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GIENS WORKSHOPS 2022/E-HEALTH AND ARTIFICIAL INTELLIGENCE

What place for intelligent automation and artificial intelligence to preserve and strengthen vigilance expertise in the face of increasing declarations?☆

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Summary In 2018, the ''Ateliers de Giens'' (Giens Workshops) devoted a workshop to artificial intelligence (AI) and led its experts to confirm the potential contribution and theoretical benefit of AI in clinical research, pharmacovigilance, and in improving the efficiency of care. The 2022 workshop is a continuation of this reflection on AI and intelligent automation (IA) by focusing on its contribution to pharmacovigilance and the applications and tasks could be optimized to preserve and strengthen medical and pharmacological expertise in pharmacovigilance. The evolution of pharmacovigilance work is characterized by many tasks with low added value, a growing volume of pharmacovigilance reporting of suspected side effects, and a scarcity of medical staff with expertise in clinical pharmacology and pharmacovigilance and human resources to support this growing need. Together, these parameters contribute to an embolization of the pharmacovigilance system at risk of missing its primary mission: to identify and characterize a risk or even a health alert on a drug. The participants of the workshop (representatives of the Regional Pharmacovigilance Centres (CRPV), the French National Agency for Safety of Medicinal Products (ANSM), patients, the pharmaceutical industry, or start-ups working in the development of AI in the field of medicine) shared their experiences, their pilot projects and their expectations on the expected potential, theoretical or proven, AI and IA. This work has made it possible to identify the needs and challenges that AI or IA represent, in the current or future modes of organization of pharmacovigilance activities. This approach led to the development of a SWOT matrix (strengths, weaknesses, opportunities, threats), a basis for reflection to identify critical points and consider four main recommendations: (1) preserve and develop business expertise in pharmacovigilance (including research and development in methods) with the integration of new technologies; (2) improve the quality of pharmacovigilance reports; (3) adapt technical and regulatory means; (4) implement a development strategy for AI and IA tools at the service of expertise.

Abbreviations

AI	intelligent automation
AI	artificial intelligence
MA	marketing authorization
ANSM	French National Agency for Safety of Medicinal Products
ARS	Regional Health Agency
CHU	University Hospital Centers
CRPV	Regional Pharmacovigilance Centres
EMA	European Medicines Agency
MedDRA	Medical Dictionary for Regulatory Activities
PBRER	Periodic Benefit Risk Evaluation Report
PMP	Risk Management Plan
PNM	non-medical personnel
PM	medical staff
PSUR	Periodic Safety Update Reports
RM	major risk
RPA	robotic process automation
SWOT	Strengths, Weaknesses, Opportunities, Threats

Introduction

In 2018, the Ateliers de Giens devoted a workshop to artificial intelligence (AI) and led its experts to confirm the potential contribution and theoretical benefit of AI in clinical research, pharmacovigilance, and in improving the efficiency of care [1]. This 2022 workshop is part of the continuity of this reflection on AI and intelligent automation (IA) by focusing on application to pharmacovigilance and more specifically on the applications and tasks they could optimize in order to preserve and strengthen medical and pharmacological expertise in pharmacovigilance. Naturally, this reflection on these novel tools (AI and IA) can be extended to other vigilances while taking into account their specificities and respective perimeters (materiovigilance, addictovigilance...). The evolution of pharmacovigilance work is characterized by: i) many tasks with low added value, repetitive, and time-consuming; ii) a growing volume of pharmacovigilance reports with a fundamental trend towards an increase in the number of cases, regardless

of health and/or media crises; iii) the scarcity of medical staff with clinical pharmacological and pharmacovigilance expertise; and iv) human resources that are not and will not be able to support the current evolution. In the very short-term, this contributes to an embolization of the pharmacovigilance system with the risk of missing its primary mission: to identify and characterize a risk or even a health alert on a drug. The participants of the workshop (representatives of the Regional Pharmacovigilance Centers (CRPV), the French National Agency for Safety of Medicinal Products (ANSM), patients, the pharmaceutical industry, or start-ups working in the development of AI in the field of medicines, first shared their experiences and expectations on the expected potential, theoretical or proven, AI and IA. This approach was facilitated by the presentation of pilot or already operational applications in the academic/institutional and industrial sectors and by the sharing of recent scientific publications on examples of artificial intelligence in pharmacovigilance. These concrete illustrations made it possible to identify the real needs and challenges that AI or IA represent, or not, in the current or future modes of organization of pharmacovigilance. This approach led to the development of a SWOT (Strengths, Weaknesses, Opportunities, Threats) matrix to determine the options offered as well as the constraints in the field of the application of AI or IA in pharmacovigilance, a basis for reflection to identify critical points and consider recommendations. The five interactive sessions between the participants, conducted remotely, also made it possible to prepare all the participants for a work inspired by Ghosh's publication [2]. At the 6th and last face-to-face working meeting in Paris, the workshop participants had to, for each pharmacovigilance task identified, reach a consensus in terms of assessed workload, potential for AI and IA application, and associated potential risk.

All the experts of the workshop unanimously agreed on the richness of these exchanges, and in the potential contribution of AI and IA to strengthen and preserve activities with high medical and pharmacological impact. The was to develop AI and IA tool that work in service of human intelligence: to support the already rare and overstretched expertise in focusing on the essentials, and to be able to benefit from technological assistance. To preserve and strengthen pharmacovigilance expertise, several critical points were discussed and led to recommendations on the use and potential risks of AI and IA.

The profession(s) of pharmacovigilance in 2022

The purpose of pharmacovigilance is to monitor, evaluate, prevent, and manage the risk of adverse reactions resulting from the use of the medicinal product [3]. In France, the pharmacovigilance system is based at the national level on the ANSM and on the territorial network made up of the French network of regional pharmacovigilance centers, located in the 31 University Hospital Centers (CHU), under the responsibility of medical pharmacologists. These CRPVs are in direct contact with health authorities (ANSM, Regional Health Agencies — ARS), health institutions, hospital or private health professionals and patients. This system also includes pharmacovigilance activities lead by pharmaceutical companies and registered patient associations.

