, evaluating, and acting upon AEs. The volume of individual case safety reports (ICSRs) increases yearly. In this landscape, embracing assistive technologies at scale becomes necessary to obtain a higher yield of AEs, to maintain compliance, and transform the PhV professional work life.

In accordance with current legislation, MAHs that have requested the authorization of a medicinal product have the obligation to monitor the safety profile of this product also by monitoring scientific literature. This activity must be regulated within the MAH's PhV system and must be carried out on a weekly basis; therefore, a considerable use of resources and time is required for this process. The project focus on the application of Artificial Intelligence (AI) to a PhV process such as the screening of medical-scientific literature. The aim of the project is to measure how much artificial intelligence can understand, evaluate and order the contents of scientific articles in order to identify an ICSR. It will be calculating the precision and accuracy with which the AI processes the data and whether it is able to directly establish the relationship between ADR and drug.

The data used to train the cognitive service of IBM Watson Knowledge Studio were an annotated corpus consisting of 74 case reports from MedLine database (PUBMED). The model developed and validated was imported into IBM Watson Discovery and 151 new articles have been tested by query into a JSB SOLUTIONS interface.

By applying the model, on a total of 151 articles, after making the queries, a list of 79 articles have been shown. All the articles have been screened to verify if they were ICSR or studies. 71 were ICSRs where the correct substance and ADR were found, 8 were false positive.

As AI is introduced to pharmacovigilance, new skills and competencies are required, these competencies are not considered all-inclusive for the field of computer science but serve as an indication of what skills a professional should acquire to work with AI in pharmacovigilance. Drug safety officers should develop the ability to understand concepts of artificial intelligence, natural language processing, machine learning and deep learning; also, should work on how to interact with and identify issues with artificial intelligence.

Keywords: MAH: Marketing-authorisation Holders; PhV: Pharmacovigilance; ICSR: Individual Case Safety Report; AI: Artificial Intelligence; ADR: Adverse Drug Reaction

Introduction

The World Health Organization defines pharmacovigilance (PhV) as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem" [1]. The goal of PhV is to improve the safe and rational use of medicines, thereby improving patient care and improving public health.

Pharmacovigilance involves, at different levels, the whole community: patients, healthcare professionals, pharmaceutical companies and academic institutions, and reports of suspected adverse reactions associated with medicinal products for human use can originate from unsolicited (spontaneous reports) or solicited sources.

Among of unsolicited sources, the medical-scientific literature represents an important source of information for monitoring the safety profile and the benefit-risk ratio of a drug in a post-marketing setting, as it allows the identification of any safety signals or new potential risk on a medicinal product.

Literature monitoring

In line with the current EMA requirement and as described in the GVP Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2), marketing-authorisation holders (MAHs) are required to monitor medical literature and to report individual cases of suspected adverse reactions for medicines for which they hold a marketing authorisation in the EEA. The literature monitoring is not limited to the search of suspected adverse drug reaction but also to special situations such as use of a medicinal product during pregnancy or breastfeeding, use of a medicinal product in a pediatric or elderly population, reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure and lack of therapeutic efficacy.

The literature monitoring is conducted at global level by 3 different processes and for each of them the MAH should have standard operating procedure (SOP) in place in order to describe methods and internal flows for literature monitoring management:

- Screening of worldwide medical and scientific literature by using reference databases
- Screening of local publications through selected national journals and newsletter
- Screening of reports identified by MLM service managed by EMA.

Screening of worldwide medical and scientific literature by using reference databases

For the period between submission and granting of a marketing authorisation, literature searching should be conducted to identify published articles that provide information that could impact on the risk-benefit assessment of the product under evaluation. Literature searches should be conducted for all products with a marketing authorisation, irrespective of commercial status. It would therefore be expected that literature searching would start on submission of a marketing authorisation application and continue while the authorisation is active.

