# Digitally transformed pharmacovigilance

## Why we need it and why it will take a while to become reality

Nets

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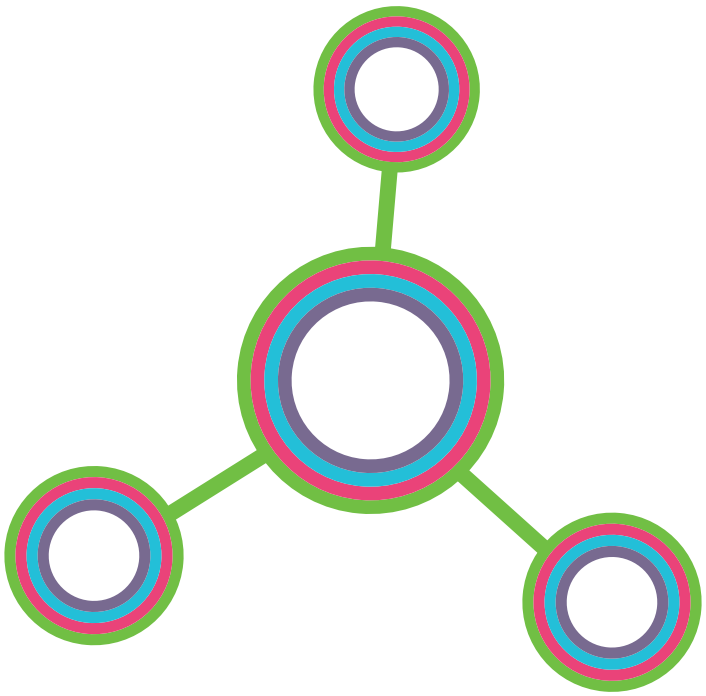


NAVITAS LIFE SCIENCES *Driving better outcomes through insights*

## Quick summary

**Pharmacovigilance is under pressure to evolve. The necessity to change is fuelled by authority interests wanting to find better ways to protect the public, while conserving healthcare spending, as well as MAH/sponsors/CROs having to deal with soaring ICSR volumes and increasingly complex global operations. Digital innovation seems to be the key to deliver major change, to harness technology advancements and the radically increasing data volumes - across clinical trials to real-world sources. The Industry has increased its effort over the past year and is discussing early pilots to understand how to apply technology to bring about new ways of working. There are significant roadblocks and concerns that may prove to make it a bumpy road ahead.**

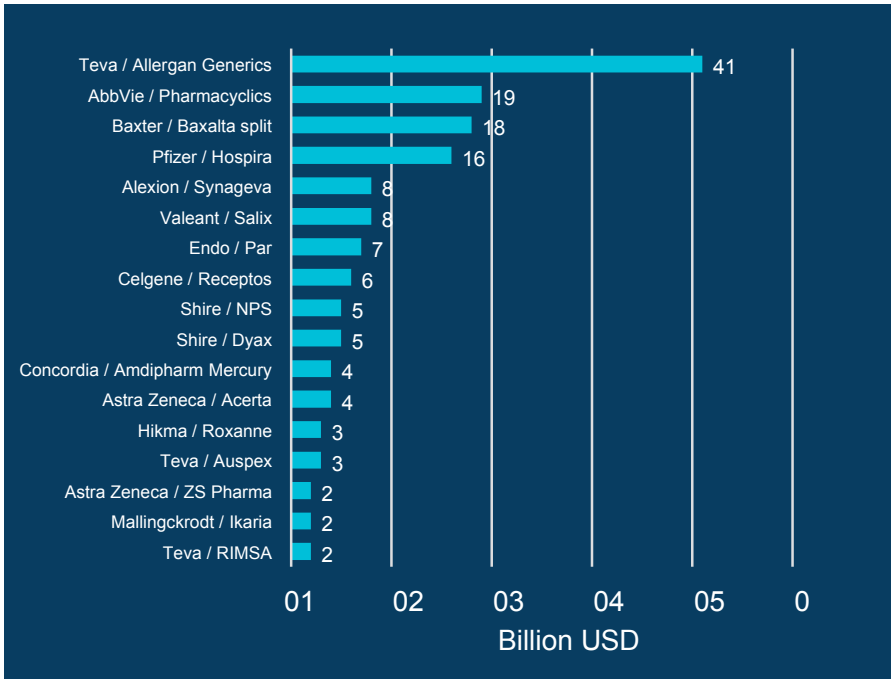
## The challenge to evolve pharmacovigilance

It is a well-established fact that ICSR volumes are increasing year by year. The 2016 benchmark at Navitas Life Sciences' pvnet®, pvconnect®, pvtech® and pvindia® (together pvnetworks®), which represents the majority of top 100 pharma companies, suggests a CAGR of approximately 20%, essentially doubling annual ICSR volumes by the end of the decade.