The reporting of adverse reactions, whether serious or not, is a regulatory obligation for health professionals and must be carried out at their CRPV or at the Reporting Portal set up by the Ministry of Health in March 2017 [4]. Patients can also report through this Reporting Portal, an approach recognized in a 2011 decree [5]. Pharmaceutical companies participate in the national pharmacovigilance system and have obligations concerning the medicines they market or they are the Exploitant. They are also subject to internal procedures given the nature of their contribution to the at the national pharmacovigilance system as Exploitants, and at the international level in connection with the status of marketing authorization holder (MAH). All pharmacovigilance activities carried out by the various actors are underpinned by regulatory obligations, governed by legislation, and regularly updated good pharmacovigilance practices.

Without going into the technical details of the work which will be detailed later, the best known mission of the CRPV (even if it is not the only one...) is the processing of pharmacovigilance notifications or declarations. Their volume continues to increase given the extension of the reporting obligation to non-serious cases, the incentive for patients to report directly, the increased number of medicinal products and classes of medicinal products marketed, the facilitation of reporting with the online availability via the internet of the reporting portal, the increasing visibility of pharmacovigilance. As an indication in 2020 alone, 42,653 declarations were managed and analyzed by the medical pharmacologists of the CRPV and then transmitted to ANSM. Nearly 750,000 declarations have been managed and analyzed in 45 years of ANSM existence, with an exponential increase between 2016 and 2020 [6]. In 2021, more than 160,000 reports were made (roughly 4 times the number made in the previous year). This increase largely related to the deployment of COVID-19 vaccination at the population level. Those reports or notifications serve as just the first step of the pharmacovigilance process. The work of processing a report or notification is very labor intensive. Provided the report is sufficiently informative, these notifications are subject to a clinical, pharmacological, chronological, semiological and bibliographic analysis. In the event of insufficient initial documentation, the pharmacovigilant shall contact the reporter again to obtain additional information in order to be able to carry out their expertise. This analysis regularly leads to correcting the diagnosis or implicating a drug that may not be the one initially suspected by the reporter. This activity is a act of diagnosis of ''drug disease'' [6].

This work is fundamental to ensure patient safety. Another public service that is provided in pharmacovigilance is responding to requests for opinions/information by health professionals. Those requests can lead to identify cases of suspected side effects, then registered in the national pharmacovigilance database at the ANSM (about 1/4 of the annual declarations come from this activity of request for information, 10,244 questions led to a declaration in 2020) [6]. This activity is fundamental in the diagnosis and management of drug disease and also contributes to the proper use of drugs. Another crucial activity

is the detection of pharmacovigilance signals (so-called ''landmark cases''/''Cas marquants''), requiring their evaluation according to procedures or identification by methods of disproportionality. The CRPV also participate in the safety of the use of medicines by providing support and expertise to ANSM. They do so by summarizing the results of national pharmacovigilance surveys [7—9]. In 2020, CRPV medical pharmacologists authored 365 expert reports (one for almost every day of the year). Most led to changes in the information or use of the drug studied [6]. At the territorial level, the CRPV also have a role in the prevention of iatrogenesis through their mission of information on medicines, training and information for health professionals at university and postgraduate level, and research and publication activity [6].

Pharmaceutical companies share this task of collecting notifications during the various activities deployed on the national territory. However, access to medical record data may be less direct than for CRPVs who are located in the Pharmacology Services of the CHU and receive the mandatory declarations. However, companies are also subject to registration, documentation and reporting obligations to the authorities of adverse reactions and special situations. These are either observations reported spontaneously to the firm by health professionals, patients or any other user of the health system, or solicited during a study or data collection program (post-authorization study, market research, early access authorization...). Pharmaceutical companies also monitor published international literature regularly and monitor non-indexed national literature in international databases for suspected adverse reactions to their drug and special situations described in these publications.

They must report the case reports/notifications they receive or identified directly, register them in the company's international pharmacovigilance database after performing a duplicate search and translation into English and finally transmit adverse reaction reports electronically to EudraVigilance or other regulatory authorities worldwide or partner firms within specified deadlines and defined modalities. This exchange of information in the majority of cases is automated in electronic format E2B (international standard for the electronic transmission of individual adverse reaction reports meeting regulatory requirements). The step of translating data into English is a specificity in the process of managing cases by pharmaceutical companies and this is the case for those operating in France compared to CRPVs. With the advent of machine translation solutions integrating AI, these tools have become more reliable and efficient to accelerate the management of pharmacovigilance cases.

Pharmaceutical companies are also required to put in place the necessary measures for the detection of signals and their processing at national level for the Exploitant and at international level for the MAH holder. The latter is also required to prepare risk management plans (RMPs), periodic safety update reports (PSURs) or Periodic Benefit Risk Evaluation Report (PBRER) and to submit them electronically to the European Medicines Agency (EMA) and other regulatory authorities in the world where the product is registered.

The multitude of sources and media of information that can report suspected adverse reactions and special situations associated with the use of their drugs require manufacturers to equip themselves with effective procedures and tools to help them process this data by integrating AI and AI.

In summary: regulatory and administrative changes in traceability, archiving, storage, activity indicators, coupled with an ever-increasing volume and a multi-source origin of data have disrupted the overall process of pharmacovigilance work, a significant part of which is time-consuming, repetitive, and without the need for expertise. Freeing up and securing time for high value-added and non-automatable activities is therefore a clearly expressed need in order to focus on clinical expertise, analysis and detection of pharmacovigilance signals, the preparation of expert reports via pharmacovigilance surveys, training and territorial animation, research and development of pharmacovigilance methods. Naturally, this reflection can be extended to other vigilances while taking into account their specificities and respective perimeters (materiovigilance, addictovigilance...) [10]. It is also important to detail the entire business process in order to identify the tasks/processes in which AI/IA/robotization/automation can be introduced in order to focus teams on tasks with high added value. Projects integrating these ''new generation'' technologies have been set up, especially at the level of pharmaceutical companies and more recently at the level of CRPV and ANSM.

