Reliable Real-world Data & Proactive Signal Detection – *The Revolution Pharmacovigilance is Crying Out for*

Signal detection in real-world drug monitoring has barely changed in 70 years, since the practice was first introduced in response to the thalidomide tragedy of the late 1950s/early 1960s. But now smart analytics, applied to robust real-world data from electronic medical records and healthcare claims, promises to make comprehensive, proactive signal detection a reliable reality. Going forward, Life Sciences R&D decision-makers, regulators and other healthcare ecosystem stakeholders will be able to continuously track adverse effects without recourse to data scientists, and without the steer of an existing hypothesis. The breakthrough could also help identify new opportunities for drug repurposing, so that Safety becomes a driver of commercial benefit as well as a protector of patients. ArisGlobal's Elizabeth Smalley explains.

In a 2022 life sciences industry report,[1] 70% of biopharmaceutical professionals indicated a maturity gap in the efficiency of safety signal analytics processing. Transforming signal detection, as well as signal validation, in ever smarter ways, promises to close that gap, boosting pharmacovigilance (PV).

And not before time. Safety signal monitoring has barely changed in 70 years, from when the practice was first introduced in response to the international thalidomide tragedy – after GPs began to observe an increase in babies being born with disabilities, including the shortening and absence of limbs, and a correlation was discovered with their mothers having taken thalidomide during pregnancy.[2] Systematic monitoring of adverse drug reactions was one of the formal regulatory responses to the tragedy which affected more than 10,000 babies around the world.

Since then, other than adapting paper-based manual reporting with some form of electronic equivalent, very little has progressed in the discipline of signal detection and analysis. Outside of the clinical environment, with its inherent limitations (as well as being highly controlled, trials' safety monitoring cannot touch the vast variety of human genomes that a drug will encounter post-market), adverse event monitoring relies too heavily on patient and clinician reporting. And, still today, too many adverse events go unreported (up to 95% in the worst cases[3]).

The Case for Change

Even once submitted, Individual Case Study Reports (ICSRs) take time to process before they are used in signal detection. Analyses of medical literature, another PV channel, also inevitably involve a time delay, while scouring of online forums yields too much noise.

With smart, sophisticated analytics technology that can filter for causal and sensitivity to substantially reduce signal 'noise' (with 40%+ more accuracy than traditional signal detection methods, as demonstrated in extensive studies conducted by ArisGlobal[4], professionals will be able to distil precise adverse event insights directly using robust real-world data from electronic medical records and healthcare claims, boosting drug safety and driving new efficiency for developers. Access to this data is being democratised, thanks to strategic partnerships designed to empower drug developers and their Safety teams with timely, reliable feeds combined with smart, intuitive analytics technology.

Moving signal detection closer to the patient will help address gaps and lag time in adverse event reporting, reducing marketing authorisation holder (MAH) risk. Indeed, the benefits will be widely felt right across the healthcare ecosystem – by patients, drug development companies, regulators, and clinicians.

Proactive, hypothesis-free signal detection along with improved signal strength is shown to reduce false positives and detection signals earlier. The incorporation of real-world data, meanwhile, means signals are detected even faster and with impressive precision – the equivalent of a thermometer quantifying the progression of an illness, or a financial credit score objectively assessing an individual's economic health/risk, enabling robust new protocols and better overall outcomes.

These developments couldn't have come at a better time. Up to now, an element of industry inertia has curbed proactive innovation in safety signal detection; typically, compliance has been the primary driver of the measures implemented.

The recent pandemic prompted swifter and more continuous vigilance as advanced vaccines were rolled out with speed, and across huge swathes of the global population. Regulators meanwhile have led the way in breakthrough innovations for signal detection and validation. Examples include EMA's adoption of DARWIN EU, a platform to generate real-world evidence (RWE) to support the decision making of EMA scientific committees and national competent authorities in EU Member States throughout regulatory processes. Meanwhile, Sentinel, FDA's national electronic system, is transforming the way researchers monitor the safety of FDA regulated medical products (here real-world data is used for validating signals, though not for detection).

Advances in AI, and Real-world Data Access

To keep pace with accelerating change and new waves of innovation in Life Sciences, drug developers have little choice but to ramp up their signal detection and analysis capabilities now. At a practical level, a combination of technology advances and more readily available real-world data is paving the way for much more robust and responsive safety vigilance.

At an artificial intelligence (AI) level, 'large language models' (next-generation neural networks) are transforming the precision with which Safety teams can distil insights from vast data sets, quickly learning and progressively honing their knowledge of what to look out for and what to discount.

The technology is so intuitive to use that Safety teams have less need for the intervention of epidemiologists or data retrieval experts, now being able to perform a deeper level of causal analysis themselves. Large language models (LLMs) are priming

the pharma industry to easily embrace all kinds of AI, something that was not true even three years ago. As a result, we can expect to see extensive adoption of proactive signal detection in record time.