Concurrently, complexity of global, end-to-end operations is increasing. Rather than achieving global harmonization of regulations, which the Industry could have hoped for, the trend currently points in opposite directions. Towards regional and country-specific dissemination of regulatory requirements, from ICSR reporting, the QPPV role, pharmacovigilance system master file formats through to aggregate reporting specificities. Meanwhile, the EU is continuing to evolve their framework around Article 57, in the pursuit of building a cross-member state database comprised of high quality data for enhanced risk management and safety monitoring capabilities. The impact for pharmaceutical enterprises will be significant from 2017 to 2020. Most significantly, the Industry will be transitioning from E2B(R2) to E2B(R3), introducing corporate-wide IDMP initiatives and adapting their signal management processes to encompass the new EVDAS.

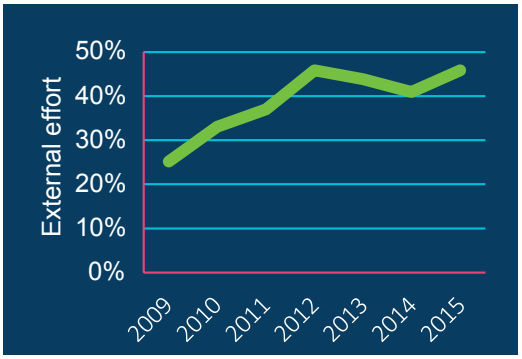
Perhaps less obvious is the impact from a changed pharma business model which has become predominantly networked and driven by merger and acquisition activities. Not many PV departments can claim to not do any due diligence activities on that account.  Merger and acquisition deals in 2015 amounted to approximately 200 bn. USD and impacted a large number of enterprises and departments, each having to adapt to a changing product portfolio. Migration and integration work has become a major effort in a PV organization alongside the fluent business partner eco system that require attention on PV reporting agreements.

**Pharma merger and acquisition activites +2 bn. USD, 2015**




Source: IMAP / MergerMarket

**PV outsourcing benchmark 2016**




Source: pvnetworks benchmark 2016

Realizing that constant headcount growth and steep cost increases is unsustainable, PV departments have been applying various measures to control the growth challenge. This includes making significant use of outsourcing partners, which provides options to handle workload pressures, and contain the headcount growth while delivering scalability that is especially important in acquisition scenarios. The Industry is getting close to the 50% mark for how much of PV is externally sourced. Outsourcing however has finite potential, as the processing still needs the same manual effort – with current utilization rates, it could be argued that most of the cost containment has already been realized by the industry today.

Extensive use of technology to reduce manual data processing and eliminating paper forms and double data entry in systems is also an integral part of PV today. The potential here is considerably more scalable as one considers recent advancements of technology for automation, but until now capabilities have been limited to fairly basic forms of data integration and scripting.

## The digital data explosion

Never has there been so much data available to access digitally. It is estimated that the size of the data available worldwide doubles approximately every 18-24 months, most aggressively increasing within the domain of unstructured data, such as text messaging, photos and video. In the healthcare and life sciences arena data growth is evident, and more sources to analyse are becoming accessible. Increasing as healthcare agencies, providers and network organizations digitize their processes and patient records. The evidence of the range of different data sources that are considered, can be observed in the industry's signal detection process. While the safety database, which is comprised of internal data, is still the most valuable at 63%; in 2016 external data across numerous source types such as claims data, electronic health record, authority databases etc. represented a noteworthy source in which 37% of identified signals have originated.