Feedback from the use of AI and IA in pharmacovigilance

Automation system within the CRPV network by the ANSM

The Medication Shield is a pharmacovigilance automation system developed by Synapse Medicine and the CRPV of Bordeaux and then implemented at the national level via an ANSM collaboration and CRPV network in April 2021, on the occasion of a software change of the national pharmacovigilance database [11,12]. This system has been integrated into an automated system, called Intake developed by ABCube, for importing reports from the National Adverse Event Reporting Portal [4]. This import system is in fact an IA airlock for the transfer between the portal and the national pharmacovigilance database, within which the pharmacovigilant can receive the case and start its evaluation. This interoperability mechanism between the portal and the national pharmacovigilance database makes it possible not to re-enter the data previously entered by the reporter, in particular concerning the patient (sex, age) and his history and the reporter himself, data that can be described as ''non-sensitive''. It is thus at this transfer airlock that Medication Shield offers assistance in coding or pre-coding reported events, subject to validation or modification of the pharmacovigilant (Fig. 1). This AI tool focuses on patient reports and some of the unstructured data in order to: i) pre-code reported adverse reactions according to Medical Dictionary for Regulatory Activities (MedDRA) terminology; ii) define the expected or unexpected nature of an adverse reaction according to the data of the summary of product characteristics; and iii) determine the severity or otherwise of the case. The ultimate objective of these

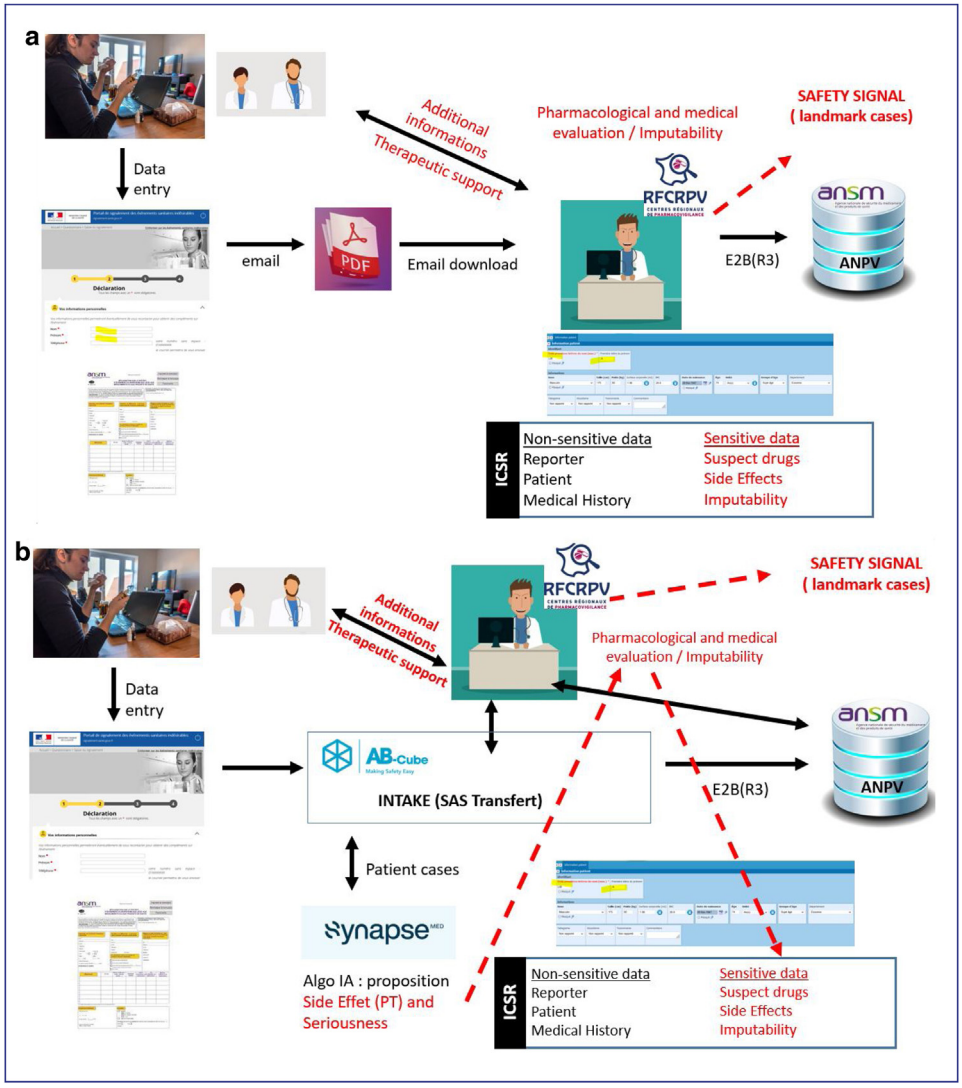

Figure 1. Management of patient reports before (a) and after implementation of the AI algorithm (b) on pharmacovigilance data, transmitted via the reporting portal, to Regional Pharmacovigilance Centres (CRPVs). Diagram of the management of pharmacovigilance notifications before the implementation of the automation system within the CRPV network. Mainly manual management with download of the report form in PDF format from the reporting portal, traceability in the internal software of the CRPV and manual entry of the data already completed by the reporters, archiving of the document in the case. RFCRPV: French Network of CRPV; ANPV: National Pharmacovigilance database; ICSR: Individual Case Safety Report; E2B(R3): International standard for data exchange; b) diagram of the management of pharmacovigilance notifications after the implementation of the automation system within the CRPV network. Integration of the automated Intake ABCube system for importing reports from the national adverse event reporting portal and the Medication Shield Synpase Medicine AI module, which allows categorization and pre-coding of adverse reactions reported by patients, all facilitating and streamlining the expert work carried out by the CRPV. PT: Preferred Term of MedDRA terminology.

coupled AI and AI devices is, given the exponential volume of patient reports, to save time for the benefit of the expert work of pharmacovigilants. This AI algorithm was initially developed on a dataset from the Bordeaux CRPV and then the Marseille CRPV to evaluate its performance [11]. Its extension at the national level during the deployment of the COVID-19 vaccination with an unprecedented volume and very heterogeneous by the reported events finally made it possible to set up a large-scale pilot phase, with its handling by a larger number of users (the teams of the 31 CRPV) and an enrichment of the AI algorithm (feedback loop with continuous enrichment of the algorithm).

