New view of Pharmacovigilance: towards real data and digital monitoring

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Summary

Pharmaceutical production is a complex high-tech process. The complexity and high cost of pharmaceutical production is due to the high safety requirements that regulatory authorities put forward for medicinal products. Manufacturers pay great attention and spend a lot of money on quality control of their products, but this control is not limited to compliance with production standards and evaluation of finished products. That is why pharmacovigilance in a modern pharmaceutical company must be effective and efficient. Fortunately, modern digital technologies make it possible to improve this area, simplifying the manufacturer’s task and in increasing the possibility of work, which significantly increases the safety of drugs. Companies process over a thousand reports of adverse reactions annually. This has generated a request for digitalization of processes and procedures in the pharmaceutical company “Darnitsa”. Pharmaceutical company “Darnitsa” became the first company to focus on digital business transformation in Ukraine. “Darnitsa” strives to achieve a more flexible and modern model of pharmaceutical business with a focus on the patient. Moving in this direction, the pharmaceutical company uses advanced solutions to increase the transparency of the process of monitoring the use of drugs and the safety of treatment in general.

As for today, all over the world, adverse drug reactions (ADRs) are a major concern for patients, clinicians, and regulatory agencies. The discovery of serious ADRs leading to substantial morbidity and mortality has resulted in mandatory phase IV clinical trials, black box warnings, and withdrawal of drugs from the market. Real-world data, data collected during routine clinical care, is being adopted by innovators, regulators, payors, and providers to inform decision making throughout the product life cycle.

The digital revolution in medicine and pharmacy has contributed to big data sets relevant for public health. While we talk a lot about technologies that transform drug development, clinical trials, and pre-clinical stage processes, it is difficult to come across materials dedicated to the new technologies in pharmacovigilance.

A less noticeable discussion around digital transformation in pharmacovigilance can be explained by two main factors: the niche nature of the field and by the highly regulated nature of the field. However, now with the increased focus on the accelerated drug approvals and the massive amount of data generated daily, it is difficult to imagine that pharmacovigilance will remain in the periphery of digital transformation.

The purpose of this article is to discuss optimal use of big data for post-marketing assessment of drug safety in big through the IT platform for pharmacovigilance and regulation - OtiPharm® Data Pro used by Pharmaceutical firm Darnitsa” - Pharmaceutical Company which has been included in TOP 25 Ukrainian companies-leaders in the introduction of digital technologies.

The safety of a drug continues to be monitored after approval and marketing in an ongoing process of pharmacovigilance [1]. This postmarket drug safety monitoring is especially important about adverse drug reactions (ADRs) that are rare, only occurring in certain subgroups, and/or only develop after long-term drug exposure. In some cases, serious ADRs are not recognized until long after a drug has been approved for market, as seen in the case of thalidomide where its use in pregnant women led to congenital malformations.

The multiple emergency drug approvals issued during the 2019 Coronavirus Disease (COVID-19) pandemic highlight the situation where post-marketing pharmacovigilance is working to maintain long-term safety. Taken together, legislative acts and regulatory practice to increase dependence on post-marketing pharmacovigilance to inform about the safety of medicines.

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In the last decade ‘big data’ has become a buzzword used in healthcare. Despite its popularity, it is not always clear what big data refers to exactly. This kind of data is generally collected routinely during administrative processes and clinical practice by different healthcare professionals: from doctors recording their patients’ medical history, drug prescriptions or medical claims to pharmacists registering dispensed prescriptions. Today big data has an important place in healthcare, including
in pharmacovigilance. The expanding role of big data in pharmacovigilance includes signal detection, substantiation and validation of drug or vaccine safety signals, and increasingly new sources of information such as social media are also being considered.

When reported by patients or healthcare professionals, ADRs are typically assessed by drug experts and pharmaceutical companies, and the results are then passed on to government agencies. This leads to substantial data loss and delays. A recent study in the United States showed that hospital staff did not report 86% of ADRs among patients [2]. Once government agencies receive the reports, they often release them with a delay of months or even years. The lack of speed and broad coverage has multiple causes, including the fact that a proper assessment of ADR data is both imperative and time-consuming; it is nevertheless in direct contrast with the public health importance of ADRs. In the European Union alone, ADRs are the cause of 5% of all hospital admissions and are responsible for an estimated 197,000 yearly deaths [3].