The marketing authorization holders must review systematically literature by using reference database such as MedLine or Embase at least once in a week. Reports of suspected adverse reactions from the medical literature, including relevant published abstracts from meetings and draft manuscripts, should be reviewed and assessed by MAH to identify and record Individual Case Safety Reports (ICSRs) originating from spontaneous reports or non-interventional post-authorisation studies.

The monitoring of scientific literature is also carried out for the purpose of preparing the periodic safety update report (PSUR) and validation of potential safety issue.

The worldwide screening process follows generally these steps:

- On weekly basis alerts from Embase\Medline with the full references are received.
- Alerts are saved in a relevant directory.
- Each abstract is assessed in order to identify an ICSR or safety information, each reference is copied in tools with relevant assessment.
- A quality control activity is performed in order to confirm the first assessment, then the results are tracked.
- The ICSR is entered into Pharmacovigilance Database and the following activities are performed: date entry; quality control and medical evaluation.

Screening of local publications through selected national journals and newsletter

MAHs should have procedures in place to monitor scientific and medical publications in local journals in countries where medicinal products have a marketing authorisation, and to bring them to the attention of the company safety department as appropriate.

The frequency of the screening is established according to the publication date of the journals.

The result is tracked in a relevant tool and the workflow is the same of the worldwide literature screening.

Screening of reports identified by MLM service managed by EMA

The European Pharmacovigilance legislation, with reference to Article 27 of Regulation (EU) No. 1235/2010 of the European Parliament, has entrusted the EMA with the responsibility for monitoring a number of substances and selected medical literature to identify suspected adverse reactions with medicines authorised in the European Union, and for entering the relevant information into the EudraVigilance database.

Therefore, in July 2015 the MLM (Monitoring Medical Literature) service was activated which, in September 2015, was extended to a greater number of groups and active substances.

The monitoring of medical literature and the entry of relevant information into EudraVigilance is carried out by EMA in order to:

- Enhance the efficiency of adverse reactions reporting;
- Provide a simplification for the pharmaceutical industry;
- Improve data quality by reducing the number of duplicates;
- Contribute to resource savings for the pharmaceutical industry;
- Support signal detection activities by national competent authorities and marketing-authorisation holders.

Marketing authorisation holders should have procedures in place to manage reports received by MLM service and shall not be required to report to EudraVigilance suspected adverse reactions recorded in the listed medical literature monitored by EMA for products containing the active substances referred to in the list of substances being monitored by EMA.

Literature case reports collection and collation is generally managed manually, requiring expertise in pharmacovigilance in order to perform many transactional activities before data are available for assessment and aggregated analyses. For a pharmaceutical company to meet its responsibilities to patients and regulatory bodies regarding the safe use and distribution of its products, improved business processes must be implemented to drive the industry forward in the best interest of patients globally. Augmented intelligent capabilities have already demonstrated success in capturing adverse events from various data sources. It has potential to provide a scalable solution for handling the ever-increasing ICSR volumes experienced within the industry by supporting pharmacovigilance professionals' decision-making [4]. Case processing activities constitute a significant portion of internal pharmacovigilance resource use, ranging up to two- thirds based on PhVNet benchmark data. When additional costs related to outsourcing are considered, case processing spending, on average, consumes most of a pharmaceutical company's overall PhV budget. Automation of adverse event (AE) case processing through artificial intelligence (AI) represents an opportunity to affect the strongest PV cost driver. The past decade has witnessed increasing application of AI methods to the field of biomedicine. Some of the recent improvements in leveraging AI techniques against publicly available consumer data have created opportunities for assessing the utility of AI techniques with the automation of PhV processes [5]. With the emergence of electronic health records, a growing body of research has explored the use of machine learning (ML) techniques to develop disease models, probabilistic clinical risk stratification models, and practice- based clinical pathways [6]. This rapid growth and the ability to process large volume of data automatically using natural language processing (NLP) and ML algorithms, have opened new opportunities for PhV.

Aims

The aim of this project is to estimate how much artificial intelligence can understand, order and evaluate the contents of scientific medical literature in order to identify an ICSR. It has been calculating the precision and accuracy with which the AI processes the data and whether it is able to directly establish the relationship between ADR and drug. According to the provided tools, the creation of an annotated body of articles is necessary as an initial service for the provision of cognitive services.