A user club made up of 8 volunteer CRPVs, the ANSM (team in charge of managing the national Pharmacovigilance database and the signal pole) and Synapse Medicine, made it possible to give feedback on this device and to propose areas for improvement. It also aims to initiate a reflection on the automation of certain low value-added tasks related to case management (download of the PDF form of the reporting portal, traceability in the CRPV's internal

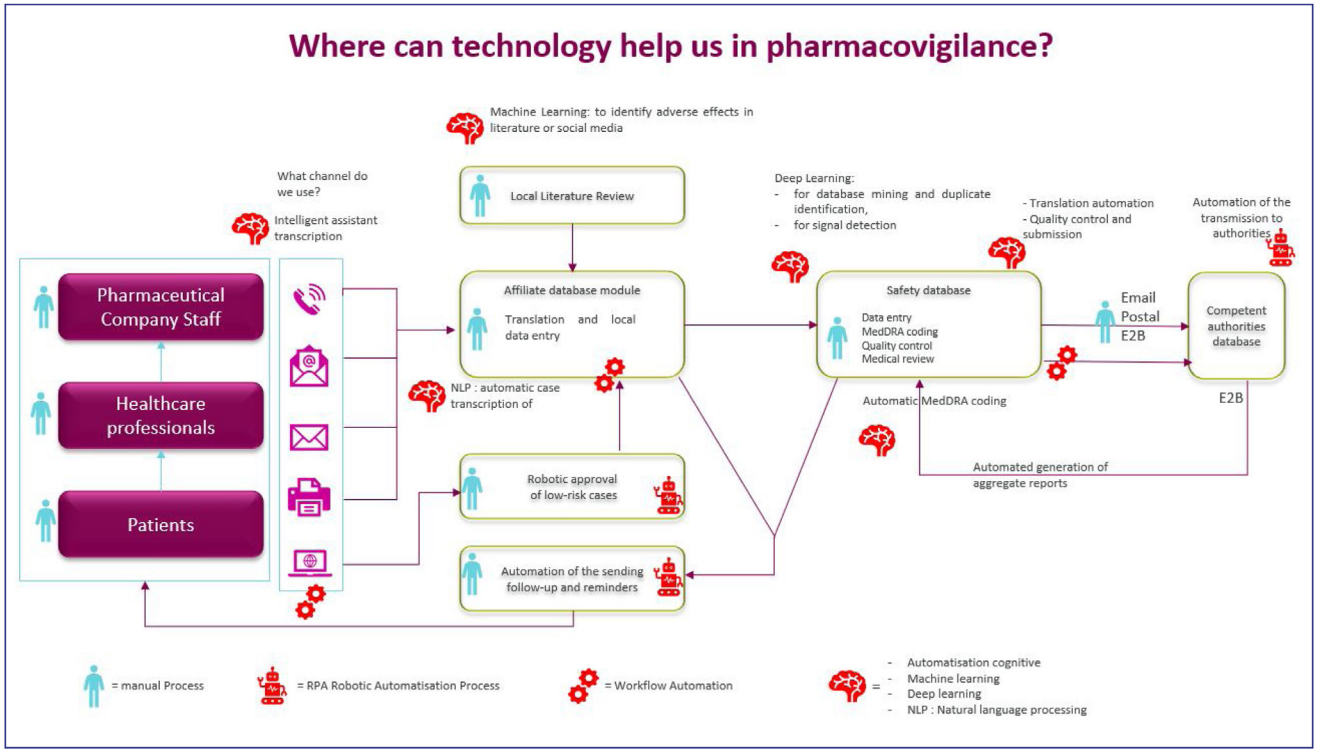

Figure 2. Contributions of technology in the different stages of pharmacovigilance in industry. Diagram of the mapping of the different stages of the management of adverse events reports in industry from receipt to submission to the authorities. Transcription and machine translation are used as soon as the data is received. Workflow automation technologies as well as robotic process automation are used at different stages to increase efficiency in case processing and sending requests to reporters for additional information or reminders. Machine or deep learning is used for the identification of adverse effects in texts such as literature or digital media.

software, archiving...) or other automation tools related to the activity of the CRPVs.

Examples of the use of AI or IA in pharmacovigilance in industry

Industry is faces with the same pressures: exponential growth in the volume of reported cases require processing, but also with the added constraints specific to pharmaceutical companies (i.e. the translation into English of notifications, the monitoring of literature, the monitoring of their data collection programs, the exchange of information with authorities and partners, signals detection and the preparation of periodic reports, several pharmaceutical companies have been interested in the integration of next-generation technologies (AI, AI, robotization, machine learning...) in pharmacovigilance activities over the past 10 years [13—15]. This work began with the analysis of the various stages of information processing from receipt and recording in the database to monitoring, signal detection, analysis and reporting (Fig. 2). The complexity of implementing these tools varied, ranging from simple programs set up at the level of an affiliate to more complex projects involving all the affiliates of the company and requiring the upgrade or replacement, and maintenance of databases to allow interoperability of systems and data communication.

The participants from pharmaceutical companies of this workshop presented projects already in place at the level of their respective companies or pilot projects deployed or being deployed in other affiliates around the world. There are thus various and varied uses of ''next generation'' technologies implemented in the management of pharmacovigilance operations such as the automation of case management (case intake). This step of case management alone can integrate several technologies such as the use of a common digital form for the reception of pharmacovigilance cases allowing automatic entry of data into the pharmacovigilance database from the dematerialized form. The use of a chatbot in medical information coupled with case intake allow to respond to users requests while integrating the ability to identify conversations involving adverse reactions and direct them to reporting forms. Automatic speech recognition technology and speech to text technology allow to transcribe telephone conversation data into text and to develop telephone call reports in structured fields that can then be used in databases. The integration of machine translation into databases allows data to be translated and entered into English regardless of the reporting language and advance the case in the workflow. Natural language processing is used to identify key data in the text of different media such as social media conversations looking for the elements to constitute a case including information about the adverse reaction and its severity, the suspected drug and patient information. The automatic categorization of the case and the robotic approval of low-risk cases defined according to criteria integrated into an algorithm allows a rapid and automatic triage of the cases received to advance them in the management process to the pharmacovigilance database

Table 1 Potential contribution of Intelligent Automation and Artificial Intelligence for the preservation of pharmacovigilance expertise: tasks concerning the treatment of reports of potential adverse drug reactions.