Public ADR reporting systems are largely unknown to the public, despite long-term governmental support. A recent study in Australia reported that only 10.4% of the general population was even aware of the national ADR reporting system [4]. This low awareness was comparable to the results reported in an earlier study in the United Kingdom, where only 8.5% of the adult population was aware of the United Kingdom ADR reporting system [5]. Among physicians, ADR reporting has been declining over time in both countries. Such declining reporting by physicians has been linked to ignorance, diffidence, lethargy, and insecurity (sorted here by decreasing frequency associated with not reporting ADRs, as identified elsewhere [6]), leading some to suggest that physicians should get paid to report ADRs [7].

In the last years, the variety of safety data sources has grown immensely, allowing pharmacovigilance to develop from a single-source passive system into a complex, holistic, dynamical process. With this change, technology has become a key to compliance, safety, and a way to stay behind all the new safety data sources.

Digital transformation in pharmacovigilance for sure has an impact on internal procedures of the department, creating a need to review and possibly restructure certain processes. 

Pharmaceutical firm “Darnitsa” is one of the largest manufacturers of finished dosage forms and pharmacological groups in Ukraine. Pharmaceutical firm “Darnitsa” specializes on the development and manufacturing (including contract manufacturing) of medicines in such pharmaceutical forms as tablets, capsules, solutions for injections and infusions, sterile powders for solution for injections, ointments, gels, creams, which are sold on the domestic market of Ukraine and abroad. Today, the company produces 210 brands of medicines [8].

Darnitsa has created an optimal hybrid model of IT infrastructure for the production company; it actively uses cloud technologies, digitized process of the drug life cycle management. Darnitsa’s IT infrastructure has been successfully tested under remote working model.

IT product of OtiPharm® Data Pro has been integrated to Pharmaceutical firm “Darnitsa”. In case of synergetic cooperation, this IT platform helps analyze internal work processes and ensures compliance with the new structure, the optimization of ADRs processing has been demonstrated in practice.

Such an example is the creation of a completely new approach for Pharmaceutical firm “Darnitsa” to the accumulation of primary data on medicines obtained from outside sources, through the creation of a single center - the “Appeals” module in the IT platform OtiPharm® Data Pro.

Calls include information about any drug-related events (quality complaints, adverse reactions, complaints, or suggestions from users etc.). In this case, the platform plays the role of an ecosystem shell, bringing together cross-functional experts in various fields (quality service, medical service, regulatory service, pharmacovigilance). The ability to conduct the necessary investigations into adverse reactions, appeal, validation, and portability (if criteria are met) provides a company-wide ecosystem.

As for today, most pharmaceutical companies continue to use traditional signal detection and investigation methods (e.g., medical assessment of individual spontaneous reports of adverse events, interventional clinical trials, database mining); a few are leveraging real-world evidence (RWE); almost none are progressing social media channels that is consistent with current PV system capabilities.

Factors that determine the effectiveness of the digital pharmacovigilance database are considered in the example of the development and analysis of the OtiPharm® Data Pro platform used by Pharmaceutical firm “Darnitsa”.

Pharmaceutical firm “Darnitsa” – Pharmaceutical company is in the top three most expensive brands in Ukraine [9].

Dmytro Shymkiv, Executive Chairman, Darnitsa Group:

“Digitalization is a part of Darnitsa’s transformation process, and we are developing rapidly in this direction. Today the company has a dynamic infrastructure that can change instantly according to the challenges and needs of the business. We improve our own processes, use modern technological solutions, achieving the synergy of digital technologies. Only in the last four years, more than EUR3.4 million have been invested in digital transformation projects”.

OtiPharm® Data Pro, in turn, is a technology that allows Pharmaceutical firm “Darnitsa” to benefit from the ability to store and analyze huge amounts of data.