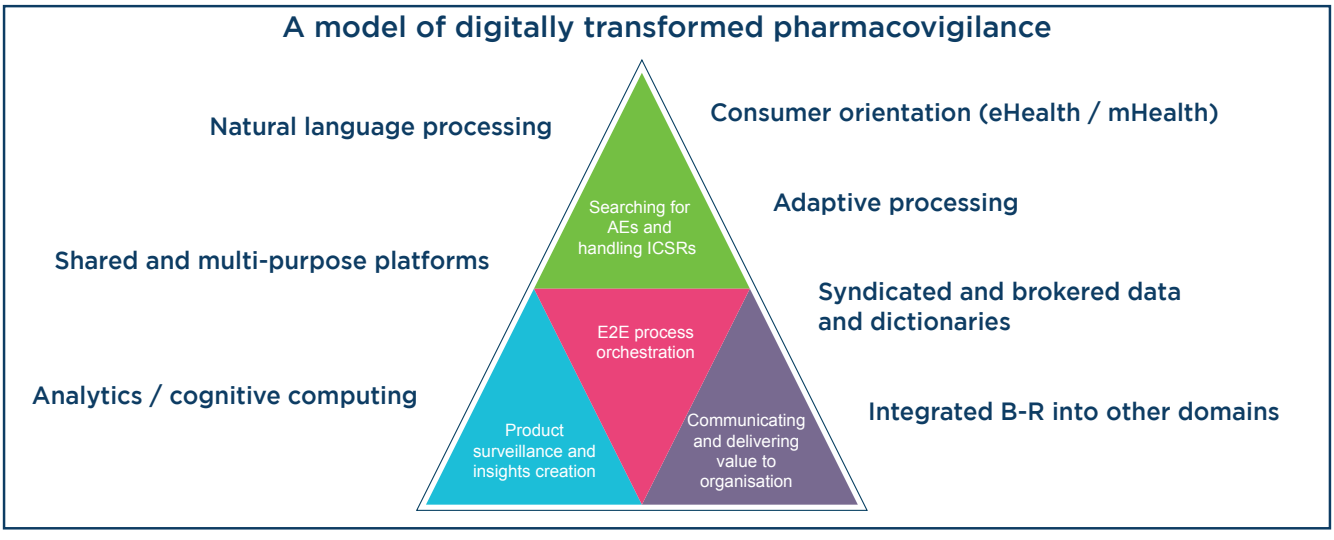
Social media is one of the leaders in global data growth and contributes to the over-representation of unstructured data. Despite this, no signals were identified from social media sources by the pvnetworks members in 2016, which begs the question of what value social media scanning has. This question stands poised against the current requirements to trawl company sponsored sites. To provide more clarity on the matter, some companies have endeavoured into pilots using natural language processing (NLP) technology. One of the most significant initiatives in this regard is the IMI Web-RADR joint venture between European agencies and volunteering public and private organizations that have a European presence. Web-

RADR objectives have partially been to improve understanding of the value of social media scanning. It is indicated that publicly accessible social media sources, in this case Twitter, overall contain less safety information when comparing to WHO VigiBase for the products investigated (38 products in total). However, Web-RADR suggests that social media does provide insights into areas that may be harder to get visibility into from traditional methods of reporting. Highlighted benefits of social media scanning include data richness of neurological & psychiatric effects, pregnancy and lifestyle treatments, misuse and abuse, as well as present added value in understanding patient tolerance and treatment discontinuation causes. While the social media data analysis of Web-RADR has concluded, it is expected that the project will contribute to added guidance for the industry within the next year, likely through an update of the EMA GVP module.

## The outline of the digital approach has been formed

Web-RADR is one project among many to experiment on how to apply new and emerging technology to the benefit of patient safety - and its operational sustainability. During 2015, Navitas Life Sciences realized that a collaborative effort was needed, to focus on collecting examples and generating knowledge on these initiatives of PV data futures. Therefore, a "PV data futures" working group was formed within the pvnetworks umbrella, to support PV technology leaders with a platform to observe and discuss the value as well as concerns on cutting edge developments. While collecting significant input during 2015-2016, the understanding of technology's pervasive potential for PV grew and became a significant turning point in 2016 in the sense that the concern for using technology as a driver for innovation now came to represent the top priority for senior PV leaders / Heads of Safety. Expanding the idea of networking and sharing knowledge to encompass the wide business interests, the pvnetworks hosted two "technology showcase" events to stimulate cross business-technology discussions from innovative yet concrete Industry pilots. The networking concept is bound to develop further, and has already spawned a new interest group on Automation in 2017.