	Processing step	Current workload	Potential contribution AI/AI	Comment (expectation, potential risk)
1	Declaration	—	Significant contribution without major risk (MR) identified	Facilitation of reporting Creation of a healthcare professional reporter account with pre-filled information Importing data from the patient ID
2	Receipt, verification of essential regulatory information, search for duplicates	Important NMS	Significant contribution without major risk (MR) identified	Non-medical time intake
3	Acknowledgement of receipt	Important NMS	Significant contribution without identified MR	Non-medical time intake
4	Initial triage (severity, known effect, specific population, recent or cautionary drug, associated information request)	Low to important for MS ± PNM (volume-dependent)	Low intake and potential MR	Sorting error: medically important event/medication under specific watch more difficult to automate than sorting on severity. In addition, sorting considers other parameters (expertise, etc.)
5	OR: initial triage: cases without priority criteria	Low to important for MS ± NMS (volume-dependent)	Low to high intake without MR identified	Ok if 100% sensitivity or classification as potentially priority if system uncertainty about non-priority + time saving + acceleration prioritization on patient declaration Attention to adaptation to business practices
	Pre-entry	Important NMS	Significant contribution without identified MR	National portal
6	File completed by source documents (information retrieval (AI) and interpretation (AI, to be annotated))	Important MS	Significant contribution and MR important	Difficulty in identifying relevant information within the medical record Access of the AI system to the medical record (confidentiality issue) System interoperability problem
7	File completed by contact of the reporter/health professional	Important MS	Low intake and potential MR	Contact pharmacovigilant-reporter allows a formal and informal collection irreplaceable in effectiveness. Reflection: could contact be targeted on the information to which the interlocutors respond most often badly? Technology that cannot replace an educational exchange with feedback
8	Follow-up follow-up/follow-up after initial pharmacovigilance-registrant contact	Low — NMS	Significant contribution without identified MR	Follow-up on outcome, pregnancy outcome, must be reflected with ways to increase the rate of return (use of smartphone application with sending SMS for example).
9	Case analysis	Important MS	Low intake and potential MR	No room for automation
10	Information retrieval (summary of product characteristics — SmPC), databases, bibliography)	Important MS	Significant contribution and potential MR	Tool to develop with functionalities to be made available, to be used or not depending on the case On SmPC drug and class If not listed, automation would be very useful on the national pharmacovigilance database (BNPV), Vigilyze, PubMed BUT useful for simple situation

Table 1 (*Continued*)

	Processing step	Current workload	Potential contribution AI/AI	Comment (expectation, potential risk)
11	Identification of landmark cases	Low for MS	Significant contribution and potential MR	Implementation of certain criteria in the entry of cases: no verification of the entire flowchart but contribution on a part and obligation of reflection
12	Completion and submission of the landmark case form	Important MS	Significant contribution without potential MR	For Pre-filling
13	Validation in the PV database	Important NMS	Significant contribution without identified MR	Quality control OK, but validation must remain manual by PM
	Reporting to authorities (industry)	Important NMS	Significant contribution without identified MR (undue)	—
14	Response — writing final letter (final opinion on the case)	Important MS	Significant contribution and potential MR	Use for response generation on automated hospitalization summaries model: automatic generation of a response proposal to be completed/validated by PV professional

and then an automatic proposal of the MedDRA coding of the reported or identified adverse event. Machine learning is used to identify adverse effects in literature or social media [16] or free text fields of databases or data collection programs conducted by pharmaceutical company. Machine learning is also used to explore the pharmaceutical company pharmacovigilance database and identify duplicate cases or in signals detection. Robotic process automation (RPA) is used at affiliate level to manage the sending of Adverse Event Report Form to reporters, to automatically send letters or emails of reminders and then classify and archive these documents in databases or computerized directories. Process automation is also used for the transmission of cases to competent authorities databases and in the preparation of periodic reports (PSUR/PBRER), particularly with regard to quantitative data responding to a targeted search on specific types of notifications (seriousness, causality, reported events, etc.).

Summary of the strengths and weaknesses of AI or IA in pharmacovigilance with regard to the opportunities and threats generated

Through discussions on the current state of organization of CRPV structures and pharmaceutical companies and the level of integration of next generation technologies in pharmacovigilance, the members of the workshop synthesized the strengths and weaknesses of these new technologies in the current pharmacovigilance environment in France, while identifying the opportunities offered and the potential risks that could be generated of the approach (Fig. 3).

Pharmacovigilance processes: AI or IA opportunities and risk levels

In order to finalize the list of tasks identified as potential candidates for intelligent automation/a contribution of artificial intelligence to procedures. Each participant was asked to, in anticipation of face-to-face group work, evaluate the workload associated with each of the listed tasks, evaluate the potential interest of intelligent automation or the use of artificial intelligence techniques to reduce processing times in the task with a view to preserving medical resources for expertise activities, and consider the potential risks of replacing humans with machines in these activities. This work was inspired by the methodology used in the publication by Gosh et al. [2].

The participants' group work aimed to finalize the reflection by reaching a consensus for each task in terms of assessed workload, potential for AI and AI, and associated potential risk. The final result of the consensus should be able to be rendered in the form of a summary table combining a categorization summary of the assessments of workload and potential contribution according to the classification detailed in Fig. 4, and a textual descriptive part of the potential risks identified and, where appropriate, the measures to contain these risks.

The summary of the evaluations carried out is detailed in 3 separate tables related to the three main pharmacovigilance activities:

- in Table 1 for activities relating to the treatment of spontaneous reports of potential adverse reactions to the medicinal product;
- in Table 2 for activities relating to the processing of requests for advice/requests for information;
- in Table 3 for signal detection activities.