Methods

AI is a subfield of computer science in which a computer system is taught to perform tasks that normally require human intelligence. Natural language processing (NLP) is the ability of a computer system to understand and interpret human language. Machine learning (ML) is an area of AI that gives computer systems the ability to learn without explicitly being programed. Cognitive services are the combination of both NLP and ML algorithms that aim to solve specific tasks that would otherwise require human intelligence [7]. In order to develop cognitive services, an annotated corpus, or data used to teach the cognitive service, must be prepared and created; data must be transcribed into a machine-readable format and contain relevant annotation labels, or tagged metadata, explaining each data entity's relevance to the learning task. The entire set of annotated, machine-readable text forms the 'annotated corpus' [4].

IBM WATSON

IBM Watson is one of the best-known cases of the use of artificial intelligence in medicine and healthcare. The two programs used in this project are related to the elaboration of the scientific language and the individuation of relative information in the contest.

IBM Watson knowledge studio

IBM Watson Knowledge Studio is an AI engine that can be taught the language of our domain with customized models to identify unique entities and relationships of an unstructured text such as a medical report. The training of Watson Knowledge Studio is done by loading a set of documents in word format, in the workspace called "ground truth", and annotating them, or by mapping their processes thus establishing the entity that connects to each other through relationships. To annotate entities, a human annotator selects a text string in a document and then applies a label that best describes and identifies the description. IBM already provides a list of entities that can be enriched depending on the type of document that needs to be annotated. Once the text is fully annotated, and switched to the relationship mode, the human annotator connects the labels associating a type of relationship that connect two entities. In this way, AI can learn how to entities are connected and the logic that is behind.

In order to get accurate results, the intervention method for the annotation of documents can be based on multiple methods, which provide the model with ever more targeted intelligence:

- General annotation applied to a large set of documents of interest; the research has been conducted by using data from MedLine database (PUBMED) and selecting articles that must be screened on routine.
- Creation and annotation of word files specially written and composed by a list of simple and immediate sentences. Those documents were used to strengthens the relation 'age of' and 'induced'\ 'induced by'
- Use of specific annotation and relations to make the connection between drug and ADR easier to get to identify. Specific relations are based on the words much associated with the correlation, such as: INDUCED; INDUCED BY; ASSOCIATED WITH; CAUSED BY; RECHALLENGE; WAS DISCONTINUED.

As shown in figure 1, entities annotated are recognizable by the colorful label and are: patient, verb, identifier, health condition, disease and substance; relations are easily identifiable by the arrows that connect the entities.

Figure 1: Example of annotation in a case report.

Based on the annotation, IBM Watson Knowledge Studio uses the ML to create personalized and specific AI models that are able to analyze an unstructured text as a human would do. It produces quantitative data on the model's performance, defined by these parameters: precision and recall (Figure 2).

Precision expresses how precise and accurate the model is, and therefore indicates what percentage of annotations produced by the model is confirmed by human annotation. Precision, also referred to as positive predictive value (PPV), is the ability of a service to correctly identify elements. The risk of having a very high precision is that the service may not capture all the correct elements, but those elements it does capture will be captured correctly. This translates to the service as having many false negatives (FNs), or elements that should have been identified but were not predicted.

Figure 2: Precision and recall formula. Predicted positive are true positive plus false positive; actual positive comprehend true positive and false negative.

On the other hand, recall calculates how many of the actual positives the model capture through labeling it as positive (true positive). The shortcoming of having a very high recall rate is that although the service may classify all the instances of identifying an element, it may classify some incorrectly. A high recall will run the risk of many false positives (FPs), or elements that were predicted by the service that should not have been. A cognitive service must therefore have a balance of both precision and recall being truly effective [7]. Also, other two parameters are important: mention and relation. Both are weighted average of the precision and recall values calculated on each entity (for mention) or relation (for relation) defined in the model.