As the evidence from pilots is collected and the industry discusses the future orientation of pharmacovigilance, structural areas of interest emerge. Concepts around how to address big data volumes, using technologies like NLP remains central. Cognitive computing, Robotic Process Automation (RPA) and Artificial Intelligence are also all concepts commonly mentioned as part of the future design, together with data brokerage and overall notion that sharing platforms may just be the better way to achieve goals in some cases. To structure the use-cases and provide a framework for discussion and measuring maturity, Navitas Life Sciences has compiled the input into a model of digitally transformed pharmacovigilance. The model basically attempts to summarize where innovative approaches unfold.



## The four pillars where transformation is expected:


Searching for AEs considers options for automation of the identification and intake of safety information from e.g.:

- Health care professional/consumer reporting
- Social media
- Literature
- Patient Support Programs / Market Research Programs
- eHealth / mHealth / EHR / PHR
- Observational
- Clinical / pre-clinical

Handling of ICSRs considers options for automation in central process steps, e.g.

- Triage
- Case entry / coding
- Med. Evaluation
- QC
- Reg. requirements
- Submission

Considers cognitive computing applied to perform safety surveillance and to create deliverables that contribute to product insights, e.g.

- Signal detection
- Risk management
- Aggregate reporting
- Health hazard evaluation

Considers the span across pharmacovigilance processes and stakeholders, where technology is applied to create cohesive data streams, from global partner/affiliate structures through to scientific teams and considers adaptive processing for a risk based approach to placing effort on most important cases and products

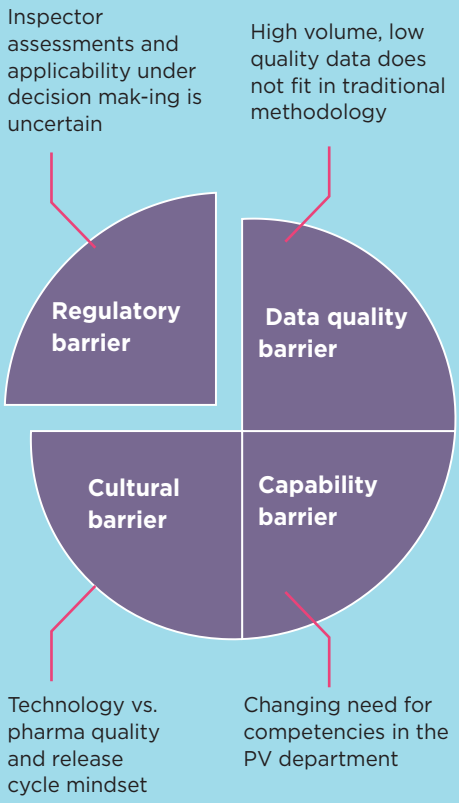
Considers pharmacovigilance in its context with other stakeholders in the enterprise as well as external parties, such as patients and media, e.g.

- Health outcomes
- Benefit-risk assessment
- Issues management
- Patient centricity and interaction
- Safety communication to regulators and HCPs

The outcome of discussions during Industry meetings point to the idea that automation should really be seen as a ladder, progressing from simple scripting to fully autonomous artificial intelligence. An understanding of where each pharma company could get the most from bringing processes up the steps of the ladder is a key question, and constructing a matrix of business process step value potential versus technological capability becomes a strategic guidance to progress by.

## 4 Key barriers for industry adopting digital innovation in PV

While the concepts and potentials are becoming more tangible, so are some of the concerns that have been identified. So far, we can condense this into 4 distinct barriers that jeopardize or potentially prohibits success, if not tackled.




## Regulatory barriers

Perhaps the greatest barrier to bringing in new technology such as NLP and cognitive computing into pharmacovigilance is the uncertain position of agency inspectorates. The risk of non-compliance during an inspectorate scrutiny is deeply embedded in the Industry. Significant efforts have been spent over the past decades on implementing a PV system that delivers high probability of success in audit and inspection settings, hence changes are always followed with a level of anxiety. Therefore, the introduction of completely automated processes using NLP and cognitive computing will set off alarms. As it rightfully should, because most legislative structures, definitions and above all consensus of how good practice looks like for NLP and cognitive computing are not present today. To summarize some key uncertainties from changing the current system to relying on digital, automated concepts:

- Inspection hand-shake: Industry PV organization and processes built since the 1960's provides a well-known framework for inspections and preparing for inspections is a rehearsed routine
- People/Training qualifications and associated documentation is the key safe-guard in the current system
- Without "good practice" references, systemic failure in technology could be escalated to licence-to-operate issue
- Lack of regulatory concepts on how to sufficiently "validate" a learning computerized system
- Lack of regulatory concepts regarding the handling of real world data e.g. by NLP
- Lack of regulatory concepts of how to produce a reliable result on surveillance of new data sources

In short, there is no certainty today on how an inspector from an authority would judge a missed signal or lack of case submissions by a fully automated process.