Among the main drivers of the transition of Pharmaceutical firm “Darnitsa” to the OtiPharm® Data Pro platform:
- **Cost and efficiency**: platform can handle large volumes of data without compromising data quality, security and privacy;
- **Scalability**: adverse event workload for life sciences companies is growing steadily. This growth requires technologies that can rapidly handle the growing volume of data;
- **Simplicity**: planform usage can simplify the life of companies by allowing them to avoid concerns about module compatibility and scaling up servers.

The task of this pharmacovigilance platform is the high-quality and convenient performance of its structuring and organizing functions, regardless of the type of internal process of working with information in the company. The base is a convenient auxiliary tool and comply with the principles of ALCOA+. An effective pharmacovigilance platform allows devoting more expert’s time to implement product safety solutions, instead optimizing processes and functions that can be automated.

This platform allows Pharmaceutical Firm “Darnitsa” to optimize and digitalize the scope of the study of critical processes of pharmacovigilance. [10]:

- continuous safety profile monitoring and benefit-risk evaluation of authorised medicinal products;
- establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimisation;
- collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of individual case safety reports (ICSRs) from any source;
- detection, investigation and evaluation of signals;
- scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports;
- meeting commitments and responding to requests from competent authorities, including provision of correct and complete information;
- interaction between the pharmacovigilance and quality defect systems;
- communication about safety concerns between marketing authorisation holders and competent authorities, in particular notifying changes to the risk-benefit balance of medicinal products;
- communicating information to patients and healthcare professionals about changes to the risk benefit balance of products for the aim of safe and effective use of medicinal products;
- keeping product information up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the applicable competent authority;
- implementation of variations to marketing authorisations for safety reasons according to the urgency required.

**Turok Viacheslav, Qualified Person of Pharmacovigilance Head of pharmacovigilance and medical instructions group of Pharmaceutical Firm “Darnitsa”**: 

“In order to effectively manage information about adverse reactions at an early stage, the developers have created an additional module “Appeals”. The module fully meets our expectations and needs. Subsequently, during the operation of the “Appeal” module, it became necessary to create additional fields for data entry and the company-developer of the platform OtiPharm® Data Pro performed this task more than a week ahead of schedule. This helped to accelerate the implementation of the new procedure in the company.”

There are approaches where a specialist or department is responsible for the full cycle of working with product information from start to finish. Instead, in other companies, the work of pharmacovigilance is divided into different stages, for which entire departments are responsible, or branches-representative offices in different countries, already with their structure of the process.

Here we approached another group of factors and analyzed how the usability of the digital platform will affect the quality of data processing.

Juhanilivari, University of Oulu, in his study of the model of success of information systems, showed that the perception quality of the system by users is a predictor of its use, and statistically affects the efficiency of the system. Also, a group of authors, led by Jung-Fan Chen from the National Kaohsiung University of Applied Sciences, Kaohsiung, Taiwan, conducted a study that identified how the “attitude to use” factor will affect the model of information technology success. The results show that the “attitude to use” is significantly and positively influenced by perceived usefulness, perceived ease of use, and user satisfaction [11].

In the case of synergistic cooperation between Pharmaceutical Firm “Darnitsa” and the IT product of OtiPharm® Data Pro, which helps companies analyze internal work processes and ensures compliance with the new structure, the optimization of ADR processing has been demonstrated in practice.

One such example is the creation of a completely new approach for Pharmaceutical Firm “Darnitsa” to the accumulation of primary data through the creation of a single center - the “Appeals” module in the OtiPharm® Data Pro IT system. Appeals include information about any events related to the drug (quality complaints, adverse reactions, complaints, or suggestions from consumers). In this case, the platform acts as a shell of the ecosystem, bringing together cross-functional experts in various fields (quality service, medical service, regulatory service, pharmacovigilance). The ability to carry out the necessary investigations regarding appeals, validation, and
transfer (if eligible) provides an ecosystem at the level of the entire pharmaceutical company.

Another critical process of pharmacovigilance is signals. Formulation of hypotheses about new possible adverse reactions is a process of signal detection.