IBM Watson discovery

The machine learning model can be imported into the IBM Watson Discovery platform, an AI program that makes it possible to search for content, concepts and relationships on a set of pdf articles by making queries. This platform links to an external interface, made by the JSB software team, trough API (Application Program Interface). In the Discovery platform has been upload 151 documents divided in case reports and observational studies or review. With the use of the JSB interface it has been possible to make queries on these 151 documents by choosing the related entities and the relationship from a drop-down list. Indicating entities and relationships, in a few seconds the list of all the documents in which the relationship is present is shown, as shown in the image below (Figure 3).

Figure 3: Example of how the queries results are shown.

Queries allow to prioritize the result because the title of the article, the entities of interest and the relationship that connects them are shown. They are therefore immediate and understandable results that facilitate the screening of articles in which to find the substance-ADR association.

Overall 151 articles have been loaded and tested. They are divided in 112 containing an ICSR and 39 observational studies. To find the correlation between substance and ADR, 4 main relationships have been used:

- INDUCED that relates SUBSTANCE (suspected) e AND DISEASE (ADR)
- CORRELATION_ADR that relates SUBSTANCE to the VERB
- INDUCED_BY that relates DISEASE (ADR) and SUBSTANCE (suspected)
- CORRELATION_ADR that relates DISEASE and VERB.

The fact of correlating the drug to the verb is necessary because it is on the verb (INDUCED-ASSOCIATED...) that has been based the correlation substance-ADR and also correlating the drug to the verb and the pathology consequent to same verb allows, during

the verification of results, to cross the query lists for INDUCED and CORRELATION_ADR and actually verify the articles in common to be sure of the result and allows to identify documents that had not been reported by the 'induced' or 'induced_by' relationship.

Results

IBM Watson knowledge studio results

To generate the model, there have been annotated 74 case reports (on average 5 pages/390 words each); 66 generally annotated, 8 specifically annotated for the correlation and 6-word files appositely created. Based on the annotations made, the results of the general ML performance (Table 1) were the following.

	Mention	Precision	Recall
Entity score	0.65	0.80	0.55
Relation score	0.45	0.64	0.35

Table 1: Final evaluation of the performance of the machine learning model.

According to these values, it is expected that the model detects in 65% of cases the entities, with an accuracy of 80%, when annotating an entity, it is correct 80% of the time and with a recall of 55% that means the model is correctly identifying 55% of all entity that would have identified a human. In 45% of cases it detects relationships, with 64% precision and 35% recall.

IBM Watson discovery and queries results

As shown in the below picture (Figure 4), on a total of 151 articles, after making the queries with the relationships mention above, a list of 79 articles have been shown.

Figure 4: Picture explanation of the results.

All the articles have been screened in order to verify if they were ICSR. Seventy-one were ICSRs where the correct substance and ADR were found (52 articles contained the relationship 'INDUCED' and 19 'INDUCED_BY'), 8 of those 79 were false positive namely observational study; they were listed because in the text was found the verb 'induced'. As a result of this research, it is possible to assert that 64% of the 112 articles have been rightly recognized as ICSRs; while it is still to discover why the remaining 41 ICSR articles haven't been found. This can be addresses to textual difficulty, the suspected ADR is not clearly reported, sometimes, the quality of information available in ICSR is poor. or finally AI presents limits in lexical recognition because it is poorly trained. However, there's an ulterior parameter that must be highlighted, the time used to perform the literature screening. While with the current method, the processing of one hundred ICSR requires at least 720 minutes (12 hours of working), with the use of the artificial intelligence the process only takes 30 minutes if it is considered the documents upload and the queries. The listed results in any cases can be a support for extraction from ADR source documents and evaluation of case validity.

Discussion

Processing medical literature involves understanding the complete text and entering the case, the details of the adverse event, drugs, patient and his/her history and so on, for further processing steps namely, Quality Review and Medical Review. Due to high data content, extracting ICSR specific information is one of the biggest challenges facing the pharmaceutical companies.