Overall, the deployment of AI/AI with a view to preserving expertise appeared to be associated with

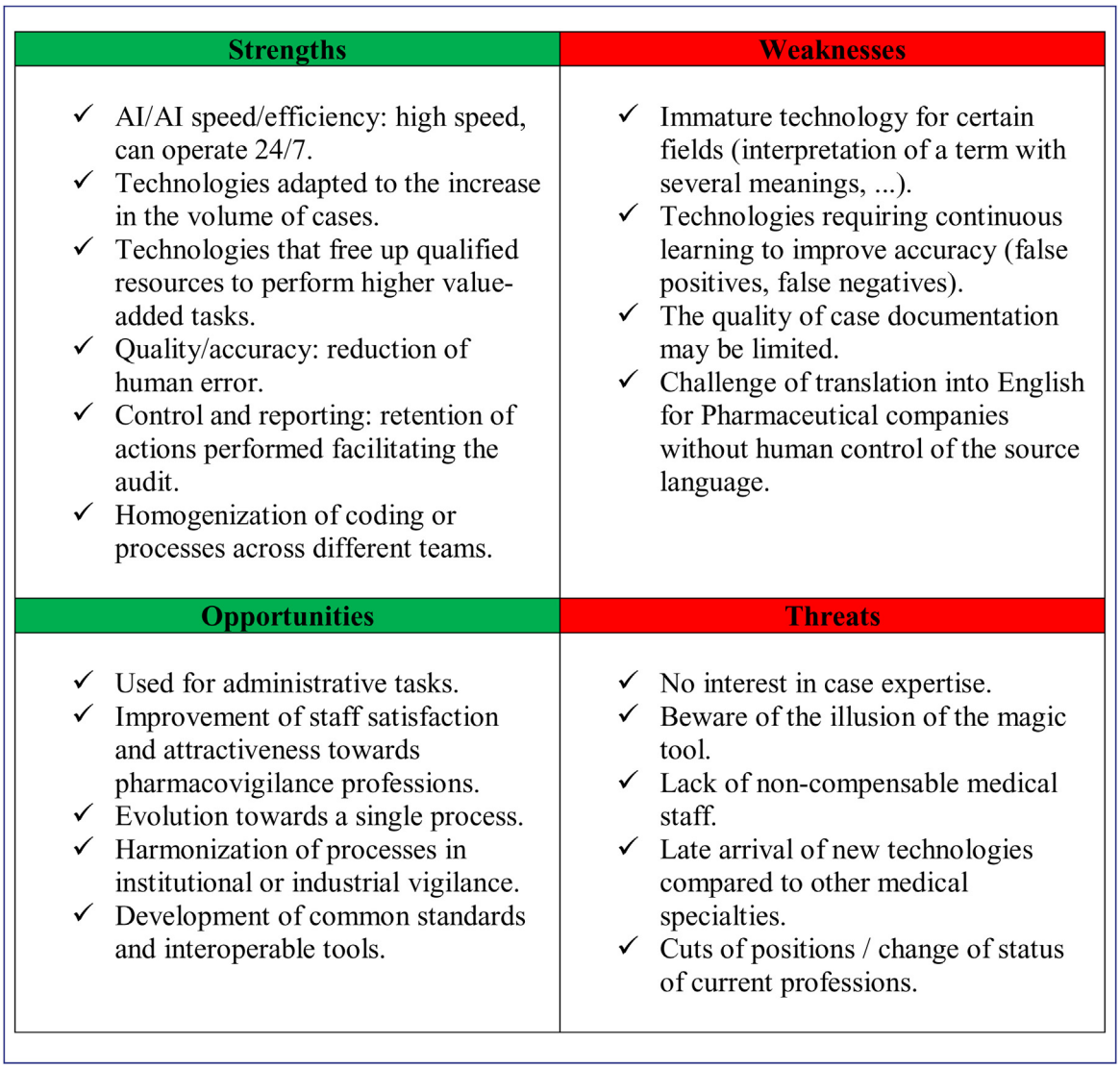

Figure 3. Strengths, Weaknesses, Opportunities, Threats (SWOT) of intelligent automation (IA) and artificial intelligence (AI) in vigilance.

Workload	Low Non-Medical Staff (NMS)	Low for medical staff (MS)	Important - NMS	Important - MS
Potential contribution	Low intake AND potential major risk (MR)	Significant contribution AND potential MR	Low intake without identified MR	Significant contribution without identified MR

Figure 4. Classification chosen to categorize, after consensus, the summary assessment of the workload associated with pharmacovigilance tasks and the potential contribution of intelligent automation or artificial intelligence to these tasks.

significant potential for all activities related to the processing of spontaneous reports of potential adverse drug reactions (14 listed) with the exception of three: initial screening of notifications for prioritisation, seeking additional information from the reporter (in particular clinical) necessary to assess the case, and medical and pharmacological analysis of the case. In addition, for four of the 11 activities with significant potential input, a theoretical risk associated with the deployment of automation or the transfer of the activity from humans to machines was identified. These were a risk related to data structuring defects for the activity of completing notification dossiers using source documents, the risk of obtaining erroneous information in the tasks of automating the search for information

Table 2 Potential contribution of Intelligent Automation (AI) and Artificial Intelligence (AI) for the preservation of pharmacovigilance expertise: tasks concerning the processing of inquiries/requests for information.

	Processing step	Current workload	Potential contribution of intelligent automation	Comment (expectation, potential risk)
1	Reception	Important NMS	Low intake and potential MR	—
2	Acknowledgement of receipt	Important NMS	Significant contribution without identified MR	—
3	Initial triage (seriousness, special population, recent drug, drug with special warnings, associated information request, known effect)	Important NMS	Low intake and potential MR	—
4	Pre-entry of questions in the local database	Important NMS	Low intake without identified MR	—
5	File completed by reporter contact/health professional	Important MS	Low intake and potential MR	The reporter contact allows a formal and informal collection; human contact has the advantage of allowing to retrieve information indirectly Reflection: if human contact is essential, could it be targeted on the part of the information to which the interlocutors most often respond badly and can the rest be done differently? Technology that cannot replace an educational exchange with feedback
6	Follow-up follow-up/follow-up after human contact	Low — NMS	Significant contribution without identified MR	Follow-up on outcome, pregnancy outcome, tool to be considered as a way to increase the rate of return
7	Analysis of the question ± of the associated case	Important MS	Low intake and potential MR	A shared system between the centres for the management of requests for information (RFI) locally would make it possible to pool work (problem of interoperability of systems): sharing tools, data, experience
8	Information retrieval (SmPC, databases, literature)	Important MS	Significant contribution and potential MR	About SmPC If not listed, an automation would be very useful on the BNPV, Vigilyze, PubMed but useful for simple situation
9	Writing the answer to the question	Important MS	Low intake and potential MR	Writing assistance (''direct mail'')
10	Sending the answer to the question and archiving	Important NMS	Significant contribution without identified MR	—