Despite not having that clarity today, it should be noted that US FDA and EMA are actively seeking to use technology advancements to improve protection of the public, in their own ways. The societal drive for digital healthcare is applying pressure on regulators and it will drive the formulation of a position on the matter. Current regulator-driven initiatives that involve automation in the analytics space, include Sentinel, IMI Web-RADR and IMI Protect. Especially Sentinel which is coming to a mature state, where both CBER, CDER and more recently CDRH are actively practicing the multi-sources analytics framework actively in regulatory decision making. The FDA is now also providing a Sentinel similar setup to other public or private entities via the IMEDS initiative.

## Capability barriers

Given that the innovations described are primarily based on technology, a question of capabilities to leverage these innovations becomes essential. There is a need for technology savvy, yet domain knowledgeable resources, to effectively place innovation in the hands of the process experts. This includes the basis of understanding of where experimentation is appropriate, but also deployment and sustainable operations. It calls for new partnerships and governance of third party engagements, with some who may hardly understand the framework which the global pharma enterprise operates within.

## Cultural barriers

The cultural aspects may also pose as a significant barrier, as there is a large gap between the aggressive (and sometimes poorly tested) release cycles of technology in comparison to the controlled, decade-long process in pharma to bring new products to market. Certainly, risk

## About the Author

**Martin Holm-Petersen** is heading the pvtech network at Navitas Life Sciences. With 10+ years of experience within the PV in the pharmaceutical industry and another 10 years in consulting, Martin is an experienced manager and pharma strategist. Including longstanding experience at Director level for a top 10 pharma company. His education background is a Masters in Science of Communication studies.

appetite and technology experimentation is not apart of the normal vocabulary in pharmacovigilance departments. As a new approach on how to integrate and calibrate mindsets would be important to success.

### Data quality barriers

The future is paved with unstructured information originating from several sources. While scanning has now been underway for some years in the pharmacovigilance context. It is not trivial to try and understand unstructured, human and sometimes broken language, especially in the light of social channels where emoji's, sarcasm and slang makes it a challenge to produce quality data for PV science. Let alone even gathering all the relevant data points constituting a valid case. Sources that lack the medical thoroughness and structure represents a paradigm on its own; pharma companies have been building processes for decades to produce high quality data, to prove efficacy and safety. There will be pressure to find new methods for bridging the two worlds of data. As previously suggested by Web-RADR, real-world data provides an alternative analytical framework with complimentary assets. A little further into the future, wearable devices that are not considered medical grade, may be part of the PV data eco system. Simply because of its pervasiveness and the potential to suggest a signal that would not be visible in traditional analytical methods of PV before months or years after.

Cyber security is yet another angle of concern, as processes are increasingly automated and feed of a larger number of data sources that rely on pervasive computing throughout its life cycle. The volatility and exposure to the enterprise grows, essentially to require substantial cybersecurity and protection measures.

## Conclusions and way forward

The Industry as well as the regulatory agencies have picked up on the potentials of technology innovation for PV. Industry dialogue and experimentation have furthermore led to a clearer idea of where value could be generated in the future. Both providing PV departments with a much-needed approach to handle some of the work effort increases, as well as improving the overall patient safety. In December 2016, The European Commission published a report "Study on Big Data in Public Health, Telemedine and Healthcare", which highlights the need for a push towards the use of real-world data and technology across the public-private sector. This extends directly from the IMI Protect and IMI Web-RADR initiatives that become defining because they are helping to determine common methodology. Initiatives to concretely do just that may gradually eliminate some of the barriers and concerns that is bound to inhibit much of the potential value creation for the years to come. The FDAs Sentinel and IMEDS similarly provides a pathway to share methods and tools. Rich Moscicki, Deputy Center Director for Science Operation, FDA CDER, recently (March 2017) underlined their commitment and enthusiasm on the back of 9 years of building and improving Sentinel: "Our investment and our reliance is being paid back in a very important way. Drug safety today is better than is has been in the past, and it points us to how drug safety can be even better in the future".

What remains central is a need to share thoughts, insights and methodologies, which will be a continued focus for the pvnetworks going forward.

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