A special section has been created in the card for high-quality support of this process.

In this section, the notification of a suspected adverse reaction goes into a semi-automatic monitoring system and remains in this state or proceeds to the next phase of approval in accordance with the information to be supplemented.

One of the most important functionalities is appeals. The appeals include information about any events related to the drug (quality complaints, adverse reactions, consumer complaints). In this case, the platform plays the role of an ecosystem shell, uniting cross functional experts in different fields (quality service, medical service, regulatory service, pharmacovigilance). The ability to conduct the necessary investigations concerning appeals, validation, and transfer (if there are criteria) to adverse reactions provides an ecosystem at the level of the entire pharmaceutical company.

Thus, we concluded that the task of the pharmacovigilance platform should be the high-quality and convenient performance of its structuring and organizing functions, regardless of the type of internal process of working with information in the company.

The database should become a convenient support tool, not a new reform challenge for employees while complying with the ALCOA+ principles developed by the FDA for working with information systems within its certification.

The goal we set ourselves was to create an intuitive ecosystem that would be an organic continuation of the expert.

One of the criteria for its achievement, which we set, is the ability of the specialist to use the base from the first briefing and save time and human resources of the company spent on the implementation of the system.

We have identified this criterion as a predictor of synergy in the interaction between different departments of the company when working with information, and the level of users should vary from basic pharmacovigilance specialist or quality department to QPPV level expert of the international company.

Conclusion

Clearly, the development of massive sources of data for future pharmacovigilance efforts creates an opportunity for capitalizing on recent advances in deep learning and anomaly detection. A continuously learning artificial intelligence system could not only learn to integrate these heterogeneous data sources for real-time ADR detection but could help identify potential cases and interface with members of the pharmacotherapy community to gather more information when needed.

Lowering case processing costs, expanding signal processing capabilities, and expediting product safety reports are compelling reasons for biopharma companies to include automation, cognitive technologies, and advanced analytics for their PV budgets. Yet we anticipate even greater gains if biopharmas leverage digital technology to create a next-generation PV learning system for improved patient safety.

The same principle was chosen as the key by Pharmaceutical Firm “Darnitsa” when choosing an IT platform for digitalization of pharmacovigilance.

The question of going the usual way of manual process control or optimizing it through digitalization was not at all.

System capabilities should include:

- Cognitive case processing to automate data intake and processing to help significantly improve the efficiency and quality of the AE life cycle.

- Aggregate and operational reporting that is scalable, user-friendly, and designed to accommodate high case volumes and large data sets.

- Signal detection, evaluation, and management that consolidate and streamline processes and systems so analysts can perform validation and assessment activities and capture results and annotations without leaving the system, leading to more efficient, accurate signal management.

- Safety metrics that leverage existing safety data, new real-world sources, and supervised and unsupervised machine learning to detect, assess, understand, and help prevent safety-related issues while uncovering benefits that can improve patient outcomes.

Taking the needs of a large pharmaceutical company Pharmaceutical Firm “Darnitsa” as an example, where tasks are clearly defined and information flows are planned, we found that modern computational algorithms make it possible to gradually simplify such activities related to pharmacovigilance as:

Collection:

- filter information;
- research in a semi-automatic mode according to the set criteria;
- receive messages pending processing by a specialist;
- accumulate undifferentiated information;

Structuring and preliminary analysis:

- processing;
- management;
- quality control;
- identification of the necessary missing information;
- coding;
classification;
- detection of duplicates;
- signal management

**Information exchange:**

- timely reporting of adverse reactions;
- sending reports;
- communication ecosystem solution:
  - opportunity to work with several cross-functional experts (quality, medical service, regulatory service, pharmacovigilance) with appeals
- fixation of investigations on appeals
- possibility to monitor the progress of investigations into appeals (complaints)

And the productivity of these processes is significantly statistically higher with a high perceived ease of use and user satisfaction.

Based on this, we conclude that an effective pharmacovigilance platform allows us to devote more expert time to the implementation of product safety solutions, instead of optimizing processes and functions that can be automated.

**References**