concerning the relationship between a medicinal product(s) and an event(s) in medically complex situations, the unacceptability of the non-identification of significant cases in the tasks relating to this activity (the automation of the identification of certain criteria seems possible), however), and the activity of drafting the summary opinion of the expertise carried out for a notification of potential adverse reaction. However, partial automation also seems possible for the latter activity (cf. Table 1).

The evaluation consensus concludes that there is less potential contribution of AI/and AI for activities related to the processing of requests for opinions/requests for

Table 3 Potential contribution of intelligent automation and artificial intelligence for the preservation of pharmacovigilance expertise: tasks concerning the signal detection activity.

Activity	Current workload	Potential contribution of intelligent automation	Comment (expectation, potential risk)
Literature watch	Low to important NMS	Low to high intake without MR identified	—
Identification of significant cases (cf. notifications table)	Low — NMS	Significant contribution and potential MR	Implementation of certain criteria in the entry of cases: no verification of the entire flowchart but contribution on a part and obligation of reflection
Completion of the landmark case form (cf. notifications table)	Low — NMS	Significant contribution without identified MR	—
Disproportionality signal — automated detection (agency/institution)	Low — NMS	Significant contribution without identified RM risk	—
	Important NMS		Low intake without identified MR
Signal of disproportionality — ad hoc study	Low — NMS	Significant contribution without identified MR	—
Signal — ad hoc pharmaco-epidemiological study	Not relevant to date	Not relevant to date	Activity of national agency to terms/team commissioned by national agency or industrial Not currently established methods for signal detection by pharmaco-epidemiological approach (research in progress)
Signal processing (agency/institution)	Important MS	Significant contribution and potential MR	In perspective: integration of the various information obtained (literature, cases, disproportionality) with automated classification subject to a weighting to be defined
Sending to the authorities	Low for MS	Low intake without identified MR	—

information concerning the medicinal product with a potential contribution considered important in only four of the 10 tasks listed, which is moreover associated with a theoretical risk for one of them (risk of obtaining erroneous information in the tasks of automating the search for information concerning complex situations, evaluations in line with that concerning the activity of processing notifications).

On the other hand, it appeared more important in terms of signal detection, an activity context in which the deployment of AI/AI was less systematically associated with identified theoretical risks. Indeed, after consensus, there was a potential contribution in the seven activities relating to the detection of listed signals, important in five activities out of the seven listed, with theoretical risk identified in only two out of five (activity of identification of landmark cases, identical to the risk identified in notification processing; categorization of signals from a management perspective at the institutional level).

Conclusions and recommendations

The objectives of this workshop were to identify the contribution of AI and AI to preserve and strengthen human expertise in pharmacovigilance. The participants of this workshop through their experience and expertise in this field, their participation in pilot or already operational AI and AI projects, and their shared reflection during these working sessions made the following recommendations.

Recommendation No. 1: preserve and develop business expertise in pharmacovigilance (including research and development in methods) with the integration of new technologies

The profession of pharmacovigilant requires specialized knowledge to carry out a pharmacological and medical analysis of adverse effects at both individual and population level.

This specialized expertise is rare, making it essential to transfer low value-added tasks to automation [17]. This requires the integration of new technologies managing these tasks more quickly, thus freeing up time to focus on tasks with high added value and thus contributing and also increasing the attractiveness of this profession [18].

Recommendation No. 2: improve the quality of pharmacovigilance reports

In recent years, the incentives for pharmacovigilance reporting or the technical systems (for example the reporting portal) set up to amplify the declaration, have not been sufficiently accompanied by a clear pedagogy on what is a quality declaration, that is to say whose content is relevant because it can be used in its subsequent analysis by pharmacovigilants and health authorities. This is a fundamental point because pharmacovigilance declarations are the basis of this activity. The insufficient quality of the data contained in the initial pharmacovigilance report requires a return to the reporter (whether health professional or patient) which is not always successful and adds an overload of work on both sides (reporting side and pharmacovigilance side). Even among health professionals, pharmacovigilance reporting is still perceived as a time-consuming administrative act and not as an accurate synthesis of a clinical observation. On the side of the general public, pharmacovigilance declarations are still too often the expression of harm or a general testimony rather than a precise description of the symptoms, the clinical diagnosis retained and its management.

The development of AI and IA is also dependent on the quality of this data. The adage ''garbage in, garbage out'' also applies to AI and IA which are ineffective on data of insufficient quality, since the initial report serves as the basis for their learning.

These observations support the recommendation that: i) education on the risk of health products aimed at the general public, students (health service of health students...); ii) the need to train or inform patients and health professionals in the use made of these declarations, in particular signal detection but also the medical and pharmacological help that pharmacovigilantes can provide when requesting opinions; iii) to provide training and information on what constitutes an informative and relevant declaration, adapted to the different targets (general public, health professionals); iv) to develop existing reporting tools more adapted to its users (reporters and pharmacovigilantes) and easily adapted to a specific emerging issue in a particular health and/or media context if necessary, and also to adapt/evolve existing tools.

Recommendation No. 3: adapt technical and regulatory means

The evolution of the pharmacovigilance profession and the ecosystem in which it operates makes it essential to modernize its work environment, as well as its more direct access to already existing and stored data. This same observation can also be applied to health professionals, who must again enter administrative and medical information already present in their patients' files when making a pharmacovigilance declaration.