AI is becoming increasingly used throughout the healthcare industry and it has been seen in the increasing uses of NLP and machine learning to automatically detect AEs and drug-drug interactions. As there has been limited success in these endeavors due to the complexity of the work but many opportunities still exist to discover the full extent to which AI can be introduced as a support structure to augment and empower the PhV professional. It became apparent that for the cognitive services to have high quality predictions, the data had to be of high quality. However, the documents could vary because of the innate way PV information were written and received by the AI. The annotated corpus was reflective of the real-world data and had representation from a variety of sources thus, the ground truth could vary because of (1) misspellings; (2) line breaks (e.g. when information was dispersed throughout a document); (3) limitations in the annotation

dictionary; and (4) annotator and reviewer bias. In fact, text-based machine learning requires training data in the form of annotated source documentation (i.e., direct indication within the document to identify the appropriate text elements and provide the contextual relation within the text).

The current pilot was undertaken to prove the ability of machine learning solutions in the application of case processing. The IBM programs proposed were used to test the ability to extract case critical information from source documents to identify valid ADR cases after training the machine- learning algorithms with annotated source documents. The project was designed to test the concept of viability of automation of safety case processing using machine learning and to help screening scientific literature. Validity was established by the presence of ADR and putative causal drug which had to be extracted and specifically coded. In addition, the pilot was used to compare the performance of the AI allowing identification of the correlation ADR-suspected drug. Increases in the number of individual case safety reports require assistive technologies such as artificial intelligence to support the drug safety (DS) professional with the increasing volume and complexity of work [8].

ML has the potential to enhance and increase the efficiency of PhV professionals' work by augmenting decision making processes when viewing machine predictions in machine-readable documents. This could allow drug safety experts to focus on other aspects of pharmacovigilance.

Conclusions

The results of this study could be used as a supporting evidence for the implementation of augmented intelligence and to increase operational efficiency and consistency of data quality during ICSR processing.

This project was designed and conduct because the advent of artificial intelligence in ICSR processing could bring about the following benefits to the pharmaceutical companies:

- Reduced cycle times: It significantly reduces cycle time achieved by processing cases faster through automation.
- Improved quality and accuracy: Achieved through standardized inputs and automated case intake and processing.
- A complementary solution of existing safety databases: Artificial Intelligence can be implemented without much disruption to the systems and processes currently managed within pharma ecosystem due to its adherence to standards requirements.
- Scalable and futuristic solution: AI allows to handle volume growth by managing the growing Adverse Events (AE) volume and diverse types of incoming data formats.
- Foundation roadmap: It lays a roadmap for use cases within and beyond.

Pharmacovigilance e.g. landscape analysis, Real World Evidence, Enterprise Knowledge Management and Quantitative Sciences.

Currently several pharmaceutical companies are implementing their services with the use of artificial intelligence to optimize the most varied processes, so in this optic the use of Artificial Intelligence in adverse event case processing can be an innovation in pharmacovigilance. The result confirmed the feasibility of using artificial intelligence to support the screening of scientific publications, even though developing a process that can read and understand a scientific text requires a deep understanding of PhV information and ML algorithms. As AI is introduced to pharmacovigilance, new skills and competencies are required, these competencies are not considered all-inclusive for the field of computer science but serve as an indication of what skills a professional should acquire to work with AI in pharmacovigilance. Drug safety officers should develop the ability to understand concepts of artificial intelligence, natural language processing, machine learning and deep learning; also, should work on how to interact with and identify issues with artificial intelligence. AI in pharmacovigilance is a novel concept and would require more effort and time to be invested in training personnel. The value of using AI methodologies in PhV is compelling; however, as PhV is highly regulated, acceptability will require assurances of quality, consistency, and standardization [8].

As with any Artificial Intelligence system, implementation as described above doesn't intend to completely replace the human element, but complements the process, and helps in identifying and bringing out seemingly hidden relationships for ensuring accurate ICSR processing in Pharmacovigilance.

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