Provided there is an appropriate interface, and that the right data preparations have been made so that Safety teams cannot be misled by the findings, Safety professionals can perform their own investigations on the fly, in a highly repeatable way. This is ultimately much more efficient and responsive than requesting a one-off, hypothesis-based study which, as well as being labour-intensive, requires that the query parameters are known up front.

Broader Benefits

The benefits of proactive signal detection, via AI-sharpened analysis of extensive and robust real-world data, in conjunction with ICSRs, are broader than simply faster speed and greater accuracy.

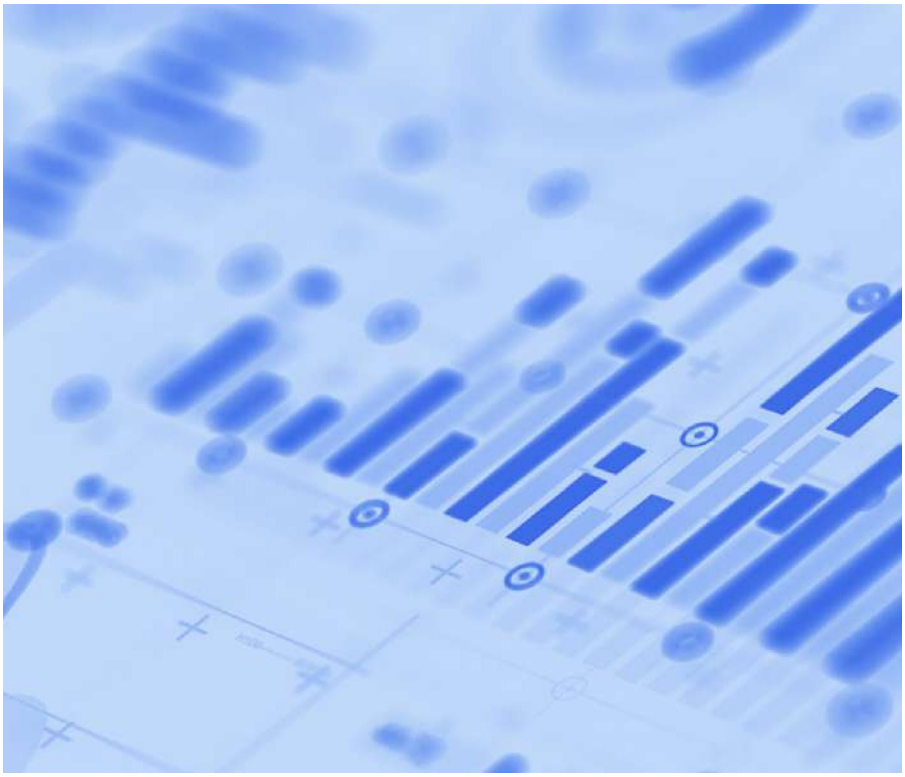
Firstly, as correlations are detected earlier and with improved precision, drug developers will be in a position to spend more time on higher value activities including innovation in drug discovery, and on delivering safer drugs to patients, sooner.

Secondly, safety-based communications will become much more targeted. Instead of stating generically that a drug may increase the risk of heart attack, the advice can specify that this risk applies specifically to women between the ages of 30 and 60 who have a pre-existing heart condition, for instance, in the context of a very specific phenotype, in other words.

Increasing the specificity of any warnings promises to keep the higher risk patients safe by improving adherence, while removing false restrictions to the size of the market. This opportunity goes hand in hand with the growing focus on personalised medicine, potentially expanding the targetable market for Drug X compared to rival Drug Y (a rival without the same targeted advice), while minimising the actual risk of safety events.

Positive Correlations: Distilling Unexpected Commercial Opportunities.

Beyond safety and compliance applications, the same mathematical modelling used in adverse event monitoring also supports signal detection in drug repurposing, potentially presenting new commercial opportunities to drug developers as previously unknown and unexpected positive



correlations are discovered. (A signal is any previously unknown information about the causality of a drug and event; it needn't be a negative outcome.) In the context of a benefit-risk profile, this is an opportunity to focus as much on the benefit as on the risk profile, and to grow the commercial potential of a drug.

In this context, Safety has an unprecedented opportunity to shine as a strategic partner to the business, rather than merely a cost centre that exists to contain risk.

Crucially, these are possibilities that leading pharma organisations are already exploring today, certainly in the context of adverse event signal detection. As a result, patient safety will go up, teams will be freed up to spend more time on drug discovery, and more time on drug repurposing, ultimately leading to more safe and effective medicines being put into the hands of patients earlier.

In an industry now so keen to innovate in all aspects of drug development and delivery, next-generation signal detection is emerging as an exciting field to watch.

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