These critical points lead to recommend: i) an upgrade of CRPV equipment given their current technological debt incompatible with the volume of data to be processed; ii) a technical reflection, in compliance with regulations, on the interoperability of information systems (Reporting Portal, Electronic Patient Record, My Health Space site, prescription assistance software) in order to optimize and facilitate the quality of the data inherent in the pharmacovigilance file; iii) facilitated adaptability and ergonomics for the national pharmacovigilance database like what can be done with VigiLyze® allowing the faster obtaining of dashboards, useful both for the individual management of a case and for the population analysis during a national pharmacovigilance survey; iv) regulatory (R)evolution: regulatory developments in recent years in the field of pharmacovigilance have led to the extension of the reporting obligation to all suspected adverse drug reactions, regardless of their seriousness. This extension, which was not accompanied by additional resources, led to a preference for the quantitative at the expense of the qualitative, really raising the question of the real contribution of this flow in relation to a smaller number of cases but more documented and contributive: always more and always faster for what added value?

Recommendation No. 4: implement a development strategy for AI and AI tools at the service of expertise

The volume of data (and their multi-source origin) and the different tasks occupying the profession of pharmacovigilant can justify the development of AI and IA tools at the service of expertise. These potential tools cannot be conceived without a co-construction from beginning to end with the different users.

These critical points lead to recommend: i) to involve the pharmacovigilant in the development of tools: the development of these tools must not be part only in a perspective of exclusively technological development. It must above all meet specifications corresponding to the needs (s) of users. Thus, these tools must not be rigid and lock users into input logics that do not correspond to their clinical reasoning; ii) to integrate into this development strategy phases of proposals and validation by pharmacovigilantes future users of the tool; iii) to integrate into these tools both automation of non-medical tasks and preparatory tasks for expertise activities; iv) to implement in this strategy a continuous process of validation/evaluation of performance and identification of new purposes.

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LL, IP: employee/shareholder of Synapse Medicine, a company that develops clinical decision support systems.

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References

[1] Diebolt V, Azancot I, Boissel FH. Participants of Giens XXXIV round table ''Hot topic N° 2''. ''Artificial intelligence'': which services, which applications, which results and which development today in clinical research? Which impact on the quality of care? Which recommendations? Therapie 2019;74:155—64.

[2] Ghosh R, Kempf D, Pufko A, Barrios Martinez LF, Davis CM, et al. Automation opportunities in pharmacovigilance: an industry survey. Pharmaceut Med 2020;34:7—18.

[3] ANSM. Bonnes pratiques de pharmacovigilance; 2022, https://ansm.sante.fr/actualites/nouvelle-edition-des-bonnes-pratiques-de-pharmacovigilance. [Consulté le 21 novembre 2022].

[4] Ministère de la Santé. Portail de signalement des événements sanitaires indésirables; 2022, https://signalement.social-sante.gouv.fr/psig_ihm_utilisateurs/index.html#/accueil. [Consulté le 21 novembre 2022].

[5] Legifrance. Arrêté du 10 juin 2011 pris pour l'application des articles R. 5121-154, R. 5121-167 et R. 5121-179 du code de la santé publique et relatif aux modalités de signalement des effets indésirables par les patients et les associations agréées de patients. JORF 2011;0136, https://www.legifrance.gouv.fr/loda/id/JORFTEXT000024153666/. [Consulté le 21 novembre 2022].

[6] Jonville-Béra AP. Vous avez dit Centre régional de pharmacovigilance ? Presse Med Form 2021;2:453—6.

[7] Abou-Taam M, Jacquot B, Ferard C, Thery AC, Mounier C, Grandvuillemin A, et al. The French pharmacovigilance surveys: a French distinctiveness, a real input. Therapie 2021;76:441—7.

[8] Soeiro T, Lacroix C, Micallef J. Adverse drug reaction monitoring: doing it the French way — act II. Therapie 2021;76:385—7.

[9] Lacroix C, Salvo F, Gras-Champel V, Gautier S, Massy N, Valnet-Rabier MB, et al. French organization for the pharmacovigilance of COVID-19 vaccines: a major challenge. Therapie 2021;76:297—303.

[10] Légifrance. Arrêté du 5 février 2021 pris en application de l'article R. 1413-61-4 du code de la santé publique définissant les missions des centres et coordonnateurs régionaux sur les vigilances relatives aux produits de santé. JORF 2021;0033, https://www.legifrance.gouv.fr/download/pdf?id=CR9_-ctqAXTRmqcijST8FodN4nZ8creyiY9Oib5-IYk. [Consulté le 21 novembre 2022].

[11] Létinier L, Jouganous J, Benkebil M, Bel-Létoile A, Goehrs C, Singier A, et al. Artificial intelligence for unstructured healthcare data: application to coding of patient reporting of adverse drug reactions. Clin Pharmacol Ther 2021;110:392—400.

[12] Martin GL, Jouganous J, Savidan R, Bellec A, Goehrs C, Benkebil M, et al. Validation of artificial intelligence to support the automatic coding of patient adverse drug reaction reports, using nationwide pharmacovigilance data. Drug Saf 2022;45:535—48.

[13] Schmider J, Kumar K, LaForest C, Swankoski B, Naim K, Caubel PM. Innovation in pharmacovigilance: use of artificial intelligence in adverse event case processing. Clin Pharmacol Ther 2019;105:954—61.

[14] Lewis DJ, McCallum JF. Utilizing advanced technologies to augment pharmacovigilance systems: challenges and opportunities. Ther Innov Regul Sci 2020;54:888—99.

[15] Hauben M, Hartford CG. Artificial intelligence in pharmacovigilance: scoping points to consider. Clin Ther 2021;43:372—9.

[16] Gartland A, Bate A, Painter JL, Casperson TA, Powell GE. Developing crowdsourced training data sets for pharmacovigilance intelligent automation. Drug Saf 2021;44:373—82.

[17] Liang L, Hu J, Sun G, Hong N, Wu G, He Y, et al. Artificial intelligence-based pharmacovigilance in the setting of limited resources. Drug Saf 2022;45:511—9.

[18] Deplanque D, de Retz S, Bellissant É, Les participants à la table ronde « Réglementation et organisationnelle » des Ateliers de Giens XXXV. Comment intéresser les médecins aux métiers du médicament et des dispositifs médicaux ? Therapie 2020;75:85—92.